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Bioorganic & Medicinal Chemistry 12 (2004) 3923–3930
Bioorganic & Medicinal Chemistry

Synthesis of 1-(ω-aminoalkyl)naphthoindolediones with antiproliferative properties

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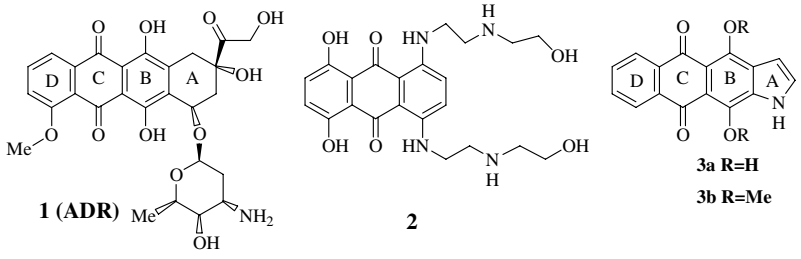
Received 5 March 2004; revised 21 April 2004; accepted 30 April 2004

Abstract—The preparation and cytotoxic properties of 4,11-dihydroxynaphtho[2,3-*f*]indole-5,10-dione derivatives carrying *N*-aminoalkyl substituents are described. The *N*-aminobutylnaphthoindolediones obtained were studied in National Cancer Institute Screening Program and demonstrated high antiproliferative activity against 60 human cancer cell lines. All *N*-(4-aminobutyl) derivatives have higher potency than adriamycin or mitoxantrone against adriamycin selected multidrug resistant breast cancer cell line NCI/ADR.

1. Introduction

The anthracycline antibiotics [daunorubicin, adriamycin (doxorubicin **1**)] have been introduced in clinical use more than 30 years ago for treatment of wide variety of cancers.[1] However, their efficacy is often limited by dose-related cumulative cardiotoxicity and the development of drug resistance. Besides, many tumors are intrinsically resistant to anthracycline antibiotics. These problems stimulate research efforts directed to the synthesis and investigation of new analogs of these antibiotics with the improved properties. Mitoxantrone (**2**) represents the most successful outcome of these efforts. However, although more active than adriamycin against some tumors, mitoxantrone has a rather narrow spectrum of antitumor activities that limits the clinical usage of this drug.[2]

The action of anthracycline antibiotics is multimodal. The anthraquinone moiety of these antibiotics and their synthetic analogs (e.g., aminoethylaminoantraquinones) determines the ability of these compounds to intercalate into DNA, thereby interfering with replication and transcription. The key enzymes, mainly topoisomerase II (Topo II), can also be inhibited by anthracyclines. Topo II is considered presently a major target of antitumor action of anthracyclines.[3] Indole derived anthracycline analogs are of special interest since a series of natural condensed indole derivatives capable of intercalating into DNA is known.[4–8] The presence of the indole moiety in the molecule can decrease the formation of semiquinones and free radicals, which frequently determine the cumulative cardiotoxicity of anthracyclines.[9] Therefore, the compounds that combine indole and anthraquinone moieties in their structures, can be



Keywords: Naphthoindolediones; O-Demethylation; N-Alkylation; Cytotoxicity.
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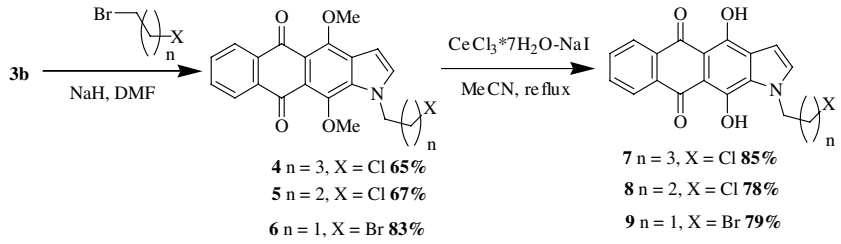
doi:10.1016/j.bmc.2004.04.042



Scheme 1.

considered as potential agents with valuable chemotherapeutic properties.

Earlier we have developed a preparative method of synthesis of 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (**3b**), based on the usage of Lemgruber–Bacho method.[10] The aim of this study was to develop the method of synthesis of aminoalkyl derivatives of 4,11-dihydroxynaphtho[2,3-*f*]indole-5,10-dione (**3a**). Compound **3a** can be considered as an analog of an anthracycline antibiotic's aglycon in which the pyrrole cycle substitutes for the cyclohexane (A) ring. The daunosamine sugar in daunorubicin or adriamycin stabilizes the complex of these antibiotics with DNA due to the interaction of amino group and DNA phosphate groups. This role can be also performed by various amino-derived 7-O-substituents.[11,12] Some other antitumor interacalators (e.g., mitonoafide, nitracrine, and crisnatol) are built similarly as in these compounds the aliphatic side chain with the terminal amino group is bonded with the flat aglycon constructed from 3 to 4 annealated cycles.[13,14] Therefore, *N*-(aminoalkyl)naphthoindoles seem to be promising intercalators with valuable properties.

The analysis of SAR for anthracyclines and other intercalators[11–14] with the side aminoalkyl chain (e.g., derivatives of ellipticine,[15] BD-40,[16] or DACA[17]) and the relationship between the length of the side aminoalkyl chain modeling daunosamine and antitumor activity demonstrate that the most active are the compounds in which the distance between the amino group and the aglycon is equivalent to five C–C bonds. Therefore, the aim of our research was the synthesis of ϖ-aminoalkyl derivatives of naphthoindoles, mostly 4-aminobutyl derivatives. To study the influence of the length of the side chain on biological properties, we also synthesized several 3-aminopropyl- and 2-aminoethyl derivatives of 4,11-dihydroxynaphtho[2,3-*f*]indole-5,10-dione.

2. Results

2.1. Chemistry

At the first step we synthesized several 1-(ϖ-halogenoalkyl)naphthoindolediones. Alkylation of 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (**3b**) in DMF at the presence of NaH at 30 °C by 1-bromo-4-chlorobutane led to 1-(4-chlorobutyl)-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (**4**) in 65% yield (Scheme 1). Similarly, alkylation of **3b** by 1-bromo-3-chloropropane or 1,2-dibromoethane afforded 1-(3-chloropropyl)- and 1-(2-bromoethyl)-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-diones (**5** and **6**), respectively.

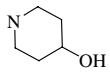
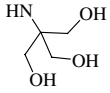
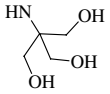
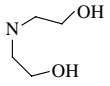
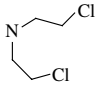
6,11-*O*-Dimethyldaunorubicin and also 6- or 11-*O*-methyl derivatives of daunorubicin have lower antineoplastic activity than daunorubicin as they form less stable complexes with DNA.[18] Therefore, the next step had to be O-demethylation of compounds **4**–**6**. Earlier we have found a convenient method of demethylation of methoxynaphtho[2,3-*f*]indole-5,10-diones with the use of $BCl_3{\cdot}SMe_2$.[19] Similarly demethylation of compounds **4**–**6** by reflux with $BCl_3{\cdot}SMe_2$ or $BBr_3{\cdot}SMe_2$ in dichloroethane (DCE) afforded dihydroxy derivatives **7**–**9** in 60–70% yields. Heating derivatives **4**–**6** with $CeCl_3$–NaI mixture in acetonitrile described earlier for selective cleavage of methoxy groups located *ortho* to carbonyl group[20] was found to be more effective. In this case the yields of 4,11-dihydroxy derivatives **7**–**9** reached 78–85%.

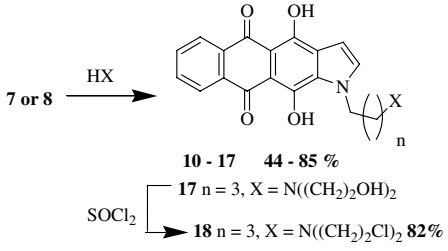
The interaction of 1-(ϖ-halogenoalkyl)naphthoindolediones **7** and **8** with primary and secondary amines gave a series of 1-(ϖ-aminoalkyl)-4,11-dihydroxynaphtho[2,3-*f*]indole-5,10-diones **10**–**17** in 44–85% yields, presented in Table 1 (Scheme 2). Treatment of diethanolamino derivative **17** with $SOCl_2$ in benzene afforded the corresponding 'nitrogen mustard' derivative **18** in 82% yield.

However, this methodology was not so successful for the synthesis of 1-(2-aminoethyl) derivatives from 1-(2-bromoethyl) derivative **9**. In this case nucleophilic substitution of bromine by an amino group competes with the intramolecular replacement by the adjacent hydroxyl group and the main product isolated was 7-hydroxy-2,3-dihydronaphtho[2,3-*f*][1,4]oxazino[2,3,4-*hi*]indole-8,13-dione (**19**). Thus, treatment of bromoethyl derivative **9** with 1-(2-hydroxyethyl)piperazine afforded the product of intramolecular cyclization **19** in 71% yield, while the desired amino derivative **20** was isolated in 11% yield (Scheme 3).

For the preparation of 1-(2-aminoethyl)-derivatives we developed the alternative methods of synthesis. The reaction of 2-hydroxyethylpyperazine and 1-(2-bromoethyl)-derivative **6** led to dimethoxyamino derivative **21** in high yield (82%, Scheme 4). Demethylation of **21** by

Table 1. Aminoalkyl derivatives of 4,11-dihydroxynaphtho[2,3-*f*]indole-5,10-dione (**10**–**18**) obtained (Scheme 2)

Compd	*n*	X	Yield, %
10	3		44
11	3		73
12	3		85
13	3		64
14	3		63
15	2		65
16	3		61
17	3		77
18	3		82



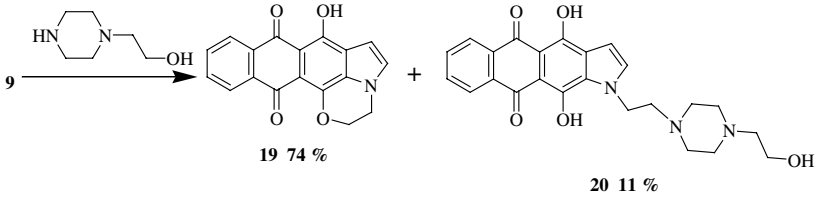
Scheme 2.

the action of $CeCl_3$–NaI mixture in boiling acetonitrile failed to yield the desired product **20**, apparently due to substitution of the terminal hydroxy group by iodine in the reaction conditions, resulting in by-reactions.[21] Treatment of **21** by $BBr_3{\cdot}SMe_2$ complex in DCE gave pyperazine derivative **20** in moderate yield. Earlier for the synthesis of 1-(2-aminoethyl) derivative of 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (**3b**) we have reported a method of direct alkylation by 2-chloroethylamino derivatives, for example, *N*,*N*-dimethyl-2-chloroethylamine.[22] The alkylation of naphthoindole **3b** with 1-(2-chloroethyl)piperidine gave **22**, demethylation of the latter by $CeCl_3$–NaI in acetonitrile afforded the corresponding piperidinoethyl derivative **23**.

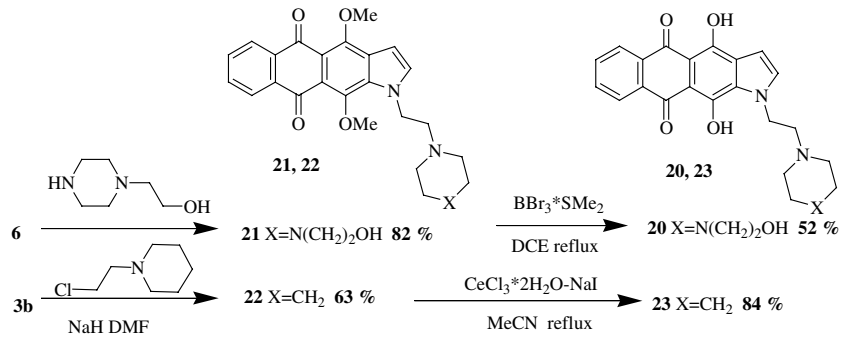
2.2. Biology

The 4,11-dihydroxynaphtho[2,3-*f*]indole-5,10-dione derivatives **10**–**17**, **20**, **23** were studied for antiproliferative activity against human cancer cell lines in National Cancer Institute Drug Screen Program. The activity of each compound was evaluated for 60 cancer cell lines.[23] The following parameters were determined for every cell line: GI_{50} (concentration inhibiting 50% net cell growth), TGI (concentration that totally inhibited 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.[24] The GI_{50} values for selected cell lines, along with MG_MID values, are shown in Table 2. Ethylamino derivatives **20** and **23** did not have significant growth inhibitory activities (GI_{50} MG_MID < 100 μM) and were excluded from Table 2.

In general all tested aminoalkylnaphthoindolediones were less cytotoxic for studied human cancer cell lines than adriamycin (GI_{50} MG_MID 0.13 μM). The most potent compound was tris(hydroxymethyl)methylamine derivative **16** (GI_{50} MG_MID 1.9 μM). It is surprising since tris(hydroxymethyl)methylamine is the least basic and the most bulky subsistent, which might have a negative effect on its interaction with DNA. It is especially notable that compound **16** had approximately 15 times lower growth inhibitory effects (GI), than adriamycin (GI_{50} MG_MID 0.13 μM) whereas for cytocidal effects (LC) this difference was smaller (LC_{50} MG_MID 31.6 and 14.5 μM, respectively). The nature of amino moiety of aminoalkyl-naphthoindolediones weakly influenced the average potency as for the majority of the compounds GI_{50} MG_MID were about 5–8 μM. However, it had significant influence on the spectrum of antiproliferative activity. All aminobutyl derivatives showed highly selective cytotoxicity for leukemia cell lines, with GI_{50} 2–5 times lower than their MG_MID. Compounds **14**, **16**, **17** had selective cytotoxicity for colon and melanoma cell lines. Furthermore, derivatives **11**, **14**, **17** exhibited significant activities against breast



Scheme 3.



Scheme 4.

Table 2. Activity (GI_{50}, μM) of naphthoindolediones **10**–**17** in the NCI in vitro 60-cell Drug Screen Program

Compd	K-562[a]	NCI-H226[b]	NCI-H460[b]	HCT3-15[c]	KM-12[c]	M-14[d]	OVCAR-8[e]	TK-10[f]	MCF-7[g]	NCI/ADR[h]	**MG_MID**[i]
10	1.8	6.6	19.1	15.8	10.5	2.8	11.4	0.5	11.2	13.1	8.5
11	2.0	5.4	11.5	3.8	5.2	2.3	5.5	1.6	6.3	4.5	7.8
12	2.6	29.5	3.8	2.7	8.5	2.5	2.5	14.8	14.1	14.5	6.5
13	1.7	23.4	2.0	2.7	1.9	2.2	6.9	1.7	2.4	12.0	6.5
14	1.6	15.0	23.9	1.4	1.4	1.7	3.5	1.5	17.0	2.3	5.1
15	9.3	60.3	10.1	14.1	11.2	14.2	14.1	1.3	12.6	10.7	10.4
16	0.5	2.8	4.6	0.6	0.6	1.9	2.1	0.5	1.0	15.8	1.9
17	2.3	64.6	4.1	1.1	1.8	2.3	2.9	6.6	6.2	2.7	5.4
1	0.1	0.05	0.5	1.6	0.3	0.2	0.15	0.1	0.02	20.0	0.13

Origin of cell lines: [a]leukemia; [b]nonsmall-cell lung cancer; [c]colon cancer; [d]melanoma; [e]ovarian cancer; [f]renal cancer; [g]breast cancer; [h]adriamycin selected multidrug resistant breast cancer cell line; [i]Mean graph midpoint over the NCI 60-cell panel.

cancer cell line NCI/ADR selected for resistance to adriamycin and other anthracyclines and their analogs. In contrast to adriamycin and other Topo II inhibitors, naphthoindolediones **12**, **13**, **15**, **17** showed about 6–15 times higher cytotoxic properties for nonsmall-cell lung (NSLC) cancer NCI-H460 than against NCI-H226 cell line; the latter expresses elevated levels of Topo II.[25]

The propylamino derivative **15** was five times less potent than its homologue **16**. The lack of antiproliferative activity of ethylamino derivatives **20** and **23** and low activity of the propylamino derivative **16** demonstrate the important role of the spacer length between the amino group and chromophore for cytotoxic activity. The optimal number of atoms between indole nitrogen atom and terminal side chain nitrogen is four, which corresponds to ~8 Å distance.

Similar results were obtained when the naphthoindolediones were studied against murine leukemia cells L1210/0.[26] While naphthoindole **3b**, **4**, **7** did not influence cell growth, all aminobutylnaphthoindolediones **10**–**18** inhibited cell growth ($IC_{50} = 1$–$8\ \mu M$) though weaker than adriamycin ($IC_{50} = 0.37\ \mu M$). 'Nitrogen mustard' derivative **18** demonstrated the greatest activity ($IC_{50} = 0.28\ \mu M$).

3. Discussion

A novel group of cytotoxic naphthoindoledione compounds was designed and synthesized. *N*-Butylamino derivatives are more potent than ethyl and propyl analogs against the majority of human tumor cells indicating the important role of the length of the spacer attaching the amino group to naphthoindoledione moiety. All aminobutyl derivatives obtained have significant activity against adriamycin resistant breast cancer cell line NCI/ADR. Bis(hydroxymethyl)ethylamino and diethanolamino derivatives **14** and **17** have 8–10 times higher cytotoxic properties against NCI/ADR cells than adriamycin and mitoxantrone. Tris(hydroxymethyl)methylamino derivative **16** is the most active against adriamycin sensitive cells used for the study, being however approximately 15 times less active than adriamycin.

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 ^{1}H (residual) 7.25 ppm, CD_3OD δ: ^{1}H (residual) 3.32 ppm, DMSO-d_6: δ ^{1}H (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. HRMS mass spectra were registered on a MAT-8430 Finnigan

instrument with data operating system SS-300 (EI, 70 eV, direct introduction, temperature of ion source 250 °C). IR spectra (as KBr disks) were determined on Perkin–Elmer-599 spectrometer. UV spectra were recorded on Hitachi-U 2000 spectrophotometer. All solutions were dried over sodium sulfate and evaporated at reduced pressure on a Buchi-211 rotary evaporator at the temperature below 45 °C.

4.1.1. 1-[4-Chlorobutyl]-4,11-dimethoxy-1*H*-naphtho[2,3-*f*]indole-5,10-dione (4). To a stirred solution of 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (**3b**; 2.0 g, 6.5 mmol) in DMF (100 mL) at 0–5 °C was portionwise added NaH (60% suspension in oil; 0.5 g, 12.5 mmol) followed after 20 min by 1-bromo-4-chlorobutane (3.5 mL, 30.0 mmol) added dropwise. The reaction mixture was stirred at 30 °C for 1 h. During this time dark red color changed to yellow, and then the reaction mixture was quenched with water (300 mL)–ice (200 g)–acetic acid (1.0 mL) mixture and Na_2CO_3 solution (10%) was added until pH 7.0 was reached. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined, washed with Na_2CO_3 (50 mL, 1 N), water, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel by hexane–ethyl acetate (10:0 → 10:4) to give crude **4** as a yellow solid. Crude **4** was twice recrystallized from toluene–heptane mixture (1:1) to afford 1-[4-butyl]-4,11-dimethoxy-1*H*-naphtho[2,3-*f*]indole-5,10-dione (**4**; 1.7 g, 65%) as yellow needles; mp 121–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (m, 2H, 6-H, 9-H), 7.71 (m, 2H, 7-H, 8-H), 7.06 (d, 1H, $J = 2.9$ Hz, 2-H), 6.85 (d, 1H, $J = 2.9$ Hz, 3-H), 4.62 (t, 2H, $J = 6.9$ Hz, NCH_2–), 4.01 (s, 3H, OMe), 3.97 (s, 3H, OMe), 3.23 (t, 2H, –CH_2Cl), 2.04 (m, 2H, 2′-CH_2–), 1.93 (m, 2H, 3′-CH_2–); IR (KBr) ν 1660 cm^{-1} (C=O); UV (ethanol) λ_{max} 251, 283, 320, 423 nm; MS m/z 397 (M^+, 100), 368 (25), 306 (16), 290 (23), 278 (21); HRMS calcd for $C_{22}H_{20}ClNO_4$ 397.1081, found 397.1086.

4.1.2. 1-[3-Chloropropyl]-4,11-dimethoxy-1*H*-naphtho-[2,3-*f*]indole-5,10-dione (5). This was similarly prepared from **3** and 1-bromo-3-chloropropane in 67% yield; mp 137–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (m, 2H, 6-H, 9-H), 7.72 (m, 2H, 7-H, 8-H), 7.05 (d, 1H, $J = 2.9$ Hz, 2-H), 6.86 (d, 1H, $J = 2.9$ Hz, 3-H), 4.75 (t, 2H, $J = 6.9$ Hz, NCH_2–), 4.01 (s, 3H, OMe), 3.97 (s, 3H, OMe), 3.23 (t, 2H, $J = 6.5$ Hz, –CH_2Cl), 2.48 (m, 2H, 2′-CH_2–); HRMS calcd for $C_{21}H_{18}ClNO_4$ 383.0924, found 383.0921.

4.1.3. 1-[2-Bromoethyl]-4,11-dimethoxy-1*H*-naphtho[2,3-*f*]indole-5, 10-dione (6). This was similarly prepared from **3** and 1,2-dibromoethane. Crude **6** was recrystallized from toluene–heptane mixture (2:1) to afford **6** in 83% yield, mp 193–195 °C (toluene); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (m, 2H, 6-H, 9-H), 7.73 (m, 2H, 7-H, 8-H), 7.05 (d, 1H, $J = 2.9$ Hz, 2-H), 6.87 (d, 1H, $J = 2.9$ Hz, 3-H), 4.90 (t, 2H, $J = 6.9$ Hz, NCH_2–), 4.01 (s, 3H, OMe), 3.98 (s, 3H, OMe), 3.64 (t, 2H, $J = 6.9$ Hz, –CH_2Br); IR (KBr) ν 1660 cm^{-1} (C=O); MS m/z 413 (M^+, 100), 398 (16), 384 (18), 290 (48), 276 (18), 248 (16); HRMS calcd for $C_{20}H_{16}BrNO_4$ 413.0262, found 413.0270.

4.1.4. 1-[4-Chlorobutyl]-4,11-dihydroxy-1*H*-naphtho[2,3-*f*]indole-5,10-dione (7). A mixture of chlorobutyl derivative **4** (1.2 g, 3.0 mmol), cerium(III) chloride heptahydrate (3.7 g, 10.0 mmol), and sodium iodide NaI (1.5 g, 10.0 mmol) in acetonitrile (150 mL) was stirred under reflux for 3 h. After complete conversion of **4** as indicated by TLC the reaction mixture was diluted with water and extracted with ethyl acetate (3 × 150 mL). The combined organic solutions were washed with brine, water (3 × 50 mL), dried, and evaporated. The residue was purified by column chromatography on silica gel by hexane–ethyl acetate (10:0 → 10:3), crystallized from toluene–heptane mixture (1:3), and dried to afford **7** (0.95 g, 85%) as red needles, mp 160–162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.18 (br d, 2H, OH), 8.43 (m, 2H, 6-H, 9-H), 7.75 (m, 2H, 7-H, 8-H), 7.06 (d, 1H, $J = 2.9$ Hz, 2-H), 6.85 (d, 1H, $J = 2.9$ Hz, 3-H), 4.55 (t, 2H, $J = 6.5$ Hz, NCH_2–), 3.23 (t, 2H, $J = 6.5$ Hz, –CH_2Cl), 2.04 (m, 2H, 2′-CH_2–), 1.93 (m, 2H, 3′-CH_2–); IR (KBr) ν 1590 cm^{-1} (C=O); UV (ethanol) λ_{max} 218, 228, 271, (451), 480, 514 nm; MS m/z 369 (M^+, 100), 306 (22), 333 (15), 292 (78), 279 (35); HRMS calcd for $C_{20}H_{16}ClNO_4$ 369.0767, found 369.0773.

4.1.5. 1-[3-Chloropropyl]-4,11-dihydroxy-1*H*-naphtho-[2,3-*f*]indole-5,10-dione (8). This was similarly prepared from **5** in 78% yield; mp 172–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.20 (s, 1H, OH), 15.18 (s, 1H, OH), 8.43 (m, 2H, 6-H, 9-H), 7.80 (m, 2H, 7-H, 8-H), 7.19 (d, 1H, $J = 2.9$ Hz, 2-H), 6.89 (d, 1H, $J = 2.9$ Hz, 3-H), 4.73 (t, 2H, $J = 6.4$ Hz, NCH_2–), 3.59 (t, 2H, $J = 6.1$ Hz, –CH_2Cl), 2.42 (m, 2H, 2′-CH_2–); MS m/z 355 (M^+, 100), 320 (42), 292 (34), 279 (15); HRMS calcd for $C_{19}H_{14}ClNO_4$ 355.0611, found 355.0609.

4.1.6. 1-[2-Bromoethyl]-4,11-dihydroxy-1*H*-naphtho[2,3-*f*]indole-5,10-dione (9). This was similarly prepared from **6** in 79% yield; mp 261–264 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.17 (s, 1H, OH), 15.12 (s, 1H, OH), 8.41 (m, 2H, 6-H, 9-H), 7.79 (m, 2H, 7-H, 8-H), 7.27 (d, 1H, $J = 2.9$ Hz, 2-H), 6.84 (d, 1H, $J = 2.9$ Hz, 3-H), 4.85 (t, 2H, $J = 6.9$ Hz, NCH_2–), 3.64 (t, 2H, $J = 6.9$ Hz, –CH_2Br); IR (KBr) ν 1585 cm^{-1} (C=O); UV (ethanol) λ_{max} 218, 228, 271, (451), 480, 514 nm; MS m/z 386 (M^+, 100), 279 (45); MS m/z 385 (M^+, 11), 306 (100), 292 (18), 279 (16), 250 (22); HRMS calcd for $C_{18}H_{12}BrNO_4$ 384.9950, found 384.9963.

4.1.7. 4,11-Dihydroxy-1-[4-(dimethylamino)butyl]-1*H*-naphtho[2,3-*f*]indole-5,10-dione (10). To the solution of chlorobutyl derivative **7** (0.10 g, 0.26 mmol) in 1,4-dioxane (10.0 mL) was added a aqueous solution (40%) of dimethylamine (1.0 mL, 7.9 mmol), the mixture was heated in a sealed tube at 100 °C for 2 h and then

evaporated. The residue was purified by column chromatography on silica gel by chloroform–methanol (10:0 → 10:4), crystallized from toluene–heptane mixture (1:5), and dried to give **10** (43 mg, 44%) as a red solid; mp 132–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.21 (br s, 2H, OH), 8.40 (m, 2H, 6-H, 9-H), 7.72 (m, 2H, 7-H, 8-H), 7.05 (d, 1H, $J = 2.8$ Hz, 2-H), 6.81 (d, 1H, $J = 2.8$ Hz, 3-H), 4.51 (t, 2H, NCH_2–), 3.32 (t, 2H, 4′-CH_2–), 2.31 (s, 6H, $N(CH_3)_2$), 1.97 (m, 2H, 2′-CH_2–), 1.58 (m, 2H, 3′-CH_2–); MS m/z 378 (35), 333 (16), 292 (24), 279 (5), 58 (100); HRMS calcd for $C_{22}H_{22}N_2O_4$ 378.1579, found 378.1591.

4.1.8. 4,11-Dihydroxy-1-[4-(4-morpholinyl)butyl]-1*H*-naphtho[2,3-*f*]indole-5,10-dione (11). The stirring solution of chlorobutyl derivative **7** (0.10 g, 0.26 mmol) and morpholine (0.20 mL, 2.2 mmol) in dry *N*-methylpyrrolidone (NMP; 2.0 mL) was heated at 110–115 °C for 1 h, cooled and quenched with water (50 mL)–HCl (1.0 mL, 36%) mixture. The mixture was extracted with ethyl acetate (3 × 20 mL). The extract was washed with brine, water, dried, and evaporated. The residue was purified by column chromatography on silica gel by chloroform–methanol (10:0 × 10:4), crystallized from toluene–heptane mixture (1:5), and dried to give **11** (0.08 g, 73%) as a red solid; mp 101–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.21 (br d, 2H, OH), 8.43 (m, 2H, 6-H, 9-H), 7.75 (m, 2H, 7-H, 8-H), 7.06 (d, 1H, $J = 2.8$ Hz, 2-H), 6.84 (d, 1H, $J = 2.8$ Hz, 3-H), 4.54 (t, 2H, NCH_2–), 3.71 (m, 4H, (–CH_2–)$_2$O), 2.40 (m, 6H, N(–CH_2–)$_3$), 1.95 (m, 2H, 2′-CH_2–), 1.59 (m, 2H, 3′-CH_2–); IR (KBr) ν 1590 cm^{-1} (C=O); UV (ethanol) λ_{max} 218, 228, 271, (450), 480, 513 nm; MS m/z 420 (58), 404 (11), 292 (22), 100 (100); HRMS calcd for $C_{24}H_{24}N_2O_5$ 420.1685, found 420.1685.

4.1.9. 4,11-Dihydroxy-1-[4-(1-piperidinyl)butyl]-1*H*-naphtho[2,3-*f*]indole-5,10-dione (12). This was similarly prepared from **7** and piperidine in 85% yield; mp 95–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.21 (br s, 2H, OH), 8.41 (m, 2H, 6-H, 9-H), 7.66 (m, 2H, 7-H, 8-H), 7.04 (d, 1H, $J = 2.8$ Hz, 2-H), 6.84 (d, 1H, $J = 2.8$ Hz, 3-H), 4.51 (t, 2H, $J = 7.1$ Hz, NCH_2–), 2.32 (m, 6H, –CH_2–), 1.90 (m, 2H, 2′-CH_2–), 1.53 (m, 6H, –CH_2–), 1.45 (m, 2H, –CH_2–); MS m/z 418 (M^+, 52), 292 (18), 279 (3), 98 (100); HRMS calcd for $C_{25}H_{26}N_2O_4$ 418.1892, found 418.1887.

4.1.10. 4,11-Dihydroxy-1-[4-(4-hydroxy-1-piperidinyl)-butyl]-1*H*-naphtho[2,3-*f*]indole-5,10-dione (13). This was similarly prepared from **7** and 4-hydroxypiperidine in 64% yield; mp 92–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.20 (br s, 2H, OH), 8.42 (m, 2H, 6-H, 9-H), 7.74 (m, 2H, 7-H, 8-H), 7.08 (d, 1H, $J = 2.8$ Hz, 2-H), 6.86 (d, 1H, $J = 2.8$ Hz, 3-H), 4.51 (t, 2H, $J = 7.3$ Hz, NCH_2–), 3.71 (m, 1H, –C*H*OH), 2.75 (m, 2H, –CH_2–), 2.39 (t, 2H, $J = 7.5$ Hz, 4′-CH_2–), 2.15 (m, 2H, 2′-CH_2–), 1.92 (m, 4H, –CH_2–), 1.61 (m, 4H, –CH_2–); MS m/z 434 (M^+, 36), 416 (12), 292 (17), 279 (4), 114 (100); HRMS calcd for $C_{25}H_{26}N_2O_5$ 434.1841, found 434.1857.

4.1.11. 4,11-Dihydroxy-1-[4-[[2-hydroxy-1-(hydroxymethyl)-1-methylethyl]amino]butyl]-1*H*-naphtho[2,3-*f*]indole-5,10-dione (14). Prepared from **7** and 2-amino-2-methyl-1,3-propanediol in 63% yield; mp 148–150 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.21 (br s, 2H, OH), 8.37 (m, 2H, 6-H, 9-H), 7.75 (m, 2H, 7-H, 8-H), 7.22 (d, 1H, $J = 2.9$ Hz, 2-H), 6.76 (d, 1H, $J = 2.9$ Hz, 3-H), 4.53 (t, 2H, $J = 7.1$ Hz, NCH_2–), 3.38 (s, 4H, (–CH_2OH)$_2$), 2.60 (t, 2H, 4-CH_2–), 1.96 (m, 2H, 2′-CH_2–), 1.53 (m, 2H, 3′-CH_2–), 0.95 (s, 3H, C–CH_3); IR (KBr) ν 3390 (OH), 1595 cm^{-1} (C=O); MS m/z 438 (M^+, 11), 407 (100), 391 (15), 334 (20), 292 (23), 279 (11); HRMS calcd for $C_{24}H_{26}N_2O_6$ 438.1791, found 438.1800.

4.1.12. 4,11-Dihydroxy-1-(4-{[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]amino}propyl)-1*H*-naphtho[2,3-*f*]indole-5,10-dione (15). This was prepared from **8** and 2-amino-2-hydroxymethyl-1,3-propanediol in 65% yield mp 163–165 °C; ^{1}H NMR (400 MHz, DMSO-d_6) 15.21 (br s, 2H, OH), 8.39 (m, 2H, 6-H, 9-H), 7.80 (m, 2H, 7-H, 8-H), 7.32 (d, 1H, $J = 2.9$ Hz, 2-H), 6.78 (d, 1H, $J = 2.9$ Hz, 3-H), 4.61 (t, 2H, $J = 7.1$ Hz, NCH_2–), 3.42 (s, 6H, (–CH_2OH)$_3$), 2.67 (t, 2H, 3′-CH_2–), 2.01 (m, 2H, 2′-CH_2–); MS m/z 440 (M^+, 23), 409 (100), 320 (42), 306 (22), 292 (68), 279 (41); HRMS calcd for $C_{23}H_{24}N_2O_7$ 440.1583, found 440.1595.

4.1.13. 4,11-Dihydroxy-1-(4-{[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]amino}butyl)-1*H*-naphtho[2,3-*f*]indole-5,10-dione (16). This was prepared from **7** and 2-amino-2-hydroxymethyl-1,3-propanediol in, 61% yield, mp 160–162 °C; ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C) 8.38 (m, 2H, 6-H, 9-H), 7.90 (m, 2H, 7-H, 8-H), 7.60 (d, 1H, $J = 2.8$ Hz, 2-H), 6.78 (d, 1H, $J = 2.8$ Hz, 3-H), 4.54 (t, 2H, $J = 7.1$ Hz, NCH_2–), 3.43 (s, 6H, (–CH_2–OH)$_3$), 2.66 (t, 2H, 4′-CH_2–), 1.92 (m, 2H, 2′-CH_2–), 1.52 (m, 2H, 3′-CH_2–); MS m/z 454 (M^+, 32), 423 (100), 407 (19), 334 (42), 292 (61), 279 (33); HRMS calcd for $C_{24}H_{26}N_2O_7$ 454.1740, found 454.1735.

4.1.14. 1-[4-[Bis(2-hydroxyethyl)amino]butyl]-4,11-dihydroxy-1*H*-naphtho[2,3-*f*]indole-5,10-dione (17). This was prepared from **7** and diethanolamine in 77% yield; mp 88–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.03 (br s, 2H, OH), 8.40 (m, 2H, 6-H, 9-H), 7.72 (m, 2H, 7-H, 8-H), 7.05 (d, 1H, $J = 2.8$ Hz, 2-H), 6.81 (d, 1H, $J = 2.8$ Hz, 3-H), 4.51 (t, 2H, $J = 6.9$ Hz, NCH_2–), 3.61 (t, 4H, (–CH_2OH)$_2$), 2.61 (t, 4H, (–CH_2N)$_2$), 2.57 (t, 2H, 4′-CH_2–), 1.92 (m, 2H, 2′-CH_2–), 1.57 (m, 2H, 3′-CH_2–); IR (KBr) ν 3390 (OH), 1595 cm^{-1} (C=O); MS m/z 438 (16), 407 (100), 391 (10), 335 (15), 292 (22), 279 (11); HRMS calcd for $C_{24}H_{26}N_2O_6$ 438.1791, found 438.1803.

4.1.15. 1-[4-[Bis(2-chloroethyl)amino]butyl]-4,11-dihydroxy-1*H*-naphtho[2,3-*f*]indole-5,10-dione (18). Thionyl chloride (0.1 mL, 1.3 mmol) was added at stirring at room temperature to the solution of diethanolamine derivative **17** (50 mg, 0.11 mmol) in dry benzene (20.0 mL). The obtained mixture was refluxed for

30 min, cooled, and quenched with $NaHCO_3$ solution (2%, 20 mL). The mixture was extracted with ethyl acetate (3×20 mL). The extract was washed with brine, water (3×20 mL), dried, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel by hexane–ethyl acetate (10:0 → 10:2), dried to afford **18** (44 mg, 82%) as a red oil, which slowly crystallized to give crystals with mp 65–68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.18 (br s, 2H, OH), 8.42 (m, 2H, 6-H, 9-H), 7.73 (m, 2H, 7-H, 8-H), 7.06 (d, 1H, $J = 2.8$ Hz, 2-H), 6.84 (d, 1H, $J = 2.8$ Hz, 3-H), 4.54 (t, 2H, $J = 6.9$ Hz, NCH_2–), 3.47 (t, 4H, $J = 6.6$ Hz, $(-CH_2Cl)_2$), 2.83 (t, 4H, $J = 6.6$ Hz, $(-CH_2)_2N$), 2.60 (t, 2H, $J = 6.5$ Hz, 4′-CH_2–), 2.12 (m, 2H, 2′-CH_2–), 1.56 (m, 2H, 3′-CH_2–); MS m/z 474 (M^+, 11), 425 (43), 420 (59), 369 (92), 334 (32), 292 (100), 279 (49); HRMS calcd for $C_{24}H_{24}Cl_2N_2O_4$ 474.1113, found 474.1128.

4.1.16. 7-Hydroxy-2,3-dihydronaphtho[2,3-*f*][1,4]oxazino-[2,3,4-*hi*]indole-8,13-dione (19) and 4,11-dihydroxy-1-{2-[4-(2-hydroxyethyl)-1-piperazinyl]ethyl}-1*H*-naphtho[2,3-*f*]indole-5,10-dione dihydrochloride (20) (Method A). The stirring solution of **9** (0.15 g, 0.39 mmol) and 1-(2-hydroxyethyl)piperazine (0.4 mL, 3.0 mmol) in dry *N*-methylpyrrolidone (2.0 mL) was heated at 100–105 °C for 1 h, cooled, and quenched with water (50 mL). The mixture was extracted with ethyl acetate (3×20 mL), the extract was washed with HCl (0.1 N, 10 mL). The combined acid solutions were used for the isolation of piperazine derivative **20**. The organic solution was washed with brine, water, dried, and evaporated. The residue was purified by column chromatography on silica gel by hexane–ethyl acetate (10:0 → 10:4) and crystallized from toluene to afford **19** (87 mg, 74%) as red crystals; mp >260 °C (subl.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.35 (s, 1H, OH), 8.21 (m, 1H, 9-H), 8.12 (m, 1H, 12-H), 7.84 (m, 2H, 10-H, 11-H), 7.64 (d, 1H, $J = 2.9$ Hz, 5-H), 6.79 (d, 1H, $J = 2.9$ Hz, 6-H), 4.66 (t, 2H, $J = 5.0$ Hz, OCH_2–), 4.45 (t, 2H, $J = 5.0$ Hz, NCH_2); UV (ethanol) λ_{max} 219, 255, 276, (450), 475, (509) nm; MS m/z 305 (100), 276 (4); HRMS calcd for $C_{24}H_{26}N_2O_6$ 305.0688, found 305.0690.

To the combined acidic solutions was added aqueous Na_2CO_3 (10%) up to pH 7.0. The solution was extracted with *n*-butanol (3×20 mL), the extract was washed with brine, water, dried, and evaporated. The residue was purified by column chromatography on silica gel by chloroform–methanol–NH_4OH (10:2:0 → 10:3:1), the red oil obtained after evaporation was dissolved in methanol (0.3 mL), and ethanolic HCl (0.1 N, 3 mL) was added. The mixture was freezed overnight and the red crystals precipitated were filtered, washed with ether, and after drying yielded **20** (21 mg, 11%), mp 186–189 °C.

4.1.17. 7-Hydroxy-2,3-dihydronaphtho[2,3-*f*][1,4]oxazino-[2,3,4-*hi*]indole-8,13-dione (19) (Method B). The stirring mixture of **21** (80 mg, 0.17 mmol) and 1 M solution $BBr_3{\cdot}SMe_2$ in dichloromethane (2.0 mL, 2.0 mmol) was mixed in dry dichloroethane (DCE, 20.0 mL) and refluxed for 1 h, cooled, quenched by the dropwise addition of methanol (2.0 mL) and then evaporated. The residue was partitioned between *n*-butanol (50 mL) and aqueous solution of $NaHCO_3$ (2%, 20 mL). The organic solution was worked up as it is described in method A to give **20** (45 mg, 52%); mp 186–189 °C (methanol); ^{1}H NMR (400 MHz, D_2O) δ 7.50 (m, 1H, 6-H), 7.46 (m, 1H, 9-H), 7.40 (m, 2H, 7-H, 8-H), 6.95 (br s, 1H, 2-H), 6.11 (br s, 1H, 3-H), 4.95 (t, 2H, NCH_2–), 4.51 (m, 4H, $(-CH_2)_2N$), 4.45 (m, 2H, CH_2OH), 4.22 (m, 2H, –CH_2N), 4.03 (m, 4H, $N(CH_2)_2$), 3.72 (m, 2H, NCH_2); MS m/z 435 (M^+, 18), 305 (15), 292 (18), 279 (52), 143 (100); HRMS calcd for $C_{24}H_{25}N_3O_5$ 435.1794, found 435.1804.

4.1.18. 4,11-Dimethoxy-1-{2-[4-(2-hydroxyethyl)-1-piperazinyl]ethyl}-1*H*-naphtho[2,3-*f*]indole-5,10-dione (21). This was synthesized from bromoethyl derivative **6** and 1-(2-hydroxyethyl)pyperazine as described for compound **11** as a yellow amorphous solid in 82% yield; mp 166–168 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.18 (m, 2H, 6-H, 9-H), 7.78 (m, 2H, 7-H, 8-H), 7.58 (d, 1H, $J = 3.1$ Hz, 2-H), 6.78 (d, 1H, $J = 3.1$ Hz, 3-H), 5.04 (t, 2H, $J = 7.1$ Hz, NCH_2–), 4.21 (m, 4H, $(-CH_2)_2$ N), 4.11 (m, 2H, CH_2OH), 4.09 (s, 3H, CH_3), 4.04 (s, 3H, CH_3), 3.90 (t, 2H, $J = 7.1$ Hz, –CH_2N), 3.56 (m, 2H, NCH_2), 3.42 (d, 2H, NCH_2), 3.34 (d, 2H, NCH_2); ^{13}C NMR (400 MHz, CD_3OD) δ 184.50 (C=O), 184.40 (C=O), 147.92 (C), 154.10 (C), 140.87 (C), 136.06 (C), 133.84 (C), 131.37 (C), 120.43 (C), 119.04 (C), 135.93 (CH), 134.60 (CH), 134.50 (CH), 127.37 (2CH), 104.19 (CH), 73.06 (CH_2), 70.60 (CH_2), 60.45 ($2CH_2$), 60.40 ($2CH_2$), 56.45 (CH_2), 43.92 (CH_2), 63.87 (CH_3), 62.36 (CH_3); UV (ethanol) λ_{max} 250, 283, 320, 423 nm; MS m/z 333 ($M^+ - C_6H_{14}N_2O$, 100), 318 (23), 304 (32), 290 (20); HRMS calcd for $C_{20}H_{15}NO_4$ 333.1001, found 333.1008. Anal. Calcd for $C_{26}H_{29}N_3O_5$: C, 67.37; H, 6.31; N, 9.07. Found: C, 67.15; H, 6.10; N, 8.97.

4.1.19. 4,11-Dimethoxy-1-[2-(1-piperidinyl)ethyl]-1*H*-naphtho[2,3-*f*]indole-5,10-dione (22). To a stirred solution of 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (**3b**; 0.20 g, 0.65 mmol) in DMF (10.0 mL) at 0–5 °C was portionwise added NaH (60% suspension in oil; 0.15 g, 3.8 mmol) and after 20 min was added 1-(2-chloroethyl)piperidine hydrochloride (0.27 g, 1.5 mmol). The reaction mixture was stirred at 30 °C for 2 h. During this time dark red color changed to yellow-brown, and then the reaction mixture was quenched with water (50 mL)–ice (20 g)–acetic acid (0.50 mL) mixture and aqueous Na_2CO_3 solution (10%) was added until pH 7.0 was reached. The aqueous layer was extracted with ethyl acetate (3×30 mL). The organic layers were combined, washed with 1 N Na_2CO_3, brine, water, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel by chloroform–methanol (10:0 → 10:4) and crystallized from toluene–heptane mixture (1:1) to produce **22** (0.17 g, 63%) as yellow crystals; mp 103–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (m, 2H, 6-H, 9-H), 7.71 (m, 2H, 7-H, 8-H), 7.29 (d, 1H, $J = 2.8$ Hz, 2-H), 6.80 (d, 1H,

$J = 2.8$ Hz, 3-H), 4.55 (t, 2H, $J = 6.9$ Hz, NCH_2–), 4.11 (s, 3H, OMe), 4.07 (s, 3H, OMe), 2.73 (t, 2H, $J = 6.9$ Hz, –CH_2N); 2.42 (m, 4H, –CH_2–), 1.60 (m, 4H, –CH_2–), 1.45 (m, 2H, –CH_2–); MS m/z 418 (M^+, 12), 387 (3), 291 (6), 262 (3), 98 (100); HRMS calcd for $C_{25}H_{26}N_2O_4$ 418.1893, found 418.1886.

4.1.20. 4,11-Dihydroxy-1-[2-(1-piperidinyl)ethyl]-1*H*-naphtho[2,3-*f*]indole-5,10-dione (23). Compound **23** was obtained from derivative **22** (0.11 g, 0.26 mmol) as it is described for compound **7**. The residue after the evaporation of the extract was purified by column chromatography on silica gel by chloroform–methanol (10:0 → 10:4) and crystallized from toluene–heptane mixture (1:1) to give **23** (85 mg, 84%) as red crystals; mp 142–144 °C; hydrochloride mp 220–223 °C (methanol); ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (m, 2H, 6-H, 9-H), 7.78 (m, 2H, 7-H, 8-H), 7.41 (d, 1H, $J = 2.6$ Hz, 2-H), 6.78 (d, 1H, $J = 2.6$ Hz, 3-H), 5.05 (t, 2H, NCH_2–), 3.68 (m, 4H, –CH_2N); 3.15 (t, 2H, –CH_2N); 2.01 (m, 2H, –CH_2–), 1.86 (m, 2H, –CH_2–), 1.60 (m, 2H, –CH_2–); UV (ethanol) λ_{max} 219, 238, 273, (450), 480, 514 nm; MS m/z 390 (M^+, 12), 292 (16), 279 (15), 98 (100); HRMS calcd for $C_{23}H_{22}N_2O_4$ 390.1594, found 390.1579.

Acknowledgements

This investigation was supported by Russian Fund for Basic Research, grant no 03-03-32090. We gratefully acknowledge extensive collaboration with Dr. V. Narayanan, Dr. E. A. Sausville, and staff of the Developmental Therapeutics Program of NCI (USA). We also thank Prof. Jan Balzarini from Rega Institute of Medical Research of the Catholic University of Leuven (Belgium).

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