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# Synthesis of regioisomeric difluoro- and 8-chloro-9-fluorobenz[*g*]isoquinoline-5,10-diones and $S_NAr$ displacements studies by diamines: bis(aminoalkyl)aminobenz[*g*]isoquinoline-5,10-diones

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**Abstract**

Convenient pathways have been developed for the synthesis of 6,7-, 6,8-, 7,9- and 8,9-difluorobenz[*g*]isoquinoline-5,10-diones and 8-chloro-9-fluorobenz[*g*]isoquinoline-5,10-dione. The crucial step in these synthesis involved the Ni-catalyzed coupling of the difluoro- or chlorofluorobenzylic zinc bromides with ethyl 3-chloroisonicotinate or ethyl 4-chloronicotinate. The reactions of the 6,7- or 8,9-difluoro regioisomers with *N,N*-dimethylethylenediamine led to quaternary salts which were formed by intramolecular displacements from the initial mono displacement products. These cyclizations could be obviated with the use of 3-dimethylaminopropylamine in the displacements which led to the desired bis(aminoalkyl)amino substitution products. Treatment of 8-chloro-9-fluorobenz[*g*]isoquinoline-5,10-dione with *N,N*-dimethylethylenediamine led to the regioselective displacement of fluoride. Treatment of this mono substitution product with excess *N,N*-dimethylethylenediamine led only to the intramolecular cyclization product which was also obtained by reaction of 8,9-difluorobenz[*g*]isoquinoline-9,10-dione with *N,N*-dimethylethylenediamine. The 6,8- and 7,9-difluoro analogues on treatment with *N,N*-dimethylethylenediamine or 3-dimethylaminopropylamine led to the expected bis substitution products. 

*Keywords:* Difluorobenz[*g*]isoquinoline-5,10-diones; Synthesis; $S_NAr$ fluoride displacements

## 1. Introduction

In previous studies dealing with the synthesis and mechanism of action of quinone anticancer agents, we have utilized $S_NAr$ displacements of fluorides by amino nucleophiles for the introduction of (aminoalkyl)amino substituents on the quinone chromophore. For example, treatment of 1,4-difluoroanthracene-9,10-dione (A=CH) or 6,9-difluorobenz[*g*]isoquinoline-5,10-dione (A=N) with *N,N*-dimethylethylenediamine led to the bis-[(2-dimethylamino)ethyl]-amino] analogues where A=CH [1] or A=N [2], respectively (Fig. 1).

The goal of the present study was the synthesis of regioisomeric bis(aminoalkyl)amino-benz[*g*]isoquinoline-5,10-diones bearing pendant side arms at positions 6,7-, 6,8-, 7,9- and 8,9 on the carbocyclic ring. The cytotoxicities of these analogues would then be compared with chemotypes bearing (aminoalkyl)amino side arms at positions 6,9 to establish the importance of the side arm positioning on antitumor activity

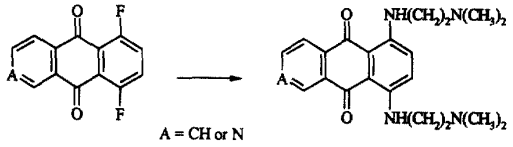


Fig. 1. $S_NAr$ fluoride displacements.

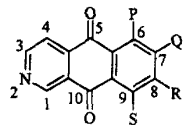


Fig. 2. Regioisomeric benz[*g*]isoquinoline-5,10-diones.

(Fig. 2). The interaction of these molecules with DNA could then be evaluated to obtain mechanistic information on the mode of cell killing for this class of drugs.

The synthetic approach to the bis(aminoalkyl)amino-benz[*g*]isoquinolines was envisioned via $S_NAr$ fluoride displacements from the appropriate regioisomeric difluoro-benz[*g*]isoquinoline-5,10-diones. However, during the

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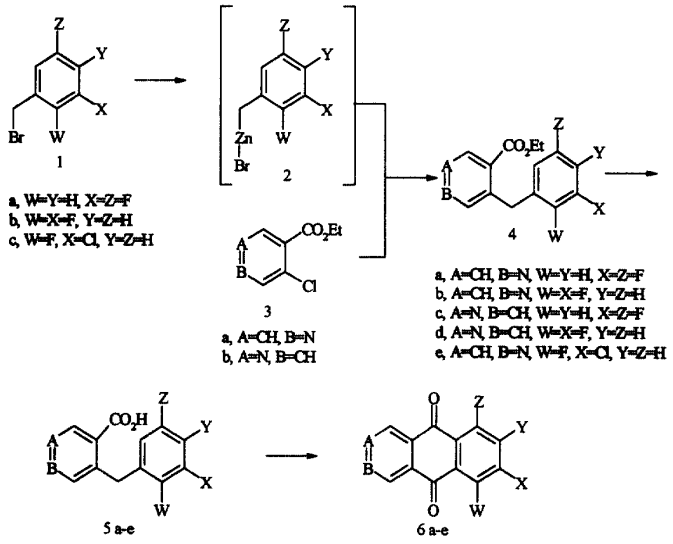
course of this study we uncovered an interesting intramolecular displacement on reaction of the difluoro analogues with adjacent fluorine atoms with *N,N*-dimethylethylenediamine. A similar intramolecular process was also found for 8-chloro-9-fluorobenz[*g*]isoquinoline-5,10-dione on treatment with *N,N*-dimethylethylenediamine. The intramolecular cyclization could be obviated by the use of 3-dimethylaminopropylamine.

## 2. Results and discussion

### *2.1. Difluoro- and 8-chloro-9-fluorobenz[g]isoquinoline-5,10-diones*

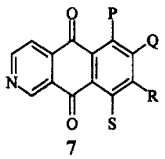
The synthetic pathways to the difluoro- and chlorofluoro chemotypes are shown in Scheme 1.




Dihalobenz[g]isoquinoline-5,10-diones

| Reactants | 6 | A | B | W | X | Y | Z |
|---|---|---|---|---|---|---|---|
| 2a, 3a | a | CH | N | H | F | H | F |
| 2b, 3a | b | CH | N | F | F | H | H |
| 2a, 3b | c | N | CH | H | F | H | F |
| 2b, 3b | d | N | CH | F | F | H | H |
| 2c, 3a | e | CH | N | F | Cl | H | H |

Scheme 1. Dihalobenz[*g*]isoquinoline-5,10-diones.




| 7 | Position | P | Q | R | S |
|---|---|---|---|---|---|
| a | 6,8 | $NH(CH_2)_2(CH_3)_2$ | H | $NH(CH_2)_2(CH_3)_2$ | H |
| b | 7,9 | H | $NH(CH_2)_2(CH_3)_2$ | H | $NH(CH_2)_2(CH_3)_2$ |
| b' | 7,9 | H | $NH(CH_2)_3(CH_3)_2$ | H | $NH(CH_2)_3(CH_3)_2$ |
| c | 8,9 | H | H | $NH(CH_2)_3(CH_3)_2$ | $NH(CH_2)_3(CH_3)_2$ |
| d | 6,7 | $NH(CH_2)_3(CH_3)_2$ | $NH(CH_2)_3(CH_3)_2$ | H | H |

Fig. 3. Regioisomeric bis-[(aminoalkyl)amino]benz[*g*]isoquinoline-5,10-diones.

Treatment of the difluorobenzyl bromides **1a–b** with zinc metal in THF readily led to the corresponding difluorobenzyl zinc bromides **2a–b** [3]. The addition of the THF solutions of 2,3-difluorobenzyl zinc bromide (**2a**) or 3,5-difluorobenzyl zinc bromide (**2b**) to ethyl 3-chloroisonicotinate (**3a**) in the presence of bistriphenylphosphinenickel(II) chloride [3] led to the coupled products **4a** and **4b**, respectively. The ester **3a** was prepared by treatment of 3-chloroisonicotinic acid (obtained by directed metallation and carboxylation of 3-chloropyridine) with DCC and ethanol in DMF as solvent [4].

In a similar manner, the couplings of ethyl 4-chloronicotinate (**3b**)[1] with **2a** or **2b** led to **4c** and **4d**, respectively. The ester **3b** was obtained by esterification of 4-chloronicotinic acid [5] using iodoethane and cesium fluoride in DMF as solvent [6]. The hydrolysis of the esters **4a–d** to the corresponding acids **5a–d** was accomplished by refluxing in aqueous sodium hydroxide followed by acidification. The cyclization and concomitant oxidations of **5a–d** with fuming sulfuric acid led to the difluorobenz[*g*]isoquinoline-5,10-diones (yields ranging from 48–75%).

Treatment of **2c** with **3a** yielded **4e** which on saponification led to **5e**. The cyclization and oxidation of **5e** was accomplished by heating in fuming sulfuric acid to yield **6e** (55%).

### 2.2. Displacement studies

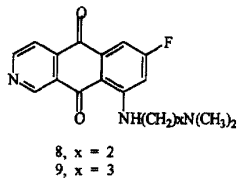
#### 2.2.1. Bis-[(aminoalkyl)amino]benz[g]isoquinoline-5,10-diones

The bis analogues **7** which have been synthesized from the difluorides **6a–d** by $S_NAr$ displacements by the appropriate amines are tabulated in Fig. 3.

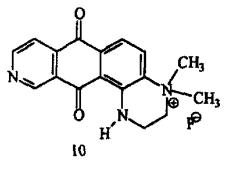
Treatment of **6a** with *N,N*-dimethylethylenediamine in pyridine at room temperature led to **7a**. In a similar manner treatment of **6c** with *N,N*-dimethylethylenediamine led to **7b** along with the mono fluoro displacement product **8**, arising from displacement of the fluoride at position 9. This structure could readily be assigned by the $^1H$ NMR absorption at $\delta$ 9.92 (m), the position of which is only consistent with strong hydrogen bonding between the HN proton and the carbonyl group. Treatment of **6c** with 3-dimethylaminopropylamine led predominantly to the monofluoro analogue **9**. Treatment of **9** with 3-dimethylaminopropylamine at 80°C led to **7b'**.

On the other hand, treatment of **6b** with *N,N*-dimethylethylenediamine in pyridine at room temperature led to the cyclic quaternary salt **10** which arises from an intramolecular $S_NAr$ displacement of the adjacent fluoride in the intermediate **11** (not isolated) formed from the initial fluoride displacement. The formulation as quaternary salt **10** is supported by the NMR spectrum of the demethylation product **12** which could be isolated in a 6% yield. The $^1H$ NMR spectrum of **12** ($CDCl_3$) exhibits an absorption at $\delta$ 10.28 which is consistent with the NH proton hydrogen bonding with the polarized carbonyl group. In order to further investigate the nature of this intramolecular cyclization, we treated the chlorofluoro analogue **6e** with *N,N*-dimethylethylenediamine in pyridine at room temperature which led predominantly to displacement of the more nucleofugal fluoride to afford **13** in good yield. Treatment of **13** with excess *N,N*-dimethylethylenediamine (10 equivalents, pyridine, 40–80°C) led to the quaternary salt **10** along with small amounts of **12**. This result supports the structure of intermediate **11** and clearly establishes the structure of the quaternary salt **10**. Of particular interest is the fact that the *intramolecular* displacement of the chloride from **13** dominates over the potential *intermolecular* displacement by the excess amine.

Treatment of **6b** with 3-dimethylaminopropylamine (45°C) led to the expected bis substitution product **7c**.




8, x = 2
9, x = 3

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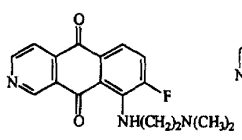


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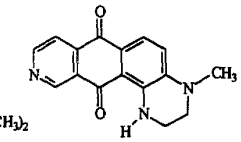


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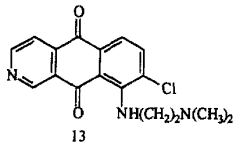


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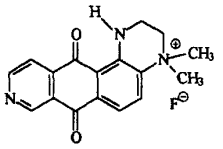
Difluoride **6d** on treatment with *N,N*-dimethylethylenediamine in pyridine at room temperature also led to a cyclized product identified as quaternary salt **14**. Longer reaction times led to the formation of a new product identified as **15**, the product arising from demethylation of **14**. Structure **15** is based on $^1H$ NMR data with an absorption at $\delta$ 10.31 indicative of strong hydrogen bonding between the carbonyl group and the HN proton.

Treatment of **6d** with 3-dimethylaminopropylamine in pyridine at room temperature led to the bis substituted product **7d** along with the monosubstituted product **16**, which exhibited in the $^1H$ NMR spectrum a multiplet for the HN at $\delta$ 9.96.

[1] In our hands this ester proved to be quite unstable and darkened on standing for a few hours at room temperature.



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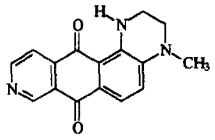

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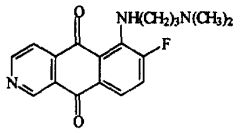

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The antitumor activities and DNA interaction studies of the bis(aminoalkyl)amino analogous which have been synthesized will be reported elsewhere in the near future.

## 3. Conclusions

A facile sequence of reactions has been developed leading to regioisomeric difluorobenz[*g*]-isoquinoline-5,10-diones and 8-chloro-9-fluorobenz[*g*]isoquinoline-5,10-dione. The fluoride displacements using *N,N*-dimethylethylenediamine occur quite readily from those regioisomers in which the fluorines are 1,3 to each other to afford the bis-[(aminoalkyl)amino]benz[*g*]isoquinoline-5,10-diones. However, when the fluorine atoms are adjacent, intramolecular $S_NAr$ substitutions occur from the initial mono displacement product when using *N,N*-dimethyethylenediamine (two methylene spacers). This intramolecular cyclization can be overcome by use of 3-dimethylaminopropylamine (three methylene spacers).

## 4. Experimental

Melting points were determined on a Thomas Hoover apparatus in open capillaries or on a Fisher–Johns block and are uncorrected. Proton NMR were recorded on a Bruker ARX-500 pulsed Fourier transform spectrometer and the data are recorded relative to tetramethylsilane as an internal standard. Mass spectra were recorded on a Finnegan MAT 4500 series automated gas-chromatograph/EI-CI mass spectrometer and recorded at mild EI. The 3,5-difluorobenzyl bromide (**1a**), 2,3-difluorobenzyl bromide (**1b**) and 2-fluoro-3-chlorobenzyl bromide (**1c**) were purchased from Oakwood Research Chemicals and used as received. Bistriphenylphosphinenickel(II) chloride was purchased from Lancaster and the zinc dust ( −325 mesh) was obtained from Aldrich and used as received. The THF was freshly distilled from potassium metal and all reactions were performed under nitrogen atmospheres. Baker analyzed 230–400 mesh silica gel was used for flash chromatography and 70–230 mesh silica gel was used for gravity chromatography. Microanalyses were performed by Robertson Microlit Laboratories, Madison, NJ.

### 4.1. Ethyl 3-chloroisonicotinate (3a)

A solution of 1,3-dicyclohexylcarbodiimide (4.8 g, 23.4 mmol) in DMF (16 ml) was added to a mixture of 3-chloroisonicotinic acid (3.7 g, 23.4 mmol), DMF (33 ml), 4-dimethylaminopyridine (0.025 g, 0.21 mmol) and ethanol (4 ml, 68 mmol) at room temperature. After allowing the mixture to stir for 20 h, the dicyclohexylurea was removed by filtration and the bulk of the DMF was removed by rotary evaporation. The ester was purified by vacuum distillation (70°C at 5 mm Hg) to yield **3a** (2.9 g, 65%) as a clear colorless oil; $^1$H NMR ($CDCl_3$): $\delta$ 8.71 (s, 1H), 8.58 (d, $J_{HH}$ = 5.4 Hz, 1H), 7.63 Hz, 3H).

### 4.2. Ethyl 4-chloronicotinate (3b)

A mixture of cesium fluoride (0.74 g, 4.9 mmol), 4-chloroisonicotinic acid (0.50 g, 3.2 mmol), iodoethane (0.78 g, 4.9 mmol) and DMF (5 ml) was stirred for 21 h at room temperature under a nitrogen atmosphere. A saturated solution of sodium carbonate (5 ml) was added and the product was extracted into dichloromethane (3 × 15 ml). The extract was dried over sodium sulfate and the solvent removed by rotary evaporation. Water (25 ml) was then added and the ester was separated and purified by column chromatography (silica gel, 1.5 cm × 4.0 cm, with 2:1 hexane:ethyl acetate as the eluent) to yield the pure ester **3b** (0.26 g, 45%) as a clear colorless liquid. The ester was used immediately to avoid decomposition; $^1$H NMR ($CDCl_3$): $\delta$ 9.02 (s, 1H), 8.57 (d, $J_{HH}$ = 5.3 Hz, 1H), 7.40 (d, $J_{HH}$ = 5.3 Hz, 1H), 4.44 (q, $J_{HH}$ = 7.0 Hz, 2H), 1.42 (t, $J_{HH}$ = 7.0 Hz, 3H).

### 4.3. Ethyl 3-(3,5-difluorobenzyl)-isonicotinate (4a)

A solution of **2a** (1.83 g, 8.85 mmol) and THF (12 ml) was slowly added to a suspension of zinc dust (0.93 g, 11.4 mmol) in THF (18 ml) at 0°C. After being allowed to stir for 3 h under a nitrogen blanket, the zinc dust was allowed to settle and the organozinc reagent was added to a solution of **3a** (1.26 g, 6.8 mmol), bistriphenylphosphinenickel(II) chloride (0.631 g, 1.32 mmol) and THF (30 ml). The mixture was stirred at room temperature for 18 h and the resultant brown mixture was quenched with aqueous ammonium chloride (10%, 60 ml). The product was extracted into ethyl acetate (90 ml) and washed with brine (3 × 15 ml). Ethyl acetate was removed by rotary evaporation to yield a yellow oil which was purified by column chromatography (silica gel, 3 cm × 20 cm; hexane:ethyl acetate 3:1) to yield the product (1.47 g, 78%); $^1$H NMR ($CDCl_3$): $\delta$ 8.65(d, $J_{HH}$ = 5.0 Hz, 1H), 8.52 (s, 1H), 7.72 (d, $J_{HH}$ = 5.0 Hz, 1H), 6.63 (m, 3H), 4.32 (m, 4H), 1.33 (t, 3H).

*4.4. Ethyl 3-(2,3-difluorobenzyl)isonicotinate (4b)*

A solution of **2b** (0.199 g, 0.96 mmol) and THF (1.5 ml) was added to a suspension of zinc dust (0.096 g, 1.47 mmol) and THF (2 ml) at 0°C. After being allowed to stir for 2.5 h the excess Zn dust was allowed to settle. The organozinc solution was then added slowly to a mixture of bistriphenylphosphinenickel(II) chloride (0.099 g, 0.15 mmol), **3a** (0.117 g, 0.63 mmol), and THF (7 ml) in a two-necked flask via cannula under nitrogen pressure. After being allowed to stir at room temperature for 24 h, the brown solution was quenched with 15 ml of 10% aqueous ammonium chloride. The product was then extracted into ethyl acetate (25 ml), washed with brine (3×20 ml) and dried over sodium sulfate. The ethyl acetate was removed by rotary evaporation to yield an orange oil which was purified by column chromatography (silica gel, 8 cm×1.5 cm, 4:1 hexane:ethyl acetate as eluent) to yield **4b** (0.128 g, 73%); $^1$H NMR ($CDCl_3$): $\delta$ 8.63 (d, $J_{HH}$=5.0 Hz, 1H), 8.56 (s, 1H), 7.71 (d, $J_{HH}$=5.0 Hz, 1H), 7.03 (m, 1H), 6.94 (m, 1H), 6.73 (m, 1H), 4.41 (s, 2H), 4.32 (q, $J_{HH}$=7.2 Hz, 2H), 1.29 (t, $J_{HH}$=7.2 Hz, 3H).

*4.5. Ethyl 4-(3,5-difluorobenzyl)nicotinate (4c)*

A solution of **2a** (0.245 g, 1.18 mmol) and THF (3 ml) was added to a suspension of zinc dust (0.123 g, 1.9 mmol) and THF (2 ml) at 0°C and allowed to warm slowly to room temperature. After being stirred at room temperature for 3 h the excess zinc was allowed to settle. The organozinc solution was then added slowly to a mixture of bistriphenylphosphinenickel(II) chloride (0.110 g, 0.21 mmol), **3b** (0.092 g, 0.54 mmol) and THF (10 ml) to a two-necked flask via cannula under nitrogen pressure. After being allowed to stir for 16 h, the brown solution was quenched with a 10% aqueous solution of ammonium chloride. The product was extracted into ethyl acetate (25 ml), washed with brine (2×30 ml), and dried over sodium sulfate. The ethyl acetate was removed by rotary evaporation to yield a yellow oil which was purified by column chromatography (silica gel, 7×2 cm, 3:1 hexane:ethyl acetate) to yield **4c** (0.106 g, 75%); $^1$H NMR ($CDCl_3$): $\delta$ 9.13 (s, 1H), 8.64 (d, $J_{HH}$=4.9 Hz, 1H), 7.03 (d, $J_{HH}$=4.9 Hz, 1H), 6.65 (m, 3H), 4.36 (m, 4H), 1.37 (t, 3H).

*4.6. Ethyl 4-(2,3-difluorobenzyl)nicotinate (4d)*

A solution of **2b** (0.30 g, 1.5 mmol) and THF (3.0 ml) was added to a suspension of zinc dust (0.21 g, 3.3 mmol) and THF (2.0 ml) at 0°C. After allowing the mixture to stir for 3 h, the excess zinc dust was allowed to settle. The organozinc solution was then slowly added to a mixture of bistriphenylphosphinenickel(II) chloride (0.1 g, 0.15 mmol), **3b** (0.18 g, 1.1 mmol) and THF (10 ml) in a two-necked flask via cannula under nitrogen pressure. After being allowed to stir for 21 h at room temperature, the brown solution was quenched with a 10% aqueous solution of ammonium chloride. The product was extracted into ethyl acetate (30 ml), washed with brine (3×30 ml), and dried over sodium sulfate. Ethyl acetate was removed by rotary evaporation to yield a yellow oil which was purified by column chromatography (silica gel, 10 cm×2 cm, 3:1 hexane:ethyl acetate) to yield **4d** (0.20 g, 66%); $^1$H NMR ($CDCl_3$): $\delta$ 9.12 (s, 1H), 8.59 (d, $J_{HH}$=5.1 Hz, 1H), 7.07 (d, $J_{HH}$=5.2 Hz, 1H), 7.03 (m, 2H), 6.82 (m, 1H), 4.46 (s, 2H), 4.37 (q, $J_{HH}$=7.4 Hz, 2H), 1.37 (t, $J_{HH}$=7.4 Hz, 3H).

*4.7. Ethyl 3-(2-fluoro-3-chlorobenzyl)isonicotinate (4e)*

A solution of **1c** (0.8 g, 3.5 mmol) and THF (4 ml) was added to a suspension of zinc dust (0.34 g, 5.2 mmol) and THF (6 ml) cooled in an ice bath over a 10 min period. The mixture was stirred for 3 h and transferred via cannula under nitrogen pressure to a mixture of **3a** (0.51 g, 2.7 mmol), bistriphenylphosphinenickel(II) chloride (0.4 g, 0.7 mmol) in THF (45 ml). The resultant brown solution was stirred for 36 h and then quenched with aqueous ammonium chloride (10%, 30 ml). The product was extracted into ethyl acetate (35 ml) and the extract washed with brine (3×25 ml). The extracts were dried over magnesium sulfate and the solvent removed by rotary evaporation. The pure ester was obtained by column chromatography (silica gel, 2.5 cm×20 cm, 3:1 hexane:ethyl acetate) to yield **4e** (0.70 g, 89%) as a colorless oil; $^1$H NMR ($CDCl_3$): $\delta$ 8.63 (d, $J_{HH}$=5.0 Hz, 1H), 8.56 (s, 1H), 7.71 (d, $J_{HH}$=5.0 Hz, 1H), 7.26 (m, 1H), 6.95 (m, 1H), 6.87 (m, 1H), 4.39 (s, 2H), 4.32 (q, $J_{HH}$=7.1 Hz, 2H), 1.31 (t, $J_{HH}$=7.3 Hz, 3H).

*4.8. 3-(3,5-Difluorobenzyl)isonicotinic acid (5a)*

A mixture of **4a** (0.170 g, 0.61 mmol) and aqueous NaOH (2 N, 3 ml) was refluxed for 2.5 h. After being allowed to cool to room temperature, an aqueous 10% solution of HCl was added dropwise until the pH reached 2.0. The resultant white solid was collected by filtration and allowed to air dry to yield **5a** (0.124 g, 82%); mp 235–237°C; $^1$H NMR (DMSO-$d_6$): $\delta$ 8.68 (s, 1H), 8.63 (d, $J_{HH}$=5.0 Hz, 1H), 7.71 (d, $J_{HH}$=5.0 Hz, 1H), 7.02 (m, 1H), 6.88 (m, 2H), 4.35 (s, 2H).

Anal. calcd. for $C_{13}H_9F_2NO_2$: C, 62.65; H, 3.64; N, 5.62. Found: C, 62.40; H, 3.45; N, 5.57%.

*4.9. 3-(2,3-Difluorobenzyl)isonicotinic acid (5b)*

A mixture of **4b** (0.367 g, 1.33 mmol) and aqueous NaOH (2 N, 6 ml) was refluxed in an oil bath for 2.5 h. After being allowed to cool to room temperature, an aqueous 10% solution of HCl was added dropwise until pH 2. The resultant white solid was collected by filtration and allowed to air dry to yield **5b** (0.296 g, 90%); mp 237–238°C; $^1$H NMR (DMSO-$d_6$): $\delta$ 8.60 (d $J_{HH}$=5.0 Hz, 1H), 8.56 (s, 1H), 7.67 (d, $J_{HH}$=5.0 Hz, 1H), 7.26 (m, 1H), 7.09 (m, 1H), 6.82 (m, 1H), 4.34 (s, 2H).

Anal. calcd. for $C_{13}H_9F_2NO_2$: C, 62.65; H, 3.64; N, 5.62. Found: C, 62.45; H, 3.58; N, 5.57%.

*4.10. 4-(3,5-Difluorobenzyl)nicotinic acid (5c)*

A mixture of **4c** (0.106 g, 0.38 mmol) and aqueous NaOH (2 N, 1.5 ml) was refluxed in an oil bath for 2.5 h. After being allowed to cool to room temperature, an aqueous solution of 10% HCl was added dropwise until the solution reached pH 2. The resultant white solid was filtered and allowed to air dry to yield **5c** (0.093 g, 97%); mp 226–229°C; $^1$H NMR (DMSO-$d_6$): $\delta$ 8.93 (s, 1H), 8.58 (d, $J_{HH}$ = 5.0 Hz, 1H), 7.28 (d, $J_{HH}$ = 5.0 Hz, 1H), 7.04 (m, 1H), 6.93 (m, 2H), 4.37 (s, 2H).

Anal. calcd. for $C_{13}H_9F_2NO_2$: C, 62.65; H, 3.64; N, 5.62. Found: C, 62.52; H, 3.62; N, 5.41%.

*4.11. 4-(2,3-Difluorobenzyl)nicotinic acid (5d)*

A mixture of **4d** (0.11 g, 0.38 mmol) and aqueous NaOH (2 N, 1.5 ml) was refluxed in an oil bath for 2.5 h. After being allowed to cool to room temperature, an aqueous solution of 10% HCl was added dropwise until the solution reached pH of 2. The resultant white solid was filtered and allowed to air dry to yield **5d** (0.09 g, 97%); mp 232–234°C; $^1$H NMR (DMSO-$d_6$): $\delta$ 8.97 (s, 1H), 8.60 (d, $J_{HH}$ = 5.1 Hz, 1H), 7.29 (m, 1H), 7.17 (d, $J_{HH}$ = 5.1 Hz, 1H), 7.11 (m, 1H), 6.91 (m, 1H), 4.44 (s, 2H).

Anal. calcd. for $C_{13}H_9F_2NO_2$: C, 62.65; H, 3.64; N, 5.62. Found: C, 62.37; H, 3.63; N, 5.53%.

*4.12. 3-(2-Fluoro-3-chlorobenzyl)isonicotinic acid (5e)*

A mixture of ester **4e** (0.68 g, 2.3 mmol) and aqueous sodium hydroxide (2 M, 5 ml) was heated at reflux for 1.5 h. The cooled solution was treated with an aqueous solution of HCl (10%) to pH 2.5. The precipitate was collected by filtration and dried to yield acid **5e** (0.55 g, 90%) as a white powder; mp 238–240°C; $^1$H NMR (DMSO-$d_6$): $\delta$ 8.62 (d, $J_{HH}$ = 5.0 Hz, 1H), 8.58 (s, 1H), 7.69 (d, $J_{HH}$ = 5.0 Hz, 1H), 7.43 (m, 1H), 7.12 (m, 1H), 6.97 (m, 1H), 4.38 (s, 2H).

Anal. calcd. for $C_{13}H_9ClFNO_2$: C, 58.77; H, 3.41; N, 5.27. Found: C, 58.42; H, 3.44; N, 4.99%.

*4.13. 6,8-Difluorobenz[g]isoquinoline-5,10-dione (6a)*

Fuming sulfuric acid (0.4 ml, 18–24% free sulfur trioxide) was slowly added to **5a** (0.06 g, 0.24 mmol) and the mixture was placed in a pre-heated oil bath at 65°C. After being kept at this temperature for 1 h, the cooled reaction mixture was quenched over ice (2 g). The resultant solution was neutralized by the cautious addition of solid sodium bicarbonate and the product extracted into dichloromethane (2×20 ml). The extracts were briefly dried over sodium sulfate and the solvent removed by rotary evaporation to yield **6a** as a yellow solid, (0.044 g, 75%); this material was crystallized from hexane:chloroform (4:1) to yield yellow needles, mp 192–194°C; $^1$H NMR ($CDCl_3$): $\delta$ 9.55 (s, 1H), 9.14 (d, $J_{HH}$ = 5.0 Hz, 1H), 8.08 (d, $J_{HH}$ = 4.9 Hz, 1H), 7.89 (m, $J_{HH}$ = 2.5 Hz, $J_{HF}$ = 1.1 Hz, $J_{HF}$ = 8.1 Hz, 1H), 7.26 (m, 1H).

Anal. calcd. for $C_{13}H_5F_2NO_2$: C, 63.68; H, 2.05; N, 5.71. Found: C, 63.39; H, 2.01; N, 5.74%.

*4.14. 8,9-Difluorobenz[g]isoquinoline-5,10-dione (6b)*

Fuming sulfuric acid (0.8 ml, 18–24% free sulfur trioxide) was slowly added to the **5b** (0.07 g, 0.27 mmol), and the mixture was placed in an oil bath which was preheated to 65°C. After being held at this temperature for 1 h, the reaction mixture was quenched over ice and the product was extracted into dichloromethane (3×20 ml). The combined extracts were dried over sodium sulfate and the solvent removed by rotary evaporation. The crude solid was purified by column chromatography (silica gel, ethyl acetate as the eluent) to yield a yellow solid (0.03 g, 48%); mp 190–192°C; $^1$H NMR ($CDCl_3$): $\delta$ 9.56 (s, 1H), 9.13 (d, $J_{HH}$ = 5.0 Hz, 1H), 8.21 (m, 1H), 8.05 (d, $J_{HH}$ = 5.1 Hz, 1H), 7.64 (m, 1H).

Anal. calcd. for $C_{13}H_5F_2NO_2$: C, 63.68; H, 2.05; N, 5.71. Found: C, 63.58 H, 1.77; N, 5.57%.

*4.15. 7,9-Difluorobenz[g]isoquinoline-5,10-dione (6c)*

Fuming sulfuric acid (1.4 ml, 33% free sulfur trioxide), was added slowly to **5c** (0.19 g, 0.76 mmol) which was in an oil bath preheated to 135°C. The reaction mixture was allowed to stir for 1.5 h. The mixture, after cooling to room temperature, was then poured over ice (5 g). The product was then extracted into dichloromethane (4×15 ml) and dried over sodium sulfate. The solvent was removed by rotary evaporation to yield a solid orange residue which was purified by column chromatography (silica gel, 2.0×8.0 cm, ethyl acetate) to yield **6c** as a yellow solid (0.11 g, 61%); mp 195–197°C; $^1$H NMR ($CDCl_3$): $\delta$ 9.51 (s, 1H), 9.12 (d, $J_{HH}$ = 5.0 Hz, 1H), 8.04 (d, $J_{HH}$ = 4.9 Hz, 1H), 7.87 (m, 1H), 7.28 (m, 1H).

Anal. calcd. for $C_{13}H_5F_2NO_2$: C, 63.68; H, 2.06; N, 5.71. Found: C, 63.60; H, 1.94; N, 5.69%.

*4.16. 6,7-Difluorobenz[g]isoquinoline-5,10-dione (6d)*

Fuming sulfuric acid (0.6 ml, 18% free sulfur trioxide) was slowly added to **5d** (0.06 g, 0.24 mmol). The reaction vessel was placed in an oil bath which was preheated to 67°C. After being allowed to react at that temperature for 1 h, the mixture was allowed to cool to room temperature and then poured over ice. The product was extracted into dichloromethane (3×20 ml) and dried over sodium sulfate. The solvent was removed by rotary evaporation to yield a solid residue. The residue was purified by column chromatography (silica gel, 1.5×5.0 cm, ethyl acetate) to yield a yellow solid (0.04 g, 66%); mp 189–191°C; $^1$H NMR ($CHCl_3$): $\delta$ 9.57

(s, 1H), 9.14 (d, $J_{HH}$=5.0 Hz, 1H), 8.22 (m, 1H), 8.07 (d, $J_{HH}$=4.9 Hz, 1H), 7.65 (m, 1H).

Anal. calcd. for $C_{13}H_5F_2NO_2$: C, 63.68; H, 2.06; N, 5.71; Found: C, 63.53; H, 2.11; N, 5.68%.

### *4.17. 8-Chloro-9-fluorobenz[g]isoquinoline-5,10-dione (6e)*

Fuming sulfuric acid (0.7 ml, 20% free sulfur trioxide) was added to acid **5e** (0.05 g, 0.2 mmol) and the resultant mixture was heated in an oil bath held at 100°C for 1 h. The reddish mixture was cooled to room temperature and poured over ice. The dione was extracted into dichloromethane (4×20 ml) and the extracts dried over magnesium sulfate. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (silica gel, 1.5 cm×8 cm, ethyl acetate as the eluent) to yield **6e** (0.03 g, 55%) as a bright yellow solid; mp 206–208°C; $^1$H NMR ($CDCl_3$): $\delta$ 9.57 (s, 1H), 9.13 (d, $J_{HH}$=5.2 Hz, 1H), 8.13 (d, $J_{HH}$=10.3 Hz, 1H), 8.04 (d, $J_{HH}$=5.0 Hz, 1H), 7.88 (m, 1H).

Anal. calcd. for $C_{13}H_5ClFNO_2$: C, 59.68; H, 1.43; N, 5.35. Found: C, 59.41; H, 1.86; N, 5.11%.

### *4.18. 6,8-Bis[[2-(dimethylamino)ethyl]amino]benz[g]isoquinoline-5,10-dione (7a)*

A solution of *N,N*-dimethylethylenediamine (0.214 g, 2.4 mmol) and pyridine (0.5 ml) was slowly added to **6a** (0.050 g, 0.20 mmol) at room temperature. The resultant red reaction mixture was allowed to stir at room temperature for 72 h. The reaction was stopped by removing the pyridine and excess amine under a stream of nitrogen. Ice water (10.0 ml) was then added to the red residue and the mixture was extracted into chloroform (5×15 ml). The solution was concentrated to yield a dark red residue which was purified by column chromatography (silica gel, 13.5 cm×2.5 cm, 9:1 chloroform:methanol with 1% ammonium hydroxide as eluent). This material was further purified by chromatotron (silica gel, 2 mm plate, 9:1 chloroform:methanol with 1% ammonium hydroxide as eluent) to yield the product **7a** as a red solid (0.037 g, 49%); mp 179–181°C; $^1$H NMR ($CDCl_3$): $\delta$ 10.03 (m, 1H), 9.38 (s, 1H), 8.97 (d, $J_{HH}$=5.2 Hz, 1H), 8.07 (d, $J_{HH}$=5.2 Hz, 1H), 6.97 (s, 1H), 5.92 (s, 1H), 5.37 (m, 1H), 3.40 (m, 2H), 3.29 (m, 2H), 2.69 (m, 2H), 2.61 (m, 2H), 2.36 (s, 6H), 2.29 (s, 6H).

Anal. calcd. for $C_{21}H_{27}N_5O_2 \cdot 0.5H_2O$: C, 65.80; H, 7.05; N, 18.28. Found: C, 65.53; H, 7.22; N, 17.89%.

### *4.19. 7,9-Bis[[2-(dimethylamino)ethyl]amino]benzo[g]isoquinoline-5,10-dione (7b) and 7-fluoro-9-[[(2-dimethylamino)ethyl]amino]benz[g]isoquinoline-5,10-dione (8)*

A solution of *N,N*-dimethylethylenediamine (0.2 g, 2.3 mmol) and pyridine (0.3 ml) was added to a mixture of **6c** (0.05 g, 0.21 mmol) and pyridine (0.2 ml) at room temperature. After allowing the mixture to stir for 48 h, the reaction was stopped by removing the pyridine and excess amine under a stream of nitrogen. Ice water (10 ml) was then added to the mixture and the crude product mixture was extracted into chloroform (5×10 ml). The combined extracts were dried over magnesium sulfate and concentrated by rotary evaporation. The crude product mixture was purified by chromatotron chromatography (silica gel, 1-mm thick, 9:1 chloroform:methanol with 1% ammonium hydroxide). Compound **8** eluted first to afford a red solid (0.019 g, 29%); mp 117–120°C; $^1$H NMR ($CDCl_3$): $\delta$ 9.92 (m, 1H), 9.56 (s, 1H), 9.01 (d, $J_{HH}$=4.9 Hz, 1H), 7.96 (d, $J_{HH}$=4.9 Hz, 1H), 7.24 (m, 1H), 6.71 (m, 1H), 3.37 (m, 2H), 2.69 (m, 2H), 2.37 (s, 6H). The disubstituted product **7b** then eluted and was isolated as a dark red solid (0.037 g, 47%); mp 145–147°C; $^1$H NMR ($CDCl_3$): $\delta$ 9.97 (m, 1H), 9.53 (s, 1H), 8.91 (d, $J_{HH}$=5.0 Hz, 1H), 7.90 (d, $J_{HH}$=5.0 Hz, 1H), 6.89 (d, $J_{HH}$=2.1 Hz, 1H), 5.94 (d, $J_{HH}$=2.1 Hz, 1H), 5.30 (m, 1H), 3.38 (m, 2H), 3.26 (m, 2H), 2.68 (m, 2H), 2.59 (m, 2H), 2.36 (s, 6H), 2.28 (s, 6H).

Anal. calcd. for $C_{21}H_{27}N_5O_2 \cdot 0.5H_2O$: C, 64.62; H, 7.18; N, 17.95. Found: C, 64.48; H, 7.03; N, 17.76%.

### *4.20. 7-Fluoro-9-[[(3-dimethylamino)propyl]amino]benz[g]isoquinoline-5,10-dione (9)*

A solution of 3-dimethylaminopropylamine (0.019 g, 0.19 mmol) and pyridine (0.3 ml) was added to a mixture of **6c** (0.021 g, 0.085 mmol) and pyridine (0.3 ml) held at room temperature. The resultant reddish mixture was allowed to stir for 6 h and the pyridine and excess amine were removed under a nitrogen stream. Water (3 ml) was added and the solid was collected by filtration. The filtrate was extracted with chloroform (3×10 ml) and the resultant solution concentrated by rotary evaporation. The combined solids were purified by column chromatography (silica gel, 6 cm×1.5 cm, gradient elution commencing with 95:5 to 80:20 chloroform:methanol) to yield **9** (0.016 g, 60%) as a red solid; mp 93–94°C (this material showed trace impurities on TLC analysis but was suitable for use in the next reaction step); $^1$H NMR ($CDCl_3$): $\delta$ 9.84 (m, 1H), 9.51 (s, 1H), 8.99 (d, $J_{HH}$=5.0 Hz, 1H), 7.95 (d, $J_{HH}$=5.0 Hz, 1H), 7.21 (d, $J_{HH}$=2.4 Hz, $J_{HF}$=8.5 Hz, 1H), 6.77 (dd, $J_{HH}$=2.4 Hz, $J_{HF}$=11.3 Hz, 1H), 3.37 (m, 2H), 2.44 (m, 2H), 2.29 (s, 6H), 1.92 (m, 2H).

### *4.21. 7,9-Bis[[3-(dimethylamino)propyl]amino]benzo[g]isoquinoline-5,10-dione (7b')*

A solution of **9** (0.016 g, 0.05 mmol) and 3-dimethylaminopropylamine (0.5 ml, neat) was heated to 80°C. After being held at that temperature for 40 min the dark purple solution was allowed to cool to room temperature. The excess amine was removed under a stream of nitrogen and the compound taken up in chloroform (5 ml), and washed with ice water (5 ml). After removal of the solvent, the product was purified by column chromatography (silica gel, 9:1 chloro-

form:methanol, 0.5 ml $NH_4OH$) to yield a red solid (0.01 g, 20%); mp 96–98°C, $^1H$ NMR ($CDCl_3$): $\delta$ 9.97 (m, 1H), 9.52 (s, 1H), 8.92 (d, $J_{HH}$ = 5.0 Hz, 1H), 7.91 (d, $J_{HH}$ = 5.0 Hz, 1H), 6.87 (d, $J_{HH}$ = 2.0 Hz, 1H), 6.12 (m, 1H), 5.95 (d, $J_{HH}$ = 2.0 Hz, 1H), 3.62 (m, 4H), 2.48 (m, 4H), 2.31 (s, 6H), 2.30 (s, 6H), 1.96 (m, 2H), 1.87 (m, 2H).

Anal. calcd. for $C_{23}H_{31}N_5O_2 \cdot 1H_2O$: C, 64.61; H, 7.78; N, 16.38 Found: C, 65.07; H, 7.47; N, 16.02%.

### *4.22. 8,9-Bis[[3-(dimethylamino)propyl]amino]benz[g]-isoquinoline-5,10-dione (7c)*

The 3-dimethylaminopropylamine (0.8 ml) was added to **6b** (0.05 g, 0.2 mmol) at room temperature. After 3 h the temperature was raised to 45°C and the reaction was allowed to stir for 2.5 h at this temperature. The reaction was stopped by removing the excess amine under a stream of nitrogen and then adding ice water (5 ml). The crude product was extracted into chloroform, dried over sodium sulfate and concentrated by allowing the solvent to evaporate in the hood. The dark blue oil was purified by column chromatography (silica gel, 2.0 cm × 5.0 cm, $CHCl_3$:MeOH (9:1), 1% $NH_4OH$ as the eluent) to yield **7c** as a dark blue solid (0.029 g, 35%); mp 83–85°C; $^1H$ NMR (deuteriotetrahydrofuran): $\delta$ 9.51 (s, 1H), 9.04 (d, $J_{HH}$ = 4.96 Hz, 1H), 8.20 (m, 1H), 8.05 (d, $J_{HH}$ = 4.96 Hz, 1H), 8.00 (d, $J_{HH}$ = 8.60 Hz, 1H), 7.43 (m, 1H), 6.98 (d, $J_{HH}$ = 8.60 Hz, 1H), 3.50 (m, 2H), 3.32 (m, 2H), 2.61 (m, 2H), 2.51 (m, 2H), 2.37 (s, 6H), 2.34 (s, 6H), 1.93 (m, 4H).

Anal. calcd. for $C_{23}H_{31}N_5O_2 \cdot 0.5H_2O$: C, 66.03; H, 7.65; N, 16.75. Found: C, 66.47; H, 7.65; N, 16.70%.

### *4.23. 1,2,3,4,7,12-Hexahydro-4,4-dimethyl-7,12-dioxoisoquino[7,6-f]quinoxalinium fluoride (10) and 1,2,3,4-tetrahydro-4-methylisoquino [7,6-f]quinoxaline-7,12-dione (12), route 1 (from 6b)*

A solution of *N,N*-dimethylethylenediamine (0.10 g, 1.2 mmol) and pyridine (0.3 ml) was added to **6b** (0.027 g, 0.11 mmol) at room temperature. The mixture turned red instantly and a red solid precipitate was visible after 20 min. The mixture was allowed to stir for 53 h while monitoring closely by TLC (silica gel, 98:2 chloroform:methanol). As the reaction proceeded, a spot corresponding to the demethylation product **12** became more intense. The reaction was stopped by removing the pyridine and excess amine under a stream of nitrogen. Chloroform (2.0 ml) was added to the red residue and the solid collected by filtration. The solid was rinsed repeatedly with chloroform until no more blue color was present in the filtrate. The solid was allowed to air dry to yield **10** (0.029 g, 83%); mp 198–201°C (dec.); $^1H$ NMR ($D_2O$): $\delta$ 8.88 (s, 1H), 8.82 (d, $J_{HH}$ = 4.4 Hz, 1H), 7.94 (d, $J_{HH}$ = 8.2 Hz, 1H), 7.70 (d, $J_{HH}$ = 4.4 Hz, 1H), 7.08 (d, $J_{HH}$ = 8.2 Hz, 1H), 3.95 (m, 2H), 3.87 (m, 2H), 3.60 (s, 6H).; MS, $M^+$ 313; *m/z* (EI) $M^+$ (279, 100%, loss of $CH_3F$). The filtrate was concentrated by rotary evaporation to yield a blue residue which was purified by column chromatography (silica gel, 2 cm × 12 cm, using gradient elution with mixtures of chloroform:methanol 97:3 to 95:5) to yield **12** (2 mg, 6%); $^1H$ NMR ($CDCl_3$): $\delta$ 10.28 (m, 1H), 9.52 (s, 1H), 8.95 (d, $J_{HH}$ = 5.0 Hz, 1H), 8.01 (d, $J_{HH}$ = 5.0 Hz, 1H), 7.71 (d, $J_{HH}$ = 8.3 Hz, 1H), 6.61 (d, $J_{HH}$ = 8.3 Hz, 1H), 3.71 (m, 2H), 3.48 (m, 2H), 3.07 (s, 3H); MS, $M^+$ 279; *m/z* (EI) $M^+$ (279, 36%).

### *4.24. 8-Chloro-9-[[(2-dimethylamino)ethyl]amino]benz[g]isoquinoline-5,10-dione (13), route 2 (from 13)*

A solution of *N,N*-dimethylethylenediamine (0.02 g, 0.23 mmol) and pyridine (0.7 ml) was added to a solution of **6e** (0.03 g, 0.10 mmol) and pyridine (0.7 ml) at room temperature. The resultant red mixture was allowed to stir for 3 h after which time starting material could no longer be detected by TLC (silica gel plate, 95:5 dichloromethane:methanol). The excess pyridine and amine were removed under a slow stream of nitrogen and purification was effected by flash chromatography (silica gel, 1.5 cm × 14 cm, 95:5 dichloromethane:methanol as the eluent) to yield **13** (0.022 g, 67%) as a red solid; mp 114–116°C; $^1H$ NMR ($CDCl_3$): $\delta$ 9.90 (m, 1H), 9.58 (s, 1H), 9.02 (d, $J_{HH}$ = 5.0 Hz, 1H), 7.97 (d, $J_{HH}$ = 4.9 Hz, 1H), 7.59 (m, 2H), 3.84 (q, $J_{HH}$ = 6.1 Hz, 2H), 2.60 (t, $J_{HH}$ = 6.2 Hz, 2H), 2.35 (s, 6H).

Anal. calcd. for $C_{17}H_{16}ClN_3O_2$: C, 61.92; H, 64.89; N, 12.74. Found: C, 62.02; H, 4.74; N, 12.69%.

### *4.25. 1,2,3,4,7,12-Hexahydro-4,4-dimethyl-7,12-dioxoisoquino[7,6-f]quinoxalinium fluoride (10) and 1,2,3,4-tetrahydro-4-methylisoquino [7,6-f]quinoxaline-7,12-dione (12) from 13*

A solution of *N,N*-dimethylethylenediamine (0.035 g, 0.4 mmol) and pyridine (0.5 ml) was added to a solution of **13** (0.012 g, 0.04 mmol) and pyridine (0.5 ml) at room temperature. After 1 h the temperature was raised to 50°C and after 4 h the temperature was raised to 80°C. After 5 h at this temperature, the pyridine and excess amine was removed under a nitrogen stream. Dichloromethane (2 ml) was added to the residue and the red solid **10** (0.009 g, 73%) was collected by filtration after rinsing thoroughly with dichloromethane. The filtrate was concentrated to afford **12** (0.004 g, 12%) which was purified by flash chromatography (silica gel, 1.5 cm × 14 cm, using 95:5 dichloromethane:methanol as the eluent).

### *4.26. 1,2,3,4,7,12-Hexahydro-4,4-dimethyl-7,12-dioxoisoquino[6,7-f]quinoxalinium fluoride (14) and 1,2,3,4-tetrahydro-4-methyl-isoquino[6,7-f]quinoxaline-7,12-dione (15)*

A solution of *N,N*-dimethylethylenediamine (0.11 g, 1.1 mmol) in pyridine (0.3 ml) was added to **6d** (0.028 g, 0.11 mmol) at room temperature. The mixture turned red instantly and a red solid precipitate was visible after 10 min. The

mixture was allowed to stir for 53 h while monitoring closely by TLC (silica gel, 98:2 chloroform:methanol). As the reaction proceeded, a spot corresponding to **15** became more intense. The reaction was stopped by removing the pyridine and excess amine under a stream of nitrogen. Chloroform (2.0 ml) was added to the red residue and the solid collected by filtration. The solid was rinsed repeatedly with chloroform until no more blue color was present in the filtrate. The solid was allowed to air dry to yield **14** (0.033 g, 94%); mp 194–197°C; $^1$H NMR ($D_2O$): $\delta$ 9.10 (s, 1H), 8.99 (d, $J_{HH}$ = 5.1 Hz, 1H), 8.13 (d, $J_{HH}$ = 8.4 Hz, 1H), 7.84 (d, $J_{HH}$ = 5.1 Hz, 1H), 7.26 (d, $J_{HH}$ = 8.4 Hz, 1H), 4.72 (m, 2H), 4.04 (m, 2H), 3.77 (s, 6H); MS, $M^+$ 313; *m/z* (EI) $M^+$ (279, 55%, loss of $CH_3F$). The filtrate was concentrated by rotary evaporation to yield a blue residue which was purified by column chromatography (silica gel, 2 cm × 9 cm, gradient elution using mixtures of chloroform:methanol 99:1 to 95:5) to yield **15** (1 mg, 3%); $^1$H NMR ($CDCl_3$): $\delta$ 10.31 (m, 1H), 9.45 (s, 1H), 8.97 (d, $J_{HH}$ = 5.0 Hz, 1H), 8.04 (d, $J_{HH}$ = 5.0 Hz, 1H), 7.71 (d, $J_{HH}$ = 8.0 Hz, 1H), 6.63 (d, $J_{HH}$ = 8.0 Hz, 1H), 3.74 (m, 2H), 3.46 (m, 2H), 3.67 (s, 3H); MS, $M^+$ 279; *m/z* (EI) $M^+$ (279, 75%).

### *4.27. 6,7-Bis[[3-(dimethylamino)propyl]amino]benzo[g]-isoquinoline-5,10-dione (**7d**) and 7-fluoro-6-[[(3-dimethylaminopropyl)]amino]benz[g]isoquinoline-5,10-dione (**16**)*

A mixture of **6d** (0.05 g, 0.21 mmol) and *N,N*-dimethylaminopropylamine (0.8 ml, neat), was stirred in a flask fitted with a condenser in an oil bath preheated to 45°C. The mixture was allowed to stir at that temperature for 10 h before having the excess amine removed under a stream of nitrogen. Water was added and the crude product mixture was extracted into chloroform (5 × 15 ml). The solvent was removed by rotary evaporation to yield a blue residue which was purified by chromatotron chromatography (silica gel, 2 mm thickness, 9:1 chloroform:methanol). The first compound to elute was **16** (0.021 g, 30%); mp 122–125°C; $^1$H NMR ($CDCl_3$): $\delta$ 9.96 (m, 1H), 9.49 (s, 1H), 9.05 (d, $J_{HH}$ = 5.0 Hz, 1H), 8.08 (d, $J_{HH}$ = 5.0 Hz, 1H), 7.60 (m 1H), 7.27 (m, 1H), 3.72 (m, 2H), 2.43 (m, 2H), 2.27 (s, 6H), 1.89 (m, 2H). Elution of the disubstituted compound **7d** followed to yield a dark blue solid (0.02 g, 30%); mp 101–104°C; $^1$H NMR ($CDCl_3$): $\delta$ 9.49 (s, 1H), 8.97 (d, $J_{HH}$ = 5.0 Hz, 1H), 8.01 (d, $J_{HH}$ = 5.0 Hz, 1H), 7.97 (d, $J_{HH}$ = 8.6 Hz, 1H), 7.33 (m, 1H), 6.77 (d, $J_{HH}$ = 8.6 Hz, 1H), 3.35 (m, 2H), 3.19 (m, 2H), 2.54 (m, 2H), 2.41 (m, 2H), 2.29 (s, 6H), 2.27 (s, 6H), 1.84 (m, 4H).

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