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Synthesis and structure–activity relationship studies of 4,11-diaminonaphtho[2,3-*f*]indole-5,10-diones

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Abstract—We describe the synthesis of derivatives of 4,11-diaminonaphtho[2,3-*f*]indole-5,10-dione and their cytotoxicity for human tumor cells that express major determinants of altered anticancer drug response, the efflux pump P-glycoprotein, and non-functional p53. Nucleophilic substitution of methoxy groups in 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione with various ethylenediamines yielded the derivatives of 4,11-diaminonaphtho[2,3-*f*]indole-5,10-dione, the indole containing analogues of the antitumor agent ametantrone. The cytotoxicity of novel compounds for multidrug resistant, P-glycoprotein-expressing tumor cells is highly dependent on the N-substituent at the terminal amino group of the ethylenediamine moiety. Whereas p53 null colon carcinoma cells were less sensitive to the reference drug doxorubicin than their counterparts with wild type p53, the majority of novel naphthoindole derivatives were equally potent for both cell lines, regardless of the p53 status.

1. Introduction

The anthracycline antibiotics, primarily adriamycin (**ADR**, doxorubicin, **1**), have the broadest range of utility among all anticancer drugs in current clinical practice.[1] However, their usage is limited by organ toxicities (mostly dose-limiting heart and bone marrow toxicity) and by emergence of multidrug resistance (MDR) in tumor cells. In an effort to design more efficacious antineoplastic agents with attenuated cardiotoxicity, new generations of synthetic analogues of anthracyclines have been developed. These include the derivatives of anthracene-9,10-dione (mitoxantrone **2** and ametantrone **3**[2]), their aza-analogues (pixantrone[3]), and anthrapyrazoles (loxanthazol[4]). Nevertheless, MDR cells are frequently resistant to the majority of these agents. This fact seriously limits the therapeutic potential of the above drugs.[5] We report here the studies of novel derivatives of naphtho[2,3-*f*]indole-5,10-dione with improved activity against MDR cells.

Recently, we have reported on the synthesis and cytotoxic properties of 1- or 3-(aminoalkyl) derivatives of 4,11-dihydroxynaphtho[2,3-*f*]indole-5,10-dione (**4**) prepared from substituted 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-diones (**5**) by demethylation reactions.[6,7] Compound **4** can be considered as a heterocyclic analogue of the aglycon of anthracycline antibiotics in which the pyrrole cycle substitutes the cyclohexane (**A**) ring. In this paper, we present the synthesis and biological properties of a series of 4,11-di(2-aminoethylamino)naphtho[2,3-*f*]indole-5,10-diones, the indole containing analogues of the antitumor agent ametantrone. In contrast to anthracyclines, ametantrone, a derivative of 1,4-diaminoanthraquinone, does not generate superoxide production and lipid microsomal peroxidation, possesses potent antioxidant properties and does not cause cardiotoxicity.[8] Pixantrone, a heterocyclic aza-analogue of ametantrone, showed low cardiotoxicity in clinical trials.[3] These data provide further evidence for the importance of amino groups (in comparison to hydroxy groups) adjacent to quinone moiety

Keywords: Naphthoindolediones; Nucleophilic substitution of methoxy group; Ametantrone; Cytotoxicity; P-glycoprotein; p53; Drug resistance; Tumor cells.
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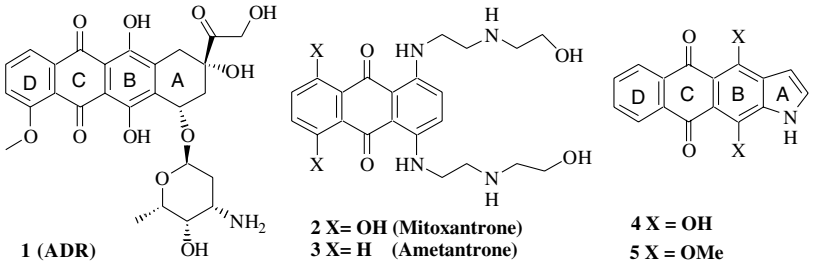


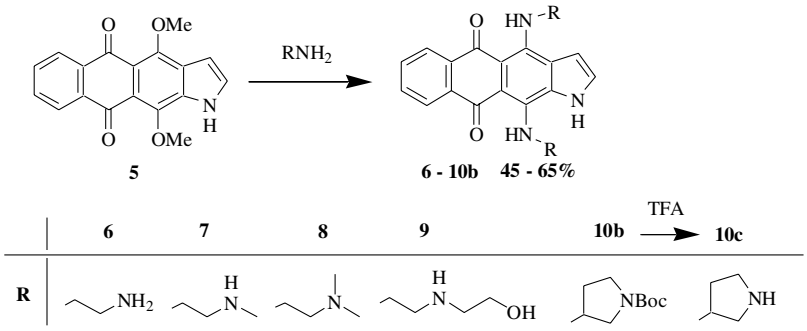
of anthracyclines for milder side effects (e.g., cardiotoxicity). One can hypothesize that the introduction of an additional pyrrole ring A in the ametantrone moiety would lead to redistribution of charges in the chromophore, which, in turn, should influence drug–DNA interactions. Given that the expression of transmembrane transporter P-glycoprotein (Pgp) and inactivation of p53 mediated death pathway(s) are the major factors of cell survival during chemotherapy,[9] we investigated the potency of novel compounds for human tumor cell lines with genetically defined determinants of anticancer drug response.

2. Results and discussion

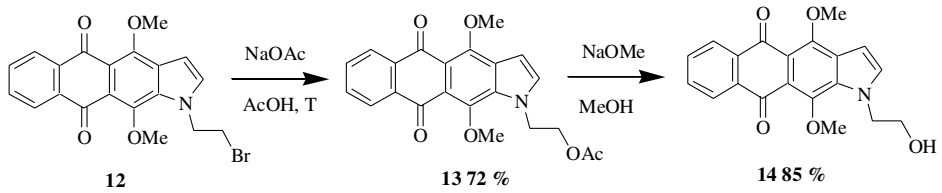
2.1. Chemistry

A traditional approach to the synthesis of 1,4-diaminoanthracene-9,10-diones from leuko derivatives of 1,4-dihydroxyanthracene-9,10-diones (e.g., quinizarine) used for the preparation of 4,11-diaminonaphtho[2,3-*f*]indole-5,10-diones failed because we could not obtain the leuko form of pyrroloquinizarine **4**. An alternative pathway to the synthesis of 1,4-diaminoanthraquinones and their analogues is based on the reactions of S_NAr substitution. We used the property of anthracene-9,10-dione moiety in which N-nucleophiles displace not only 'good'[10] leaving groups (such as halogens, sulfo- and nitro groups) but also 'poor' leaving groups (hydroxy, aryloxy, and alkoxy groups, and hydride ion). Aromatic substitution of methoxy groups by amines is seldom used for the synthesis of aminoanthracene-9,10-diones.[11,12] We demonstrated the efficacy of similar approach based on the use of methoxynaphtho[2,3-*f*]indole-5,10-diones for the preparation of derivatives of aminonaphtho[2,3-*f*]indole-5,10-diones. 4,11-Dimethoxynaphtho[2,3-*f*]indole-5,10-dione (**5**) reacted with primary alkylamines under milder conditions than 4,11-dimethoxyanthracene-9,10-dione, which reacts with primary alkylamines under photolytic conditions.[12] This is probably due to an additional stabilization of the S_NAr reaction intermediate, the Meisenheimer ion, by heterocyclic ring in naphthoindolediones. Therefore, the reaction of naphthoindoledione **5** with ethylenediamine and its derivatives is a convenient method for the preparation of corresponding derivatives of 4,11-diaminonaphtho[2,3-*f*]indole-5,10-diones **6**–**9** (Scheme 1). The reactivity of ethylenediamines as nucleophiles in substitution reaction of S_NAr-type with naphthoindole **5** is decreased in the following sequence: ethylenediamine > *N*-methylethylenediamine > *N*,*N*-dimethylethylenediamine. The methoxy groups in naphthoindole **5** can also be substituted by secondary amines. This can explain the formation of mixture of products which was difficult to separate when naphthoindole **5** was treated with 3-aminopyrrolidine. To diminish the side reactions, we used 3-amino-Boc-pyrrolidine **10a**, which reacted with naphthoindole **5** significantly slower than ethylenediamine or its *N*-alkyl derivatives. After boiling in dioxane with Boc-derivative **10a** for several days, compound **10b** was obtained. Subsequent cleavage of protecting group with trifluoroacetic acid led to di(pyrrolidin-3-yl)derivative **10c**.

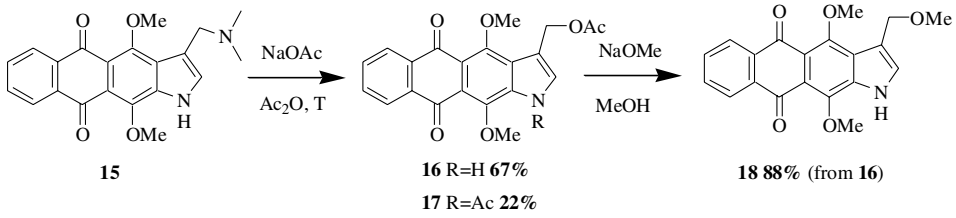
To address the role of substituents in the pyrrole fragment for antiproliferative activity, we synthesized a series of 1- and 3-derivatives of 4,11-dimethoxynaphtho[2,3-*f*]-indole 5,10-dione (**5**). We prepared 1-methyl-4,11-dimethoxynaphtho[2,3-*f*]indole 5,10-dione (**11**)[13] and bromoethyl derivative **12**.[6] In the latter compound, the halogen was replaced by treatment by acetate; subsequent hydrolysis of ester **13** yielded *N*-(2-hydroxyethyl)naphthoindole **14** (Scheme 2).



Scheme 1.



Scheme 2.

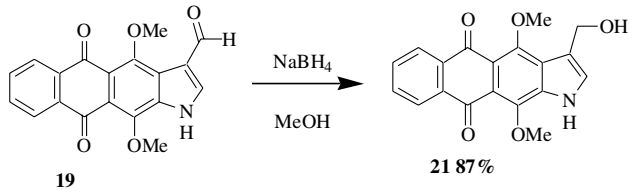


Scheme 3.

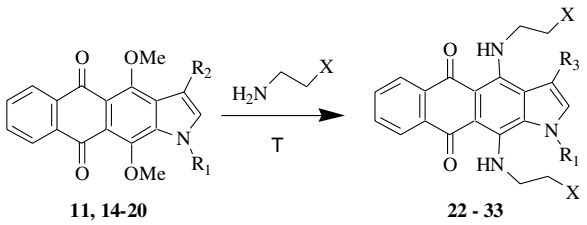
Similarly to gramine,[14] the dimethylamino group in the Mannich base **15**[15] was substituted by acetate upon boiling in acetic anhydride to yield acetoxymethyl derivative **16** and a minor product, diacetyl derivative **17** (Scheme 3). Treatment of **16** or **17** with sodium methoxide led to 3-methoxymethylnaphthoindole **18**.

Vilsmeyer and Friedel–Crafts reactions led to 3-acyl derivatives of naphthoindole **5**, for example, 3-formyl and 3-acetyl-4,11-dimethoxynaphtho[2,3-*f*]indole 5,10-dione (**19**, **20**).[15] The reduction of 3-formyl-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (**19**) by $NaBH_4$ produced indole-3-yl-carbinol **21** in high yield (Scheme 4).

The 1- and 3-substituted 4,11-dimethoxynaphtho[2,3-*f*]-indole-5,10-diones **11**, **14**–**21** were transformed into compounds **22**–**33** by treatment with various diamines; however, the lability of some substituents in the pyrrole fragment in some cases made these reactions problematic (Scheme 5). The interactions of diamines with Mannich base **15** yielded along with desired compounds **26**–**28**, the respective unsubstituted compounds **6**–**8** whose amounts increased with time of reaction. Interestingly, although Mannich bases **26**–**28** were stable when stored as crystals, the unsubstituted compounds **6**–**8** were formed in solutions by retro-Mannich reaction. The latter process easily occurs for these compounds, probably due to steric tensions between bulky substituents in positions 3 and 4 of chromophore and to the resonance stabilization of leaving group (imine ion). The nucleophilic replacement of acetoxy group by *N*,*N*-dimethylethylenediamine in 3-acetoxymethyl derivatives **16** and **17** led to gramine-type compound **29** (see Table 1).



Scheme 4.



Scheme 5.

2.2. Biology

The 4,11-diaminonaphtho[2,3-*f*]indole-5,10-dione derivatives **6**–**9**, **22**, **26**–**28**, and **33** were tested in a panel of 60 human cancer cell lines in National Cancer Institute Drug Screen Program.[16] The following parameters were determined: GI_{50} (concentration inhibiting 50% net cell growth) and LC_{50} (concentration leading to 50% net cell death). For each of these parameters the averaged values of mean graph midpoint (MG_MID) were calculated.[17] The GI_{50} values for naphthoindoles for selected cell lines, along with MG_MID values, are shown in Table 2; **ADR** (**1**) was used as a reference compound.

The comparison of data for compounds **6**–**9** demonstrated that alkylation of amino group in the side chains decreased the cytotoxicity (see GI_{50}MG_MID values, Table 2). The most potent derivatives **6** and **7** (GI_{50}MG_MID 0.25 and 0.32 μM) were 2–3 times less potent than **1**. However, activity against **ADR** selected, MDR breast cancer cells NCI/ADR strongly depended on structural features of amino groups in the side chains. The ratios of GI_{50} for NCI/ADR versus MCF-7 cells for **ADR** and naphthoindoles with primary amino and ethanolamino substituents **6** and **9** were approximately 1000, 400, and

Table 1. 4,11-Diaminonaphtho[2,3-*f*]indole-5,10-diones prepared from 1- or 3-derivatives of 4,11-dimethoxynaphtho[2,3-*f*]indole 5,10-dione (**5**) (Scheme 5)

Compound	Starting		Compound	Products			Yield (%)
	R_1	R_2		X	R_1	R_3	
11	Me	H	**22**	NH_2	Me	H	60
11	Me	H	**23**	NHMe	Me	H	64
11	Me	H	**24**	NMe_2	Me	H	68
14	$(CH_2)_2OH$	H	**25**	NH_2	$(CH_2)_2OH$	H	55
15	H	CH_2NMe_2	**26**	NH_2	H	CH_2NMe_2	46
			6	NH_2	H	H	15
15	H	CH_2NMe_2	**27**	NHMe	H	CH_2NMe_2	54
			7	NHMe	H	H	12
15	H	CH_2NMe_2	**28**	NMe_2	H	CH_2NMe_2	57
			8	NMe_2	H	H	10
16	H	CH_2OAc	**29**	NMe_2	H	$CH_2NH(CH_2)_2NMe_2$	52
18	H	CH_2OMe	**30**	NMe_2	H	CH_2OMe	58
19	H	CHO	**31**	NMe_2	H	CHO	41
20	H	Ac	**32**	NMe_2	H	Ac	46
21	H	CH_2OH	**33**	NMe_2	H	CH_2OH	47

Table 2. Activity (GI_{50}, μM) of naphthoindolediones **6–9**, **22**, **26–28**, **33** and **ADR** (**1**) in the NCI in vitro 60-cell line Drug Screen Program

Compound	Molt-4[a]	NCI-H226[b]	NCI-H460[b]	HCT-15[c]	KM-12[c]	M-14[d]	OVCAR-8[e]	TK-10[f]	MCF-7[g]	NCI/ADR[h]	MG_MID[i]
1	0.01	0.05	0.5	1.6	0.3	0.2	0.15	0.1	0.02	20.0	0.13
6	0.01	1.5	0.9	0.8	0.2	1.5	0.1	0.1	0.03	13.1	0.25
7	0.03	0.2	0.1	0.1	5.2	0.08	0.1	0.2	0.08	1.3	0.32
8	0.2	9.5	0.5	0.2	0.5	3.6	0.4	1.5	0.4	1.0	1.0
9	1.1	4.2	7.6	50.3	4.5	7.5	2.4	6.0	1.6	>100	3.2
22	0.06	15.0	0.4	2.7	0.5	2.7	1.5	2.5	0.4	8.5	1.2
26	1.5	1.6	11.2	7.8	1.7	3.6	0.7	4.8	1.1	22.5	1.9
27	0.4	6.7	2.0	5.7	5.6	11.2	3.3	10.1	1.4	12.2	2.5
28	0.5	15.0	2.2	1.7	1.7	2.5	2.5	2.1	2.1	4.5	2.5
33	0.5	7.4	1.9	1.9	1.0	1.7	2.7	2.5	2.0	4.1	3.2

Origin of cell lines: [a]leukemia; [b]non-small cell lung cancer; [c]colon cancer; [d]melanoma; [e]ovarian cancer; [f]renal cancer; [g]breast cancer; [h]**ADR** selected multidrug resistant breast cancer cell line; [i]Mean Graph Midpoint over the NCI 60-cell panel.

>100, respectively. In striking contrast, the corresponding ratios for methyl- and dimethylamino derivatives **7** and **8** were 16.0 and 2.5, respectively (Table 2). These compounds inhibited the growth of NCI/ADR cells at low micromolar concentrations ($GI_{50} \sim 1$ μM), whereas GI_{50} of **1** was 20 μM (Table 2). Besides derivatives 4,11-diaminonaphtho[2,3-*f*]indole-5,10-dione **6** and **7** had selective toxicity for leukemia, colon and renal cancer cells, and demonstrated more potent cytocidal effects than, **1** (LC_{50}MG_MID 6.3, 10.1 and 14.5 μM, respectively). The potencies of 1- or 3-substituted analogues **22**, **26–28**, and **33** were lower than those of their parent naphthoindoles **6–8**.

We next tested naphthoindoles **6–10c**, **22–25**, **27**, and **29–33** for cytotoxicity against cells that express Pgp, the transporter responsible for the most well-documented MDR phenotype.[18] Each of these agents was less toxic than **1** for human leukemia cell line K562 (Table 3). However, for methyl- and dimethylamino derivatives **7** and **8** the mean ratios of IC_{50} for K562i/S9 versus K562 cells were 3.1 and 4.8, respectively, compared to 14.3 for **1** and to 22.0 for ametantrone analogue **9**, respectively (Table 3). These results are in agreement with the data for analogues of pixantrone, whose derivatives with methyl- and dimethylamino groups in the side chains have been reported to overcome MDR in the LoVo/DX cell line.[19,20] The cyclic variation in diamine side chain of derivatives of 4,11-diaminonaphtho[2,3-*f*]indole-5,10-dione yielded the inactive analogue **10c**. Other 1- or 3-substituted derivatives **22–33** were less potent than their unsubstituted analogues **7**, **8** for K562 cells, nor were these compounds active for Pgp-expressing K562i/S9 cells.

Finally, we were interested whether p53 plays a role in cytotoxicity of novel derivatives of 4,11-diaminonaphtho[2,3-*f*]indole-5,10-dione **6–9**, **22–24**. Given that p53-inactivating mutations are the most frequent genetic events in cancer, and the loss of p53 function can confer resistance to DNA damaging agents including **ADR**,[21] the potency for p53-deficient cells would provide an advantage for these compounds as potential chemotherapeutic drugs. The cytotoxicity of **6–9** for HCT116 colon carcinoma cells was 8–30 times lower than that for reference drugs **1** or **2** and for previously reported derivatives of 4,11-dihydroxynaphtho[2,3-*f*]indole-5,10-dione[7] (Table 3). However, whereas the loss of p53 rendered cells more resistant to **ADR**, all tested naphthoindoles were equally toxic for $p53^{+/+}$ cells and

Table 3. A 50% growth inhibitory concentration (IC_{50}) of 4,11-diaminonaphtho[2,3-*f*]indole-5,10-dione derivatives, **ADR** (**1**) and mitoxantrone (**2**) against K562 and HCT116 cells and their sublines

Compound	IC_{50} (μM)		RI[a]	IC_{50} (μM)		RI[b]
	K562	K562i/S9		HCT116	HCT116p53KO	
1	0.14 ± 0.04	2.0 ± 0.1	14.3	1.4 ± 0.1	4.4 ± 0.4	3.1
2	0.9 ± 0.2	2.0 ± 0.4	2.2	1.2 ± 0.1	2.0 ± 0.2	1.6
6	3.0 ± 0.4	25.0 ± 0.8	8.3	33.2 ± 1.1	32.9 ± 1.0	1.0
7	0.8 ± 0.1	2.5 ± 0.2	3.1	11.1 ± 0.4	11.3 ± 0.4	1.0
8	1.0 ± 0.1	4.8 ± 0.3	4.8	13.3 ± 0.6	16.0 ± 0.5	1.2
9	2.2 ± 0.2	48 ± 2	22.0	>50	>50	—
10c	>50	nt[c]	—	nt[c]	nt[c]	—
22	9.1 ± 0.8	23.0 ± 1.2	2.5	1.5 ± 0.2	3.0 ± 0.3	2.0
23	1.4 ± 0.2	7.6 ± 1.1	5.4	2.4 ± 0.3	2.9 ± 0.4	1.2
24	1.1 ± 0.1	2.1 ± 0.3	1.9	1.3 ± 0.1	1.6 ± 0.1	1.2
25	1.4 ± 0.2	>50	>50	nt[c]	nt[c]	—
27	1.8 ± 0.5	nt[c]	—	nt[c]	nt[c]	—
29	1.1 ± 0.2	>50	>50	nt[c]	nt[c]	—
30	2.0 ± 0.6	>50	>25	nt[c]	nt[c]	—
31	2.1 ± 0.7	nt[c]	—	nt[c]	nt[c]	—
32	2.0 ± 0.5	nt[c]	—	nt[c]	nt[c]	—
33	>50	nt[c]	—	nt[c]	nt[c]	—

[a] RI, resistance index = IC_{50} (K562i/S9)/IC_{50}(K562).
[b] RI, resistance index = IC_{50} (HCT116p53KO)/IC_{50} (HCT116).
[c] Not tested.

their isogenic $p53^{-/-}$ subline. Interestingly, methylation of heterocyclic nitrogen in 4,11-diaminonaphtho[2,3-*f*]indole-5,10-dione moiety (**22**–**24**) resulted in a 10- to 20-fold increase of activity against HCT116 cells compared with unsubstituted congeners **6**–**8**. Thus, compound **24** showed the activity close to **1** or **2** and was almost equally potent for $p53^{+/+}$ HCT116 cells and their $p53^{-/-}$ subline (Table 3).

3. Conclusions

We have developed a convenient method for preparing the derivatives of 4,11-diaminonaphtho[2,3-*f*]indole-5,10-dione based on a facilitated ability of 4,11-dimethoxynaphtho[2,3-*f*]indole 5,10-diones to substitute methoxy groups for alkylamines. Using S_NAr reactions, a series of indole containing analogues of ametantrone was prepared. Testing of the derivatives of 4,11-dimethoxynaphtho[2,3-*f*]indole 5,10-dione in a broad panel of human cancer cell lines showed that their antiproliferative activity was close to that of **ADR**. The introduction of a substituent in position 1 or 3 of naphtho[2,3-*f*]indole-5,10-dione chromophore resulted in diminished cytotoxicity. Importantly, the naphthoindoles carrying *N*-methyl- or *N*,*N*-dimethylamino groups have remarkable activity against Pgp-positive MDR cells. Finally, the majority of novel analogues were potent for colon carcinoma cell lines, regardless of the p53 status.

4. Experimental

4.1. General

NMR spectra were registered on a Varian VXR-400 instrument operated at 400 MHz (^{1}H NMR). Chemical shifts were measured in CD_3OD, DMSO-d_6 or $CDCl_3$ using these solvents as internal standards ($CDCl_3$: δ^1H (residual) 7.25 ppm, DMSO-d_6: δ^1H (residual) 2.50 ppm). Analytical TLC was performed on Silica Gel F_{254} plates (Merck) and column chromatography on Silica Gel Merck 60. Melting points were determined on a Buchi SMP-20 apparatus and are uncorrected. Mass-spectra were obtained on an SSQ 710 Finnigan instrument. IR spectra (as KBr disks) were determined on Perkin-Elmer-599 spectrometer. UV spectra were recorded on Hitachi-U2000 spectrophotometer. All solutions were dried over sodium sulfate and evaporated at reduced pressure on a Buchi-R200 rotary evaporator at the temperature below 45 °C. All products were dried under high vacuum at room temperature.

4.2. Cell lines, drugs, and viability assay

The K562 human leukemia cell line (American Type Culture Collection; ATCC, Manassas, VA) and its variant K562i/S9 that expresses Pgp after *MDR*1/Pgp gene transfer and immunoflow cytometry-based sorting of Pgp-positive cells,[22] HCT116 colon carcinoma cell line (ATCC) with wild type p53 ($p53^{+/+}$), and HCT116p53KO subline (both alleles of p53 deleted by homologous recombination[23]) ($p53^{-/-}$) were cultured in RPMI-1640 supplemented with 5% fetal calf serum (BioWhittaker, Belgium), 2 mM L-glutamine, 100 U/ml penicillin, and 100 μg/ml streptomycin at 37 °C, 5% CO_2 in humidified atmosphere. Cells in logarithmic phase of growth were used in all experiments. Novel compounds were dissolved in 10% aqueous DMSO as 10 mM stock solutions followed by serial dilutions in water immediately before experiments. The cytotoxicity of novel agents was determined in a formazan conversion assay (MTT test).[24,25] Briefly, cells (5×10^3 in 190 μL of culture medium) were plated into a 96-well

plate (Becton Dickinson, Franklin Lakes, NJ) and treated with 0.05% DMSO (vehicle control) or with increasing concentrations of tested compounds (each dose in duplicate) for 72 h. After the completion of drug exposure, 50 μg of 3-(4,5-dimethylthiazolyl-2)-2,5-diphenyl tetrazolium bromide (Sigma Chemical Co., St. Louis, MO) was added into each well for an additional 3 h. Formazan was dissolved in acidified DMSO, and the absorbance at $\lambda = 540$ nm was measured. Cell viability at given drug concentration was calculated as percentage of absorbance in wells with drug treated cells to that of vehicle control cells (100%).

4.3. 4,11-Bis[(2-aminoethyl)amino]-1*H*-naphtho[2,3-*f*]indole-5,10-dione (6)

A mixture of 4,11-dimethoxy-1*H*-naphtho[2,3-*f*]indole-5,10-dione (**5**[26]; 0.10 g, 0.31 mmol) and ethylenediamine (3.0 mL) was heated at 50 °C for 1.5–2 h. During this time yellow color changed to dark violet and after complete conversion of **5** (as determined by TLC), the reaction mixture was cooled and quenched with water. Aqueous acetic acid was added (1.0 M) until pH 8.0 was reached, the solution was saturated by $(NH_4)_2SO_4$, and the product was extracted with *n*-butanol (3×30 mL). The extract was twice washed with brine, dried, and evaporated. The residue was purified by column chromatography with chloroform–methanol–concd NH_4OH (10:2:0 → 10:4:1) as eluting solvent. The solid residue obtained after evaporation was crystallized from ethanol–1,4-dioxane mixture (1:1) to afford **6** (66 mg, 56%) as dark blue crystals, mp 154–158 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.16 (t, 1H, $J = 5.5$ Hz, NH), 11.88 (t, 1H, $J = 7.5$ Hz, NH), 8.35 (m, 2H, 6-H, 9-H), 7.35 (m, 2H, 7-H, 8-H), 7.30 (d, 1H, $J = 3.0$ Hz, 3-H), 6.98 (d, 1H, $J = 3.0$ Hz, 2-H), 3.95 (q, 2H, $^1J = 6.0$ Hz, $^2J = 5.5$ Hz, HNCH_2–), 3.82 (m, 2H, HNCH_2–), 3.14 (m, 4H, –CH_2NH$_2$); MS *m*/*z* 363 (M^+, 100), 343 (29), 313 (80), 291 (32), 261 (82), 204 (10); UV (ethanol) λ_{max} (log ε) 228 (4.3), 262 (4.6), 336 sh (3.7), 377 sh (3.5), 482 sh (3.4), 510 sh (3.9), 540 (4.3), 580 (4.4) nm; IR (KBr) ν 3550–3300 (NH), 1590 cm^{-1} (C═O); Anal. Calcd for $C_{20}H_{21}N_5O_2 \cdot H_2O$: C, 62.98; H, 6.08; N, 18.36. Found: C, 63.11; H, 6.42; N, 18.31.

4.4. 4,11-Bis{[2-(methylamino)ethyl]amino}-1*H*-naphtho[2,3-*f*]indole-5,10-dione (7)

This was prepared similarly from naphthoindole **5** and *N*-methylethylenediamine (50 °C, 3–3.5 h) as dark blue needles in 61% yield, mp 145–147 °C (benzene); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.03 (t, 1H, $J = 4.8$ Hz, NH), 11.64 (t, 1H, $J = 7.6$ Hz, NH), 8.36 (m, 2H, 6-H, 9-H), 7.63 (m, 2H, 7-H, 8-H), 7.07 (d, 1H, $J = 3.0$ Hz, 3-H), 6.88 (d, 1H, $J = 3.0$ Hz, 2-H), 3.99 (q, 2H, $^1J = 5.8$ Hz, $^2J = 5.5$ Hz, HNCH_2–), 3.75 (m, 2H, HNCH_2–), 3.09 (t, 2H, $J = 6.0$ Hz, –CH_2NHMe), 3.01 (t, 2H, $J = 5.0$ Hz, –CH_2NHMe), 2.60 (s, 3H, –NHCH_3), 2.57 (s, 3H, –NHCH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 181.46 (C═O), 178.24 (C═O), 148.96 (C), 142.85 (C), 135.66 (C), 134.57 (C), 130.00 (C), 120.72 (C), 108.31 (C), 103.64 (C), 131.37 (CH), 130.56 (CH), 125.83 (CH), 125.57 (CH), 125.30 (CH), 107.92 (CH), 52.33 (CH_2), 51.40 (CH_2), 46.42 (CH_2), 45.59 (CH_2), 36.59 (CH_3), 36.21 (CH_3); MS *m*/*z* 391 (M^+, 100), 348 (41), 316 (56), 290 (82), 276 (22); UV (ethanol) λ_{max} (log ε) 228 (4.3), 262 (4.6), 340 sh (3.7), 376 sh (3.5), 477 sh (3.4), 505 sh (3.9), 538 (4.3), 578 (4.4) nm; IR (KBr) ν 3550–3300 (NH), 1590 cm^{-1} (C═O); Anal. Calcd for $C_{22}H_{25}N_5O_2$: C, 67.50; H, 6.44; N, 17.89. Found: C, 67.42; H, 6.40; N, 17.69.

4.5. 4,11-Bis{[2-(dimethylamino)ethyl]amino}-1*H*-naphtho[2,3-*f*]indole-5,10-dione (8)

A solution of naphthoindole **5**[26] (0.10 g, 0.31 mmol) and *N*,*N*-dimethylethylenediamine (3.0 mL) was heated at 50 °C for 4–5 h. After complete conversion of **5** (as determined by TLC) the reaction mixture was cooled, quenched with water, and acidified by aqueous acetic acid (1.0 M) to pH 8.0. The product was extracted with ethyl acetate (4×30 mL). The residue obtained after the evaporation of the extract was purified by column chromatography with chloroform–methanol (10:1 → 2:1) as eluent. The solid obtained after evaporation was crystallized from benzene–*n*-heptane mixture (1:4) and dried to afford **6** (84 mg, 65%) as dark blue needles, mp 141–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.85 (br s, 1H, NH), 13.01 (t, 1H, $J = 6.8$ Hz, NH), 11.90 (t, 1H, $J = 7.8$ Hz, NH), 8.40 (m, 2H, 6-H, 9-H), 7.64 (m, 2H, 7-H, 8-H), 7.21 (d, 1H, $J = 3.0$ Hz, 3-H), 7.03 (d, 1H, $J = 3.0$ Hz, 2-H), 4.00 (m, 2H, HNCH_2–), 3.76 (m, 2H, HNCH_2–), 2.87 (t, 2H, $J = 4.5$ Hz, –CH_2NMe$_2$), 2.83 (t, 2H, $J = 6.8$ Hz, –CH_2NMe$_2$), 2.50 (s, 6H, –N(CH_3)$_2$), 2.39 (s, 6H, –N(CH_3)$_2$); MS *m*/*z* 419 (M^+, 55), 361 (34), 286 (11), 58 (100); UV (ethanol) λ_{max} (log ε) 228 (4.3), 265 (4.5), 336 sh (3.6), 374 sh (3.5), 477 sh (3.3), 507 sh (3.9), 538 (4.3), 579 (4.4) nm; Anal. Calcd for $C_{24}H_{29}N_5O_2$: C, 68.71; H. 6.97; N. 16.69 Found: C, 68.44; H, 6.55; N, 16.36.

4.6. 4,11-Bis[{2-[(2-hydroxyethyl)amino]ethyl}amino]-1*H*-naphtho[2,3-*f*]indole-5,10-dione (9)

This was prepared similarly from naphthoindole **5** and 2-[(2-hydroxyethyl)amino]ethylamine (50 °C, 2–3 h) (as described for compound **6**) in 45% yield, mp 148–150 °C (ethanol); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.16 (t, 1H, $J = 5.3$ Hz, NH), 12.02 (t, 1H, $J = 7.0$ Hz, NH), 8.35 (m, 2H, 6-H, 9-H), 7.65 (m, 2H, 7-H, 8-H), 7.36 (d, 1H, $J = 2.8$ Hz, 3-H), 6.98 (d, 1H, $J = 2.8$ Hz, 2-H), 4.01 (q, 2H, $^1J = 6.0$ Hz, $^2J = 5.3$ Hz, HNCH_2–), 3.79 (m, 2H, HNCH_2–), 3.66 (m, 4H, –CH_2OH), 3.11 (m, 4H, –CH_2NH–), 2.84 (m, 4H, –NHCH_2–); MS *m*/*z* 451 (M^+, 100), 378 (43), 316 (48), 290 (100), 262 (25), 190 (5); UV (ethanol) λ_{max} (log ε) 229 (4.4), 265 (4.6), 337 sh (3.8), 374 sh (3.6), 479 sh (4.1), 506 sh (4.0), 538 (4.4), 579 (4.5) nm; IR (KBr) ν 3550–3300 (NH, OH), 1590 cm^{-1} (C═O); Anal. Calcd for $C_{24}H_{29}N_5O_4$: C, 63.84; H, 6.47; N, 15.51. Found: C, 63.52; H, 6.32; N, 15.90.

4.7. *tert*-Butyl 3-amino-1-pyrrolidinecarboxylate (10a)

To a well-stirred solution of 3-amino-1-pyrrolidine dihydrochloride (1.0 g, 3.2 mmol) in water–isopropanol

(20.0–20.0 mL) a solution of Boc_2O (1.44 g, 3.3 mmol) in isopropanol (20.0 mL) and solution of NaOH (1 N) were added within 3 h dropwise at pH 6.0. The mixture was stirred overnight, solution of NaOH (1 N) was added until pH 10.0 was reached, the resulting solution was concentrated to 20–30 mL volume, and the products were extracted with *n*-butanol (4 × 40 mL). The organic layers were combined, washed with brine, dried, and evaporated. Mono and di-Boc derivatives of 3-amino-1-pyrrolidine were separated by column chromatography with chloroform–methanol-concd NH_4OH (10:1:0 → 10:3:0.8) to give *tert*-butyl 3-amino-1-pyrrolidinecarboxylate (**10a**; 0.76 g, 64%); ^1H NMR (400 MHz, $CDCl_3$) δ 3.48 (m, 1H, CH), 3.44 (m, 1H, CH), 3.28 (m, 1H, CH), 2.97 (m, 1H, CH), 1.96 (m, 1H, CH), 1.67 (br s, 2H, NH_2), 1.58 (m, 1H, CH), 1.38 (s, 9H, $CO_2(CH_3)_3$); ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.47 (C=O), 78.98 (C), 51.17, 50.34 (CH), 54.20, 53.84 (CH_2), 44.15, 43.77 (CH_2), 34.44, 33.99 (CH_2), 28.29 ($CO(CH_3)_3$); MS *m*/*z* 186 (M^+, 21), 129 (100), 113 (82), 85 (35); Anal. Calcd for $C_9H_{18}N_2O_2$: C, 58.04; H, 9.74; N, 15.04. Found: C, 58.31; H, 9.62; N, 14.59.

4.8. 4,11-Bis{[1-(*tert*-butoxycarbonyl)-3-pyrrolidinyl]amino}-1*H*-naphtho[2,3-*f*]indole-5,10-dione (10b)

To a solution of naphthoindole **5** (0.1 g, 0.31 mmol) in 1,4-dioxane (3.0 mL) *tert*-butyl 3-amino-1-pyrrolidinecarboxylate **10a** (0.3 g, 1.6 mmol) was added and the mixture was refluxed for 72–90 h. After conversion of **5** (as determined by TLC), the reaction mixture was cooled and quenched with water. The product was extracted with ethyl acetate (3 × 30 mL). The residue after extract evaporation was purified by column chromatography on silica gel with chloroform–methanol (10:0 → 5:1), the solid obtained after evaporation was crystallized from toluene–*n*-heptane mixture (1:2) and dried to afford **10b** (0.10 g, 53%) as dark blue solid, mp 135–138 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 13.01 (br d, 1H, NH), 11.70 (br dd, 1H, NH), 11.90 (br d, 1H, NH), 8.35 (m, 2H, 6-H, 9-H), 7.68 (m, 2H, 7-H, 8-H), 7.20 (d, 1H, 3-H), 6.72 (d, 1H, 2-H), 4.62 (m, 1H, HNC*H*), 4.55 (m, 1H, HNC*H*), 3.61 (br m, 8H, CH), 2.22 (br m, 4H, CH), 1.46 (s, 18H, $-CO_2(CH_3)_3$); MS *m*/*z* 615 (M^+, 100), 559 (29), 515 (84), 503 (38), 459 (28), 415 (25), 316 (41); UV (ethanol) λ_{max} (log ε) 229 (4.3), 265 (4.6), 370 sh (3.7), 500 sh (3.8), 514 sh (3.9), 537 (4.1), 579 (4.2) nm; Anal. Calcd for $C_{34}H_{41}N_5O_6$: C, 66.32; H, 6.71; N, 11.37. Found: C, 66.48; H, 6.54; N, 11.31.

4.9. 4,11-Bis(3-pyrrolidinylamino)-1*H*-naphtho[2,3-*f*]indole-5,10-dione dihydrochloride (10c)

A solution of Boc-derivative **10b** (85.0 mg, 0.3 mmol) in trifluoroacetic acid was stirred for 2 h under dry argon flow. The mixture was evaporated, the residue was dissolved in water (20 mL), and aq 2% $NaHCO_3$ was added until pH 9.0 was reached. The product was extracted after addition of $(NH_4)_2SO_4$ (10.0 g) with *n*-butanol (3 × 30 mL), washed with brine, dried, evaporated, and purified by flash chromatography on a silica gel pad with chloroform–methanol–concd NH_4OH (10:2:0.1 → 10:4:1). The residue obtained after evaporation was dissolved in methanol, a solution of HCl in diethyl ether (0.1 N, 3.0 mL) was added. The precipitated crystals were filtered, washed with ether, and dried to yield dihydrochloride dipyrrolidinyl derivative **10c** (55 mg, 84%), mp 237–239 °C (dec.); ^1H NMR (400 MHz, DMSO-d_6) δ 13.13 (br s, 1H, NH), 12.28 (br s, 1H, NH), 12.11 (br s, 1H, NH), 9.80 (br s, 2H, $^+NH_2$), 9.38 (br s, 2H, $^+NH_2$), 8.28 (m, 2H, 6-H, 9-H), 7.77 (m, 2H, 7-H, 8-H), 7.66 (t, 1H, J = 2.9 Hz, 3-H), 7.13 (br s, 1H, 2-H), 5.21 (m, 2H, CH), 3.70 (m, 2H, CH), 3.35 (m, 4H, CH), 3.23 (m, 1H, CH), 3.12 (m, 1H, CH), 2.45 (m, 1H, CH), 2.38 (m, 1H, CH), 2.14 (m, 1H, CH), 2.01 (m, 1H, CH); MS *m*/*z* 415 (M^+, 100), 346 (11), 316 (18), 288 (21), 262 (12); UV (ethanol) λ_{max} (log ε) 227 (4.2), 270 (4.6), 334 sh (3.6), 370 sh (3.5), 497 sh (3.7), 512 sh (3.8), 535 (4.0), 576 (4.1) nm; Anal. Calcd for $C_{24}H_{25}N_5O_2 \cdot 2HCl$: C, 59.02; H, 5.57; Cl, 14.52; N, 14.34. Found: C, 59.23; H, 5.71; Cl, 14.18; N, 14.17.

4.10. 1-(2-Acetoxyethyl)-4,11-dimethoxy-1*H*-naphtho[2,3-*f*]indole-5,10-dione (13)

To a warm solution of 1-(2-bromoethyl)-4,11-dimethoxy-1*H*-naphtho[2,3-*f*]indole-5,10-dione (**12**;[6] 0.2 g, 0.5 mmol) in acetic acid (10.0 mL) sodium acetate (0.50 g, 6.1 mmol) was added, the mixture was refluxed for 24 h and then evaporated. The resulting solid was dissolved in water and the product was extracted with ethyl acetate (4 × 30 mL). The organic layers were combined, washed with Na_2CO_3 (50 mL, 1 N), brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography with chloroform–methanol (10:1 → 10:3) to give crude **13**. Crude **13** was recrystallized from toluene–*n*-heptane mixture (1:1) to afford **13** in 72% yield, mp 137–138 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (m, 2H, 6-H, 9-H), 7.72 (m, 2H, 7-H, 8-H), 7.21 (d, 1H, J = 3.1 Hz, 3-H), 6.84 (d, 1H, J = 3.1 Hz, 2-H), 4.70 (t, 2H, J = 5.2 Hz, $-CH_2-$), 4.48 (t, 2H, J = 5.2 Hz, $-CH_2O-$), 4.12 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 2.06 (s, 3H, OAc); MS *m*/*z* 393 (M^+, 100), 378 (22), 336 (35), 292 (21), 276 (18); Anal. Calcd for $C_{22}H_{19}NO_6$: C, 67.17; H, 4.87; N, 3.56. Found: C, 67.01; H, 4.71; N, 3.55.

4.11. 1-(2-Hydroxyethyl)-4,11-dimethoxy-1*H*-naphtho[2,3-*f*]indole-5,10-dione (14)

To a stirring solution of acetoxy derivative **13** (0.11 g, 0.3 mmol) in methanol (20.0 mL) was added 0.1 N MeONa (3.0 mL) and the mixture was stirred overnight. The resulting solution was evaporated and water was added. The product was extracted with ethyl acetate (4 × 30 mL), organic layers were combined, washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography with chloroform–methanol (10:2 → 10:5) to give **14** (89 mg, 85%); 124–125 °C (toluene–*n*-heptane (1:1)); ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (m, 2H, 6-H, 9-H), 7.72 (m, 2H, 7-H, 8-H), 7.30 (d, 1H, J = 3.1 Hz, 3-H), 6.80 (d, 1H, J = 3.1 Hz, 2-H), 4.59 (t, 2H, J = 5.1 Hz, $-CH_2-$), 4.09 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 4.04 (m, 2H,

–CH_2OH), 1.92 (t, 1H, J = 5.0 Hz, OH); MS m/z 351 (M^+, 81), 319 (35), 290 (100), 276 (35), 248 (20); Anal. Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.11; H, 4.70; N, 3.81.

4.12. 3-(Acetoxymethyl)-4,11-dimethoxy-1*H*-naphtho[2,3-*f*]indole-5,10-dione (16) and 3-(Acetoxymethyl)-1-acetyl-4,11-dimethoxy-1*H*-naphtho[2,3-*f*]indole-5,10-dione (17)

The solution of 4,11-dimethoxy-3-[(dimethylamino)methyl]-1*H*-naphtho[2,3-*f*]indole-5,10-dione (**15**;[15] 0.20 g, 0.55 mmol) and sodium acetate (0.50 g, 6.1 mmol) in acetic anhydride (5.0 mL) was refluxed for 30 min. After cooling, the mixture was poured in water (20 mL) and stirred for 1 h. The products were extracted with ethyl acetate (4 × 30 mL). The organic layers were combined, washed with Na_2CO_3 (2 × 50 mL, 1 N), brine, dried, and evaporated. The products were separated by chromatographic fractionation with chloroform–methanol (10:0 → 10:3) and after crystallization from benzene–*n*-heptane mixture (1:2) were isolated **16** (0.14 g, 67%) and **17** (49 mg, 22%). **16**: R_f = 0.32 (chloroform–methanol, 10:3); mp 140–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (br s, 1H, NH), 8.26 (m, 2H, 6-H, 9-H), 7.74 (m, 2H, 7-H, 8-H), 7.48 (d, 1H, J = 2.5 Hz, 2-H), 5.47 (s, 2H, –CH_2O), 4.10 (s, 3H, OCH_3), 4.09 (s, 3H, OCH_3), 2.10 (s, 3H, OAc); MS m/z 379 (M^+, 100), 336 (22), 319 (68), 290 (44), 272 (81); Anal. Calcd for $C_{21}H_{17}NO_6$: C, 66.49; H, 4.52; N, 3.69. Found: C, 66.19; H, 4.50; N, 3.75.

The diacetyl derivative **17**: R_f = 0.52 (chloroform–methanol, 10:3); mp 215–218 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (m, 2H, 6-H, 9-H), 7.78 (m, 2H, 7-H, 8-H), 7.76 (s, 1H, 2-H), 5.48 (s, 2H, –CH_2O), 4.10 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3), 2.74 (s, 3H, NAc); 2.15 (s, 3H, OAc); MS m/z 421 (M^+, 100), 379 (55), 336 (38), 319 (39), 290 (74), 272 (91); Anal. Calcd for $C_{23}H_{19}NO_7$: C, 65.55; H, 4.54; N, 3.32. Found: C, 65.39; H, 4.59; N, 3.44.

4.13. 4,11-Dimethoxy-3-(methoxymethyl)-1*H*-naphtho[2,3-*f*]indole-5,10-dione (18)

This was synthesized from acetoxy derivatives **16** or **17** as described for compound **14** in 82–88% yield; 95–97 °C (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (br s, 1H, NH), 8.25 (m, 2H, 6-H, 9-H), 7.72 (m, 2H, 7-H, 8-H), 7.40 (d, 1H, J = 2.4 Hz, 2-H), 4.81 (s, 2H, –CH_2O), 4.09 (s, 6H, OCH_3), 3.52 (s, 3H, –CH_2OCH_3); MS m/z 351 (M^+, 100), 336 (42), 306 (38), 272 (48); Anal. Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H. 4.88; N. 3.99. Found: C, 68.12; H, 4.62; N, 3.84.

4.14. 4,11-Dimethoxy-3-(hydroxymethyl)-1*H*-naphtho[2,3-*f*]indole-5,10-dione (21)

To a stirring solution of 4,11-dimethoxy-3-formyl-1*H*-naphtho[2,3-*f*]indole-5,10-dione (**19**[15]; 0.17 g, 0.5 mmol) in hot THF (20 mL) were added methanol (20 mL) and, after cooling, $NaBH_4$ (15.0 mg, 0.4 mmol). The mixture was stirred for 1 h and evaporated. The residue was quenched with water (50 mL), and AcOH solution (5%) was added until pH 7.0 was reached. The product was extracted with ethyl acetate (4 × 30 mL), organic layers were combined, washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography on silica gel pad with chloroform–methanol (10:3 → 1:1) to give 0.15 g (87%) carbinol derivative **21**; 132–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (br s, 1H, NH), 8.26 (m, 2H, 6-H, 9-H), 7.75 (m, 2H, 7-H, 8-H), 7.35 (d, 1H, 2-H), 4.89 (s, 2H, –CH_2OH), 4.18 (s, 3H, OCH_3), 4.11 (s, 3H, OCH_3), 3.20 (br s, 1H, OH); MS m/z 337 (M^+, 100), 322 (32), 279 (21), 272 (61), 2621 (15); Anal. Calcd for $C_{19}H_{15}NO_5$: C, 67.65; H, 4.48; N, 4.15. Found: C, 67.80; H, 4.59; N, 4.10.

4.15. 4,11-Bis[(2-aminoethyl)amino]-1-methyl-1*H*-naphtho[2,3-*f*]indole-5,10-dione (22)

This was synthesized from 4,11-dimethoxy-1-methyl-1*H*-naphtho[2,3-*f*]indole-5,10-dione (**11**)[13] and ethylenediamine as described for compound **6** in 60% yield; mp 167–168 °C (benzene–*n*-heptane, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.61 (t, 1H, J = 6.5 Hz, NH), 9.88 (t, 1H, J = 6.5 Hz, NH), 8.30 (m, 2H, 6-H, 9-H), 7.67 (m, 2H, 7-H, 8-H), 7.22 (d, 1H, J = 3.2 Hz, 3-H), 6.99 (d, 1H, J = 3.2 Hz, 2-H), 4.15 (s, 3H, NCH_3), 3.93 (q, 2H, ^1J = 5.6 Hz, ^2J = 6.0 Hz, HNCH_2–), 3.31 (q, 2H, ^1J = 5.6 Hz, ^2J = 6.0 Hz, HNCH_2–), 2.76 (m, 4H, –CH_2NH_2); MS m/z 378 (M^+, 70), 393 (27), 313 (68), 279 (22), 261 (100), 204 (10); IR (KBr) ν 3500–3300 (NH), 1585 cm^{-1} (C=O); Anal. Calcd for $C_{21}H_{23}N_5O_2$: C, 66.83; H, 6.14; N, 18.55. Found: C, 67.02; H, 6.29; N, 18.30.

4.16. 1-Methyl-4,11-bis{[2-(methylamino)ethyl]amino}-1*H*-naphtho[2,3-*f*]indole-5,10-dione (23)

This was synthesized from 4,11-dimethoxy-1-methyl-1*H*-naphtho[2,3-*f*]indole-5,10-dione (**11**) and *N*-methylethylenediamine as described for compound **6** (50 °C, 2–3 h, the product was extracted with toluene) in 64% yield; mp 78–80 °C (*n*-pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.52 (t, 1H, J = 4.3 Hz, NH), 9.61 (t, 1H, J = 6.6 Hz, NH), 8.36 (m, 2H, 6-H, 9-H), 7.67 (m, 2H, 7-H, 8-H), 7.06 (d, 1H, J = 3.0 Hz, 3-H), 6.97 (d, 1H, J = 3.0 Hz, 2-H), 4.15 (s, 3H, NCH_3), 3.98 (q, 2H, ^1J = 5.5 Hz, ^2J = 6.1 Hz, HNCH_2–), 3.31 (q, 2H, ^1J = 6.1 Hz, ^2J = 5.1 Hz, HNCH_2–), 2.77 (t, 2H, J = 6.1 Hz, –CH_2NHMe), 2.77 (t, 2H, J = 6.1 Hz, –CH_2NHMe), 2.56 (s, 3H, –NHCH_3), 2.39 (s, 3H, –NHCH_3); MS m/z 405 (M^+, 81), 362 (22), 330 (54), 304 (100), 289 (20); Anal. Calcd for $C_{23}H_{27}N_5O_2$: C, 68.13; H, 6.71; N, 17.27. Found: C, 67.91; H, 6.80; N, 17.05.

4.17. 4,11-Bis{[2-(dimethylamino)ethyl]amino}-1-methyl-1*H*-naphtho[2,3-*f*]indole-5,10-dione (24)

This was synthesized from 4,11-dimethoxy-1-methyl-1*H*-naphtho[2,3-*f*]indole-5,10-dione (**11**) as described for compound **8** in 68% yield; mp 97–99 °C (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.48 (t, 1H,

J = 4.3 Hz, NH), 9.52 (t, 1H, J = 6.5 Hz, NH), 8.36 (m, 2H, 6-H, 9-H), 7.66 (m, 2H, 7-H, 8-H), 7.06 (d, 1H, J = 3.0 Hz, 3-H), 6.99 (d, 1H, J = 3.0 Hz, 2-H), 4.15 (s, 3H, NCH_3), 3.96 (q, 2H, ^1J = 5.2 Hz, ^2J = 6.8 Hz, HNCH_2–), 3.31 (q, 2H, ^1J = 7.1 Hz, ^2J = 6.8 Hz, HNCH_2–), 2.77 (t, 2H, J = 6.8 Hz, –CH_2NMe$_2$), 2.77 (t, 2H, J = 6.8 Hz, –CH_2NMe$_2$), 2.39 (s, 6H, –N(CH_3)$_2$), 2.21 (s, 6H, –N(CH_3)$_2$); MS m/z 433 (M$^+$, 44), 388 (17), 330 (54), 58 (100); Anal. Calcd for $C_{25}H_{31}N_5O_2$: C, 69.26; H, 7.21; N, 16.15. Found: C, 69.01; H, 6.99; N, 16.04.

4.18. 4,11-Bis{[2-(dimethylamino)ethyl]amino}-1-(2-hydroxyethyl)-1*H*-naphtho[2,3-*f*]indole-5,10-dione (25)

This was synthesized from dimethoxynaphthoindole **14** as described for compound **8** in 55% yield; mp 112–113 °C (toluene–*n*-heptane, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.22 (t, 1H, J = 4.8 Hz, NH), 8.98 (t, 1H, J = 7.0 Hz, NH), 8.32 (m, 2H, 6-H, 9-H), 7.66 (m, 2H, 7-H, 8-H), 7.18 (d, 1H, J = 3.2 Hz, 3-H), 6.98 (d, 1H, J = 3.2 Hz, 2-H), 4.65 (t, 2H, J = 5.2 Hz, CH_2CH$_2$OH), 3.92 (m, 2H, CH$_2$CH_2OH), 3.91 (m, 2H, HNCH_2–), 3.18 (q, 2H, J = 6.7 Hz HNCH_2–), 2.75 (t, 2H, J = 6.7 Hz, –CH_2NMe$_2$), 2.54 (t, 2H, J = 6.7 Hz, –CH_2NMe$_2$), 2.37 (s, 6H, –N(CH$_3$)$_2$), 2.25 (s, 6H, –N(CH$_3$)$_2$); MS m/z 463 (M$^+$, 15), 445 (34), 400 (7), 360 (13), 342 (54), 58 (100); UV (ethanol) λ_{max} (log ε) 232 (4.2), 270 (4.5), 363 sh (3.5), 492 sh (3.5), 511 sh (3.8), 548 (4.0), 590 (4.0) nm; Anal. Calcd for $C_{26}H_{33}N_5O_3$: C, 67.36; H, 7.18; N, 15.11. Found: C, 67.53; H, 7.01; N, 15.35.

4.19. 4,11-Bis[(2-aminoethyl)amino]-3-[(dimethylamino)methyl]-1*H*-naphtho[2,3-*f*]indole-5,10-dione (26)

This was synthesized from 4,11-dimethoxy-3-[(dimethylamino)methyl]-1*H*-naphtho[2,3-*f*]indole-5,10-dione (**15**)[15] as described for compound **6** (35 °C, 4 h). After evaporation of extract, the separation of the residue by column chromatography with chloroform–methanol-concd NH_4OH (10:2:0 → 10:4:1) gave **6** (R_f = 0.71, chloroform–methanol–NH_4OH, 10:4:0.6; 15%) and gramine derivatives **26** (R_f = 0.62, chloroform–methanol–NH_4OH, 10:4:0.6; 46%), mp 145–147 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.27 (t, 1H, NH), 9.83 (br s, 1H, NH), 8.30 (m, 2H, 6-H, 9-H), 7.62 (m, 2H, 7-H, 8-H), 7.10 (s, 1H, 2-H), 3.74 (m, 2H, HNCH_2–), 3.62 (s, 2H, CH_2NMe$_2$), 3.19 (t, 2H, J = 6.0 Hz, HNCH_2–), 3.12 (t, 2H, J = 5.1 Hz, –CH_2NH$_2$), 2.91 (t, 2H, J = 6.0 Hz, –CH_2NH$_2$), 2.29 (s, 6H, –N(CH$_3$)$_2$); MS m/z 420 (M$^+$, 7), 402 (84), 374 (100), 359 (25), 328 (78), 298 (83), 58 (32); Anal. Calcd for $C_{23}H_{28}N_6O_2$: C, 65.69; H, 6.71; N, 19.99. Found: C, 65.51; H, 6.54; N, 19.79.

4.20. 3-[(Dimethylamino)methyl]-4,11-bis{[2-(methylamino)ethyl]amino}-1*H*-naphtho[2,3-*f*]indole-5,10-dione (27)

This was synthesized from gramine **15**[15] and *N*-methylethylenediamine as described for compound **6** (35 °C, 7–8 h). After evaporation of the extract, the separation of the residue by column chromatography with chloroform–methanol–concd NH_4OH (10:2:0 → 10:4:1) gave **7** (R_f = 0.73, chloroform–methanol–NH_4OH, 10:4:0.6; 12%) and gramine derivatives **27** (R_f = 0.63, chloroform–methanol–NH_4OH, 10:4:0.6; 54%), mp 116–118 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.22 (t, 1H, J = 6.5 Hz, NH), 9.90 (br s, 1H, NH), 8.29 (m, 2H, 6-H, 9-H), 7.61 (m, 2H, 7-H, 8-H), 7.11 (s, 1H, 2-H), 3.75 (m, 2H, HNCH_2–), 3.60 (s, 2H, CH_2NMe$_2$), 3.26 (t, 2H,J = 6.0 Hz, HNCH_2–), 2.98 (t, 2H, J = 5.2 Hz, –CH_2NHMe), 2.82 (t, 2H, J = 6.0 Hz, –CH_2NHMe), 2.56 (s, 3H, –NHCH_3), 2.37 (s, 3H, –NHCH_3), 2.29 (s, 6H, –N(CH$_3$)$_2$); MS m/z 403 (M$^+$-HNMe$_2$, 100), 391 (11), 332 (18), 316 (55), 288 (38), 260 (18), 58 (20); UV (ethanol) λ_{max} (log ε) 229 (4.2), 270 (4.5), 374 sh (3.6), 499 sh (3.8), 512 sh (3.9), 540 (4.1), 576 (4.1) nm; Anal. Calcd for $C_{25}H_{32}N_6O_2$: C, 66.94; H. 7.19; N. 18.74. Found: C, 67.12; H, 7.35; N, 18.76.

4.21. 4,11-Bis[[2-(dimethylamino)ethyl]amino]-3-[(dimethylamino)methyl]-1*H*-naphtho[2,3-*f*]indole-5,10-dione (28)

This was synthesized from gramine **15** and *N*,*N*-dimethylethylenediamine as described for compound **6** (35 °C, 14–16 h). After evaporation of the extract, the purification of the residue by column chromatography with chloroform–methanol–concd NH_4OH (10:2:0 → 10:4:0.5) gave **8** (R_f = 0.51, chloroform–methanol, 5:2; 10%) and gramine derivatives **28** (R_f = 0.39, chloroform–methanol, 5:2; 57%), mp 112–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.18 (br s, 1H, NH), 11.53 (t, 1H, NH), 10.11 (br s, 1H, NH), 8.30 (m, 2H, 6-H, 9-H), 7.60 (m, 2H, 7-H, 8-H), 7.09 (s, 1H, 2-H), 3.71 (m, 2H, HNCH_2–), 3.62 (s, 2H, CH_2NMe$_2$), 3.24 (t, 2H, HNCH_2–), 2.80 (t, 2H, –CH_2NMe$_2$), 2.52 (t, 2H, –CH_2NMe$_2$), 2.45 (s, 6H, –N(CH_3)$_2$), 2.27 (s, 6H, –N(CH_3)$_2$), 2.19 (s, 6H, –N(CH_3)$_2$); MS m/z 476 (M$^+$, 7), 433 (9), 419 (20), 405 (25), 361 (22), 316 (81), 58 (100); Anal. Calcd for $C_{27}H_{36}N_6O_2$: C, 68.04; H. 7.61; N. 17.63. Found: C, 68.11; H, 7.44; N, 17.77.

4.22. 4,11-Bis{[2-(dimethylamino)ethyl]amino}-3-({[2-(dimethylamino)ethyl]amino}methyl)-1*H*-naphtho[2,3-*f*]indole-5,10-dione (29)

This was synthesized from 3-acetoxymethyl derivatives **16** or **17** as described for compound **8**, in 46–52% yield; mp 121–122 °C (benzene–*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.45 (t, 1H, NH), 10.01 (br s, 1H, NH), 8.34 (m, 2H, 6-H, 9-H), 7.66 (m, 2H, 7-H, 8-H), 7.23 (s, 1H, 2-H), 4.17 (s, 2H, –CH_2NHCH$_2$–), 3.74 (m, 2H, HNCH_2–), 3.42 (t, 2H, J = 6.8 Hz, HNCH_2–), 2.84 (t, 2H, J = 4.5 Hz, –CH_2NMe$_2$), 2.74 (t, 2H, J = 6.2 Hz, –CH$_2$NHCH_2–), 2.52 (t, 2H, J = 6.8 Hz, –CH_2NMe$_2$), 2.49 (s, 6H, –N(CH_3)$_2$), 2.45 (t, 2H, J = 6.2 Hz, –CH_2NMe$_2$), 2.25 (s, 6H, –N(CH_3)$_2$), 2.14 (s, 6H, –N(CH_3)$_2$); ^{13}C NMR (400 MHz, $CDCl_3$) δ 182.36 (C=O), 182.20 (C=O), 148.25 (C), 143.10 (C), 135.24 (C), 135.01 (C), 130.45 (C), 123.86 (C), 117.75 (C), 110.35 (C), 107.28 (C), 131.75 (CH), 131.74 (CH), 127.48 (CH),126.24 (CH), 125.73 (CH), 61.66 (CH$_2$), 59.57 (CH$_2$), 57.89 (CH$_2$), 49.16 (CH$_2$), 46.05 (CH$_2$), 45.50 (CH$_2$), 45.26 (CH$_2$),

46.29 ($2CH_3$), 45.60 ($2CH_3$), 45.15 ($2CH_3$); MS *m*/*z* 519 (M^+, 4), 474 (3), 433 (12), 419 (79), 372 (41), 316 (100), 290 (26); Anal. Calcd for $C_{29}H_{41}N_7O_2$: C, 67.02; H, 7.95; N, 18.87. Found: C, 67.09; H, 7.73; N, 18.71.

4.23. 4,11-Bis{[2-(dimethylamino)ethyl]amino}-3-(methoxymethyl)-1*H*-naphtho[2,3-*f*]indole-5,10-dione (30)

This was synthesized from 3-methoxymethyl derivative **18** as described for compound **8**, in 58% yield; mp 82–84 °C (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.89 (br s, 1H, NH), 11.58 (t, 1H, J = 7.5 Hz, NH), 10.96 (br s, 1H, NH), 8.36 (m, 2H, 6-H, 9-H), 7.66 (m, 2H, 7-H, 8-H), 7.29 (s, 1H, 2-H), 4.72 (s, 2H, CH_2O), 3.74 (m, 2H, $HNCH_2$–), 3.63 (t, 2H, $HNCH_2$–), 3.47 (s, 3H, $-OCH_3$), 2.74 (t, 2H, $-CH_2NMe_2$), 2.52 (t, 2H, $-CH_2NMe_2$), 2.48 (s, 6H, $-N(CH_3)_2$), 2.25 (s, 6H, $-N(CH_3)_2$); MS *m*/*z* 463 (M^+, 12), 449 (21), 431 (100), 386 (42), 373 (81), 328 (94), 313 (39); Anal. Calcd for $C_{26}H_{33}N_5O_3$: C, 67.36; H. 7.18; N. 15.11. Found: C, 67.50; H, 7.11; N, 15.14.

4.24. 4,11-Bis{[2-(dimethylamino)ethyl]amino}-3-formyl-1*H*-naphtho[2,3-*f*]indole-5,10-dione (31)

This was synthesized from 4,11-dimethoxy-3-formyl-1*H*-naphtho[2,3-*f*]indole-5,10-dione **19**[15] as described for compound **8**, in 41% yield; mp 176–178 °C (benzene–*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.04 (t, 1H, J = 7.5 Hz, NH), 10.17 (s, 1H, –CHO), 10.03 (br s, 1H, NH), 8.34 (m, 2H, 6-H, 9-H), 7.91 (s, 1H, 2-H), 7.70 (m, 2H, 7-H, 8-H), 3.71 (m, 2H, $HNCH_2$–), 3.41 (m, 2H, $HNCH_2$–), 2.90 (t, 2H, J = 4.6 Hz, $-CH_2NMe_2$), 2.57 (t, 2H, J = 6.6 Hz, $-CH_2NMe_2$), 2.56 (s, 6H, $-N(CH_3)_2$), 2.25 (s, 6H, $-N(CH_3)_2$); ^{13}C NMR (400 MHz, $CDCl_3$) δ 186.20 (HC═O), 183.65 (C═O), 181.92 (C═O), 146.62 (C), 141.35 (C), 135.46 (C), 134.81 (C), 131.62 (C), 134.61 (C), 126.44 (C), 122.70 (C), 109.71 (C), 132.24 (CH), 131.81 (CH), 126.36 (CH), 125.82 (CH), 122.37 (CH), 61.73 (CH_2), 59.71 (CH_2), 47.70 (CH_2), 45.43 (CH_2), 46.22 ($2CH_3$), 45.59 ($2CH_3$); MS *m*/*z* 447 (M^+, 18), 402 (14), 389 (100), 344 (82); Anal. Calcd for $C_{25}H_{29}N_5O_3$: C, 67.09; H, 6.53; N, 15.65. Found: C, 67.00; H, 6.47; N, 15.54.

4.25. 3-Acetyl-4,11-bis{[2-(dimethylamino)ethyl]amino}-1*H*-naphtho[2,3-*f*]indole-5,10-dione (32)

This was synthesized from 3-acetyl-4,11-dimethoxy-1*H*-naphtho[2,3-*f*]indole-5,10-dione (**20**)[15] as described for compound **8**, in 46% yield; mp 105–108 °C (benzene–*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.87 (t, 1H, NH), 10.35 (br s, 1H, NH), 8.30 (m, 2H, 6-H, 9-H), 7.79 (s, 1H, 2-H), 7.65 (m, 2H, 7-H, 8-H), 3.64 (m, 2H, $HNCH_2$–), 3.16 (t, 2H, $HNCH_2$–), 2.86 (t, 2H, $-CH_2NMe_2$), 2.63 (t, 2H, $-CH_2NMe_2$), 2.61 (s, 3H, $-COCH_3$), 2.54 (s, 6H, $-N(CH_3)_2$), 2.25 (s, 6H, $-N(CH_3)_2$); MS *m*/*z* 461 (M^+, 12), 403 (41), 358 (54), 58 (100); UV (ethanol) λ_{max} (log ε) 223 (4.3), 268 (4.5), 355 sh (3.6), 511 sh (3.7), 553 (4.0), 589 (4.0) nm; Anal. Calcd for $C_{26}H_{31}N_5O_3$: C, 67.66; H. 6.77; N. 15.17. Found: C, 67.21; H, 6.61; N, 15.14.

4.26. 4,11-Bis{[2-(dimethylamino)ethyl]amino}-3-(hydroxymethyl)-1*H*-naphtho[2,3-*f*]indole-5,10-dione (33)

This was synthesized from carbinol **21** as described for compound **8**, in 47% yield; mp 132–134 °C (benzene–*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (br s, 1H, NH), 8.32 (m, 2H, 6-H, 9-H), 7.69 (m, 2H, 7-H, 8-H), 7.21 (s, 1H, 2-H), 4.83 (s, 2H, CH_2OH), 3.78 (m, 2H, $HNCH_2$–), 3.39 (t, 2H, $HNCH_2$–), 2.85 (t, 2H, J = 4.5 Hz, $-CH_2NMe_2$), 2.63 (t, 2H, J = 7.0 Hz, $-CH_2NMe_2$), 2.51 (s, 6H, $-N(CH_3)_2$), 2.32 (s, 6H, $-N(CH_3)_2$); MS *m*/*z* 449 (M^+, 35), 433 (25), 419 (100), 330 (38), 316 (82), 286 (28); UV (ethanol) λ_{max} (log ε) 228 (4.2), 262 (4.5), 370 sh (3.6), 496 sh (3.8), 514 sh (3.9), 539 (4.1), 579 (4.1) nm; Anal. Calcd for $C_{25}H_{31}N_5O_3$: C, 66.79; H, 6.95; N, 15.58. Found: C, 66.52; H, 6.74; N, 15.34.

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