Design of Antineoplastic Agents Based on the "2-Phenylnaphthalene-Type" Structural Pattern. 4. Synthesis and Biological Activity of 2-Chloro-3-(substituted phenoxy)-1,4-naphthoquinones and Related 5,8-Dihydroxy-1,4-naphthoquinones

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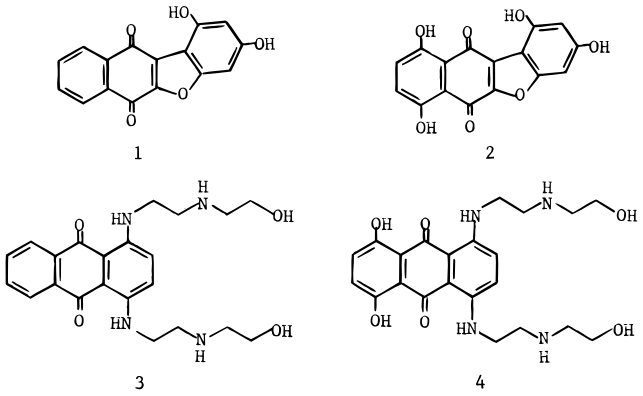
The intermediate in the preparation of 1,3,7,10-tetrahydroxybenzo[*b*]naphtho[2,3-*d*]furan-6,11-dione (**2**), 2-chloro-5,8-dimethoxy-3-(3,5-dimethoxyphenoxy)-1,4-naphthoquinone (**8h**), and corresponding hydroxyl, methoxyl, and acetoxyl analogues was found to possess interesting inhibitory activities in a number of cytotoxic test systems. Activities were also noticed in some 5,8-dihydroxy-1,4-naphthoquinone derivatives. A structure−activity discussion of compounds of this series is presented. The newly uncovered biological activity of 2-chloro-3-(substituted phenoxyl)-1,4-naphthoquinones and 2,3-bis(substituted phenoxy)-1,4-naphthoquinones may suggest an approach for the development of new classes of antineoplastic agents.

Introduction

On the basis of the "2-phenylnaphthalene-type" structural pattern hypothesis developed in our laboratory,[1] a number of novel compounds conforming to this pattern were designed, synthesized, and evaluated biologically.[2] Many of these compounds displayed interesting antineoplastic properties, particularly in the series of benzo[*b*]naphtho[2,3-*d*]furan-6,11-diones which showed outstanding activity against the growth of human promyelocytic leukemia cells (HL-60), small-cell lung cancers (SCLC) sensitive and resistant to cisplatin (SCLC/CDDP), National Cancer Institute's disease-oriented primary antitumor 60-cell line panel, and drug-oriented primary topoisomerase II-mediated DNA cleavages.[2b]

The activity of the benzo[*b*]naphtho[2,3-*d*]furan-6,11-diones, represented by the 1,3-dihydroxyl compound **1**, suggested that synthesis of derivatives with the addition of two hydroxyl groups at positions 7 and 10 (i.e., structure **2**) may be of interest. The logic is that the two added hydroxyl functions *peri* to the quinone carbonyl functions can form hydrogen-bonding linkages with the neighboring carbonyls and should readily form metal chelation in vivo for improved biological activity.[3] A similar arrangement is thought to be responsible for the drastic enhancement of the antineoplastic action of mitoxantrone (**4**) over that of ametantrone (**3**).[4]



Chemistry

1,3-Dihydroxybenzo[*b*]naphtho[2,3-*d*]furan-6,11-dione (**1**), as we reported previously,[2b] was prepared by the condensation of 2,3-dichloro-1,4-naphthoquinone with phloroglucinol (**6a**). However, attempted synthesis of the 1,3,7,10-tetrahydroxy analogue **2** by condensing 2,3-dichloronaphthazarin (**5a**; prepared by the Friedel−Crafts condensation of dichloromaleic anhydride with 1,4-dimethoxybenzene in the presence of a molten $AlCl_3$−NaCl mixture,[5] and the crude product was purified by means of a Soxhlet extractor) with **6a** under the same reaction conditions failed to yield the desired product. After a number of studies, compound **2** was finally obtained by the following route.

Methylation of **5a** with CH_3I and Ag_2O in $CHCl_3$[5] gave a mixture of 2,3-dichloro-5,8-dimethoxy-1,4-naphthoquinone (**5b**) and 6,7-dichloro-5,8-dimethoxy-1,4-naphthoquinone (**7**) (Chart 1). These compounds were separated by recrystallization with a mixture of $CHCl_3$ and

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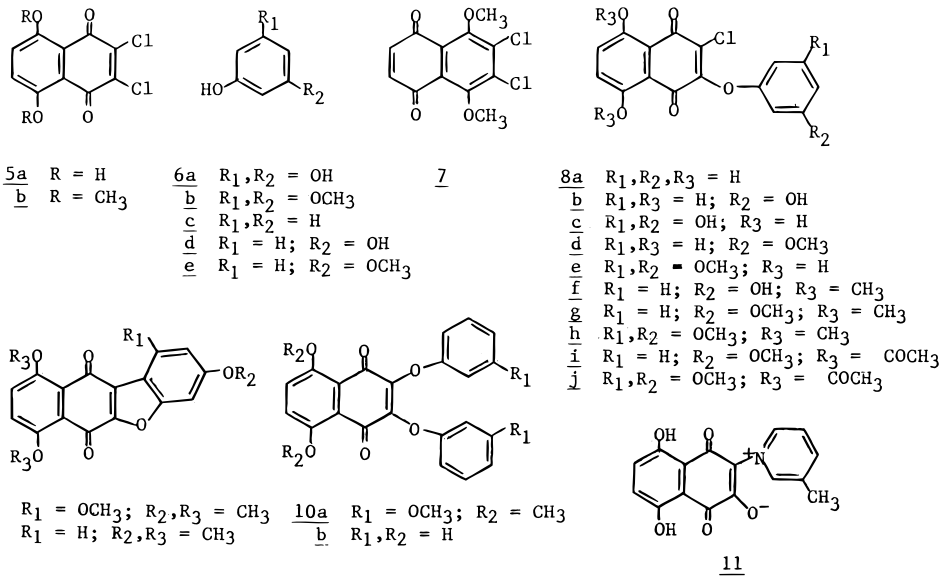
Chart 1



CCl_4;[5] the red crystalline **5b** was treated with 3,5-dimethoxyphenol (**6b**) and Na_2CO_3 in DMSO at room temperature to yield 2-chloro-5,8-dimethoxy-3-(3,5-dimethoxyphenoxy)-1,4-naphthoquinone (**8h**). Treatment of **8h** with palladium(II) acetate and Na_2CO_3 led to cyclization to yield 1,3,7,10-tetramethoxybenzo[*b*]-naphtho[2,3-*d*]furan-6,11-dione (**9a**). Demethylation of **9a** with pyridine hydrochloride gave the desired target compound **2**, albeit in low yield. Compound **9b** was obtained in a similar manner from **5b** and 3-methoxyphenol (**6e**) via the intermediate **8g**. Other chlorophenoxyl compounds (**8a**−**8h**) were prepared from **5a** or **5b** with the appropriate phenols (**6a**−**6e**) and Na_2CO_3 at room temperature. Two acetoxy derivatives (**8i** and **8j**) were obtained by treating **8d** and **8e**, respectively, with acetyl chloride.

Reactions between 2,3-dichloro-5,8-dimethoxy-1,4-naphthoquinone (**5b**) and 3-methoxyphenol (**6e**) as well as between 2,3-dichloronaphthazarin (**5a**) and phenol (**6c**) in the presence of Na_2CO_3 at elevated temperature resulted in the replacement of both chloro groups with the formation of compounds **10a** and **10b**, respectively, in high yields.

Results and Discussion

Preliminary biological evaluation of the cyclized compound 1,3,7,10-tetrahydroxybenzo[*b*]naphtho[2,3-*d*]furan-6,11-dione (**2**) indicated that it indeed possessed valuable, but not outstanding, cytotoxicity. The corresponding tetramethoxy compound **9a** and trimethoxy compound **9b** were totally inactive. On the other hand, evaluation of the intermediate chlorophenoxy compounds (including both the tetramethoxyl compound **8h** and the tetrahydroxyl compound **8c**) revealed that exciting inhibitory activity was found in several in vitro biological systems. This interesting information led us to evaluate other related chlorophenoxy analogues (**8a**−**8j**), and inhibitory activities were again found in these compounds. There is little difference in activity among the hydroxyl, the methoxyl, or the acetoxyl substitutions, and similar inhibitory action was uniformly observed throughout the entire series. With the exception of the topoisomerase II data, activity found in one of the cell lines tested is often echoed in other series. As mentioned previously, during preparation of these chlorophenoxy intermediates from the dichloro-1,4-naphthoquinones, when the reaction temperature was higher than room temperature, both chlorine atoms were replaced by the phenoxy functions. The resulting diphenoxy compounds **10a** and **10b** also showed cytotoxic activities.

It is of interest to note that two starting materials, 2,3-dichloronaphthazarin (**5a**) and 2,3-dichloro-5,8-dimethoxynaphthoquinone (**5b**), also showed sensational cytotoxic activities. The isomeric 6,7-dichloro-5,8-dimethoxy-1,4-naphthoquinone (**7**), on the other hand, possessed no inhibitory activity.

Not all 5,8-dihydroxynaphthoquinone derivatives are expected to possess cytotoxicity. A naphthoquinone oxopyridinium inner salt **11**, synthesized by us earlier by refluxing **8b** with 3-picoline,[6] was found to be without inhibitory action in our tests. Since the topoisomerase II inhibition could not be correlated with the observed activity and the mere presence of a quinoid structure may not be sufficient for explaining the structure−activity relationship, it would be difficult to address the exact mechanism of activity of these compounds. Compounds **8b**, **8g**, and **8h** have recently been found to possess activity in the in vivo hollow fiber assays[7] at the National Cancer Institute. Test data are listed in Table 1.

Experimental Section

All melting points were taken on a Thomas-Hoover melting point apparatus. NMR spectra were determined by the NMR laboratory of The University of Kansas, Lawrence, KS, and were obtained on a Bruker AM-500 (500 MHz for ^1H and 125.77 MHz for ^{13}C) spectrometer with Me_4Si as an internal standard. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.3% of the theoretical values. Mass spectra were determined by The University of Kansas Mass Spectrometry Laboratory, Lawrence, KS.

2,3-Dichloronaphthazarin (5a). A mixture of 100 g of $AlCl_3$ and 20 g of NaCl was melted in a large casserole. To the

Table 1. Inhibitory Action of 2-Chloro-3-phenoxy-1,4-naphthoquinones and Related Compounds

compd	IC_{50} (μM) HL-60[a]	IC_{50} (μM) SCLC[b]	NCI screen[c]	topo II-mediated DNA cleavage activities[d]
1	0.22	1.03	++	>100 000
2	0.39	1.5	+++	2000
5a	0.049	0.3	ND	ND
5b	0.22	1.0	ND	200
7	1.00	0.75	ND	10
9a	127.9	>10	+	2
9b	14.5	1.0	ND	2
8a	0.22	0.25	+++	4000
8b	0.16	0.45	++[e]	100
8c	0.25	0.5	++	200
8d	0.2	0.5	++	800
8e	0.07	0.75	++	50
8f	0.067	0.3	++	10
8g	0.44	2.0	++[e]	20
8h	0.12	2.0	++[e]	100
8i	0.2	5.0	++	200
8j	0.5	1.1	++	50
10a	0.16	1.0	+++	0
10b	0.13	0.1	+++	500
11	30.0	>10.0	ND	0.5

[a] Inhibitory concentration for established anticancer agent *m*-AMSA is 0.055 μM and for compound **1**[2b] is 0.22 μM. [b] Cytotoxicity against SCLC for mitoxantrone[4a] is 0.02 μM, for adriamycin is 0.04 μM, and for VP-16 is 0.5 μM. [c] National Cancer Institute preclinical 60-human tumor cell line drug discovery screen:[8] complete inhibition of cell growth detected [log IC_{50} (M)] for at least one cell line at −7, +++; −6, ++; −5, +; inactive, −; ND, not determined. [d] Relative activity to induce mammalian DNA topoisomerase II-mediated DNA cleavage is based on the effective doses which caused 50% of topoisomerase II-mediated DNA fragmentation of linearized 8.4-kb YEpTG DNA. The cleavage activity of VP-16 (a potent topoisomerase II drug) to stimulate topo II-mediated DNA cleavage is taken as 100 000. [e] Active in the in vivo hollow fiber assays at the National Cancer Institute.[7] Descriptions of all the assay tests were given in one of our previous publications.[2b]

molten mass was added portionwise, with continuous and vigorous stirring (with a large stirring rod and a thermometer), an intimate mixture of 11.7 g (0.08 mol) of 99% 1,4-dimethoxybenzene and 28.2 g (0.16 mol) of 97% dichloromaleic anhydride at 140−150 °C. After the addition was complete, the reaction temperature was raised to 170−175 °C for 5 min with continuous stirring. The hot melt was quickly but carefully added, with stirring, to 1000 mL of cold water containing 700 mL of concentrated HCl. The resulting mixture was allowed to stand overnight at room temperature to complete the hydrolysis. The solid was collected by filtration under suction and washed thoroughly with H_2O and dried. The crude dark brown solid was purified with heptane (using a Soxhlet extractor, 3 days) as shining magenta crystals, mp 197−198 °C (lit. mp 195 °C[5]). The yield was 20.4 g (93.4%).

2-Chloro-3-phenoxynaphthazarin (8a). A mixture of 2 g (7.7 mmol) of **5a**, 2 g (21 mmol) of phenol (**6c**), and 2.5 g (24 mmol) of Na_2CO_3 in 120 mL of DMSO was stirred at 35−40 °C for 4 h. The reaction mixture was diluted with H_2O, and its pH was adjusted to 2−3 by means of 2 N HCl. The final volume was 1000 mL. The crude product (2.3 g) was collected by filtration and was purified by silica gel column chromatography using CH_2Cl_2 as eluent to give pure **8a** (1.95 g, 80% yield) as brown crystals, mp 165−167 °C. MS: *m*/*z* 316 (M^+). Anal. ($C_{16}H_9ClO_5$) C, H, Cl.

2-Chloro-3-(3-hydroxyphenoxy)naphthazarin (8b) was prepared by stirring a mixture of 4 g (15 mmol) of **5a**, 5.6 g (51 mmol) of resorcinol (**6d**), and 6.4 g (60 mmol) of Na_2CO_3 in 200 mL of DMSO at room temperature for 3 h. After the reaction mixture (which still contain some insoluble sodium salt) was diluted with H_2O and its pH adjusted to 2−3 with 2 N HCl, the isolated crude product was purified by silica gel column chromatography (CH_2Cl_2:EtOAc, 5:1) to give 3.5 g (70% yield) of pure **8b** as dark red crystals, mp 198 °C. ^{1}H NMR ($CDCl_3$): δ 12.40, 12.09, 7.32, 7.30, 7.19, 6.62, 6.59, 6.55, 4.97. ^{13}C NMR ($CDCl_3$): δ 180.2, 179.2,160.2,159.8,157.3, 156.9, 153.3, 134.2, 131.0, 130.6, 130.5, 111.3, 110.7, 110.4, 108.5, 104.2. MS: *m*/*z* 332 (M^+). Anal. ($C_{16}H_9ClO_6$) C, H, Cl.

2-Chloro-3-(3,5-dihydroxyphenoxy)naphthazarin (8c) was prepared in a similar manner by stirring 0.9 g of **5a**, 0.45 g of phloroglucinol (**6a**), 0.45 g of Na_2CO_3, and 45 mL of DMSO for 2 h. Silica gel column purification (CH_2Cl_2:EtOAc, 9:1 then 1:1) gave 35% yield of pure **8c** as a brown solid, mp 138 °C. ^{1}H NMR (DMSO): δ 12.03 (s, 1H, C8-OH), 11.72 (s, 1H, C5-OH), 9.50 (s, 2H, C3′- and C5′-OH), 7.43 (d, J = 8.2 Hz, 1H, C7-H), 7.40 (d, J = 8.2 Hz, 1H, C6-H), 5.98 (s, 1H, C4′-H), 5.95 (s, 2H, C2′ and C6′-H). MS: *m*/*z* 348 (M^+). Anal. ($C_{16}H_9ClO_7$) C, H, Cl.

2-Chloro-3-(3-methoxyphenoxy)naphthazarin (8d) was prepared by stirring a mixture of 0.4 g of **5a**, 0.3 g of 3-methoxyphenol (**6e**), 0.4 g of Na_2CO_3, and 15 mL of DMSO at room temperature for 3 h. Silica gel column (CH_2Cl_2) was used for purification. The yield of this brownish red solid was 73%, mp 153−154 °C. MS: *m*/*z* 346 (M^+). Anal. ($C_{17}H_{11}ClO_6$) C, H, Cl.

2-Chloro-3-(3,5-dimethoxyphenoxy)naphthazarin (8e) was prepared in a similar manner by stirring 3.2 g of **5a**, 2.8 g of 3,5-dimethoxyphenol (**6b**), 3.2 g of Na_2CO_3, and 100 mL of DMSO at room temperature for 3.5 h and by purifying the crude product through a silica gel column (CH_2Cl_2) as a brown-red solid. The yield was 65%, mp 168 °C. MS: *m*/*z* 376 (M^+). Anal. ($C_{18}H_{13}ClO_7$) C, H, Cl.

2-Chloro-5,8-dimethoxy-3-(3-hydroxyphenoxy)-1,4-naphthoquinone (8f) was prepared by stirring 1.2 g of **5b**, 1.0 g of resorcinol (**6d**), 1.4 g of Na_2CO_3, and 120 mL of DMSO at room temperature for 11 h. After recrystallization from 1-BuOH, pure **8f** was obtained as a red solid in 50% yield, mp 207 °C. ^{1}H NMR (DMSO): δ 9.66 (s, 1H, C3′-OH), 7.61 (d, J = 8.8 Hz, 1H, C7-H), 7.58 (d, J = 8.8 Hz, 1H, C6-H), 7.07 (s, 1H, C2′H), 6.41−6.50 (m, 3H, C4′-, C5′- and C6′-H), 3.88 (s, 3H, C8-OCH_3), 3.82 (s, 3H, C5-OCH_3). MS: *m*/*z* 360 (M^+). Anal. ($C_{18}H_{13}ClO_6$) C, H, Cl.

2-Chloro-5,8-dimethoxy-3-(3-methoxyphenoxy)-1,4-naphthoquinone (8g) was prepared by stirring 1.0 g of **5b**, 0.6 g of 3-methoxyphenol (**6e**), 0.6 g of Na_2CO_3, and 40 mL of DMSO at room temperature for 8 h. Pure product was obtained by recrystallization from EtOH as a red solid. The yield was 89%, mp 174−175 °C. MS: *m*/*z* 374 (M^+). Anal. ($C_{19}H_{15}ClO_6$) C, H, Cl.

2-Chloro-5,8-dimethoxy-3-(3,5-dimethoxyphenoxy)-1,4-naphthoquinone (8h) was prepared by stirring 2.0 g of **5b**, 1.2 g of 3,5-dimethoxyphenol (**6b**), 1.2 g of Na_2CO_3, and 80 mL of DMSO at room temperature for 2 h. It was recrystallized from 1-BuOH to give 2.6 g (93% yield) of **8h** as red crystals, mp 184−185 °C. MS: *m*/*z* 404 (M^+). Anal. ($C_{20}H_{17}ClO_7$) C, H, Cl.

2-Chloro-5,8-diacetoxy-3-(3-methoxyphenoxy)-1,4-naphthoquinone (8i). A red-colored mixture of 0.15 g of **8d** and 5 mL of CH_3COCl was refluxed for 23 h. The reaction solution was evaporated under reduced pressure to yield a red oily syrup. To this was added 100 mL of Et_2O with stirring. Soon a yellow solid was formed. It was collected and recrystallized from CCl_4 to give 0.14 g (75% yield) of **8i** as yellow crystals, mp 148 °C. MS: *m*/*z* 430 (M^+). Anal. ($C_{21}H_{15}ClO_8$) C, H, Cl.

2-Chloro-5,8-diacetoxy-3-(3,5-dimethoxyphenoxy)-1,4-naphthoquinone (8j) was prepared in a manner similar to that for preparing **8i** from 0.2 g of **8e** and 5 mL of CH_3COCl. After the product was recrystallized from CCl_4, the yield of yellow crystalline **8j** was 80%, mp 173−174.5 °C. MS: *m*/*z* 460 (M^+). Anal. ($C_{22}H_{17}ClO_9$) C, H, Cl.

1,3,7,10-Tetramethoxybenzo[*b*]naphtho[2,3-*d*]furan-6,11-dione (9a). A mixture of 2.0 g of **8h**, 0.5 g of $Pd(OAc)_2$, and 0.75 g of Na_2CO_3 in 60 mL of dimethylacetamide was heated at 120−130 °C in an oil bath under N_2 for 8 h and cooled. The pH of the solution was adjusted to 3 with 2 N HCl, and H_2O was added to make the final volume 1 L. The resulting precipitate was collected by filtration (1.5 g) and purified via silica gel column chromatography (CH_2Cl_2:EtOAc,

3:1 then 2:1) to give 0.9 g of **9a**, mp 265 °C. The crude product could also be purified by recrystallization from 1-BuOH. MS: *m*/*z* 368 (M^+). Anal. ($C_{20}H_{16}O_7$) C, H.

1,3,7,10-Tetrahydroxybenzo[*b*]naphtho[2,3-*d*]furan-6,11-dione (2). A mixture of 0.4 g of **9a** and 8 g of pyridine hydrochloride in a round bottom flask, attached with a condenser and a $CaCl_2$ drying tube, was heated in an oil bath at 190−195 °C, with stirring, for 30 min. The reaction mixture was cooled to ca. 80 °C and acidified with 2 N HCl. After standing overnight at room temperature, the crude product was purified through a silica gel column (EtOAc:MeOH, 3:1) to give 100 mg (27% yield) of **2** as a black solid, mp >300 °C. MS: *m*/*z* 312 (M^+). Anal. ($C_{16}H_8O_7$) C, H.

3,7,10-Trimethoxybenzo[*b*]naphtho[2,3-*d*]furan-6,11-dione (9b) was prepared and isolated in a manner similar as that for the preparation of **9a** from 0.9 g of **8g**, 0.2 g of $Pd(OAc)_2$, 0.3 g of Na_2CO_3, and 30 mL of dimethylacetamide. The crude product was purified through a silica gel column (CH_2Cl_2:EtOAc, 3:1) to give 0.1 g (12% yield) of dark brown solid, mp 260−263 °C. Purification of the crude product could also be conducted by stirring it in 50 mL of CH_2Cl_2 and the insoluble solid recrystallized from DMF, with similar yield. MS: *m*/*z* 338 (M^+). Anal. ($C_{19}H_{14}O_6$) C, H.

2,3-Bis(3-methoxyphenoxy)-5,8-dimethoxynaphthoquinone (10a). A mixture of 1 g (3.4 mmol) of **5b**, **1** g (8 mmol) of 3-methoxyphenol (**6e**), and 0.9 g (8.6 mmol) of Na_2CO_3 in 50 mL of DMSO was heated at 105−115 °C for 5 h. The reaction mixture was cooled and diluted with 600 mL of H_2O. It was then acidified with 2 N HCl to pH 2. The crude solid was isolated by filtration and recrystallized from 1-BuOH to give 1.4 g (88% yield) of pure product as orange needles, mp 180 °C. MS: *m*/*z* 462 (M^+). Anal. ($C_{26}H_{22}O_8$) C, H.

2,3-Diphenoxynaphthazarin (10b). A mixture of 2 g (7.7 mmol) of **5a**, 2 g (21 mmol) of phenol (**6c**), and 2.5 g (24 mmol) of Na_2CO_3 in 120 mL of DMSO was heated at 80−85 °C for 3.5 h. The reaction mixture was cooled and diluted with H_2O to a total volume of 1000 mL. It was then acidified to pH 3 with 2 N HCl. The crude product was collected by filtration and purified by silica gel column chromatography using CH_2Cl_2 as the eluent to give 2 g (70% yield) of pure product as red crystals, mp 219−220 °C. MS: *m*/*z* 374 (M^+). Anal. ($C_{22}H_{14}O_6$) C, H.

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