# The Synthesis of 6,9-Bis[(aminoalkyl)amino] Substituted Benzo[g]quinoxaline-, Benzo[g]quinazoline- and Benzo-[g]phthalazine-5,10-diones *via* Regiospecific Displacements



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The synthesis of 6,9-difluoro substituted benzo[g]quinoxaline-5,10-diones (**3A**), benzo[g]quinazoline-5,10-diones (**3B**) and benzo[g]phthalazine-5,10-diones (**3C**) have been accomplished. Treatment of **3A, 3B** or **3C** with diamines or *N*-(*t*-butoxycarbonyl)ethylenediamine led to the corresponding 6,9-bis[(aminoalkyl)amino]-substituted analogues related to **2A, 2B** and **2C**, respectively. The mono-substituted derivatives **4h** and **4i** could be isolated from displacements commencing from **3A**. A competitive ring-opening of the pyrimidine ring of **2C** occurred during the reaction with *N,N*-dimethylethylenediamine. Removal of the BOC-protecting group from **2Ac** led to the hydrochloride salt **2Ab**. A novel synthetic pathway to 6,9-dihydroxybenzo[g]-phthalazine-5,10-dione (**21a**) was developed. Conversion of **21a** to the ditosylate **21b** was readily accomplished. Treatment of **21b** with *N,N*-dimethylethylenediamine or *N*-(*t*-butoxycarbonyl)ethylenediamine led to **2Ca** and **2Cc**, respectively. Removal of the BOC-protecting group from **2Cc** with trifluoroacetic acid followed by ion-exchange led to the hydrochloride salt **2Cb**. Treatment of ditosylate **21b** with *N*-(*t*-butoxycarbonyl)ethylenediamine also led to the mono-substituted analogue **25a** along with a small amount of the O-S cleavage product **25b**. Treatment of **25a** with *N,N*-dimethylethylenediamine led to the unsymmetrically substituted derivative **25c** which was converted into the trifluoroacetate salt **25d**.

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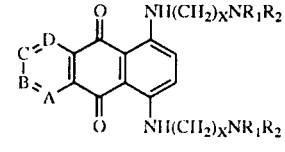
Anthracene-9,10-diones with specific 1,4-bis[(aminoalkyl)amino] substituents such as **1a** or **1b** have shown outstanding anticancer activities [1-4]. Mitoxantrone (**1b**) is not completely devoid of toxic side effects and the search for chemotypes with higher therapeutic efficacies and fewer toxic effects is still an important endeavor. In addition, the search for new compounds effective against MDR cell lines is of paramount importance [5].

**1a**, X = H
**b**, X = OH

The introduction of heteroatoms into the anthracene-9,10-dione chromophore is a relatively unexplored area [6-9]. These bioisosteres could have altered molecular interactions with biomolecules (such as DNA intercalation) and different properties such as cellular drug uptake and physiological distribution.

The scope of this manuscript is to describe synthetic pathways which lead to three regioisomeric chemotypes related to **2** using $S_NAr$-like displacements from the respective difluorides **3** and in one case from a related ditosylate.



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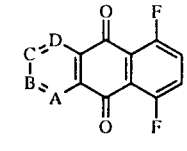


**3**

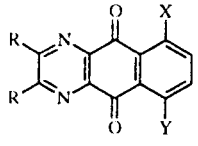
Series A, A = D = N, B = C = CH
Series B, A = C = N, B = D = CH
Series C, B = C = N, A = D = CH

a, $R_1 = R_2 = CH_3$, x = 2
b, $R_1 = R_2 = H$, x = 2
c, $R_1 = H$, $R_2 = CO_2C(CH_3)_3$, x = 2
d, $R_1 = R_2 = H$, x = 3

## A. 6,9-Bis[(aminoalkyl)amino]benzo[g]quinoxaline-5,10-diones (Series A).

An analysis of the prior literature data did not lead to any potential intermediates which could be utilized for the preparation of these regiospecifically substituted benzo[g]-quinoxaline-5,10-diones. Although the analogues **4a** [10], **4b** [11], **4c** [12] and **4d** [13] are known, attempts to nitrate **4a** were unsuccessful [10]. The synthesis of **4e** [13] has been accomplished but no attempts to prepare **4f** by decarbethoxylation of this bis-urethane were mentioned. The preparation of **4g** [10] has been accomplished *via* a cyclodehydration route in a very low yield (6%). The preparation of 7,10 disubstituted derivatives of benzo[b]phen-

azine-6,11-quinones **5** have been reported [14]. The analogue **6** has been prepared *via* a one pot bis-acylation strategy in a very poor yield [15].



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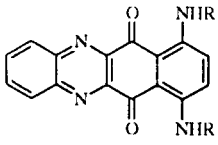
a, R = X = H, Y = $OCH_3$
b, R = X = H, Y = $NO_2$
c, R = X = H, Y = $NH_2$
d, R = $CH_3$, X = H, Y = $OCH_3$
e, R = $CH_3$, X = Y = $NHCO_2Et$
f, R = $CH_3$, X = Y = $NH_2$
g, R = H, X = Y = OH
h, R = H, X = F, Y = $NH(CH_2)_2N(CH_3)_2$
i, R = H, X = F, Y = $NH(CH_2)_2NHCO_2C(CH_3)_3$



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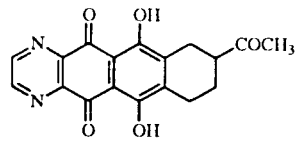
a, R = H
b, R = $CH_3$
c, R = $C_6H_5$



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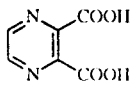
The exceptional ease of displacement of suitably positioned fluorides by diamines (a formal $S_NAr$ process) which we have previously utilized for the preparation of substituted anthracene-9,10-dione analogues provided the synthetic rational for the preparation of this series of diaza bioisosteres and the subsequent regioisomers [1]. The target synthon was the difluoro analogue **3A**.

Commercially available diacid **7** was readily converted into the anhydride **8** by refluxing in acetic anhydride or by treatment with DCC in THF. Friedel-Crafts acylation of 1,4-difluorobenzene with anhydride **8** in the presence of aluminum chloride led to keto acid **9**. Cyclodehydration of **9** with fuming sulfuric acid (30% sulfur trioxide) at 140° yielded **3A**.



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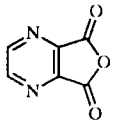

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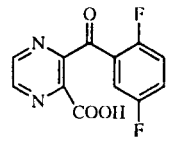

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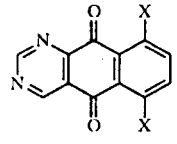
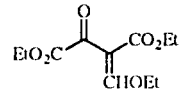
The ipso fluoride displacements from **3A** were initially investigated using *N,N*-dimethylethylenediamine for the preparation of **2Aa**. Upon addition of this diamine to a pyridine solution of **3A**, an immediate blue coloration appeared (probably a charge transfer complex). The fluoride displacements proceeded quite slowly and the mixture was allowed to stir for several days to effect nearly complete bis-substitution to yield **2Aa**. If the reaction period was shortened, the mono-substituted analogue **4h** could be isolated by column chromatography. This latter compound would be useful for the preparation of unsymmetrically substituted analogues. Displacements of the fluorides of **3A** by ethylenediamine (pyridine as solvent) led to several products of unknown structure, but none of the desired **2Ab**. This latter compound was prepared by treatment of *N*-(*tert*-butoxycarbonyl)ethylenediamine (DMSO as solvent) to form **2Ac** and **4i**. Treatment of the bis-BOC analogue with anhydrous hydrogen chloride gas led to **2Ab** (isolated as the hydrochloride salt). The reaction of **3A** with 1,3-diaminopropane (neat or in pyridine as solvent) led to **2Ad** (isolated as the dimaleate salt).

B. 6,9-Bis[(Aminoalkyl)amino]benzo[*g*]quinazoline-5,10-dione (Series B).

The synthesis of benzo[*g*]quinazoline-5,10-dione (**10a**) [12] and the 6,9-bis urethane **10b** [13] have been reported. Following a strategy similar to that described for the **A** series, the target molecule was the difluoro analogue **3B**.



10a, X = H
b, X = $NHCO_2Et$
c, X = $NH_2$



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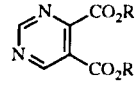
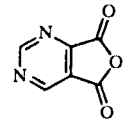


12a, R = Et
b, R = H



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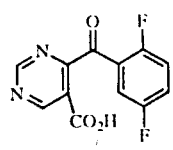
Diethyl ethoxymethyleneoxalacetate (**11**) and formamidine acetate on being refluxed in a benzene solution readily yielded diethyl pyrimidine-4,5-dicarboxylate (**12a**). Hydrolysis of this diester **12a** under basic conditions led to pyrimidine-4,5-dicarboxylic acid (**12b**). The anhydride **13** was obtained by treatment of this diacid with DCC in THF. However, this anhydride proved difficult to work with because of its extremely hygroscopic nature [16]. Treatment of **13** with 2-lithio-1,4-difluorobenzene [17] led to keto acid **14**. The diester **12a** on treatment with 2-lithio-1,4-difluorobenzene in THF followed by saponification of the resulting ester and acidic workup also led to the keto acid **14**. This formulation is based on the expected greater electrophilicity of the ester and anhydride carbonyl groups at position 4 [18,19]. The cyclization of **14** in fuming sulfuric acid (30% sulfur trioxide) at 110° led to reasonable yields of the desired difluoro analogue **3B**.



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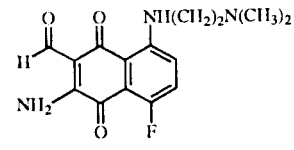
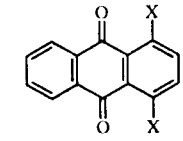


15 (or regioisomer)



16a, X = OH
b, X = $NH(CH_2)_2N(CH_3)_2$
c, X = $NH_2$

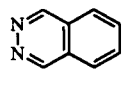
Our initial attempts to prepare **2Ba** by displacements of the fluorides from **3B** with *N,N*-dimethylethylenediamine in pyridine or DMSO as the solvent were unsuccessful. Numerous side products, which were formed from opening of the pyrimidine ring, proved difficult to separate from the desired bis-substitution product. When chloroform was used as the solvent for the reaction of **3B** with *N,N*-dimethylethylenediamine, only two major products were formed and **2Ba** could be isolated by chromatography.

A dark red material was also isolated and $^1H$ nmr spectroscopic analysis was consistent with the structural formulation **15**. Integral comparisons indicated a mono substitution pattern and the presence of F was indicated by $^{19}F$-$^1H$ couplings. The mass spectrum indicated a parent peak at 306 which corresponds to the molecular mass of **15**. Precedents exist for the ring-opening reactions of pyrimidines with nucleophiles [20,21] and compounds such as **3B** are further activated at C-2 by the quinone moiety.

An alternate pathway for the synthesis of 1,3-diaza (B series) was pursued. A prior study had reported that treatment of quinizarin (**16a**) with *N,N*-dimethylethylenediamine led to **16b** [22]. We have found that treatment of **16c** with *N,N*-dimethylethylenediamine also led to **16b**. Based on this conversion of the carbocyclic analogue, the preparation of **10c** was attempted. However, the synthesis of analogue **10c** by decarbethoxylation of the bis-urethane **10b** [13] under acidic or basic conditions was unsuccessful. Numerous decomposition products were formed from which no **10c** could be isolated. An attempt to prepare **2Ba** by heating **10b** with *N,N*-dimethylethylenediamine in water was unsuccessful.

C. 6,9-Bis[(aminoalkyl)amino]benzo[g]phthalazine-5,10-diones (Series C).

Numerous investigations in the phthalazine arena (which even date back to the last century) have been reported and various substituted analogues have been prepared [23,24,25].



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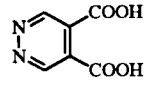

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Route 1.

As in the **A** or **B** series, our target synthon was difluoride **3C**, which was prepared by the following reaction sequence. Phthalazine (**17**) was oxidized with a hot aqueous solution of sodium permanganate to yield the pyridazine-4,5-dicarboxylic acid **18**. This diacid was converted to the anhydride **19** by treatment with DCC in THF. The keto acid **20** was obtained by treatment of anhydride **19** with 2-lithio-1,4-difluorobenzene in THF at −80°. The dione **3C** was obtained by heating this keto acid in fuming sulfuric acid (30% sulfur trioxide) at 105° for 3 hours.

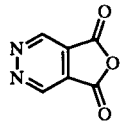
The analogues **2Ca** and **2Cc** were obtained by treatment of **3C** with *N,N*-dimethylethylenediamine or *N*-(*tert*-butoxycarbonyl)ethylenediamine, respectively.

Route 2.

The second approach towards the construction of these 2,3-diaza chemotypes is based on the introduction of the pyridazine ring in a late stage of the synthesis using a direct transformation of a furan ring to a pyridazine ring. This strategy is illustrated in the retrosynthetic analysis in Scheme I.

The synthetic pathway to **21b** commenced from commercially available diethyl 3,4-furandicarboxylate (**23a**). Saponification of this diester led to **23b** which was readily converted into the dichloride **23c** by treatment with thionyl chloride in toluene. Friedel-Crafts bis-acylation of **24** with **23c** [26,27] in dichloromethane at room temperature in the presence of aluminum chloride followed by a brief reflux to effect demethylation led to **22a** (variable yields of 40 to 63%). During the early stages of this reaction the intermediates **22b** and **22c** could be detected by tlc.

The crucial step is the conversion of **22a** to **21a**. Few precedents exist for this type of transformation [28]. On treatment of **22a** with hydrazine at room temperature followed by air oxidation under alkaline conditions, **21a** (89%) was isolated. It might be noted that in the Clauson-



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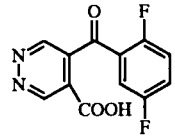

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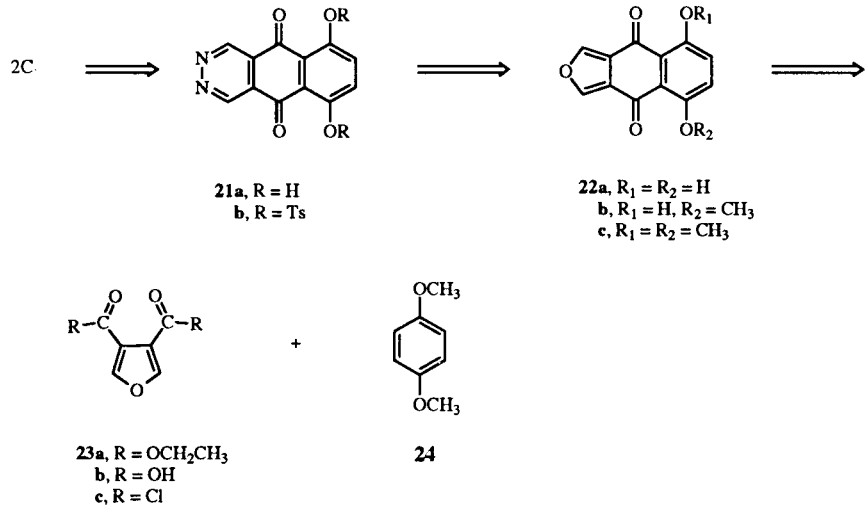
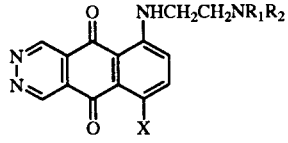
Scheme 1



Kaas [29] method of pyridazine synthesis, a furan is treated with bromine in methanol to yield a 2,5-dimethoxy-2,5-dihydrofuran. These products are hydrolyzed by aqueous acetic acid to yield the intermediate ene-diones (or the aldehyde analogues) which react with hydrazine to yield the corresponding pyridazines. In comparison to the Clauson-Kaas methodology, the reaction sequence involved in the transformation of **22a** to **21a** is reversed in that the furan ring initially reacts with the hydrazine and then oxidation of the resultant intermediate occurs. The incorporation of hydrazine into **22a** is activated by the neighboring carbonyl moieties.

Treatment of **21a** with *p*-toluenesulfonyl chloride in pyridine at room temperature yielded the ditosylate **21b**. The displacement of the tosylate groups in **21b** by *N,N*-dimethylethylenediamine or *N*-(*t*-butoxycarbonyl)ethylenediamine in pyridine at room temperature led to **2Ca** (32%) or **2Cc** (35%), respectively. The bis-substitution product **2Ca** (9%) can also be obtained by reaction of the lecuo form of **21a** which was prepared *in situ* by reduction with sodium dithionite followed by oxidation on workup.

In the reaction of **21b** with a limited amount of *N*-(*t*-butoxycarbonyl)ethylenediamine, **2Cc** along with **25a** (30%) and **25b** (14%) could be isolated. The O-S bond cleavage occurs *via* a nucleophilic attack of the amino nitrogen at the S atom of the tosylate grouping [30]. The deprotection of **2Cc** was accomplished with trifluoroacetic acid to initially yield the trifluoroacetate salt, followed by anion exchange with Dowex 1 x 8-200 Cl- form to yield **2Cb**.



**25a**, $R_1 = H$, $R_2 = CO_2C(CH_3)_3$, X = OTs
**b**, $R_1 = H$, $R_2 = CO_2C(CH_3)_3$, X = OH
**c**, $R_1 = R_2 = CH_3$, $X = NH(CH_2)_2NHCO_2C(CH_3)_3$
**d**, $R_1 = R_2 = CH_3$, $X = NH(CH_2)_2NH_2$

Attempts to react **21b** with ethylenediamine or 2-[(2-aminoethyl)amino]ethanol led to complex product mixtures from which none of the desired bis-substitution products could be isolated.

The synthesis of an unsymmetrically substituted 6,9-bis-[(aminoalky)amino]benzo[*g*]phthalazine-5,10-dione was also accomplished. Compound **25a** on reaction with *N,N*-dimethylethylenediamine in pyridine led to **25c** (68%). The deprotected analogue **25d** (as the trifluoroacetate salt) was obtained by treatment of **25c** with trifluoroacetic acid in dichloromethane.

Conclusions.

The difluoro and ditosyloxy synthons described not only permit facile synthetic access to the compounds described, but should find application in displacement processess with other nucleophilies to lead to a plethora of additional substitution products.

The biological data for the regioisomeric diaza compounds will be published elsewhere.

## EXPERIMENTAL

Melting points were determined on a Buchi 535 apparatus or a Thomas Hoover apparatus and are uncorrected. The nmr spectra were recorded on a Bruker AC 200 spectrometer (200 MHz), a

Bruker WP-270SY or a WM-250 pulsed FT spectrometer. The ir spectra were recorded on a Perkin Elmer FT-IR model 1710 spectrophotometer in potassium bromide. Mass spectra were recorded on a Finnigan MAT 4610 mass spectrometer. Elemental analyses were performed by Redox S.n.c. (Cologno Monzese, Milan, Italy) or Robertson Labs (Madison, NJ). Commercially available reagents were used as received unless otherwise stated. The solvent used were of analytical grade or better. The solvents were dried over molecular sieves of suitable type (**3A** or **4A**). Baker analyzed 80-200 mesh silica gel or Merck silica gel 60 (230-400 mesh) was used for column chromatography.

6,9-Bis[[2-(dimethylamino)ethyl]amino]benzo[g]quinoxaline-5,10-dione (**2Aa**).

A solution of **3A** (100 mg, 0.41 mmole) and *N,N*-dimethylethylenediamine (1.5 ml) was magnetically stirred at rt for 66 hours. The excess diamine was removed under a slow stream of nitrogen and the crude blue solid was purified by column chromatography over silica gel. The initial eluent was chloroform followed by 95:5 chloroform:methanol which eluted the mono-substituted analogue **4h**. The desired **2Aa** was eluted by chloroform:methanol v/v mixtures of 90:10 and 85:15. The removal of the eluents led to a blue solid (77 mg, 49%), mp 210-212°; $^1$H nmr (deuteriochloroform): δ 11.38 (t, 2H), 8.99 (s, 2H), 7.32 (s, 2H), 3.48 (q, 4H), 2.70 (t, 4H), 2.32 (s, 12H).

*Anal.* Calcd. for $C_{20}H_{26}N_6O_2$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.48; H, 6.45; N, 21.77.

6,9-Bis[[2-[(*t*-butoxycarbonyl)amino]ethyl]amino]benzo[g]quinoxaline-5,10-dione (**2Ac**).

A mixture of **3A** (102 mg, 0.41 mmole) and *N-t*-butoxycarbonylethylenediamine (664 mg, 4.14 mmoles) in dimethyl sulfoxide (1 ml) was stirred at room temperature for 70 hours. The deep blue solution was poured over crushed ice (40 g) and the resulting solid collected by filtration and dried under vacuum. Purification by column chromatography over silica gel with chloroform/methanol gradient elution (99:1, 95:5, 90:10, 100 ml) gave a minor red and major blue band. Removal of the eluents by rotary evaporation led to a red solid **4i** (26 mg, 17%) and blue solid **2Ac** (84 mg, 38%), mp 237-239°; $^1$H nmr (deuteriochloroform): δ 11.39 (t, 2H), 9.01 (s, 2H), 7.41 (s, 2H), 5.18 (t, 2H), 3.63 (br m, 4H), 3.44 (q, 4H), 1.49 (s, 18H).

*Anal.* Calcd. for $C_{26}H_{34}N_6O_6$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.22; H, 6.32; N, 15.92.

6,9-Bis[[2-aminoethyl]amino]benzo[g]quinoxaline-5,10-dione Trihydrochloride (**2Ab**).

Hydrogen chloride gas was bubbled through a magnetically stirred solution of **2Ac** (30 mg, 0.063 mmole) in chloroform (10 ml) for 15 minutes. The dark blue precipitate was collected by filtration, washed with chloroform (2 x 5 ml) and dried under vacuum (25 mg, 96%); $^1$H nmr (deuterium oxide): δ 8.99 (s, 2H), 6.73 (s, 2H), 3.74 (br m, 4H), 3.44 (br m, 4H).

*Anal.* Calcd. for $C_{16}H_{21}Cl_3N_6O_2$: C, 44.10; H, 4.86; N, 19.29; Cl, 24.31. Found: C, 44.61; H, 5.26; N, 19.17.

6,9-Bis[[3-aminopropyl]amino]benzo[g]quinoxaline-5,10-dione Dimaleate (**2Ad**).

A solution of **3A** (200 mg, 0.83 mmole) and 1,3-diaminopropane (3 ml) was stirred at room temperature for 48 hours. The excess diamine was removed by a gentle stream of nitrogen. The residue was triturated with petroleum ether (4 x 15 ml) and dried under vacuum overnight. The blue solid (230 mg) was dissolved in a mixture of methanol (15 ml) and ethyl acetate (5 ml). Maleic acid (191 mg) in ethyl acetate (5 ml) was added dropwise to the blue stirred solution. Ethyl acetate was added slowly until precipitation of the salt was induced. The mixture was allowed to stand for a few hours and the solid was collected by filtration (319 mg, 68%); $^1$H nmr (DMSO-$d_6$): δ 11.09 (t, 2H), 9.07 (s, 2H), 7.76 (br, 4H), 7.58 (s, 2H), 6.00 (s, 4H), 3.61 (q, 4H), 2.92 (t, 4H), 1.93 (t, 4H).

*Anal.* Calcd. for $C_{26}H_{30}N_6O_{10}$: C, 52.23; H, 5.16; N, 14.32. Found: C, 51.90; H, 5.46; N, 14.00.

6,9-Bis[[2-(dimethylamino)ethyl]amino]benzo[g]quinazoline-5,10-dione (**2Ba**).

A solution of *N,N*-dimethylethylenediamine (230 mg, 2.61 mmoles) and chloroform (4 ml) was added dropwise to a stirred solution of **3B** (58 mg, 0.23 mmole) and chloroform (10 ml) under a nitrogen blanket. The stopped solution was stirred at room temperature for 70 hours. The chloroform and excess diamine were removed by a stream of nitrogen. Purification by preparative thin layer chromatography (silica gel, 10 x 15 cm, 0.25 mm thickness) with chloroform/methanol (95:5) separated a red and blue band. Each band was collected and rinsed with chloroform/methanol (50:50, 15 ml). The silica gel was removed by filtration and each filtrate was concentrated by rotary evaporation to yield a red solid **15** (19 mg), mp 174-180°; $^1$H nmr (deuteriochloroform): δ 10.36 (s, 1H), 9.98 (br s, 2H), 7.37 (t, 1H), 7.01 (dd, 1H), 3.43 (q, 2H), 2.66 (t, 2H), 2.36 (s), 2.35 (s) [ratio 22:78] and **2Ba** as a blue solid (44 mg, 53%); $^1$H nmr (deuteriochloroform): δ 11.58 (br t, 1H), 11.12 (br t, 1H), 9.78 (s, 1H), 9.57 (s, 1H), 7.35 (s, 2H), 3.56 (q, 4H), 2.71 (t, 4H), 2.37 (s, 6H), 2.36 (s, 6H).

*Anal.* Calcd. for $C_{20}H_{26}N_6O_2$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.45; H, 6.44; N, 21.62.

6,9-Bis[[2-(dimethylamino)ethyl]amino]benzo[g]phthalazine-5,10-dione (**2Ca**).

From **3C**.

A solution of **3C** (61 mg, 0.25 mmole) and *N,N*-dimethylethylenediamine (1 ml) was stirred at rt for 4 hours. The excess diamine was removed under a slow nitrogen stream and the residue was placed under vacuum. The resultant solid was purified by column chromatography over silica gel (2.25 x 6.5 cm). A minor red band (mono-substituted analogue) eluted with 20:80 methanol:chloroform. The major blue band was eluted from the column with 50:50:0.5 methanol:chloroform:ammonium hydroxide (300 ml). The eluents were removed by rotoevaporation to yield **2Ca** as a blue solid (76 mg, 81%), mp 208-210°; $^1$H nmr (deuteriochloroform): δ 11.45 (t, 2H), 9.98 (s, 2H), 7.33 (s, 2H), 3.56 (q, 4H), 2.69 (t, 4H), 2.37 (s, 12H).

*Anal.* Calcd. for $C_{20}H_{26}N_6O_2$: C, 62.80; H, 6.86; N, 21.96. Found: C, 62.40; H, 6.93; N, 21.58.

From **21b**.

A solution of **21b** (0.16 g, 0.91 mmole) and *N,N*-dimethylethylenediamine (1.0 ml, 9.15 mmoles) in pyridine (10 ml) was stirred at room temperature under a nitrogen blanket for 24 hours. The solvent was removed at reduced pressure, the residue taken up in chloroform (50 ml), the extract washed with a sodium bicarbonate solution (3%, 2 x 15 ml), dried over sodium sulfate and concentrated to dryness. The residue was purified by silica gel column

chromatography with the eluent chloroform:methanol:triethylamine 95:4:1. Removal of the eluents and recrystallization of the residue from dichloromethane:pentane led to **2Ca** (36 mg, 32%) as small blue crystals.

From **21a**.

Under a nitrogen atmosphere, a stirred mixture of **21a** (63 mg, 0.26 mmole), sodium dithionite (97 mg, 0.557 mmole) and anhydrous sodium carbonate (17 mg, 0.16 mmole) in degassed and dry ethanol (7 ml) was heated at reflux for 1.5 hours. *N,N*-Dimethylethylenediamine (0.43 ml, 3.90 mmoles) was added and the mixture was refluxed for an additional 12 hours. The solvent was removed by distillation under reduced pressure, the residue taken up in chloroform (15 ml) and the solution stirred in an open vessel at room temperature for 0.5 hour. The solvent was removed under reduced pressure and the residue purified by chromatography to yield **2Ca** (15 mg, 9%).

6,9-Bis[[2-aminoethyl]amino]benzo[*g*]phthalazine-5,10-dione Trihydrochloride (**2Cb**).

To a stirred solution of **2Cc** (240 mg, 0.456 mmole) in dry dichloromethane (20 ml) under a nitrogen atmosphere at 0°, trifluoroacetic acid (10 ml) was added during 15 minutes. The reaction mixture was stirred for an additional 15 minutes and the mixture was concentrated by distillation at reduced pressure while keeping the bath temperature at about 15°. The residue was taken up in absolute ethanol (15 ml) and the mixture concentrated to dryness with a rotary evaporator while keeping the bath at room temperature. The resulting sky-blue solid was dissolved in distilled water (15 ml) and then treated with thoroughly washed (with methanol and distilled water) Dowex® 1 x 8-200 ion-exchange resin, $Cl^-$ form (20 ml, Aldrich). The mixture was stirred vigorously at room temperature for 45 minutes, then applied to a chromatographic column (20 mm inner diameter) which was packed with the same ion-exchange resin (60 ml) and eluted with water. The fractions containing the products were filtered through a MILLEX® -GS 0.22 μm filter and the filtrate concentrated to dryness with a rotary evaporator while keeping the bath temperature at room temperature. The residue was taken up in absolute ethanol (30 ml), in which it was partially soluble and the mixture was concentrated to dryness. The residue was treated with ethanol (5 ml) and ether (5 ml) and the solid collected by filtration under a nitrogen blanket. The product **2Cb** was obtained as a blue solid (178 mg, 90%), mp >225°; $^1$H nmr (deuterium oxide): δ 9.45 (s, 2H), 7.40 (s, 2H), 3.90 (m, 4H), 3.37 (br t, 4H).

*Anal.* Calcd. for $C_{16}H_{21}Cl_3N_6O_2$: C, 44.10; H, 4.86; N, 19.29; Cl, 24.31. Found: C, 44.61; H, 5.25; N, 19.25; Cl, 23.58.

6,9-Bis[[2-[*N*-(*t*-butoxycarbonyl)amino]ethyl]amino]benzo[*g*]-phthalazine-5,10-dione (**2Cc**).

From **3C**.

A solution of **3C** (75 mg, 0.31 mmole) and *N*-(*t*-butoxycarbonyl)-ethylenediamine (49 mg, 3.0 mmoles) in dimethyl sulfoxide (2.5 ml) was stirred at room temperature for 25 hours. The blue mixture was quenched with cold water and the precipitate collected by filtration. The aqua-blue solid was washed with water (3 x 50 ml) and dried *in vacuo*. Purification by column chromatography (silica gel, 1.75 x 15 cm) with chloroform/methanol (95:5) eluted a blue band. Removal of the eluent by rotary evaporation gave **2Cc** (140 mg, 87%), mp 220-221°; $^1$H nmr (deuteriochloroform): δ 11.58 (br t, 2H), 9.82 (s, 2H), 7.45 (s, 2H), 5.68 (br s, 2H), 3.68 (br s, 4H), 3.52 (br, 4H), 1.54 (s, 18H).

*Anal.* Calcd. for $C_{26}H_{34}N_6O_6$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.01; H, 6.80; N, 15.66.

From **21b**.

A mixture of **21b** (357 mg, 0.648 mmole) and *N*-(*t*-butoxycarbonyl)ethylenediamine (1.04 g, 6.48 mmoles) in dry pyridine (5 ml) was stirred under nitrogen at room temperature for 18 hours and then at 50° for an additional 12 hours. The solvent was removed by distillation under reduced pressure and the resultant residue purified by column chromatography over silica gel using chloroform containing up to 3% methanol. On removal of the eluents, the residue was recrystallized from pentane:dichloromethane:methanol 60:20:1 (50 ml) to yield **2Cc** (120 mg, 35%).

6,9-Difluorobenzo[*g*]quinoxaline-5,10-dione (**3A**).

A solution of the keto acid **9** (0.31 g, 1.17 mmoles) in fuming sulfuric acid (1 ml, 30% sulfur trioxide was heated in an oil bath at 140-145° for 4 hours. The reaction mixture was quenched in ice water (30 ml) and neutralized with solid sodium bicarbonate. The mixture was continuously extracted with chloroform and removal of the chloroform yielded a tan solid (0.20 g, 69%), mp 238-241° dec; $^1$H nmr (deuteriochloroform): δ 9.08 (s, 2H), 7.57 (t, 2H).

*Anal.* Calcd. for $C_{12}H_4F_2N_2O_2$: C, 58.55; H, 1.64; N, 11.38. Found: C, 58.25; H, 1.90; N, 11.00.

6,9-Difluorobenzo[*g*]quinazoline-5,10-dione (**3B**).

A stirred mixture of **14** (40 mg, 0.151 mmole) and fuming sulfuric acid (30% sulfur trioxide, 0.5 ml) was covered with a cotton drying tube and heated to 95° for 2 hours. The dark red mixture was cooled, quenched over ice (2 g) and neutralized with solid sodium bicarbonate. The tan-yellow mixture was extracted with dichloromethane (5 x 5 ml). The extracts were dried with sodium sulfate and the dichoromethane was removed by rotary evaporation to yield a yellow solid (19.8 mg, 54%), mp 206-208°; $^1$H nmr (deuteriochloroform): δ 9.73 (s, 1H), 9.70 (s, 1H), 7.60 (m, 2H).

*Anal.* Calcd. for $C_{12}H_4F_2N_2O_2$: C, 58.55; H, 1.64; N, 11.38. Found: C, 58.46; H, 1.77; N, 11.21.

6,9-Difluorobenzo[*g*]phthalazine-5,10-dione (**3C**).

The mixture of **20** (211 mg, 0.80 mmole) in fuming sulfuric acid (30% sulfur trioxide, 2 ml) was stirred and heated in an oil bath to 105° for 3 hours. The red-brown solution was cooled and quenched over ice water (10 ml). After neutralizing the mixture with solid sodium bicarbonate, the mixture was extracted with dichloromethane (6 x 10 ml). The extracts were dried with sodium sulfate and the dichloromethane was removed by rotary evaporation to yield a yellow solid (94 mg, 48%), mp 255-258°; $^1$H nmr (deuteriochloroform): δ 9.95 (s, 2H), 7.67 (t, 2H).

*Anal.* Calcd. for $C_{12}H_4F_2N_2O_2$: C, 58.55; H, 1.64; N, 11.38. Found: C, 58.24; H, 1.86; N, 10.98.

6-Fluoro-9-[[2-(dimethylamino)ethyl]amino]benzo[*g*]quinoxaline-5,10-dione (**4h**).

A mixture of **3A** (100 mg, 0.40 mmole) and *N,N*-dimethylethylenediamine (704 mg, 8 mmoles) in pyridine (1 ml) was stirred at room temperature for 48 hours. The pyridine and excess diamine were removed by a nitrogen stream and the resultant solid was

dried under vacuum for 24 hours. Purification by column chromatography (silica gel, 2.25 x 18 cm) with choloroform/methanol gradient elution (90:10, 200 ml; 75:25, 300 ml) gave the major red and minor blue bands. Removal of the eluents from the major red band by rotary evaporation yielded a red solid (65 mg, 52%), mp 176-177°; $^1$H nmr (deuteriochloroform): δ 10.38 (br t, 1H), 9.05 (s, 1H), 9.00 (s, 1H), 7.43 (t, 1H), 7.15 (dd, 1H), 3.48 (q, 2H), 2.76 (t, 2H), 2.38 (s, 6H).

*Anal.* Calcd. for $C_{16}H_{15}FN_4O_2$: C, 61.14; H, 4.81; N, 17.82. Found: C, 60.80; H, 5.00; N, 17.45.

Furo[3,4-*b*]pyrazine-5,7-dione (**8**).

Method A.

A mixture of **7** (2.0 gm, 11.9 mmoles) and acetic anhydride (6 ml) was refluxed for 5 minutes. The hot orange mixture was cooled to −20° and the resultant white crystals were collected by filtration, washed with ether (3 x 10 ml) and dried in a desiccator to yield **8** (1.68 g, 94%), mp 221-223°; lit [31] mp 221° dec; $^1$H nmr (deuteriochloroform): δ 9.16 (s).

Method B.

The diacid **7** (0.51 g, 3.0 mmoles) was added in portions to a solution of DCC (0.62 g, 3.0 mole) in THF (50 ml) and the stoppered flask was magnetically stirred overnight. The insoluble dicyclohexylurea was removed by filtration and the filtrate concentrated under vacuum. The resultant tan solid was sublimed (bath temperature 115°, 0.3 mm) to yield pure **8** (0.42 g, 92%).

2-(2′,5′-Difluorobenzoyl)pyrazine-3-carboxylic Acid (**9**).

A mixture of anhydride **8** (2.0 g, 13.3 mmoles) and aluminum chloride (4.6 g, 34.4 mmoles) in 1,4-difluorobenzene (44 ml) was refluxed for 16 hours. The excess 1,4-difluorobenzene was recovered by distillation and the remaining brown solid quenched with ice-water. The solid was collected by filtration, dried, and taken up in chloroform. The mixture was filtered to remove insoluble material and the filtrate with 10% sodium hydroxide. The aqueous layer was acidified with 10% sulfuric acid and extracted with chloroform. The chloroform was evaporated to yield **9** (2.62 g, 75%) as a light tan solid. The material was recrystallized from ligroin-chloroform to give yellow needles, mp 151-153°; $^1$H nmr (deuteriochloroform): δ 8.93 (d, 1H), 8.79 (d, 1H), 7.80 (m, 1H), 7.30 (m, 1H), 7.05 (m, 1H).

*Anal.* Calcd. for $C_{12}H_6N_2O_3F_2 \cdot 0.25H_2O$: C, 53.36; H, 2.39; N, 10.42. Found: C, 53.30; H, 2.33; N, 10.36.

Diethyl Ethoxymethyleneoxalacetate (**11**).

A solution of diethyl oxalacetate (22.17 g, 0.118 mole), triethyl orthoformate (31.22 g, 0.211 mole) and acetic anhydride (34.37 g, 0.337 mole) was heated at 120° for 1 hour with a static hot water fractional distillation setup. The mixture was heated for an additional 2 hours at 140°. Purification of the brown oil by vacuum distillation gave an *E*/*Z* mixture (50:50) of a pale yellow liquid (22.20 g, 77%), bp 151-157° (0.25 mm Hg), lit [32] bp 146° (0.2 mm); $^1$H nmr (deuteriochloroform): δ 7.89 (s, 1H), 7.88 (s, 1H) [areas of about 1:1 for the H on HC(OEt)], 4.31 (m, 8H), 4.24 (q, 2H), 4.20 (q, 2H), 1.44 (t, 3H), 1.42 (t, 3H), 1.35 (t, 6H), 1.27 (t, 6H).

Diethyl Pyrimidine-4,5-dicarboxylate (**12a**).

A mixture of **11** (9.98 g, 0.041 mole) and formamidine acetate (4.78 g, 0.046 mole) in benzene (300 ml) was refluxed with a Dean-Stark water trap for 2.5 hours. The benzene was removed by rotary evaporation and the resultant yellow oil was purified by vacuum distillation to give a clear colorless liquid (9.55 g, 68%), bp 102-104°, lit [33] oil; $^1$H nmr (deuteriochloroform): δ 9.36 (s, 1H), 9.27 (s, 1H), 4.48 (q, 2H), 4.42 (q, 2H), 1.41 (t, 3H), 1.39 (t, 3H).

Pyrimidine-4,5-dicarboxylic Acid (**12b**).

An aqueous solution of sodium hydroxide (4*N*, 5 ml, 20 mmoles) was added to **12a** (1.81 g, 8.07 mmoles). After heating to 50° for 3 hours, the yellow solution was neutralized with hydrochloric acid (4*N*, 5 ml). The volume of water was reduced to 4 ml and the mixture was allowed to stand overnight. The crystals which separated were collected by filtration, pulverized and placed in a vacuum desiccator to yield **12b** (1.25 g, 90%), mp 216-217°; $^1$H nmr (DMSO-$d_6$): δ 9.40 (s, 1H), 9.27 (s, 1H).

Furo[3,4-*d*]pyrimidine-5,7-dione (**13**).

Dicyclohexylcarbodimide (615 mg, 3.04 mmoles) was added to a solution of **12b** (502 mg, 3.00 mmoles) in THF (50 ml). The mixture was stirred overnight at room temperature and some insoluble material which separated was removed by filtration. The THF was removed by rotary evaporation and the resultant white solid was sublimed to yield **13** (261 mg, 58%), mp 137° dec; $^1$H nmr (acetone-$d_6$): δ 9.82 (s, 1H), 9.67 (s, 1H).

4-(2′,5′-Difluorobenzoyl)pyrimidine-5-carboxylic Acid (**14**).

From Diester **12a**.

Sec-butyllithium (1.32 *M*, in cyclohexane, 1.80 ml, 2.38 mmoles) was added dropwise to a stirred solution of 1,4-difluorobenzene (229 mg, 2.01 mmoles) in THF (20 ml) at −76° over 15 minutes under a nitrogen blanket. After an additional 45 minutes, the yellow mixture was added dropwise *via* cannula into a stirred solution of **12a** (306 mg, 1.36 mmoles) in THF (35 ml) at −77° under nitrogen. The yellow solution was gradually warmed to room temperature over 16 hours. The reddish solution was acidified with hydrogen chloride gas to yield a yellow-brown solution. After the solvent was removed by rotary evaporation, the crude keto ester was saponified with sodium hydroxide (4*N*, 10 ml) by heating at 70° for 10 minutes. The solution was acidified with dilute hydrochloric acid and the resulting tan solid was collected by filtration to yield **14** (279 mg, 79%), mp 180-183°; $^1$H nmr (deuteriochloroform): δ 9.37 (s, 1H), 9.34 (s, 1H), 7.78 (m, 1H), 7.27 (m, 1H), 7.03 (dt, 1H).

*Anal.* Calcd. for $C_{12}H_6F_2N_2O_3 \cdot 0.25H_2O$: C, 54.44; H, 2.28; N, 10.47. Found: C, 54.41; H, 2.17; N, 10.40.

From Anhydride **13**.

Sec-butyllithium (1.32 *M* in cyclohexane, 1.25 ml, 1.65 mmoles) was added dropwise by syringe into a stirred mixture of 1,4-difluorobenzene (156 mg, 1.37 mmoles) in THF (5 ml) at −78° under a nitrogen atmosphere. After stirring for an additional 15 minutes, the yellow mixture was added dropwise *via* a cannula into a stirred solution of **13** (222 mg, 1.48 mmoles) in THF (35 ml) at −78° under nitrogen. The solution was warmed to room temperature and the solvents were removed under reduced pressure. The resultant solid was dissolved in a saturated sodium bicarbonate solution (10 ml) and this solution was acidified with dilute hydrochloric acid. The tan solid (156 mg, 43%) which separated was collected by filtration.

Pyridazine-4,5-dicarboxylic Acid (**18**).

A sodium permanganate solution (1.6 *M*, 200 ml) was added to a stirred mixture of **17** (6.0 g, 46.1 mmoles) and aqueous sodium hydroxide (2 *N*, 20 ml) at 90° over 2.5 hours. After refluxing overnight, the manganese dioxide was removed by filtration and washed with hot water (2 x 100 ml). The filtrate was acidified with acetic acid until the effervescence ceased, concentrated to 50 ml and made basic with concentrated ammonium hydroxide. A saturated solution of barium chloride (12.3 g) was added dropwise to the stirred solution at 50°. The resulting barium salt (13.0 g) was collected by filtration and dried *in vacuo*. The white solid was suspended in hot water (300 ml) and acidified with concentrated sulfuric acid. The barium sulfate was removed by filtration and the filtrate reconcentrated to 50 ml. The precipitate was collected by filtration, washed with ice water (3 x 20 ml) and dried to yield a white solid (5.1 g, 66%), mp 210-213°, lit [34] mp 212-213°; $^1$H nmr (DMSO-$d_6$): $\delta$ 9.56 (s).

Furo[3,4-*d*]pyridazine-5,7-dione (**19**).

The diacid **18** (0.502 g, 3.0 mmoles) was added to a stirred solution of dicyclohexylcarbodiimide (0.615 g, 3.0 mmoles) in tetrahydrofuran (50 ml). The mixture was stirred overnight at room temperature. After removal of the insoluble material by filtration, the filtrate was concentrated under reduced pressure. Vacuum sublimation (97°, 0.03 mm Hg) of the brown residue gave a pale yellow solid (0.41 g, 92%), mp 180° darkening 215° dec, lit [35] mp 170° darkening, 180-190° dec; $^1$H nmr (acetone-$d_6$): $\delta$ 10.11 (s).

4-(2′,5′-Difluorobenzoyl)pyridazine-5-carboxylic Acid (**20**).

Sec-butyllithium (1.32 *M* in cyclohexane, 1.25 ml, 1.65 mmoles) was added dropwise by syringe over 0.25 hour to a stirred solution of 1,4-difluorobenzene (162 mg, 1.42 mmoles) in tetrahydrofuran (5 ml) at −84° under a nitrogen blanket. The yellow mixture was stirred for an additional 45 minutes at −80° and then added *via* a cannula over 5 minutes to a stirred solution of **19** (220 mg, 1.46 mmoles) in tetrahydrofuran (40 ml) at −80° by nitrogen pressure. The mixture was warmed to room temperature overnight and neutralized with ammonium chloride. After removal of tetrahydrofuran by rotary evaporation, the resultant tan solid was treated with an aqueous sodium bicarbonate solution (10 ml) and washed with ether (10 ml). The aqueous phase was acidified with aqueous hydrochloric acid. The precipitate was collected by filtration, washed with cold water (3 x 10 ml) and dried to give an off-white solid (230 mg, 59%), mp 202-205°; $^1$H nmr (deuteriochloroform/perdeuteriomethane, 70/30): $\delta$ 9.72 (s, 1H), 9.25 (s, 1H), 7.74 (m, 1H), 7.34 (m, 1H), 7.10 (m, 1H).

*Anal.* Calcd. for $C_{12}H_6F_2N_2O_3 \cdot 0.28H_2O$: C, 54.34; H, 2.28; N, 10.45. Found: C, 54.36; H, 2.25; N, 10.43.

6,9-Dihydroxybenzo[*g*]phthalazine-5,10-dione (**21a**).

Compound **22a** (2.12 g, 9.21 mmoles) was added portionwise to hydrazine hydrate (80%, 18 ml, 0.46 mole) during a 0.3 hour period with stirring at 0°. The reaction mixture was stirred for 17 hours at room temperature and then cautiously poured into hydrochloric acid (6*N*, 60 ml) while cooling to 0°. The resultant black-deep green solid was collected by filtration, washed with cold water and suspended in sodium hydroxide (1*N*, 40 ml). The mixture was heated to 80° for 0.25 hour, then cooled to room temperature and stirred for 18 hours under a gentle flow of air. Water (15 ml) and concentrated hydrochloric acid (3.1 ml) were added to the deep-blue reaction mixture. A dark-red solid separated which was collected by filtration, washed with water followed by a small amount of methanol and dried. The product **21a** was obtained as a dark-red solid (1.98 g, 89%), mp >220°; $^1$H nmr (deuteriochloroform): $\delta$ 12.65 (s, 2H, exchangeable with deuterium oxide), 10.07 (s, 2H), 7.47 (s, 2H); ms: (EI 70 eV, direct introduction) m/z (relative intensity) 242 ($M^+$, 100%), 187 (13%), 159 (24%), 108 (16%); ir (potassium bromide): 974, 1147, 1196, 1258, 1444, 1560, 1629, 3073, 3436 cm$^{-1}$. This material was sufficiently pure for use in subsequent reactions.

6,9-Bis[(4-methylphenyl)sulfonyloxy]benzo[*g*]phthalazine-5,10-dione (**21b**).

The *p*-toluenesulfonyl chloride (2.60 g, 13.64 mmoles) was added over a 2 minute period to a stirred suspension of **21a** (1.50 g, 6.2 mmoles) in dry pyridine (15 ml) under a nitrogen atmosphere. The mixture was stirred at room temperature for 23 hours, the solvent was removed by distillation under reduced pressure and the remaining residue was purified by column chromatography over silica gel using dichloromethane:ethyl acetate 20:1 as the eluent. The ditosylate **21b** was obtained as a yellow solid (1.57 g, 46%). An analytical sample was recrystallized from acetonitrile, mp 240° dec; $^1$H nmr (deuteriochloroform): $\delta$ 9.80 (s, 2H), 7.90 (d, 4H), 7.65 (s, 2H), 7.40 (d, 4H), 2.47 (s, 6H).

*Anal.* Calcd. for $C_{26}H_{18}N_2O_8S_2$: C, 56.31; H, 3.22; N, 5.08; S, 11.61. Found: C, 56.72; H, 3.30; N, 5.09; S, 11.65.

5,8-Dihydroxynaphtho[2,3-*c*]furan-4,9-dione (**22a**).

To a vigorously stirred mixture of aluminum chloride (11.6 g, 87 mmoles) and 1,4-dimethoxybenzene (4.82 g, 34.9 mmoles) in dry dichloromethane (230 ml) under a nitrogen blanket at room temperature, was added a solution of **23c** (5.60 g, 29 mmoles) in dry dichloromethane (70 ml) and the stirring was continued for 18 hours. Dichloromethane was added (100 ml) and the mixture was refluxed for 6 hours. The mixture was quenched by addition of a saturated solution of oxalic acid (75 ml) and hydrochloric acid (2*N*, 100 ml). The solvent was removed by distillation under reduced pressure. Ethyl acetate (1000 ml) was added to the resulting suspension until the solid completely dissolved. The extract was washed with a saturated sodium bicarbonate solution (100 ml), a saturated sodium chloride solution (2 x 100 ml) and dried over sodium sulfate. The residue which was obtained on concentration was recrystallized from chloroform (250 ml) to yield **22a** (3.12 g, 46%) as red-orange blades. An additional amount of pure **22a** could be obtained by chromatography of the mother liquor over silica gel with the eluent dichloromethane:pentane 3:1 (1.14 g, 17%), mp 219-221°, lit [27] 223-226°; $^1$H nmr (deuteriochloroform): $\delta$ 12.80 (s, 2H, exchangeable with deuterium oxide), 8.27 (s, 2H), 7.29 (s, 2H).

Small amounts of **22b** and **22c** were isolated from purifications by chromatography.

Furan-3,4-dicarboxylic Acid (**23b**).

A sodium hydroxide solution (3*N*, 585 mmoles, 195 ml) was added dropwise over a period of 0.75 hour to a solution of **23a** (51.4 g, 279 mmoles) in methanol:water (5:1, 300 ml). The mixture was stirred for an additional 1.5 hours at room temperature and heated at reflux for 0.75 hour. The reaction mixture was concentrated to half volume and acidified with hydrochloric acid (6*N*, 100 ml). The resultant white precipitate was extracted with ethyl

acetate (400 ml) and the aqueous phase was saturated with sodium chloride (20 g). This was extracted with ethyl acetate (3 x 50 ml), the extracts were combined and washed with saturated sodium chloride (50 ml) and dried over sodium sulfate. The solvent was removed by distillation at reduced pressure and the residue was dried under vacuum at 60° for 4 hours. The crude product (43.1 g, 99%) was used for the next step without further purification. A sample recrystallized from ethyl acetate:hexane melted at 210-212°, lit [36] 210-212°; $^1$H nmr (deuteriochloroform): δ 11.25 (br s, 2H), 8.09 (s, 2H).

3,4-Furandicarbonyl Dichloride (**23c**).

A mixture of **23b** (20.0 g, 128 mmoles), thionyl chloride (50 ml, 685 mmoles) and dry toluene (50 ml) was refluxed for 3 hours. The reaction mixture was concentrated to dryness and the residue kept under vacuum at room temperature for 20 hours. The product **23c** was obtained as a beige solid (24.3 g, 98%) and was used in the next step without further purification; mp 69-71°, lit [37] mp 71-72°.

6-[[2-(*t*-Butoxycarbonylamino)ethyl]amino]-9-[(4-methylphenyl)-sulfonyloxy]benzo[g]phthalazine-5,10-dione (**25a**).

A mixture of **21b** (1.08 g, 1.96 mmoles) and *N*-(*t*-butoxycarbonyl)ethylenediamine (706 mg, 4.41 mmoles) in dry pyridine (15 ml) was stirred for 10 hours under a nitrogen atmosphere at room temperature. The solvent was removed under reduced pressure and the residue was taken up in dichloromethane (60 ml). This solution was washed with water (2 x 50 ml), dried over sodium sulfate and evaporated to dryness. The product was purified by column chromatography over silica gel with the eluent chloroform:methanol 100:1 and the crude product on removal of the eluents was recrystallized from a 1:1 dichloromethane:pentane mixture (40 ml). The product **25a** was obtained as violet needles with a bronze reflection (714 mg, 68%), mp 178-179° dec; $^1$H nmr (deuteriochloroform): δ 10.20 (br t, 1H, exchangeable with deuterium oxide) 9.91 (s, 1H), 9.68 (s, 1H), 7.86 (d, 2H), 7.46 (d, 1H), 7.35-7.25 (m, 3H), 3.40-3.65 (m, 4H), 4.86 (br s, 1H, exchangeable with deuterium oxide), 2.42 (s, 3H), 1.46 (s, 9H).

6-[[2-(*t*-Butoxycarbonylamino)ethyl]amino]-9-hydroxybenzo[g]-phthalazine-5,10-dione (**25b**).

This compound was isolated as a blue solid during a chromatographic purification of **2Cc** (silica gel, chloroform:methanol 100:1); $^1$H nmr (deuteriochloroform): δ 13.17 (br s, 1H, exchangeable with deuterium oxide), 10.88 (br s, 1H, exchangeable with deuterium oxide), 10.06 (s, 1H), 9.96 (s, 1H), 7.53 (d, 1H), 7.36 (d, 1H), 4.92 (br s, 1H, exchangeable with deuterium oxide), 3.68 (q, 2H), 3.47 (q, 2H), 1.48 (s, 9H).

6-[[2-(*t*-Butoxycarbonylamino)ethyl]amino]-9-[[2-(dimethylamino)-ethyl]amino]benzo[g]phthalazine-5,10-dione (**25c**).

A mixture of **25a** (700 mg, 1.30 mmoles) and *N,N*-dimethylethylenediamine (1.42 ml, 13.0 mmoles) in dry pyridine (7.0 ml) was stirred under a nitrogen atmosphere at room temperature for 18 hours. The mixture was concentrated to dryness and the resulting residue was purified by column chromatography over silica gel with the eluents chloroform:methanol from 100% to 93% chloroform. The product **25c** was obtained as a blue solid (390 mg, 66%); $^1$H nmr (deuteriochloroform): δ 11.37-11.60 (m, 2H, exchangeable with deuterium oxide), 9.93 (s, 1H), 9.37 (s, 1H), 7.45 (d, 1H), 7.30 (d, 1H), 5.23 (br t, 1H, exchangeable with deuterium oxide), 3.40-3.70 (m, 6H), 2.70 (t, 2H), 2.37 (s, 6H), 1.48 (s, 9H).

6-[(2-Aminoethyl)amino]-9-[[2-(dimethylamino)ethyl]amino]benzo-[g]phthalazine-5,10-dione Tris(trifluoroacetate) (**25d**).

To a stirred solution of **25c** (18 mg, 0.037 mmole) in dry dichloromethane (2 ml) under a nitrogen atmosphere at 0°, trifluoroacetic acid (0.5 ml) was added over a 5 minute period. The mixture was stirred for 0.5 hour and the solvent removed by distillation under reduced pressure with a rotary evaporator while keeping the bath at room temperature. The residue was taken up in absolute ethanol (5 ml) and the mixture was concentrated to dryness using a rotary evaporator and this procedure was repeated one more time using a 1:1 isopropyl alcohol/ethanol mixture. The product **25d** was obtained as a blue solid (25 mg, 90%); $^1$H nmr (deuterium oxide): δ 9.54 (br s, 2H), 7.44 (br s, 2H), 3.80-4.05 (m, 4H), 3.55 (t, 2H), 3.36 (t, 2H), 3.01 (s, 6H).

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