$$\Delta G_{m,calc} = \max_{b \in B_m} \Delta G(\mathbf{b}) \quad (3)$$

where B_m is the set of geometrically feasible binding modes for molecule m, and $\Delta G(\mathbf{b})$ is the total interaction energy for the mode **b**. (In this paper we take the convention that algebraically greater values denote better interaction.) Since the interaction energy of a molecule is assumed to be the sum of its atomic contributions, we have

$$\Delta G(\mathbf{b}) = \sum_{\text{region r}} \sum_{\substack{\text{atoms a} \\ \text{in r}}} \epsilon_{r,\text{type(a)}} \quad (4)$$

where $\epsilon_{r,\text{type(a)}}$ is the interaction energy parameter between the site region r and the atom-type of atom a. Once these interaction parameters are determined, they can be used to calculate the binding energy of a molecule outside the original set of compounds. However, if no solution can be found, the proposed site geometry is rejected, a more complex one is considered, and the above procedure is repeated until the ligand molecules of the set can be fitted to the experimental data.

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Registry No. 1, 50-32-8; 2, 215-58-7; 3, 218-01-9; 4, 129-00-0; 5, 27208-37-3; 6, 206-44-0; 7, 56-49-5; 8, 134-32-7; 9, 153-78-6; 10, 610-49-1; 11, 947-73-9; 12, 17573-21-6; 13, 57404-88-3; 14, 58886-98-9; 15, 37571-88-3; 16, 82911-12-4.

1,4-Dihydronaphthoquinones, Hydroindoloquinones, Benzofurans, and Benzothiophenes as Inhibitors of 5-Lipoxygenase. Synthesis and Structure–Activity Studies

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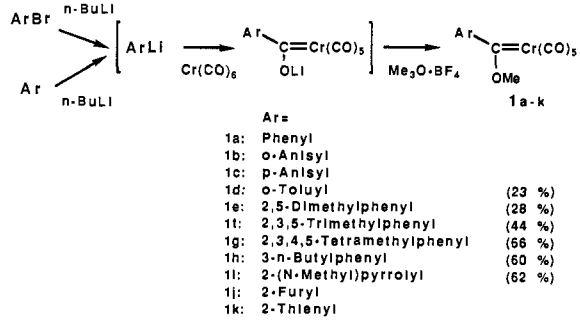
A series of substituted 1,4-dihydronaphthoquinones, hydroindoloquinones, benzofuran-4,7-dihydroquinones, and benzothiophene-4,7-dihydroquinones were synthesized and evaluated for inhibitory activity against 5-lipoxygenase. These compounds were found to be active in vitro for LTC_4/D_4 inhibition with the potencies (IC_{50}'s) ranging from 0.2 to 85 μM. Active 1,4-dihydronaphthoquinone acetates ($IC_{50} < 20$ μM) were evaluated in an ex vivo LTB_4 inhibition assay. The acetates of 1,4-dihydronaphthoquinones containing the alkyl substituent(s) (2-*n*-butyl, 11, and 2,3-diethyl, 15) exhibited the best activity in LTC_4/D_4 inhibition (IC_{50} = 0.2–0.4 μM, in vitro) as well as in LTB_4 inhibition (60–75% inhibition).

The metabolism of arachidonic acid (AA), catalyzed by the enzyme 5-lipoxygenase, produces 5-hydroperoxy-6,8,11,14-eicosatetraenoic acid (5-HPETE), which undergoes further bioconversions to 5-hydroxy-6,8,11,14-eicosatetraenoic acid (5-HETE) and to the leukotrienes (LTA_4, LTB_4, LTC_4, LTD_4, and LTE_4).[1] These potent biological substances have been implicated as important mediators of inflammation and allergic reactions. For example, LTC_4 and LTD_4 are potent bronchioconstrictors of human bronchi,[2] LTB_4 is a powerful chemotactic factor for leukocytes,[3] and inhibition of 5-lipoxygenase may be of therapeutic value in the treatment of inflammatory and allergic diseases. On the basis of current knowledge of the enzymatic mechanisms of related lipoxygenases,[4] it is reasonable to assume that the reaction of oxygen with AA to form 5-HPETE requires a metal species, putatively iron, in the active site of the enzyme. Considering this premise, there are several examples of rationally designed inhibitors of 5-lipoxygenase. Common approaches involve the preparation of acetylenic,[5] allenic,[6] aryl,[7] or dimethyl[8] analogues of AA. Other approaches include the synthesis of analogues of 5-HPETE[9] or LTA_4.[10] We have found that

Scheme I



Scheme II

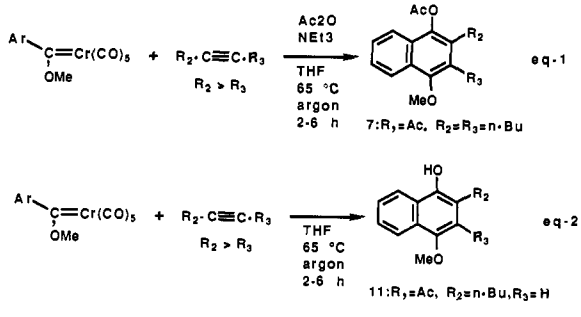


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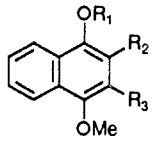
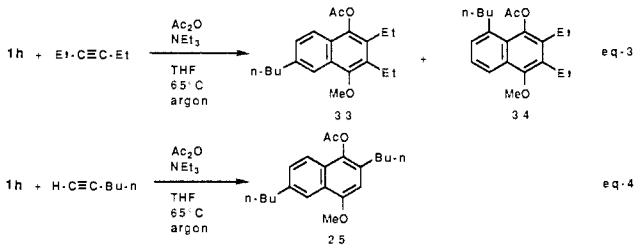
Table I. In Vitro and ex Vivo Assessment of Inhibitory Potencies



no.	R_1	R_2	R_3	LTC/D[a] IC_{50}, μM	LTB_4[b] % inhibn
2	Ac	Ph	Ph	11.02	
3	Ac	Ph	CO_2Et	5.81	
4	Ac	$CH(OP)CH_3$[d]	OEt	23.88	
5	Ac	CO_2Et	Et	3.76	
6	Ac	CO_2Et	n-C_5H_{11}	8.92	
7	Ac	n-Bu	n-Bu	6.02	29.2[c]
8	Ac	n-Bu	Et	0.99	-28.0
9	Ac	n-Bu	Me	0.20	
10	Ac	n-C_5H_{11}	CO_2Et	0.94	
11	Ac	n-Bu	H	0.44	61.1[c]
12	Ac	n-Pr	n-Pr	1.43	
13	Ac	Et	n-Bu	1.13	-39.4
14	Ac	Et	CO_2Et	1.16	
15	Ac	Et	Et	0.40	74.8[c]
16	H	n-Bu	H	1.47	
17	CH_3	n-Bu	H	40.92	
18	CH_3	$CH(OH)CH_3$[e]	OEt	85.99	
19	CH_3	$CH=CH_2$	OEt	inactive	

[a] IC_{50} is the concentration causing 50% inhibition of LTC/D production based on interpolation of a log dose vs response plot. Activity was expressed as percent of control based on duplicate determinations. [b] A dose of 50 mg/kg with male Sprague-Dawley rats. Each compound was tested in five rats. [c] P value is less than 0.05 compared to nontreated, vehicle-administered control. [d] P = $SiMe_2$-t-Bu, ref 12a. [e] Reference 12b.

Scheme III



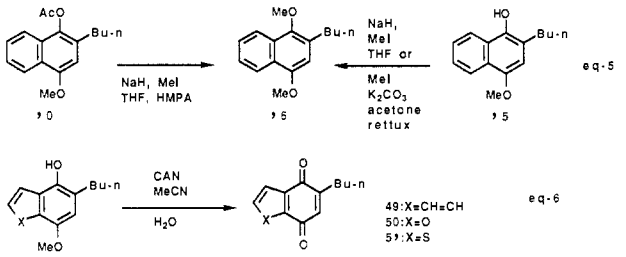
fused-aromatic 1,4-dihydroquinones effectively inhibit leukotriene formation.

We herein report the synthesis and the structure–activity studies (SAR) of 1,4-dihydronaphthoquinones, 1,4-dihydroindoloquinones, benzofurans, and benzothiophenes as a novel and new class of potent irreversible inhibitors of 5-lipoxygenase.

Chemistry

The synthetic pathway for preparation of pentacarbonyl(arylmethoxycarbene)chromium(0) (**1a–k**) and the compounds listed in Table I–IV is illustrated in Scheme I–III. The aryl chromium carbene complexes (**1a–c**, **1j**, **1k**) were prepared according to the literature.[11] The other

Scheme IV



carbene complexes (**1d–i**) were prepared in a similar fashion by the reaction of aryllithium with chromium hexacarbonyl and sequential methylation with trimethyloxonium tetrafluoroborate (Scheme I).[11] The corresponding aryllithium was generated either by a lithium–halogen exchange reaction of an aryl bromide and n-butyllithium at 25 °C in n-hexane (for **1a–h**) or direct lithiation of an aromatic ring with n-butyllithium in THF at −30 °C (for **1i**).[12] The acetate derivatives of 1,4-dihydronaphthoquinone, 1,4-dihydroindroquinone, benzofuran, and benzothiophene were prepared by the alkyne–carbene cycloaddition with in situ protection developed in our laboratories[13] (eq 1, Scheme II). A solution of the complex with the alkyne (1–2 molar equiv) in THF in the presence of acetic anhydride (1–2 molar equiv) and triethylamine (1–2 molar equiv) was heated at 65 °C (bath temperature) under argon. TLC analysis indicated that the reaction was complete within 5-10 h. After chromatographic purification, the product was characterized by mass, IR, and ^1H NMR spectral analysis. The acetate derivatives (**2–11**, **20–41**, and **47**) were prepared in this manner from the corresponding carbene complexes and alkynes. The reaction of the complex with an alkyne without acetic anhydride and triethylamine in THF at 65 °C produced free phenols[14] such as **16**, **42–46**, and **48** (eq 2, Scheme II). The regiochemistry of two functional groups, R_2 and R_3, was determined according to the literature.[15] The reaction of **1h** with 3-hexyne in THF under the conditions for the cycloaddition with in situ protection provided two regioisomers, 6-n-butylnaphthalene (**33**) and 8-n-butylnaphthalene (**34**), in a 1:1 ratio (eq 3, Scheme III). On the other hand, the reaction of **1h** with 1-hexyne under the identical conditions produced only 6-n-butyl derivative **25** (eq 4, Scheme III). It is presumed that, in the 1-hexyne reaction, the cycloaddition to the para position to the n-butyl substituent became more favored due to avoidance of the steric interaction between two butyl groups in the cyclization to the ortho position. The dimethyl derivatives of 1,4-dihydronaphthoquinone (**17–19**) were prepared either by methylation of the free phenol or by conversion of the acetate to the methyl ether[16] (eq 5, Scheme IV). For example, treatment of **10** with sodium hydride (2 molar equiv) and excess methyl iodide in THF and HMPA di-

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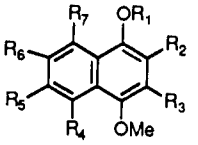
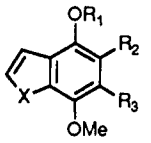
Table II. In Vitro and ex Vivo Assessment of Inhibitory Potencies



no.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	LTC/D[a] IC_{50}, μM	LTB_4[b] % inhibn
20	Ac	*n*-Bu	H	H	H	OMe	H	1.38	−41.1
21	Ac	*n*-Bu	H	OMe	H	H	H	0.26	17.5
22	Ac	*n*-Bu	H	Me	H	Me	Me	11.86	35.4[c]
23	Ac	*n*-Bu	H	Me	H	H	Me	7.35	19.1
24	Ac	*n*-Bu	H	Me	H	H	H	0.62	31.8[c]
25	Ac	*n*-Bu	H	H	*n*-Bu	H	H	0.48	19.2
26	Ac	*n*-Bu	H	Me	Me	Me	Me	44.05	41.2[c]
27	Ac	Et	Et	OMe	H	H	H	0.89	−13.1
28	Ac	Et	Et	H	H	OMe	H	0.69	−64.6
29	Ac	Et	Et	Me	H	Me	Me	15.67	14.7
30	Ac	Et	Et	Me	H	H	H	0.83	40.6[c]
31	Ac	Et	Et	Me	H	H	Me	13.01	50.6[c]
32	Ac	Et	Et	Me	Me	Me	Me	37.32	−4.9
33	Ac	Et	Et	H	*n*-Bu	H	H	0.94	17.0
34	Ac	Et	Et	H	H	H	*n*-Bu	14.12	30.5

[a] IC_{50} is the concentration causing 50% inhibition of LTC/D production based on interpolation of a log dose vs response plot. Activity was expressed as percent of control based on duplicate determinations. [b] A dose of 50 mg/kg with male Sprague–Dawley rats. Each compound was tested in five rats. [c] *P* value is less than 0.05 compared to nontreated, vehicle-administered control.

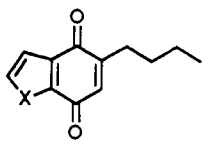
Table III. In Vitro Assessment of Inhibitory Potencies



no.	X	R_1	R_2	R_3	LTC/D[a] IC_{50}, μM
35	NMe	Ac	Ph	Ph	inactive
36	NMe	Ac	Ph	H	3.86
37	NMe	Ac	*n*-Bu	Me	0.76
38	NMe	Ac	*n*-Bu	H	0.72
39	NMe	Ac	Et	Et	2.03
40	NMe	Ac	Me	*n*-Bu	0.76
41	O	Ac	*n*-Bu	H	0.11
42	O	H	*n*-Bu	H	11.94
43	O	H	*n*-Bu	*n*-Bu	1.15
44	O	H	Ph	Ph	4.39
45	O	H	Ph	H	2.20
46	O	H	Ph	Me	1.25
47	S	Ac	*n*-Bu	H	0.46
48	S	H	*n*-Bu	H	1.05

[a] IC_{50} is the concentration causing 50% inhibition of LTC/D production based on interpolation of a log dose vs response plot. Activity was expressed as percent of control based on duplicate determinations.

Table IV. In Vitro Assessment of Inhibitory Potencies



no.	X	LTC/D[a] I_{50}, μM
49	CH=CH	2.24
50	O	2.05
51	S	23.50

[a] IC_{50} is the concentration causing 50% inhibition of LTC/D production based on interpolation of a log dose vs response plot. Activity was expressed as percent of control based on duplicate determinations.

rectly formed **16**. 1,4-Quinones **49–51** were generated by oxidation of the corresponding free phenols (**16**, **41**, **48**) with ceric ammonium nitrate in acetonitrile and water at 0 °C (eq 6, Scheme IV).

Biological Data and Discussion

Initial evaluation of the compounds was performed with the in vitro LTC_4/D_4 inhibition assay. Active compounds were assayed in an ex vivo inhibition assay. Results are expressed in Tables I–IV. We first prepared a series of 1-acetoxy-4-methoxynaphthalenes by varying the substituents (R_2, R_3) at the 2- and 3-positions and examined the resulting compounds for LTC_4/D_4 inhibitory activity (Table I). Compounds bearing a sterically bulky group or a strong electron-withdrawing group, such as a phenyl and an ester group (**2–6**), have shown marginal activity at the high concentrations. The alkyl-substituted derivatives, such as **7–9**, **11–13**, and **15**, showed significantly higher activity. The substituent at the 2-position appears to be more important in comparison to that of the 3-position. For example, compounds **10** and **14** are the regioisomers of **5** and **6**, even though they carry the electron-withdrawing group, they expressed a 5–10 fold higher potency than **5** and **6**. The 2,3-dialkyl-substituted derivatives (**7–9**, **12**, **13**, **15**) as well as the 2-alkyl-substituted compound (**11**) showed consistently high activity (IC_{50} = 0.1–1.5 μM) with the exception of **7**. Among these compounds, **9**, **11**, and **15** significantly inhibited LTC_4 formation (IC_{50} = 0.3 μM). By removal of the acetyl ester at the 1-position of **11**, there was no loss in activity (**16**), although the free phenols of this class are unstable to oxidation, particularly when R_2 and R_3 are electron-rich substituents and are readily converted to the corresponding quinones. Changing the acetate to the methyl ether (**11** to **17**) significantly reduced the activity. These observations indicated that the presence of the acetate and the alkyl substituent at the 2-position (next to the acetate) seem to be essential to high potency.

We next investigated the effect of the substituents at the 5–8-positions of the naphthalene ring, keeping the other substituents constant (R_1 = Ac, R_2 = *n*-Bu, R_3 = H, or R_1 = Ac, R_2 = R_3 = Et), based on two active structures (**11** and **15**). The alkyl or alkyloxy groups were introduced in various positions of these structures (Table II). Replacement of all four hydrogens at the 5–8-positions with

four methyl groups (26, 32) resulted in profound loss of potency (IC_{50} = 40 μM). Introduction of di- and trimethyl groups to the naphthalene ring (22, 29, 31, 33) rendered them less active in the order dimethyl > trimethyl substitution. Monomethyl-substituted derivatives (24, 30), the *n*-butyl derivatives (25, 33, 34), and the methoxy derivatives (20, 21, 27, 28) were found to be active. However, the activity was not higher than those of 9, 11, and 15.

5,6-Substituted hydroindoloquinone acetates 35–40, benzofuran-4,7-hydroquinones 41–46, and benzothiophene-4,7-hydroquinones 47, 48 were prepared in order to examine the effect of the heteroaromatic rings fused to the 1,4-hydrobenzoquinone. Various functional groups were introduced into the 5- and 6-positions. As observed before, the presence of the aryl, the bulky alkyl, and the electron-withdrawing substituents at these position(s) (35, 36, 44, 45) resulted in a considerable decrease in the potency, while compounds with the alkyl substituents (37–43, 47, 48) maintained comparative activity to that of 11 and 15. 1,4-Dihydroquinones 16, 42, and 48 were converted to the corresponding 1,4-quinones in order to investigate if 5-lipoxygenase could catalyze oxidation of the free phenol, derived from the acetate by hydrolysis, to the quinone.[17] As shown in Table IV, oxidation may be involved since quinones 49–51 and the methyl ether derivative 17 (Table I) were found to be less active than those of dihydroquinones 16, 42 and 48 and the acetate derivatives 11, 41 and 47.

The ex vivo experiments determining LTB_4 inhibition were performed with the compounds having high activity in LTC_4/D_4 assay as described above. The results are illustrated in Tables I and II. Among the compounds tested, 7, 22, 26, 30, and 34 presented good activity (30–50% inhibition) and 21, 23, 25, 29, and 33 were marginally active (10–20% inhibition). However, 8, 13, 20, 28, and 32 resulted in enhancement of LTB_4 formation. Compounds 11 and 15 expressed the best inhibition (60–80% inhibition).

In summary, 1,4-dihydronaphthoquinones have been demonstrated to be potent inhibitors of 5-lipoxygenase. The alkyl substituent attached next to the acetate (at the 2-position) seems to have a great influence on the magnitude of this potency in both LTC_4/D_4 and LTB_4 inhibition. Many of these analogues have IC_{50}'s for 5-lipoxygenase inhibition equal to those of the hydroxamic acid analogues (0.5–1.0 μM) and in excess of the phenidone analgoue BW755C (43 μM).[18a-c] In addition, the in vivo potencies of our more active compounds (11 and 15) appear to be equivalent to those reported for the more active hydroxamic acid analogues.[18a,b] The potent inhibition provided by the 1,4-dihydronaphthoquinone analogues suggests a possible strategy for designing pharmaceutically useful inhibitors of 5-lipoxygenase.

Experimental Section

Determination of LTC_4/D_4 Inhibitory Potencies. Compounds were initially evaluated at a concentration of 10 μg/mL for their ability to inhibit the formation of LTC_4/D_4 in rat peritoneal mononuclear cells which were challenged with the calcium ionophore A23187 in the presence of cysteine[19] and activity was expressed as the percent of control based on duplicate determinations. Follow-up determinations were employed to derive estimates of IC_{50}. The production of LTC_4/D_4 was initially determined with a bioassay on the atropinized, mepyramine-treated guinea pig ileum,[19] but more recently, a selective radioimmunoassay for LTC_4, which is the predominant sulfidopeptide leukotriene produced by these cells, was employed.[20] Results are expressed in Tables I–IV as IC_{50}. Compounds which showed the highest potency in this assay were evaluated in an ex vivo LTB_4 inhibition assay.

Determination of LTB_4 Inhibitory Potencies in ex Vivo. Male Sprague–Dawley rates (225–275 g) were fasted for 18 h prior to dosing. Each rat was orally dosed with 1.0 mL of a solution of the test compound calculated to give a dose of 50 mg/kg. Each compound was tested in five rats. Statistics were performed with SAS programs using GLM procedure and Wilcoxin's rank sum for estimating statistical significance. Control rats received 1.0 mL of vehicle. Two hours postdosing, rats were anesthetized and approximately 2 mL of heparinized blood was obtained from the vena cava of each rat. Blood (1.0 mL) was then simulated with calcium ionophore (A23187, 30 μM) for 30 min at 37 °C. Plasma was obtained by centrifugation and assayed for LTB_4 content by radioimmunoassay.[21] Percent inhibition of LTB_4 synthesis was determined by comparing the average LTB_4 value of the rats receiving the test compound vs the average LTB_4 value of the control rats. Data is presented in Tables I and II.

Synthesis. All melting points were obtained with a Thomas Hoover Capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on either a Perkin-Elmer Model 297 or a Digilab Model FTS 140 instrument. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on either a Varian FT-80A or a Bruker AM 300 MHz spectrometer. Chemical shifts are reported as values in parts per million relative to tetramethylsilane (δ 0.000) as an internal standard. Mass spectral data were obtained with either a Varian MAT CH7-A or a CEC 21-110B. Combustion analyses were obtained with a Perkin-Elmer 240B Elemental Analyzer. Analytical data indicated by the elemental symbols were within ±0.4% theoretical values unless noted.

All chromatographic isolations were accomplished by using a flash colum packed with silica gel 60 (230–400 mesh ASTM). Dry solvents were freshly distilled from an appropriate drying agent and stored under an argon atmosphere. Tetrahydrofuran (THF) was predried over 4-Å molecular sieve and distilled over sodium benzophenone ketyl immediately prior to use at atmospheric pressure under argon. All other solvents and reactants were ACS reagent grade unless described otherwise. "Ether" refers to anhydrous diethyl ether which is supplied by Mallinckrodt and Baker. *n*-Butyllithium (*n*-BuLi) was purchased from Aldrich as a 1.6 M solution in *n*-hexane. Trimethyloxonium tetrafluoroborate ($Me_3O{\cdot}BF_4$) was obtained from Alfa Co. and was used without further purification. Chromium hexacarbonyl [$Cr(CO)_6$] was purchased from Pressure Chemical Co. Pentacarbonyl(phenylmethoxycarbene)chromium(0) (**1a**), pentacarbonyl(*o*-anisylmethoxycarbene)chromium(0) (**1b**), pentacarbonyl(*p*-anisylmethoxycarbene)chromium(0) (**1c**), pentacarbonyl(2-furylmethoxycarbene)chromium(0) (**1j**), and pentacarbonyl(2-thienylmethoxycarbene)chromium(0) (**1k**) were synthesized by the literature procedure.[12] The syntheses of carbene complexes **1g** and 1i are given as examples. Other arylcarbene complexes were prepared according to these procedures. Physical data for compounds not explicitly described in this section are included in Table V.

Preparation of Pentacarbonyl[(2,3,4,5-tetramethylphenyl)methoxycarbene]chromium(0) (1g). To a solution of 2,3,4,5-tetramethylbromobenzene (16.6 g, 0.08 mol) in dry *n*-hexane (150 mL), prepared under argon, was added *n*-BuLi (48.9 mL, 0.08 mol, 1.6 M *n*-hexane solution) via a syringe over a period

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(21) Leukotriene B_4 (H-3) Assay Kit Protocol, Amersham Corp., Arlington Heights, IL.

Table V. Summary of Physical Data for Compounds Not Included in the Experimental Section

no.	mp, °C	formula	anal.
2	oil	$C_{25}H_{20}O_3$	C, H
3	oil	$C_{22}H_{20}O_5$	C, H
4	oil	$C_{32}H_{34}O_5Si$	C, H
5	oil	$C_{18}H_{20}O_5$	C, H
8	oil	$C_{19}H_{24}O_3$	C, H
9	oil	$C_{18}H_{22}O_3$	C, H
12	oil	$C_{19}H_{24}O_3$	C, H
13	oil	$C_{19}H_{24}O_3$	C, H
14	oil	$C_{18}H_{20}O_5$	C, H
18	oil	$C_{16}H_{20}O_4$	C, H
19	oil	$C_{16}H_{18}O_3$	C, H
20	66–69	$C_{18}H_{22}O_4$	C, H
21	69–71	$C_{18}H_{22}O_4$	C, H
22	70–72	$C_{20}H_{26}O_3$	C, H
24	56–59	$C_{18}H_{22}O_3$	C, H
27	oil	$C_{18}H_{22}O_4$	C, H
28	66–69	$C_{18}H_{22}O_4$	C, H
29	oil	$C_{20}H_{26}O_3$	C, H
30	56–59	$C_{18}H_{22}O_3$	C, H
31	87–90	$C_{19}H_{24}O_3$	C, H
32	oil	$C_{21}H_{28}O_3$	C, H
36	88.5–90	$C_{18}H_{17}NO_3$	C, H, N
37	oil	$C_{17}H_{23}NO_3$	C, H, N
38	oil	$C_{16}H_{21}NO_3$	C, H, N
39	oil	$C_{16}H_{21}NO_3$	C, H, N
40	oil	$C_{17}H_{23}NO_3$	C, H, N
42	65–67	$C_{13}H_{16}O_3$	C, H
43	oil	$C_{17}H_{24}O_3$	C, H
44	210.5–211	$C_{21}H_{16}O_3$	C, H
45	oil	$C_{15}H_{12}O_3$	C, H
46	90–91	$C_{16}H_{14}O_3$	C, H
47	oil	$C_{15}H_{18}O_3S$	C, H, S
48	71–72	$C_{13}H_{16}O_2S$	C, H, S
50	43–44	$C_{12}H_{12}O_3$	C, H
51	38–39	$C_{12}H_{12}O_2S$	C, H, S

of 20 min at 0 °C and the resulting solution was stirred at 25 °C for 4 days under argon. During this procedure, a white solid was precipitated. In a separate round-bottom flask, evacuated and filled with argon, were placed $Cr(CO)_6$ (18.5 g, 0.08 mol) and ether (350 mL), and the suspension was cooled with a wet-ice bath. To this suspension was introduced a solution of lithium tetramethylbenzene using a liquid-transferring cannula (a white solid was dissolved by addition of anhydrous ether). The resulting dark red solution was stirred at 25 °C for 1 h and the solvent was removed by rotary evaporation (bath temperature was kept below 45 °C). The remaining brown residue was dissolved in H_2O (200 mL), $Me_3O{\cdot}BF_4$ (10.4 g, 0.07 mol) was added portionwise to the aqueous solution, and the aqueous layer was extracted with ether (3 × 400 mL). The extracts were combined, washed with saturated aqueous $NaHCO_3$ (1 × 500 mL) and brine (3 × 500 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed under nitrogen using a flash column (silica gel, 700 g). Elution by 10% ether in *n*-hexane gave **1g** (17.1 g, 66%) as orange-red needles: MS *m/e* 368 (M^+), 340 ($M^+ - CO$), 312 ($M^+ - 2\ CO$), 284 ($M^+ - 3\ CO$), 256 ($M^+ - 4\ CO$), 228 ($M^+ - 5\ CO$), 52 (Cr); IR (Nujol) 2061, 1985, 1949, 1922, 1727 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.40 (1 H, s, C_6-H), 4.09 (3 H, s, $C_{carbene}$-OCH_3), 2.24 (3 H, s, C_2-CH_3), 2.16 (6 H, s, C_3-CH_3, C_4-CH_3), 1.97 (3 H, s, C_5-CH_3). The carbene complexes **1d–f** and **1h** were prepared in a similar manner from the corresponding bromides.[22]

Preparation of Pentacarbonyl[(*N*-methylpyrrol-2-yl)-methoxycarbene]chromium(0) (1i). In a 500-mL three-necked round-bottomed flask, evacuated and filled with argon three times, was placed *N*-methylpyrrole (9 mL, 0.1 mol) and THF (100 mL) via a syringe and the flask was cooled at −78 °C (dry ice/acetone bath). *n*-BuLi (62 mL, 0.1 mol, 1.6 M in *n*-hexane solution) was introduced slowly to the amine solution via a syringe over a period of 20 min and the resulting solution was stirred at −20 °C for 15 h under argon. In a 1000-mL three-necked round-bottomed flask, evacuated and filled with argon three times, were placed $Cr(CO)_6$ (22 g, 0.1 mol) and anhydrous ether (150 mL), and to this cooled (wet-ice bath) suspension was introduced the yellow solution of lithium pyrrole using a liquid-transferring cannula. During this procedure, $Cr(CO)_6$ was dissolved and the solution turned deep red. The solvent was removed by rotary evaporation (bath temperature was kept under 45 °C) and the black residue was dissolved in H_2O (200 mL). $Me_3O{\cdot}BF_4$ (15 g, 0.101 mol) was added portionwise to the aqueous solution and the aqueous layer was extracted with ether (3 × 300 mL). The extracts were combined, washed with aqueous $NaHCO_3$ solution (2 × 200 mL) and brine (3 × 300 mL), dried (Na_2SO_4), filtered, and concentrated to give a dark red oil. Purification by flash column chromatography (elution by ether/*n*-hexane 1/1) gave **1b** as yellow needles (19.6 g, 62%): MS *m/e* 315 (M^+), 287 ($M^+ - CO$), 259 ($M^+ - 2\ CO$), 231 ($M^+ - 3\ CO$), 203 ($M^+ - 4\ CO$), 175 ($M^+ - 5\ CO$), 160, 145, 132, 52 (Cr); IR (Nujol) 2053, 1984, 1400, 1343, 1323 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.73 (1 H, d, d, J = 1.5, 2.4 Hz, C_5-H in pyrrole), 6.79 (1 H, d, d, J = 1.5, Hz, C_3-H in pyrrole), 6.28 (1 H, d, d, J = 2.4 Hz, C_4-H in pyrrole), 4.71 (3 H, s, OCH_3), 3.73 (3 H, s, NCH_3). Anal. ($C_{12}H_9NO_6Cr$) C, H, N.

General Procedure for the Reaction of the Aryl Chromium Carbene Complex with Alkyne in the Presence of Ac_2O and NEt_3 in THF: Preparation of 1-Acetoxy-2,3-di-*n*-butyl-4-methoxynaphthalene (7). In a 1000-mL three-necked round-bottom flask, equipped with two rubber septa and a 6-in. air condenser with an argon–vacuum inlet, was placed **1a** (5.0 g, 15.2 mmol) and the flask was evacuated and filled with argon three times. THF (450 mL), dry 5-decyne (5.47 mL, 30.4 mmol), dry Ac_2O (2.87 mL, 30.4 mmol), and dry NEt_3 (4.24 mL, 30.4 mmol) were added to this flask via a syringe, and the solution was heated at 65 °C (bath temperature) for 10 h under argon. The mixture was cooled and the solvent was removed by rotary evaporation. The black residue was chromatographed using a flash column (silica gel, 450 g). Elution by 7% ether in *n*-hexane gave **7** (2.2 g, 48%) as a yellow oil: MS *m/e* 328 (M^+), 286, 271, 204, 43; IR (neat) 1764, 1595, 1359, 1206, 763 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.20–7.10 (4 H, m, C_5-H, C_6-H, C_7-H, C_8-H), 3.91 (3 H, s, $ArOCH_3$), 3.15–2.15 (4 H, m, 2 $ArCH_2CH_2CH_2CH_3$), 2.45 (3 H, s, $ArOCOCH_3$), 2.00–0.50 14 H, m, 2 $ArCH_2CH_2CH_2CH_3$). Anal. ($C_{21}H_{28}O_3$) C, H.

Preparation of 1-Acetoxy-2-(ethoxycarbonyl)-3-*n*-pentyl-4-methoxynaphthalene (6) and 1-Acetoxy-2-*n*-pentyl-3-(ethoxycarbonyl)-4-methoxynaphthalene (10). A solution of **1a** (5.0 g, 16.0 mmol), dry ethyl *n*-octynoate (5.0 mL, 24 mmol), dry Ac_2O (4.0 mL, 42 mmol), and dry NEt_3 (6.0 mL, 42 mmol) in THF (450 mL) was heated at 65 °C for 6 h under argon. Purification by flash column chromatography (silica gel, 250 g; 10% ether in *n*-hexane) gave a 1:2 mixture of **6** and **10** (2.78 g, 49%). Extensive flash column chromatography (silica gel, 450 g; 10% ether in *n*-hexane) isolated both **6** and **10** as yellow oils. **6**: high-resolution MS mol wt 358.1784, calcd 358.1780; IR (neat) 1775, 1727, 1595, 1359, 1284, 1225, 1197, 1160, 1075, 1031 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.20–8.00 (1 H, m, C_8-H), 7.90–7.70 (1 H, m, C_5-H), 7.65–7.40 (2 H, m, C_6-H, C_7-H), 4.41 (2 H, q, J = 7.0 Hz, $ArCO_2CH_2CH_3$), 3.92 (3 H, s, $ArOCH_3$), 3.05–2.80 (2 H, m, $ArCH_2CH_2CH_2CH_2CH_3$), 2.40 (3 H, s, $ArOCOCH_3$), 1.80–1.20 (6 H, m, $ArCH_2CH_2CH_2CH_2CH_3$), 1.40 (3 H, t, J = 7.0 Hz, $ArCO_2CH_2CH_3$), 1.05–0.80 (3 H, m, $ArCH_2CH_2CH_2CH_2CH_3$). Anal. ($C_{21}H_{26}O_5$) C, H. **10**: high-resolution MS mol wt 358.1791, calcd 358.1780; IR (neat) 1767, 1728, 1596, 1360, 1286, 1226, 1205, 1160, 1109, 1027 cm^{-1}); ^1H NMR ($CDCl_3$) δ 8.25–8.14 (1 H, m, C_8-H), 7.80–7.45 (3 H, m, C_5-H, C_6-H, C_7-H), 4.46 (2 H, q, J = 7.0 Hz, $ArCO_2CH_2CH_3$), 4.00 (3 H, s, $ArOCH_3$), 2.47 (3 H, s, $ArOCOCH_3$), 2.75–2.50 (2 H, m, $ArCH_2CH_2CH_2CH_2CH_3$), 1.80–1.20 (6 H, m, $ArCH_2CH_2CH_2CH_2CH_3$), 1.41 (3 H, t, J = 7.0 Hz, $ArCO_2CH_2CH_3$), 1.10–0.80 (3 H, m, $ArCH_2CH_2CH_2CH_2CH_3$). Anal. ($C_{21}H_{26}O_5$) C, H.

Preparation of 1-Acetoxy-2-*n*-butyl-4-methoxynaphthalene (11). A solution of **1a** (1.0 g, 3.2 mmol), dry 1-hexyne (1.0 mL, 8.7 mmol), dry Ac_2O (0.3 mL, 3.2 mmol), and dry NEt_3 (0.9 mL, 3.2 mmol) in THF (90 mL) was heated at 60 °C for 1 h under argon. Purification by flash column chromatography (silica gel, 200 g; 10% ether in *n*-hexane) gave 11 (715

(22) 3-*n*-Butylphenyl bromide for formation of **1h** was prepared according to the literature: Buchi, V. J.; Kollev, R. J.; Perlia, X. *Arzheim.-Forsch. (Drug Res.)* **1974**, *24*, 1957. Other bromides were commercially available.

mg, 82%) as white needles: mp 49–50 °C; high-resolution MS mol wt 272.1412, calcd 272.1412; IR (Nujol) 1761, 1597, 1370, 1202, 1162, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.25–8.10 (1 H, m, C_8-H), 7.75–7.40 (3 H, m, C_5-H, C_6-H, C_7-H), 6.65 (1 H, s, C_3-H), 3.98 (3 H, s, $ArOCH_3$), 2.75–2.50 (2 H, m, $ArCH_2CH_2CH_2CH_3$), 2.45 (3 H, s, $ArOCOCH_3$), 1.80–0.80 (7 H, m, $ArCH_2CH_2CH_2CH_3$). Anal. ($C_{17}H_{20}O_3$) C, H.

Preparation of 1-Acetoxy-2,3-diethyl-4-methylnaphthalene (15). A solution of **1a** (2.0 g, 6.4 mmol), dry 3-hexyne (2.0 mL, 18 mmol), dry Ac_2O (0.65 mL, 7.04 mmol), and dry NEt_3 (0.9 mL, 7.04 mmol) was heated at 65 °C for 2 h under argon. Purification by flash column chromatography (silica gel, 250 g; 15% ether in *n*-hexane) gave **15** (1.3 g, 75%) as a yellow oil: high-resolution MS mol wt 272.1412, calcd 272.1412; IR (neat) 1762, 1594, 1452, 1357, 1208, 1096 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.10–7.85 (1 H, m, C_8-H), 7.70–7.30 (3 H, m, C_5-H, C_6-H, C_7-H), 3.94 (3 H, s, $ArOCH_3$), 2.47 (3 H, s, $ArOCOCH_3$), 2.80–2.50 (4 H, m, 2 $ArCH_2CH_3$), 1.25 (3 H, t, J = 7.4 Hz, $ArCH_2CH_3$), 1.20 (3 H, t, J = 7.5 Hz, $ArCH_2CH_3$). Anal. ($C_{17}H_{20}O_3$) C, H.

Prepation of 1-Acetoxy-2-*n*-butyl-4-methoxy-5,8-dimethylnaphthalene (24). A solution of **1e** (1.0 g, 2.9 mmol), dry 1-hexyne (0.67 mL, 5.9 mmol), dry Ac_2O (0.56 mL, 5.9 mmol), and dry NEt_3 (0.82 mL, 5.9 mmol) in THF (90 mL) was heated at 65 °C for 4 h under argon. Purification by flash column chromatography (silica gel, 250 g; 15% ether in *n*-hexane) gave **24** (390 mg, 44%) as white needles: mp 54–57 °C; MS *m/e* 300 (M^+), 258, 243, 215, 201, 43; IR (Nujol) 1749, 1618, 1592, 1215, 831, 814 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.01 (2 H, m, C_6-H, C_7-H), 6.63 (1 H, s, C_3-H), 3.86 (3 H, s, $ArOCH_3$), 2.78–2.20 (2 H, m, $ArCH_2CH_2CH_2CH_3$), 2.78 (3 H, s, C_8-CH_3), 2.65 (3 H, s, C_5-CH_3), 2.34 (3 H, s, $ArOCOCH_3$), 1.85–0.70 (7 H, m, $ArCH_2CH_2CH_2CH_3$). Anal. ($C_{19}H_{24}O_3$) C, H.

Preparation of 1-Acetoxy-2,6-di-*n*-butyl-4-methoxynaphthalene (26). A solution of **1h** (2.0 g, 5.54 mmol), dry 1-hexyne (1.25 mL, 10.9 mmol), dry Ac_2O (1.02 mL, 10.9 mmol), and dry NEt_3 (1.51 mL, 10.9 mmol) in THF (180 mL) was heated at 65 °C for 4 h under argon. Purification by flash column chromatography (silica gel, 300 g; 10% ether in *n*-hexane) gave **26** (911 mg, 51%) as a yellow oil: MS *m/e* 328 (M^+), 286, 243, 229, 187; IR (neat) 2957, 2932, 1761, 1464, 1366, 1201, 836 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05–9.95 (1 H, m, C_8-H), 7.60–7.50 (1 H, m, C_5-H), 7.40–7.30 (1 H, m, C_7-H), 6.30 (1 H, s, C_3-H), 3.95 (3 H, s, $ArOCH_3$), 2.80–2.50 (4 H, m, 2 $ArCH_2CH_2CH_2CH_3$), 2.44 (3 H, s, $ArOCOCH_3$), 1.80–1.25 (8 H, m, 2 $ArCH_2CH_2CH_2CH_3$), 1.05–0.85 (6 H, m, 2 $ArCH_2CH_2CH_2CH_3$). Anal. ($C_{21}H_{28}O_3$) C, H.

Preparation of 1-Acetoxy-2-*n*-butyl-4-methoxy-5,6,7,8-tetramethylnaphthalene (27). A solution of **1g** (510 mg, 1.38 mmol), dry 1-hexyne (0.32 mL, 2.76 mmol), dry Ac_2O (0.26 mL, 2.76 mmol), and dry NEt_3 (0.39 mL, 2.76 mmol) in THF (70 mL) was heated at 65 °C for 20 h under argon. Purification by flash column chromatography (silica gel, 100 g; 10% ether in *n*-hexane) gave **27** (240 mg, 54%) as white crystals; mp 94–95 °C; MS *m/e* 328 (M^+), 286, 271, 243, 43; IR (Nujol) 1746, 1620, 1572, 1206, 828 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.47 (1 H, s, C_3-H), 3.84 (3 H, s, C_4-OCH_3), 2.85–2.20 (2 H, m, $ArCH_2CH_2CH_2CH_3$), 2.68 (3 H, s, C_8-CH_3), 2.54 (3 H, s, C_5-CH_3), 2.29 (9 H, m, C_6-CH_3, C_7-CH_3, $ArOCOCH_3$), 1.85–0.75 (7 H, m, $ArCH_2CH_2CH_2CH_3$). Anal. ($C_{21}H_{28}O_3$) C, H.

Preparation of 1-Acetoxy-2,3-diethyl-4-methoxy-6-*n*-butylnaphthalene (33) and 1-Acetoxy-2,3-diethyl-4-methoxy-8-*n*-butylnaphthalene (34). A solution of **1h** (4.0 g, 10.9 mmol), dry 3-hexyne (2.47 mL, 21.7 mmol), dry Ac_2O (2.05 mL, 21.7 mmol), and dry NEt_3 (3.03 mL, 21.7 mmol) in THF (360 mL) was heated at 65 °C for 5 h under argon. Purification by flash column chromatography (silica gel, 450 g; 10% ether in *n*-hexane) gave a 1:1 mixture of **33** and **34** (3.77 g, 53%). Extensive column chromatography (flash column, silica gel, 500 g; 5% ether in *n*-hexane) isolated both **33** and **34** as yellow oils. **33**: high-resolution MS mol wt 328.2034, calcd 328.2038; IR (neat) 1765, 1451, 1368, 1348, 1203, 1026 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78 (1 H, s, C_5-H), 7.54–7.50 (1 H, m, C_8-H), 7.36–7.30 (1 H, m, C_7-H), 3.94 (3 H, s, $ArOCH_3$), 2.90–2.70 (6 H, m, 2 $ArCH_2CH_3$ and $ArCH_2CH_2CH_2CH_3$), 2.48 (3 H, s, $ArOCOCH_3$), 1.70–1.60 (2 H, m, $ArCH_2CH_2CH_2CH_3$), 1.45–1.30 (2 H, m, $ArCH_2CH_2CH_2CH_3$), 1.25–1.15 (6 H, m, 2 $ArCH_2CH_3$), 1.00–0.85 (3 H, m, $ArCH_2CH_2CH_2CH_3$). Anal. ($C_{21}H_{28}O_3$) C, H. **34**: high-resolution MS mol wt 328.2049, calcd 328.2038. IR (neat) 1762, 1594, 1455, 1367, 1202, 1171, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.96–7.90 (1 H, m, C_5-H), 7.35–7.20 (2 H, m, C_6-H, C_7-H), 3.94 (3 H, s, $ArOCH_3$), 2.90–2.75 (6 H, m, 2 $ArCH_2CH_3$, $ArCH_2CH_2CH_2CH_3$), 2.43 (3 H, s, $ArOCOCH_3$), 1.55–1.15 (10 H, m, 2 $ArCH_2CH_3$, $ArCH_2CH_2CH_2CH_3$), 1.10–0.90 (3 H, m, $ArCH_2CH_2CH_2CH_3$). Anal. ($C_{21}H_{28}O_3$) C, H.

Preparation of 1-Methyl-4-acetoxy-5,6-diphenyl-7-methoxyindole (35). A solution of **1h** (1.5 g, 4.8 mmol) diphenylacetylene (1.5 g, 8.4 mmol), dry Ac_2O (0.9 mL, 9.6 mmol), and dry NEt_3 (0.7 mL, 4.8 mmol) in THF (150 mL) was heated at 65 °C for 5 h under argon. Purification by flash column chromatography (silica gel, 250 g; 50% ether in *n*-hexane) gave **36** (390 mg, 22%) as yellow needles: mp 158–159.5 °C; high-resolution MS mol wt 371.1511, calcd 371.1521; IR (Nujol) 1761, 1599, 1202 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13 (10 H, b s, 2 C_6H_5), 6.99 (1 H, *d*, J = 3.1 Hz, C_2-H), 6.32 (1 H, d, J = 3.1 Hz, C_3-H), 4.03 (3 H, s, $ArOCH_3$), 3.36 (3 H, s, NCH_3), 2.01 (3 H, s, $ArOCOCH_3$). Anal. ($C_{24}H_{21}NO_3$) C, H, N.

Preparation of 4-Acetoxy-6-*n*-butyl-7-methoxybenzofuran (43). A solution of **1j** (1.0 g, 3.3 mmol), dry 1-hexyne (0.77 mL, 8.25 mmol), dry Ac_2O (0.31 mL, 3.3 mmol), and dry NEt_3 (0.46 mL, 3.3 mmol) in THF (100 mL) was heated at 65 °C for 24 h under argon. Purification by flash column chromatography (silica gel, 250 g; 30% ether in *n*-hexane) gave **43** (590 mg, 68%) as white crystals: mp 49–50 °C; high-resolution MS mol wt 262.1211, calcd, 262.1205; IR (Nujol) 1761, 1490, 1349, 1208 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.54 (1 H, d, J = 2.2 Hz, C_2-H), 6.63 (1 H, s, C_7-H), 6.55 (1 H, d, J = 2.2 Hz, C_3-H), 3.99 (3 H, s, C_7-OCH_3), 2.75–2.40 (2 H, m, $ArCH_2CH_2CH_2CH_3$), 2.37 (3 H, s, $ArOCOCH_3$), 1.75–1.05 (4 H, m, $ArCH_2CH_2CH_2CH_3$), 1.00–0.75 (3 H, m, $ArCH_2CH_2CH_2CH_3$). Anal. ($C_{15}H_{18}O_4$) C, H.

General Procedure for Formation of Free Phenol by Reaction of Carbene Complex with Alkyne in THF. Preparation of 1-Hydroxy-2-*n*-butyl-4-methoxynaphthalene (16). In a 250-mL three-necked round-bottom flask, equipped with two rubber septa and a 6-in. air condenser with an argon–vacuum inlet, was placed **1a** (1.0 g, 3.2 mmol) and the flask was evacuated and filled with argon three times. THF (90 mL) and dry 1-decyne (1.0 mL, 3.2 mmol) were added to the flask via a syringe, and the solution was heated at 65 °C (bath temperature) for 2 h under argon. The mixture was cooled and the solvent was removed by rotary evaporation. The black residue was chromatographed with a flash column (silica gel, 200 g). Elution with 5% ether in *n*-hexane gave **16** (695 mg, 94%) as a white, low-melting solid: MS *m/e* (230 (M^+), 187, 173, 132; IR (Nujol) 3400, 1635, 1599, 1466, 1312, 1282 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.25–7.95 (2 H, m, C_5-H, C_8-H), 7.55–7.25 (2 H, m, C_6-H, C_7-H), 3.95 (3 H, s, $ArOCH_3$), 2.95–2.55 (3 H, m, ArOH, $ArCH_2CH_2CH_2CH_3$), 1.80–1.25 (4 H, m, $ArCH_2CH_2CH_2CH_3$), 1.10–0.75 (3 H, m, $ArCH_2CH_2CH_2CH_3$). Anal. ($C_{15}H_{18}O_2$) C, H. Compounds **42–46** and **48** were prepared in a similar fashion.

Direct Conversion of Acetate to Methyl Ether. Preparation of 1,4-Dimethyl-2-*n*-butylnaphthalene (17) from 11. A solution of **11** (1.0 g, 3.7 mmol) in THF (20 mL) was added to a cooled (wet-ice bath) suspension of NaH (600 mg, 12.5 mmol, 50% oil dispersion, washed with dry *n*-hexane) in THF (80 mL) under argon. The mixture was stirred at this temperature for 1 h and dry methyl iodide (2.0 mL, 32.1 mmol) was added all at once via a syringe. The resulting solution was stirred at 25 °C for 72 h under argon and poured into a mixture of ice water (100 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 × 100 mL). The extracts were combined, washed (brine, 3 × 100 mL), dried (Na_2SO_4), filtered, and concentrated. The yellow residue was chromatographed with a flash column (silica gel, 250 g). Elution by 10% ether in *n*-hexane gave the recovered **11** (300 mg, 30%) and **17** (620 mg, 69%) as a yellow oil: MS *m/e* 244 (M^+), 229, 187; IR (neat) 1665, 1628, 1597, 1461, 1371, 1265, 1223, 1123, 1097 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.30–7.90 (2 H, m, C_5-H, C_8-H), 7.60–7.35 (2 H, m, C_6-H, C_7-H), 6.61 (1 H, s, C_3-H), 3.97, 3.87 (2 × 3 H, 2 s, 2 $ArOCH_3$), 2.90–2.60 (2 H, m, $ArCH_2CH_2CH_2CH_3$), 1.90–1.30 (4 H, m, $ArCH_2CH_2CH_2CH_3$), 1.10–0.75 (3 H, m, $ArCH_2CH_2CH_2CH_3$). Anal. ($C_{16}H_{20}O_2$) C, H.

Oxidation of 1,4-Dihydroquinone to 1,4-Quinone. Preparation of 2-*n*-Butyl-1,4-naphthoquinone (49). To a cooled (wet-ice bath) solution of **16** (1.0 g, 4.3 mmol) in CH_3CN (10 mL)

was added dropwise a solution of CAN (5.0 g, 9.1 mmol) in H_2O (5 mL) and the resulting solution was stirred at this temperature for 2 h. The mixture was diluted with H_2O (20 mL) and the aqueous layer was extracted with ether (3 × 100 mL). The extracts were combined, washed (brine, 3 × 100 mL), dried ($MgSO_4$), filtered, and concentrated. The brown residue was chromatographed using a flash column (silica gel, 250 g). Elution by 5% ether in *n*-hexane gave **49** (850 mg, 92%) as yellow needles; mp 37-38 °C; MS *m/e* 214 (M^+), 199, 172; IR (Nujol) 1654, 1520, 1400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.20-8.00 (2 H, m, C_5-H, C_8-H), 7.80-7.50 (2 H, m, C_6-H, C_7-H), 6.65 (1 H, s, C_3-H), 3.00-2.80 (2 H, m, $ArCH_2CH_2CH_2CH_3$), 2.00-1.30 (4 H, m, $ArCH_2CH_2CH_2CH_3$), 1.20-0.95 (3 H, m, $ArCH_2CH_2CH_2CH_3$). Anal. ($C_{14}H_{14}O_2$) C, H. Quinones **50** and **51** were prepared in a similar fashion from **42** and **48**, respectively.

Registry No. **1a**, 27436-93-7; **1b**, 27436-99-3; **1c**, 27437-03-2; **1d**, 123332-48-9; **1e**, 123332-49-0; **1f**, 123332-50-3; **1g**, 123332-51-4; **1h**, 123357-80-2; **1i**, 84153-34-4; **1j**, 34741-93-0; **1k**, 62589-23-5; **2**, 99107-53-6; **3**, 107536-17-4; **4**, 107536-14-1; **5**, 107536-22-1; **6**, 107536-20-9; **7**, 123332-22-9; **8**, 123332-23-0; **9**, 123332-24-1; **10**, 107536-19-6; **11**, 99107-52-5; **12**, 123332-25-2; **13**, 123332-26-3; **14**, 107536-21-0; **15**, 99120-56-6; **16**, 99107-70-7; **17**, 123332-27-4; **18**, 121444-82-4; **19**, 121444-83-5; **20**, 123332-28-5; **21**, 123332-29-6; **22**, 123332-30-9; **23**, 123332-31-0; **24**, 123332-32-1; **25**, 123332-33-2; **26**, 123332-34-3; **27**, 123332-35-4; **28**, 123332-36-5; **29**, 123332-37-6; **30**, 123332-38-7; **31**, 123332-39-8; **32**, 123332-40-1; **33**, 123332-41-2; **34**, 123332-42-3; **35**, 99107-56-9; **36**, 99497-21-9; **37**, 99497-22-0; **38**, 99107-54-7; **39**, 99107-55-8; **40**, 99497-23-1; **41**, 99107-57-0; **42**, 99107-50-3; **43**, 123332-43-4; **44**, 120255-00-7; **45**, 123332-44-5; **46**, 123332-45-6; **47**, 99107-58-1; **48**, 99107-51-4; **49**, 34491-88-8; **50**, 123332-46-7; **51**, 123332-47-8; *o*-MeC_6H_4Br, 95-46-5; *m*-BuC_6H_4Br, 54887-20-6; $Cr(CO)_6$, 13007-92-6; BuC≡CBu, 1942-46-7; $CH_3(CH_2)_4C{\equiv}CCO_2Et$, 10519-20-7; BuC≡CH, 693-02-7; EtC≡CEt, 928-49-4; PhC≡CPh, 501-65-5; $HC{\equiv}C(CH_2)_7CH_3$, 764-93-2; 5-lipoxygenase, 80619-02-9; 2,5-dimethylbromobenzene, 553-94-6; 2,3,5-trimethylbromobenzene, 31053-99-3; 2,3,4,5-tetramethylbromobenzene, 40101-36-8; *N*-methylpyrrole, 96-54-8.

Some Benzyl-Substituted Imidazoles, Triazoles, Tetrazoles, Pyridinethiones, and Structural Relatives as Multisubstrate Inhibitors of Dopamine β-Hydroxylase. 4.[1] Structure-Activity Relationships at the Copper Binding Site

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Structure-activity relationships (SAR) were determined for novel multisubstrate inhibitors of dopamine β-hydroxylase (DBH; EC 1.14.17.1) by examining the effects upon in vitro inhibitory potencies resulting from structural changes at the copper-binding region of inhibitor. Attempts were made to determine replacement groups for the thione sulfur atom of the prototypical inhibitor 1-(4-hydroxybenzyl)imidazole-2-thione described previously. The synthesis and evaluation of oxygen and nitrogen analogues of the soft thione group demonstrated the sulfur atom to be necessary for optimal activity. An additional series of imidazole-2-thione relatives was prepared in an effort to probe the relationship between the pK_a of the ligand group and inhibitor potency. In vitro inhibitory potency was shown not to correlate with ligand pK_a over a range of approximately 10 pK_a units, and a rationale for this is advanced. Additional ligand modifications were prepared in order to explore bulk tolerance at the enzyme oxygen binding site and to determine the effects of substituting a six-membered ligand group for the five-membered imidazole-2-thione ligand.

Recently we reported some multisubstrate inhibitors of dopamine β-hydroxylase (DBH; EC 1.14.17.1), the mixed-function oxidase that catalyzes the hydroxylation of dopamine to norepinephrine.[1-5] Kinetic characterization of these inhibitors has led to structural insights to the active site of DBH[3] while the pharmacological activity of certain DBH inhibitors lends support to the notion that inhibiting DBH might offer a novel approach to the treatment of cardiovascular disorders such as hypertension.[1,2,5] Previous structure-activity relationship (SAR) studies of these DBH inhibitors demonstrated a striking dependence of potency upon substitution patterns at the portion of inhibitor that mimics the phenethylamine substrate,[5] as well as the dependence upon the length and substitution patterns of the bridging chain.[4] The prototype of this class of inhibitor, 1-(4-hydroxybenzyl)imidazole-2-thione, was designed on the basis of a capacity to bind a hypothesized binuclear active site as illustrated in Figure 1. Evidence in support of a direct binding of inhibitor to one copper atom has already been presented,[3,6] but further evidence to support the hypothesized binuclear copper site shown in Figure 1 is lacking. Indeed, EXAFS (extended X-ray absorption fine structure) studies have failed to detect a Cu···Cu interaction in either the resting Cu^{2+} or reduced, catalytically competent Cu^{1+} oxidation state of DBH.[6] For this reason and because of the stringent SAR shown at the bridging chain and phenethylamine mimic portions of inhibitor, it became of interest to explore inhibitory potency as a function of modifications of the copper-binding portion of inhibitor. In this paper we re-

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