Analogues of Amonafide and Azonafide with Novel Ring Systems

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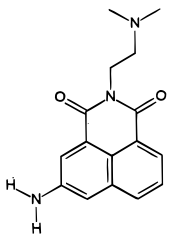
Received November 22, 1999

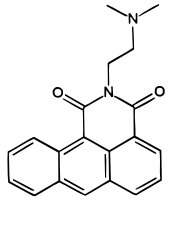
Three new types of amonafide and azonafide analogues were synthesized and screened in a panel of human solid tumor cells and murine L1210 leukemia cells. The structural types included tetrahydroazonafides, which have the naphthalene chromophore of amonafide within the anthracene nucleus of azonafide; phenanthrene analogues, in which the linear anthracene nucleus is replaced by the bent phenanthrene nucleus; and azaphenanthrenes. The tetrahydroazonafides were generally intermediate in potencies between amonafide and azonafide against the tumor cells, but some of them had high potencies against the L1210 cells and were more potent against the MDR strain than the sensitive strain. The phenanthrene and azaphenanthrene analogues showed no improvement on the potencies of the anthracenes.

Introduction

Previous articles in this series have described the preparation and antitumor properties of 2-[2′-(dimethylamino)ethyl]-1,2-dihydro-3*H*-dibenz[*de,h*]isoquinoline-1,3-dione (**2**), known as azonafide, and many analogues with structural variations in the side chain and the anthracene nucleus.[1−5] These compounds have been compared with each other in terms of qualitative and quantitative structure−activity relationships (SARs), and their mode of action (intercalation with inhibition of topoisomerase II) has been studied. They have also been compared with amonafide (**1**), the first compound of this general type, which was discovered by Braña and co-workers, who also made numerous analogues and studied the mode of action and SARs.[6−8]



1, amonafide



2, azonafide

The present article describes the synthesis and antitumor activities of three new types of structures related to azonafide. One type has a tetrahydroanthracene nucleus and thus represents the naphthalene chromophore of amonafide in the anthracene nucleus of azonafide**.** A second type has the linear anthracene chromophore of azonafide replaced by the bent phenanthrene chromophore. It was designed to answer the question of how this change in geometry would influence the DNA binding and antitumor potency of the molecule. The third structural type is the aza analogue of the phenanthrene chromophore, which was designed to determine the effect of replacing carbon by nitrogen on antitumor activity.

Chemistry

Synthesis of the tetrahydroazonafides **12** and **13** began with 6-[(trimethylacetyl)amino]-1,2,3,4-tetrahydroanthracene (**4**),[2] which was converted into a mixture of diones **6** and **7** by oxalyl chloride and aluminum chloride in CS_2 (Scheme 1). This mixture was separated as previously described.[2] Oxidation of these diones with alkaline hydrogen peroxide afforded the corresponding anhydrides **9** and **10**. Treatment of the anhydrides with *N*,*N*-dimethylethylenediamine in a mixture of ethanol and toluene at reflux temperature then furnished the desired isomeric (trimethylacetyl)aminotetrahydroazonafides **12** and **13** in good yields. 4-Acetylaminotetrahydroazonafide (**11**) was prepared from 6-acetylamino-1,2,3,4-tetrahydroanthracene (**3**)[2] by a route parallel to the one described for **12** and **13**. Oxalylation of **3** gave only a single isomer (**5**), which was converted into **11** in moderate yield.

Acid hydrolysis of **12** and **13** afforded the corresponding amines **14** and **15**. Treatment of **14** with nitrous acid then gave the parent tetrahydroazonafide **16** in low yield.

Phenanthrene analogues of azonafide are 5-[2′-(dimethylamino)ethyl]-5,6-dihydro-4*H*-dibenz[*de,g*]-4,6-diones. The parent compound in this series (**20**) was prepared from the known phenanthrene-8,9-dicarboxylic acid anhydride (**17**)[9] by treatment with *N*,*N*-dimethylethylenediamine in ethanol at reflux (Scheme 2). Nitration of anhydride **17** with nitric and sulfuric acids gave a mixture of the 1- and 4-nitro derivatives, **18** and **19**, which were purified by column chromatography on silica gel and then separated by PTLC on silica gel. The yields of the pure isomers were low. Treatment of these nitro compounds with *N*,*N*-dimethylethylenediamine gave the phenanthrene analogues of azonafide, **21** and **23**, respectively. Reduction of each of these compounds by catalytic hydrogenation afforded the corresponding amines **22** and **24**. Each of the amines was treated with sodium nitrite in hydrochloric acid, and each one gave a mixture of the corresponding chloro and hydroxy

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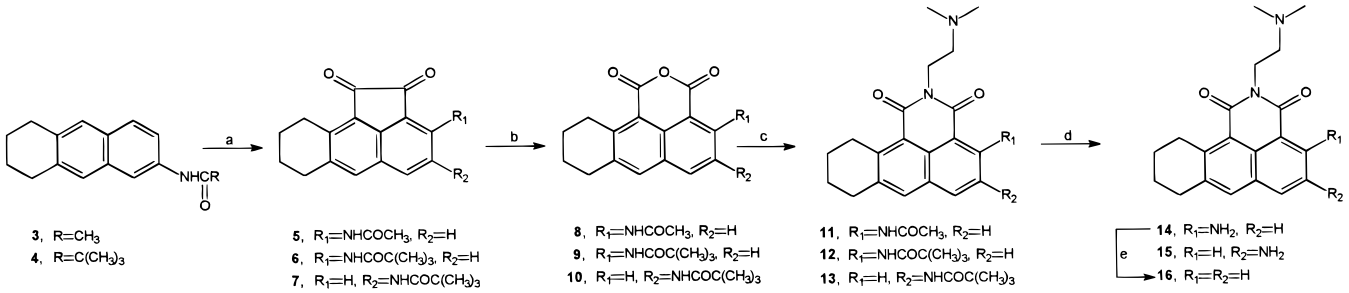
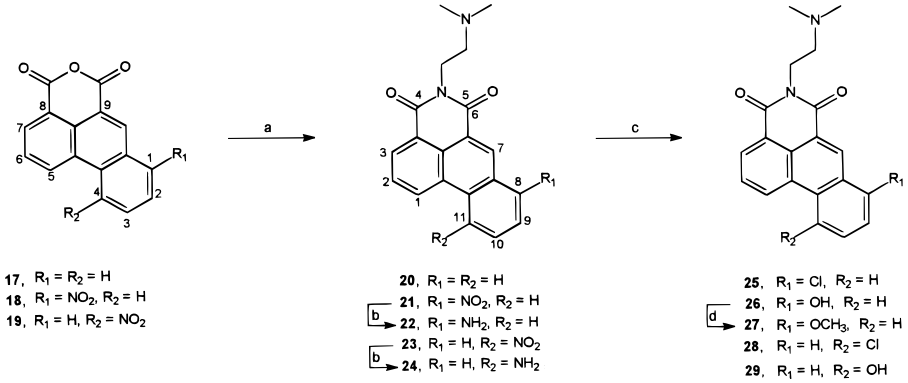
10.1021/jm9905817 CCC: $19.00
Published on Web 07/27/2000

Scheme 1. Synthesis of Tetrahydroazonafides[a]



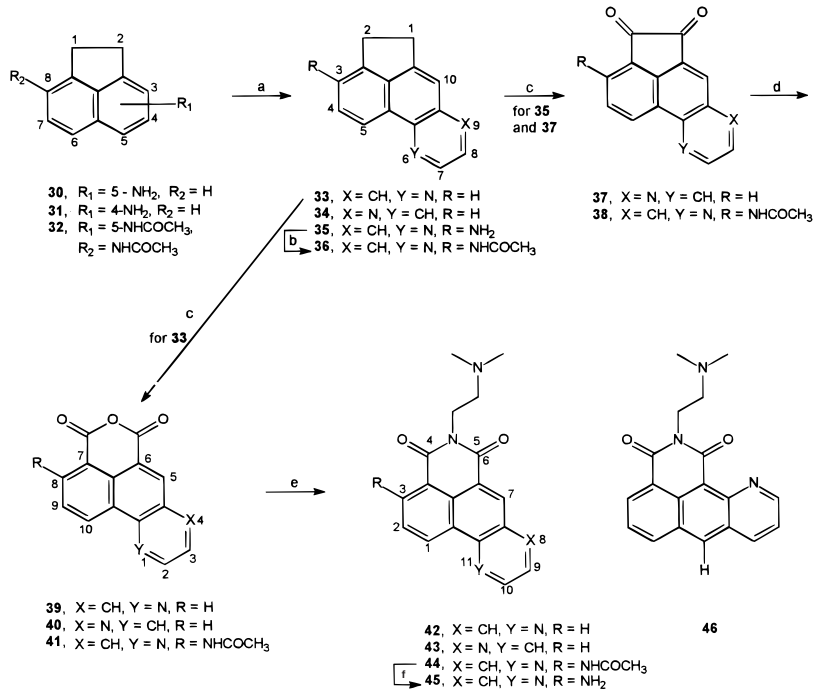
[a] Reagents: (a) ClCOCOCl, $AlCl_3$, CS_2; (b) H_2O_2, NaOH; (c) $H_2N(CH_2)_2N(CH_3)_2$; (d) HCl, EtOH; (e) $NaNO_2$, HCl, 0 °C.

Scheme 2. Synthesis of Phenanthrene Analogues[a]



[a] Reagents: (a) $H_2N(CH_2)_2N(CH_3)_2$; (b) H_2, Pd/C; (c) $NaNO_2$, HCl, 0 °C, **23** or **25** then △; (d) CH_2N_2.

Scheme 3. Synthesis of Azaphenanthrene Analogues[a]



[a] Reagents: (a) glycerol, Ac_2O_5, H_2SO_4; (b) Ac_2O, pyr; (c) $K_2Cr_2O_7$, AcOH, 100 °C; (d) H_2O_2, NaOH; (e) $H_2N(CH_2)_2N(CH_3)_2$; (f) HCl, EtOH.

derivatives. Thus, **22** gave **25** and **26**, both of which were obtained in low yields after separation by PTLC on silica gel. Likewise, **24** gave **28** and **29**. 8-Hydroxy derivative **26** was converted into methoxy derivative **27** by diazomethane.

Four different azaphenanthrene analogues of azonafide (**42**−**45**), with nitrogen replacing CH at either the 8 or the 11 position, were prepared from aminoacenaphthenes as shown in Scheme 3. When the Skraup reaction[10] was run on 5-aminoacenaphthene (**30**), the product was 1,2-dihydroindeno[1,7-*gh*]quinoline **33**. Oxidation of **33** with potassium dichromate in acetic acid gave anhydride **39** directly, and treatment with *N*,*N*-dimethylethylenediamine in ethanol and toluene at

Table 1. Activity of Compounds Against Human and Murine Tumor Cells in Culture[a]

	potency against tumor cells: IC_{50} (nM)									
	melanoma	ovarian	L12110 leukemia		MCF7 breast[e]			WiDr colon[f]		lung
compd	UA375[b]	OVCAR3[c]	sens	resist[d]	sens	D40	mitox	sens	resist	A549[g]
11	132	48	60	36	40	130	40	31	240	32
12	8752	656	2186	1749	950	2000	1300	750	800	750
13	4273	4273	984	1530	1700	1300	1000	1200	1500	850
14	187	80	11	2	120	110	130	79	450	13
15	610	488	73	26	240	900	320	230	1600	170
16	223	70	11	8	100	230	150	130	220	18
20	564	564	197	165	220	500	280	240	420	220
21	175	50	50	50	150	170	180	135	175	154
22	1083	541	54	54	550	590	550	280	525	280
23	751	626	751	501	360	620	440	800	2400	950
24	244	68	54	50	130	290	150	240	460	37
25	513	513	769	513	60	80	19	20	110	22
26	540	810	810	1350	625	560	340	320	500	420
27	520	20	520	1560	860	820	900	900	1300	870
28	179	385	256	231	160	286	150	220	380	45
29	405	675	540	540	625	675	390	260	2300	160
42	309	862	43	26	210	400	320	195	370	220
43	617	986	493	367	170	320	230	110	260	32
44	212	424	424	127	270	290	270	130	195	150
45	117	466	233	186	270	310	310	160	210	170
1	2031	2180	625	625	1100	1800	1200	1100	2200	1100
2	71	57	7	7	18	70	20	13	94	10
doxorubicin	112	35	35	3884	28	1172	28	53	130	22
mitoxantrone	48	6	10	39	9	72	41	8	488	3

[a] The murine leukemia experiments utilized the MTT assay (Alley, M. C.; Scudiero, D. A.; Monks, A.; Hursey, M. L.; Czerwinsky, M. J.; Fine, D. L.; Mayo, J. D.; Schoemaker, R. R.; Boyd, M. R. Feasibility of Drug Screening with Panels of Human Tumor Cell Lines Using a Microculture Tetrazolium Assay. *Cancer Res.* **1988**, *48*, 589−601). Determination of cytotoxicity against breast, colon, lung, ovarian, and melanoma tumors utilized the sulforhodamine B assay (Skehan, P.; Strong, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokesh, H.; Kenney, S.; Boyd, M. R. New Colorimetric Assay for Anticancer-Drug Screening. *J. Natl. Cancer Inst.* **1990**, *82*, 1107−1112). [b] A human melanoma cell line obtained from the University of Arizona Cancer Center. [c] A human ovarian cancer cell line obtained from the NCI. It is resistant to standard clinical agents. [d] A MDR strain that expresses increased levels of P-glycoproteins. [e] A human mammary carcinoma including a sensitive cell line and cell lines resistant to doxorubicin (D40) and mitoxantrone (mitox). The D40 strain is P-glycoprotein-positive and the mitox strain is P-glycoprotein-negative. [f] A human colon carcinona including sensitive and MDR cell lines. It is MRP-positive but non-P-glycoprotein. [g] A non-small-cell, drug-resistant cell line that does not produce P-glycoprotein.

reflux then afforded 8-azaphenanthrene derivative **42** (5-[2′-(dimethylamino)ethyl]-5,6-dihydro-4*H*-quinolino-[6,7,8-*de*]isoquinoline-4,6-dione).

When 3,6-di(acetylamino)acenaphthene (**32**, indicated as 5,8 in Scheme 3) was treated under the conditions of the Skraup reaction, the product (**35**) had undergone hydrolysis of the 3-acetylamino group. The resulting 3-amino group was re-acetylated to give **36** in quantitative yield in order to protect it before oxidation in the next step**.** The Skraup reaction on 4-aminoacenaphthene (**31**) can go in either of two directions to give a linear azaanthracene nucleus or a bent azaphenanthrene nucleus. When this reaction was run, a single product (**34**) with the bent chromophore was obtained. Evidence for this structure was provided by a NOE experiment on compound **43**, derived from **34**, as described below.

Treatment of either **34** or **36** with potassium dichromate in acetic acid gave the diones **37** and **38**, respectively. In contrast to **33**, they were not further oxidized to the anhydrides under these conditions. The desired anhydrides **40** and **41** were obtained in high yields by treating **37** and **38** with alkaline hydrogen peroxide. Introduction of the side chains by treatment with *N*,*N*-dimethylethylenediamine then provided the azaphenanthrene analogues **43** and **44** of azonafide. The acetyl group of **44** was hydrolyzed by HCl to give amino analogue **45** in high yield.

The structure of **43** was shown to be an azaphenanthrene by its NMR spectrum (Experimental Section) when irradiation of the singlet for H-7 showed no NOE to a *peri* resonance signal. In the corresponding azaanthracene structure **46**, the singlet from the indicated hydrogen could make NOEs to two *peri* hydrogens.

Antitumor activity

The inhibitory potencies (IC_{50}) of the new compounds related to azonafide and amonafide against a variety of human and murine tumor cells in culture are compared with those of the parent compounds, doxorubicin, and mitoxantrone in Table 1. In this table, the human tumor cell lines include a melanoma; a resistant ovarian carcinoma; a breast carcinoma with strains that are sensitive, resistant to doxorubicin because of P-glycoproteins, and resistant to mitoxantrone; a colon carcinoma including sensitive and multidrug-resistant strains; and a non-small-cell-resistant lung carcinoma. These antitumor potencies were determined by the sulforhodamine B assay. The murine cell line was L1210 leukemia with a sensitive and a multiple drug-resistant (P-glycoprotein positive) strain. Drug potencies against these strains were determined by the MTT assay.

As indicated in Table 1, none of the new compounds is more potent than azonafide (**2**) against tumor cells in the panel. Among the tetrahydroazonafides, potencies vary greatly depending on the substituents. The best compounds are more potent than amonafide (**1**) but less potent than azonafide against solid tumors. Two of these compounds, **14** and **16,** the 4-amino derivative and the parent compound, have high potencies against murine L1210 leukemia, and they are more potent against the

multidrug-resistant (MDR) strain than the sensitive strain. Tetrahydroazonafides **11** and **15** have moderately high potencies against L1210 leukemia, and they also are more potent against the MDR strain.

None of the phenanthrene analogues is as potent as azonafide, which indicates that the bent phenanthrene structure is less desirable than the linear anthracene structure. Compounds **21** and **24**, which have nitro or amino substituents, have moderately good potencies against a variety of tumor cells and are as active against MDR murine leukemia cells as against the sensitive ones. None of the azaphenanthrenes has significant potency against solid tumors. The parent azaphenanthrene (**42**) does have moderate potency against L1210 leukemia cells, especially the MDR strain.

Conclusions

The tetrahydroazonafides are significant because of their high potencies against MDR L1210 leukemia cells and lung carcinoma cells; however, this significance is tempered by lack of potency, compared with azonafide, against the other solid tumors. Overall, their potencies fall between those of amonafide and azonafide, which correlates with their structural feature of a naphthalene chromophore within an anthracene nucleus.

Phenanthrene analogues are less potent than azonafide against tumor cells, indicating that the linear anthracene chromophore is preferred. The azaphenanthrene analogues prepared thus far show no advantages over the phenanthrenes. Despite the last observation, it might be appropriate to prepare some additional azaanthracene analogues of azonafide. For example, compound **46** with a nitrogen atom at the 11 position should be coplanar, and this property might enhance its ability to intercalate DNA compared with azonafide. Azonafide has an 11-hydrogen that encounters steric hindrance from the 1-carbonyl group, resulting in distortion of its nucleus from coplanarity.

Experimental Section

Melting points were recorded on a Mel-Temp apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Brucker WM-250 MHz spectrometer using deuteriochloroform as solvent (unless stated otherwise) and tetramethylsilane as the internal standard. NMR shift values (δ) are expressed in ppm. Elemental analyses were performed by Desert Analytics, Inc., Tucson, AZ.

Preparation of 2-[2′-(Dimethylamino)ethyl]-1,2,8,9,10,-11-hexahydro-4-(trimethylacetyl)amino-3*H*-dibenz[*de,h*]-isoquinoline-1,3-dione (12). 3-(Trimethylacetyl)amino-1,2,7,8,9,10-hexahydrocyclopentano[*de*]anthracene-1,2-dione (**6**) was prepared from **4** as previously described.[2] A suspension of 405 mg of **6** in 20 mL of dioxane and 3 mL of 2 N NaOH was treated at room temperature with 2.5 mL of 30% H_2O_2. The mixture was stirred for 1 h, diluted with 100 mL of water, and then acidified with dilute H_2SO_4. The resulting precipitate was washed well with water and dried in air to give 410 mg (97%) of 2-(trimethylacetyl)aminoanthracene-1,9-dicarboxylic acid anhydride **(9)**. This crude product was used directly in the next step.

A suspension of 1 equiv of **9** in a mixture of ethanol and toluene (1:1) was heated under reflux with 1.4 equiv of *N*,*N*-dimethylethylenediamine for 24 h. The solvent was evaporated and the residue was crystallized from hexanes to afford an 86% yield of **12** (based on **9**) as crystals: mp 144−146 °C; ^{1}H NMR 1.43 (s, 9, CH_3), 1.85−1.92 (m, 4, H-9 + H-10), 2.37 (s, 6, NCH_3), 2.61−2.66 (t, 2, NCH_2), 3.02−3.06 (t, 2, H-8), 3.57−3.61 (t, 2, H-11), 4.33−4.38 (t, 2, $CONCH_2$), 7.81 (s, 1, H-7), 7.99−8.03 (d, 1, H-5), 9.11−9.14 (d, 1, H-6), 13.22 (s, 1, NH). Anal. ($C_{25}H_{31}N_3O_3$) C, H, N.

Preparation of 2-[2′-(Dimethylamino)ethyl]-1,2,8,9,10,-11-hexahydro-5-(trimethylacetylamino)-3*H*-dibenz[*de,h*]-isoquinoline-1,3-dione (13). This compound was prepared from 4-(trimethylacetyl)-1,2,7,8,9,10-hexahydrocyclopentano-[*de*]anthracen-1,2-dione (**7**)[4] by the procedure described above for **12**. The intermediate 3-(trimethylacetyl)aminoanthracene-1,9-dicarboxylic acid anhydride **(10)** was obtained in 64% crude yield. It was converted directly into **13**, which was obtained in 88% yield (based on anhydride **10)**. After purification by PTLC on silica gel with 7.5% CH_3OH in $CHCl_3$ as solvent, followed by crystallization from hexanes containing the least amount of toluene, it had: mp 176−178 °C; ^{1}H NMR 1.41 (s, 9, CH_3), 1.83−1.89 (m, 4, H-9 + H-10), 2.36 (s, 6, NCH_3), 2.59−2.64 (t, 2, CH_2N), 2.96−3.00 (t, 2, H-8), 3.44−3.48 (t, 2, H-11), 4.24−4.28 (t, 2, $CONCH_2$), 7.65 (s, 1, H-7), 7.97 (s, 1, NH), 8.056−8.064 (d, 1, H-4, $J_{4,6}$ = 2.278), 8.626−8.633 (d, 1, H-6, $J_{6,4}$=2.274). For analysis, **13** was converted into its hydrochloride salt, which crystallized from methanol as a sesquihydrate: mp 256 °C dec. Anal. ($C_{25}H_{31}N_3O_3$·1.5H_2O) C, H, N.

Preparation of 4-Acetylamino-2-[2′-(dimethylamino)-ethyl]-1,2,8,9,10,11-hexahydro-3*H*-dibenz[*de,h*]isoquino-line-1,3-dione (11). A solution of 0.97 g of 7-amino-1,2,3,4-tetrahydroanthracene[2] in 25 mL of dry THF containing 1.5 mL of triethylamine was stirred at room temp for 8 h with 1 mL of acetic anhydride. The solvent was evaporated and the residue was treated with water and allowed to stand overnight. The solid that formed was collected by filtration and then crystallized from toluene−hexanes (1:1) to give 0.8 g (68%) of 2-acetylamino-5,6,7,8-tetrahydroanthracene (**3**): mp 157−158 °C; ^{1}H NMR 1.84 (br s, 4, H-2 + H-3), 2.2 (s, 3, CH_3), 2.92−3.03 (br d, 4, H-1 + H-4), 7.32−7.34 (s, 1, H-6), 7.44 (s, 1, H-9), 7.45 (s, 1, H-10), 7.5 (br s, 1, NH), 7.62−7.63 (d, 1, H-5), 8.01 (s, 1, H8). Anal. ($C_{16}H_{17}NO_3$·1.5H_2O) C, H, N.

Friedel−Crafts acylation of **3** with oxalyl chloride, following the procedure described in the literature for preparation of **6**,[2] gave 3-acetylamino-7,8,9,10-tetrahydroaceanthralene (**5**) as the sole isomer in 10% yield: mp 229−231 °C (after recrystallization from methanol containing the least amount of dioxane); ^{1}H NMR 1.87−1.93 (m, 4, H-8 + H-9), 2.34 (s, 3, CH_3), 3.00−3.07 (t, 2, H-7), 3.36−3.42 (t, 2, H-10), 7.78 (s, 1, H-6), 7.98−8.02 (d, 1, H-4), 8.74−8.77 (d, 1, H-5), 9.45 (br s, 1, NH).

Without further purification, **5** was converted directly into crude 2-acetylaminoanthracene-1,9-dicarboxylic acid anhydride **(8)** in 59% yield by the procedure described for **9**, and then **8** was converted into **11** by the procedure described for **12**. After purification by PTLC on silica gel with 5% methanol in chloroform as solvent, an 87% yield of **11** (based on **8**) was obtained: mp 174−176 °C (after crystallization from hexanes containing the least amount of toluene); ^{1}H NMR 1.82−1.92 (m, 4, H− 9 + H-10), 2.37 (s, 3, $COCH_3$), 2.38 (s, 6, CH_3), 2.60−2.66 (t, 2, NCH_2), 3.01−3.06 (t, 2, H-8), 3.55−3.60 (t, 2, H-11), 4.30−4.36 (t, 2, $CONCH_2$), 7.80 (s, 1, H-7), 7.97−8.01 (d, 1, H-5), 9.02−9.06 (d, 1, H-6), 12.97 (s, 1, NH). Anal. ($C_{22}H_{25}N_3O_3$·1.5H_2O) C, N; H: calcd, 6.89; found, 6.07.

Preparation of 4-Amino-2-[2′-(dimethylamino)ethyl]-1,2,8,9,10,11-hexahydro-3*H*-dibenz[*de,h*]isoquinoline-1,3-dione (14). A mixture of 35 mg (0.08 mol) of **12**, 15 mL of ethanol, and 2 mL of 37% HCl was heated under reflux for 20 h and then concentrated. The residue was dissolved in methanol, made slightly alkaline with methanolic NaOH and then concentrated under reduced pressure. The solid residue was purified by PTLC on silica gel with 5% methanol in chloroform as solvent. This procedure gave 22 mg (79%) of **14**: mp 197−199 °C (after crystallization from toluene−hexanes (1:1)); ^{1}H NMR 1.80−1.91 (m, 4, H-9 + H-10), 2.39 (s, 6, CH_3), 2.62−2.67 (t, 2, NCH_2), 2.94−2.98 (t, 2, H-8), 3.55−3.59 (t, 2, H-11), 4.31−4.36 (t, 2, $CONCH_2$), 6.81−6.84 (d, 1, H-5), 7.61 (s, 1, H-7), 7.65−7.68 (d, 1, H-6). Anal. ($C_{20}H_{23}N_3O_2$) C, H, N.

Preparation of 5-Amino-2-[2′-(dimethylamino)ethyl]-1,2,8,9,10,11-hexahydro-3*H*-dibenz[*de,h*]isoquinoline-1,3-

dione (15). This compound was prepared from **13** in 84% yield using the procedure described for **14**. After crystallization from hexanes containing the least amount of toluene it had: mp 184−185 °C; ^{1}H NMR 1.82−1.90 (m, 4, H-9 + H-10), 2.37 (s, 6, CH_3), 2.61−2.66 (t, 2, NCH_2), 2.99−3.03 (t, 2, H-8), 3.50−3.54 (t, 2, H-11), 4.05 (s, 2, NH_2), 4.29−4.34 (t, 2, $CONCH_2$), 7.17−7.18 (d, 1, H-4), 7.64 (s, 1, H-7), 7.97−7.98 (d, 1, H-6); HRMS (FAB$^+$) calcd for $C_{20}H_{23}N_3O_2{\cdot}H^+$ 338.1868, found MH^+ 338.1866.

Preparation of 2-[2′-(Dimethylamino)ethyl]-1,2,8,9,10,-11-hexahydro-3*H*-dibenz[*de,h*]isoquinoline-1,3-dione (16). A solution of 45 mg (0.65 mmol) of sodium nitrite in 1 mL of water was added at 0 °C to a solution of 200 mg (0.59) of **14** in 10 mL of 37% HCl. After stirring at 0 °C for 1 h and at room temperature for 15 min, the mixture was heated under reflux for 1 h. It was then concentrated to dryness and the residue was dissolved in methanol. The solution was neutralized with excess solid $NaHCO_3$ and then filtered. The filtrate was evaporated to dryness and the residue was purified by PTLC on silica gel with 5% methanol in chloroform to give in the first band 40 mg (21%) of **16**: mp 122−124 °C (after crystallization from hexanes); ^{1}H NMR 1.82−1.95 (m, 4, H-9 + H-10), 2.41 (s, 6, CH_3), 2.67−2.72 (t, 2, NCH_2), 3.03−3.07 (t, 2, H-8), 3.54−3.58 (t, 2, H-11), 4.31−4.36 (t, 2, $CONCH_2$), 7.59−7.64 (t, 1, H-5), 7.85 (s, 1, H-7), 8.00−8.04 (d, 1, H-4), 8.49−8.52 (d, 1, H-6). Anal. ($C_{20}H_{22}N_2O_2{\cdot}HCl{\cdot}0.25H_2O$) C, H, N.

Unreacted starting material (8 mg, 4%) was recovered from the second band.

Preparation of 5-[2′-(Dimethylamino)ethyl]-5,6-dihydro-4*H*-dibenz[*de,g*]isoquinoline-4,6-dione (20). A suspension of 124 mg (0.5 mmol) of phenanthrene-8,9-dicarboxylic acid anhydride (**17**)[9] in 40 mL of toluene was heated under reflux for 2 h with a solution of 52 mg (0.7 mmol) of *N*,*N*-dimethylethylenediamine in 5 mL of ethanol. The solvent was removed and the residue (135 mg, 85% crude yield) was crystallized from hexanes−toluene (2;1) to afford **20** as pale yellow crystals: 159−161 °C; ^{1}H NMR 2.38 (s, 6, CH_3), 2.66−22.71 (t, 2, NCH_2), 4.33−4.38 (t, 2, $CONCH_2$), 7.69−7.75 (t, 1, H-9), 7.8−7.88 (m, 2, H-2 + H-10), 8.07−8.11 (d, 1, H-8), 8.58−8.61 (d, 1, H-3), 8.65−8.68 (d, 1, H-11), 8.88−8.91 (s over d, 2, H-1 + H-7). Anal. ($C_{20}H_{18}N_2O_2$) C, H, N.

Preparation of 5-[2′-(Dimethylamino)ethyl]-5,6-dihydro-8-nitro-4*H*-dibenz[*de,g*]isoquinoline-4,6-dione (21) and 5-[2′-(Dimethylamino)ethyl]-5,6-dihydro-11-nitro-4*H*-dibenz[*de,g*]isoquinoline-4,6-dione (23). To a stirred solution of 1.534 g (6.18 mmol) of **17** in 100 mL of concentrated H_2SO_4 was added at −10 °C a solution of 640 mg (7.11 mmol) of 70% HNO_3 in 4 mL of concentrated H_2SO_4. The mixture was stirred at −5 to −10 °C for 15 min and then poured into ice water. The yellow precipitate containing nitro derivatives **18** and **19** that formed (1.65 g) was collected, washed with water and dried in air. It was then suspended in 80 mL of absolute ethanol and 40 mL of toluene, treated with 644 mg (7.32 mmol) of *N*,*N*-dimethylenediamine, and the mixture was heated at reflux for 16 h. The solvent was evaporated and the residue was purified by chromatography on a silica gel column with 5% methanol in chloroform as solvent. The resulting 715 mg of yellow solid was resolved into its two components by PTLC on silica gel with toluene−methanol (9:1) (or with $CHCl_3$−Et_3N, 140:1.3) as solvent. The first yellow fraction gave 359 mg (18%) of **21**: mp 203−205 °C (after crystallization from methanol); ^{1}H NMR 2.39 (s, 6, CH_3), 2.7−2.73 (t, 2, NCH_2), 4.36−4.41 (t, 2, $CONCH_2$), 7.92−8.03 (m, 2, H-2 + H-10), 8.30−8.34 (d, 1, H-9), 8.72−8.75 (d, 1, H-11), 8.97−9.04 [t (d over d), 2, H-1 + H-3], 9.49 (s, 1, H-7). Anal. ($C_{20}H_{17}N_3O_4{\cdot}H_2O$) C, H, N.

The second yellow band gave 352 mg (17%) of **23** as a yellow solid: mp 220−222 °C; ^{1}H NMR 2.37 (s, 6, CH_3), 2.67−2.72 (t, 2, NCH_2), 4.34−4.40 (t, 2, $CONCH_2$), 7.77−7.87 (m, 2, H-2 + H-9), 7.92−8.03 (d, 1, H-8), 8.39−8.43 (d, 1, H-3), 8.68−8.72 (d, 1, H-1), 8.97 (s, 1, H-7). Anal. ($C_{20}H_{17}N_3O_4{\cdot}0.5H_2O$) C, H; N: calcd, 11.29; found, 10.17.

Preparation of 8-Amino-5-[2′-(dimethylamino)ethyl]-5,6-dihydro-4*H*-dibenz[*de,g*]isoquinoline-4,6-dione (22). This compound was prepared from **21** in 78% yield by catalytic hydrogenation using 10% Pd/C in a methanol−acetic acid mixture at room temperature and a hydrogen pressure of 40 psi for 4 h. Purification by PTLC on silica gel with chloroform−methanol (9:1) as solvent gave **22**: mp > 360 °C; ^{1} H NMR 2.40 (s, 6, CH_3), 2.71−2.76 (t, 2, NCH_2), 4.34−4.40 (t, 2, $CONCH_2$), 4.49 (s, 2, NH_2), 7.19−7.22 (d, 1, H-9), 7.49−7.62 (m,2, H-2 + H-10), 7.77−7.84 (t, 1, H-2), 8.54−8.57 (d, 1, H-3), 8.83 (s, 1, H-7), 9.54−9.58 (d, 1, H-1); HRMS (FAB$^+$) calcd for $C_{20}H_{19}N_3O_2{\cdot}H^+$ 334.1555, found MH^+ 334.1560.

Preparation of 11-Amino-5-[2′-(dimethylamino)ethyl]-5,6-dihydro-4*H*-dibenz[*de,g*]isoquinoline-1,3-dione (24). This compound was prepared from **23** by the method described above for **22**. A 78% yield of product was obtained: mp 227−229 °C; ^{1}H NMR 2.41 (s, 6, CH_3), 2.72−2.77 (t, 2, NCH_2), 4.34−4.40 (t, 2, $CONCH_2$), 4.74 (s, 2, NH_2), 6.90−6.94 (d, 1, H-10), 7.51−7.57 (t, 1, H-9), 7.74−7.80 (t, 1, H-2), 7.94−7.98 (d, 1, H-8), 8.52−8.55 (d, 1, H-3), 8.77−8.81 (d, 1, H-1), 8.96 (s, 1, H-7); HRMS (FAB$^+$) calcd for $C_{20}H_{19}N_3O_2{\cdot}H^+$ 334.1555, found 334.1556.

Preparation of 8-Chloro-5-[2′-(dimethylamino)ethyl]-5,6-dihydro-4*H*-dibenz[*de,g*]isoquinoline-4,6-dione (25) and 5-[2′-(Dimethylamino)ethyl]-5,6-dihydro-8-hydroxy-4*H*-dibenz[*de,g*]isoquinoline-4,6-dione (26). To a cold (0 °C) solution of 258 mg (0.775 mmol) of **22** in 14 mL of 37% HCl was added a solution of 63 mg (0.913 mmol) of sodium nitrite in 0.5 mL of water. The mixture was stirred at 0 °C for 1 h, then at room temperature overnight, and finally at 85 °C for 0.5 h. The mixture was neutralized with solid $NaHCO_3$ and extracted with chloroform. This extract was concentrated and the residue was purified by PTLC on silica gel with 3% methanol in chloroform as solvent. The first band gave 93 mg (34%) of **25**: mp 179−181 °C (after crystallization from methanol); ^{1}H NMR 2.41 (s, 6, CH_3), 2.71−2.77 (t, 2, NCH_2), 4.34−4.40 (t, 2, $CONCH_2$), 7.58−7.64 (t, 1, H-10), 7.82−7.93 [m (d over t), 2, H-2 + H-9], 8.01−8.05 (d, 1, H-11), 8.64−8.68 (d, 1, H-3), 8.87 (s, 1, H-7), 10.17−10.21 (d, 1, H-1). Anal. ($C_{20}H_{17}ClN_2O_2$) C, H, N.

The second band afforded 37 mg (14%) of **26**: mp 260−265 °C (after crystallization from methanol); ^{1}H NMR ($CDCl_3$ + DMSO-d_6) 2.39 (s, 6, CH_3), 2.70−2.75 (t, 2, NCH_2), 4.27−4.33 (t, 2, $CONCH_2$), 7.25−7.28 (t, 1, H-9), 7.48−7.55 [m, 2, H-10 + H-11], 7.64−7.70 (t, 1, H-2), 8.32−8.35 (d, 1, H-3), 8.64 (s, 1, H-7), 9.84−9.88 (d, 1, H-1), 11.20 (br s, 1, OH); HRMS (EI) calcd for $C_{20}H_{18}N_2O_3$ 334.13742, found M^+ 334.131700.

Preparation of 11-Chloro-5-[2′-(dimethylamino)ethyl]-5,6-dihydro-4*H*-dibenz[*de,g*]isoquinoline-4,6-dione (28) and 5-[2′-(Dimethylamino)ethyl]-5,6-dihydro-11-hydroxy-4*H*-dibenz[*de,g*]isoquinoline-4,6-dione (29). These two compounds were prepared from **24** following the procedure described for **25** and **26**. The first band on the PTCL plate gave **28** in 22% yield: mp 178−181 °C (after crystallization from methanol−ether); ^{1}H NMR 2.40 (s, 6, CH_3), 2.70−2.75 (t, 2, NCH_2), 4.34−4.40 (t, 2, $CONCH_2$), 7.72−7.80 (m, 2, H-9 + H-10), 7.85−7.91 (t, 1, H-2), 8.56−8.59 (d, 1, H-8), 8.85−8.88 (d, 1, H-1), 9.33 (s, 1, H-7). Anal. ($C_{20}H_{17}ClN_2O_2{\cdot}0.5H_2O$) C, H, N.

From the second band was obtained a 16% yield of **29**, which was crystallized from the methanol containing the least amount of chloroform. It decomposed without melting above 200 °C: ^{1}H NMR ($CDCl_3$ + CF_3COOD) 3.14 (s, 6, CH_3), 3.65−3.73 (t, 2, NCH_2), 4.65−4.73 (t, 2, $CONCH_2$), 7.48−7.51 (s over d, 2, H-10 + OH), 7.88−7.94 (t, 1, H-9], 8.00−8.08 (t, 1, H-2), 8.50−8.53 (d, 1, H-8), 8.57−8.61 (d, 1, H-3), 8.83 (s, 1, H-7), 8.89−8.93 (d, 1, H-1); HRMS (EI) calcd for $C_{20}H_{18}N_2O_3$ 334.13742, found M^+ 334.132100.

Preparation of 5-[2′-(Dimethylamino)ethyl]-5,6-dihydro-8-methoxy-4*H*-dibenz[*de,g*]isoquinoline-4,6-dione (27). A solution of 26 mg (0.08 mmol) of **26** in 30 mL of chloroform and 30 mL of anhydrous methanol was treated with excess etherial diazomethane. The mixture was stirred at 0 °C for 3 h and then stored in a refrigerator overnight. After further stirring at 0 °C for 2 h, the solvent was removed and the residue was purified by PTLC on silica gel with 5% methanol

in chloroform (or 15% methanol in toluene) as solvent. This procedure gave 16 mg (59%) of **27** which was crystallized from a mixture of hexanes−toluene−methanol (least amount). It gave a dihydrochloride salt: mp 252−255 °C; ^{1}H NMR (free base) 2.41 (s, 6, CH_3), 2.71−2.78 (t, 2, NCH_2), 4.18 (s, 3, OCH_3), 4.34−4.40 (t, 2, $CONCH_2$), 7.31−7.35 (d, 1, H-9), 7.62−7.74 (m, 2, H-10 + H-11), 7−77−7.84 (t, 1, H-2), 8.57−8.62 (d, 1, H-3), 8.87 (s, 1, H-7), 9.88−9.91 (d, 1, H-1); HRMS (EI) calcd for $C_{21}H_{20}N_2O_3$ 348.147390, found M^+ 348.147500.

Preparation of 1,2-Dihydroindenoquinolines 33−36. A mixture of 8.0 g of 5-aminoacenaphthene (**30**), 12.6 g of glycerol, 10.5 g of As_2O_5, and 13.5 g of H_2SO_4 (95−99%) was heated under gentle reflux for 1 h. It was then cooled and basified with aqueous ammonia. The resulting precipitate was collected, washed with water, dried, and extracted with boiling chloroform. This extract was concentrated and the residue was purified by chromatography on a column of neutral alumina with hexanes−benzene (1:1) as solvent. This procedure gave 3.5 g (36%) of 1,2-dihydroindeno[1,7-*gh*]quinoline **33**: mp 58−59 °C (after crystallization from *n*-pentane); ^{1}H NMR 3.34 (m, 4, CH_2), 7.37 (s, 1, H-10), 7.42−7.47 (q, 1. H-8), 7.65−7.71 (t, 1, H-4), 8.06−8.10 (dd, 1, H-9, $J_{9,8} = 8.091$, $J_{9,7} = 1.716$), 8.72−8.75 (d, 1, H-5), 8.89−8.91 (dd, 1, H-7, $J_{7,8} = 4.395$, $J_{7,9} = 1.707$). Anal. ($C_{15}H_{11}N$) C, H, N.

In a similar manner, 1,2-dihydroindeno[1,7-*fg*]quinoline (**34**) was prepared from 4-aminoacenaphthene (**31**)[11] in 40% yield. After PTLC on silica gel with 3% methanol in chloroform as solvent and crystallization from *n*-pentane, it had: mp 120−122 °C; ^{1}H NMR 3.34 (m, 4, CH_2), 7.43−7.46 (q, 1, H-7), 7.47−7.49 (d, 1, H-3), 7.60−7.65 (t, 1, H-4), 7.72 (s, 1, H-10), 8.20−8.23 (d, 1, H-6), 8.78−8.81 (d, 1, H-5), 8.88−8.91 (dd, 1, H-8). Anal. ($C_{15}H_{11}N$) C, H, N.

3-Amino-1,2-dihydroindeno[1,7-*gh*]quinoline (**35**) was prepared from **32** according to the literature procedure.[10] It was then converted into its acetyl derivative **36** in quantitative yield by acetic anhydride in THF: mp 226−227 °C (after crystallization from methanol); ^{1}H NMR ($CDCl_3$ + DMSO-d_6) 2.22 (s, 3, CH_3), 3.39 (m, 4, CH_2), 7.45−7.50 (q, 1, H-8), 7.94−7.97 (d, 1. H-4), 8.12−8.15 (d, 1, H-9), 8.61−8.63 (s, 1, H-5), 8.84−8.86 (d, 1, H-7), 9.55 (s, 1, NH). Anal. ($C_{17}H_{14}N_2O$) C, H, N.

Preparation of Benzo[*f*]quinoline-6,7-dicarboxylic Acid Anhydride (40). A solution of 0.8 g of **34** in 10−15 mL of acetic acid and 4.5 g of powdered $Na_2Cr_2O_7$ was stirred and heated on a steam bath for 4 h. The mixture was then diluted with excess water and the precipitate that formed was collected and washed well with water. This procedure gave 745 mg (82%) of indeno[1,7-*fg*]quinoline-1,2-dione **37**: mp 333−335 °C (after crystallization from acetic acid); ^{1}H NMR (DMSO-d_6) 7.95−7.99 (q, 1, H-7), 8.09−8.14 (t, 1, H-4), 8.60−8.62 (d, 1, H-6), 8.88 (s, 1, H-10), 9.19−9.20 (d, 1, H-8), 9.36−9.38 (d, 1, H-3) 9.41−9.44 (d, 1, H-5).

Without further purification, a suspension of 500 mg of **37** in 10 mL of dioxane and 3 mL of 2 N NaOH was treated with 3 mL of 30% H_2O_2 and the mixture was stirred at room temperature for 45 min. The mixture was diluted with water, acidified with dilute H_2SO_4 to pH. 6, and the yellow precipitate was collected. Crystallization from acetic acid gave 516 mg (97%) of **40**: mp 338−340 °C; ^{1}H NMR (DMSO-d_6 + CF_3-COOD) 8.11−8.16 (t, 1, H-9), 8.21−8.25 (q, 1, H-2), 8.66−8.68 (d, 1, H-1), 9.03 (s, 1, H-5), 9.38−9.39 (d, 1, H-3), 9.40−9.42 (d, 1, H-8) 9.81−9.84 (d, 1, H-10). Anal. ($C_{15}H_7NO_3$) C, H, N.

Preparation of 8-Acetylaminobenzo[*f*]quinoline-6,7-dicarboxylic Acid Anhydride (41). Compound **36** was converted into dione **38** by the procedure described for **37**. The crude dione was obtained in 659 mg (74%) yield from 0.8 g of **36**. It had mp 339−341 °C and was insoluble in common organic solvents. Without further purification, it was converted into **41** by the procedure described above for **40**, except that the reaction mixture had to be filtered after it was diluted with water. From 500 mg of **38** was obtained 408 mg (77%) of **41**: mp 350−352 °C; ^{1}H NMR (DMSO-d_6) 2.36 (s, 3, CH_3), 7.85−7.89 (q, 1, H-3), 8.82−8.85 (d, 1, H-9), 9.12−9.16 (s over d, 2, H-4 + H-5), 9.23−9.24 (s, 1, H-2), 9.52−9.55 (d, 1, H-10), 11.38 (s, 1, NH). Anal. ($C_{17}H_{10}N_2O_4$) C, H, N.

Preparation of Benzo[*h*]quinoline-6,7-dicarboxylic Acid Anhydride (39). A solution of 1.0 g of **33** in 10 mL of acetic acid and 4.5 g of powdered $Na_2Cr_2O_7$ was stirred and heated on a steam bath for 4 h. The mixture was then diluted with excess water and the precipitate that formed was collected and washed well with water. This procedure gave 750 mg (82%) of **39**: mp 330−332 °C (after crystallization from toluene); ^{1}H NMR (DMSO-d_6) 7.90−7.94 (q, 1, H-3), 8.08−8.14 (t, 1, H-9), 8.63−8.66 (d, 1, H-4), 8.84−8.87 (s, 1, H-8), 9.11 (s, 1, H-5), 9.25−9.27 (d, 1, H-2) 9.53−9.56 (d, 1, H-10). Anal. ($C_{15}H_7NO_3$) C, H, N.

Preparation of 5-[2′-(Dimethylamino)ethyl]-5,6-dihydro-4*H*-quinolino[6,7,8-*de*]isoquinoline-4,6-dione (42). A suspension of one equivalent of **39** and 1.25−1.4 equiv of *N*,*N*-dimethylethylenediamine in a toluene−ethanol mixture (2:1) was heated under reflux for 18 h and then allowed to cool. The resulting clear solution was concentrated to dryness and the residue was purified by PTLC on silica gel with 5% methanol in chloroform as solvent. Crystallization of the product from methanol gave 53% of **42**: mp 150−152 °C; ^{1}H NMR 2.38 (s, 6, CH_3), 2.67−2.72 (t,2, NCH_2), 4.35−4.40 (t, 2, $CONCH_2$), 7.66−7.70 (q, 1, H-9), 7.93−7.98 (t, 1, H-2), 8.40−8.43 (d, 1, H-8), 8.70−8.72 (d, 1, H-3), 8.90 (s, 1, H-7), 9.14−9.16 (d, 1, H-10), 9.52−9,55 (d, 1, H-1). The dihydrochloride salt was used for microanalysis. Anal. ($C_{15}H_{17}N_3O_2$·2HCl·0.75H_2O) C, H, N.

Preparation of 5-[2′-(Dimethylamino)ethyl]-5,6-dihydro-4*H*-quinolino[7,6,5-*de*]isoquinoline-4,6-dione (43). This compound was prepared by the procedure described for **42.** It was obtained in 60% yield from **40**: mp 190−192 °C (after crystallization from methanol); ^{1}H NMR 2.38 (s, 6, CH_3), 2.69−2.73 (t,2, NCH_2), 4.35−4.40 (t, 2, $CONCH_2$), 7.73−7.77 (q, 1, H-10), 7.91−7.96 (t, 1, H-2), 8.66−8.68 (d, 1, H-3), 8.87−8.90 (d, 1, H-1), 8.96−9.00 (d, 1, H-11), 9.11 (s, 1, H-7), 9.13−9.14 (d, 1, H-9). Irradiation of H-7 showed no NOE to a *peri* proton resonance signal, thus supporting structure **43** over its linear isomer **46**. The compound was converted into its dihydrochloride salt for analysis: mp 254−257 °C dec. Anal. ($C_{19}H_{17}N_3O_2$·2HCl·2H_2O) C, H, N.

Preparation of 3-Acetylamino-5-[2′-(dimethylamino)-ethyl]-5,6-dihydro-4*H*-quinolino[6,7,8-*de*]isoquinoline-4.6-dione (44). This compound was prepared by the procedure described for **42.** It was obtained in 76% yield from **41**: mp 270−272 °C (after crystallization from toluene−ethanol (1:1)); ^{1}H NMR 2.38 (s, 6, CH_3), 2.40 (s, 3, CH_3CO), 2.65−2.69 (t,2, NCH_2), 4.32−4.36 (t, 2, $CONCH_2$), 7.60−7.64 (q, 1, H-9), 8.34−8.37 (d, 1, H-8), 8.89 (s, 1, H-7), 9.11−9.13 (d, 1, H-10), 9.23−9.27 (d, 1, H-2), 9.42−9.45 (d, 1, H-1). Anal. ($C_{21}H_{20}N_4O_3$) C, H, N.

Preparation of 3-Amino-5-[2′-(dimethylamino)ethyl]-5,6-dihydro-4*H*-quinolino[6,7,8-*de*]isoquinoline-4.6-dione (45). A mixture of 115 mg (0.3 mmol) of **44**, 30 mL of absolute ethanol, and 30 mL of 37% HCl was heated under reflux for 48 h and then evaporated to dryness. The residue was dissolved in 5 mL of water and made basic with dilute KOH solution, whereupon **45** crystallized in 95 mg (93%) yield: mp 224−226 °C (after recrystallization from toluene); ^{1}H NMR ($CDCl_3$ + DMSO-d_6) 2.38 (s, 6, CH_3), 2.64−2.69 (t,2, NCH_2), 4.30−4.35 (t, 2, $CONCH_2$), 7.22−7.25 (d, 1, H-2), 7.48−7.53 (q, 1, H-9), 8.32−8.35 (d, 1, H-8), 8.82 (s, 1, H-7), 9.00−9.02 (d, 1, H-10), 9.07−9.10 (d, 1, H-1). Elemental analysis was determined on the HCl salt, which was prepared by treating a solution of the base in ethanol with excess HCl and concentrating the mixture to dryness. Anal. ($C_{19}H_{18}N_4O_2$·2HCl·1.25H_2O) C, H, N.

Acknowledgment. This project was supported by Grant GM 52795 awarded by the National Institute of General Medical Sciences, DHHS, and by a grant from the AmpliMed Corp., Tucson, AZ. We thank Dr. Neil Jacobsen at the University of Arizona Chemistry Department for 2D-NMR studies.

Supporting Information Available: ^{1}H NMR spectra of compounds **15**, **22**, **24**, **26**, **27**, and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM9905817