# The Synthesis of 3-Bromo-2,4,5-trifluorobenzoic Acid and its Conversion to 8-Bromoquinolonecarboxylic Acids



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A series of 8-bromo-4-oxo-3-quinolinecarboxylic acids was prepared *via* the borate ester, **8**. The key intermediate in the synthesis of the final products **10a-10d** was 3-bromo-2,4,5-trifluorobenzoic acid (**3**), conveniently prepared in two steps from the known oxazoline, **1**. The preparation of **10a-10d** is a significant improvement of the literature procedure currently available for the synthesis of these compounds.

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As part of a study to optimize the quinolone antibacterials against mycobacterial infections, specifically *Mycobacterium tuberculosis*, we were interested in examining the effect of the 8-substituent of quinolone antibacterials on mycobacterial activity. In particular, we were most interested in preparing and evaluating a series of 8-bromo substituted analogs. We found during our study that although several 8-bromo-4-oxo-3-quinolinecarboxylic acids have been reported in the patent literature [1-2], very little synthetic or physical data were available for these compounds. Furthermore, a number of the synthetic steps described for the preparation of such derivatives were low yielding and involved difficult separations. The present report describes, in detail, an improved preparation of and synthetic data for 8-bromo substituted quinolones using a procedure from 2-(2,4,5-trifluorophenyl)-4,4-dimethyl-2-oxazoline (**1**).

The key intermediate in the synthesis of the 8-bromo quinolones is 3-bromo-2,4,5-trifluorobenzoic acid (**3**). Two syntheses of **3** have previously been used during the preparation of 8-bromo substituted quinolones, one involving a ten-step sequence from 3-chloro-4-fluoroaniline [1] and another consisting of a three-step synthesis from tetrafluorophthalonitrile [3]. We decided to prepare **3** using the latter approach, although we were aware that the initial reaction involving bromination of tetrafluorophthalonitrile with lithium bromide resulted in a reported 1:1 mixture of starting material to the desired brominated derivative. Using several modifications of the literature approach, we were never successful in significantly altering the outcome of the reaction. Furthermore, attempts to separate the two components by distillation proved difficult. We eventually abandoned this approach and examined alternative methods for the preparation of **3**.

Initially, it appeared that direct bromination of the commercially available 2,4,5-trifluorobenzoic acid should afford the desired **3**; however, a number of attempts to brominate this analog resulted in an incomplete conversion of starting material to the product. For example, treatment of 2,4,5-trifluorobenzoic acid with 2.25 equivalents of

Scheme 1

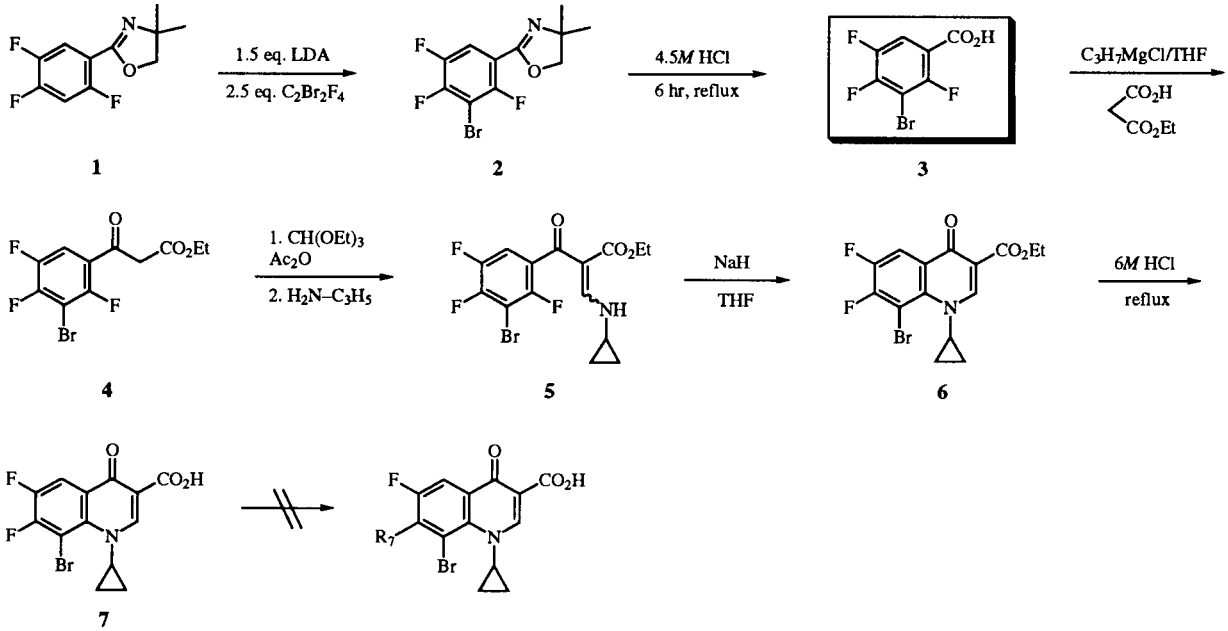


Table 1

Summary of the Reaction Conditions for the Synthesis of Compound **2**

| Equivalents of Lithium diisopropylamide [a] | Electrophile | Ratios of **1** to **2** [b] | Comments |
|---|---|---|---|
| 1.05 | $Br_2$ | 40:60 | Decomposition overnight |
| 1.05 | $(CF_2Br)_2$ | 40:60 | **1** and **2** separated by chromatography |
| 1.25 | $(CF_2Br)_2$ | 10:90 | **1** and **2** separated by chromatography |
| 1.25 | $(CCl_2Br)_2$ | 10:90 | bromine reagent solid |
| 1.50 | $(CF_2Br)_2$ | 10:90 | **1** and **2** separated by chromatography |

[a] Lithium diisopropylamide was prepared *in situ* by the treatment of diisopropylamine with *n*-butyllithium. [b] Ratios determined by gas chromatography.

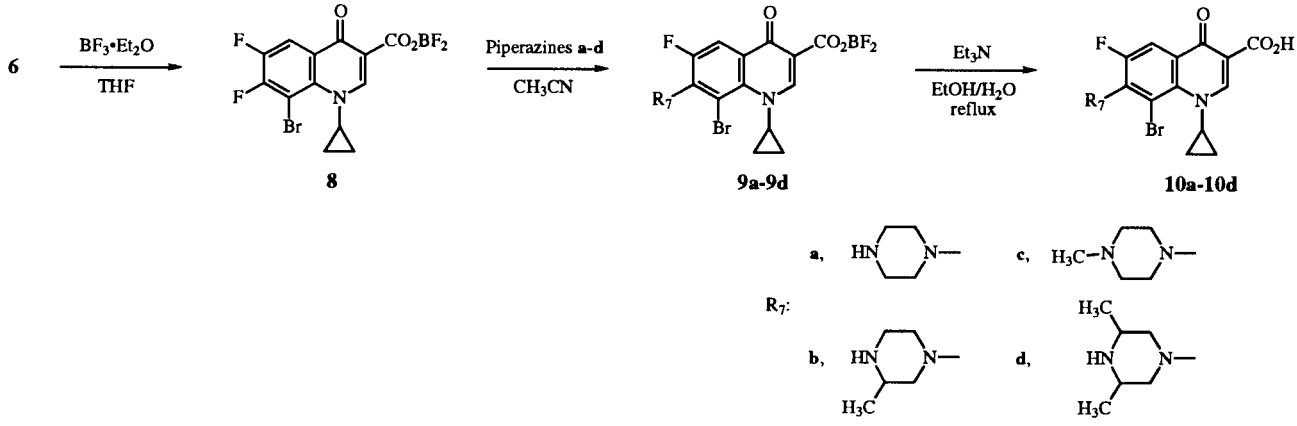
lithium diisopropyl amide followed by quenching with 1,2-dibromotetrafluoroethane gave a 60:40 mixture of starting material to the desired product, 3-bromo-2,4,5-trifluorobenzoic acid (**3**). Use of butyl lithium as the base gave only a 90:10 mixture of starting material to product, **3**. We next investigated an approach that involved the extension of work previously described from our laboratories for the synthesis of 5-methyl substituted quinolones [4]. Specifically, we felt that treatment of the known oxazoline derivative **1** [4] with lithium diisopropyl amide followed by quenching with an appropriate bromine electrophile should afford the brominated analog **2** (Scheme 1). Indeed, treatment of **1** with 1.05 equivalents of lithium diisopropyl amide followed by quenching with bromine as the electrophile produced a new product which was observed by gas chromatography (Table 1) but which proved to be unstable. Substitution of 1,2-dibromotetrafluoroethane for bromine in the presence of 1.05 equivalents lithium diisopropyl amide gave a 40:60 mixture of starting material to product, **2**, which was isolated by column chromatography and characterized by nmr. Increasing the amount of lithium diisopropyl amide from 1.05 equivalents to 1.25 equivalents gave a 10:90 mixture of **1:2**. Similar results were obtained when 1,2-dibromotetrachloroethane was substituted for 1,2-dibromotetrafluoroethane or when 1.5 equivalents of lithium diisopropyl amide and 1,2-dibromotetrafluoroethane were used in the reaction. In summary, we found that the best conditions for the conversion of **1** to **2** involved the use of 1.5 equivalents of lithium diisopropyl amide and the volatile 1,2-dibromotetrafluoroethane as the bromine source. We were never able to completely convert **1** to **2**; however, each compound was easily separable by column chromatography. Yields for the synthesis of **2** from **1** typically ranged from 80-90%.

Acid hydrolysis of **2** gave the key intermediate 3-bromo-2,4,5-trifluorobenzoic acid (**3**) in 45% yield. Unfortunately, attempts to increase the yield of the hydrolysis reaction failed. For example, base hydrolysis of the oxazoline furnished a modest amount of desired material **3** along with several unidentified by-products. The structural properties of **3** were confirmed by $^1H$ nmr, $^{19}F$ nmr and ms, and the purity was established by gas chromatography and elemental analyses. Comparison of our data with that reported previously for **3** provided nearly identical results [1,3]. The two step yield for the preparation of **3** from **1** *via* **2** was 38%. For comparison, the reported three step yield for the synthesis of **3** from tetrafluorophthalonitrile was 36% [3].

Conversion of the bromo acid **3** to the β-ketoester **4** using triethyl orthoformate in acetic anhydride proceeded in good yield. The keto ester **4** was converted to the cyclopropyl enamine **5** which was cyclized directly with sodium hydride to afford the quinolone ester **6**. The ester **6** was initially hydrolyzed to the free acid **7** using 6*M* hydrochloric acid, since we anticipated using conventional methods [5] to couple heterocyclic side-chains with the quinolone acid. Such a method was previously utilized for the preparation of 8-bromo-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid [1]. However, attempts to couple **7** with 4 equivalents of piperazine in refluxing acetonitrile were unsuccessful, as no product formation was detected. Addition of triethylamine to the reaction mixture did not enhance reactivity, and decomposition resulted upon treatment of the reaction mixture with 2.0 equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene. An examination of the patent [1] describing the synthesis of 8-bromo-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid revealed that similar problems were encountered during the coupling procedure; although the piperazine substituted analog was prepared using dimethyl sulfoxide as the reaction solvent, the reported yield was <10%. At this point we sought an alternative synthesis for this compound, one that would provide us with sufficient material for our biological studies and the latitude to prepare other derivatives.

We were aware that similar coupling problems had been encountered in the past during the synthesis of a variety of 8-alkoxyquinolone derivatives [6]. In that case, the decreased reactivity of the 7-fluoro substituent to displacement was overcome by converting the 3-ethyl ester to the boron difluoride chelate. Subsequent coupling of the borate ester of the 8-alkoxy derivatives with a variety of heterocyclic side chains followed by deprotection furnished the desired final products. Using this approach,

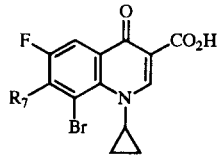
Scheme 2

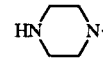
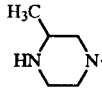
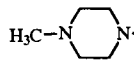
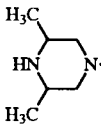



we treated the quinolone ethyl ester **6** with boron trifluoride etherate to give the boron difluoride chelate **8** (Scheme 2). The reaction of **8** with piperazine in acetonitrile at 40° overnight proceeded smoothly to afford the penultimate intermediate **9a**. Deprotection of **9a** using-triethylamine in refluxing aqueous ethanol provided 8-bromo-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid (**10a**) in 47% yield over the two steps. The overall yield for the preparation of **10a** from **6** *via* **8** was 37%. In contrast, the reported two step yield for the synthesis of **10a** from **6** *via* the acid **7** was only 7% [1]. Analysis of the physical data for **10a** showed it to be consistent with the previously reported literature values [1]. Using the procedure described for **10a**, a variety of other substituted piperazine derivatives **10b-10d** were synthesized. A summary of the physical and analytical data for **10a-10d** is presented in Table 2.

Preliminary biological evaluation of quinolones **10a-10d** demonstrated that they had equal or greater activity than both ciprofloxacin and sparfloxacin against mycobacteria These compounds will be included in a manuscript investigating the role of the 8-position of quinolone antibacterials on mycobacterial activity.

Table 2
Synthetic and Physical Data for Analogs **10a-10d** [a]




| Compound # | $R_7$ | mp (°C) | Yield [b] % | Molecular Formula | Analysis Data | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Theoretical | | | Found | | |
| | | | | | C | H | N | C | H | N |
| **10a** |  | 217-218 | 47 | $C_{17}H_{17}BrFN_3O_3 \cdot 1.5H_2O$ | 46.70 | 4.61 | 9.61 | 46.63 | 4.30 | 9.35 |
| **10b** |  | 199-200 | 54 | $C_{18}H_{19}BrFN_3O_3 \cdot 1.5H_2O$ | 47.90 | 4.91 | 9.31 | 47.80 | 4.67 | 9.10 |
| **10c** |  | 204-205 | 88 | $C_{18}H_{19}BrFN_3O_3$ | 50.96 | 4.51 | 9.90 | 51.33 | 4.39 | 9.67 |
| **10d** [7] |  | 210 (dec) | 50 | $C_{19}H_{21}BrFN_3O_3$ | 52.07 | 4.83 | 9.59 | 52.18 | 5.01 | 8.97 |

[a] See Experimental for method of preparation and purification. [b] Two step yield from the borate ester **8**.

## EXPERIMENTAL

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Gas chromatography was performed on a Shimadzu GC-8A instrument. Proton magnetic resonance (nmr) were determined at either 300 or 400 MHz with a Varian Unity 300/400 spectrometer. The chemical shift values are expressed in δ values relative to the internal standard tetramethylsilane. Mass spectra were recorded on a Finnigan TSQ-70 spectrometer. Elemental analyses were performed in house on a Perkin-Elmer 240 elemental analyzer or sent to Robertson Microlit Laboratories, Madison, NJ. Malinckrodt silica gel 60 (230-400 mesh) was used for gravity or flash chromatography.

3-Bromo-2,4,5-trifluorobenzoic Acid (**3**).

To a -78° solution of diisopropylamine (16.8 g, 166 mmoles) in 50 ml of dry tetrahydrofuran was added *n*-butyllithium (1.6*M*, 131 mmoles) dropwise. The reaction was stirred at -78° for 30 minutes then treated dropwise with 2-(2,4,5-trifluorophenyl)-4,4-dimethyl-2-oxazoline [4] (**1**, 20.0 g, 87.3 mmoles), dissolved in 50 ml of tetrahydrofuran. The dark orange solution was stirred at -78° for 1 hour, then quenched with 1,2-dibromotetrafluoroethane (5.7 g, 219 mmoles). The reaction was allowed to warm to room temperature, and the solution was extracted into ethyl acetate and washed with 1*N* hydrochloric acid. The organic fractions were collected, dried over sodium sulfate and filtered. The filtrate was concentrated to dryness and the residue was put over silica gel eluting with 90:10 hexanes:diethyl ether to give 20.9 g (84%) of **2**; $^1$H nmr (deuteriochloroform): δ 7.72-7.66 (m, 1H), 4.08 (s, 2H), 1.35 (s, 6H).

The purified oxazoline was dissolved in 100 ml of 4.5 *M* hydrochloric acid and the solution was refluxed for 6 hours, cooled to room temperature, and concentrated to dryness. The resultant gray gum was suspended in water and the *p*H of the solution adjusted to 8 with sodium bicarbonate. The water layer was washed with diethyl ether then acidified to *p*H = 2 with 6 *M* hydrochloric acid. The acidified aqueous layer was extracted with ethyl acetate, which was dried over sodium sulfate, filtered and concentrated to an oil. The oil was co-evaporated with hexanes/diethyl ether to yield 7.6 g (45%) of **3** as a white solid. A small sample was recrystallized from hexanes/dichloromethane to provide the analytical sample, mp 122-123°; $^1$H nmr (deuteriochloroform): δ 7.86-7.81 (m, 1H); $^{19}$F nmr (deuteriochloroform): δ -138, -116, -102; MS (m/z, relative intensity) 257 (98), 256 (97), 255 (100), 254 (94).

*Anal.* Calcd. for $C_7H_2BrF_3O_2$: C, 32.97; H, 0.79. Found: C, 32.86; H, 0.71.

Ethyl 3-Bromo-2,4,5-trifluoro-β-oxobenzenepropanoate (**4**).

A solution of 17.2 g (67.5 mmoles) of **3**, 9.0 g (70.9 mmoles) of oxalyl chloride and 50 ml of dichloromethane was treated with three drops of dimethylformamide and stirred for 18 hours at room temperature. The mixture was concentrated to dryness, co-evaporated three times with dichloromethane and the crude acid chloride was used without further purification.

A solution of 17.7 g (134 mmoles) of ethyl hydrogen malonate in 50 ml of tetrahydrofuran was cooled to -78° and treated dropwise with 134 ml (268 mmoles) of 2*M* isopropylmagnesium chloride. The solution was stirred at -78° for 30 minutes then the acid chloride, diluted in 100 ml of tetrahydrofuran, was added dropwise. The reaction mixture was warmed to room temperature and poured into 100 ml of 1*M* hydrochloric acid. The mixture was extracted with ethyl acetate, and the organic layer was washed with 1*M* hydrochloric acid and 1.05 equivalents of sodium bicarbonate. The organic layer was collected, dried over sodium sulfate, filtered and concentrated to an oil. The oil was co-evaporated with diethyl ether and hexanes to provide 17.5 g (80%) of **4** as an off white solid. A small sample was recrystallized from hexanes/dichloromethane to afford the analytical sample, mp 84-85°; $^1$H nmr (deuteriochloroform): δ 12.7 (s, 0.3 H, OH of tautomer), 7.80-7.67 (m, 1H, ArH), 5.81 (s, 0.3H, vinyl proton enol of tautomer), 4.27-4.16 (m, 2H, $OCH_2$), 3.95 (d, 2H, $CH_2CO_2Et$ of ketone tautomer), 1.32-1.25 (m, 3H, $OCH_2CH_3$); ms: (m/z, relative intensity) 327 (28), 325 (30), 324 (16), 239 (98), 237 (100).

*Anal.* Calcd. for $C_{11}H_8BrF_3O_3$: C, 40.64; H, 2.48. Found: C, 40.76; H, 2.50.

Ethyl 8-Bromo-1-cyclopropyl-6,7-difluoro-1,4-dihydro 4-oxo-3-quinolinecarboxylate (**6**).

A solution of 17.2 g (53 mmoles) of **4** in 18 ml (106 mmoles) of triethyl orthoformate and 12 ml of acetic anhydride was heated at 130° for 3 hours. The mixture was concentrated in high vacuum and co-evaporated three times with toluene to give an oil. The oil was diluted with 100 ml of diethyl ether then 3.2 g (55.6 mmoles) of cyclopropylamine was added dropwise. The solution was stirred for 18 hours at room temperature, concentrated to dryness and the resultant oil diluted with 100 ml of tetrahydrofuran. To this solution was added 2.65 g (66.3 mmoles) of 60% sodium hydride-mineral oil portionwise over 30 minutes. The reaction was stirred for 1.5 hours at room temperature, quenched with 25 ml of water, and the *p*H of the solution was adjusted to 7 with acetic acid. The volatile solvents were evaporated and the solid collected by filtration to afford 18 g (90%) of **6**. A small sample was recrystallized from dichloromethane/hexanes to furnish pure **6**, mp 162-163°; $^1$H nmr (deuteriochloroform): δ 8.65 (s, 1H), 8.25-8.21 (dd, 1H), 4.38-4.32 (q, 2H), 4.27-4.22 (m, 1H), 1.38-1.33 (t, 3H), 1.29-1.24 (m, 2H), 0.99-0.95 (m, 2H); ms: (m/z, relative intensity) 374 (100), 372 (96).

*Anal.* Calcd. for $C_{15}H_{12}BrF_2NO_3 \cdot 0.25H_2O$:C, 47.83; H, 3.34; N, 3.72. Found: C, 47.91; H, 3.32; N, 3.69.

8-Bromo-1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (**7**).

A solution of 2.7 g (7.3 mmoles) of **6** in 50 ml of 6*M* hydrochloric acid was heated at reflux for 3 hours and cooled to room temperature. The brown solid was collected by filtration, washed with water and diethyl ether. The resultant white solid was dried at 40° for 18 hours to give 1.2 g (48%) of pure **7**, mp 216-217°; $^1$H nmr (DMSO-$d_6$): δ 14.21 (s, 1H), 8.90 (s, 1H), 8.31-8.29 (dd, 1H), 4.48-4.46 (m, 1H), 1.30-1.11 (m, 4H); ms: (m/z, relative intensity) 346 (81), 344 (76), 328 (100), 326 (89).

*Anal.* Calcd. for $C_{13}H_8BrF_2NO_3$: C, 45.38; H, 2.34; N, 4.07. Found: C, 45.28; H, 2.45; N, 3.86.

8-Bromo-1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid Boron Difluoride Chelate (**8**).

A solution of 15 g (40 mmoles) of **6**, 70 ml of freshly distilled boron trifluoride etherate and 100 ml of tetrahydrofuran was heated at 70° for 18 hours. The reaction was cooled to room temperature, diluted with 50 ml of diethyl ether and the solid was collected by filtration and washed with diethyl ether to give

12.3 g (78%) of **8**. A small sample was recrystallized from hexanes/dichloromethane/acetone to provide pure **8** as a white powder, mp >290°; $^1$H nmr (DMSO-$d_6$): 9.34 (s, 1H), 8.60-8.55 (m, 1H), 4.74-4.69 (m, 1H), 1.33-1.23 (m, 4H); ms: (m/z, relative intensity) 394 (45), 392 (13), 374 (98), 372 (100).

*Anal.* Calcd. for $C_{13}H_7BBrF_4NO_3 \cdot 1.25H_2O$: C, 37.67; H, 2.31, N, 3.38. Found: C, 37.43; H, 1.86; N, 3.37.

General Method for the Preparation of the Quinolone Derivatives **10a-10d**.

8-Bromo-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic Acid (**10a**).

A solution of 1.1 g (2.8 mmoles) of **8**, 964 mg piperazine (11.2 mmoles) and 80 ml of acetonitrile was heated at 40° for 18 hours. The reaction was cooled to room temperature and the solid collected by filtration. The crude solid was suspended in water, the *p*H of the solution adjusted from 8.5 to 7.3 with 1*M* hydrochloric acid and the precipitate collected and washed with water to provide a quantitative yield of **9a**.

This solid was dissolved in a mixture of 2.2 ml of triethylamine (16.8 mmoles), 40 ml of ethanol, and 10 ml of water and stirred at reflux for 18 hours. The reaction was cooled to room temperature, concentrated to dryness and the residue co-evaporated two times with ethanol. The residue was dissolved in water, the *p*H of the solution was adjusted from 5.5 to 7.5 with 1*N* sodium hydroxide and the solid was collected by filtration. The material was washed with water then with a mixture of diethyl ether/ethanol to yield 518 mg (47%) of pure **10a**, mp 217-218°; $^1$H nmr (DMSO-$d_6$) : δ 8.81 (s, 1H), 7.92-7.89 (d, 1H), 4.42-4.38 (m, 1H), 3.20-3.19 (m, 4H), 2.83-2.81 (m, 4H), 1.14-1.09 (m, 2H), 0.87-0.83 (m, 2H); ms: (m/z relative intensity) 412 (94), 410 (100).

*Anal.* Calcd. for $C_{17}H_{17}BrFN_3O_3 \cdot 1.5H_2O$: C, 46.70; H, 4.61; N, 9.61. Found: C, 46.63; H, 4.30; N, 9.35.

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[7] After repeated analysis, a more satisfactory value was available.