Synthesis and Antiviral Activity of Helioxanthin Analogues

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A series of natural product analogues based on helioxanthin (**2**), with particular attention to modification of the lactone ring and methylenedioxy group, were synthesized and evaluated for their antiviral activities. Among them, lactam derivative **18** and helioxanthin cyclic hydrazide **28** exhibited significant in vitro antiviral activity against hepatitis B virus (EC_{50} = 0.08 and 0.03 μM, respectively). Compound **18** showed the most potent antiviral activity against hepatitis C virus (55% inhibition at 1.0 μM). Compound **12**, an acid-hydrolyzed product of helioxanthin cyclic imide derivative **9**, was found to exhibit broad-spectrum antiviral activity against hepatitis B virus (EC_{50} = 0.8 μM), herpes simplex virus type 1 (EC_{50} = 0.15 μM) and type 2 (EC_{50} < 0.1 μM), Epstein−Barr virus (EC_{50} = 9.0 μM), and cytomegalovirus (EC_{50} = 0.45 μM). Helioxanthin lactam derivative **18** also showed marked inhibition of herpes simplex virus type 1 (EC_{50} = 0.29 μM) and type 2 (EC_{50} = 0.16 μM). The cyclic hydrazide derivative of helioxanthin **28** and its brominated product **42** exhibited moderately potent activities against human immunodeficiency virus (EC_{50} = 2.7 and 2.5 μM, respectively). Collectively, these molecules represent a novel set of antiviral compounds with unique structural features.

Introduction

Arylnaphthalene lignan lactones are natural product molecules found in plant species, many exhibiting diverse biological activities, such as phosphodiesterase inhibition,[1] leukotriene biosynthesis inhibition,[2] hypolipidemic,[3] antitumoral,[4] and antiviral activities.[5,6] Helioxathin is an arylnaphthalene lignan lactone isolated from the root of *Heliopsis scabra* Dunal (Compositae)[7] and the whole plant of *Taiwania cryptomerioides* Hayata (Taxodiaceae).[8] The total synthesis of this molecule has been carried out by both inter- and intramolecular Diels−Alder reactions[9−11] and a benzannulation strategy.[12]

Recently, we have reported that helioxanthin and its analogues exhibit significant in vitro antiviral activity against hepatitis B virus (HBV) and flavivirus. It was found that helioxanthin and its analogues decreased cellular RNA levels of HBV and antigen expression as well as selective inhibition of HBV replication in a cell culture model.[13] In the past, anti-HBV nucleotide analogues such as (−)-(2*R*,5*S*)-1-[2-(hydroxymethyl)-oxathiolan-5-yl]cytosine (3TC), 9-[2-(phosphonomethoxy)-ethyl]adenine (PMEA), and 9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]guanine (PCV) have been evaluated in clinical trials. However, HBV-infected patients often experience a recurrence of HBV after a period of treatment with 3TC or PCV. This recurrence is commonly due to the emergence of viral resistance.[14,15] Some of the resistant viruses even gain cross resistance to the other anti-HBV nucleotide analogues.[16] With the intensive efforts in the search for effective antiviral agents against drug-resistant HBV, a number of nucleotide analogues have been developed and are currently under clinical evaluation for the treatment of 3TC-resistant HBV infections.[16,17]

We also have reported that helioxanthin and its analogues unexpectedly exhibit exceptional anti-HBV activity against 3TC-resistant HBV.[13] Because HBV replicates via the reverse transcription of a 3.5-kb pregenomic RNA, the inhibitory action of helioxanthin must be in an early stage of the viral life cycle. Helioxanthin and its analogues have a unique mechanism of antiviral action, different from those of the anti-HBV nucleotide analogues that inhibit HBV only during viral DNA synthesis. This class of compounds offers a unique characteristic in anti-HBV chemotherapy. Therefore, it was of interest to synthesize additional analogues of helioxanthin for the evaluation of structure−activity relationships and the development of more selective and potent antiviral agents.

For the reasons stated above, we synthesized a series of helioxanthin analogues, particularly through the modification of the lactone ring and methylenedioxy group of helioxanthin (**2**). The analogues were examined on their antiviral activities against HBV, hepatitis C virus (HCV), herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), Epstein−Barr virus (EBV), cytomegalovirus (CMV), and human immunodeficiency virus (HIV). Herein, we report a full account of the synthesis and biological evaluation of helioxanthin analogues with significant antiviral activity.

Chemistry

Helioxanthin (**2**) was synthesized using a previously described approach,[11] hydrolyzed with alkali, and es-

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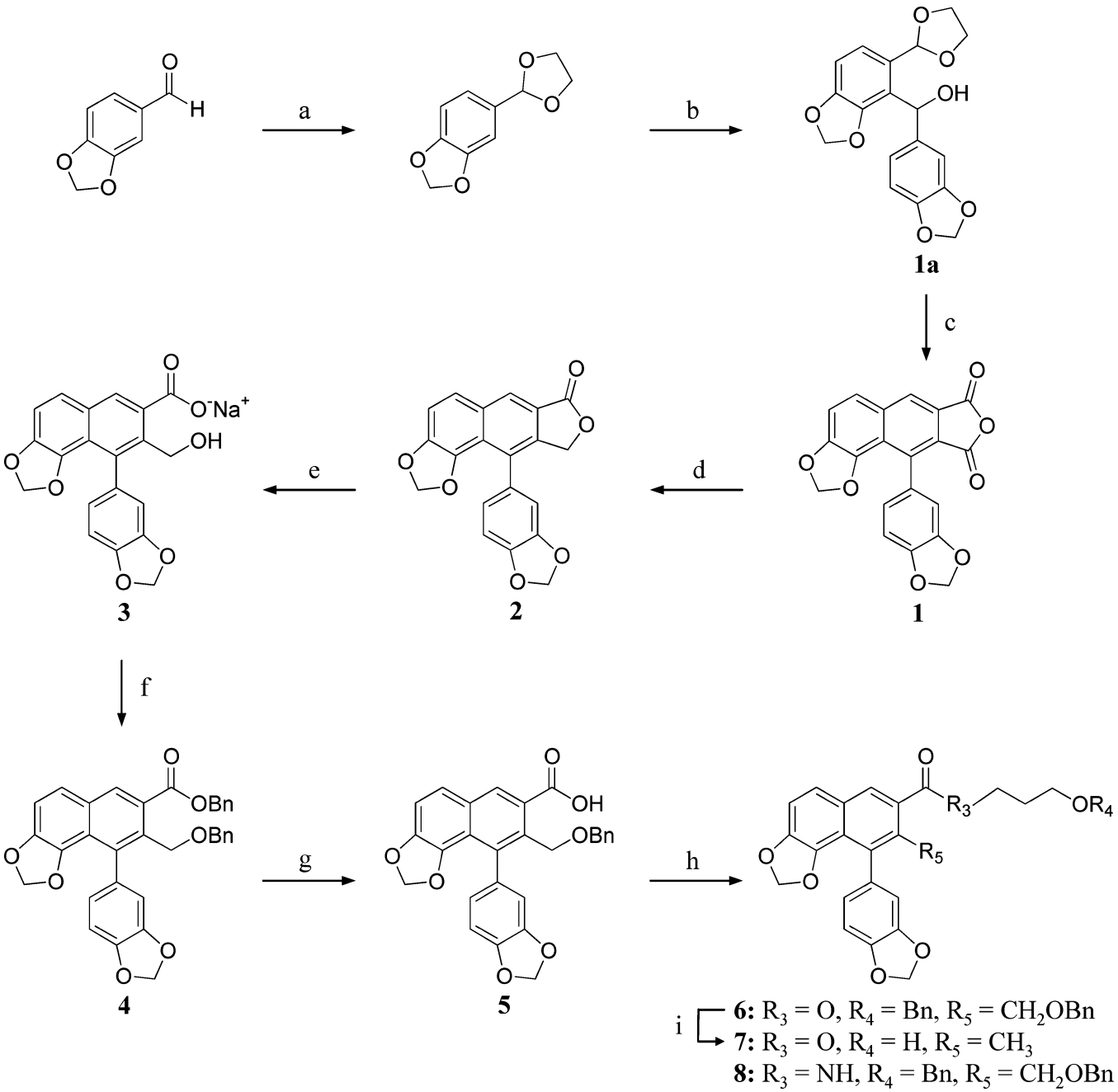
Scheme 1[a]



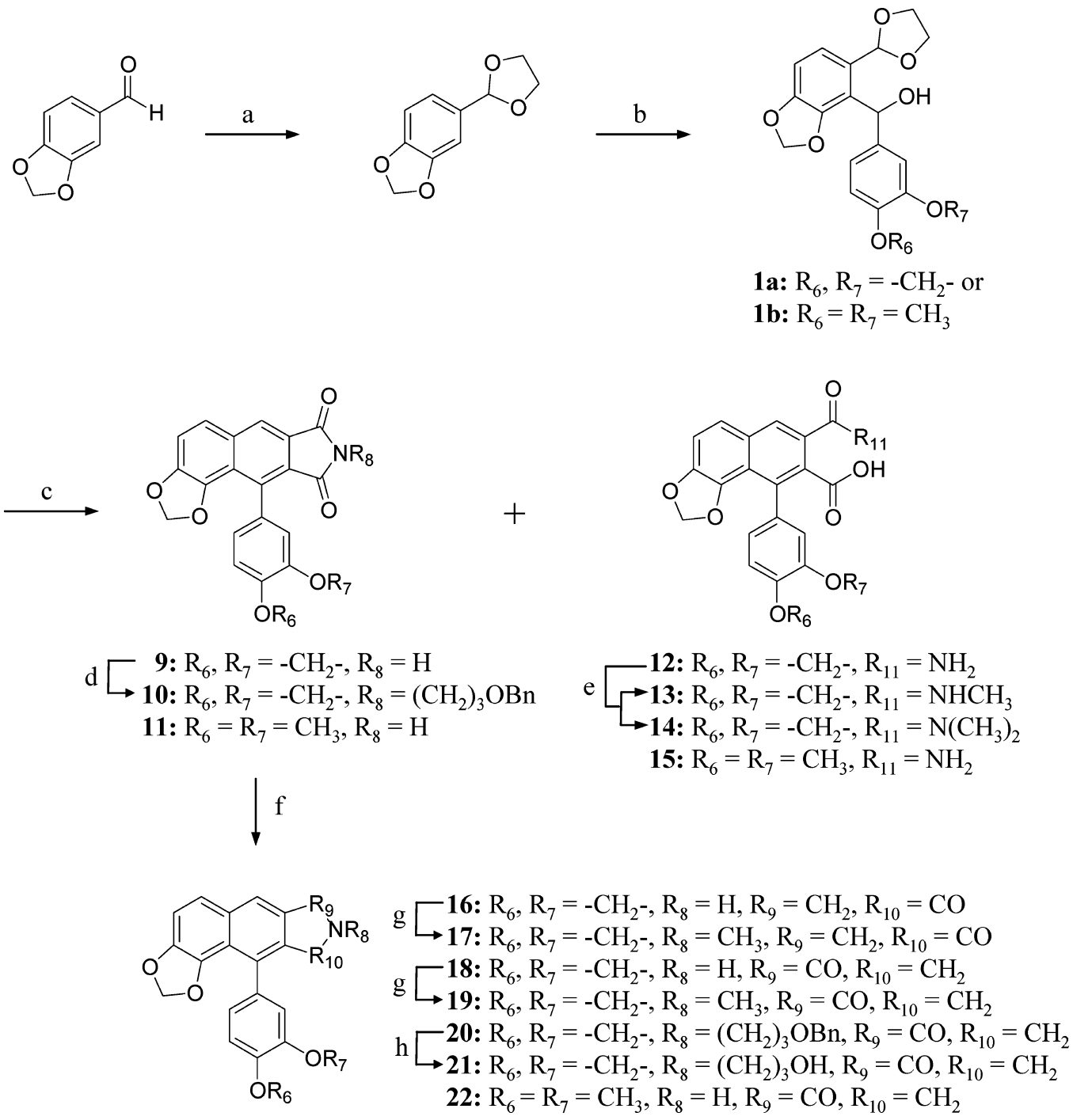
[a] Reagents and conditions: (a) $HO(CH_2)OH$, *p*-toluenesulfonic acid, reflux; (b) *n*-BuLi, piperonal, −78 ×b0°C to room temperature; (c) maleic anhydride, AcOH, Ac_2O, CH_2Cl_2, 140 °C, 24 h; (d) $NaBH_4$, THF, 0 °C, 3h; (g) NaOH−MeOH/H_2O (4:1), 70°C, 1 h; (h) $HO(CH_2)_3OBn$ (for **6**) or $H_2N(CH_2)_3OBn$ (for **8**, DCC, DMAP (for **6**) or 1-HOBt (for **8**), CH_2Cl_2, 0 °C; (i) Pd/C, THF, H_2, room temperature, 14 h.

terified with a mixture of alkali hydroxide and benzyl bromide to yield compound **4**. The benzyl ester group of compound **4** was cleaved by alkaline hydrolysis to the corresponding carboxylic acid and was coupled with 3-benzyloxy-1-propanol using 1,3-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) to afford compound **6**. Similarly, the coupling of compound **5** to 3-(benzyloxy)propylamine in the presence of DCC and 1-hydroxybenzotriazole hydrate (1-HOBt) in CH_2Cl_2 gave compound **8**.

The cyclic imides **9** and **11**, which exist as an imide/imidol tautomers, respectively, were prepared by the Diels−Alder reaction of the corresponding hydroxyacetals and maleimide, as depicted in Scheme 2. Compounds **12** and **15**, the acid-hydrolyzed products of imides **9** and **11**, were formed from the Diels−Alder reaction products. Lactams **16**, **18**, and **22** were prepared by the selective reduction of imides **9** and **11** with zinc dust in glacial acetic acid. Compounds **12**, **16**, and **18** were further reacted with iodomethane in KOH/DMSO to afford the N-methylated products **13**, **14**, **17**, and, **19**. Similarly, the reaction of imide **9** with trimethylsilyldiazomethane ($TMSCHN_2$) gave the O-methylated product **23**.

Mitsunobu reaction of benzyloxyalkyl alcohol with imide **9** in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine (PPh_3) in THF afforded a *N*-(benzyloxyalkyl)imide **10**, which was selectively reduced with zinc dust in acetic acid to give the corresponding lactam **20**. Debenzylation of compound

Scheme 2[a]



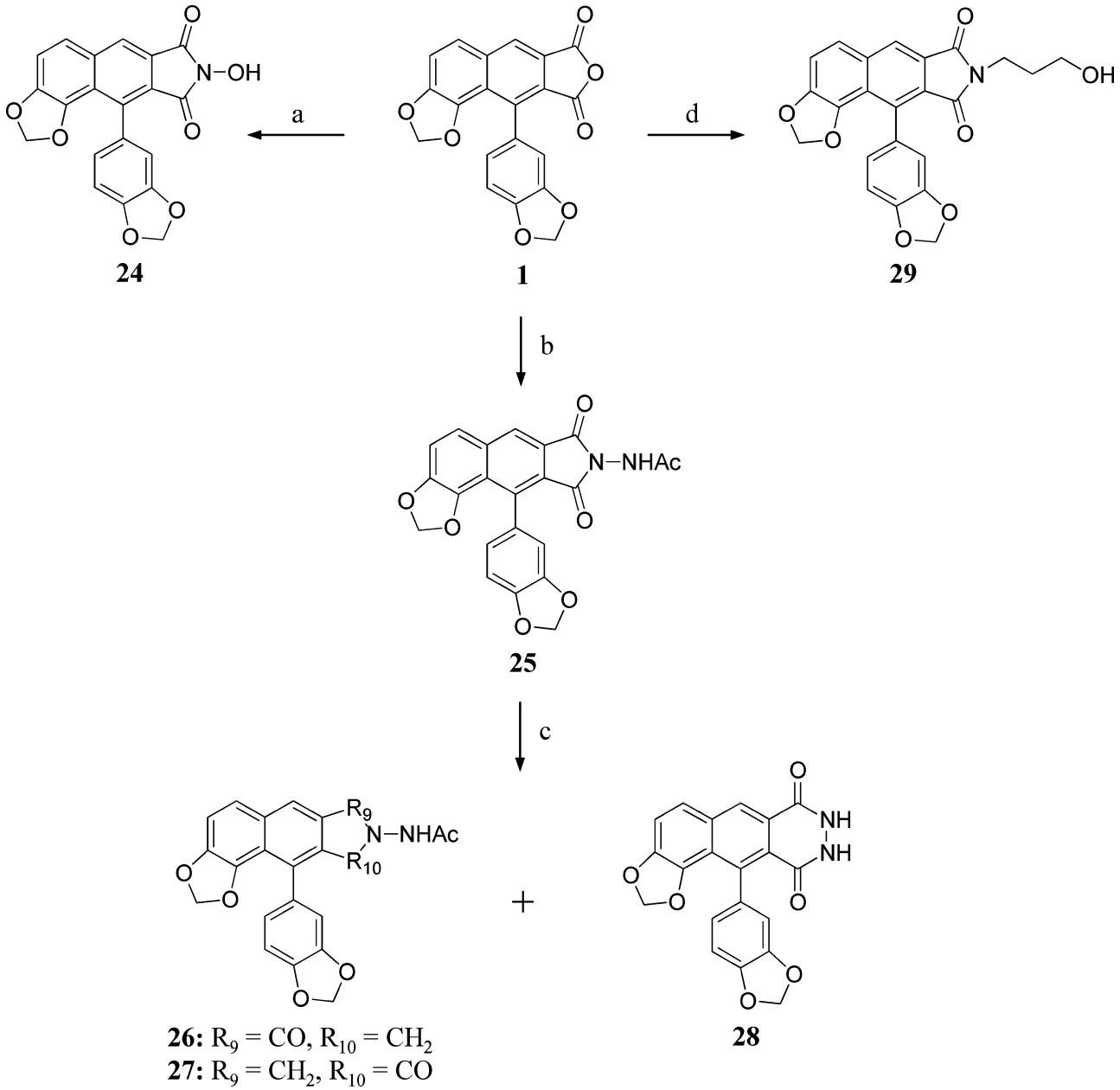
[a] Reagents and conditions: (a) $HO(CH_2)OH$, *p*-toluenesulfonic acid, reflux; (b) *n*-BuLi, piperonal (for **9** and **12**) or 3,4-dimethoxybenzaldehyde (for **11** and **15**), −78 °C to room temperature; (c) maleimide, AcOH, Ac_2O, CH_2Cl_2, 140 °C, 24 h; (d) $HO(CH_2)_3OBn$, PPh_3, DEAD, THF, 0 °C to room temperature; (e) KOH/DMSO, MeI, 24 h; (f) Zn/AcOH, 100 °C, 48 h; (g) KOH/DMSO, MeI, 1 h; (h) Pd/C, THF, H_2, room temperature, 20 h.

20 with Pd/C under hydrogen atmosphere provided *N*-(hydroxyalkyl)lactam **21**.

The *N*-hydroxyimide **24** and *N*-(hydroxyalkyl)imide **29** were synthesized by reaction of anhydride **1** with the respective hydroxyamine and hydroxyalkylamine, as shown in Scheme 3. The reaction of anhydride **1** with hydrazine hydrate in glacial acetic acid gave a *N*-acetoimidoimide **25**, which was converted to the cyclic hydrazide product **28**, as well as the lactams **26** and **27** by reaction with zinc dust in acetic acid.

Anhydride **1** was reacted with $TMSCHN_2$ in a methanolic THF solution to give bis-ester **30**, which was hydrolyzed with KOH in MeOH to yield compounds **31** and **32** (Scheme 4). The hydroxyacetal **1a** was subjected to Diels−Alder addition with diethyl acetylenedicarboxylate (DEADC) to afford compound **33**, which was converted to lactone **34** by reduction with lithium aluminum hydride (LAH). The conversion of imide **9** to diamide **36** was achieved by treatment with a mixture of concentrated ammonium hydroxide in THF at 40 °C.

Scheme 3[a]



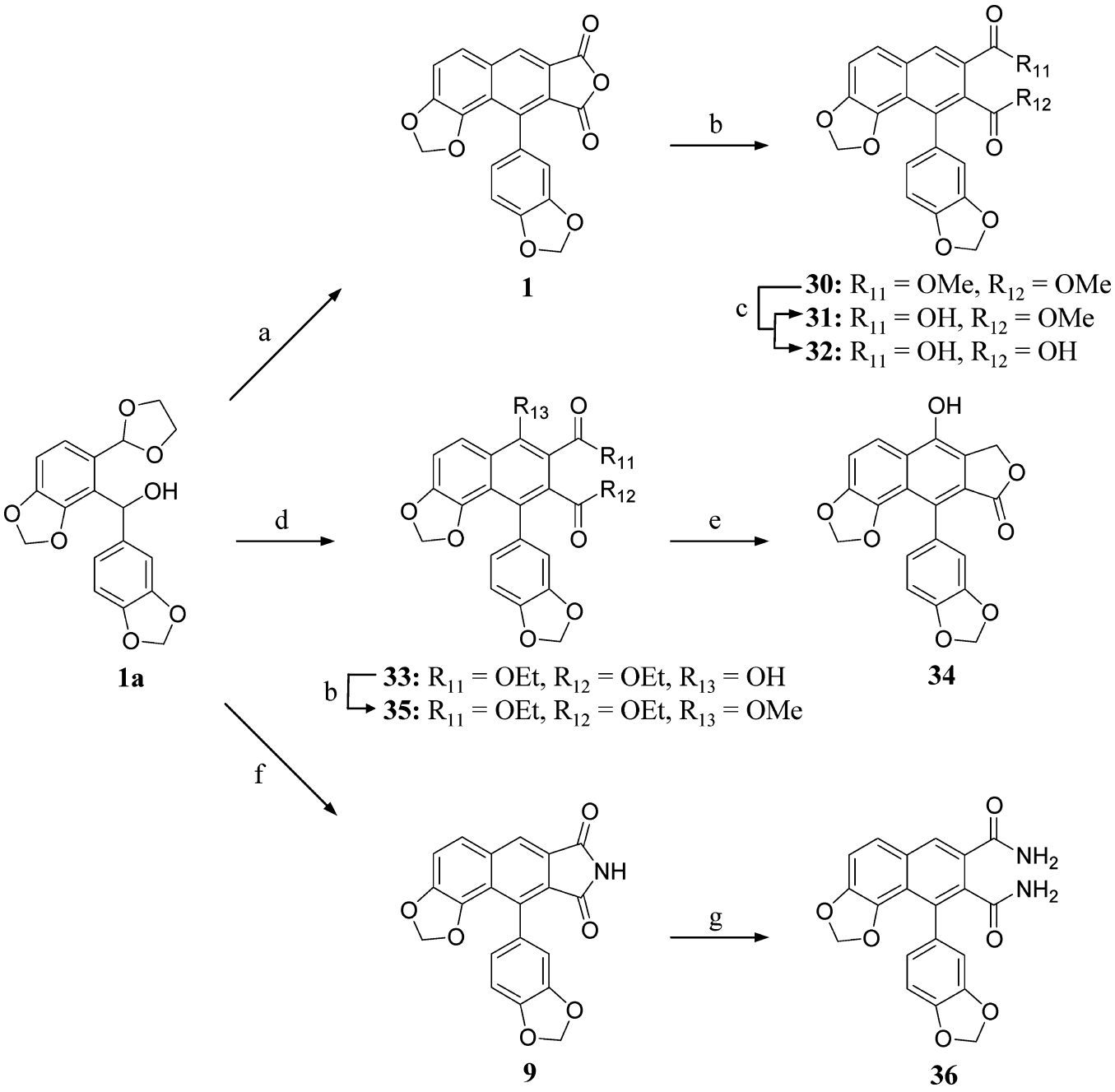
[a] Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, $N(Et)_3$, EtOH, reflux, 12 h; (b) $NH_2NH_2{\cdot}H_2O$, AcOH, reflux, 24 h; (c) Zn/AcOH, 100 °C, 5 h; (d) $H_2N(CH_2)_3OH$, toluene, reflux 3 h.

Compounds **2**, **18**, and **28** were treated with *N*-halosuccinimides in the presence of a catalytic amount of concentrated sulfuric acid to afford compounds **37**–**43**, which were selectively halogenated at the C-5 position (Scheme 5). The 5-halolactones **37**–**39** were subsequently hydrolyzed with NaOH in MeOH to yield compounds **44**–**46**.

Results and Discussion

Conservative estimates place the number of persons chronically infected with hepatitis B virus (HBV) at more than 300 million.[15] Currently approved agents of chronic HBV treatment include interferon-α and the nucleoside analogues lamivudine[18] and adefovir dipivoxil.[19] However, the side effects of interferon and the viral resistance of nucleoside analogues make the current treatment regimens far from satisfactory. New anti-HBV drugs with novel mechanisms of action are desperately needed. Helioxanthin and its derivatives are the first small molecules, described thus far, that have the ability to decrease HBV RNA. This very unique feature not only has clinical significance but also basic research value, because an understanding of their mechanism may lead to alternate therapies. Due to the growing number of patients harboring lamivudine resistant virus strains, new drugs with different mechanisms are needed for inclusion in and development of combination therapy regimens. However, this class of compound may lead to a new area of RNA interference. This may be the reason this class of compounds could target more than one virus. The different structure of these compounds may recognize, interact, and interfere with different RNA secondary structure, which is the subject of further investigation. For the reasons stated

Scheme 4[a]

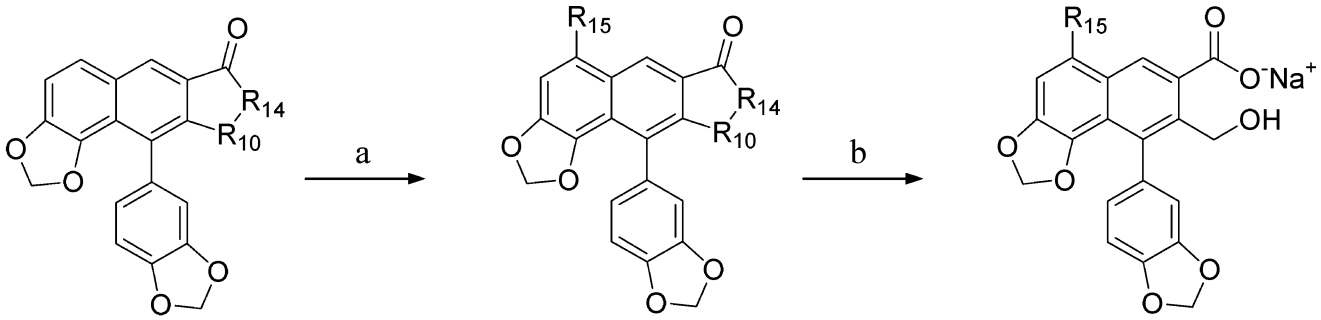


[a] Reagents and conditions: (a) maleic anhydride, AcOH, Ac_2O, CH_2Cl_2, 140 °C, 24 h; (b) $TMSCHN_2$, MeOH/THF (1:2), room temperature, 12 h; (c) KOH/MeOH, reflux 2−24 h; (d) DEADC, AcOH, CH_2Cl_2, 140 °C, 24 h; (e) LAH, THF, 0 °C to room temperature, 2 h; (f) maleimide, AcOH, Ac_2O, CH_2Cl_2, 140 °C, 24 h; (g) NH_4OH, THF, 40 °C, 72 h. ×b0

above and to achieve an optimal therapeutic window for this novel structure, the synthesis and biological investigation of additional helioxanthin derivatives were undertaken.

Of these analogues, the lactam **18** and the cyclic hydrazide **28** derivatives of helioxanthin (**2**) exhibited significant in vitro anti-HBV activity (EC_{50} = 0.08 and 0.03 μM, respectively), with compound **18** showing the most potent anti-HCV activity (55% inhibition at 1.0 μM). Compound **12**, the acid-hydrolyzed product of the cyclic imide **9**, was also more active than helioxanthin against HBV (EC_{50} = 0.8 μM). Compounds **15** and **22**, containing dimethoxy moieties instead of methylenedioxy groups in the C ring of compounds **12** and **18**, displayed potent antiviral activities against HCV (64 and 80% inhibition at 3.0 μM, respectively) as well as HBV (EC_{50} = 0.8 and 0.9 μM, respectively). The most potent anti-HSV compounds were **12** and **18**, which showed marked inhibition of HSV-1 (EC_{50} = 0.15 and 0.29 μM, respectively) and HSV-2 (EC_{50} < 0.1 and 0.16 μM, respectively). Compound **12** was also found to exhibit broad-spectrum antiviral activity against HSV-1 (EC_{50} = 0.15 μM), HSV-2 (EC_{50} < 0.1 μM), EBV (EC_{50} = 9.0 μM), and CMV (EC_{50} = 0.45 μM). This compound was about 140 and 210 times more potent than the reference drug acylclovir (EC_{50} = 21 μM) against HSV-1 and HSV-2, respectively. The cyclic hydrazide **28** and its brominated product **42** showed moderately potent anti-HIV activities (EC_{50} = 2.7 and 2.5 μM, respectively).

Scheme 5[a]



2: $R_{10} = CH_2$, $R_{14} = O$
18: $R_{10} = CH_2$, $R_{14} = NH$
28: $R_{10} = CO$, $R_{14} = NHNH$

37: $R_{10} = CH_2$, $R_{14} = O$, $R_{15} = Cl$
38: $R_{10} = CH_2$, $R_{14} = O$, $R_{15} = Br$
39: $R_{10} = CH_2$, $R_{14} = O$, $R_{15} = I$
40: $R_{10} = CH_2$, $R_{14} = NH$, $R_{15} = Br$
41: $R_{10} = CO$, $R_{14} = NHNH$, $R_{15} = Cl$
42: $R_{10} = CO$, $R_{14} = NHNH$, $R_{15} = Br$
43: $R_{10} = CO$, $R_{14} = NHNH$, $R_{15} = I$

44: $R_{15} = Cl$
45: $R_{15} = Br$
46: $R_{15} = I$

[a] Reagents and conditions: (a) *N*-chlorosuccinimide (for **37** and **41**), *N*-bromosuccinimide (for **38** and **42**), or *N*-iodosuccinimide (for **39** and **43**), CH_3CN or THF, conc H_2SO_4 (cat.), room temperature or reflux, 20−48 h; (b) aqueous NaOH, MeOH, 70 °C, 1−3 h.

We have previously reported that helioxanthin (**2**) exhibited antiviral activity against HBV, whereas retro-helioxanthin was much less active.[13] Alkaline hydrolysis of the lactone ring in helioxanthin, followed by coupling with alkyl chains (**3**−**7**), resulted in a large decrease in antiviral potency. In addition, the introduction of halogen atoms at the C-5 position of helioxanthin (**2**) and its alkaline-hydrolyzed derivative **3** both produced a significant loss in activity, as seen in compounds **37**−**39** and **44**−**46**. Therefore, it is likely that the introduction of substituents at the C-5 position is not desirable for improving the antiviral potency of helioxanthin.

We found that compound **12**, the acid-hydrolyzed product of cyclic imide **9**, exhibited potent antiviral activities against HBV and CMV as well as HSV. However, it is interesting to note that modifications of the carboxylic acid and amide groups in compound **12**, by dicarboxylic acid and diamide substituents, resulted in a significant loss of activity as seen in compounds **12**, **32**, and **36**.

The reduction of imide **9** yielded a lactam **18** and a retro-lactam **16**. The lactam **18** was more potent than compound **12** against HBV and HCV and as potent as compound **12** against HSV. In contrast, the retro-lactam **16** was not active at all. This finding indicates that the "up" carbonyl group of the lactam **18** is an important feature for the antiviral activity.

Comparing the antiviral activities of compounds **15** and **22** with those of compounds **12** and **18**, respectively, we found that the replacement of a methylenedioxy group by two methoxy substituents in the C ring exhibited more or less decreased activities. It would appear that the introduction of a substituent larger than the methylenedioxy group is not desirable for increased potency.

Compounds **10**, **13**, and **14**, the alkylated products of compounds **9** and **12**, turned out to be inactive. Moreover, modifications of the NH group in the lactam **18** resulted in the reduction of antiviral activities as shown in compounds **19**−**21** and **26**. Therefore, these findings indicate that the presence of a free NH group at this position is critical for antiviral activity.

The cyclic hydrazide **28** showed the most potent anti-HBV activity among those helioxanthin analogues tested. In addition, compound **28** exhibited moderately potent activity against HIV. It would therefore be promising to study helioxanthin analogues that contain a six-membered ring instead of the five-membered ring found in the lactam.

Helioxanthin is an interesting antiviral natural product with a potentially novel mode of action, as suggested by its unique ability to lower cellular RNA levels. The structurally novel helioxanthin analogues described herein are a promising class of anti-viral compounds that exhibit a wide spectrum of activity. Current and future efforts involve the development of more specific and potent derivatives for anti-viral drug therapy.

Experimental Section

General Methods. All of the solvents and reagents were obtained from commercial suppliers and were used without purification. Unless otherwise specified, reactions were performed under a nitrogen atmosphere with exclusion of moisture. All of the reaction mixtures were magnetically stirred and monitored by thin-layer chromatography (TLC) using Si250F precoated plates from J. T. Baker (0.25 mm). Flash column chromatography was performed on 32−63 D 60 Å silica gel from ICN SiliTech (ICN Biomedicals GmbH). Melting points were determined with an electrothermal capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-400 (400 MHz) or GE QE-plus 300 (300 MHz) spectrometer, chemical shifts (δ) are reported in parts per million (ppm) using chloroform-*d* (δ 7.24 ppm for ^1H and δ 77.23 ppm for ^{13}C) or DMSO-d_6 (2.50 ppm for ^1H and δ 39.43 ppm for ^{13}C) as internal references (Cambridge Isotope Labs, Inc.), and signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br s (broad singlet). Mass spectra were conducted at the Mass Spectrometry Laboratory of the University of Illinois.

10-Benzo[1,3]dioxol-5-yl-9*H*-furo[3′,4′:6,7]naphtho[1,2-*d*][1,3]dioxol-7-one (2). 10-Benzo[1,3]dioxol-5-yl-furo[3′,4′:

Table 1. Antiviral Activities of Helioxanthin and Helioxanthin Analogues

	antiviral activities (EC_{50}, μM)							cytotoxicity (ID_{50}, μM)	
compd	HBV	HCV[a]	HSV-1	HSV-2	EBV	CMV	HIV[b]	MT-2	CEM
1	>10	>10	>50	>50	>20	17.6	>100	>100	>50
2	1.0	3(64)	2	35	>20	7.3	>2.5(T)	2.5	31
3	3.4 >10	10(25)	9	25	>20	2.5	>10(T)	10	30
4	>10	10(71)	>50	>50	>20	ND[c]	>100	>100	>50
5	>10	>10	>25	>25	>20	ND	>48(T)	48	>50
6	>23	10(55)	>50	>50	>20	ND	>100	>100	>50
7	>10	>10	>25	>25	>15	ND	>10(T)	10	46
8	ND	>10	>25	>25	>15	3.7	>100	>100	10
9[d]	>10	ND	ND	ND	ND	ND	ND	ND	ND
10	ND	10(62)	>50	>50	>5	ND	>100	>100	>100
11[d]	0.8	ND	ND	ND	ND	ND	ND	ND	ND
12	>20	3(58)	0.15	<0.1	9	0.45	>5(T)	5	8.4
13	>10	>10	12	>25	>20	ND	>26(T)	26	29
14	0.8	>10	>50	>50	>20	ND	>70(T)	70	76
15	>10	3(64)	0.8	>3	>20	ND	>10(T)	10	3
16	>10	>10	>50	>50	>20	ND	>100	>100	90
17	0.08	3(29)	14	14	>20	ND	>26(T)	26	27
18	1.6	1(55)	0.29	0.16	11	ND	>4(T)	4	4.5
19	>20	>3	0.67	1	>20	ND	>8(T)	8	6
20	>20	10(85)	13	>20	>20	ND	>28(T)	28	67
21	0.9	10(58)	5	7	>20	ND	5	22	22
22	>10	3(80)	0.6	0.5	>20	ND	>16(T)	16	5
23	>5	>10	>50	>50	>20	ND	>100	>100	>100
24	>10	>10	>30	>30	>5	4.1	>16(T)	16	17
25	1	>10	>40	>40	>20	ND	>100	>100	93
26	>20	>10	5	10	13	ND	>7(T)	7	40
27	0.03	10(25)	17	40	>20	ND	>25(T)	25	32
28	>5	10(74)	1.4	1.4	>25	ND	15(T)	16	50
29	>20	>10	>30	>30	>5	8.1	>22(T)	22	27
30	>20	10(93)	>50	>50	>20	ND	>28(T)	28	50
31	>20	>10	>50	>50	>20	ND	>90(T)	90	74
32	>10	>10	>50	>50	>20	ND	>100	>100	>100
33	>10	10(62)	>50	>50	>10	ND	>15(T)	15	39
34	>20	>10	23	28	>10	ND	>13(T)	13	31
35	>20	10(60)	>50	>50	>20	ND	>24(T)	24	>100
36	>10	>10	>50	>50	>20	ND	>100	>100	>100
37	>60	>10	23	>25	>20	8.8	>50(T)	50	27
38	>40	>10	>50	>50	>15	ND	>100	>100	100
39	>20	>10	>25	>25	>10	ND	>80(T)	80	70
40	>10	10(32)	6.5	>20	>20	ND	>54(T)	54	38
41	>20	10(60)	7	>40	>20	ND	>30(T)	30	>100
42	>10	3(45)	16	>20	>20	ND	6	>100	28
43	>10	10(52)	>40	>40	>20	ND	2	35	40
44	>10	>10	>50	>50	>20	>20	>60(T)	60	>100
45	>18	ND	>50	>50	>20	>20	>50(T)	50	46.5
46	ND	10(36)	>50	>50	>20	>20	>80(T)	80	>100
ACV	0.02	ND	8	21	ND	ND	ND	ND	ND
3TC	ND	ND	ND	ND	0.4	ND	ND	ND	ND
ddC	ND	ND	ND	ND	ND	ND	0.8	70	5
Interferon		10u/ml (90)	ND	ND	ND	ND	ND	ND	ND

[a] The values in parentheses are percent inhibition. [b] (T) indicates toxicity. [c] Not determined. [d] Low solubility.

6,7]naphtho[1,2-*d*][1,3]dioxole-7,9-dione (**1**) was synthesized using a literature procedure.[11] To a mixture of sodium borohydride (218 mg, 5.8 mmol) in dry THF (100 mL) was added dropwise anhydride **1** (1.90 g, 5.25 mmol) in dry THF (100 mL) at 0 °C. The mixture was stirred at room temperature for 1 h and then acidified to pH 1−2 with 10% aqueous HCl solution. After being stirred for 1 h, the mixture was extracted with ether (3 × 100 mL), concentrated in vacuo, and chromatographed using $CHCl_3$ to give a lactone **2** (1.44 g, 79%) as a pale yellow powder. Mp: 242−244 °C. ^{1}H NMR (DMSO-d_6) δ: 8.56 (s, 1H, H4), 7.93 (d, 1H, H5, J = 8.4 Hz), 7.50 (d, 1H, H6, J = 8.4 Hz), 7.01 (d, 1H, H2′, J = 1.5 Hz), 6.95 (d, 1H, H5′, J = 8.1 Hz), 6.87 (dd, 1H, H6′, J = 1.5, 8.1 Hz), 6.08 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 15.6 Hz, J = 0.9 Hz), 5.99 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 6.0 Hz, J = 0.9 Hz), 5.28 (s, 2H, lactone-CH_2−). MS (FAB, positive) *m/z*: 349 $[M + H]^+$.

9-Benzo[1,3]dioxol-5-yl-8-hydroxymethyl-naphtho[1,2-*d*][1,3]dioxole-7-carboxylic Acid Monosodium Salt (3). Aqueous NaOH solution (1 N, 2.9 mL) was added to a solution of **2** (100 mg, 0.29 mmol) in MeOH (10 mL). The mixture was stirred at 70 °C for 1 h. The solvent was evaporated to give a crude product, which was purified by silica gel column chromatography using CH_2Cl_2/MeOH (3:1, v/v) to afford **3** (110 mg, 98%) as a white powder. Mp: 128−130 °C. ^{1}H NMR (DMSO-d_6) δ: 8.16 (s, 1H, H4), 7.52 (d, 1H, H5, J = 8.7 Hz), 7.24 (d, 1H, H6, J = 8.7 Hz), 6.88 (d, 1H, H5′, J = 8.4 Hz), 6.73 (s, 1H, H2′), 6.64 (d, 1H, H6′, J = 8.4 Hz), 6.05 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 18.9 Hz), 5.79 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 8.4 Hz), 4.16 (s, 2H, 2-CH_2OH).

9-Benzo[1,3]dioxol-5-yl-8-benzyloxymethyl-naphtho-[1,2-*d*][1,3]dioxole-7-carboxylic Acid Benzyl Ester (4). A mixture of **3** (78 mg, 0.2 mmol), benzyl bromide (0.38 mL, 3.2 mmol), and powdered KOH (168 mg) was heated at 140 °C for 3 h and then cooled to room temperature. The mixture was diluted with water (100 mL) and extracted with EtOAc (3 × 100 mL). The extract was washed with water (3 × 100 mL),

dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using CH_2Cl_2 to give **4** (56 mg, 51%) as a colorless liquid. ^{1}H NMR ($CDCl_3$) δ: 8.27 (s, 1H, H4), 7.51 (d, 1H, H5, J = 8.4 Hz), 7.23−7.44 (m, 10H, 2 × OCH_2Ph), 7.22 (d, 1H, H6, J = 8.4 Hz), 6.82 (d, 1H, H5′, J = 7.8 Hz), 6.77 (d, 1H, H2′, J = 1.5 Hz), 6.71 (dd, 1H, H6′, J = 1.5, 7.8 Hz), 6.05 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 10.2 Hz, J = 1.2 Hz), 5.84 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 4.8 Hz, J = 1.2 Hz), 5.34 (s, 2H, 3-$COOCH_2$Ph), 4.67 (s, 2H, 2-CH_2OCH_2Ph), 4.32 (s, 2H, 2-CH_2OBn). MS (EI) *m/z*: 546 $[M]^+$.

9-Benzo[1,3]dioxol-5-yl-8-benzyloxymethyl-naphtho-[1,2-*d*][1,3]dioxole-7-carboxylic Acid (5). A solution of **4** (56 mg, 0.1 mmol) and NaOH (16 mg, 0.4 mmol) in MeOH/H_2O (4:1, 2 mL) was heated at 70 °C for 12 h. The solvent was evaporated to dryness, and the residue was dissolved in water. The aqueous solution was acidified to pH 1−2 with 10% aqueous HCl solution and extracted with ether (3 × 50 mL). The extract was washed with water and brine and dried over $MgSO_4$. The evaporation of solvent yielded **5** (32 mg, 70%) as a white powder. Mp: 219−221 °C. ^{1}H NMR (DMSO-d_6) δ: 8.27 (s, 1H, H4), 7.70 (d, 1H, H5, J = 8.7 Hz), 7.38 (d, 1H, H6, J = 8.7 Hz), 7.17−7.25 (m, 5H, OCH_2Ph), 6.89 (d, 1H, H5′, J = 8.1 Hz), 6.79 (d, 1H, H2′, J = 1.5 Hz), 6.65 (dd, 1H, H6′, J = 1.5, 8.1 Hz), 6.06 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 18.0 Hz, J = 0.6 Hz), 5.85 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 9.3 Hz, J = 0.9 Hz), 4.53 (s, 2H, 2-CH_2OCH_2Ph), 4.24 (s, 2H, 2-CH_2OBn). MS (FAB, positive) *m/z*: 457 $[M + H]^+$.

9-Benzo[1,3]dioxol-5-yl-8-benzyloxymethyl-naphtho-[1,2-*d*][1,3]dioxole-7-carboxylic Acid 3-Benzyloxy-propyl Ester (6). To a stirred solution of 3-benzyloxy-1-propanol (16.6 mg, 0.1 mmol), 1,3-dicyclohexylcarbodiimide (31 mg, 0.15 mmol), and 4-(dimethylamino)pyridine (14.6 mg, 0.12 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise compound **5** (54.8 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The mixture was stirred for 4 h at room temperature and concentrated in vacuo. The residue was chromatographed over silica gel using CH_2Cl_2/MeOH (50:1, v/v) to give **6** (61.2 mg, 84%) as a yellow liquid. ^{1}H NMR ($CDCl_3$) δ: 8.16 (s, 1H, H4), 7.47 (d, 1H, H5, J = 8.7 Hz), 7.20−7.45 (m, 11H, H6 + 2 × OCH_2Ph), 6.82 (d, 1H, H5′, J = 7.8 Hz), 6.76 (d, 1H, H2′, J = 1.5 Hz), 6.70 (dd, 1H, H6′, J = 1.5, 7.8 Hz), 6.06 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 9.9 Hz, J = 1.5 Hz), 5.84 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 4.5 Hz, J = 1.5 Hz), 4.65 (s, 2H, OCH_2Ph), 4.53 (s, 2H, OCH_2Ph), 4.42 (t, 2H, 3-$COOCH_2(CH_2)_2OBn$, J = 6.3 Hz), 4.35 (s, 2H, 2-CH_2OBn), 3.62 (t, 2H, 3-$COO(CH_2)_2CH_2OBn$, J = 6.3 Hz), 2.06 (quintet, 2H, 3-$COOCH_2CH_2CH_2OBn$, J = 6.3 Hz). MS (EI) *m/z*: 604 $[M]^+$.

9-Benzo[1,3]dioxol-5-yl-8-methyl-naphtho[1,2-*d*][1,3]-dioxole-7-carboxylic Acid 3-Hydroxy-propyl Ester (7). A mixture of **6** (48 mg, 0.079 mmol) and 10% Pd/C (12 mg) in dry THF (5 mL) was stirred for 14 h at room temperature under 1 atm of hydrogen. The mixture was filtered, and the filtrate evaporated at reduced pressure. The residue was purified by column chromatography on silica gel using CH_2Cl_2/MeOH (40:1, v/v) to yield **7** (30 mg, 93%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 8.32 (s, 1H, H4), 7.50 (d, 1H, H5, J = 8.7 Hz), 7.18 (d, 1H, H6, J = 8.7 Hz), 6.87 (d, 1H, H5′, J = 7.8 Hz), 6.72 (d, 1H, H2′, J = 1.5 Hz), 6.68 (dd, 1H, H6′, J = 1.5, 7.8 Hz), 6.05 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 9.6 Hz, J = 1.5 Hz), 5.83 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 1.5 Hz, J = 1.5 Hz), 4.54 (t, 2H, 3-$COOCH_2(CH_2)_2OH$, J = 6.3 Hz), 3.83 (t, 2H, 3-$COO(CH_2)_2CH_2OH$, J = 6.3 Hz), 2.34 (s, 3H, 2-CH_3), 2.06 (quintet, 2H, 3-$COOCH_2CH_2CH_2OH$, J = 6.3 Hz). MS (EI) *m/z*: 408 $[M]^+$.

9-Benzo[1,3]dioxol-5-yl-8-benzyloxymethyl-naphtho-[1,2-*d*][1,3]dioxole-7-carboxylic Acid (3-Benzyloxy-propyl)-amide (8). To a stirred solution of 3-amino-1-propanol (7.51 g, 0.1 mol) in THF (150 mL) was added 60% sodium hydride dispersion in mineral oil (4 g, 0.1 mol) in small portions at room temperature. The mixture was stirred for 30 min under nitrogen, and benzyl bromide (11.9 mL, 0.1 mol) was added. The mixture was stirred for 10 h at room temperature and concentrated in vacuo. The residue was partitioned between 1 N aqueous HCl solution and CH_2Cl_2. The aqueous layer was alkalified to pH 10 with 10% aqueous NaOH solution and extracted with CH_2Cl_2 (3 × 100 mL). The extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography using CH_2Cl_2/MeOH (3:1 to 2:1, v/v) to give 3-(benzyloxy)propylamine (1.37 g, 8.3%) as a yellow oil. To a mixture of **5** (32 mg, 0.07 mmol) and 3-(benzyloxy)propylamine (11.6 mg, 0.07 mmol), and 1-hydroxybenzotriazole hydrate (9.5 mg, 0.07 mmol) in CH_2Cl_2 (5 mL) was added dropwise 1,3-dicyclohexylcarbodiimide (14.4 mg, 0.07 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The reaction mixture was stirred for 18 h at room temperature and concentrated in vacuo. The residue was purified by silica gel column chromatography using CH_2Cl_2/MeOH (30:1, v/v) to afford **8** (36 mg, 85%) as a pale yellow liquid. ^{1}H NMR ($CDCl_3$) δ: 8.05 (s, 1H, H4), 7.44 (d, 1H, H5, J = 8.7 Hz), 7.19−7.28 (m, 11H, H6 + 2 × OCH_2Ph), 6.78−6.82 (m, 3H, H2′ + H5′ + H6′), 6.06 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 6.9 Hz, J = 1.5 Hz), 5.84 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 4.2 Hz, J = 1.5 Hz), 4.45 (s, 4H, 2 × OCH_2Ph), 4.38 (s, 2H, 2-CH_2OBn), 3.55 (m, 4H, 3-$CONHCH_2CH_2CH_2OBn$), 1.87 (quintet, 2H, 3-$CONHCH_2CH_2CH_2OBn$, J = 6.3 Hz). MS (FAB, positive) *m/z*: 604 $[M + H]^+$.

10-Benzo[1,3]dioxol-5-yl-1,3-dioxa-8-aza-dicyclopenta-[*a*,*g*]naphthalene-7,9-dione (9) and 9-Benzo[1,3]dioxol-5-yl-7-carbamoyl-naphtho[1,2-*d*][1,3]dioxole-8-carboxylic Acid (12). The hydroxyacetal **1a** (7.34 g, 21.3 mmol), maleimide (2.07 g, 21.3 mmol), acetic anhydride (7 mL), CH_2Cl_2 (7 mL), and glacial acetic acid (3 mL) were heated at 140 °C for 24 h. The cooled mixture was diluted with CH_2Cl_2 (100 mL), washed with 5% $NaHCO_3$ solution (3 × 100 mL), dried over $MgSO_4$, and concentrated under vacuum. The silica gel column chromatography of the crude product using CH_2Cl_2/acetone (30:1 to 3:1, v/v) gave two fractions. The first fraction eluted with CH_2Cl_2/acetone (30:1, v/v) gave a yellow solid that was then recrystallized from acetone to give an imide **9** (1.33 g, 17%). Mp: 306−308 °C. ^{1}H NMR (DMSO-d_6) δ: 8.61 (s, 1H, H4), 7.98 (d, 1H, H5, J = 8.7 Hz), 7.62 (d, 1H, H6, J = 8.7 Hz), 6.93 (d, 1H, H2′, J = 1.5 Hz), 6.92 (d, 1H, H5′, J = 7.8 Hz), 6.79 (dd, 1H, H6′, J = 1.5, 7.8 Hz), 6.09 (AB, 2H, 3′,4′-OCH_2O-, $\Delta\delta$ = 5.7 Hz), 5.99 (AB, 2H, 7,8-OCH_2O-, $\Delta\delta$ = 4.5 Hz). MS (FAB, positive) *m/z*: 362 $[M + H]^+$.

The second fraction eluted with CH_2Cl_2/acetone (3:1, v/v) afforded a pale yellow solid (**12**, 1.66 g, 21%) that was identified as the acid hydrolysis product of imide **9**. Mp: 207−209 °C. ^{1}H NMR ($CDCl_3$) δ: 8.31 (s, 1H, H4), 7.62 (s, 1H, 2-COOH), 7.60 (d, 1H, H5, J = 8.4 Hz), 7.27 (d, 1H, H6, J = 8.4 Hz), 6.87−6.92 (m, 3H, H2′ + H5′ + H6′), 6.03 (s, 2H, 3′,4′-OCH_2O−), 5.97 (s, 2H, 7,8-OCH_2O-). ^{13}C NMR (DMSO-d_6) δ: 169.40, 146.52, 146.46, 145.13, 140.95, 138.70, 130.88, 130.08, 129.13, 128.45, 124.63, 123.35, 122.72, 119.83, 110.95, 109.85, 107.61, 100.91, 79.11, 44.28. MS (FAB, positive) *m/z*: 336 $[M - CONH_2 + H]^+$. Regiochemical assignment of the carboxylate and carboxamide groups for compound **12** was carried out by direct comparison with the chemical shifts for H-4, H-5, and H-6 in compound **32**. The chemical shits of H-4 (8.61 ppm), H-5 (7.98 ppm), and H-6 (7.62 ppm) in compound **12** are downfield shifted compared with the chemical shifts of H-4 (8.25 ppm), H-5 (7.53 ppm), and H-6 (7.24 ppm) in compound **32**, indicating that they are adjacent to the carboxamide in compound **12**, rather than the carboxylate as in compound **32**.

10-Benzo[1,3]dioxol-5-yl-8-(3-benzyloxy-propyl)-1,3-dioxa-8-aza-dicyclopenta[*a*,*g*]naphthalene-7,9-dione (10). A solution of diethyl azodicarboxylate (52 mg, 0.3 mmol) in dry THF (3 mL) was added dropwise to a stirred solution of **9** (108 mg, 0.3 mmol), 3-benzyloxy-1-propanol (50 mg, 0.3 mmol), and triphenylphosphine (79 mg, 0.3 mmol) in dry THF (6 mL) at 0 °C over 30 min. The mixture was stirred at room temperature for 30 h and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with *n*-hexane/EtOAc (2:1, v/v) to give **10** (56 mg, 37%) as a yellow powder. Mp: 153−155 °C. ^{1}H NMR ($CDCl_3$) δ: 8.24 (s, 1H, H4), 7.66 (d, 1H, H5, J = 8.4 Hz), 7.35 (d, 1H, H6, J = 8.4 Hz), 7.24−7.26 (m, 5H, OCH_2Ph), 6.78−6.91 (m, 3H, H2′ + H5′ + H6′), 6.07 (AB, 2H, 3′,4′-OCH_2O−,

$\Delta\delta$ = 15.3 Hz, J = 1.5 Hz), 5.95 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 5.4 Hz, J = 1.2 Hz), 4.45 (s, 2H, OCH_2Ph), 3.80 (t, 2H, $NCH_2(CH_2)_2OBn$, J = 6.0 Hz), 3.54 (t, 2H, $N(CH_2)_2CH_2OBn$, J = 6.0 Hz), 2.01 (quintet, 2H, $NCH_2CH_2CH_2OBn$, J = 6.0 Hz). MS (EI) *m/z*: 509 $[M]^+$.

10-(3,4-Dimethoxy-phenyl)-1,3-dioxa-8-aza-dicyclopenta[*a*,*g*]naphthalene-7,9-dione (11) and 7-Carbamoyl-9-(3,4-dimethoxy-phenyl)-naphtho[1,2-*d*][1,3]dioxole-8-carboxylic Acid (15). The acetal (2.25 g, 11.6 mmol) of piperonal was dissolved in dry THF (40 mL) under nitrogen and cooled to −78 °C, and *n*-butyllithium (1.6 M in hexanes, 7.98 mL, 12.8 mmol) was added dropwise over 30 min. The mixture was stirred for 15 min and then at 0 °C for 20 min. The mixture was again cooled to −78 °C, followed by dropwise addition of 3,4-dimethoxybenzaldehyde (1.93 g, 11.6 mmol) in THF (15 mL). After being stirred for 20 min, the solution was gradually warmed to room temperature and stirred for another 1.5 h, followed by the addition of water (100 mL). The resulting mixture was extracted with ether (3 × 100 mL), dried over $MgSO_4$, and concentrated to provide a crude hydroxyacetal **1b** (4.18 g). The crude product was employed in the following reaction without further purification.

The hydroxyacetal **1b** (4.18 g, 11.6 mmol), maleimide (1.13 g, 11.6 mmol), acetic anhydride (4 mL), CH_2Cl_2 (4 mL), and glacial acetic acid (1.8 mL) were heated at 140 °C for 24 h. The cooled mixture was diluted with CH_2Cl_2 (100 mL), washed with 5% $NaHCO_3$ solution (3 × 100 mL), dried over $MgSO_4$, and concentrated in vacuo. The silica gel column chromatography of the crude product using CH_2Cl_2/acetone (30:1 to 3:1, v/v) gave two fractions. The first fraction eluted with CH_2Cl_2/acetone (30:1, v/v) gave a yellow solid, which was then recrystallized from acetone to give imide **11** (800 mg, 18%). Mp 288−290 °C. ^{1}H NMR (DMSO-d_6) δ: 8.60 (s, 1H, H4), 7.98 (d, 1H, H5, J = 8.7 Hz), 7.62 (d, 1H, H6, J = 8.7 Hz), 6.88−6.96 (m, 3H, H2′ + H5′ + H6′), 5.98 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 3.3 Hz), 3.81, 3.68 (each s, 2 × 3H, 3′-OCH_3 + 4′-OCH_3). MS (FAB, positive) *m/z*: 378 $[M + H]^+$.

The second fraction eluted with CH_2Cl_2/acetone (3:1, v/v) afforded a white solid (**15**, 213 mg, 5%), which was identified as the acid hydrolysis product of imide **11**. Mp: 240−242 °C. ^{1}H NMR (DMSO-d_6) δ: 8.42 (s, 1H, H4), 7.70 (d, 1H, H5, J = 8.7 Hz), 7.41 (d, 1H, H6, J = 8.7 Hz), 6.96−7.00 (m, 3H, H2′ + H5′ + H6′), 5.98 (s, 2H, 7,8-OCH_2O-), 3.79, 3.74 (each s, 2 × 3H, 3′-OCH_3 + 4′-OCH_3). MS (FAB, positive) *m/z*: 352 $[M - CONH_2 + H]^+$.

9-Benzo[1,3]dioxol-5-yl-7-methylcarbamoyl-naphtho-[1,2-*d*][1,3]dioxole-8-carboxylic Acid (13) and 9-Benzo-[1,3]dioxol-5-yl-7-dimethylcarbamoyl-naphtho[1,2-*d*][1,3]-dioxole-8-carboxylic Acid (14). To DMSO (3 mL) was added powdered KOH (64 mg, 1.1 mmol). After the mixture was stirred for 5 min, compound **12** (108 mg, 0.28 mmol) was added, followed immediately by iodomethane (0.035 mL, 0.57 mmol). The mixture was stirred for 24 h and poured into water (30 mL), and then the product was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extract was washed with water (5 × 30 mL), dried over $MgSO_4$, and concentrated in vacuo. The resulting product was purified by column chromatography on silica gel using CH_2Cl_2/acetone (10:1, v/v) to yield **13** (20 mg, 18%) as a pale yellow powder and **14** (80 mg, 71%) as a pale yellow oil, respectively. **13.** Mp: 223−225 °C. ^{1}H NMR ($CDCl_3$) δ: 8.26 (s, 1H, H4), 7.60 (d, 1H, H5, J = 8.7 Hz), 7.57 (s, 1H, 2-COOH), 7.25 (d, 1H, H6, J = 8.7 Hz), 6.87−6.92 (m, 3H, H2′ + H5′ + H6′), 6.04 (s, 2H, 3′,4′-OCH_2O−), 5.97 (s, 2H, 7,8-OCH_2O−), 3.07 (d, 3H, 3-$CONHCH_3$, J = 4.8 Hz). **14.** ^{1}H NMR ($CDCl_3$) δ: 7.85 (s, 1H, H4), 7.52 (d, 1H, H5, J = 8.7 Hz), 7.32 (s, 1H, 2-COOH), 7.25 (d, 1H, H6, J = 8.7 Hz), 6.86−6.92 (m, 3H, H2′ + H5′ + H6′), 6.03 (s, 2H, 3′,4′-OCH_2O−), 5.95 (s, 2H, 7,8-OCH_2O−), 3.12 (s, 6H, 3-$CON(CH_3)_2$).

10-Benzo[1,3]dioxol-5-yl-7,8-dihydro-1,3-dioxa-8-aza-dicyclopenta[*a*,*g*]naphthalen-9-one (16) and 10-Benzo-[1,3]dioxol-5-yl-8,9-dihydro-1,3-dioxa-8-aza-dicyclopenta-[*a*,*g*]naphthalen-7-one (18). Compound **9** (181 mg, 0.5 mmol) was dissolved in glacial acetic acid (5 mL), and the freshly activated zinc dust (328 mg) was added thereto and then heated in an oil bath at 100 °C for 48 h. The insoluble solid was filtered off, and the majority of acetic acid was removed with a rotary evaporator. The obtained residue was neutralized to pH 7 with 10% aqueous NaOH solution and extracted with $CHCl_3$ (3 × 100 mL). The extract was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel, eluting with CH_2Cl_2/acetone (3:1 to 2:1, v/v) to give two fractions. The first (minor) and the second (major) fractions afforded a retro-lactam **16** (12 mg, 7%) and a lactam **18** (56 mg, 32%) as pale yellow solids, respectively. **16.** Mp: 267−269 °C. ^{1}H NMR (DMSO-d_6) δ: 8.48 (s, 1H, NH), 7.99 (s, 1H, H4), 7.64 (d, 1H, H5, J = 8.7 Hz), 7.42 (d, 1H, H6, J = 8.7 Hz), 6.83 (d, 1H, H5′, J = 7.8 Hz), 6.80 (d, 1H, H2′, J = 1.5 Hz), 6.66 (dd, 1H, H6′, J = 1.5, 7.8 Hz), 6.04 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 3.9 Hz), 5.86 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 5.4 Hz), 4.38 (br s, 2H, lactam-CH_2−). MS (FAB, positive) *m/z*: 348 $[M + H]^+$. **18.** Mp: 252−254 °C. ^{1}H NMR (DMSO-d_6) δ: 8.59 (s, 1H, NH), 8.27 (s, 1H, H4), 7.83 (d, 1H, H5, J = 8.7 Hz), 7.41 (d, 1H, H6, J = 8.7 Hz), 6.98 (s, 1H, H2′), 6.94 (d, 1H, H5′, J = 7.8 Hz), 6.84 (d, 1H, H6′, J = 7.8 Hz), 6.07 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 14.4 Hz), 5.93 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 6.0 Hz), 4.17 (br s, 2H, lactam-CH_2−). ^{13}C NMR (DMSO-d_6) δ: 169.83, 146.98, 146.91, 145.58, 141.40, 139.14, 131.33, 130.53, 129.59, 128.90, 125.07, 123.79, 123.16, 120.28, 111.38, 110.28, 108.04, 101.35, 79.55, 44.71. MS (FAB, positive) *m/z*: 348 $[M + H]^+$.

10-Benzo[1,3]dioxol-5-yl-8-methyl-7,8-dihydro-1,3-dioxa-8-aza-dicyclopenta[*a*,*g*]naphthalen-9-one (17). Powdered KOH (11.2 mg, 0.2 mmol) was added to DMSO (1 mL). After the mixture was stirred for 5 min, compound **16** (18 mg, 0.05 mmol) was added, followed immediately by iodomethane (0.006 mL, 0.1 mmol). The mixture was stirred for 1 h and poured into water (15 mL), then the product was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extract was washed with water (5 × 20 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using CH_2Cl_2/acetone (10:1, v/v) to provide **17** (12 mg, 66%) as a pale yellow powder. Mp: 242−244 °C. ^{1}H NMR ($CDCl_3$) δ: 7.79 (s, 1H, H4), 7.50 (d, 1H, H5, J = 8.4 Hz), 7.29 (d, 1H, H6, J = 8.4 Hz), 6.83−6.88 (m, 3H, H2′ + H5′ + H6′), 6.04 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 21.6 Hz, J = 1.5 Hz), 5.89 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 2.4 Hz), 4.46 (s, 2H, lactam-CH_2−), 3.14 (s, 3H, NCH_3). MS (FAB, positive) *m/z*: 362 $[M + H]^+$.

10-Benzo[1,3]dioxol-5-yl-8-methyl-8,9-dihydro-1,3-dioxa-8-aza-dicyclopenta[*a*,*g*]naphthalen-7-one (19). Powdered KOH (11.2 mg, 0.2 mmol) was added to DMSO (1 mL). After the mixture was stirred for 5 min, compound **18** (18 mg, 0.05 mmol) was added, followed immediately by iodomethane (0.006 mL, 0.1 mmol). The mixture was stirred for 1 h and poured into water (15 mL), then the product was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extract was washed with water (5 × 20 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using CH_2Cl_2/acetone (10:1, v/v) to give **19** (12 mg, 66%) as a pale yellow powder. Mp: 234−236 °C. ^{1}H NMR ($CDCl_3$) δ: 8.30 (s, 1H, H4), 7.66 (d, 1H, H5, J = 8.4 Hz), 7.26 (d, 1H, H6, J = 8.4 Hz), 6.81−6.91 (m, 3H, H2′ + H5′ + H6′), 6.06 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 8.4 Hz, J = 1.2 Hz), 5.92 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 7.8 Hz, J = 1.5 Hz), 4.26 (q, 2H, lactam-CH_2-, J = 6.3 Hz), 3.18 (s, 3H, NCH_3). MS (EI) *m/z*: 361 $[M]^+$.

10-Benzo[1,3]dioxol-5-yl-8-(3-benzyloxy-propyl)-8,9-dihydro-1,3-dioxa-8-aza-dicyclopenta[*a*,*g*]naphthalen-7-one (20). Compound **10** (40 mg, 0.08 mmol) was dissolved in glacial acetic acid (3 mL), the freshly activated zinc dust (206 mg) was added thereto, and then the mixture was heated in an oil bath at 100 °C for 48 h. The insoluble solid was filtered off, and the majority of acetic acid was removed with a rotary evaporator. The obtained residue was neutralized to pH 7 with 10% aqueous NaOH solution and extracted with $CHCl_3$ (3 × 50 mL). The combined organic extract was washed with water (2 × 100 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was chromatographed with *n*-hexane/EtOAc

(2:1 to 1:1, v/v) to afford **20** (26 mg, 66%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 8.30 (s, 1H, H4), 7.66 (d, 1H, H5, J = 8.4 Hz), 7.28 (d, 1H, H6, J = 8.4 Hz), 7.25 (br s, 5H, OCH_2Ph), 6.77−6.90 (m, 3H, H2′ + H5′ + H6′), 6.06 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 9.6 Hz, J = 1.2 Hz), 5.92 (AB, 2H, 7,8-OCH_2O-, $\Delta\delta$ = 4.8 Hz, J = 1.2 Hz), 4.47 (s, 2H, OCH_2Ph), 4.25 (q, 2H, q, lactam-CH_2−, J = 6.6 Hz), 3.73 (t, 2H, $NCH_2(CH_2)_2OBn$, J = 6.0 Hz), 3.56 (t, 2H, $N(CH_2)_2CH_2OBn$, J = 6.0 Hz), 1.98 (quintet, 2H, $NCH_2CH_2CH_2OBn$, J = 6.0 Hz). MS (EI) *m/z*: 495 $[M]^+$.

10-Benzo[1,3]dioxol-5-yl-8-(3-hydroxy-propyl)-8,9-dihydro-1,3-dioxa-8-aza-dicyclopenta[*a*,*g*]naphthalen-7-one (21). The mixture of **20** (16 mg, 0.032 mmol) and 10% Pd/C (4 mg) in dry THF (3 mL) was stirred for 20 h at room temperature under 1 atm of hydrogen. The Pd/C was removed by filtration and the solvent evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using CH_2Cl_2/acetone (3:1 to 2:1, v/v) to yield **21** (9 mg, 69%) as a white solid. Mp: 213-215 °C. ^{1}H NMR ($CDCl_3$) δ: 8.31 (s, 1H, H4), 7.67 (d, 1H, H5, J = 8.4 Hz), 7.28 (d, 1H, H6, J = 8.4 Hz), 6.82−6.92 (m, 3H, H2′ + H5′ + H6′), 6.07 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 8.7 Hz, J = 1.2 Hz), 5.93 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 4.8 Hz, J = 1.2 Hz), 4.28 (q, 2H, lactam-CH_2−, J = 4.8 Hz), 3.77 (t, 2H, $NCH_2(CH_2)_2OH$, J = 4.8 Hz), 3.59 (t, 2H, $N(CH_2)_2CH_2OH$, J = 4.8 Hz), 2.65 (br s, 1H, OH), 1.81 (quintet, 2H, $NCH_2CH_2CH_2OH$, J = 4.8 Hz). MS (EI) *m/z*: 405 $[M]^+$.

10-(3,4-Dimethoxy-phenyl)-8,9-dihydro-1,3-dioxa-8-aza-dicyclopenta[*a*,*g*]naphthalen-7-one (22). Compound **11** (400 mg, 1.06 mmol) was dissolved in glacial acetic acid (10 mL), and freshly activated zinc dust (695 mg) was added thereto, then heated in an oil bath at 100 °C for 48 h. The insoluble solid was filtered off, and the majority of acetic acid was removed with a rotary evaporator. The obtained residue was neutralized to pH 7 with 10% aqueous NaOH solution and then extracted with $CHCl_3$ (3 × 100 mL). The extract was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel, eluting with CH_2Cl_2/acetone (3:1 to 2:1, v/v) to give **22** (95 mg, 25%) as a pale yellow solid. Mp: 258 °C (dec). ^{1}H NMR ($CDCl_3$) δ: 8.36 (s, 1H, H4), 7.69 (d, 1H, H5, J = 8.7 Hz), 7.29 (d, 1H, H6, J = 8.7 Hz), 6.86−6.95 (m, 3H, H2′ + H5′ + H6′), 5.90 (s, 2H, 7,8-OCH_2O-), 4.35 (q, 2H, lactam-CH_2−, J = 22.8 Hz), 3.99, 3.88 (each s, 2 × 3H, 3′-OCH_3 + 4′-OCH_3). MS (FAB, positive) *m/z*: 364 $[M + H]^+$.

10-Benzo[1,3]dioxol-5-yl-7-methoxy-1,3-dioxa-8-aza-dicyclopenta[*a*,*g*]naphthalen-9-one (23). Compound **9** (29 mg, 0.08 mmol) was dissolved in a mixture of MeOH (3 mL) and THF (6 mL). To the solution was added trimethylsilyldiazomethane (2 M in hexanes, 0.2 mL, 0.4 mmol). The mixture was stirred for 18 h at room temperature and concentrated in vacuo. The crude material was purified by column chromatography on silica gel using CH_2Cl_2/MeOH (30:1, v/v) to provide **23** (22 mg, 73%) as a yellow powder. Mp: 306−308 °C. ^{1}H NMR ($CDCl_3$) δ: 8.27 (s, 1H, H4), 7.67 (d, 1H, H5, J = 8.4 Hz), 7.35 (d, 1H, H6, J = 8.4 Hz), 6.83−6.92 (m, 3H, H2′ + H5′ + H6′), 6.07 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 15.6 Hz, J = 1.5 Hz), 5.96 (AB, 2H, 7,8-OCH_2O-, $\Delta\delta$ = 4.2 Hz, J = 1.5 Hz), 3.15 (s, 3H, OCH_3). MS (EI) *m/z*: 375 $[M]^+$.

10-Benzo[1,3]dioxol-5-yl-8-hydroxy-1,3-dioxa-8-aza-dicyclopenta[*a*,*g*]naphthalene-7,9-dione (24). Hydroxyamine hydrochloride (20.9 mg, 0.3 mmol) and triethylamine (0.04 mL, 0.3 mmol) were dissolved in EtOH (30 mL). After the mixture was stirred for 10 min, anhydride **1** (109 mg, 0.3 mmol) was added. The mixture was refluxed overnight and concentrated in vacuo. The resulting product was purified by silica gel column chromatography using CH_2Cl_2/acetone (2:1, v/v) to afford **24** (16 mg, 15%) as a yellow powder. Mp: 255 °C (dec). ^{1}H NMR (DMSO-d_6) δ: 10.78 (s, 1H, OH), 8.40 (s, 1H, H4), 7.89 (d, 1H, H5, J = 8.7 Hz), 7.54 (d, 1H, H6, J = 8.7 Hz), 6.94 (s, 1H, H2′), 6.90 (d, 1H, H5′, J = 7.8 Hz), 6.79 (d, 1H, H6′, J = 7.8 Hz), 6.08 (s, 2H, 3′,4′-OCH_2O−), 5.96 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 5.7 Hz). MS (FAB, positive) *m/z*: 378 $[M + H]^+$.

***N*-(10-Benzo[1,3]dioxol-5-yl-7,9-dioxo-7,9-dihydro-1,3-dioxa-8-aza-dicyclopenta[*a*,*g*]naphthalen-8-yl)-acetamide (25).** A solution of anhydride **1** (145 mg, 0.4 mmol) in glacial acetic acid (10 mL) was refluxed with hydrazine hydrate (0.023 mL, 0.48 mmol) for 24 h under nitrogen and then poured, after cooling, into ice water. The resulting precipitate was filtered and dried under reduced pressure. The residue was purified by column chromatography on silica gel using CH_2Cl_2/MeOH (30:1 to 20:1, v/v) to give **25** (143 mg, 86%) as a yellow solid. Mp: 281−283 °C. ^{1}H NMR ($CDCl_3$) δ: 8.34 (s, 1H, H4), 7.69 (d, 1H, H5, J = 8.7 Hz), 7.46 (s, 1H, N*H*Ac), 7.38 (d, 1H, H6, J = 8.7 Hz), 6.84−6.87 (m, 3H, H2′ + H5′ + H6′), 6.06 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 16.5 Hz, J = 1.5 Hz), 5.98 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 5.4 Hz, J = 1.2 Hz), 2.17 (s, 3H, $NHCOCH_3$). MS (EI) *m/z*: 418 $[M]^+$.

***N*-(10-Benzo[1,3]dioxol-5-yl-7-oxo-7,9-dihydro-1,3-dioxa-8-aza-dicyclopenta[*a*,*g*]naphthalen-8-yl)-acetamide (26), *N*-(10-Benzo[1,3]dioxol-5-yl-9-oxo-7,9-dihydro-1,3-dioxa-8-aza-dicyclopenta[*a*,*g*]naphthalen-8-yl)-acetamide (27), and 11-Benzo[1,3]dioxol-5-yl-8,9-dihydro-1,3-dioxa-8,9-diaza-cyclopenta[*a*]anthracene-7,10-dione (28).** Compound **25** (113 mg, 0.27 mmol) was dissolved in glacial acetic acid (2 mL), the freshly activated zinc dust (196 mg) was added thereto, then heated in an oil bath at 100 °C for 5 h. The insoluble solid was filtered off, and the majority of acetic acid was removed with a rotary evaporator. The obtained residue was neutralized to pH 7 with 10% aqueous NaOH solution, and then the mixture was extracted with $CHCl_3$ (3 × 100 mL). The extract was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel using CH_2Cl_2/acetone (7:1 to 1:1, v/v) to afford a lactam **26** (52 mg, 48%, pale yellow powder), a retro-lactam **27** (16 mg, 15%, yellow powder), and a hydrazino compound **28** (20 mg, 20%, yellow powder), respectively. **26**. Mp: 274−276 °C. ^{1}H NMR ($CDCl_3$) δ: 8.51 (s, 1H, N*H*Ac), 8.34 (s, 1H, H4), 7.64 (d, 1H, H5, J = 8.7 Hz), 7.28 (d, 1H, H6, J = 8.7 Hz), 6.78−6.89 (m, 3H, H2′ + H5′ + H6′), 6.06 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 11.1 Hz, J = 1.2 Hz), 5.94 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 5.1 Hz, J = 1.2 Hz), 4.54 (m, 2H, lactam-CH_2−), 2.14 (s, 3H, $NHCOCH_3$). MS (EI) *m/z*: 404 $[M]^+$. **27**. Mp: 278−280 °C. ^{1}H NMR ($CDCl_3$) δ: 8.44 (s, 1H, N*H*Ac), 7.79 (s, 1H, H4), 7.50 (d, 1H, H5, J = 8.7 Hz), 7.30 (d, 1H, H6, J = 8.7 Hz), 6.74−6.84 (m, 3H, H2′ + H5′ + H6′), 6.02 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 18.3 Hz, J = 0.9 Hz), 5.89 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 1.2 Hz), 4.72 (s, 2H, lactam-CH_2−), 1.99 (s, 3H, $NHCOCH_3$). MS (EI) *m/z*: 404 $[M]^+$. **28**. Mp: 318−320 °C. ^{1}H NMR ($CDCl_3$) δ: 9.71(s, 1H, NH), 8.98 (s, 1H, NH), 7.93 (s, 1H, H4), 7.81 (d, 1H, H5, J = 8.7 Hz), 7.43 (d, 1H, H6, J = 8.7 Hz), 6.93 (d, 1H, H5′, J = 7.8 Hz), 6.86 (d, 1H, H2′, J = 1.2 Hz), 6.82 (dd, 1H, H6′, J = 1.2, 7.8 Hz), 6.11 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 9.4 Hz, J = 1.2 Hz), 5.97 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 6.3 Hz, J = 1.2 Hz). ^{13}C NMR (DMSO-d_6) δ: 159.84, 147.38, 147.01, 146.49, 141.94, 136.78, 133.32, 130.46, 130.18, 128.25, 125.61, 125.49, 124.29, 122.29, 121.29, 113.97, 111.28, 107.96, 102.00, 101.55. MS (EI) *m/z*: 376 $[M]^+$.

10-Benzo[1,3]dioxol-5-yl-8-(3-hydroxy-propyl)-1,3-dioxa-8-aza-dicyclopenta[*a*,*g*]naphthalene-7,9-dione (29). To a stirred solution of anhydride **1** (109 mg, 0.3 mmol) in toluene (40 mL) was added dropwise 3-amino-1-propanol (27 mg, 0.36 mmol) in toluene (5 mL) at 0 °C. The mixture was stirred at room temperature for 1 h and then heated under a Dean−Stark trap for 3 h. After water ceased to distill, the reaction mixture was cooled, washed successively with water (2 × 50 mL), 5% aqueous $NaHCO_3$ solution (2 × 50 mL), and water (2 × 50 mL), and then dried over $MgSO_4$. The solvent was removed in vacuo, and the resulting product was purified by column chromatography on silica gel using CH_2Cl_2/acetone (3:1 to 1:1, v/v) to provide **29** (10 mg, 11%) as a pale yellow powder. Mp: 150−152 °C. ^{1}H NMR ($CDCl_3$) δ: 8.27 (s, 1H, H4), 7.56 (d, 1H, H5, J = 8.4 Hz), 7.26 (d, 1H, H6, J = 8.4 Hz), 6.86−6.91 (m, 3H, H2′ + H5′ + H6′), 6.04 (s, 2H, 3′,4′-OCH_2O−), 5.97 (s, 2H, 7,8-OCH_2O−), 3.69−3.76 (m, 4H, $NCH_2CH_2CH_2$-OH), 1.83 (m, 2H, $NCH_2CH_2CH_2OH$).

9-Benzo[1,3]dioxol-5-yl-naphtho[1,2-*d*][1,3]dioxole-7,8-dicarboxylic Acid Dimethyl Ester (30). Compound **1** (108.6 mg, 0.3 mmol) was dissolved in a mixture of MeOH (4 mL) and THF (8 mL). To the solution was added trimethylsilyldiazomethane (2 M in hexanes, 1.0 mL, 2.0 mmol). The mixture was stirred for 12 h at room temperature and then concentrated in vacuo. The residue was purified by chromatography on silica gel using *n*-hexane/EtOAc (2:1, v/v) to afford **30** (67 mg, 55%) as a pale yellow powder. Mp: 157−159 °C. ^{1}H NMR ($CDCl_3$) δ: 8.53 (s, 1H, H4), 7.58 (d, 1H, H5, J = 8.7 Hz), 7.27 (d, 1H, H6, J = 8.7 Hz), 6.79−6.82 (m, 3H, H2′ + H5′ + H6′), 6.03 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 10.2 Hz, J = 1.5 Hz), 5.89 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 7.2 Hz, J = 1.5 Hz), 3.94, 3.66 (each s, 2 × 3H, 2 × OCH_3). MS (EI) *m/z*: 408 $[M]^+$.

9-Benzo[1,3]dioxol-5-yl-naphtho[1,2-*d*][1,3]dioxole-7,8-dicarboxylic Acid 8-Methyl Ester (31). Compound **30** (20 mg, 0.05 mmol) was refluxed with a 1 M solution of KOH in MeOH (10 mL) for 2 h. The solution was cooled, and the solvent was removed under reduced pressure. The remaining solid was dissolved in water (10 mL) and acidified to pH 1−2 with 10% aqueous HCl solution. The precipitate was collected by filtration, washed with water, and dried. The product was purified by column chromatography on silica gel using CH_2Cl_2/MeOH (20:1 to 10:1, v/v) to give **31** (11 mg, 56%) as a pale yellow powder. Mp: 273−275 °C. ^{1}H NMR ($CDCl_3$) δ: 8.54 (s, 1H, H4), 7.49 (d, 1H, H5, J = 8.1 Hz), 7.20 (d, 1H, H6, J = 8.1 Hz), 6.76−6.82 (m, 3H, H2′ + H5′ + H6′), 6.03 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 11.1 Hz), 5.88 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 7.2 Hz), 3.62 (s, 3H, OCH_3). MS (FAB, positive) *m/z*: 395 $[M + H]^+$.

9-Benzo[1,3]dioxol-5-yl-naphtho[1,2-*d*][1,3]dioxole-7,8-dicarboxylic Acid (32). Compound **30** (20 mg, 0.05 mmol) was refluxed with 1 M solution of KOH in MeOH (10 mL) for 24 h. Completion of the reaction, followed by a workup as described for the isolation of **31**, gave a residue that was purified by silica gel column chromatography. Elution with CH_2Cl_2/MeOH (2:1, v/v) as eluent yielded **32** (12 mg, 63%) as a yellow powder. Mp: 253 °C (dec). ^{1}H NMR (DMSO-d_6) δ: 8.25 (s, 1H, H4), 7.53 (d, 1H, H5, J = 8.7 Hz), 7.24 (d, 1H, H6, J = 8.7 Hz), 6.72−6.82 (m, 3H, H2′ + H5′ + H6′), 5.99 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 18.9 Hz), 5.81 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 6.0 Hz). MS (FAB, positive) *m/z*: 381 $[M + H]^+$.

9-Benzo[1,3]dioxol-5-yl-6-hydroxy-naphtho[1,2-*d*][1,3]-dioxole-7,8-dicarboxylic Acid Diethyl Ester (33). Hydroxyacetal **1a** (3.44 g, 10 mmol), diethyl acetylenedicarboxylate (1.70 g, 10 mmol), CH_2Cl_2 (4.5 mL), and glacial acetic acid (3 mL) were heated at 140 °C for 24 h. The cooled mixture was diluted with CH_2Cl_2 (100 mL), washed with 5% $NaHCO_3$ solution (3 × 100 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was chromatographed over silica gel using *n*-hexane/EtOAc/triethylamine (3:1:0.1, v/v/v), followed by crystallization from ether to afford **33** (741 mg, 16%) as a white powder. Mp: 192−194 °C. ^{1}H NMR ($CDCl_3$) δ: 12.76 (s, 1H, 4OH), 8.15 (d, 1H, H5, J = 8.7 Hz), 7.21 (d, 1H, H6, J = 8.7 Hz), 6.77−6.81 (m, 3H, H2′ + H5′ + H6′), 6.01 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 13.5 Hz, J = 1.5 Hz), 5.86 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 5.7 Hz, J = 1.5 Hz), 4.41, 4.01 (each q, 2 × 2H, 2 × OCH_2CH_3, J = 7.2 Hz), 1.37, 1.06 (each t, 2 × 3H, 2 × OCH_2CH_3, J = 7.2 Hz). MS (EI) *m/z*: 452 $[M]^+$.

10-Benzo[1,3]dioxol-5-yl-6-hydroxy-7*H*-furo[3′,4′:6,7]-naphtho[1,2-*d*][1,3]dioxol-9-one (34). A solution of **33** (45.2 mg, 0.1 mmol) in THF (1 mL) was added dropwise to a suspension of lithium aluminum hydride (7.6 mg, 0.2 mmol) in THF (1 mL) at 0 °C. The mixture was stirred at room temperature for 2 h, quenched with aqueous saturated Na_2SO_4 solution, and extracted with $CHCl_3$ (2 × 30 mL). After evaporation of organic solvent, the residue was purified by column chromatography on silica gel using CH_2Cl_2/MeOH (20:1, v/v) to give **34** (36 mg, 99%) as a yellow powder. Mp: 257 °C (dec). ^{1}H NMR (DMSO-d_6) δ: 10.67 (s, 1H, 4OH), 7.94 (d, 1H, H5, J = 9.0 Hz), 7.44 (d, 1H, H6, J = 9.0 Hz), 6.84 (d, 1H, H5′, J = 8.1 Hz), 6.79 (d, 1H, H2′, J = 1.5 Hz), 6.66 (dd, 1H, H6′, J = 1.5, 8.1 Hz), 6.04 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 6.0 Hz, J = 0.6 Hz), 5.88 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 6.3 Hz, J = 0.9 Hz), 5.32 (s, 2H, lactone-CH_2−). MS (FAB, positive) *m/z*: 365 $[M + H]^+$.

9-Benzo[1,3]dioxol-5-yl-6-methoxy-naphtho[1,2-*d*][1,3]-dioxole-7,8-dicarboxylic Acid Diethyl Ester (35). Compound **33** (95 mg, 0.21 mmol) was dissolved in a mixture of MeOH (3 mL) and THF (6 mL). To the solution was added (trimethylsilyl)diazomethane (2 M in hexanes, 0.6 mL, 1.2 mmol). The mixture was stirred for 12 h at room temperature and then concentrated in vacuo. The crude material was purified by column chromatography on silica gel using CH_2Cl_2 to afford **35** (97 mg, 99%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 7.86 (d, 1H, H5, J = 8.7 Hz), 7.26 (d, 1H, H6, J = 8.7 Hz), 6.75−6.82 (m, 3H, H2′ + H5′ + H6′), 6.00 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 11.7 Hz, J = 1.2 Hz), 5.87 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 9.0 Hz, J = 1.2 Hz), 4.39 (q, 2H, OCH_2CH_3, J = 7.2 Hz), 4.06 (s, 3H, 4-OCH_3), 4.03 (q, 2H, OCH_2CH_3, J = 7.2 Hz), 1.38, 1.04 (each t, 2 × 3H, 2 × OCH_2CH_3, J = 7.2 Hz); MS (EI) *m/z*: 466 $[M]^+$.

9-Benzo[1,3]dioxol-5-yl-naphtho[1,2-*d*][1,3]dioxole-7,8-dicarboxylic Acid Diamide (36). Compound **9** (72 mg, 0.2 mmol) was added to a mixture of concentrated ammonium hydroxide (2 mL) and THF (2 mL). The suspension was stirred at 40 °C for 72 h and concentrated in vacuo. Silica gel column chromatography of the crude product with CH_2Cl_2/MeOH (4:1 to 1:1, v/v) provided **36** (23 mg, 30%) as a pale yellow powder. Mp: 298 °C (dec). ^{1}H NMR (CD_3OD) δ: 8.18 (s, 1H, H4), 7.55 (d, 1H, H5, J = 8.4 Hz), 7.21 (d, 1H, H6, J = 8.4 Hz), 6.72−6.86 (m, 3H, H2′ + H5′ + H6′), 5.93 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 13.2 Hz, J = 0.9 Hz), 5.80 (AB, 2H, 7,8-OCH_2O-, $\Delta\delta$ = 7.2 Hz, J = 0.9 Hz). MS (FAB, positive) *m/z*: 402 $[M + H + Na]^+$.

10-Benzo[1,3]dioxol-5-yl-5-chloro-9*H*-furo[3′,4′:6,7]naphtho[1,2-*d*][1,3]dioxol-7-one (37). A stirred solution of **2** (104 mg, 0.3 mmol), *N*-chlorosuccinimide (80 mg, 0.6 mmol), and concentrated H_2SO_4 (10 μL) in THF (5 mL) was heated to reflux for 24 h and then diluted with $CHCl_3$ (50 mL). The reaction mixture was washed with 10% aqueous $Na_2S_2O_3$ solution (50 mL) and water (2 × 50 mL), dried over $MgSO_4$, and concentrated in vacuo. The product was purified by column chromatography on silica gel eluting with $CHCl_3$ to afford **37** (56 mg, 49%) as a brown solid. Mp: 267 °C (dec). ^{1}H NMR ($CDCl_3$) δ: 8.91 (s, 1H, H4), 7.47 (s, 1H, H6), 6.76−6.91 (m, 3H, H2′ + H5′ + H6′), 6.08 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 8.7 Hz, J = 1.5 Hz), 5.97 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 8.7 Hz, J = 1.5 Hz), 5.22 (q, 2H, lactone-CH_2−, J = 8.7 Hz). MS (EI) *m/z*: 384 $[M + 2]^+$, 382 $[M]^+$.

10-Benzo[1,3]dioxol-5-yl-5-bromo-9*H*-furo[3′,4′:6,7]naphtho[1,2-*d*][1,3]dioxol-7-one (38). To a solution of **2** (15.4 mg, 0.044 mmol) in THF (1 mL) were added *N*-bromosuccinimide (10.7 mg, 0.06 mmol) and concentrated H_2SO_4 (5 μL). The solution was stirred at room temperature for 20 h and then diluted with EtOAc (30 mL). The same workup and purification procedure as described for the isolation of **37** gave product **38** (12 mg, 64%) as a pale yellow powder. Mp: 256 °C (dec). ^{1}H NMR ($CDCl_3$) δ: 8.89 (s, 1H, H4), 7.65 (s, 1H, H6), 6.76−6.91 (m, 3H, H2′ + H5′ + H6′), 6.08 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 8.7 Hz, J = 1.5 Hz), 5.97 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 7.8 Hz, J = 1.5 Hz), 5.22 (q, 2H, lactone-CH_2−, J = 8.4 Hz). MS (EI) *m/z*: 428 $[M + 2]^+$, 426 $[M]^+$.

10-Benzo[1,3]dioxol-5-yl-5-iodo-9*H*-furo[3′,4′:6,7]naphtho[1,2-*d*][1,3]dioxol-7-one (39). To a solution of **2** (14 mg, 0.04 mmol) in acetonitrile (1 mL) were added *N*-iodosuccinimide (13.6 mg, 0.06 mmol) and concentrated H_2SO_4 (5 μL). The mixture was stirred at room temperature for 36 h, concentrated at reduced pressure, and diluted with ether (30 mL). The same workup and purification procedure as described for the isolation of **37** afforded product **39** (10.5 mg, 55%) as a yellow powder. Mp: 255 °C (dec). ^{1}H NMR ($CDCl_3$) δ: 8.78 (s, 1H, H4), 7.93 (s, 1H, H6), 6.75−6.90 (m, 3H, H2′ + H5′ + H6′), 6.08 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 8.7 Hz, J = 1.5 Hz), 5.97 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 7.8 Hz, J = 1.5 Hz), 5.23 (q, 2H, lactone-CH_2-, J = 8.7 Hz). MS (EI) *m/z*: 474 $[M]^+$.

10-Benzo[1,3]dioxol-5-yl-5-bromo-8,9-dihydro-1,3-dioxa-8-aza-dicyclopenta[*a*,*g*]naphthalen-7-one (40). To a solu-

tion of **18** (14 mg, 0.04 mmol) in THF (5 mL) were added *N*-bromosuccinimide (11 mg, 0.06 mmol) and concentrated H_2SO_4 (10 μL). The solution was stirred at room temperature for 24 h and then diluted with EtOAc (30 mL). Completion of the reaction, followed by the workup as described for the isolation of **37**, gave a residue that was purified by silica gel column chromatography. Elution with CH_2Cl_2/acetone (10:1 to 5:1, v/v) as eluent yielded **40** (12 mg, 70%) as a pale brown solid. Mp: 285 °C (dec). ^{1}H NMR ($CDCl_3$) δ: 8.81 (s, 1H, H4), 7.63 (s, 1H, H6), 6.77−6.91 (m, 3H, H2′ + H5′ + H6′), 6.07 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 7.5 Hz, J = 1.2 Hz), 5.93 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 6.0 Hz, J = 1.2 Hz), 4.34 (m, 2H, lactam-CH_2−). MS (FAB, positive) *m/z*: 428 $[M + 2]^+$, 426 $[M]^+$.

11-Benzo[1,3]dioxol-5-yl-5-chloro-8,9-dihydro-1,3-dioxa-8,9-diaza-cyclopenta[*a*]anthracene-7,10-dione (41). To a solution of **28** (39.5 mg, 0.11 mmol) in THF (1 mL) were added *N*-chlorosuccinimide (28 mg, 0.21 mmol) and concentrated H_2SO_4 (10 μL). The solution was stirred at room temperature for 48 h and then diluted with EtOAc (30 mL). Completion of the reaction, followed by the workup as described for the isolation of **37**, gave a residue that was purified by silica gel column chromatography. Elution with CH_2Cl_2/acetone (10:1, v/v) as eluent afforded **41** (15.6 mg, 35%) as a yellow powder. Mp: 316 °C (dec). ^{1}H NMR (DMSO-d_6) δ: 12.58 (s, 1H, NH), 9.10 (s, 1H, NH), 8.01 (s, 1H, H4), 7.73 (s, 1H, H6), 7.04 (d, 1H, H5′, J = 7.8 Hz), 7.03 (d, 1H, H2′, J = 1.5 Hz), 6.86 (dd, 1H, H6′, J = 1.5, 7.8 Hz), 6.14 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 23.1 Hz), 6.05 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 12.2 Hz).^{13}C NMR (DMSO-d_6) δ: 159.09, 147.12, 146.63, 145.58, 141.48, 136.05, 134.10, 129.17, 126.21, 125.64, 125.44, 123.82, 123.40, 122.84, 121.12, 114.43, 110.75, 107.58, 102.29, 101.17. MS (EI) *m/z*: 396 $[M - NH_2 + 2]^+$, 394 $[M - NH_2]^+$.

11-Benzo[1,3]dioxol-5-yl-5-bromo-8,9-dihydro-1,3-dioxa-8,9-diaza-cyclopenta[*a*]anthracene-7,10-dione (42). To a solution of **28** (13 mg, 0.035 mmol) in THF (1 mL) were added *N*-bromosuccinimide (9.4 mg, 0.053 mmol) and concentrated H_2SO_4 (5 μL). The solution was stirred at room temperature for 48 h and then diluted with EtOAc (20 mL). The same workup and purification procedure as described for the isolation of **41** gave product **42** (9 mg, 57%) as a yellow powder. Mp: 310 °C (dec). ^{1}H NMR (DMSO-d_6) δ: 12.54 (s, 1H, NH), 9.04 (s, 1H, NH), 8.13 (s, 1H, H4), 7.69 (s, 1H, H6), 7.00 (d, 1H, H5′, J = 7.8 Hz), 6.99 (d, 1H, H2′, J = 1.5 Hz), 6.82 (dd, 1H, H6′, J = 1.5, 7.8 Hz), 6.11 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 17.4 Hz, J = 0.6 Hz), 6.02 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 9.3 Hz, J = 0.9 Hz). MS (FAB, positive) *m/z*: 441 $[M - NH_2 + H + 2]^+$, 439 $[M - NH_2 + H]^+$.

11-Benzo[1,3]dioxol-5-yl-5-iodo-8,9-dihydro-1,3-dioxa-8,9-diaza-cyclopenta[*a*]anthracene-7,10-dione (43). To a solution of **28** (13.3 mg, 0.035 mmol) in acetonitrile (1 mL) were added *N*-iodosuccinimide (11.9 mg, 0.053 mmol) and concentrated H_2SO_4 (5 μL). The solution was stirred at room temperature for 48 h and diluted with EtOAc (20 mL). The same workup and purification procedure as described for the isolation of **41** yielded **43** (9 mg, 51%) as a brown solid. Mp: 300 °C (dec). ^{1}H NMR (DMSO-d_6) δ: 12.59 (s, 1H, NH), 9.10 (s, 1H, NH), 8.38 (s, 1H, H4), 7.79 (s, 1H, H6), 7.10 (d, 1H, H5′, J = 7.8 Hz), 7.09 (d, 1H, H2′, J = 1.7 Hz), 6.92 (dd, 1H, H6′, J = 1.7, 7.8 Hz), 6.22 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 22.8 Hz, J = 0.7 Hz), 6.10 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 13.5 Hz, J = 0.9 Hz). MS (EI): *m/z* 486 $[M - NH_2]^+$.

9-Benzo[1,3]dioxol-5-yl-5-chloro-8-hydroxymethyl-naphtho[1,2-*d*][1,3]dioxole-7-carboxylic Acid Monosodium Salt (44). Aqueous NaOH solution (1.56 mL, 1 N) was added to a solution of **37** (57 mg, 0.15 mmol) in MeOH (25 mL). The mixture was stirred at 70 °C for 1 h. The solvent was evaporated to give crude product, which was purified by silica gel column chromatography using CH_2Cl_2/MeOH (3:1, v/v) to afford **44** (55 mg, 87%) as a white powder. Mp: 220 °C (dec). ^{1}H NMR (DMSO-d_6) δ: 8.39 (s, 1H, H4), 7.54 (s, 1H, H6), 6.89 (d, 1H, H5′, J = 8.7 Hz), 6.73 (d, 1H, H2′, J = 1.5 Hz), 6.63 (dd, 1H, H6′, J = 1.5, 8.7 Hz), 6.05 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 18.9 Hz), 5.81 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 8.1 Hz), 4.12 (s, 2H, 2-CH_2OH). MS (FAB, positive) *m/z*: 425 $[M + H + 2]^+$, 423 $[M + H]^+$.

9-Benzo[1,3]dioxol-5-yl-5-bromo-8-hydroxymethyl-naphtho[1,2-*d*][1,3]dioxole-7-carboxylic Acid Monosodium Salt (45). Conversion of **38** (65 mg, 0.15 mmol) to **45** was accomplished using a procedure similar to that described for **44**. The residue obtained was purified by silica gel column chromatography using CH_2Cl_2/MeOH (3:1, v/v) to provide **45** (64 mg, 91%) as a yellow powder. Mp: 205 °C (dec), ^{1}H NMR (DMSO-d_6) δ: 8.29 (s, 1H, H4), 7.69 (s, 1H, H6), 6.88 (d, 1H, H5′, J = 7.8 Hz), 6.72 (d, 1H, H2′, J = 1.5 Hz), 6.62 (dd, 1H, H6′, J = 1.5, 7.8 Hz), 6.05 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 18.6 Hz), 5.81 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 8.4 Hz), 4.13 (s, 2H, 2-CH_2OH). MS (FAB, positive) *m/z*: 469 $[M + H + 2]^+$, 467 $[M + H]^+$.

9-Benzo[1,3]dioxol-5-yl-8-hydroxymethyl-5-iodo-naphtho[1,2-*d*][1,3]dioxole-7-carboxylic Acid Monosodium Salt (46). Conversion of **39** (64 mg, 0.135 mmol) to **46** was accomplished using a procedure similar to that described for **44**. The residue obtained was purified by silica gel column chromatography using CH_2Cl_2/MeOH (3:1, v/v) to give **46** (62 mg, 89%) as a pale yellow powder. Mp: 212 °C (dec). ^{1}H NMR (DMSO-d_6) δ: 8.27 (s, 1H, H4), 7.86 (s, 1H, H6), 6.88 (d, 1H, H5′, J = 7.8 Hz), 6.71 (d, 1H, H2′, J = 1.2 Hz), 6.62 (dd, 1H, H6′, J = 1.2, 7.8 Hz), 6.04 (AB, 2H, 3′,4′-OCH_2O−, $\Delta\delta$ = 18.3 Hz), 5.79 (AB, 2H, 7,8-OCH_2O−, $\Delta\delta$ = 8.4 Hz), 4.13 (s, 2H, 2-CH_2OH). MS (FAB, positive) *m/z*: 515 $[M + H]^+$.

In Vitro Antiviral Assays. The antiviral assays for HBV,[18] HSV-1,[20] HSV-2,[20] EBV,[21] CMV,[22] and HIV[23] were performed according to the previously described procedures. Anti-HCV activities were tested in the Huh-Luc/neo cell line, which was kindly given to us by Dr. Bartenschlager of University of Heidelberg, Germany. Cells were seeded into a 48-well plate and grown until confluent. Varying concentrations of drug were added into the media (DMEM, 10% dFBS), and the cells were incubated for 3 days. At the end of the 3-day treatment, the medium was removed, and 50 μL of Passive lysis buffer (Promega) was added. The cell lysate was then shaken at room temperature for 15 min. An aliquot of 30 μL/well cell lysate was transferred to a 96-well plate, 100 μL/well of luciferase activity assay substrate was added to each well, and the activity on the plate was immediately read with a luminometer (Amersham).

Cell Cytotoxicity Assays. The cytotoxicity of test compounds was determined on both MT-2[23] and CEM[24] cell lines according to the previously reported procedures.

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Supporting Information Available: HPLC chromatograms for helioxanthine, **12**, **18**, **28**, and **42**. This information is available free of charge via the Internet at http://pubs.acs.org.

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