A General Synthesis of 4-Substituted 6-(2-Imidazolinylamino)-5,8-dimethylquinolines

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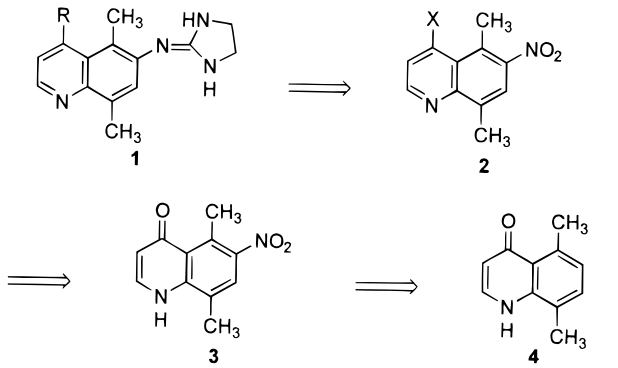
Received October 24, 1997

A general synthesis of 4-substituted 6-(2-imidazolinylamino)-5,8-dimethylquinolines **1** has been developed. All new compounds were synthesized from a common intermediate, 5,8-dimethyl-6-nitro-4-quinolone **3**, the structure of which was confirmed by X-ray crystallography. This methodology involved the conversion of **3** into either a 4-chloro- or 4-bromoquinoline followed by the introduction of various 4-substituents late in the synthetic sequence. Substituents introduced in this way include alkyl (**18a**), alkoxy (**12a**, **12b**), halo (**9**, **12c**, **16**), cyano (**18b**), thioalkyl (**12d**), acetamido (**14**), carboxamido (**19**), and hydroxy (**10**). This work illustrates the utility of 4-haloquinoline intermediates in the general synthesis of 4-substituted quinolines.

Introduction

In the context of our search for new adrenergic compounds,[1] we wished to develop a general synthesis for 4-substituted 6-(2-imidazolinylamino)-5,8-dimethylquinolines of type **1** (Scheme 1). The chemistry of quinolines has been well reviewed,[2−5] and there are two major strategies for constructing the quinoline nucleus.[2] A common approach involves cyclization of an aniline with a three-carbon piece. The Skraup reaction[6] and the milder Doebner−von Miller reaction provide a variety of substituted quinolines, while the Beyer method and the Combes method uniquely afford 2,4-disubstituted compounds.[2,3] Also in this category are the Knorr synthesis, which provides 2-quinolones, and the Conrad−Limpach method, which affords 4-quinolones.[2,3] A second major approach to quinoline construction involves the reaction of an aniline, substituted in the 2-position with a carbonyl group, and a two-carbon unit. Examples include the Friedlander method[7] which begins with a 2-aminobenzaldehyde or 2-aminophenyl ketone, the Pfitzinger method[3] which begins with isatin, and the von Niementowski[4] reaction which starts with anthranilic acid.

Scheme 1. Retrosynthetic Analysis



All of the above methods have limited flexibility for the introduction of 4-substituents in quinolines because the ring cyclization reactions generally establish the substitution pattern and functionality. We wished to develop a synthetic approach that would allow us to introduce various substituents at the 4-position with maximum efficiency. Ideally these compounds would be synthesized from a common intermediate and allow for the introduction of the R group (alkyl, alkoxy, halo, cyano, thioalkyl, acetamido, carboxamido, hydroxy) late in the synthetic sequence. The development of this chemistry is described in this report.

Results and Discussion

Examination of the retrosynthetic analysis (Scheme 1) shows that the nitro and halogen substituents of 4-halo-6-nitroquinoline **2** can be converted to the 6-(2-imidazolinylamino) functionality and the R group, respectively, found in **1**. Halogenation[4,8] of 5,8-dimethyl-6-nitroquinolone **3** will give **2**, and nitration of known 5,8-

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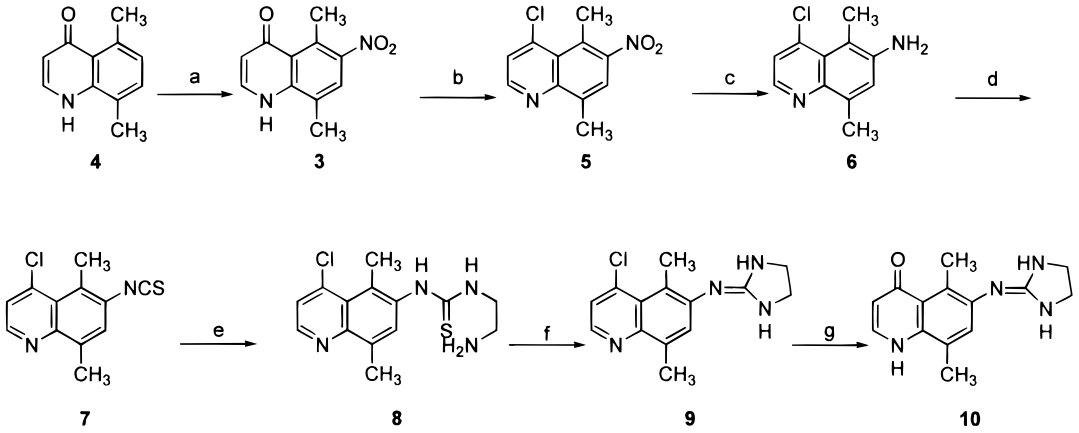
S0022-3263(97)01959-2 CCC: $15.00
Published on Web 08/05/1998

Scheme 2[a]



[a] Key: (a) HNO_3/H_2SO_4; (b) $POCl_3$; (c) $SnCl_2$; (d) DPT/DMAP; (e) ethylenediamine; (f) $Hg(OAc)_2$; (g) HCl/2-PrOH.

dimethylquinolone **4**[9−11] will give rise to the key intermediate, nitroquinolone **3**. The regiochemical outcome of this nitration, accomplished with nitric acid and sulfuric acid (Scheme 2), was determined by X-ray crystallography. Compound **3** was transformed into both the 4-chloroquinoline and 4-bromoquinoline for further elaboration.

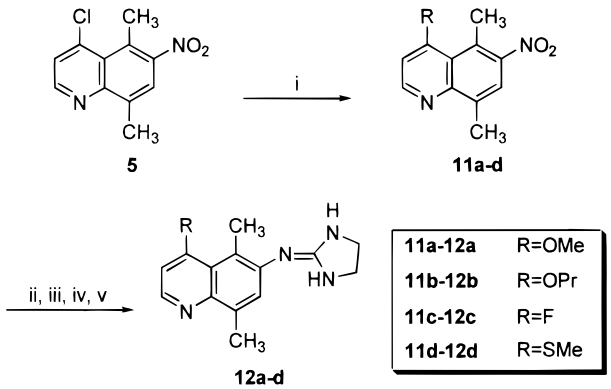
Conversion of nitroquinolone **3** to the corresponding 4-chloroquinoline **5** is indicated in Scheme 2. By heating **3** in an excess of phosphorus oxychloride, **5** was obtained in an 84% yield and used without further purification. The chloroquinoline **5** subsequently served as a precursor to seven desired 4-substituted aminoimidazolines. The 4-chloro amino derivative **6** was formed in a straightforward manner by reducing the nitro functionality of **5** with tin chloride. From **6**, a three-step procedure was used to generate the aminoimidazoline, which involved first forming the isothiocyanate **7** using di-2-pyridyl thionocarbonate (DPT) and 4-(dimethylamino)pyridine (DMAP) in methylene chloride.[12] Compound **7** was converted to the thiourea **8** with ethylenediamine, and this was followed by cyclization to aminoimidazoline **9** using mercuric acetate. We have found this three-step procedure (isothiocyanate, thiourea, cyclization) to be a convenient and general way to convert amines into aminoimidazolines. Most final aminoimidazolines were converted to and characterized as salts (see Table 1). The quinolone analogue **10** was obtained in one step directly from **9** by hydrolysis in a hydrochloric acid/2-propanol/water mixture. Low solubility of quinolone intermediates precluded direct conversion of **3** into **10**. Initially we treated **9** with dilute hydrochloric acid, but no reaction was observed. Addition of 2-propanol subsequently led to quinolone formation. Heindel and Fine[13] have shown that certain 4-chloroquinolines can be converted into 4-quinolones upon treatment with refluxing alcohols. In theory, the 4-haloimidazolines such as **9** could have been used as intermediates to a variety of 4-substituted quinolines. The aminoimidazolines are generally very polar and difficult to handle, so we instead chose the nitro compounds of type **2** as intermediates.

Table 1. Purification of Free Base and Salt Formation

free base	solvent system[a]	salt[c]	
9	8:2:0.1 CH_2Cl_2/MeOH/NH_4OH	1.0 acetate	0.25 H_2O
12a	9:1:0.1 $CHCl_3$/MeOH/NH_4OH	2.0 HCl	0.5 H_2O
12b	9:1:0.1 $CHCl_3$/MeOH/NH_4OH	0.5 fumarate	0.75 H_2O
12c	8:2:0.1 CH_2Cl_2/MeOH/NH_4OH	1.0 fumarate	0.1 H_2O
12d	100% MeOH	1.0 acetate	0.5 H_2O
14	1:1 CH_2Cl_2/MeOH up to 1:1:0.1 CH_2Cl_2/MeOH/NH_4OH[b]	2.0 HCl	1.0 H_2O
16	8:2:0.1 CH_2Cl_2/MeOH/NH_4OH	1.0 acetate	
18a	8:2:0.1 CH_2Cl_2/MeOH/NH_4OH	2.0 HCl	1.0 H_2O
18b	9:1:0.1 $CHCl_3$/MeOH/NH_4OH	1.0 acetate	0.75 H_2O

[a] Solvent system for chromatography of free bases. [b] Gradient elution used. [c] Salts were formed by dissolving free base in methanol, adding 1.0 equiv of acid, and precipitating with diethyl ether.

Scheme 3[a]



[a] Key: (i) **11a**: $NaOCH_3$; **11b**: n-PrOH/HCl; **11c**: FD-KF; **11d**: $NaSCH_3$; (ii) **12a** and **12b**: $SnCl_2$; **12c**: H_2, 10% Pd/C; **12d**: H_2, 5% Pd/C; (iii) DPT/DMAP; (iv) ethylenediamine; (v) $Hg(OAc)_2$.

Two methods were employed to convert chloroquinoline **5** into 4-alkoxy-substituted compounds (Scheme 3). Methoxy compound **11a** was formed in 84% yield by treating **5** with sodium methoxide in methanol. The nitro group was reduced with tin chloride to the amine, followed by the preparation of the aminoimidazoline **12a**. On the other hand, propoxy compound **12b** was obtained in similar yield by treating **5** with *n*-propanol and hydrochloric acid at room temperature.[14] From **11b**, a tin chloride reduction formed the amine, followed by the

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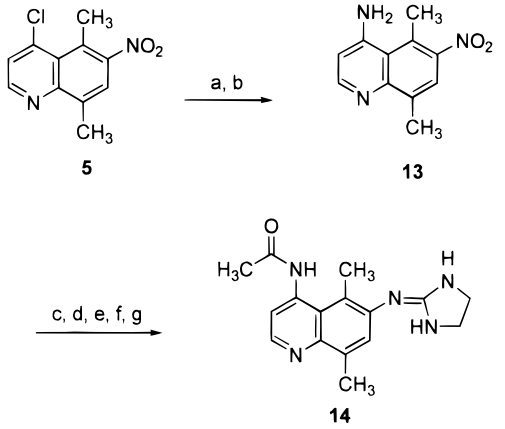
Scheme 4[a]

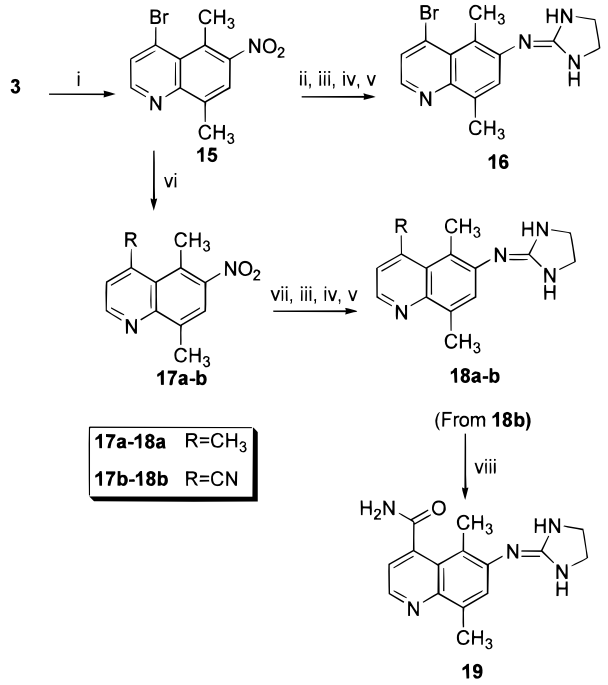


[a] Key: (a) NaN_3; (b) $NaBH_4$; (c) acetic anhydride/Et_3N; (d) H_2, 5% Pd/C; (e) DPT/DMAP; (f) ethylenediamine; (g) $Hg(OAc)_2$.

preparation of the aminoimidazoline **12b**. Compound **5** also served as a substrate for the synthesis of a 4-fluoro derivative. 4-Fluoroquinolines are known to have limited chemical stability under certain conditions, and preparations have been attempted using the Schiemann reaction.[15] Recently, the combination of 2-trifluoromethylaniline and lithium enolates has been reported to provide 4-fluoroquinolines.[16] It is known that 2-chloroquinoline can be converted into 2-flouroquinoline using anhydrous potassium fluoride.[17] Using a similar procedure, 4-chloroquinoline **5** was converted into 4-fluoroquinoline **11c** through the use of freeze-dried potassium fluoride (FD-KF) in hot DMSO.[18] From **11c**, a tin reduction in ethanol resulted in the displacement of the fluorine atom by ethanol. Atmospheric hydrogenation using palladium on carbon in ethyl acetate resulted in a 94% yield of 6-amino-4-fluoroquinoline which was followed by the preparation of the aminoimidazoline, **12c**. A methylthioquinoline, **11d**, was synthesized by the reaction of **5** with sodium thiomethoxide. The nitro functional group of **11d** was reduced with hydrogen using palladium on carbon to give the amine, which was followed by the preparation of the aminoimidazoline, **12d**.

The synthesis of the 4-acetamido compound **14** is shown in Scheme 4. A common method of obtaining quinolines substituted in the 4-position with a primary amino group is to treat 4-chloroquinoline with ammonia in sealed vessels.[4] We have found an alternate approach to 4-aminoquinolines which involves first the displacement of the 4-chloro group with azide.[19] This is followed by reduction with sodium borohydride, a reduction that has proven useful in the conversion of 9-chloroacridines into 9-aminoacridines.[20] Accordingly, chloroquinoline **5** was converted to 4-aminoquinoline **13** via the azide. Treatment of **13** with refluxing acetic anhydride provided a diacetylated material. This structural assignment was based on mass spectral data, a single carbonyl resonance

Scheme 5[a]



[a] Key: (i) $POBr_3$; (ii) iron/acetic acid; (iii) DPT/DMAP; (iv) ethylenediamine; (v) $Hg(OAc)_2$; (vi) **17a**: $PdCl_2(PPh_3)_2/(CH_3)_3Al$/LiCl, DMF; **17b**: CuCN; (vii) $SnCl_2$; (viii) H_2SO_4.

in the ^{13}C NMR spectra, and similar structural assignments of acetylated 5-aminoacridines.[21] The 6-nitro group was reduced to the 6-amino compound using hydrogen and palladium on carbon. In the subsequent preparation of the aminoimidazoline, hydrolysis of one of the acetyl groups occurred during the mercuric acetate promoted cyclization to afford the monoacetamide analogue, **14**.

The introduction of certain groups required the use of a 4-bromoquinoline intermediate (Scheme 5). The use of phosphorus oxybromide and dimethylaniline in toluene has been documented[8] as a way to transform 4-quinolones to 4-bromoquinolines, but in our system, this reaction resulted in complex mixtures. By replacing the dimethylaniline with pyridine, bromoquinoline **15** was obtained in 40−50% yield and could be used without further purification. Reduction of the nitro group of **15** was initially attempted with tin chloride, but a mixture of 4-chloro- and 4-bromoaminoquinolines resulted. We were able to obtain 6-amino-4-bromoquinoline by reducing the nitro group with iron and acetic acid. This was followed by the preparation of the 4-bromo aminoimidazoline, **16**.

4-Alkylquinolines can be synthesized from anilines using a Doebner−von Miller approach.[22] Unfortunately, this strategy requires a separate quinoline ring synthesis for each desired 4-alkyl substituent. We have found bromoquinoline **15** to be an effective substrate for a Stille coupling reaction (Scheme 5).[23] Reaction of **15** with trimethylaluminum, bis(triphenylphosphine)palladium(II) chloride, and lithium chloride in DMF provided trimethylquinoline **17a**. The nitro group was reduced using tin

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chloride to give the amine, which was followed by the preparation of the aminoimidazoline, **18a**. Compound **15** can also serve as a substrate for the introduction of a nitrile in the 4-position. A 4-cyanoquinoline, **17b**, was obtained by treating **15** with cuprous cyanide in DMF. This was followed by a tin chloride reduction and further elaboration to provide the aminoimidazoline, **18b**. A 4-carboxamido derivative **19** was obtained directly from **18b** by hydrolysis with sulfuric acid.

Conclusions

We have developed a general strategy for the late-stage introduction of various substituents into the 4-position of 6-imidazolinylaminoquinolines. All groups were introduced via a common intermediate, nitroquinolone **3**, thereby avoiding the resynthesis of the entire quinoline ring system for each desired compound. Nitroquinolone **3** can be easily converted into 4-haloquinolines **5** or **15**. Replacement of the halogen with the desired substituent and formation of the aminoimidazoline groups complete the synthesis of the desired compounds.

Experimental Section

Liquid chromatography was performed by using flash column chromatography conditions (silica gel 60, particle size 40−63 μm purchased from EM Science of Gibbstown, NJ) or by filtering through a fritted glass funnel packed with a layer of sand/flash silica gel/sand, using a water aspirator vacuum (hereafter this will be referred to as an aspirator vacuum column). Thin-layer chromatography (TLC) was accomplished using silica gel GF (250 μm) on prescored plates (10 × 20 cm) obtained from Analtech Inc., Newark, DE. Proton (300 MHz) and carbon-13 (75 MHz) nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded using $CDCl_3$ as a solvent except where noted. Mass spectra (MS) were obtained using chemical ionization or ion spray. Melting points were uncorrected. Elemental analyses were obtained from Oneida Research Services, Whitesboro, NY. The free bases **9**, **12a**, **12b**, **12c**, **12d**, **14**, **16**, **18a**, and **18b** were purified and characterized as salts (see Table 1).

5,8-Dimethyl-4-quinolone (4)[9−11] was prepared as described in the literature.

5,8-Dimethyl-6-nitro-4-quinolone (3). Quinolone **4** (5.0 g, 0.0289 mol) and sulfuric acid (30 mL) were combined and stirred at room temperature for 10 min. The resulting dark green solution was placed in an ice−water bath, and nitric acid (2.73 g, 0.0298 mol, 1.9 mL, 15.4 M) was added dropwise. The reaction became orange-red in color. After the addition was complete, the reaction was allowed to stir for 15 min in the ice water bath. The reaction mixture was then poured into a stirring solution of ice−water (400 mL). The mixture became a creamy beige color and was allowed to stir until it warmed to room temperature. The pale tan solid was filtered, washed with water, vacuum-dried, and recrystallized from ethanol to give **3** (4.4 g, 70% yield) as a yellow solid. Mp: 274−300 °C (dec). ^{1}H NMR (DMSO-d_6): δ 2.43 (s, 3 H); 2.75 (s, 3 H); 5.60 (br s, 1 H); 6.16 (d, J = 7.4 Hz, 1 H); 7.83 (d, J = 7.4 Hz, 1 H); 7.87 (s, 1 H). ^{13}C NMR (DMSO-d_6): δ 17.27, 17.60, 112.46, 123.57, 126.60, 131.92, 139.58, 142.48, 146.50, 179.64. MS (CI) m/z 219 $[M + H]^+$. Anal. Calcd for $C_{11}H_{10}N_2O_3 \cdot H_2O$: C, 55.92; H, 5.12; N, 11.86. Found: C, 55.69; H, 4.81; N, 11.56.

4-Chloro-5,8-dimethyl-6-nitroquinoline (5). Nitroquinolone **3** (2.70 g, 12.42 mmol) and phosphorus oxychloride (38.02 g, 248.53 mmol, 23.1 mL) were combined and heated to an oil bath temperature of 95 °C. The reaction was monitored by TLC for loss of starting material and cooled to room temperature after 2 h. The reaction was poured slowly into a stirring mixture of ice−water (200 mL) and basified with concentrated ammonium hydroxide. This mixture was extracted with chloroform (3 × 75 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and rotary evaporated to give **5** (2.4 g, 82% unpurified yield). Compound **5** was used without purification in the next step. Mp: 120−121 °C. ^{1}H NMR: δ 2.75 (s, 3 H); 2.91 (s, 3 H); 7.55 (d, J = 4.6 Hz, 1 H); 7.69 (s, 1 H); 8.78 (d, J = 4.6 Hz, 1 H). ^{13}C NMR: δ 18.96, 19.24, 123.57, 125.13, 126.14, 126.97, 138.62, 144.09, 149.87, 150.69. MS (CI): m/z 237 $[M + H]^+$.

6-Amino-4-chloro-5,8-dimethylquinoline (6). Chloronitroquinoline **5** (1.40 g, 5.94 mmol), ethanol (50 mL), and tin chloride dihydrate (6.68 g, 29.61 mmol) were combined and heated to reflux. After 30 min, the reaction was cooled to room temperature, poured into crushed ice (200 g), and basified with concentrated ammonium hydroxide (30 mL). This mixture was extracted with chloroform (3 × 250 mL), dried over K_2CO_3, filtered, and rotary evaporated. The crude material was purified by flash column chromatography, eluting with 20% ethyl acetate in hexane, to give **6** (0.686 g, 56% yield) as a solid. (In most subsequent cases, 4-substituted amines were used without further purification). ^{1}H NMR: δ 2.67 (s, 6 H); 3.8−4.0 (br s, 2 H); 7.07 (s, 1 H); 7.34 (d, J = 4.6 Hz, 1 H); 8.45 (d, J = 4.6 Hz, 1 H). ^{13}C NMR (DMSO-d_6): δ 16.01, 18.49, 106.76, 122.76, 123.49, 126.76, 135.06, 137.83, 142.60, 143.59, 145.98. MS (CI): m/z 207 $[M + H]^+$.

4-Chloro-6-isothiocyanato-5,8-dimethylquinoline (7). Chloroaminoquinoline **6** (0.637 g, 3.08 mmol), di-2-pyridylthionocarbonate (DPT) (1.10 g, 4.76 mmol), 4-(dimethylamino)-pyridine (DMAP) (0.101 g, 0.82 mmol), and methylene chloride (60 mL) were combined and stirred for 5 h. The reaction mixture was rotary evaporated and purified by a vacuum aspirator column, eluting with 10% ethyl acetate in hexane. The compound-containing fractions were combined to give **7** (0.583 g, 76% yield) as a pale tan solid. Mp: 134−135 °C. ^{1}H NMR: δ 2.69 (s, 3 H); 2.94 (s, 3 H); 7.42 (s, 1H); 7.46 (d, J = 4.6 Hz, 1 H); 8.67 (d, J = 4.6 Hz, 1 H). ^{13}C NMR: δ 18.67, 19.16, 124.42, 126.25, 28.05, 128.45, 129.74, 137.17, 137.85, 142.59, 148.01, 148.23. MS (CI): m/z 249 $[M + H]^+$. Anal. Calcd for $C_{12}H_9N_2ClS$: C, 57.94; H, 3.65; N, 11.27. Found: C, 58.06; H, 3.94; N, 11.09.

6-[*N*-(2-Aminoethyl)thioureido]-4-chloro-5,8-dimethylquinoline (8). Chloroisothiocyanate **7** (1.27 g, 5.12 mmol) in toluene (30 mL) was added dropwise to a stirring solution of ethylenediamine (1.53 g, 25.60 mmol, 1.71 mL) and toluene (10 mL). Additional toluene (20 mL) was added to rinse in the isothiocyanate. The reaction was stirred overnight at room temperature. The resulting white precipitate was filtered and washed well with toluene to obtain **8** (1.60 g, 100% crude yield). This material was used in the next step without further purification. ^{1}H NMR (DMSO-d_6): δ 2.58 (s, 3 H); 2.66 (m, 5 H); 3.43 (br t, 2 H); 7.50 (s, 1 H); 7.61 (d, J = 4.6 Hz, 1 H); 8.67 (d, J = 4.6 Hz, 1 H). ^{13}C NMR (DMSO-d_6): δ 18.10, 18.40, 42.08, 46.77, 123.79, 125.69, 127.82, 131.31, 134.96, 136.91, 141.23, 147.88, 181.51. MS (CI): m/z 309 $[M + H]^+$.

4-Chloro-6-(2-imidazolinylamino)-5,8-dimethylquinoline (9). Thiourea **8** (0.401 g, 1.30 mmol), methanol (50 mL), and mercuric acetate (0.497 g, 1.56 mmol) were combined and stirred at room temperature. After 2.5 h, the black mixture was filtered through Celite, which was washed well with methanol. Compound **9** was purified (Table 1) and converted to a salt to give (0.242 g, 81% yield) a white solid as the monoacetate 0.25 hydrate. Mp: 205−208 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.86 (s, 3 H); 2.57 (s, 3 H); 2.68 (s, 3 H); 3.39 (s, 4 H); 7.31 (s, 1 H); 7.55 (d, J = 4.4 Hz, 1 H); 8.56 (d, J = 4.4 Hz, 1 H). ^{13}C NMR (DMSO-d_6): δ 17.87, 18.95, 22.53, 42.56, 123.15, 124.00, 126.74, 129.49, 135.68, 140.73, 144.98, 146.49, 147.10, 158.38, 173.81. MS (CI): m/z 275 $[M + H]^+$. Anal. Calcd for $C_{14}H_{15}N_4Cl \cdot CH_3CO_2H \cdot 0.25\ H_2O$: C, 56.64; H, 5.79; N, 16.51; Cl, 10.45. Found: C, 56.83, H, 5.69; N, 16.27; Cl, 10.49.

6-(2-Imidazolinylamino)-5,8-dimethyl-4-quinolone (10). Free base **9** (0.25 g, 0.92 mmol) was combined with 1 N hydrochloric acid (18.54 mL) and 2-propanol (12 mL). After stirring at 60 °C for 48 h, the mixture was rotary evaporated and recrystallized (methanol/ether) to give **10** (0.097 g, 29% yield) as the dihydrochloride 1.5 hydrate salt. Mp: > 350 °C (some dec seen at 200 °C). ^{1}H NMR (DMSO-d_6): δ 2.55 (s, 3

H); 2.67 (s, 3 H); 3.60 (s, 4 H); 6.00 (br s, 1 H); 6.90 (d, $J = 6.9$ Hz, 1 H); 7.54 (s, 1 H); 8.20 (s, 1 H); 8.29 (d, $J = 6.9$ Hz, 1 H); 10.58 (s, 1 H); 13.00 (br s, 1 H). ^{13}C NMR (DMSO-d_6): δ 17.16, 18.33, 43.17, 108.43, 121.88, 127.56, 131.98, 133.03, 133.58, 139.65, 143.03, 159.14, 175.35. MS (CI): m/z 257 $[M + H]^+$. Anal. Calcd for $C_{14}H_{16}N_4O \cdot 2HCl \cdot 1.5H_2O$: C, 47.20; H, 5.94; N, 15.73. Found: C, 47.44; H, 5.79; N, 15.91.

4-Methoxy-5,8-dimethyl-6-nitroquinoline (11a). Chloronitroquinoline **5** (1.52 g, 6.44 mmol), sodium methoxide (2.26 g, 41.83 mmol), and methanol (25 mL) were combined and refluxed under argon. The reaction was monitored by TLC and, upon completion, was diluted with methanol (50 mL) and water (100 mL). The mixture was extracted with methylene chloride (2 × 200 mL). The combined organic layers were dried over K_2CO_3, filtered, and rotary evaporated. The residue was purified by flash column chromatography, eluting with 30% ethyl acetate in hexane, to give **11a** as a solid (1.26 g, 84% yield). Mp: 162−164 °C. ^{1}H NMR (DMSO-d_6): δ 2.56 (s, 3 H); 2.58 (s, 3 H); 3.93 (s, 3 H); 7.03 (d, $J = 5.2$ Hz, 1 H); 7.74 (s, 1 H); 8.72 (d, $J = 5.2$ Hz, 1 H). ^{13}C NMR (DMSO-d_6): δ 17.93, 18.17, 56.27, 103.42, 120.01, 122.72, 126.27, 136.50, 148.37, 149.07, 152.40, 165.55. MS (CI): m/z 233 $[M + H]^+$.

6-(2-Imidazolinylamino)-4-methoxy-5,8-dimethylquinoline (12a). Methoxynitroquinoline **11a** was reduced to the methoxyaminoquinoline by the procedure used to prepare **6** (99% yield). This amine was used without further purification and converted in three steps to **12a** following the procedures previously described for the preparation of **7** (43% yield), **8** (84% yield), and **9** (92% yield). Purification and conversion of **12a** to the salt gave (0.304 g, 60% yield) the dihydrochloride hemihydrate. Mp: > 300 °C. ^{1}H NMR (DMSO-d_6): δ 2.64 (s, 3 H); 2.71 (s, 3 H); 3.61 (s, 4 H); 4.21 (s, 3 H); 7.50 (d, $J = 5.0$ Hz, 1 H); 7.75 (s, 1 H); 8.37 (s, 2 H); 8.95 (d, $J = 5.0$ Hz, 1 H); 11.12 (s, 1 H). ^{13}C NMR (DMSO-d_6): δ 17.85, 18.78, 43.14, 58.84, 103.37, 120.84, 129.10, 130.94, 133.41, 133.48, 139.08, 146.26, 158.42, 171.08. MS (CI): m/z 271 $[M + H]^+$. Anal. Calcd for $C_{15}H_{18}N_4O \cdot 2HCl \cdot 0.5H_2O$: C, 51.14; H, 6.01; N, 15.90. Found: C, 51.01; H, 6.12; N, 15.69.

5,8-Dimethyl-6-nitro-4-propoxyquinoline (11b). Chloronitroquinoline **5** (0.294 g, 1.24 mmol), 1-propanol (30 mL), and 12 N hydrochloric acid (1 mL) were combined and stirred at room temperature for 16 h. The reaction mixture was rotary evaporated to dryness and then diluted with methylene chloride (50 mL), water (100 mL), and concentrated ammonium hydroxide (5 mL). The mixture was extracted with methylene chloride (2 × 200 mL). The combined organic layers were dried over K_2CO_3, filtered, and rotary evaporated to give **11b** (0.269 g, 83% yield) as a solid. This was used in the next step without further purification. ^{1}H NMR: δ 1.08 (t, $J = 7.4$ Hz, 3 H); 1.90 (m, 2 H); 2.68 (s, 3 H); 2.77 (s, 3 H); 4.06 (t, $J = 6.3$ Hz, 2 H); 6.74 (d, $J = 5.0$ Hz, 1 H); 7.61 (s, 1 H); 8.71 (d, $J = 5.0$ Hz, 1 H). ^{13}C NMR: δ 10.81, 18.65, 18.76, 22.16, 70.92, 102.75, 123.25, 127.68, 136.63, 151.69, 165.53. MS (CI): m/z 261 $[M + H]^+$.

6-(2-Imidazolinylamino)-5,8-dimethyl-4-propoxyquinoline (12b). Propoxynitroquinoline **11b** was reduced to the propoxyaminoquinoline by the procedure used to prepare **6** (98% yield), and this amine was used in the next step without further purification. The above amine was converted in three steps to **12b** following the procedures previously described for the preparation of **7** (76% yield), **8** (72% yield), and **9** (99% yield). Purification and conversion of **12b** to the salt gave (0.101 g, 64% yield) the hemifumarate 0.75 hydrate. Mp: 230−238 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.03 (t, $J = 7.4$ Hz, 3 H); 1.84 (m, 2 H); 2.56 (s, 3 H); 2.62 (s, 3 H); 3.53 (s, 4 H); 4.09 (t, $J = 6.2$ Hz, 2 H); 6.29 (s, 1 H); 6.95 (d, $J = 5.2$ Hz, 1 H); 7.30 (s, 1 H); 8.60 (d, $J = 5.2$ Hz, 1 H). ^{13}C NMR (DMSO-d_6): δ 10.76, 17.27, 18.40, 21.73, 42.37, 70.23, 102.45, 120.82, 126.98, 128.40, 134.20, 134.84, 147.59, 149.45, 159.14, 163.60, 169.99, 181.47. MS (CI): m/z 299 $[M + H]^+$. Anal. Calcd for $C_{17}H_{22}N_4O \cdot 0.5C_4H_4O_4 \cdot 0.75H_2O$: C, 61.68; H, 6.95; N, 15.15. Found: C, 62.07; H, 6.54; N, 15.02.

4-Fluoro-5,8-dimethyl-6-nitroquinoline (11c). Chloronitroquinoline **5** (0.50 g, 2.11 mmol), dimethyl sulfoxide (12 mL), and freeze-dried potassium fluoride [FD-KF obtained by freeze-drying a 5% aqueous solution of KF[18] (0.184 g, 3.17 mmol)] were combined and heated to an oil bath temperature of 165 °C. The reaction was monitored by TLC for the disappearance of starting material. After 1 h, the reaction was cooled to room temperature and diluted with water (10 mL). The reaction mixture was filtered, and the precipitate was washed well with water and ethyl acetate. The organic−aqueous filtrate was separated. The aqueous phase was back extracted with ethyl acetate (1 × 10 mL). The combined organic layers were washed with water (4 × 50 mL), dried over Na_2SO_4, filtered, and evaporated. The crude material was purified by an aspirator vacuum column, eluting with 20% ethyl acetate in hexane, to give **11c** (0.128 g, 27% yield) as a yellow solid. Mp: 136−137 °C. ^{1}H NMR: δ 2.75 (s, 3 H); 2.78 (d, $J_{H-F} = 6.5$ Hz, 3 H); 7.18 (dd, $J_{H-F} = 12.7$ Hz, $J_{H-H} = 4.9$ Hz, 1 H); 7.74 (s, 1 H); 8.92 (dd, $J_{H-F} = 7.8$ Hz, $J_{H-H} = 4.9$ Hz, 1 H). ^{13}C NMR (DMSO-d_6): δ 16.28, 16.46, 17.81, 108.67, 108.92, 118.10, 118.20, 123.58, 124.63, 137.09, 148.48, 149.66, 153.09, 153.22, 165.45, 169.04. MS (CI): m/z 221 $[M + H]^+$.

4-Fluoro-6-(2-imidazolinylamino)-5,8-dimethylquinoline (12c). Nitrofluoroquinoline **11c** (0.8 g, 3.63 mmol), 10% palladium on carbon (0.242 g), and ethyl acetate (100 mL) were combined and placed under a hydrogen atmosphere. The reaction was monitored by TLC for loss of starting material. After 6 h, the reaction was filtered through Celite, and the solid was washed well with ethyl acetate. Evaporation and vacuum-drying of the filtrate gave an amine (0.65 g, 94% yield). The above amine was converted in three steps to **12c** following the procedures previously described for the preparation of **7** (65% yield), **8** (assumed 100% yield), and **9** (75% yield). Purification and conversion of **12c** to the salt gave (0.091 g, 63% yield) the monofumarate 0.1 hydrate. (Note: decomposition occurs upon standing in methanol). Mp: 118 °C (dec). ^{1}H NMR (MeOD-d_4): δ 2.69 (d, $J_{H-F} = 7.1$ Hz, 3 H); 2.71 (s, 3 H); 3.76 (s, 4 H); 6.65 (s, 2 H); 7.31 (dd, $J_{H-F} = 13.0$ Hz, $J_{H-H} = 5.0$ Hz, 1 H); 7.52 (s, 1 H); 8.84 (dd, $J_{H-F} = 7.8$ Hz, $J_{H-H} = 5.0$ Hz, 1 H). ^{13}C NMR (DMSO-d_6): δ 16.25, 16.41, 18.43, 43.03, 107.86, 108.10, 119.44, 119.54, 126.27, 129.93, 134.16, 135.63, 136.23, 149.31, 149.33, 150.81, 150.93, 159.97, 165.05, 168.60, 169.20. MS (CI): m/z 259 $[M + H]^+$. Anal. Calcd for $C_{14}H_{15}N_4F \cdot C_4H_4O_4 \cdot 0.1H_2O$: C, 57.47; H, 5.14; N, 14.90. Found: C, 57.23; H, 5.19; N, 14.60.

5,8-Dimethyl-4-methylthio-6-nitroquinoline (11d). Chloronitroquinoline **5** (0.30 g, 1.26 mmol) was combined with dimethylformamide (4 mL) and sodium thiomethoxide (0.16 g, 2.29 mmol). The resulting red mixture was stirred at room temperature for 30 min. The reaction was quenched with saturated ammonium hydroxide (5 mL), followed by extraction with ethyl acetate (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and rotary evaporated. The residue was purified by flash column chromatography, eluting with 50% ethyl acetate in hexane, to give **11d** (0.242 g, 77% yield) as a yellow solid. ^{1}H NMR: δ 2.60 (s, 3 H); 2.74 (s, 3 H); 2.94 (s, 3 H); 7.16 (d, $J = 4.8$ Hz, 1 H); 7.68 (s, 1 H); 8.69 (d, $J = 4.8$ Hz, 1 H). ^{13}C NMR: δ 16.81, 19.02, 19.85, 116.82, 123.00, 127.29, 127.95, 137.90, 148.65, 148.82, 149.48, 152.74. MS (CI): m/z 249 $[M + H]^+$.

6-(2-Imidazolinylamino)-5,8-dimethyl-4-methylthioquinoline (12d). Methylthionitroquinoline **11d** (0.24 g, 0.97 mmol) was combined with ethyl acetate (5 mL) and 5% palladium on carbon (100 mg). The mixture was stirred for 2 h under hydrogen at atmospheric pressure. The reaction was monitored by TLC, and an excess of palladium on carbon was added as needed. After stirring for an additional 3 h under 1 atm of hydrogen, the mixture was filtered through silica gel and rotary evaporated. The residue was purified by flash column chromatography, eluting with 25% ethyl acetate in hexane, to give the amine (0.20 g, 94% yield) as a yellow solid. This amine was converted in three steps to **12d** following the procedures previously described for the preparation of **7**, **8**, and **9**. Purification and conversion of **12d** to the salt gave (0.120 g, 18% yield) of the monoacetate hemihydrate. (An additional 0.465 of free base was recovered that was not converted to the salt.) Mp: 235−258 °C (dec). ^{1}H NMR (D_2O): δ 1.74 (s, 3 H); 2.16 (s, 3 H); 2.27 (s, 3 H); 2.42 (s, 3 H);

3.61 (s, 4 H); 6.74 (br s, 1 H); 7.11 (br s, 1H); 7.92 (br s, 1 H). ^{13}C NMR (D_2O): δ 16.85, 19.06, 19.42, 24.27, 43.91, 117.36, 128.24, 129.64, 131.78, 132.08, 137.30, 146.94, 148.09, 154.09, 160.12, 181.82. MS (CI): *m/z* 287 $[M + H]^+$. Anal. Calcd for $C_{15}H_{18}N_4S\cdot CH_3CO_2H\cdot 0.5H_2O$: C, 57.44; H, 6.52; N, 15.76. Found: C, 57.79; H, 6.45; N, 15.57.

4-Amino-5,8-dimethyl-6-nitroquinoline (13). Chloronitroquinoline **5** (2.03 g, 8.57 mmol) was combined with sodium azide (1.11 g, 17.1 mmol) and DMSO (20 mL). The mixture was stirred at room temperature overnight, followed by heating with a heat gun until all of the solid had dissolved. This mixture was allowed to cool to room temperature, diluted with water (50 mL), and extracted with ethyl acetate (4 × 75 mL). The combined organic layers were washed with water (1 × 50 mL), dried over $MgSO_4$, filtered, and rotary evaporated to give the azide as a yellow solid. This was used directly in the next step without further purification. Mp: 138−140 °C. ^{1}H NMR: δ 2.74 (s, 3 H); 2.82 (s, 3 H); 7.24 (d, J = 5.3 Hz, 1 H); 7.69 (s, 1 H); 8.87 (d, J = 5.3 Hz, 1 H). ^{13}C NMR: δ 18.75, 19.03, 111.50, 121.04, 123.93, 127.06, 137.77, 148.86, 149.84, 150.19, 150.59. MS (CI): *m/z* 244 $[M + H]^+$. The azidonitroquinoline (2.08 g, 8.57 mmol) was combined with methanol (20 mL). To this stirring mixture was added sodium borohydride (1.35 g, 35.2 mmol) in portions over 6 h until all the starting material was consumed. The excess methanol was removed, and the residue was diluted with water (20 mL). The aqueous mixture was extracted with ethyl acetate (4 × 40 mL). The combined organic phases were dried over $MgSO_4$, filtered, and rotary evaporated. The residue was purified by flash column chromatography, eluting with 50% ethyl acetate in hexane. The compound-containing fractions were combined to give **13** (1.56 g, 84% yield over two steps) as an orange solid. Mp: 149−151 °C. ^{1}H NMR (DMSO-d_6): δ 2.51 (s, 3H); 2.74 (s, 3 H); 6.60 (s, 2 H); 6.71 (d, J = 5.3 Hz, 1 H); 7.72 (s, 1 H); 8.32 (d, J = 5.3 Hz, 1 H). ^{13}C NMR (DMSO-d_6): δ 18.25, 18.45, 106.54, 118.12, 122.22, 128.51, 135.81, 146.51, 149.89, 150.36, 155.15. MS (CI): *m/z* 218 $[M + H]^+$.

4-(*N*−Acetylamino)-6-(2-imidazolinylamino)-5,8-dimethylquinoline (14). A mixture of aminonitroquinoline **13** (0.30 g, 1.38 mmol), triethylamine (0.5 mL), and acetic anhydride (4 mL) was heated to reflux for 2 h. The mixture was cooled to room temperature, and the excess of acetic anhydride was removed under vacuum. The residue was purified by flash column chromatography, eluting with 50% ethyl acetate in hexane. The compound-containing fractions were combined to give diacetylaminonitroquinoline (0.413 g, 99% yield) as a white solid. Mp: 137−139 °C. ^{1}H NMR (DMSO-d_6): δ 2.20 (s, 6 H); 2.35 (s, 3 H); 2.73 (s, 3 H); 7.75 (d, J = 4.8 Hz, 1 H); 7.98 (s, 1 H); 9.13 (d, J = 4.8 Hz, 1 H). ^{13}C NMR (DMSO-d_6): δ 15.72, 18.25, 26.89, 123.02, 123.23, 125.07, 125.28, 138.66, 146.46, 149.08, 150.25, 152.17, 172.10. MS (CI): *m/z* 302 $[M + H]^+$. The diacetylaminonitroquinoline was reduced to the 6-aminoquinoline by the procedure used to prepare the amine precursor of **12d** (90% yield). The above was converted in three steps to **14** following the procedures previously described for the preparation of **7** (85% yield), **8**, and **9** (88% over steps **8** and **9**). Purification and conversion of **14** to the salt gave (0.122 g, 74% yield) the dihydrochloride monohydrate. Mp: 230−250 °C (dec). ^{1}H NMR (MeOH-d_4): δ 2.42 (s, 3 H, CH_3); 2.79 (s, 3 H); 2.84 (s, 3 H); 3.84 (s, 4 H); 7.85 (s, 1 H); 8.67 (d, J = 7.7 Hz, 1 H); 8.90 (d, J = 7.7 Hz, 1 H). ^{13}C NMR (MeOH-d_4): δ 17.63, 17.93, 25.00, 44.41, 114.93, 124.20, 130.91, 132.09, 134.62, 136.17, 141.18, 145.03, 154.21, 160.00, 171.55. MS (CI): *m/z* 298 $[M + H]^+$. Anal. Calcd for $C_{16}H_{19}N_5O\cdot 2.0HCl\cdot H_2O$: C, 61.62; H, 6.21; N, 23.96. Found: C, 61.38; H, 6.21; N, 23.67.

4-Bromo-5,8-dimethyl-6-nitroquinoline (15). Nitroquinolone **3** (1.00 g, 4.58 mmol), toluene (15 mL), pyridine (0.74 mL, 9.17 mmol), and phosphorus oxybromide (1.05 g, 3.66 mmol) were combined and heated to an oil bath temperature of 90 °C. The reaction was monitored by TLC for loss of starting material and cooled to room temperature after 30 min. The reaction was diluted with water (10 mL), and the mixture was extracted with methylene chloride (3 × 100 mL). The combined organic layers were washed with water (2 × 100 mL), dried over Na_2SO_4, filtered, and rotary evaporated to give **15** (0.700 g, 55% crude yield) which was used without purification. Mp: 121−122 °C. ^{1}H NMR: δ 2.64 (s, 3 H); 2.83 (s, 3 H); 7.60 (s, 1 H); 7.72 (d, J = 4.5 Hz, 1 H); 8.54 (d, J = 4.5 Hz, 1 H). ^{13}C NMR (DMSO-d_6): δ 18.91, 19.56, 123.40, 127.10, 129.32, 132.52, 138.61, 149.50, 149.65, 150.63. MS (CI): *m/z* 281 $[M + H]^+$ and 283 $[M + H (+2)]^+$.

4-Bromo-6-(2-imidazolinylamino)-5,8-dimethylquinoline (16). Bromonitroquinoline **15** (1.40 g, 4.98 mmol) was combined with powdered iron (0.64 g, 11.50 mmol), acetic acid (40 mL), and water (60 mL). The suspension was heated to an oil bath temperature of 70 °C. After 1.5 h, the reaction was cooled to room temperature and filtered, and the precipitate was washed well with methylene chloride and water. The aqueous organic mixture was extracted with methylene chloride (3 × 140 mL). The combined organic layers were dried over Na_2SO_4, filtered, and rotary evaporated. The crude material was purified using an aspirator vacuum column, eluting with 20% ethyl acetate in hexane (material loaded on column with 100% methylene chloride). The compound-containing fractions were combined and evaporated to give the amine (0.522 g, 42% yield) as a yellow solid. The above amine was converted in three steps to **16** following the procedures previously described for the preparation of **7** (98% yield), **8** (95% yield), and **9** (assumed 100%). Conversion to the salt gave (0.88 g, 100% yield) the monoacetate. Mp: 152−154 °C. ^{1}H NMR (DMSO-d_6): δ 1.81 (s, 3 H); 2.55 (s, 3 H); 2.70 (s, 3 H); 3.34 (s, 4 H); 7.27 (s, 1 H); 7.76 (d, J = 4.5 Hz, 1 H); 8.39 (d, J = 4.5 Hz, 1 H). ^{13}C NMR (MeOH-d_4): δ 18.98, 19.12, 24.19, 44.18, 129.10, 130.02, 130.38, 130.95, 132.97, 135.56, 138.98, 149.39, 149.86, 160.85, 180.64. MS (CI): *m/z* 319 $[M + H]^+$ and *m/z* 321 $[M + H (+2)]^+$. Anal. Calcd for $C_{14}H_{15}N_4Br\cdot CH_3CO_2H$: C, 50.67; H, 5.05; N, 14.77. Found: C, 50.91; H, 5.03; N, 14.88.

4,5,8-Trimethyl-6-nitroquinoline (17a). Bromonitroquinoline **15** (0.89 g, 3.17 mmol), DMF (22 mL), trimethylaluminum (0.24 g, 3.33 mmol, 1.66 mL of a 2.0 M solution in toluene), lithium chloride (0.40 g, 9.52 mmol), and bis-(triphenylphosphine)palladium(II) chloride (0.11 g, 0.15 mmol) were combined and heated in an 80 °C oil bath for 18 h. After being cooled to room temperature, the reaction was quenched with water (50 mL). This mixture was extracted with methylene chloride (6 × 50 mL). The combined organic layers were washed with water (2 × 200 mL), dried over Na_2SO_4, filtered, and rotary evaporated to dryness. The material was purified by an aspirator vacuum column using a gradient elution of 10% ethyl acetate in hexane up to 25% ethyl acetate in hexane. The compound-containing fractions were combined to give **17a** (0.36 g, 48% yield) as a solid. Mp: 119−121 °C. ^{1}H NMR: δ 2.77 (s, 3H); 2.80 (s, 3H); 2.93 (s, 3 H); 7.29 (d, J = 4.4 Hz, 1 H); 7.70 (s, 1 H); 8.81 (d, J = 4.4 Hz, 1 H). ^{13}C NMR: δ 18.78, 19.27, 25.64, 122.42, 125.51, 127.30, 128.78, 137.94, 147.15, 148.74, 149.93. MS (CI): *m/z* 217 $[M + H]^+$.

6-(2-Imidazolinylamino)-4,5,8-trimethylquinoline (18a). Trimethylnitroquinoline **17a** was reduced to the amine by the procedure used to prepare **6** (72% yield). The resulting residue was purified by flash column chromatography, eluting with 25% ethyl acetate in hexane. The compound-containing fractions were combined to give the amine (0.37 g, 72% yield) as a solid. The above amine was converted in three steps to **18a** following the procedures previously described for the preparation of **7** (89% yield), **8** (70% yield), and **9** (50% yield). Purification and conversion to the salt (0.35 g, 63% yield) gave the dihydrochloride monohydrate. ^{1}H NMR (DMSO-d_6): δ 2.71 (s, 3 H); 2.78 (s, 3 H); 3.10 (s, 3 H); 3.64 (s, 4 H); 5.0−6.0 (br s, 1 H); 7.71 (s, 1 H); 7.81 (d, J = 5.0 Hz, 1 H), 8.41 (s, 1 H); 8.93 (d, J = 5.0 Hz, 1 H); 11.20 (s, 1 H). ^{13}C NMR (DMSO-d_6): δ 18.20, 18.52, 26.26, 42.71, 125.21, 129.88, 131.17, 131.35, 131.91, 134.04, 139.70, 144.34, 157.33, 158.23. MS (CI): *m/z* 255 $[M + H]^+$. Anal. Calcd for $C_{15}H_{18}N_4\cdot 2HCl\cdot H_2O$: C, 52.18; H, 6.42; N, 16.23. Found: C, 51.94; H, 6.30; N, 16.12.

4-Cyano-5,8-dimethyl-6-nitroquinoline (17b). Bromonitroquinoline **15** (0.20 g, 0.71 mmol) was combined with DMF (4 mL) and copper(I) cyanide (0.19 g, 2.13 mmol). After refluxing for 1 h, the mixture was cooled to room temperature,

filtered, and the solid was washed with methylene chloride and water. The aqueous organic phases were extracted with methylene chloride (3 × 100 mL). The combined organic layers were washed with water (1 × 100 mL), dried over Na_2SO_4, filtered, and rotary evaporated. The crude material was purified by aspirator vacuum column, eluting with 15% ethyl acetate in hexane. The compound-containing fractions were combined and evaporated to give **17b** (0.069 g, 43% yield) as a solid. Mp: 191−192 °C. ^{1}H NMR: δ 2.80 (s, 3 H); 3.02 (s, 3 H); 7.83 (s, 1 H); 7.92 (d, J = 4.3 Hz, 1 H); 9.12 (d, J = 4.3 Hz, 1 H). ^{13}C NMR: δ 16.25, 18.28, 118.04, 118.78, 124.48, 125.02, 125.89, 129.18, 139.45, 148.60, 149.63, 150.48. MS (CI): m/z 228 $[M + H]^+$.

4-Cyano-6-(2-imidazolinylamino)-5,8-dimethylquinoline (18b). The cyanonitroquinoline **17b** was reduced to the amine by the procedure used to prepare **6** (92% yield)**.** This amine was used in the next step without further purification. The above amine was converted in three steps to **18b** following the procedures previously described for the preparation of **7** (87% yield), **8** (95% yield), and **9** (assume 100% yield). Purification and conversion of **18b** to the salt gave (0.391 g, 100% yield) the monoacetate 0.75 hydrate. Mp: 221−232 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.84 (s, 3 H); 2.61 (s, 3 H); 2.69 (s, 3 H); 3.42 (s, 4 H); 7.42 (s, 1 H); 8.95 (d, J = 4.3 Hz, 1 H); 9.82 (d, J = 4.3 Hz, 1 H). ^{13}C NMR (DMSO-d_6): δ 15.14, 18.45, 22.47, 42.51, 114.89, 120.16, 121.82, 125.99, 128.50, 129.85, 136.17, 145.36, 145.70, 146.40, 158.48, 173.88. MS (CI): m/z 266 $[M + H]^+$. Anal. Calcd for $C_{15}H_{15}N_5 \cdot CH_3CO_2H \cdot 0.75H_2O$: C, 60.25; H, 6.10; N, 20.67. Found: C, 60.46; H, 6.55; N, 20.34.

4-Carboxamido-6-(2-imidazolinylamino)-5,8-dimethylquinoline (19). Compound **18b** (0.300 g, 1.13 mmol) and concentrated sulfuric acid (2 mL) were combined and heated to an oil bath temperature of 100 °C for 5 min. The yellow solution was cooled to room temperature, poured into an ice−water mixture (60 mL), and basified with 50% sodium hydroxide (6 mL). A yellowish white precipitate formed, which was filtered and washed with chloroform. The material was vacuum-dried and used as the free base to give **19** (0.145 g, 30% yield) as a hemihydrate. Mp: 291−292 °C (decomposition begins at around 72 °C). ^{1}H NMR (DMSO-d_6): δ 2.36 (s, 3 H); 2.57 (s, 3 H); 3.27 (s, 4 H); 5.86 (br s, 2 H); 7.16 (s, 1 H); 7.21 (d, J = 4.2 Hz, 1 H); 7.62 (br s, 1 H); 7.89 (br s, 1 H); 8.60 (d, J = 4.2 Hz, 1 H). ^{13}C NMR (DMSO-d_6/D_2O): δ 14.68, 18.65, 42.22, 119.81,121.01, 124.95, 128.64, 134.63, 142.75, 144.93, 145.27, 148.56, 157.60; 173.16. MS [ion spray (mobile phase methanol, 0.1% formic acid, 2 mM ammonium acetate)]: m/z 284 $[M + H]^+$. Anal. Calcd for $C_{15}H_{17}N_5O \cdot 0.5H_2O$: C, 49.49; H, 5.97; N, 18.04. Found: C, 49.58; H, 5.92; N, 17.67.

Acknowledgment. The authors wish to thank Starks Associates (Buffalo, NY) for their help in the synthesis of compound **4**.

Supporting Information Available: X-ray crystallography studies on the structure of **3** and melting points, ^{1}H, ^{13}C, and mass spectra data for 6-amino, 6-isothiocyanato, and 6-thioureido compounds (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO971959G