In Vivo Antitumor Activity of 6-Benzyl-1,3-benzodioxole Derivatives against the P388, L1210, B16, and M5076 Murine Models

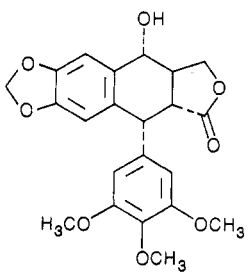
Leonard Jurd,† V. L. Narayanan,‡ and Kenneth D. Paull*‡

Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland 20892, and Western Regional Research Center, Agricultural Research Center, U.S. Department of Agriculture, Berkeley, California 94710. *Received February 26, 1987*

A series of 6-benzyl-1,3-benzodioxoles have been synthesized and evaluated against the in vivo ip P388 murine lymphocytic leukemia. Selected actives against this system were tested against the additional in vivo systems L1210, B16, M5076, and MX1. The most active of the 6-benzyl-1,3-benzodioxoles tested were as effective as podophyllotoxin as experimental antitumor agents in vivo, but larger doses were required. Three of the P388-active series members were active against the in vitro astrocytoma assay, which detects compounds that interfere with or bind to tubulin.

Medicinal chemists have often attempted to modify complex natural products to yield simpler synthetic compounds with similar biological activities.[1] We report here a series of synthetic compounds that incorporate structural features consistent with at least some of the biological activity of a natural product. The natural product is podophyllotoxin, the biological activity is experimental antitumor activity presumably mediated by a binding to tubulin at the colchicine binding site, and the synthetic series is the 6-benzyl-1,3-benzodioxoles (BBDs).

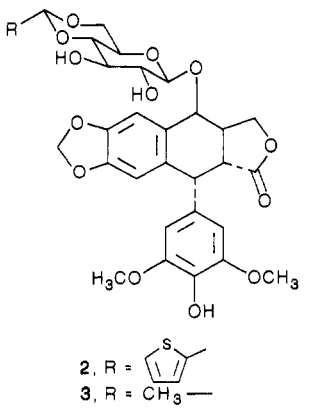
The key facts about podophyllotoxin particularly relevant to this paper are its structure (1) and the generally accepted mechanism of action of its cytotoxicity. The



1

isolation of podophyllotoxin was first reported in 1880.[2] The structure accepted today was reported over seven decades later.[3] The chemistry of podophyllotoxin was reviewed in detail some years ago,[4] and the history, chemistry, and bioactivity of the podophyllotoxins were reviewed recently.[5]

There are two podophyllotoxin derivatives of growing interest to oncologists. These are teniposide (2) and etoposide (3). In antitumor tests of the type described in this paper, these two compounds perform on an entirely dif-



2, R =

3, R = CH_3—

ferent plane, giving much better results than any other podophyllotoxin derivatives of which we are aware, and neither bind nor inhibit tubulin at relevant concentrations.[6] It is believed that interaction with topoisomerases is important in the production of their outstanding antitumor properties.[7,8] DNA topoisomerases have been reviewed in detail.[9,10]

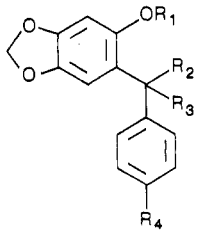
The BBDs reported here belong to a series initially synthesized to discover safer insect-control agents.[11,12] For example, 5-ethoxy-6-[1-(4-methoxyphenyl)ethyl]-1,3-benzodioxole (8) effectively sterilized male houseflies when fed at concentrations as low as 0.05%. Further effects on insects by members of this series have been observed and reported.[13-16]

The National Cancer Institute began its study of the experimental antitumor activity of the BBDs in 1976, when Jurd submitted the first example for screening. Since then, 161 BBDs have been evaluated against the ip in vivo P388 murine leukemia.[19] A selection of five of the 16 BBDs active against the P388 system were evaluated in the NCI Tumor Panel.[20] Recent reports describe the synthesis and

† U.S. Department of Agriculture.
‡ National Cancer Institute.

(1) Albert, A. *Selective Toxicity, The Physico-chemical Basis of Therapy*, 7th ed.; Albert, A., Ed.; Chapman and Hall: New York, 1985; Part 1, p 271.
(2) Podwyssotski, V. *Pharm. J. Trans.* **1881**, *12*, 217.
(3) Hartwell, J. L.; Schrecker, A. W.; *J. Am. Chem. Soc.* **1951**, *73*, 2909.
(4) Hartwell, J. L.; Schrecker, A. W.; *Fortschr. Chem. Org. Naturst.* **1958**, *15*, 83.
(5) Jardine, I. *Anticancer Agents Based on Natural Product Models*; Cassady, J. M., Douros, J. D., Ed.; Academic: New York, 1980; p 319.
(6) Loike, J. J. D.; Horwitz, S. B. *Biochemistry* **1976**, *15*, 5435.
(7) Ross, W.; Rowe, T.; Glisson, B.; Yalowich, J.; Liu, L. *Cancer Res.* **1984**, *44*, 5857.
(8) Kohn, K. W. *Concepts, Clinical Developments, and Therapeutic Advances in Cancer Chemotherapy*; Muggia, Franco, Ed.; Martinus-Nijhoff: Norwell, MA, 1987; p 3.
(9) Zwelling, L. A. *Cancer Metastasis Rev.* **1985**, *4*, 263.
(10) Wang, J. C. *Annu. Rev. Biochem.* **1985**, *54*, 665.
(11) Jurd, L.; Fye, R. L.; Morgan, J., Jr. *J. Agric. Food Chem.* **1979**, *27*, 1007.
(12) Langley, P. A.; Trewern, M. A.; Jurd, L. *Bull. Entomol. Res.* **1982**, *72*, 473.
(13) Van Mellaert, H.; De Loof, A.; Jurd, L. *Entomol. Exp. Appl.* **1983**, *33*, 83.
(14) Dame, D. A.; Jurd, L. *Mosq. News* **1983**, *43*, 50.
(15) Rawlins, S. C.; Jurd, L.; Snow, J. W. *J. Econ. Entomol.* **1982**, *75*, 728.
(16) Chang, F.; Hsu, C. L.; Jurd, L.; Williamson, D. L. *Ann. Entomol. Soc. Am.* **1984**, *77*, 147.
(17) Igarashi, K. S.; Ikeyama, S.; Takeuchi, M.; Sugino, Y. *Cell Struct. Funct.* **1978**, *3*, 103.
(18) Batra, J. K.; Jurd, L.; Hamel, E. *Mol. Pharmacol.* **1985**, *27*, 94.
(19) Developmental Therapeutics Program, Division of Cancer Treatment, NCI. In vivo cancer models. U.S. Government Printing Office: Washington, DC, 1984; DHHS Publication No. (NIH)84-2635.

Table I 4'-Substituted 6-Benzyl-1,3-benzodioxoles



compd	R_1	R_2	R_3	R_4	P388[a] act.: ILS	mp (bp), °C	formula[b]
4	Me	Me	H	OMe	78	(184/1 mm)	$C_{17}H_{18}O_4$[c]
5	Me	Me	H	OEt	78	71–72	$C_{18}H_{20}O_4$
6	Et	Me	H	OEt	71	60–61	$C_{19}H_{22}O_4$
7	Pr	Me	H	OEt	41	49–50	$C_{20}H_{24}O_4$
8	Et	Me	H	OMe	25	95	$C_{18}H_{20}O_4$[c]
9	allyl	Me	H	OMe	88	52–53	$C_{19}H_{20}O_4$
10	Pr	Me	H	OMe	30	84	$C_{19}H_{22}O_4$[c]
11	Et	Me	Me	OMe	35	79–80	$C_{19}H_{22}O_4$
12	Me	Me	H	OH	–	90–91	$C_{16}H_{16}O_4$
13	Me	Me	H	OPr	–	64–65	$C_{19}H_{22}O_4$
14	Me	Me	H	OBu	–	53–54	$C_{20}H_{24}O_4$
15	Me	Me	H	H	–	(176/5 mm)	$C_{16}H_{16}O_3$[c]
16	Me	Me	H	F	–	45–46	$C_{16}H_{15}FO_3$
17	Me	Me	H	Br	–	87–88	$C_{16}H_{15}BrO_3$
18	Me	Me	H	OCH_2CO_2H	–	120	$C_{18}H_{18}O_6$
19	Me	Me	H	$OCH_2C_6H_5$	–	95–96	$C_{23}H_{22}O_4$
20	Me	Et	H	OEt	—	77–78	$C_{19}H_{22}O_4$
21	Me	Me	Me	OMe	–	90–91	$C_{18}H_{20}O_4$
22	Me	Et	H	OMe	–	68–69	$C_{18}H_{20}O_4$
23	Me	H	H	OMe	–	56–57	$C_{16}H_{16}O_4$[c]
24	Me	CH_2CO_2Me	H	OMe	–	83–84	$C_{19}H_{20}O_6$
25	Me	CH_2CO_2H	H	OMe	–	166–167	$C_{18}H_{18}O_6$
26	CH_2CH_2OH	Me	H	OEt	–	67–68	$C_{19}H_{22}O_5$
27	CH_2CO_2Et	Me	H	OEt	–	77–78	$C_{21}H_{24}O_6$
28	Bu	Me	H	OMe	–	56	$C_{20}H_{24}O_4$[c]
29	penyl	Me	H	OMe	–	(183–185/5 mm)	$C_{21}H_{26}O_4$[c]
30	hexyl	Me	H	OMe	–	(213–215/1.5 mm)	$C_{22}H_{28}O_4$[c]
31	CH_2CH_2OH	Me	H	OMe	–	110–111	$C_{18}H_{20}O_5$
32	CH_2CO_2H	Me	H	OMe	–	100–101	$C_{18}H_{18}O_6$
33	CH_2CO_2Et	Me	H	OMe	–	80	$C_{20}H_{22}O_6$
34	Ac	Me	H	OMe	–	76	$C_{18}H_{18}O_5$[c]
35	H	Me	H	OMe	–	93–94	$C_{16}H_{16}O_4$
36	Me	Me	Me	H	–	(147/0.5 mm)	$C_{17}H_{18}O_3$[c]
37	Et	Me	Me	H	–	78–79	$C_{18}H_{20}O_3$[c]
38	Pr	Me	Me	H	–	94	$C_{19}H_{22}O_3$[c]
39	Pr	Me	Me	OMe	–	88–89	$C_{20}H_{24}O_4$
40	allyl	Me	Me	OMe	–	78	$C_{20}H_{22}O_4$
41	allyl	Et	H	OMe	–	97–98	$C_{20}H_{22}O_4$
42	allyl	Me	H	F	–	53–54	$C_{18}H_{17}FO_3$

[a] Tests were conducted according to the NCI protocol previously described (see ref 19); CD2F1 mice were inoculated intraperitoneally with 0.1 mL of suspension containing 10^6 P388 cells on day 0. A suspension of the BBD was given by ip injection on day 1 and each day thereafter for a total of 5 days. The BBD is evaluated as "+" if the ILS of the confirmatory test is >20%. [b] All new BBDs had satisfactory analyses for C and H. [c] See ref 11.

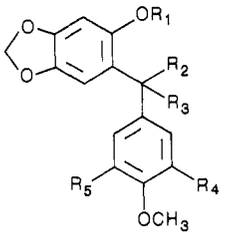
testing of a closely related group of morpholino derivatives of the BBDs tested at the NCI as part of this series.[21,22]

Chemistry. The new 1,3-benzodioxoles evaluated in these studies were synthesized by adaptation of a recently described procedure,[11] in which sesamol was condensed in aqueous acid media with an appropriately substituted benzylic alcohol. The resulting phenolic 1,3-benzodioxoles were then alkylated to yield the compounds listed in the tables. Compound **43** and similar ethanolic derivatives were prepared by initial alkylation with ethyl bromoacetate and subsequent reduction of the ester grouping to the alcohol.

In Vivo P388 Activity. The initial testing of this large series of 161 compounds was carried out by using the then-current NCI ip in vivo P388 prescreen protocol. As a general rule, unless the first dose–response testing covering the range of 200 to 50 mg/kg showed either activity or toxicity, the compound was considered negative and not retested. When testing of the series began, a 20% increased life span (ILS) or more on the first test was grounds for retesting. However, series members submitted after October 1984 needed at least a 27% ILS[15] in the first test in order to be retested. In all cases, an ILS of 20% upon retesting for confirmation of initial activity was sufficient to consider the series member active against P388. A total of nine series members considered active against P388 are listed in Tables I and II. Selected P388-negative examples are listed in these tables after the actives for structure–activity comparison purposes. The actives in Tables I and II are denoted by the highest ILS achieved and negatives by the symbol –. The range of

(20) Venditti, J. M.; Wesley, R. A.; Plowman, J. *Advances in Pharmacology and Chemotherapy*; Garattini, S., Goldin, A., Hawking, F., Eds.; Academic: New York, 1984; Vol. 20, p 1.
(21) Jurd, L. *J. Heterocycl. Chem.* **1985**, *22*, 993.
(22) Batra, J. K.; Jurd, L.; Hamel, E. *Biochem. Pharmacol.* **1986**, *35*, 4013.

Table II. 4′-Methoxy-6-benzyl-1,3-benzodioxoles



compd	R_1	R_2	R_3	R_4	R_5	P388[a] act.: ILS	mp °C	formula[b]
8	Et	Me	H	H	H	25		
11	Et	Me	Me	H	H	35		
4	Me	Me	H	H	H	78		
9	allyl	Me	H	H	H	88		
43	CH_2CH_2OH	Me	H	OMe	OMe	80	97–99	$C_{20}H_{24}O_7$
44	Et	H	H	H	H	–	101	$C_{17}H_{18}O_4$[c]
45	Et	Me	H	Me	H	–	81–82	$C_{19}H_{22}O_4$
46	Et	Et	H	H	H	–	108	$C_{19}H_{22}O_4$
47	Et	Me	H	OMe	H	–	80–81	$C_{19}H_{22}O_5$
48	Et	CH_2CO_2H	H	H	H	–	144–145	$C_{19}H_{20}O_6$
49	Et	Me	H	OMe	OMe	–	86–87	$C_{20}H_{24}O_6$
50	Et	H	H	OMe	OMe	–	103–104	$C_{19}H_{22}O_6$
51	Me	Me	H	OMe	H	–	90–91	$C_{18}H_{20}O_5$
52	Me	Me	H	OMe	OMe	–	104–105	$C_{19}H_{22}O_6$
53	allyl	Me	H	OMe	OMe	–	70	$C_{21}H_{24}O_6$
54	CH_2CH_2OH	Me	H	OMe	H	–	82–83	$C_{19}H_{22}O_6$
55	CH_2CO_2Et	Me	H	OMe	OMe	–	87–88	$C_{22}H_{26}O_8$
56	Pr	Me	H	OMe	OMe	–	62–63	$C_{21}H_{26}O_6$

[a] See *a* in Table I. [b] All new BBDs had satisfactory analyses for C and H, except for 48, which gave M^+ 358. [c] See ref. 11.

Table III. P388 Activity of the 6-Benzyl-1,3-benzodioxoles

compd	ILS[a] (dose, mg/kg)
3 etoposide	219 (16),[b] 3/6 cures
9	88 (200), 84 (800), 41 (200), 39 (400)[b]
43	80 (400), 66 (200), 61 (400), 49 (400)
4	78 (100), 76 (100), 74 (200), 53 (100)
5	78 (200), 61 (400), 56 (200), 31 (200)
5-fluorouracil	73 (20)[b]
6	71 (5), 56 (200), 36 (50)
1 podophyllotoxin	52 (8)[b]
7	41 (240), 26 (100)
11	35 (480), 25 (240)
10	30 (400)[b], 21 (200), 14 (400), 12 (400)
8	25 (100), 23 (100)

[a] Increased life span, %. [b] Tested in the same control.

observed ILSs for the actives and the optimal dose in milligrams/kilogram are presented in Table III.

The P388-active compounds in Table I have either methoxyl or ethoxyl substitution at R_4. Inactive compounds **12–19** are identical with active compounds 4 and 5 except in the R_4 position. Small changes at the benzhydryl carbon substituents R_2 and R_3 as in compounds **20–25**, **39**, and **40** usually destroyed activity. Compound **11** is an exception to that rule. Either methoxyl or ethoxyl at R_1 is compatible with activity. Compounds **7**, **9**, and **10** demonstrate that propoxy and allyloxy are also acceptable, but larger and more polar groups as in **26–35** give inactive compounds. Neither the acetyloxy nor the phenolic hydroxyl at R_1 in **34** and **35**, respectively, is compatible with activity. Compounds **36–40** and **21** resemble active **11** at R_2 and R_3 but are inactive. Compound **9** has the best activity of all the BBDs tested in the NCI Tumor Panel. However, additional 5-allyloxy examples **40–42** proved negative.

Compounds **44–48** in Table II show the deleterious effect on activity of small changes to active compounds **8** and **11** at the R_2, R_3, and R_4 positions. Compounds **49** and **50** have enhanced similarity to podophyllotoxin because of the presence of additional methoxyl groups at R_4 and R_5 but are, nevertheless, inactive. Compounds **51–53** explore the effect of additional methoxyls on active examples **4** and **9**. These changes result in inactive compounds. It appears that the substitution of a (2-hydroxyethyl)oxy group at R_1 reverses the negative impact on activity of the methoxyl substitutions at R_4 and R_5. Compound **43**, having the (2-hydroxyethyl)oxy at R_1 and methoxyls at both R_4 and R_5, is active; but compounds **54** and **31** show that if either one or both of the methoxyls are lost, so is the activity. Compounds **52–56** and **49** demonstrate the importance of the (2-hydroxyethyl)oxy R_1 substitution.

The compounds in Table III are arranged in an approximate order of their ILS against the P388 leukemia. The variability in ILS values makes it difficult to assign rank order precisely, but certain observations can be made. The glycosidic, 4′-demethylepipodophyllotoxin etoposide is markedly superior to the listed BBDs, 5-FU, or podophyllotoxin. BBDs **9**, **43**, **4**, and **5** give about the same life extension as either 5-FU or podophyllotoxin, but require larger doses to achieve the same effect.

In Vivo Tumor Panel Testing. The Tumor Panel is a set of in vivo tumor models used by the NCI to establish the basis for decisions that could lead to the clinical trial of an experimental antitumor agent. The tumor systems comprising the Tumor Panel have changed from time to time, and the Panel testing of this series has involved some of these changes. However, all of the BBDs discussed here were evaluated against the L1210 leukemia, the B16 melanoma, the M5076 reticulum cell sarcoma, and the MX1 mammary xenograft. No BBD showed activity against the latter system; Table IV provides the results of tests against L1210, B16, and M5076.

The topoisomerase-effecting etoposide (**3**) is markedly superior to the tubulin-binding **1**, **9**, **5**, **43**, **4**, or **8** against the L1210 leukemia tumor model or the B16 melanoma model. Reproducible activity at a modest level was demonstrated for **9**, **5**, and **43** in routine testing against L1210. A direct comparison test of **1** and **9** in L1210 using a five-injection protocol resulted in an ILS of 31 for **1**, but **9** was inactive. (These tests are not shown in Table IV.) When another direct comparison test of **1** and **9** against

Table IV. Tumor Panel[a]

compd	L1210[b] ILS [cures]	L1210[b] (dose, mg/kg)	B16[c] ILS [cures]	B16[c] (dose, mg/kg)	M5076[d] ILS	M5076[d] (dose, mg/kg)
3	>511 [4/8]	(8)	>185 [6/10]	(10)	87	(32)
	118 [2/10]	(4)	>176 [3/6]	(8)	72	(32)
9	43	(200)	55	(200)	58	(800)[g]
	39	(200)	27	(100)	33	(400)
	inactive	(400)[e]	inactive	(200)[f]		
5	50	(200)	42	(200)	49	(500)
	24	(200)	29	(100)	27	(500)
1			28	(1)[f]	46	(4)[g]
	inactive	e	inactive			
43	43	(200)	inactive		inactive	
	33	(200)				
4	inactive		inactive		inactive	
8	inactive		inactive		inactive	

[a] See ref 19 and 20. [b,c] Both tumors were grown ip, and drug was injected once a day for 9 days; for details, see ref 19. [d] Tumor was grown ip, and drug was given in four injections spaced 4 days apart; for details, see ref 19. [e,f,g] Each represents a pair of experiments performed with the same control group to enhance comparability of the results.

L1210 was attempted, using a nine-injection schedule, both 1 and 9 were inactive. Because of the variability inherent in this type of testing, particularly with insoluble compounds like 9, it is not at all uncommon for compounds that previously reproduced at very modest activity levels to fail some additional retests (insoluble compounds are administered by using appropriate suspending agents, e.g., klucel or Tween 80). While we remain unknowing if 1 or 9 is more active against L1210, it is abundantly clear that neither has much activity. Almost the identical situation occurred when B16 tests were performed. Routine B16 tests gave reproducible modest activity levels for both 5 and 9. Earlier tests of 1 in B16 gave negative results. When a direct comparison of 1 and 9 against B16 was attempted, 9 was negative and 1 gave weakly positive results. As for L1210, it is unclear if 1 or 9 is more active against B16, but it is clear that neither has much activity.

Etoposide proved only slightly superior to 1, 5, or 9 against the M5076 tumor. Routine tests of 9 and 5 against this tumor gave reproducible and modest levels of activity. This time, however, direct comparison tests between 1 and 9 gave positive results for both compounds, and nearly equal levels of activity were observed. The dose potency difference was, however, significant.

In Vitro Astrocytoma Assay. A few of the first BBDs found active against P388 were also tested in vitro in the astrocytoma assay.[17] Activity in this assay depends on the ability of the test compound to inhibit the dibutyryl-cAMP-induced change of an immature glioma cell to a mature, differentiated astrocyte. Compounds that interfere with or bind to tubulin, e.g., colchicine or podophyllotoxin, are detected by this assay. On the basis of the structure of the BBDs and the fact that some were active against P388, it was felt likely that the activity was mediated by tubulin binding. All three of the compounds tested, 8, 4, and 9, proved active in this assay (Table V).

Conclusions. An extensive series of 6-benzyl-1,3-benzodioxoles have been prepared and tested in vivo against the ip P388 murine lymphocytic leukemia. Selected actives from this prescreen were tested in the additional tumor systems L1210, B16, M5076, and MX1. The most effective of the 6-benzyl-1,3-benzodioxoles tested were as active as podophyllotoxin against the model systems used but required larger doses to achieve the activity. The presence of a BBD-like substructure within the podophyllotoxin structure, the observed in vivo activity against P388 leukemia, and the in vitro activity against the astrocytoma assay system[17] suggested that the mechanism of cytotoxicity of the BBDs and podophyllotoxin might be related. A recent paper by Batra et al.[18] confirmed that the BBDs, like podophyllotoxin, have significant antimitotic activity and that the BBDs, like podophyllotoxin, are competitive inhibitors of the binding of colchicine to tubulin. There is no basis to believe that any of the BBDs reported here share any of the mechanism of antitumor activity reported for etoposide or teniposide, i.e., interaction with topoisomerase 2.

Table V. In Vitro Astrocytoma Assay[a]

compd	dose μg/mL	% astrocyte reversal #1	% astrocyte reversal #2
8	100	91–up	71–90
	10	31–50	31–50
	1	16–30	16–30
4	100	16–30	16–30
	10	6–15	0–5
	1	0–5	0–5
9	100	51–70	31–50
	10	6–15	31–50
	1	0–5	0–5
colchicine	10	91–up	91–up
	1	51–70	51–70
	0.1	0–5	0–5

[a] See ref 17.

Experimental Section

Boiling and melting points are uncorrected. ^{1}H NMR spectra were determined in $CDCl_3$ with a Me_4Si internal standard on a modified Varian HA-100 instrument. The synthesis of some of the benzodioxoles listed in Table I has been described previously.[11] The preparation of representative new benzodioxoles is described below. Other new benzodioxole derivatives listed in Tables I and II were prepared by similar procedures.

5-(2-Propenyloxy)-6-[1-(4-methoxyphenyl)ethyl]-1,3-benzodioxole (9). A solution of 6-[1-(4-methoxyphenyl)-ethyl]-1,3-benzodioxol-5-ol (54.4 g)[11] and 3-bromopropene (24.2 g) in acetone (100 mL) was refluxed with potassium carbonate (50 g) for 4 h. The mixture was concentrated and diluted with an excess of water. The oily product crystallized; it was recrystallized from acetone–methanol to give 9 as colorless needles (40.8 g): mp 53–54 °C; MS, *m/e* 312 (64.1), 297 (9.2), 271 (52.5), 255 (9.3), 241 (17.4), 225 (5.9), 213 (11.7), 163 (12.2), 147 (9.3) 133 (100.0), 121 (7.45); ^{1}H NMR δ 1.47 (3 H, d, J = 7 Hz), 3.72 (3 H, s), 4.36 (2 H, m), 4.47 (1 H, q, J = 7Hz), 5.22 (2 H, m), 5.79 (2 H, s), 5.95 (1 H, m), 6.46 (1 H, s), 6.63 (1 H, s), 6.75 (2 H, d, J = 8 Hz), 7.10 (2 H, d, J = 8 Hz). Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.1; H, 6.45. Found: C, 73.0; H, 6.49.

6-[1-(4-Ethoxyphenyl)ethyl]-1,3-benzodioxol-5-ol. A solution of 4-ethoxyacetophenone (32.8 g) in ethanol (100 mL) was treated with sodium borohydride (3.8 g). After 2 h, an excess of water was added to precipitate 1-(4-ethoxyphenyl)ethanol (30.4 g) as colorless needles, mp 51–52 °C. Without further purification 1-(4-ethoxyphenyl)ethanol (33.2 g) was refluxed with sesamol (27.6

g) and oxalic acid (2 g) in acetic acid (60 mL) and water (5 mL) for 5 h. Water was added to precipitate an oil, which was extracted with ether and distilled to give 6-[1-(4-ethoxyphenyl)ethyl]-1,3-benzodioxol-5-ol as a slightly yellow oil, bp 220–225 °C (0.5 mm) (52 g). It crystallized from benzene–Skellysolve F as colorless needles: mp 86–87 °C; ^{1}H NMR δ 1.35 (3 H, t, J = 7 Hz), 1.50 (3 H, d, J = 7 Hz), 3.95 (2 H, q, J = 7 Hz), 4.8 (2 H, q, J = 7 Hz), 4.58 (1 H, s), 5.82 (2 H, s), 6.32 (1 H, s), 6.67 (1 H, s), 6.78 (2 H, d, J = 8 Hz), 7.06 (2 H, d, J = 8 Hz). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.3; H, 6.34. Found: C, 71.4; H, 6.36.

The above product (10 g) was methylated by refluxing it with methyl iodide (15 mL), acetone (30 mL), and potassium carbonate (10 g) for 8 h. The mixture was concentrated and diluted with water. The crystalline product was recrystallized from methanol to give the ***O*-methyl derivative 5** as colorless needles (9.2 g): mp 71–72 °C; ^{1}H NMR δ 1.32 (3 H, d, J = 7 Hz), 1.46 (3 H, d, J = 7 Hz), 3.65 (3 H, s), 3.94 (2 H, q, J = 7 *hz*), 4.32 (1 H, q, J = 7 Hz), 5.89 (2 H, s), 6.45 (1 H, s), 6.58 (1 H, s), 6.74 (2 H, d, J = 8 Hz), 7.10 (2 H, d, J = 8 Hz). Anal. Calcd for $C_{18}H_{20}O_4$: C, 72.0; H, 6.71. Found: C, 71.8; H, 6.71. the ***O*-ethyl derivative 6**, prepared similarly with ethyl iodide, crystallized from acetone–methanol as colorless thick needles, mp 60–61 °C. Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.6; H, 7.05. Found: C, 72.6; H, 7.11. The ***n*-propyl ether 7** crystallized from methanol as colorless needles, mp 49–50 °C. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.1; H, 7.37. Found: C, 73.3; H, 7.45.

6-[1-(4-Methoxyphenyl)-1-methylethyl]-1,3-benzodioxol-5-ol. A mixture of sesamol (27.6 g), 1-(4-methoxyphenyl)-1-methylethanol (33.2 g), oxalic acid (2 g), acetic acid (60 mL), and water (5 mL) was refluxed for 3 h and diluted with water. The oily product was extracted with chloroform and distilled to give the above benzodioxol-5-ol as a colorless oil, bp 210–212 °C (0.5 mm), which crystallized from methanol as colorless needles (41 g): mp 87–88 °C; ^{1}H NMR δ 1.57 (6 H, s), 3.73 (3 H, s), 4.27 (1 H, s), 5.85 (2 H, s), 6.30 (1 H, s), 6.77 (1 H, s), 6.97 (1 H, s), 6.99 (2 H, d, J = 8 Hz), 7.24 (2 H, d, J = 8 Hz). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.3; H, 6.34; $M^{\bullet+}$, 286.1205. Found: C, 71.7; H, 6.52; $M^{\bullet+}$, 286.1216.

The above phenolic benzodioxole was alkylated in the usual way to give ethers **21** and **11**. ***O*-Methyl derivative 21**: colorless needles from methanol; mp 90–91 °C; ^{1}H NMR δ 1.57 (6 H, s), 3.15 (3 H, s), 3.70 (3 H, s), 5.84 (2 H, s), 6.40 (1 H, s), 6.69 (2 H, d, J = 8 Hz), 6.93 (1 H, s), 7.04 (2 H, d, J = 8 Hz). Anal. Calcd for $C_{18}H_{20}O_6$: C, 72.0; H, 6.71; $M^{\bullet+}$, 300.1361. Found: C, 72.1; H, 6.74; $M^{\bullet+}$, 300.1352. ***O*-Ethyl derivative 11**: colorless needles from methanol; mp 79–80 °C; ^{1}H NMR δ 0.85 (3 H, t, J = 7 Hz), 1.58 (6 H, s), 3.43 (2 H, q, J = 7 Hz), 3.74 (3 H, s), 5.85 (2 H, s), 6.29 (1 H, s), 6.70 (2 H, d, J = 9 Hz), 6.95 (1 H, s), 7.06 (2 H, d, J = 9 Hz). Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.6; H, 7.05. Found: C, 72.8; H, 7.12.

6-[1-(3,4,5-Trimethoxyphenyl)ethyl]-1,3-benzodioxol-5-ol. 1-(3,4,5-Trimethoxyphenyl)ethanol was conveniently prepared by reduction of 3,4,5-trimethoxyacetophenone (100 g) with sodium borohydride (10 g) in ethanol (200 mL). The oil obtained on adding water to the reaction mixture was distilled to give 1-(3,4,5-trimethoxyphenyl)ethanol as a colorless oil (92 g): bp 164–165 °C (0.5 mm); ^{1}H NMR δ 1.41 (3 H, d, J = 7 Hz), 3.21 (1 H, s), 3.79 (3 H, s), 4.76 (1 H, q, J = 7 Hz), 6.57 (2 H, s). A mixture of this ethanol derivative (42.4 g), sesamol (27.6 g), oxalic acid (2 g), acetic acid (60 mL), and water (5 mL) was refluxed for 4 h and diluted with water. The solid product was crystallized from methanol to yield the above 1,3-benzodioxol-5-ol as colorless prisms (57 g): mp 130–131 °C; ^{1}H NMR δ 1.51 (3 H, d, J = 7 Hz), 3.78 (9 H, s), 4.26 (1 H, q, J = 7 Hz), 5.10 (1 H, s), 5.86 (2 H, s), 6.38 (1 H, s), 6.47 (2 H, s), 6.77 (1 H, s). Anal. Calcd for $C_{18}H_{20}O_6$: C, 65.0; H, 6.07. Found: C, 65.0; H, 6.05.

A solution of the above-described phenol (10 g) and ethyl bromoacetate (5.1 g) in acetone (20 mL) was refluxed in the presence of potassium carbonate (10 g) for 6 h, concentrated, and diluted with water. The product was extracted with ether. Removal of the ether left an oil, which crystallized from methanol to give **55** as colorless needles (10.2 g): mp 87–88 °C; ^{1}H NMR δ 1.25 (3 H, t, J = 7 Hz), 1.49 (3 H, d, J = 7 Hz), 3.78 (9 H, s), 4.20 (2 H, q, J = 7 Hz), 4.42 (2 H, s), 4.53 (1 H, q, J = 7 Hz), 5.85 (2 H, s), 6.40 (1 H, s), 6.50 (2 H, s), 6.66 (1 H, s). Anal. Calcd for $C_{22}H_{26}O_8$: C, 63.1; H, 6.26. Found: C, 63.1; H, 6.28.

A solution of the ester **55** (4.2 g) in monoglyme (8 mL) was refluxed for 3.5 h with sodium borohydride and lithium chloride (1.3 g). The product (3.2 g) crystallized on adding water (50 mL) and Skellysolve F (30 mL) to the cooled reaction mixture. The product was recrystallized from methanol.

2-[[6-[1-(3,4,5-Trimethoxyphenyl)ethyl]-1,3-benzodioxol-5-yl]oxy]ethanol (43): separated as colorless needles: mp 97–98 °C; ^{1}H NMR δ 1.78 (1 H, s), 3.78 (9 H, s), 3.88 (4 H, m), 4.33 (1 H, q, J = 7 Hz), 5.89 (2 H, s), 6.40 (2 H, s), 6.48 (1 H, s), 6.75 (1 H, s); MS, m/e 376 (100.0), 361 (47.6), 317 (9.8), 285 (7.9), 211 (17.0), 168 (25.9). Anal. Calcd for $C_{20}H_{24}O_7$: C, 63.8; H, 6.43. Found: C, 63.7; H, 6.42.

Registry No. **4**, 71712-16-8; **5**, 90632-70-5; **6**, 90632-69-2; **7**, 109335-88-8; **8**, 71712-17-9; **9**, 95385-60-7; **10**, 71712-18-0; **11**, 95385-64-1; **12**, 75393-99-6; **13**, 95385-56-1; **14**, 95385-58-3; **15**, 71712-21-5; **16**, 90632-71-6; **17**, 109335-89-9; **18**, 109335-90-2; **19**, 109335-91-3; **20**, 109335-92-4; **21**, 95385-63-0; **22**, 109335-93-5; **23**, 71712-07-7; **24**, 109335-94-6; **25**, 109335-95-7; **26**, 109335-96-8; **27**, 109335-97-9; **28**, 71712-19-1; **29**, 75393-88-3; **30**, 95385-61-8; **31**, 95385-62-9; **32**, 109335-98-0; **33**, 109335-99-1; **34**, 71712-01-1; **35**, 71712-15-7; **36**, 71712-26-0; **37**, 71712-47-5; **38**, 71712-48-6; **39**, 109336-00-7; **40**, 109336-01-8; **41**, 109336-02-9; **42**, 109336-03-0; **43**, 95385-72-1; **44**, 71712-08-8; **45**, 109336-04-1; **46**, 109336-05-2; **47**, 95385-66-3; **48**, 109336-06-3; **49**, 95385-70-9; **50**, 109336-07-4; **51**, 95385-65-2; **52**, 95385-69-6; **53**, 109336-08-5; **54**, 95385-68-5; **55**, 109336-09-6; **56**, 95385-71-0; $BrCH_2CH{=}CH_2$, 106-95-6; *p*-$EtOC_6H_4Ac$, 1676-63-7; *p*-$EtOC_6H_4CH_2OH$, 6214-44-4; *p*-$Me_2C(OH)C_6H_4OMe$, 7428-99-1; $BrCH_2CO_2Et$, 105-36-2; sesamol, 533-31-3; 6-(1-(4-ethoxyphenyl)ethyl)-1,3-benzodioxol-5-ol, 109336-10-9; 6-(1-(4-methoxyphenyl)-1-methylethyl)-1,3-benzodioxol-5-ol, 109336-11-0; 3,4,5-trimethoxyacetophenone, 1136-86-3; 1-(3,4,5-trimethoxyphenyl)ethanol, 36266-40-7; 6-(1-(3,4,5-trimethoxyphenyl)ethyl)-1,3-benzodioxol-5-ol, 109336-12-1.