N-tert-Butoxycarbonyl-*N*-Substituted Hydrazines in S_NAr Displacements. Synthetic Pathways to *N*-1-Substituted Anthrapyrazoles, Aza-Anthrapyrazoles and Aza-Benzothiopyranoindazoles

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The synthesis of several *N-tert*-butoxycarbonyl(Boc)-protected-*N*-substituted hydrazines has been accomplished. The use of these protected hydrazines in S_NAr substitutions leads to products in which the most nucleophilic nitrogen displaces the leaving group. Treatment of these compounds with trifluoroacetic acid readily removes the Boc-protecting group and the intermediates readily undergo cyclizations to yield *N*-1-substituted aza-benzothiopyranoindazoles, anthrapyrazoles and aza-anthrapyrazoles. Side chain buildup was employed in the synthesis of several aza-anthrapyrazoles.

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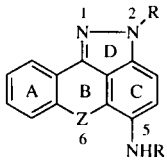
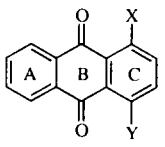
Anthrapyrazoles **1** [1-5] and benzothiopyranoindazoles **2** [6-8] holding specific distal side arms at N-2 and C-5, and with hydroxyl substituents in the A–ring, have been shown to be potent antitumor agents. The introduction of the pyrazole D-ring with an N-2 substituent into an A-B-C ring system can readily be accomplished by treatment of 1,4-dichloroanthracene-9,10-dione (**3a**), or related disubstituted analogues [3,4], with a monosubstituted hydrazine. The S_NAr displacement of the chloride occurred by the most nucleophilic nitro-

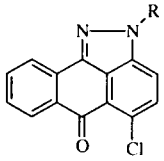


1, Z = C=O, anthrapyrazole
2, Z = S, benzothiopyranoindazole
R = R_1 = alkylamino group

gen of the hydrazine moiety which bears the substituent to yield intermediate **3b**, which subsequently, under the reaction conditions, underwent cyclization to the pyrazole **4**. Further treatment of these substrates with an amine displaced the C-5 chloride to yield analogues related to **1**.



3a, X = Y = Cl
b, X = N(NH_2)R, Y = Cl



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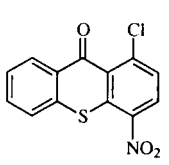
The benzothiopyranoindazoles have been prepared [6-8] in a similar manner by reaction of 1-chloro-4-nitro-9*H*-thioxanthen-9-one (**5**) with the appropriate hydrazine to afford 5-nitrobenzothiopyranoindazoles **6**. Functional group elaboration of the nitro group and the N-2 side arm, led to the desired *N*-2, C-5-disubstituted chemotypes **2**.



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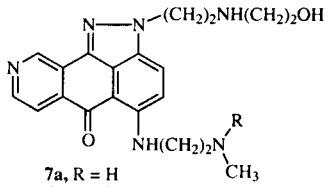
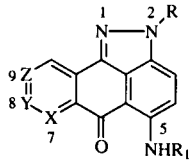
With the goal of developing anthrapyrazole chemotypes with reduced side effects and a wider range of antitumor activity, we have synthesized aza-anthrapyrazoles which bear a nitrogen atom in the anthrapyrazole chromophore and lack hydroxyl substitution [9,10]. Analogues such as **7a** and **7b** have exhibited potent antitumor activities and are candidates for clinical trails. This heteroatom substitution methodology has been utilized for the preparation of aza-benzothiopyranoindazoles **8** [11] commencing from the respective nitro analogues. Since the displacement of substitutents on tricyclic electrophilic ring skeletons by alkylhydrazines have generally led to *N*-2-substituted pyrazole analogues, we were interested in developing a



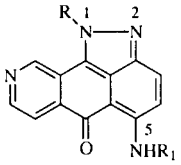
7a, R = H
b, R = CH_3



8a, X = N, Y = Z = CH
b, Y = N, X = Z = CH
c, Z = N, X = Y = CH

convenient synthetic pathway, which would lead to *N*-1 substituted chemotypes **9** (holding distal side arms shown in **7a** and **7b**). This pathway could also be utilized for the synthesis of *N*-1 substituted anthrapyrazoles and aza-benzothiopyranoindazoles.

Two examples of N-1-alkyl anthrapyrazoles have been previously reported. Anthrapyrazole **10a** [1] reacted with



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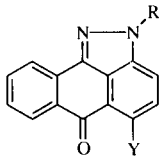
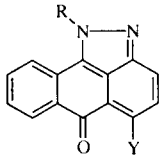
sodium hydride to form the anion, which on quenching with ethyl iodide yielded regioisomers **10b** and **11a** (3:1 ratio) which were chromatographically separated.

Addition of sodium hydroxide to **10c,** followed by addition of dimethyl sulfate led to regioisomers **10d** and **11b** [12,13].

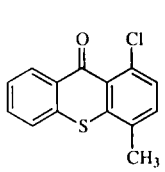




10a, R = H, Y = Cl
b, R = CH_2CH_3, Y = Cl
c, R = H, Y = H
d, R = CH_3, Y = H
e, R = CH_3, Y = Cl
f, R = $(CH_2)_2OH$, Y = Cl
g, R = $(CH_2)_2N(CH_3)_2$, Y = Cl

11a, R = CH_2CH_3, Y = Cl
b, R = CH_3, Y = H

Thioxanthenone **12** reacted with *N*-(2-dimethylaminoethyl)hydrazine to afford benzothiopyranoindazole **13** in a low yield (10%), along with the major regioisomer **14,** that could be separated by tedious chromatography [14].



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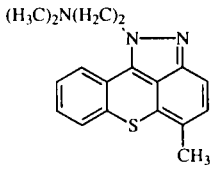

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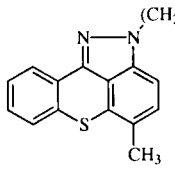

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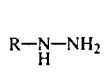
We wish to report the synthesis of *N-tert*-butoxycarbonyl(Boc)-protected hydrazines and studies of their S_NAr displacements on tricyclic substrates holding nucleofugal groups as a viable synthetic route to intermediates, which on removal of the Boc-protecting group, readily cyclized to afford *N*-1 substituted aza-benzothiopyranoindazoles, anthrapyrazoles and aza-anthrapyrazoles.

Results and Discussion.

In order to effect displacements at the unsubstituted nitrogen of alkyl substituted hydrazines, the nitrogen atom holding the substituent was protected with a Boc group. The S_NAr displacement by these Boc-protected hydrazines on the appropriate substrates occurs only at the most nucleophilic nitrogen. Removal of the Boc-protecting group from the 1,2-disubstituted-hydrazine intermediate triggers the cyclization to form the 1-substituted pyrazole moiety.

A) Preparation of the *N*-Boc hydrazines.

The reaction of methylhydrazine (**15a**), 2-(hydroxyethyl) hydrazine (**15b**) or 2-(dimethylamino) ethylhydrazine (**15c**) with di-*tert*-butyldicarbonate in ethanol led regioselectively to the Boc-protected hydrazines **16a**, [15-17], **16b** [18], and **16c**, respectively. Of particular interest is the highly regioselective formation of **16a** and **16c**, in which the ^1H nmr of the crude products showed no evidence for the presence of the regioisomers **17a** and **17c**, respectively.



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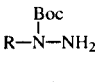

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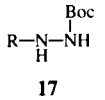
a, R = CH_3
b, R = $(CH_2)_2OH$
c, R = $(CH_2)_2N(CH_3)_2$



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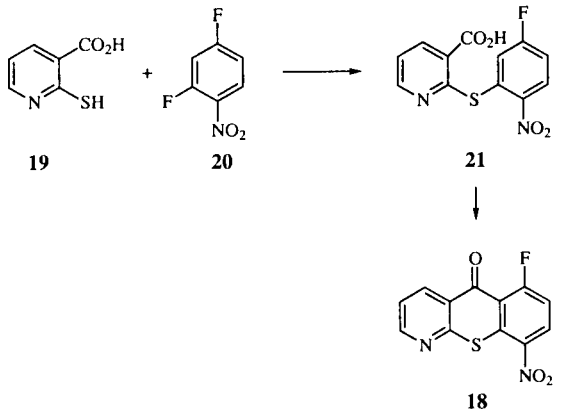
In the crude product from **15b**, about 10% of regioisomer **17b** could be detected by proton nmr (based on the integral of Boc-methyl groups at δ 1.48 and 1.46 ppm for **16b** and **17b**, respectively). The chemical shifts of the signals assigned to the methylene protons of the two regioisomers were significantly different, with **16b** giving signals at δ 3.61 and 3.80 ppm and **17b** at 2.93 and 3.71 ppm. Pure **16b** was obtained by chromatography and recrystallization while **17b** was only obtained in 75% purity.

B) Displacement Studies.

a) 1-Methyl-1-*H*- and 2-methyl-2-*H*-pyrido[3',2':5,6]thiopyrano[4,3,2-*cd*]indazoles.

The preparative route to 6-fluoro-9-nitro-5*H*[1]-benzothiopyrano[2,3-*b*]pyridine-5-one (**18**) is shown in Scheme 1.

Scheme 1

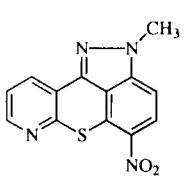


19 **20** **21**

18

Treatment of 2-mercaptonicotinic acid (**19**) with 2 equivalents of sodium ethoxide in ethanol followed by addition of 2,4-difluoronitrobenzene (**20**) led to 3-carboxy-2-(2-nitro-5-fluorophenylthio)-pyridine (**21**). Cyclization of **21** was accomplished by heating in fuming sulfuric acid to yield **18**.

Methyl hydrazine was reacted with **18** to afford 2-methyl-5-nitro-2*H*-pyrido[3',2':5,6]thiopyrano[4,3,2-*cd*]indazole (**22**). Heating **18** with **16a** led to **23** which on addition of trifluoroacetic acid in dichloromethane led to 1-methyl-5-nitro-1*H*-pyrido[3',2';5,6]thiopyrano[4,3,2-*cd*]indazole (**24**).



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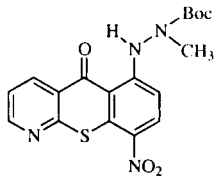

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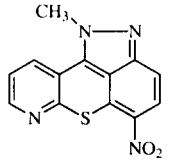

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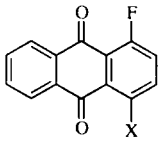
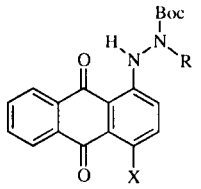
b) *N*-1-substituted–anthra[1,6-*cd*]pyrazol-6-(1*H*)-one and *N*-2-substituted-anthra-[1,6-*cd*]pyrazol-6-(2*H*)-one.

Methylhydrazine (**15a**) and 1-fluoroanthracene-9,10-dione (**25a**) reacted in pyridine at room temperature for 19 hours to yield 2-methylanthra[1,6-*cd*] pyrazol-6-(2*H*)-one (**10d**, 88%). However, reaction of **25a** with **16a** in pyridine (65° for 24 hours) afforded about 85% of recovered dione along with the cleavage product, 1-aminoanthracene-9,10-dione (about 15%). From the reaction conditions it appears that the presence of the Boc-group considerably lowers the nucleophilic character of the unsubstituted nitrogen atom.



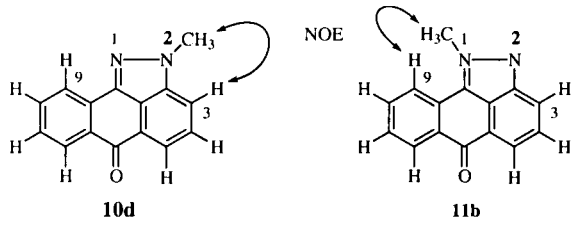
25a, X = H
b, X = Cl



26a, X = H, R = CH_3
b, X = Cl, R = CH_3
c, X = Cl, R = $(CH_2)_2OH$
d, X = Cl, R = $(CH_2)_2N(CH_3)_2$

On the other hand, **25a** reacted with neat **16a** in the presence of diisopropylethyl amine (100°, 19 hours) to give 70% of the desired product **26a**. This material on addition of trifluoroacetic acid led to removal of the protecting group and subseqent cyclization to afford 1-methylanthra[1,9-*cd*]pyrazol-6-(1*H*)-one (**11b**).

Further evidence for the correctness of the structure of **10d** and **11b** was obtained from ^1H and 2D-NOESY nmr experiments. The two compounds displayed significant chemical shift differences in their ^1H nmr spectra in deuteriochloroform. For example, protons of the methyl groups resonate at δ 4.25 and 4.63 ppm for **10d** and **11b**, respectively. The final elucidation of the structures of **10d** and **11b** was achieved by 2D-NOESY experiments. The methyl substituents of compounds **10d** and **11b** showed strong NOE interactions with protons at C-3 and C-9, respectively (Figure 1).

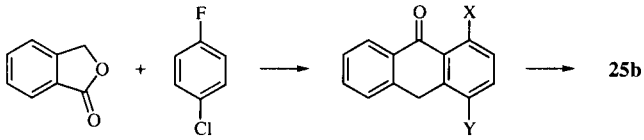


10d **11b**

Figure 1. 2D-NOESY of **10d** and **11b**.

The displacements were then investigated using 1-fluoro-4-chloranthracene-9,10-dione (**25b**),which was prepared *via* the route shown in Scheme 2.

Scheme 2

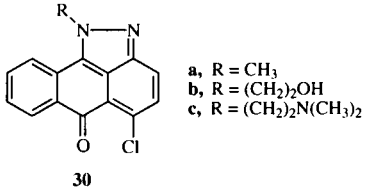


27 **28** **29a**, X = F, Y = Cl
b, X = Cl, Y = F

A mixture of phthalide (**27**) [19], 1-chloro-4-fluorobenzene (**28**) and aluminum chloride was heated at reflux to afford a reasonable yield of the regioisomeric anthrones **29a** and **29b**. Oxidation of this crude mixture with chromium trioxide in acetic acid led to **25b**.

Treatment of dione **25b** with **15a-c** led to **10e-g** while reaction with **16a-c led** to **26b-d**, respectively. Interestingly, in the nmr spectrum of **26c** in dimethyl sulfoxide-d_6, one of the methylenes gives two broad signals at δ 3.38 and 3.78 ppm, respectively, for each proton, while the other methylene exhibits a 2-H multiplet pattern at δ 3.58 ppm. This phenomenon is probably due to restricted rotation about the C-C bond on the sidearm. When the nmr was recorded at 70°, the 3.38 and 3.78 ppm signals coalesced into a multiplet pattern at δ 3.61 ppm.

Compounds **26b-d** were readily cyclized into the *N*-1-substituted analogues **30a-c,** respectively, on removal of the protecting group with trifluoroacetic acid.

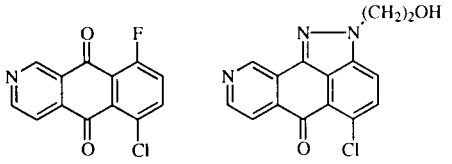


30

a, R = CH_3
b, R = $(CH_2)_2OH$
c, R = $(CH_2)_2N(CH_3)_2$

c) 5-Substituted-1-(2-substituted)indazolo[4,3-*gh*]-isoquinolin-6(1*H*)-ones.

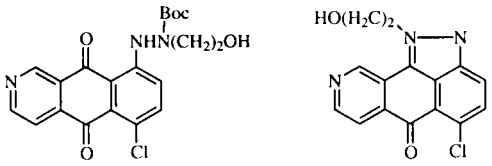
The reaction of 6-chloro-9-fluorobenz[*g*]isoquinoline-5,10-dione (**31**) [20] with **15a** has been previously reported to yield **32**, which was then converted into **7a** and **7b** [9].



31 32

Treatment of 6-chloro-9-fluorobenz[g]isoquinoline-5,10-dione (**31**) [20] with the Boc-protected hydrazine **16b** led to **33**. As previously discussed for **26c**, the nmr spectrum of **33** in dimethyl sulfoxide-d_6 showed three separate signals for the two methylene groups. Again, one methylene group gave 2 separate signals for two different protons at δ 3.27 and 3.77 ppm, while the other methylene exhibited a multiplet pattern at δ 3.59 ppm. The nmr at 70° exhibited a multiplet pattern for both methylene groups at δ 3.63 ppm (4H).

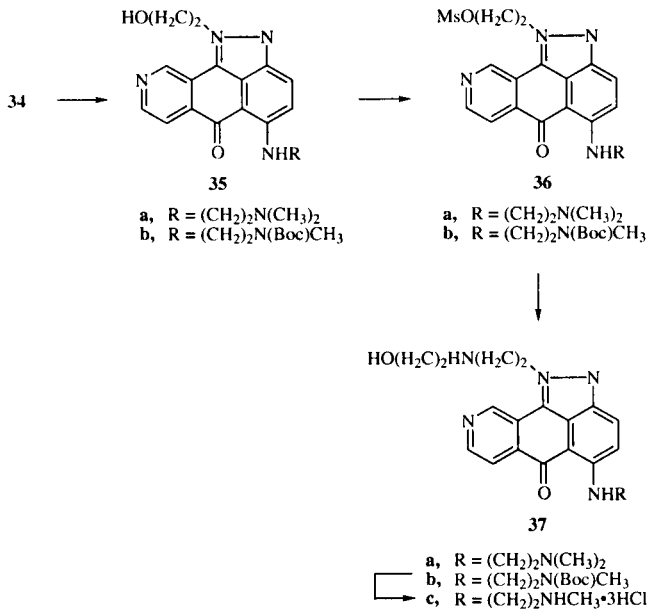
Addition of trifluoroacetic acid to **33** removed the Boc-protecting group and the resultant amino group underwent cyclization to afford 1-(2-hydroxyethyl)-5-chloroindazolo[4,3-*gh*]isoquinolin-6(1*H*)-one (**34**).



33 34

The subsequent synthetic pathway leading from **34** to the 1,5-disubstituted indazolo[4,3-*gh*]isoquinoline-6-ones is outlined in Scheme 3.

Scheme 3



Analogue **34** reacted with 2-(dimethylamino)ethylamine or [2-[*N*-methyl-*N*-(*t*-butoxycarbonyl)amino]ethyl]amine in pyridine at 100° to yield intermediates **35a** and **35b**, respectively. The buildup of the side arms was accomplished by reacting **35a** and **35b** with methanesulfonyl chloride in dichloromethane in the presence of triethylamine to afford the corresponding mesylates **36a** and **36b**. These intermediates, without isolation or purification, were dissolved in pyridine and heated with ethanolamine to yield **37a** as the free base and **37b** as the Boc-protected analogue, respectively. Addition of concentrated hydrochloric acid to **37b** removed the Boc-group to yield the trihydrochloride salt **37c**.

The comparisons of antitumor activity between the 1-substituted analogues **37a** and **37c**, along with the 2-substituted chemotypes **7a** and **7b**, will be detailed in a separate publication.

EXPERIMENTAL

General.

Melting points were determined on Buchi 535, Thomas-Hoover or a Fisher-Johns apparatus and are uncorrected. Proton and carbon-13 nmr spectra were recorded on either a Bruker AC-200 or Bruker ARX 500 pulsed Fourier transform spectrometer. Microanalyses were performed by Redox s.n.c., Cologno Monzese, Milan, Italy or by Robertson Microlit Laboratories, Madison, NJ, USA.

1-Methylhydrazinecarboxylic acid 1,1-dimethylethyl ester (**16a**).

A solution of di-*tert*-butyl dicarbonate (14.27 g, 65.4 mmoles) and dry ethanol (30.0 ml) was added dropwise over 1.5 hours to a solution of methylhydrazine (3.0 g, 65.3 mmoles) and dry ethanol (30.0 ml) which was being cooled in an ice bath. After completion of the addition, the solution was allowed to warm to room temperature and stirring was continued for 15 hours. The solvent was removed by rotary evaporation to yield **16a** (8.23 g, 86%) as a clear colorless liquid which was sufficiently pure, as indicated by nmr, for use in the displacement reactions; ^{1}H nmr (deuteriochloroform): δ 4.05 (br s, 2H), 3.05 (s, 3H), 1.47 (s, 9H).

1-(2-Hydroxyethyl)hydrazinecarboxylic acid 1,1-dimethylethyl ester (**16b**).

A solution of di-*tert*-butyl dicarbonate (2.92 g, 13.38 mmoles) and dry ethanol (8 ml) was added over 1 hour under a nitrogen atmosphere to a solution of 2-hydroxyethylhydrazine (1.02 g, 13.4 mmoles) and dry ethanol (10 ml) which was cooled in an ice bath. After the addition was complete, the solution was allowed to warm up to room temperature and stirring was continued for 16 hours. The solvent was removed by rotary evaporation to yield a colorless, viscous material, which was 90% pure, by ^{1}H nmr and tlc (silica gel, 95:5 dichloromethane:methanol as the eluent, developed in an iodine chamber). The crude product (2.34 g, 99%) was purified by flash chromatography (silica gel, 2 cm by 22 cm using 95:5 dichloromethane:methanol as the eluent) to yield **16b** (1.44 g, 61%), which was then recrystallized from hexane to yield white needles; mp 32-33°; ^{1}H nmr [18] (deuteriochloroform): δ 4.12 (br s, 2H), 3.81 (q, J = 5.2 Hz, 2H), 3.56 (t,

J = 5.0 Hz, 2H), 3.11 (t, J = 5.4 Hz, 1H), 1.48 (s, 9H); ^{13}C nmr (deuteriochloroform) δ 158.3, 81.0, 62.1, 51.7, 28.4.

1-(2-Dimethylaminoethyl)hydrazinecarboxylic acid 1,1-dimethylethyl ester (**16c**).

A solution of di-*tert*-butyl dicarbonate (2.24 g, 10.3 mmoles) in dry ethanol (10.0 ml) was added dropwise over a 45 minute period to a solution of 2-(dimethylamino)ethylhydrazine (1.01 g, 9.8 mmoles) in dry ethanol (10.0 ml) which was cooled in an ice bath. The solution was allowed to warm to room temperature and stirring was continued for 25 hours. The solvent was removed by rotary evaporation to yield a colorless, viscous liquid. This crude product showed only trace impurities by ^1H nmr and tlc (silica gel plate, 9:1 dichloromethane:methanol:0.25% ammonium hydroxide, and developed in an iodine chamber). The product was purified by flash column chromatography (silica gel, 2 cm x 20 cm, using 9:1 dichloromethane:methanol with 0.25% ammonium hydroxide as the eluent). The middle fractions were combined and the solvent removed by rotary evaporation to yield **16c** (1.31 g, 66 %) as a thick, colorless liquid; ^1H nmr (deuteriochloroform): δ 4.03 (s, 2H), 3.46 (t, J = 6.6 Hz, 2H), 2.47 (t, J = 6.6 Hz, 2H) 2.25 (s, 6H), 1.47 (s, 9H).

Anal. Calcd. for $C_9H_{21}N_3O_2$: C, 53.18; H, 10.41; N, 20.67. Found: C, 53.30; H, 10.38; N, 20.44

3-Carboxy-2-(2-nitro-5-fluorophenylthio)-pyridine (**21**).

To a solution of sodium ethoxide, prepared by adding sodium (1.5 g, 0.064 mole) to anhydrous ethanol (100 ml), 2-mercaptonicotinic acid (**19**, 5.0 g, 0.032 mole) was added. The resultant white suspension was then treated with 2,4-difluoronitrobenzene (**20**, 5.1 g, 0.032 mole). The mixture was placed in an oil bath and heated at reflux for 2 hours. The mixture was cooled and the residue washed with ethanol. The filtrate was concentrated to dryness and ether (75 ml) was added to the residue. The solid was collected by filtration, dried and dissolved in water (100 ml). The aqueous phase was acidified to *p*H 1 by addition of concentrated sulfuric acid. The resultant solid was collected by filtration to afford **21** (6.6 g, 99%), which was recrystallized from ethyl cellosolve; mp 237-238°; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.39 (dd, J = 1.8, 4.8 Hz, 1H), 8.28 (dd, J = 1.7, 7.8 Hz, 1H), 8.18 (dd, J = 5.1, 9.0 Hz, 1H), 7.65 (dd, J = 2.7, 8.7 Hz, 1H), 7.53 (m, 1H), 7.31 (dd, J = 4.8, 7.8 Hz, 1H).

Anal. Calcd. for $C_{12}H_7FN_2O_4S$. C, 48.98; H, 2.40; N, 9.52. Found: C, 48.91; H, 2.31; N, 9.49.

6-Fluoro-9-nitro-5*H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-one (**18**).

Acid **21** (0.50 g, 1.7 mmoles) was added to fuming sulfuric acid (1.8 ml, 18-24% sulfur trioxide) and the mixture was placed in an oil bath preheated to 75°. The bath temperature was raised to 120° over a 1.5 hour interval. The mixture was quenched over ice (60 ml) and the resultant solid collected by filtration to yield **21** (0.49 g, quantitative). Recrystallization was effected from dimethyl formamide to afford **18** (0.40 g, 80%) as yellow crystals; mp 241-243 dec; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.92 (dd, J = 1.6, 4.5 Hz, 1H), 8.82 (dd, J = 4.5, 9.2 Hz, 1H), 8.60 (dd, J = 1.9, 8.0 Hz, 1H), 7.68 (dd, J = 4.6, 8.0 Hz, 1H), 7.65 (dd, J = 1.4, 9.4 Hz, 1H).

Anal. Calcd. for $C_{12}H_5FN_2O_3S$: C, 52.18; H, 1.82; N, 10.14. Found: C, 51.83; H, 1.76; N, 9.99.

2-Methyl-5-nitro-2*H*-pyrido[3',2':5,6]thiopyrano[4,3,2-*cd*]-indazole (**22**).

A solution of **15a** (0.041 g, 0.89 mmole) and anhydrous dimethylformamide (1.0 ml) was slowly added to a solution of **18** (0.10 g, 0.37 mmole) and anhydrous dimethylformamide (5.0 ml) at 0°. The mixture was allowed to warm up to room temperature and stirred overnight (21 hours), before being poured over ice water (15 ml). The resultant solid was collected by filtration, rinsed with water (30 ml) and ether (15 ml) to yield **22** (0.10 g, 86%) as an orange-yellow solid; mp >300° (recrystallized from acetonitrile); ^1H nmr (dimethyl sulfoxide-d_6): δ 8.62 (d, J = 4.4 Hz, 1H), 8.46 (dd, J = 1.6, 7.9 Hz, 1H), 8.24 (d, J = 9.3 Hz, 1H), 7.55 (dd, J = 4.8, 7.9 Hz, 1H), 7.52 (d, J = 9.3 Hz, 1H), 4.17 (s, 3H).

Anal. Calcd. for $C_{13}H_8N_4O_2S$: C, 54.93; H, 2.84; N, 19.71. Found: C, 54.79; H, 2.67; N, 19.84.

9-Nitro-6-{2-[1,1-dimethylethoxy)carbonyl]-2-methylhydrazino}-5*H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-one (**23**).

A solution of **16a** (0.10 g, 0.71 mmole) and dry pyridine (0.5 ml) was added to a mixture of **18** (0.1 g, 0.36 mmole) and pyridine (1.0 ml) at room temperature under a nitrogen blanket. This mixture was allowed to stir at room temperature for 20 hours until tlc (silica gel plate, using 98:2 dichloromethane:methanol as the eluent) indicated that no more starting material was present. The pyridine was removed under a stream of nitrogen and the product isolated by flash chromatography (silica gel, 1 cm x 16 cm, using 98:2 dichloromethane:methanol as the eluent) to yield **23** (0.105 g, 72%) as a bright yellow solid; mp 192-193°; ^1H nmr (deuteriochloroform): δ 12.34 (s, 1H), 8.84 (dd, J = 1.8, 4.5 Hz, 1H), 8.73 (dd, 1.8, 7.9 Hz, 1H), 8.59 (d, J = 9.7 Hz, 1H), 7.49 (dd, J = 4.5, 7.9 Hz, 1H), 6.90 (d, J = 9.6 Hz, 1H), 3.28 (s, 3H), 1.44 (s, 9H).

Anal. Calcd. for $C_{18}H_{18}N_4O_5S$: C, 53.72; H, 4.51; N, 13.92. Found: C, 53.56; H, 4.30; N, 13.77.

1-Methyl-5-nitro-1*H*-pyrido[3',2':5,6]thiopyrano[4,3,2-*cd*]indazole (**24**).

Trifluoroacetic acid (1.0 ml) was added to a solution of **23** (0.068 g, 0.17 mmole) and dichloromethane (2.0 ml) at 0° under a nitrogen blanket. The solution was allowed to warm up to room temperature and continue stirring for 11 hours. The solvent was removed under a stream of nitrogen and ethanol (5.0 ml) was added to the orange residue. The ethanol was removed by rotary evaporation and water (2.0 ml) was added to the solid. The *p*H was adjusted to 10 using 1*M* sodium hydroxide before extraction in dichloromethane (5 x 10 ml). The combined extracts were dried over magnesium sulfate and the solvent removed by rotary evaporation to yield **24** (0.025 g, 61%) as a bright yellow solid; mp >300° (recrystallized from actonitrile); ^1H nmr (dimethyl sulfoxide-d_6): δ 8.64 (m, 2H), 8.11 (d, J = 9.5 Hz, 1H), 7.61 (m, 1H), 7.35 (d, J = 9.5 Hz, 1H), 4.52 (s, 3H).

Anal. Calcd. For $C_{13}H_8N_4O_2S$: C, 54.93; H, 2.84; N, 19.71. Found: C, 54.70; H, 2.66; N, 19.68.

2-Methylanthra[1,9-*cd*]pyrazol-6(2*H*)-one (**10d**).

A solution of **15a** (0.16 g, 3.5 mmoles) and dry pyridine (0.5 ml) was added to a solution of 1-fluoroanthracene-9,10-dione (**25a**, 0.12 g, 0.54 mmole) and dry pyridine (1.0 ml). The resultant red-orange solution, which slowly deposited a precipitate, was allowed to stir at room temperature for 19 hours. The pyridine was removed under a stream of nitrogen to leave a reddish-orange residue, which was broken up and stirred well in water (5 ml). The solid was collected by filtration and rinsed well with water (5 x 5-10 ml). The solid was recrystallized from methanol to yield orange needles (0.11 g, 88%); mp 184-185°; lit mp [12] 189-190°; ^1H nmr (deuteriochloroform): δ 8.45 (m, 1H), 8.20 (m,

1H), 8.05 (d, J = 6.0 Hz, 1H), 7.69 (m, 3H), 7.54 (m, 1H), 4.25 (s, 3H); ^{13}C nmr (deuteriochloroform) δ183.6, 139.4, 138.7, 133.3, 133.2, 131.8, 129.2, 128.2 (2 resonances closely spaced), 126.4, 123.6, 122.5, 120.6, 114.6, 36.3.

1{2-[(1,1-Dimethylethoxy)carbonyl]-2-methylhydrazino}-anthracene-9,10-dione (**26a**).

A solution of **16a** (0.68 g, 0.47 mmole) and diisopropylethylamine (0.065 g, 0.5 mmole) was added to 1-fluoroanthracene-9,10-dione (**25a**, 0.055 g, 0.24 mmole) at room temperature and the mixture was stirred for 5 minutes. The resultant suspension was placed in an oil bath which was preheated to 60°. The temperature was slowly increased to 100° and the mixture allowed to stir at that temperature for 19 hours. The mixture was removed from the oil bath and allowed to cool to room temperature. At this point tlc (silica gel, developed in dichloromethane) indicated that only a small amount of the starting material **25a** remained along with an intense orange spot. The orange solution was poured over ice water and extracted into dichloromethane (3 x 15 ml). The combined extracts were dried over magnesium sulfate and the solvent removed by rotary evaporation to yield a red, waxy residue. The product was purified by flash chromatography (silica gel, 1 cm x 16 cm, using dichloromethane as the eluent) to yield **26a** (0.059 g, 70%) as a red, glassy residue; mp 138-140°; ^1H nmr (deuteriochloroform): δ 10.64 (s, 1H), 8.25 (m, 2H), 7.75 (m, 3H), 7.25 (m, 1H), 7.15 (d, 1H), 3.28 (s, 3H), 1.38 (s, 9H).

Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 67.93; H, 5.71; N, 7.88.

1-Methylanthra[1,9-*cd*]pyrazol-6(1*H*)-one (**11b**).

Trifluoroacetic acid (1.0 ml) was slowly added *via* syringe to a solution of **26a** (0.059 g, 0.17 mmole) and dichloromethane (1.0 ml) which was cooled in an ice bath. The solution was allowed to warm up to room temperature and stirring was continued for 11 hours. The solvent was then removed under a stream of nitrogen and then ethanol (2 ml) was added to the orange residue. The ethanol was removed by rotary evaporation and water (0.5 ml) was added. The mixture was basified (*p*H 10) using 1*M* sodium hydroxide. The product was extracted into dichloromethane (4 x 20 ml) and the combined extracts were dried over magnesium sulfate. The solvent was removed by rotary evaporation to yield a yellow-orange solid which was purified by flash chromatography (1 cm x 16 cm, using 99:1 dichloromethane:methanol as the eluent) to yield **11b** (0.029 g, 73%) as a bright yellow solid; mp 226-227°; lit [12] mp 228-229°; ^1H nmr (deuteriochloroform): δ 8.53 (m, 1H), 8.11 (m, 1H), 8.04 (m, 1H), 7.95 (m, 1H), 7.72 (m, 1H), 7.52 (m, 1H), 7.61 (m, 1H), 4.62 (s, 3H). ^{13}C nmr (deuteriochloroform): δ 182.9, 145.9, 133.0, 132.7, 130.3, 128.7, 128.3, 128.1, 127.7, 126.4, 123.9, 123.4, 122.9, 121.9, 41.2.

1-Chloro-4-fluoroanthracene-9,10-dione (**25b**).

Aluminum chloride (5.2 g, 0.04 mole) was added to a mixture of phthalide (**27**, 2.5 g, 0.02 mole) and 1-chloro-4-fluorobenzene (**28**, 12.4 g, 0.095 mole) and the mixture was placed in an oil bath preheated to 95° and held at this temperature for 4 hours. The excess 1-chloro-4-fluorobenzene was removed by gentle heating under water aspiration and the dark mass was decomposed by careful addition of water. This mixture was distilled to remove any residual reactant and the tacky residue was dissolved in dichloromethane, dried over sodium sulfate and concentrated to a yellow semi-solid. Addition of ether led to the crude anthrones **29a** and **29b** (0.95 g) as a yellow solid. Additional material (0.70 g) was collected from the ether filtrate on cooling. This combined material (0.90 g, 0.003 mole) was placed in glacial acetic acid (20 ml) and chrominum trioxide (0.6 g, 0.006 mole) in acetic acid (20 ml) and water (2 ml) was added. The mixture was allowed to stir for 24 hours and then quenched into ice water. The yellow solid was collected by filtration and dried to afford **25b** (0.86 g) which was recrystallized from ethanol; mp 187-188°; lit [21] mp 174-175°; ^1H nmr (deuteriochloroform): δ 8.24 (m, 2H), 7.81 (m, 3H), 7.41 (m, 1H).

5-Chloro-2-methylanthra[1,6-*cd*]pyrazol-6(2*H*)-one (**10e**).

To a solution of **25b** (0.046 g, 0.18 mmole) and dry pyridine (1.0 ml) at 0° was added a solution of **15a** (0.026 g, 0.52 mmole) in pyridine (0.5 ml) under a nitrogen blanket. Upon addition of the hydrazine solution, the yellow solution instantly turned red followed by the formation of a yellow precipitate. After allowing the mixture to stir for 1.5 hours the reaction was stopped by removing the solvent under a stream of nitrogen. Residual pyridine was removed under vaccum pump overnight before adding water (2.0 ml). The solid was collected by filtration and washed well with water. The solid was allowed to air dry overnight and recrystallized from acetonitrile to afford **10e** (0.043 g, 88%) as yellow needles; mp 275-277°; lit [1] mp 266-277°; ^1H nmr (deuteriochloroform): δ 8.47 (d, J = 7.8 Hz, 1H), 8.19 (d, J = 7.7 Hz, 1H), 7.71 (m, 1H), 7.60 (s, 2H), 7.55 (m, 1H), 4.24 (s, 3H).

4-Chloro-1-{2-[(1,1-dimethylethoxy)carbonyl]-2-methylhydrazino}anthracene-9,10-dione (**26b**).

A mixture of **16a** (0.455 g, 3.1 mmoles), diisopropylethylamine (0.016 g, 0.18 mmole), and **25b** (0.024 g, 0.09 mmole) was heated from 60° to 100° over a three hour period. The mixture was then allowed to react at 100° for an additional 2 hours before being allowed to cool to room temperature. Water (1.0 ml) was added to the mixture and the resultant waxy solid collected by filtration. This crude product was washed thoroughly with water and allowed to air dry. The product was purified by flash chromatography (silica gel, 1 cm x 15 cm, using dichloromethane as the eluent) to yield **26b** (0.024 g, 69%) as an orange solid; mp 160-161°; ^1H nmr (deuteriochloroform): δ 10.9 (s, 1H), 8.23 (m, 2H), 7.75 (m, 2H), 7.59 (d, J = 9.3 Hz, 1H), 7.11 (d, J = 9.3 Hz, 1H), 3.27 (s, 3H), 1.39 (s, 9H).

Anal. Calcd. for $C_{20}H_{19}ClN_2O_4$: C, 62.10; H, 4.95; N, 7.24. Found: C, 61.94; H, 5.02; N 7.18.

5-Chloro-1-methylanthra[1,9-*cd*]pyrazol-6(1*H*)-one (**30a**).

To a solution of **26b** (0.019 g, 0.05 mmole) and dichloromethane (0.05 ml) was added trifluoroacetic acid (0.25 ml) at 0° under a nitrogen atmosphere. The solution was allowed to warm to room temperature and stirring was continued overnight. The solvent was removed under a light stream of nitrogen followed by addition of ethanol (2.0 ml). The mixture was stirred thoroughly before removing the ethanol by rotary evaporation. Water (0.5 ml) was added to the solid residue and made basic (*p*H 11) with 1 *M* sodium hydroxide. The product was extracted into dichloromethane (3 x 20 ml) and the extracts dried over magnesium sulfate. The solvent was removed by rotary evaporation to yield **30a** (0.011 g, 85%) as a bright yellow solid; mp 234-235°; ^1H nmr (deuteriochloroform): δ 8.54 (dd, J = 1.3, 7.9 Hz, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.91 (d, J = 8.9 Hz, 1H), 7.72 (m, 1H), 7.53 (m, 1H), 7.51 (d, J = 8.8 Hz, 1H), 4.62 (s, 3H).

Anal. Calcd. for $C_{15}H_9ClN_2O \cdot 0.5\ H_2O$: C, 64.61; H, 3.63; N, 10.09. Found: C, 64.36; H, 3.67; N,10.01.

5-Chloro-2-(2-hydroxyethyl)anthra[1,9-*cd*]pyrazol-6(2*H*)-one (**10f**).

A solution of **15b** (0.037 g, 0.49 mmole) and anhydrous dimethylformamide (0.75 ml) was added to a solution of **25b** (0.048 g, 0.18 mmole) and anhydrous dimethylformamide (2.25 ml) over 1 minute at 0° under a nitrogen atmosphere. After stirring for 3 hours at this temperature, the solution was slowly poured into ice water (5.0 ml). The resultant solid was collected by filtration to yield **10f** (0.053 g, 98%) as a brown solid. The product was recrystallized from ethyl acetate to yield **10f** as bright yellow needles; mp 210-211°; lit [1] mp 209-211°; ^{1}H nmr (deuteriochloroform): δ 8.26 (m, 1H), 8.11 (m, 1H), 8.06 (d, J = 8.7 Hz, 1H), 7.79 (m, 1H), 7.66 (d, J = 8.6 Hz, 1H), 7.59 (m, 1H), 4.95 (t, J = 5.1 Hz, 1H), 4.61 (t, J = 5.2 Hz, 2H), 3.88 (m, 2H).

5-Chloro-1-{2-[(1,1-dimethylethoxy)carbonyl]-2-{2-hydroxyethyl]hydrazino}anthracene-9,10-dione (**26c**).

A solution of **16b** (0.647 g, 3.7 mmoles) and diisopropylethylamine (0.71 g, 4.0 mmoles) was added to **25b** (0.055 g, 0.21 mmole) at room temperature. The mixture was placed in an oil bath which was preheated to 60° and the temperature was raised to 95°. The solution which formed after 1.5 hours at that temperature was allowed to stir for 22 hours before being allowed to cool to room temperature. Water (2.0 ml) was added to the mixture and the resultant tacky solid was collected by filtration and washed thoroughly with water before being allowed to air dry overnight. The product was purified by flash chromatography (silica gel, 1 cm x 16 cm, using 99:1 dichloromethane:methanol as the eluent) to yield **26c** (0.051 g, 59%) as a glassy, red solid; mp 140-141°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 10.84 (s, 1H, partially exchangeable with D_2O), 8.16 (m, 2H), 7.88 (m, 2H), 7.72 (d, J = 9.4 Hz, 1H), 7.32 (d, J = 9.4 Hz, 1H), 4.91 (m, 1H, exchangeable with D_2O), 3.78 (br s, 1H), 3.58 (m, 2 H), 3.38 (br s, 1H), 1.32 (s, 9H).

Anal Calcd. for $C_{21}H_{21}ClN_2O_6$: C, 60.51; H, 5.08; N, 6.72. Found: C, 59.84; H, 5.23; N, 6.49.

5-Chloro-1-(2-hydroxyethyl)anthra[1,9-*cd*]pyrazol-6(1*H*)-one (**30b**).

Trifluoroacetic acid (1.0 ml) was added to a solution of **26c** (0.051 g, 0.12 mmole) and dichloromethane (1.0 ml) at 0° under a nitrogen atmosphere. The solution was allowed to warm up to room temperature and stir overnight before removing the solvent under a stream of nitrogen. Ethanol (2.0 ml) was added to the orange residue and stirred thoroughly before concentrating to dryness by rotary evaporation. Water (1.0 ml) was then added and the pH adjusted to 10 using 1*M* sodium hydroxide. The product was extracted into dichloromethane (5 x 15 ml) and the extracts dried over magnesium sulfate. The solvent was removed by rotary evaporation to yield the crude product as a yellow solid which was purified by flash chromatography (silica gel, 2 cm x 15 cm, using 99:1 dichloromethane:methanol as the eluent) to yield **30b** (0.029 g, 83%); mp 221-222°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.37 (m, 1H), 8.31 (m, 1H), 8.14 (d, J = 8.8 Hz, 1H), 7.85 (m, 1H), 7.63 (m, 1H), 7.61 (d, J = 8.8 Hz, 1H, overlapping with the 6.63 signal), 5.11 (m, 1H), 5.01 (t, J = 5.7 Hz, 2H), 4.01 (m, 2H).

Anal. Calcd. for $C_{16}H_{11}ClN_2O_2$: C, 64.33; H, 3.71; N, 9.38. Found: C, 64.24; H, 3.60; N, 9.17.

4-Chloro-1-{(2-dimethylaminoethyl)-2-[(1,1-dimethylethoxy)-carbonyl]hydrazino}-anthracene-9,10-dione (**26d**).

A solution of diisopropylethyl amine (0.04 g, 0.31 mmole) and **16c** (0.65 g, 3.2 mmoles) was added to **25b** (0.059 g, 0.23 mmole) at room temperature, then placed in an oil bath which was preheated to 70°. The temperature was raised to 95° at which point a dark red solution formed. This solution was allowed to stir at this temperature for 22 hours before cooling to room temperature. Water (2.0 ml) was added and the mixture stirred thoroughly. The resultant solid was collected by filtration and rinsed with water. The product was purified by flash chromatography (silica gel, 1 cm x 15 cm, using 98:2 dichloromethane: methanol with 0.25% ammonium hydroxide) to yield **26d** (0.08 g, 79%) as a bright red solid; mp 129-131° ; ^{1}H nmr (deuteriochloroform): δ 10.96 (s, 1H), 8.22 (m, 2H), 7.72 (m, 2H), 7.55 (d, J= 9.4 Hz, 1H), 7.33 (d, J= 9.4 Hz, 1H), 3.83 (br s, 1H), 3.50 (br s, 1H), 2.57 (br s, 1H), 2.47 (br s, 1H), 2.29 (s, 6H), 1.38 (s, 9H). ^{13}C NMR (deuteriochloroform): δ 184.9, 182.6, 155.3, 151.5, 139.0, 133.7, 133.7, 133.6, 133.5, 130.1, 126.9, 126.5, 124.5, 119.2, 115.2, 81.5, 56.7, 47.4, 45.5, 28.1.

Anal. Calcd. for $C_{23}H_{26}ClN_2O_4$: C, 62.23; H, 5.90; N, 9.47. Found: C, 61.54; H, 5.84; N, 9.32.

5-Chloro-1-[(2-dimethylamino)ethyl]anthra[1,9-*cd*]pyrazol-6(1*H*)-one (**30c**).

Trifluoroacetic acid (2.0 ml) was added to a solution of **26d** (0.05 g, 0.12 mmole) and dichloromethane (2.0 ml) at 0°. The solution was allowed to warm up to room temperature and stirring was continued overnight. The solvent was removed under a stream of nitrogen to yield an orange residue. Water (2.0 ml) was added and the solution basified (*p*H 10) using 1*M* sodium hydroxide. The product was extracted into dichloromethane (3 x 15 ml) and the combined extracts dried over magnesium sulfate. The solvent was removed by rotary evaporation to yield an orange solid. This solid was purified by flash chromatography (silica gel, 1 cm x 15 cm, using 98:2 dichloromethane:methanol as the eluent) to yield the product **30c** (0.036 g, 88%) as a yellow solid; mp 135-136°; ^{1}H nmr (deuteriochloroform): δ 8.50 (m, 1H), 7.89 (m, 2H), 7.69 (m, 1H), 7.52 (m, 2H), 4.96 (t, J = 7.5 Hz, 2H), 3.02 (t, J = 7.5 Hz, 2H), 2.40 (s, 6H).

Anal. Calcd. for $C_{18}H_{16}ClN_3O$: C, 66.36; H, 4.95; N, 12.90. Found: C, 66.14; H, 5.08; N, 12.72.

5-Chloro-2-[(2-dimethylamino)ethyl]anthra[1,6-*cd*]pyrazol-6(2*H*)-one (**10g**).

A solution **15c** (0.067 g, 0.65 mmole) and dry pyridine (0.5 ml) was added to a solution of **25b** (0.033 g, 0.13 mmole) and dry pyridine (0.5 ml) at room temperature. After allowing to stir 20 hours, the pyridine was removed under a stream of nitrogen. Water (2.0 ml) was added and the solid collected by filtration to yield an orange solid. The product was purified by flash chromatography (silica gel, 1 cm x 12 cm, using 95:5 dichloromethane:methanol as the eluent) to yield **10g** (0.031 g, 71%) as an orange solid; mp 199-201°; ^{1}H nmr (deuteriochloroform): δ 8.43 (m, 1H) 8.17 (m, 1H), 7.68 (m, 1H), 7.61 (m, 1H), 7.52 (m, 2H), 4.58 (t, J = 6.6 Hz, 2H), 2.91 (t, J = 6.6 Hz, 2H), 2.32 (s, 6H).

Anal. Calcd. for $C_{18}H_{16}ClN_3O$: C, 66.36; H, 4.95; N, 12.90. Found: C, 66.07; H, 5.11; N, 12.71.

6-Chloro-9-{2-[(1,1-dimethylethoxy)carbonyl]2-(2-hydroxyethyl)hydrazino}benz[*g*]isoquinoline-5,10-dione (**33**).

A solution of **16b** (0.63 g, 3.6 mmoles) and diisopropylethylamine (0.09 g, 0.70 mmole) was added to **31** (0.11 g, 0.44

mmole) at room temperature. The mixture was placed in an oil bath, which had been preheated to 90°. The reaction was allowed to proceed at this temperature for 20 hours and then cooled to room temperature. Water (5.0 ml) was added and the resultant tacky solid was collected by filtration and washed well with water. The residue was allowed to air dry overnight and was purified by flash chromatography (silica gel, 1 cm x 16 cm, using 98:2 dichloromethane:methanol as the eluent) to yield **33** (0.13 g, 71%) as a red solid; mp 170-171°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 10.85 (s, 1H, partially exchangeable with D_2O), 9.35 (s, 1H), 9.07 (d, J = 5.0 Hz, 1H), 7.95 (d, J = 5.0 Hz, 1H), 7.75 (d, J = 9.3 Hz, 1H), 7.36 (d, J = 9.3 Hz, 1H), 4.91 (m, 1H, exchangeable with D_2O), 3.77 (br s, 1H), 3.59 (m, 2H), 3.27 (br s, 1H), 1.36 (s, 9H).

Anal. Calcd. for $C_{20}H_{20}ClN_3O_5$: C, 57.49; H, 4.82; N, 10.06. Found: C, 57.12; H, 4.71; N, 9.91.

5-Chloro-1-(2-hydroxyethyl)indazolo[4,3-*gh*]isoquinolin-6(1*H*)-one (**34**).

Trifluoroacetic acid (2.0 ml) was added to a solution of dichloromethane (2.0 ml) and **33** (0.03 g, 0.07 mmole) which was cooled in an ice bath. The solution was allowed to warm to room temperature and stirring was contined for 11 hours. The solvent was removed under a stream of nitrogen. Water (2.0 ml) was added to the solid residue and the *p*H adjusted to 11 using 1*M* sodium hydroxide. The product was isolated by continuous extraction into dichloromethane. Removal of the solvent led to **34** (0.014 g, 62%) as a bright yellow solid; mp 244-245°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 9.70 (s, 1H), 8.85 (d, J = 5.1 Hz, 1H), 8.24 (d, J = 8.8 Hz, 1H), 8.17 (d, J = 5.1 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 5.12 (m, 1H), 5.08 (t, J = 5.5 Hz, 2H), 4.04 (m, 2H).

Anal. Calcd. for $C_{15}H_{10}ClN_3O_2$: C, 60.11; H, 3.36; N, 14.02. Found: C, 59.77; H, 3.34; N, 13.78.

5-[[2-(Dimethylamino)ethyl]amino]-1-(2-hydroxyethyl)indazolo[4,3-*gh*]isoquinolin-6(1*H*)-one (**35a**).

A mixture of **34** (750 mg, 2.5 mmoles) and 2-(dimethylamino)-ethylamine (2.23 ml, 20 mmoles) in anhydrous pyridine (11.3 ml) was heated at 100° for 3 hours. The solvent was removed by rotary evaporation, the residue was taken up with brine (75 ml) and the mixture was extracted with tetrahydrofuran:ethyl acetate (1:1, 10 x 50 ml). The combined organic layers were dried over sodium sulfate and concentrated to dryness. The residue was taken up with ethanol (7.0 ml). The mixture was stirred at room temperature for 15 minutes and after addition of *t*-butyl methyl ether (56 ml) stirring was continued for an additional 2 hours. The solid was collected by filtration, washed with *t*-butyl methyl ether and dried under vacuum at 40° to constant weight (750 mg, 85%); mp 221-223°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 10.05 (br t, J = 5.1 Hz, 1H), 9.73 (d, J = 0.8 Hz, 1H), 8.75 (d, J = 5.3 Hz, 1H), 8.30 (dd, J = 5.3 Hz, 0.8 Hz, 1H), 8.11 (d, J = 9.4 Hz, 1H), 7.28 (d, J = 9.4 Hz, 1H), 5.11 (t, J = 5.5 Hz, 1H), 5.00 (t, J = 5.7 Hz, 2H), 3.99 (q, J = 5.7 Hz, 2H), 3.66 (q, J = 5.7 Hz, 2H), 2.61 (t, J = 6.1 Hz, 2H), 2.27 (s, 6H).

Anal. Calcd. for $C_{19}H_{21}N_5O_2 \cdot 0.5\ H_2O$: C, 63.32; H, 6.15; N, 19.43. Found: C, 63.40; H, 6.25; N, 19.33.

1-(2-Hydroxyethyl)-5-{[2-[*N*-[(1,1-dimethylethoxy)carbonyl]-*N*-methylamino]ethyl]amino}indazolo[4,3-*gh*]isoquinolin-6(1*H*)-one (**35b**).

A mixture of **34** (1.5 g, 5.00 mmoles) and [2-{*N*-methyl-*N*-(*t*-butoxycarbonyl)amino]ethyl}amine (7.0 g, 40 mmoles) in anhydrous pyridine (10.5 ml) was heated at 100° for 5 hours. The solvent was removed by rotary evaporation, the residue was taken up with water (66 ml) and the mixture was stirred at room temperature overnight. The solid was collected by filtration and thoroughly washed with water. The wet solid was suspended in 2-propanol (6.5 ml) and stirred for 15 minutes, then *t*-butyl methyl ether was added (65 ml) and the mixture was stirred for an additional 2 hours. The solid was collected by filtration, washed repeatedly with *t*-butyl methyl ether and dried under vacuum at 40° to constant weight to yield **35b** (1.80 g, 82%), mp 149-151°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 10.00 (br. t, J = 6.3 Hz, 1H), 9.72 (s, 1H), 8.74 (d, J = 5.3 Hz, 1H), 8.27 (d, J = 5.3 Hz, 1H), 8.09 (d, J = 9.4 Hz, 1H), 7.31 (d, J = 9.4 Hz, 1H), 5.10 (t, J = 5.5 Hz, 1H), 4.99 (t, J = 5.5 Hz, 2H), 3.99 (q, J = 5.5 Hz, 2H), 3.78 (q, J = 5.5 Hz, 2H), 3.50 (br t, 2H), 2.85 (s, 3H), 1.34 (brs, 4H, part of the split Boc signal), 1.21 (brs, 5H; part of the split Boc signal).

5-{[2-(Dimethylamino)ethyl]amino}-1-{2-[(2-hydroxyethyl)-amino]ethyl}indazolo[4,3-*gh*]isoquinolin-6(1*H*)-one (**37a**).

To a stirred suspension of **35a** (422 mg, 1.20 mmoles) in anhydrous dichloromethane (21 ml), triethylamine (0.285 ml, 2.04 mmoles) and methanesulfonyl chloride (0.144 ml, 1.80 mmoles) were added and the mixture was stirred at room temperature for 1.5 hours. The reaction mixture was diluted with additional dichloromethane (50 ml) and washed with water (30 ml). The aqueous phase was extracted with dichloromethane (2 x 30 ml) then the combined organic phases were dried over sodium sulfate and concentrated to dryness to yield **36a**. The crude product was then taken up with pyridine (5 ml), ethanolamine (5 ml) was added and the mixture was stirred at 60° for 2 hours. The reaction mixture was concentrated under vacuum to remove most of pyridine, 2-propanol (5 ml) was added and the mixture was stirred at room temperature overnight. The solid was collected by filtration, washed with 2-propanol and taken up with brine (25 ml). The mixture was brought to pH 10-11 by addition of 2N sodium hydroxide and extracted into dichloromethane (10 x 20 ml). The organic extracts were dried over sodium sulfate and concentrated to dryness. The residue was triturated with 2-propanol at room temperature for 30 minutes, hexane (2.5 ml) was added and the mixture was stirred at room temperature for 2 hours. The solid was collected by filtration and dried under vacuum at 40° to constant weight to give **37a** (190 mg, 40%) as a red solid mp; 155-157°; ^{1}H nmr (dimethyl sulfoxide-d_6) δ 10.04 (br t, J = 5.3 Hz, 1H), 9.67 (s, 1H), 8.77 (d, J = 5.3 Hz, 1H), 8.31 (d, J = 5.3 Hz, 1H), 8.11 (d, J = 9.4 Hz, 1H), 7.27 (d, J = 9.4 Hz, 1H), 5.00 (t, J = 6.5 Hz, 2H), 4.44 (t, J = 5.3 Hz, 1H), 3.66 (q, J = 5.7 Hz, 2H), 3.37 (q, J = 5.3 Hz, 2H), 3.17 (t, J = 6.5 Hz, 2H), 2.67-2.54 (m, 4H), 2.26 (s, 6H).

Anal. Calcd. for $C_{21}H_{26}N_6O_2 \cdot 0.5\ H_2O$: C, 62.51; H, 6.76; N, 20.83. Found: C, 62.17; H, 6.33; N, 20.75.

5-{[2-{*N*-[(1,1-Dimethylethoxy)carbonyl]-*N*-methylamino}ethyl]-amino}-1-[2-[(2-hydroxyethyl)amino]ethyl]indazolo[4,3-*gh*]-isoquinolin-6(1*H*)-one (**37b**).

To a stirred suspension of **35b** (1.31 g, 3.00 mmoles) in anhydrous dichloromethane (53 ml), triethylamine (0.71 ml, 5.10 mmoles) and methanesulfonyl chloride (0.397 ml, 4.50 mmoles) were added and the mixture was stirred at room temperature for 1.5 hours. The reaction mixture was diluted with dichloromethane (150 ml) and washed with water (70 ml). The aqueous phase was extracted with dichloromethane (50 ml), the combined organic phases were dried over sodium sulfate and concentrated to dryness to yield **36b**. This crude material was taken up with pyridine

(31 ml), ethanolamine (15.5 ml) was added, and the mixture was stirred at 60° for 3 hours. The reaction mixture was concentrated under vacuum to remove most of the pyridine, 2-propanol (15 ml) was added and the mixture was stirred at room temperature for 3 hours. The solid was collected by filtration, washed with 2-propanol and dried under vacuum to afford 1.15 g of crude product. This material was suspended in 2*N* sodium hydroxide (5.8 ml) and kept under vigorous stirring for 30 minutes, then collected by filtration and washed with water. The solid was dissolved in hot 2-propanol (3.5 ml) and the solution was filtered through a microfiber glass filter, which was then washed with additional 2-propanol (5 ml). The filtrate was concentrated to half volume and, as the product started crystallizing, hexane (10 ml) was added and the mixture was stirred at room temperature for 3 hours. The solid was collected by filtration and dried under vacuum at 40° to constant weight to give **37b** (1.12 g, 78%) as a red solid; mp 162-165°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 10.00 (br t, J = 6.0 Hz, 1H), 9.66 (s, 1H), 8.77 (d, J = 5.3 Hz, 1H), 8.28 (d, J = 5.3 Hz, 1H), 8.10 (d, J = 9.4 Hz, 1H), 7.31 (d, J = 9.4 Hz, 1H), 4.99 (br t, J = 6.0 Hz, 2H), 4.43 (br t, J = 4.7 Hz, 1H), 3.86-3.66 (m, 2H), 3.59-3.25 (m, 4H), 3.16 (t, J = 6.5 Hz, 2H), 2.84 (s, 3H), 2.59 (t, J = 5.5 Hz, 2 H), 1.32 (br s, 4H, part of the split Boc signal), 1.16 (br. s, 5H; part of the split Boc signal).

Anal. Calcd. for $C_{25}H_{32}N_6O_4$: C 62.48; H 6.71; N 17.49. Found: C 62.10; H 6.73; N 17.12

1-{2-[(2-Hydroxyethyl)amino]ethyl}-5-{[2-(methylamino)-ethyl]amino}indazolo[4,3-*gh*]isoquinoline-6(1*H*)-one trihydrochloride (**37c**).

Compound **37b** was dissolved in a mixture of water (1.36 ml), concentrated hydrochloric acid (1.04 ml) and ethanol (1.20 ml) and the resulting solution was stirred at room temperature for 2 hours. Additional ethanol (13.2 ml) was added and the resulting suspension was stirred at room temperature for 3 hours. The solid was collected by filtration and dried under vacuum at 40° to constant weight to give **37c** (550 mg, 90%) as a red solid; mp 272-274°; ^{1}H nmr (deuterium oxide) δ 9.37 (s, 1H), 8.71 (d, J = 6.0 Hz, 1H), 8.44 (d, J = 6.0 Hz, 1H), 8.06 (d, J = 9.4 Hz, 1H), 7.22 (d, J = 9.4 Hz, 1H), 5.18 (t, J = 5.5 Hz, 2H), 4.04 (t, J = 6.1 Hz, 2H), 3.97-3.93 (m, 4H), 3.46 (t, J = 5.9 Hz, 2H), 3.39-3.29 (m, 2H), 2.79 (s, 3H).

Anal. Calcd. for $C_{20}H_{27}Cl_3N_6O_2 \cdot 0.5H_2O$: C, 48.16; H, 5.66; N, 16.85; Cl, 21.32. Found: C, 48.14; H, 5.48; N, 16.43; Cl, 20.5.

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