5-HT_1 and 5-HT_2 Binding Profiles of the Serotonergic Agents α-Methylserotonin and 2-Methylserotonin

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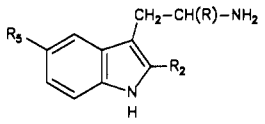
α-Methyl-5-hydroxytryptamine (α-Me-5-HT; **2**) and 2-methyl-5-hydroxytryptamine (2-Me-5-HT; **3**) are considered to be 5-HT_2-selective and 5-HT_3-selective agents, respectively. These agents were synthesized and examined at serotonin (5-HT) binding sites because there is relatively little documentation as to their selectivity and because they have not been previously examined at the newly discovered 5-HT_{1D} and 5-HT_{1E} sites. As previously reported, 2-Me-5-HT possesses a low affinity (K_i > 500 nM) for 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, and 5-HT_2 sites; this agent also displays a low affinity for 5-HT_{1D} (K_i = 1220 nM) and 5-HT_{1E} (K_i > 10 000 nM) sites. However, α-Me-5-HT displays little selectivity for 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, and 5-HT_{1D} sites (K_i = 42, 85, 150, and 150 nM, respectively) and a very low affinity for 5-HT_{1E} (K_i > 10 000 nM) sites. Depending upon the radioligand used to label the sites, α-Me-5-HT displays either a low affinity (K_i = 880 nM with [^{3}H]ketanserin) or a high affinity (K_i = 3 nM with [^{3}H]DOB) for 5-HT_2 sites. These results suggest that α-Me-5-HT is not as selective as previously considered and that caution should be used when employing this agent in pharmacological studies because it may act as a mixed 5-HT_1/5-HT_2 agonist.

The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT; **1**) binds with high affinity (K_i values = 2–35 nM) at several populations of central 5-HT_1 sites (i.e., 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C} sites).[1,2] To this extent, 5-HT is considered to be a nonselective 5-HT_1 agent. 5-HT also binds, though with an apparent lower affinity (K_i = 500–2000 nM), at [^{3}H]ketanserin-labeled 5-HT_2 sites.[1,2] However, interpretation of the 5-HT_2 binding data is complicated by the demonstration that [^{3}H]ketanserin may label multiple agonist affinity states.[3] α-Methylation of tryptamine derivatives reduces their affinity for 5-HT_1 sites but has little effect on their binding at 5-HT_2 sites.[2,4] 5-Hydroxy-α-methyltryptamine (α-Me-5-HT; **2**), for example, has been used by some investigators as a 5-HT_2-selective agent (e.g. see ref 5–7). 2-Methylation of 5-HT significantly reduces its affinity for 5-HT_1 and 5-HT_2 sites,[2] and 2-methyl 5-HT (2-Me-5-HT; **3**) is considered a 5-HT_3-selective agent.[8] Recently, two new populations of central 5-HT_1 sites have been reported: 5-HT_{1D}[9–11] and 5-HT_{1E}[12] sites. Interestingly, these two types of 5-HT sites appear to be the predominant 5-HT_1 sites in human frontal cortex.[10,12] Because there is relatively little documentation supporting the selectivity of these agents, and in light of the discovery of the two new 5-HT_1 binding sites, it was felt that a reevaluation of α-Me-5-HT (**2**) and 2-Me-5-HT (**3**) was in order. Also, the affinity of α-Me-5-HT for the agonist high-affinity state of the 5-HT_2 sites has not been previously reported and was deemed to be an important parameter in determining the 5-HT site selectivity of this agent.



1 R = R_2 = H; R_5 = OH

2 R = CH_3; R_2 = H; R_5 = OH

3 R = H; R_2 = CH_3; R_5 = OH

4 R = H; R_2 = CH_3; R_5 = OCH_3

Chemistry

α-Me-5-HT (**2**) has been prepared by several groups of investigators,[14–16] but perhaps the method of Ash and Wragg[14] [i.e., via 5-(benzyloxy)-3-(2′-nitropropenyl)indole] is the most convenient. We essentially repeated the latter synthesis except that the intermediate 5-(benzyloxy)-α-methyltryptamine was isolated as its hydrochloride salt **5** and not as the hygroscopic sulfate salt. Attempts to remove the benzyl group by hydrogenolysis of the salt resulted in a product that we were unable to crystallize. Conversion of the product to the free base and formation of the maleate salt gave the desired product in 18% yield. However, hydrogenolysis of the freshly prepared free base of **5** gave a 72% yield of α-Me-5-HT (as its maleate salt).

The synthesis of 2-Me-5-HT (**3**) and its *O*-methyl ether **4** have also been previously reported,[16] but the route to both compounds seemed rather cumbersome. This is particularly true in light of the recent commercial availability of 5-methoxy-2-methylindole. Compounds **3** and **4** were conveniently prepared in this study by the Speeter–Anthony method. The appropriate 5-(benzyloxy)- or 5-methoxy-2-methylindole was converted to its glyoxylamide,

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Table I. Affinity of 5-HT, α-Me-5-HT, 2-Me-5-HT and 2-Methyl-5-methoxytryptamine for Central 5-HT_1 and 5-HT_2 Binding Sites

	K_i values,[a] nM			
site	5-HT (1)	α-Me-5-HT (2)	2-Me-5-HT (3)	2-methyl-5-methoxytryptamine (4)
5-HT_{1A}	2 (±1)	42 (±12)	1200 (±110)	1300 (±100)
5-HT_{1B}	5 (±1)	85 (±20)	520 (±165)	800 (±60)
5-HT_{1C}	10 (±3)	150 (±15)	650 (±80)	690 (±200)
5-HT_{1D}	3 (±1)	150 (±25)	1220 (±200)	1060 (±145)
5-HT_{1E}	4 (±1)	>10000	>10000	>10000
5-HT_2	950 (±90)	880 (±150)	>10000	>10000

[a] K_i values are followed by SEM in parenthesis; SEM not determined where K_i values exceed 10000 nM.

which was subsequently reduced to the corresponding amine with $LiAlH_4$. In the case of **3**, the benzyloxy protecting group was removed by hydrogenolysis. Although treatment of **4** with 48% HBr reportedly gives a good yield of **3**,[17] we found this reaction to be unsuccessful. Shaw[17] has previously reported that both compounds, isolated as their hydrochloride salts, were very hygroscopic. Although we were able to isolate a small amount of **3** as its hydrochloride salt, clearly it was too hygroscopic to be handled. We were unable to isolate a good sample of the hydrochloride salt of **4**. As a consequence, both **3** and **4** were isolated as their more stable maleate salts.[18]

Results

The results of the radioligand binding studies are shown in Table I. In addition to **1–3**, the *O*-methyl ether of **3** (i.e., 2-methyl-5-methoxytryptamine; **4**) was also included in order to determine the importance of a free hydroxy group on receptor affinity. Other than for 5-HT (**1**), none of the tryptamine analogues display affinity for 5-HT_{1E} sites (i.e. K_i < 10000 nM), and only 5-HT (**1**) binds at 5-HT_{1D} sites with appreciable affinity. α-Me-5-HT (**2**) binds at 5-HT_{1D} sites, but only with modest affinity (K_i = 150 nM). Apparently, α-methylation reduces the 5-HT_{1D} affinity of 5-HT by 50-fold. In order to provide additional support for this observation, the affinity of **2** was compared with that of 5-methoxytryptamine (5-HT_{1D} K_i = 4 ± 1 nM), and α-methyltryptamine (5-HT_{1D} K_i = 1180 ± 80 nM) was compared with tryptamine (5-HT_{1D} K_i = 23 ± 2 nM); in both cases there is a 40–50-fold decrease in affinity upon introduction of the α-methyl group. With regard to the role of the hydroxy versus methoxy group, a comparison of the results for **3** and **4** suggests a negligible effect for O-methylation. α-Me-5-HT displays different affinity for 5-HT_2 sites depending upon the radioligand employed. With use of [^{3}H]ketanserin to label 5-HT_2 sites, α-Me-5-HT displays a rather low affinity (K_i = 880 nM), whereas, with [^{3}H]DOB as the radioligand, α-Me-5-HT displays a high affinity (K_i = 3 nM). The affinity of α-Me-5-HT (K_i = 880 and 3 nM) is comparable to that of 5-HT (950 and 5 nM) independent of whether [^{3}H]-ketanserin or [^{3}H]DOB is used as the radioligand to label 5-HT_2 sites.

Discussion

Engel and co-workers[2] have previously published 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, and 5-HT_2 binding data for compounds **1–3**. For the most part, there is little (less than a 3-fold) difference between their results and those reported in Table I. There are, however, several significant differences worthy of mention. The 5-HT_{1B} affinities reported by Engel et al.[2] for α-Me-5-HT (**2**) and 2-Me-5-HT (**3**) (K_i = 1000 and 36300 nM, respectively) are 12- and 70-fold lower than those determined in the present study. Perhaps the observed differences might be related to the different radioligands used to label 5-HT_{1B} sites in the two studies and, by themselves, may not be all that important. However, the affinity of α-Me-5-HT (**2**) at 5-HT_2 sites was reported to be about 7-fold higher (K_i = 125 nM) than that found in the present study (K_i = 880 nM). As a consequence, according to the data shown in Table I, α-Me-5-HT does not appear to be as selective for 5-HT_2 sites as previously thought. Indeed, there is less than a 4-fold difference in its affinity for 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, and 5-HT_{1D} sites, and its affinity for each of these sites is greater than its affinity for [^{3}H]ketanserin-labeled 5-HT_2 sites. In fact, even with the data of Engel et al.,[2] α-Me-5-HT would not be considered a 5-HT_2-selective agent.

The low affinity of α-Me-5-HT for 5-HT_2 sites is seemingly inconsistent with the finding that it acts as a 5-HT_2 receptor agonist in peripheral tissue preparations; furthermore, its apparent lack of selectivity is in contrast to the results of Leff and Martin,[19] who have used this agent to assist in the classification or differentiation of peripheral "5-HT_1-like" versus 5-HT_2 receptors. Previous radioligand binding studies have convincingly demonstrated that a large variety of 5-HT receptor agonists display higher affinities for the high-affinity state of 5-HT_2 sites labeled by [^{3}H]DOB than for the overall population of 5-HT_2 sites (predominantly the agonist low-affinity state) labeled by [^{3}H]ketanserin.[3] This prompted us to examine α-Me-5-HT at [^{3}H]DOB-labeled 5-HT_2 sites. The results with [^{3}H]-DOB indicate that α-Me-5-HT does have a high affinity, and some degree of selectivity, for 5-HT_2 sites. This would explain its potency in the isolated tissue studies. However, even if the 3-nM K_i value is used in comparison with the K_i values obtained for the binding of α-Me-5-HT at subpopulations of 5-HT_1 sites, it is entirely possible that in pharmacological studies using α-Me-5-HT high doses of this agent may also be capable of acting as a 5-HT_1 agonist. Indeed, α-Me-5-HT has already been demonstrated to act as a 5-HT_1 receptor agonist in isolated tissue studies.[19]

Several significant findings emerge from the present study. 2-Me-5-HT (**3**), as previously reported, shows little affinity for 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, and 5-HT_2 sites. In addition, this agent binds at the newly discovered 5-HT_{1D} and 5-HT_{1E} sites with a much lower affinity than 5-HT. From this standpoint, 2-Me-5-HT may still be considered at 5-HT_3-selective agent. Its *O*-methyl ether (**4**) possesses a binding profile similar to that of **3** itself. This may be important in future in vivo studies because it seems that the polar nature of the hydroxyl group offers potential problems with penetration of the blood–brain barrier. On the other hand, O-methylation of 5-HT decreases its affinity for 5-HT_3 recognition sites (neuroblastoma cell membranes) by 100-fold; thus, additional studies with **4** are necessary in order to determine its affinity for 5-HT_3

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sites. α-Me-5-HT (2) also binds at each of the 5-HT_1 sites with a lower affinity than 5-HT, but as with 5-HT, it displays relatively little selectivity for 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, or 5-HT_{1D} sites. α-Me-5-HT (2) binds with a rather low affinity at [^{3}H]ketanserin-labeled 5-HT_2 sites, but it does show a high affinity at [^{3}H]DOB-labeled sites. Nevertheless, α-Me-5-HT (2) should be used as a 5-HT_2-selective agent with caution: high concentrations or doses of this agent should be capable of stimulating 5-HT receptors in a nonselective manner. This agent might still find use as a pharmacological tool by virtue of the fact that, unlike 5-HT, it does *not* bind at 5-HT_{1E} sites.

Experimental Section

Synthesis. Proton magnetic resonance spectra (^{1}H NMR) were obtained with a JEOL FX90Q spectrometer with tetramethylsilane as an internal standard; infrared spectra were recorded with a Nicolet 5ZDX FT-IR spectrometer. Spectral data were consistent with the assigned structures. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analysis was performed by Atlantic Microlab and values are within 0.4% of the theoretical values.

(±)-5-Hydroxy-α-methyltryptamine [3-(2-Aminopropyl)-5-hydroxyindole; α-Me-5-HT] Maleate (2). 5-(Benzyloxy)-3-(2-nitropropenyl)indole[14] (0.7 g, 2.2 mmol) was reduced with $LiAlH_4$ (0.25 g, 6.6 mmol) according to the procedure of Ash and Wragg[14] and a solution of the crude product in anhydrous Et_2O was treated with an HCl(g)-saturated solution of Et_2O to afford 0.5 g (69%) of hydrochloride salt **5** as white crystals, mp 261–262 °C (lit.[15] mp 257–258 °C). [A small sample of the free base was converted to the sulfate salt for purposes of comparison, mp 141–142 °C (lit.[14] mp 139–142 °C).] *O*-Benzyl derivative **5** (3 g, 9.5 mmol) was dissolved in H_2O (150 mL) and the cloudy solution was made alkaline (pH 8) by the addition of 2 N NaOH solution. The mixture was extracted with 3 portions of Et_2O (75, 50, and 25 mL) and the combined Et_2O extract was washed with H_2O (3 × 10 mL), dried (Na_2SO_4), and evaporated to dryness. A solution of the crude free base in 95% EtOH (50 mL) was hydrogenated at 50 psi in the presence of 10% Pd/C (1 g) until the theoretical amount of H_2 had been consumed (ca. 4 h). The catalyst was removed by filtration and the solvent was evaporated under reduced pressure; the free base was dissolved in a minimal amount of cold MeOH and treated with a saturated solution of maleic acid in anhydrous Et_2O to afford 2.1 g (72%) of the product as fine, white needles after recrystallization from MeOH/anhydrous Et_2O, mp 191–192 °C. Anal. ($C_{11}H_{14}N_2O \cdot C_4H_4O_4$) C, H, N.

5-Hydroxy-2-methyltryptamine [3-(2-Aminoethyl)-5-hydroxy-2-methylindole; 2-Me-5-HT] Maleate (3). A solution of 3-(2-aminoethyl)-5-(benzyloxy)-2-methylindole (6) (1.7 g, 6.1 mmol) in absolute EtOH (100 mL) containing 10% Pd/C (0.24 g) was hydrogenated at room temperature until hydrogen uptake was slightly in excess of the theoretical value. The suspension was filtered to remove the catalyst and the filtrate was evaporated under reduced pressure to afford an oil. A solution of the oily residue in MeOH (5 mL) was treated with a solution of maleic acid (1 g) in anhydrous Et_2O (150 mL); the salt that precipicated upon standing was collected by filtration and recrystallized from MeOH/anhydrous Et_2O to give 1.2 g (62%) of the product as a white powder, mp 195–196 °C. [A small amount was converted to the very hygroscopic hydrochloride salt for purpose of identification, mp 232–234 °C (lit.[17] mp 230–231 °C).] Anal. ($C_{11}H_{14}N_2O \cdot C_4H_4O_4$) C, H, N.

2-Methyl-5-methoxytryptamine [3-(2-Aminoethyl)-5-methoxy-2-methylindole] Maleate (4). A suspension of glyoxylamide **7** (0.7 g, 3 mmol) and $LiAlH_4$ (1 g, 26.4 mmol) in dry THF was heated at reflux for 4 days. The reaction mixture was allowed to cool to room temperature and a solution of sodium potassium tartrate (3.2 mL of a 650 mg/mL aqueous solution) was added in a dropwise manner at room temperature. The insoluble material was removed by filtration and the filtrate was evaporated under reduced pressure to yield an oily residue. A solution of the oil in Et_2O (20 mL) was extracted with 2 N HOAc; the aqueous phase was basified (to pH 8) with 2 N NaOH solution, and the basic solution was extracted with Et_2O (2 × 25 mL). The combined Et_2O solution was dried ($MgSO_4$) and treated with an absolute EtOH solution of maleic acid (0.5 g/5 mL). The precipitate that formed upon standing was collected by filtration and recrystallized from absolute EtOH/anhydrous Et_2O to yield 0.15 g (15%) of the product as a finely divided white powder, mp 176–177 °C. Anal. ($C_{12}H_{16}N_2O \cdot C_4H_4O_4$) C, H, N.

3-(2-Aminoethyl)-5-(benzyloxy)-2-methylindole (6). A solution of oxalyl chloride (1 mL, 11.9 mmol) in anhydrous Et_2O (15 mL) was added to a stirred solution of 5-(benzyloxy)-2-methylindole[20] (2.5 g, 10.6 mmol) in Et_2O (30 mL) at 0 °C. The ice bath was removed and the mixture was allowed to stir for an additional 1 h. At this time, the reaction mixture was diluted by the dropwise addition of petroleum ether (bp 60–80 °C) (150 mL), and the solid product that formed was collected by filtration and immediately added to concentrated NH_4OH (20 mL). The basic solution was allowed to stir at room temperature for 4 h and the product was collected by filtration, washed with H_2O (3 × 10 mL), air-dried, and recrystallized from acetone/hexanes to afford 2 g (91%) of the glyoxylamide as an off-white powder, mp 232–234 °C. A suspension of this amide (3.5 g, 11.4 mmol) and $LiAlH_4$ (2.8 g, 73.9 mmol) in dry THF was heated at reflux for 4 days. The reaction mixture was allowed to cool to room temperature and excess $LiAlH_4$ was decomposed by the addition of a saturated solution of sodium potassium tartrate (5 mL) at 0 °C. The suspension was filtered and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure to afford an oily product. A solution of the oil in Et_2O (50 mL) was extracted with 2 N HOAc (20, 10, and 5 mL) and the combined acid solution was made alkaline (to pH 8) by the addition of 2 N NaOH. The basic solution was extracted with Et_2O (3 × 15 mL) and the combined Et_2O fractions were washed with H_2O (10 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give 1.2 g (38%) of the amine as a colorless oil. [A small sample was converted to the picrate for purpose of identification, mp 208–210 °C (lit.[17] mp 207–208 °C).] The crude product was used in the preparation of **3**.

5-Methoxy-2-methylindole-3-glyoxylamide (7). Method A. A solution of oxalyl chloride (1.5 mL) in anhydrous Et_2O (20 mL) was added over a 10-min period to a stirred solution of 5-methoxy-2-methylindole (2.5 g, 15.4 mmol) in anhydrous Et_2O (40 mL) at 0 °C. The ice bath was removed and the reaction mixture was allowed to stir for an additional 1 h. At this time, the solution was diluted by the dropwise addition of petroleum ether (bp 60–80 °C; 150 mL) at 0 °C. The solid product that formed was collected by filtration to afford 2.7 g (69%) of the unstable glyoxylyl chloride. A suspension of this material (1 g) in absolute EtOH (20 mL) was allowed to stir at room temperature for 4 h and was then diluted by the addition of H_2O (20 mL). The precipitated material was collected by filtration, air-dried, and recrystallized from MeOH to give 1 g (98%) of the ethyl ester as small needles: mp 120–122 °C; ^{1}H NMR ($CDCl_3$) δ 1.4 (t, 3 H, CH_2CH_3), 2.6 (s, 3 H, CH_3), 3.9 (s, 3 H, OCH_3), 4.3 (q, 2 H, $-CH_2-$), 6.75–7.55 (m, 3 H, ArH), 8.8 (b s, 1 H, NH, D_2O exchangeable). The ethyl ester (1 g, 3.8 mmol) in concentrated NH_4OH solution (10 mL) was allowed to stir at room temperature for 4 h; the solid yellow material was collected by filtration and recrystallized from acetone/hexanes to afford 0.52 g (80%) of the product as yellow crystals, mp 244–246 °C. The amide was used without further characterization.

Method B. The glyoxylyl chloride (1 g) prepared in method A was suspended in concentrated NH_4OH solution (10 mL) and the mixture was allowed to stir for 4 h. The reaction mixture was filtered and the solid material was air-dried and recrystallized from acetone/hexanes to give 0.5 g (80%) of the product as yellow crystals, mp 244–246 °C. The products prepared by methods A and B were identical with regard spectroscopic and thin-layer chromatographic character.

Radioligand Binding. Methods used in the radioligand binding studies have already been reported in detail.[4,10] Following decapitation, the brain of male Sprague–Dawley rats were removed and placed in 0.9% ice-cold saline, and dissected over ice until the tissue was prepared. Tissues were stored in ice-cold saline for not longer than 1 h and, following blot drying and weighing,

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were prepared and frozen at -30 °C until used. Bovine and human tissues were used in some assays (see below). Freshly dissected (or frozen) tissue was homogenized (Polytron setting 6 for 20 s) in 30 volumes of ice-cold buffer containing 50 mM Tris·HCl (pH 7.4 at 37 °C; pH 8.0 at 4 °C), 0.5 mM Na_2EDTA, and 10 mM $MgSO_4$, and centrifuged at 30000*g* for 15 min. The supernatant was discarded; the pellet was resuspended and preincubated for 15 min at 37 °C. The homogenate membranes were washed twice by centrifugation and resuspension. The final assay buffer contained 10 μM parglyine, and 0.1% ascorbate was added last to the incubation medium. Protein determinations were made by the Lowry method.

5-HT_{1A} sites were labeled with 0.1 nM [^{3}H]-8-hydroxy-2-(di-*n*-propylamino)tetralin ([^{3}H]OH-DPAT) (157 Ci/mmol; New England Nuclear) and 4 mg wet weight of rat hippocampal tissue. 8-OH-DPAT (1 μM) was used to determine nonspecific binding. The 5-HT_{1B} receptor was labeled with 2.0 nM [^{3}H]-5-HT (28.3 Ci/mmol; New England Nuclear) and 8 mg of rat striatal membrane homogenate. 5-HT (10^{-6} M) was used to define nonspecific binding, and 10^{-7} M 8-OH-DPAT and mesulergine were included to block 5-HT_{1A} and 5-HT_{1C} receptors, respectively. 5-HT_{1C} sites were labeled with 1 nM [^{3}H]-5-HT and 10 mg of rat frontal cortical tissue homogenate; 20 nM spiperone was used to mask 5-HT_2 sites. 5-HT_{1D} sites were labeled with 10 nM [^{3}H]-5-HT and 10 mg of bovine caudate homogenate; 1 μM pindolol was used to block 5-HT_{1A} and 5-HT_{1B} istes, and 100 nM mesulergine was used to block 5-HT_{1C} sites. 5-HT_{1E} sites were labeled with 2 nM [^{3}H]-5-HT and 10 mg of human cortical homogenate in the presence of 100 nM 5-carboxamidotryptamine to block any 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} sites and 100 nM mesulergine was used to block 5-HT_{1C} 5-HT_1 sites. 5-HT_2 binding studies were conducted as previously reported.[3]

Eleven concentrations of nonradioactive competing drugs were made fresh daily in assay buffer, and assays were performed in (at least) triplicate. Following incubation with membranes and radioligand at 37 °C for 30 min, samples were rapidly filtered over glass-fiber filters (Schleicher and Schuell) and were washed with 10 mL of ice-cold 50 mM Tris·HCl buffer. Individual filters were inserted into vials and equilibrated with 5 mL of scintillation fluid (Scinti-Verse, Fisher) for 6 h before counting at 50% efficiency in a Beckman 3801 counter. Results were analyzed with an updated version of the program EBDA[21] in order to determine IC_{50}, K_i, and Hill values.

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Registry No. **2**, 304-52-9; **3**, 78263-90-8; **4**, 6260-79-3; **5**·HCl, 1453-99-2; **6**, 18658-09-8; **7**, 124224-49-3; 5-(benzyloxy)-3-(2-nitropropenyl)indole, 101731-72-0; oxalyl chloride, 79-37-8; 5-(benzyloxy)-2-methylindole, 124224-50-6; 5-methoxy-2-methylindole, 1076-74-0.

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3-Hydroxy-3-methylglutaryl-coenzyme A Reductase Inhibitors. 6.[1] *trans*-6-[2-(Substituted-1-naphthyl)ethyl(or ethenyl)]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-ones

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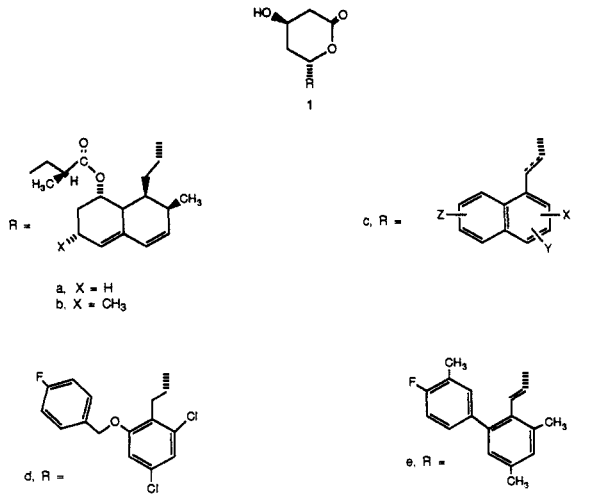
A variety of *trans*-6-[2-(substituted-1-naphthyl)ethyl(or ethenyl)]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-ones were prepared and, upon conversion to their 3,5-dihydroxy carboxylates, were found to have good inhibitory activity against the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the rate-determining enzyme in cholesterogenesis. The most active compounds are 2,4,6- and 2,4,7-trichloro derivatives and would be expected to display about the same potency as the standard compactin (**1a**) upon resolution.

The enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase catalyzes the rate-determining step and point of natural regulation of cholesterogenesis. Potent inhibitors of this enzyme (e.g. **1a**) have been shown to lower cholesterol blood levels in animals and man by about 30%.[2] The results of the Lipid Research Clinics Coronary Primary Prevention Trial showed that reduction in blood cholesterol by even a modest 10% results in significantly diminished risk of coronary heart disease.[3] Thus cholesterol blood level lowering by a **1a** and similar inhibitors can be expected to significantly reduce the risk of coronary heart disease. In pursuit of this goal, we wanted to prepare wholly synthetic analogues of **1a** and **1b** without the complex stereochemistry. We began with some simple probes with modest activity.[4] Nonetheless these probes pointed the way to classes of compounds which after further ex-



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