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Synthesis and thromboxane A2 antagonist activity of N-benzyltrimetoquinol analogs

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subjected to preparative (precoated silica gel F-254, 0.5 mm) TLC. The compound obtained from the appropriate band was then purified by radial chromatography by using a chromatatron with a solvent system of methanol/chloroform (10:90 v/v). The single UV absorbing band was eluted with the same solvent system and collected in 25-mL fractions (total of 10). The compound was obtained in the first three (25 mL) fractions. The fractions were combined, and the solvent was removed in vacuo to give a light green syrup. Trituration of this syrup with diethyl ether gave a crystalline solid, which was recrystallized from methanol to obtain 0.03 g (27.27%) of **17**: mp 150–151 °C; ^{1}H NMR (Me_2SO-d_6) δ 6.83 (d, 1, J = 3.6 Hz, C-6-H), 6.74 (br s, 2, exchangeable with D_2O, C-4-NH_2), 6.40 (d, 1, J = 3.5 Hz, C-5-H), 5.32 (s, 2, CH_2), 4.6 (br s, 1, exchangeable with D_2O, OH), 3.4 (m, 4, CH_2CH_2); UV λ_{max} nm ($\epsilon \times 10^4$) pH 1, 206 (2.0), 232 (3.0), 262 (1.4), 299 (1.0); pH 11, 226 (2.8), 262 (1.6), 282 (1.2). Anal. ($C_9H_{13}N_5O_2 \cdot {}^1/_2H_2O$) C, H, N.

Biological Evaluations. (a) Cells and Viruses. KB cells, an established human cell line derived from an epidermoid oral carcinoma, were routinely grown in minimal essential medium (MEM) with Hanks salts [MEM(H)] supplemented with 5% fetal bovine serum. African green monkey kidney (BSC-1) cells and diploid cell cultures of human foreskin fibroblast (HFF) cells were grown in MEM with Earle salts [MEM(E)] supplemented with 10% fetal bovine serum. Cells were passaged according to conventional procedures as detailed previously.[37] The plaque-purified isolate, P_0, of the Towne strain of HCMV was used in all experiments and was a gift of Dr. Mark Stinski, University of Iowa. The S-148 strain of HSV-1 was provided by Dr. T. W. Schafer of Schering Corp. Stock preparations of HCMV and HSV-1 were prepared and titered as described elsewhere.[20]

(b) Assays for Antiviral Activity. HCMV plaque reduction experiments were performed using monolayer cultures of HFF cells by a procedure similar to that referenced above for titration of HCMV, with the exceptions that the virus inoculum (0.2 mL) contained approximately 50 PFU of HCMV and the compounds to be assayed were dissolved in the overlay medium. HSV-1 plaque reduction experiments were performed with use of monolayer cultures of BSC-1 cells. The assay was performed exactly as referenced above for HSV-1 titration assays except that the 0.2 mL of virus suspension contained approximately 100 PFU of HSV-1 and the compounds to be tested were dissolved in the overlay medium.

(c) Cell Cytotoxicity Assays. Two basic tests for cellular cytotoxicity were routinely employed for compounds examined in antiviral assays. Cytotoxicity produced in HFF and BSC-1 cells was estimated by visual scoring of cells not affected by virus infection in the plaque reduction assays described above. Cytopathology was estimated at 35- and 60-fold magnification and scored on a zero to four plus basis on the day of staining for plaque enumeration. Cytotoxicity in KB cells was determined by measuring the effects of compounds on the incorporation of radioactive precursors into DNA, RNA and protein as detailed elsewhere.[20]

(d) Data Analysis. Dose–response relationships were constructed by linearly regressing the percent inhibition of parameters derived in the preceeding sections against log drug concentrations; 50% inhibitory (I_{50}) concentrations were calculated from the regression lines. The three I_{50} concentrations for inhibition of DNA, RNA, and protein synthesis were averaged to give the values reported in Table I for KB cell cytotoxicity. Samples containing positive controls (acyclovir, ganciclovir, or vidarabine) were used in all assays. Results from sets of assays were rejected if inhibition by the positive control deviated from its mean response by more than 1.5 standard deviations.

Acknowledgment. We thank Lisa Coleman for expert technical assistance. This project was supported with Federal funds from the Department of Health and Human Services under contract number NO1-AI-42554. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

Registry No. 1, 59277-89-3; 2, 57564-94-0; 3, 81777-40-4; 4, 114199-78-9; 5, 114199-79-0; 6, 114199-80-3; 7, 86625-99-2; 8, 114199-81-4; 9, 114220-98-3; 10, 114199-82-5; 11, 90213-66-4; 12, 114199-83-6; 13, 114199-84-7; 14, 114199-85-8; 15, 114199-86-9; 16, 114199-87-0; 17, 114199-88-1; pyrrolo[2,3-*d*]pyrimidine-2,4-dione, 39929-79-8; 2-acetamido-4-chloro-7-[(2-acetyloxyethoxy)-methyl]pyrrolo[2,3-*d*]pyrimidine, 114199-89-2; ganciclovir, 82410-32-0.

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Synthesis and Thromboxane A_2 Antagonist Activity of *N*-Benzyltrimetoquinol Analogues

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It is currently believed that the platelet thromboxane A_2 (TXA_2/PGH_2) receptor is different from the vascular TXA_2/PGH_2 receptor. While the majority of TXA_2 receptor antagonists are structurally related to the prostaglandins, trimetoquinol (TMQ) represents a unique nonprostanoid antagonist. TMQ also possesses β-adrenergic activity; however, an *N*-benzyl substituent on TMQ has been shown to impart some selectivity for platelet antiaggregatory activity versus β-adrenergic activity. In this study, we examined the synthesis and TXA_2 antagonist activity of a series of substituted *N*-benzyl analogues of TMQ. While these analogues showed an apparent direct correlation between platelet antiaggregatory activity and electron-donating ability of the *N*-benzyl substituents, no such correlation could be demonstrated for the inhibition of contractile responses. Thus, nonprostanoid TXA_2 antagonists can be used to demonstrate differences between platelet and vascular TXA_2/PGH_2 responses.

Thromboxane A_2 (TXA_2) is a potent vasoconstrictor and platelet aggregatory agent that mediates its effects by receptor-stimulated breakdown of polyphosphoinositides.[1-3] Inhibition of TXA_2 at the receptor level is thus a useful approach to the treatment of various ischemic and thrombotic disorders.[4] The TXA_2 receptor is usually

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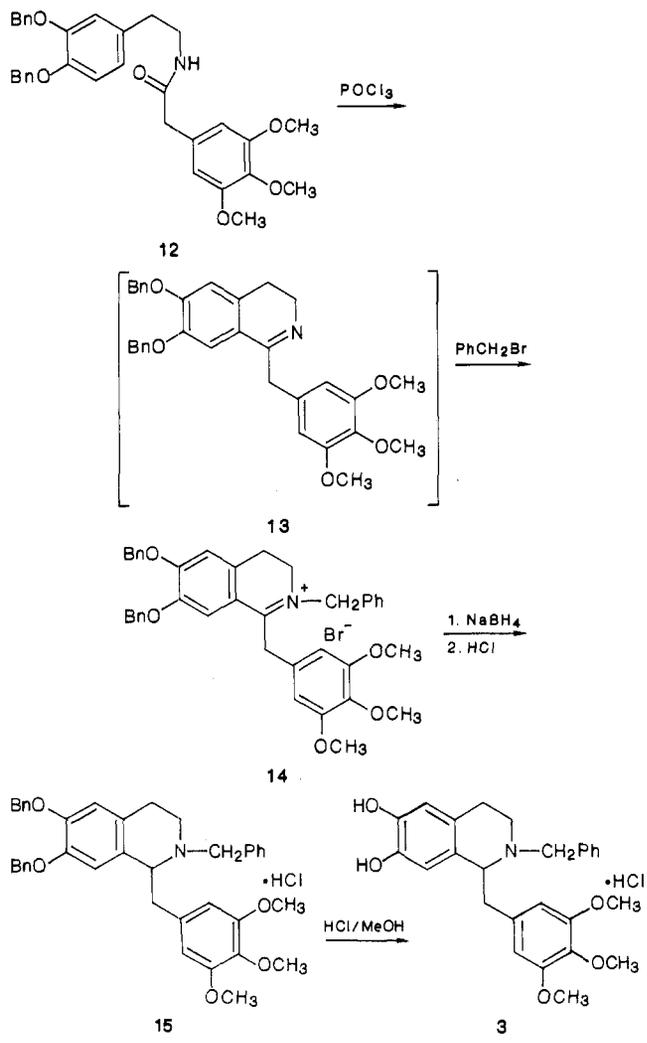
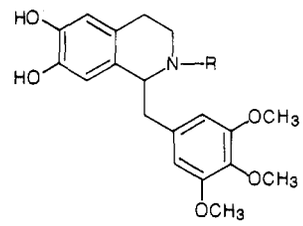
Scheme I

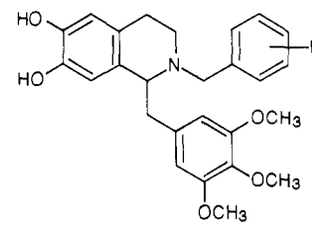


referred to as the TXA_2/PGH_2 receptor since both of these endogenous agents produce similar biological effects.[5] Further evidence that the cyclic endoperoxide PGH_2 acts at the same receptor as TXA_2 comes from the fact that the stable endoperoxide analogues U46619 and U44609 mimic the effects of TXA_2.[5] It is currently believed that the platelet TXA_2/PGH_2 receptor is different from the vascular TXA_2/PGH_2 receptor.[6,7] This is a result of pharmacological studies of stable agonists and antagonists of the TXA_2/PGH_2 receptor. In these studies, both agonists and antagonists showed different rank order potencies in platelets compared with blood vessels. Mais et al.[7] have designated the platelet receptor α for aggregation and the vascular receptor τ for tone. These receptors have not been completely characterized; however, efforts to understand the TXA_2/PGH_2 receptor(s) have intensified.[8]

A number of TXA_2 receptor antagonists have been reported.[9,10] While the majority of these compounds are structurally related to the prostaglandins, a few unique nonprostanoid structures have TXA_2 receptor antagonistic activity. One of these unique nonprostanoid compounds is trimetoquinol (**1**, TMQ). Originally reported as a β-adrenergic agonist,[11,12] TMQ was first examined for platelet antiaggregatory activity in 1976 by Shtacher et al.[13] due to its structural similarity to the antiaggregatory agent papaverine. Trimetoquinol has been subsequently shown to stereoselectively inhibit platelet aggregation induced by arachidonic acid, collagen, U46619, U44069, and TXA_2.[14] It has also been shown to inhibit the secondary wave of platelet aggregation and secretion induced by ADP. The platelet antiaggregatory activity of TMQ is thought to be mediated by a different mechanism than its β-adrenergic activity since the *S*-(−)-isomer of TMQ is more potent in β-adrenoceptor systems[12] while the *R*-(+)-isomer is more potent in platelet systems.[14] On the basis of its inhibitory profile, TMQ was proposed to be a TXA_2 receptor antagonist.[14] This mechanism of action has been questioned;[15] however, recent studies from our laboratory substantiate the claim that R-(+)-TMQ is a stereospecific antagonist of TXA_2/PGH_2 receptor sites in platelets.[16-18]



1: R = H
2: R = CH_3
3: R = CH_2Ph
4: R = CH_2CH_2OH
5: R = CH_2CH_2Cl



6: R = 4-CH_3
7: R = 4-Cl
8: R = 4-OCH_3
9: R = 4-NO_2
10: R = 3,4-Cl_2
11: R = 4-NH_2

Recently, Adejare et al.[19] reported the synthesis, β-adrenergic agonist activity, and platelet antiaggregatory activity of a series of N-substituted TMQ analogues (**2**–**5**). One of the most interesting findings of this study was that the larger the N-substituent, the lower the β-adrenergic activity but the higher the platelet antiaggregatory activity. Thus, *N*-benzyl-TMQ (**3**) was the most potent in this series against U46619-induced platelet aggregation, but it was the least potent β-adrenoceptor agonist. Although *N*-benzyl-TMQ was about 30-fold less potent than *R*-(+)-TMQ in inhibiting U46619-induced aggregation, it offers some promise for the development of selective antagonists of TXA_2 receptor-mediated biological responses.

In an effort to utilize the finding by Adejare et al.[19] that *N*-benzyl-TMQ provides separation of the biological effects of TMQ, this study sought to examine the synthesis and

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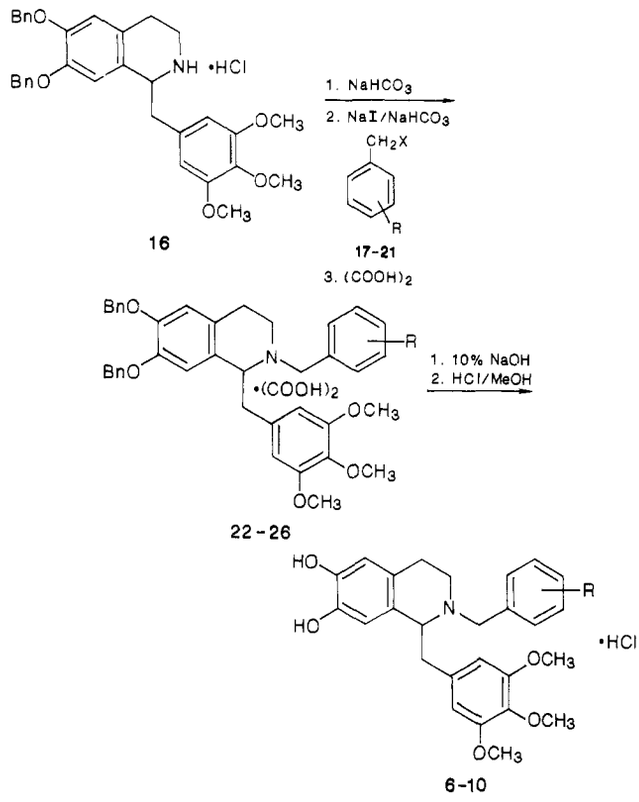
Scheme II



6, 17, 22: R = 4-CH_3 (17: X = Br)
7, 18, 23: R = 4-Cl (18: X = Cl)
8, 19, 24: R = 4-OCH_3 (19: X = Cl)
9, 20, 25: R = 4-NO_2 (20: X = Br)
10, 21, 26: R = 3, 4-Cl_2 (21: X = Cl)

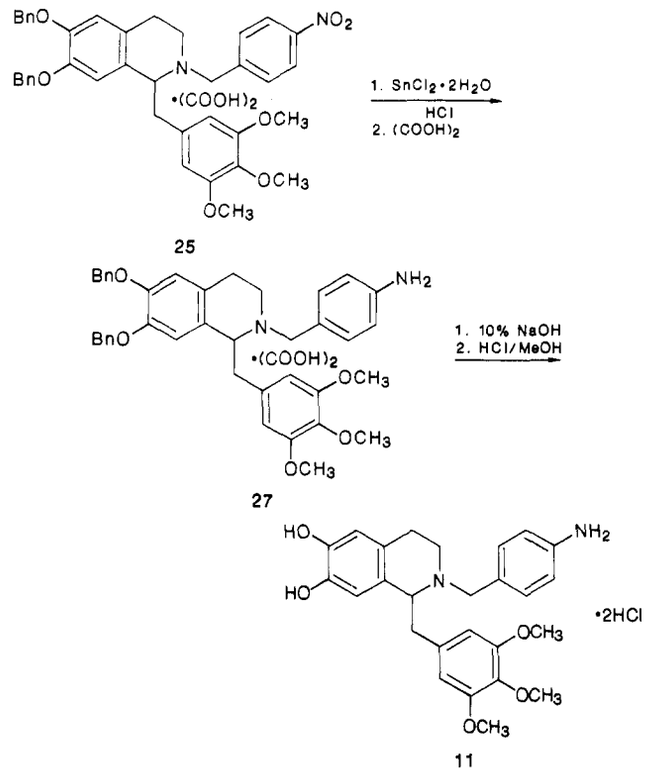
TXA_2 antagonist activity of a series of substituted *N*-benzyl analogues of TMQ (**6–11**). These compounds were designed so as to include substituents with significantly different physical parameters. In this manner, it was hoped that some rough, general structure–activity relationships could be established for this portion of the molecule. Although a quanitative structure–activity relationship (QSAR) analysis was not the objective here, the substituents were chosen from a variety of QSAR cluster sets. These sets are valuable in choosing substituents that have nonoverlapping physical parameters.[20] The *N*-benzyl analogues of TMQ were evaluated for their TXA_2 antagonist activity in both platelets and blood vessels in an effort to determine if nonprostanoid TXA_2 antagonists have different structural requirements for α versus τ receptors.

Chemistry

The synthesis of *N*-benzyltrimetoquinol (**3**) as reported by Adejare et al.[19] is outlined in Scheme I. Bischler–Napieralski cyclization of amide **12** gave the unstable imine **13**. This imine was then reacted with benzyl bromide to give imminium salt **14**. Reduction of this salt followed by salt formation gave tetrahydroisoquinoline **15**. Selective cleavage of the *O*-benzyl protecting groups in the presence of the *N*-benzyl group was achieved by using a 1:1 mixture of methanol and concentrated HCl.

Initially, it was felt that the target compounds **6–10** could be obtained by the above literature procedure if appropriately substituted benzyl halides were used in place of benzyl bromide in the alkylation of imine **13**. Additionally, the 4-amino analogue **11** was envisioned to arise from reduction of an intermediate in the synthesis of the 4-nitro analogue **9**. This approach, although quite logical in design, was an unexpected and disappointing failure. We were able to repeat Adejare's procedure with benzyl bromide as the alkylating agent; however, the use of other benzyl halides, such as 4-chlorobenzyl chloride or 4-nitrobenzyl bromide, in the alkylation of imine **13** failed to provide the desired products despite the use of a variety of solvents and conditions. Repeated reactions of imine **13** with α-bromo-*p*-xylene did eventually give the desired product; however, the yield was too low to make this a viable route to the desired catechol **6**. Since this route to the desired compounds was not encouraging, an alternate approach was taken (Scheme II).

Scheme III



The reduction of imine **13** followed by salt formation provided tetrahydroisoquinoline **16**.[21] After conversion to the free base, **16** was allowed to react with benzyl halides **17–21** in the presence of sodium bicarbonate and a catalytic amount of sodium iodide[22] to give tetrahydroisoquinolines **22–26**. Despite numerous attempts, the HCl salts of these compounds refused to crystallize. They were therefore isolated as their oxalate salts. Both sodium bicarbonate and sodium iodide are essential to the above reaction. The reaction does not go to completion without sodium bicarbonate to neutralize the hydrochloric or hydrobromic acid that is formed, and the reaction goes very slowly, if at all, without sodium iodide. This reaction was run in refluxing ethanol except when 4-methoxybenzyl chloride was used as the alkylating agent. This reagent was heat sensitive and tended to decompose at higher temperatures, leading to multiple products. This problem was overcome by running the reaction at room temperature. Although this required a much longer time (48 vs

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Table I. Inhibition of U46619-Induced Human Platelet Aggregation and [^{14}C]Serotonin Secretion by N-Substituted TMQ Analogues

compound	IC_{50},[a] μM	
	aggregation	secretion
(±)-TMQ	0.77 ± 0.09	0.75 ± 0.04
3	67.4 ± 8.67	66.4 ± 15.3
6	55.9 ± 10.69	40.4 ± 9.00
7	119.3 ± 16.37	127.5 ± 19.46
8	50.2 ± 6.92	56.2 ± 7.04
9	295.9 ± 25.65	268.9 ± 47.54
10	256.9 ± 13.60	264.5 ± 25.57
11	27.0 ± 6.21	27.1 ± 3.32

[a] Values represent the mean ± SEM of data from three different preparations with 0.5–0.7 μM of U46619.

Table II. Inhibition of ADP-Induced Human Platelet Aggregation and [^{14}C]Serotonin Secretion by N-Substituted TMQ Analogues

compound	IC_{50},[a] μM	
	aggregation[b]	secretion
3	67.5 ± 5.12	54.1 ± 11.32
9	358.9 ± 8.63	288.7 ± 6.17
11	40.0 ± 3.24	29.1 ± 0.93

[a] Values represent the mean ± SEM of data from three different preparations with 1.5–1.9 μM of ADP. [b] Each compound only blocked the secondary wave of aggregation to ADP. No detectable inibition of primary wave ADP induced aggregation was observed.

4 h), no decomposition of 4-methoxybenzyl chloride was seen. Once tetrahydroisoquinolines **22–26** were obtained, selective cleavage of the *O*-benzyl protecting groups afforded the desired catechols **6–10** as their hydrochloride salts.

The 4-amino analogue **11** was synthesized from nitro tetrahydroisoquinoline **25** as shown in Scheme III. Reduction of the nitro group was accomplished by using stannous chloride and hydrochloric acid.[23] Amino tetrahydroisoquinoline **27** was then isolated as its monooxalate salt. Cleavage of the *O*-benzyl groups as before gave the amino catechol **11** as the dihydrochloride salt.

Biological Results and Discussion

The substituted *N*-benzyl analogues of TMQ (**6–11**) were evaluated for their ability to inhibit U46619-induced human platelet aggregation and [^{14}C]serotonin secretion. These results are shown in Table I. For comparison, the values for (±)-TMQ and *N*-benzyl-TMQ (**3**) are also shown. As evidenced by the table, there appears to be a direct correlation between platelet antiaggregatory activity and electron-donating ability of the *N*-benzyl substituents. Electron-donating substituents (NH_2, OCH_3, CH_3) increased the U46619 inhibitory activity of the compounds relative to *N*-benzyl-TMQ, while electron-withdrawing substituents (Cl, NO_2) decreased the activity. The rank order of inhibitory potency against U46619-mediated aggregation was (±)-TMQ > 4-NH_2-*N*-benzyl-TMQ (**11**) > 4-OCH_3-*N*-benzyl-TMQ (**8**) > 4-CH_3-*N*-benzyl-TMQ (**6**) > *N*-benzyl-TMQ (**3**) > 4-Cl-*N*-benzyl-TMQ (**7**) > 3,4-Cl_2-*N*-benzyl-TMQ (**10**) > 4-NO_2-*N*-benzyl-TMQ (**9**). Additionally, *N*-benzyl-TMQ and analogues **9** and **11** inhibited the secondary waves of aggregation and secretion induced by ADP with similar IC_{50} values and with an identical rank order of inhibition as they did against U46619 (Table II). Schild plot analyses of several concentrations of **11** on the inhibition of U46619-induced platelet aggregation and serotonin release responses revealed pA_2 and slope values of 4.55 and −0.95, and 4.37 and −0.95, respectively (n = 3). Slope values were not significantly different from unity, and the results are consistent with a competitive interaction of U46619 and **11** in this system. These findings suggest that the electron density of the *N*-benzyl aromatic ring is important for platelet antiaggregatory and antisecretory activity, and that increasing the electron density of this ring leads to more potent inhibitors of endoperoxide and thromboxane A_2 responses mediated by TXA_2/PGH_2 α receptors.

Table III. Inhibition of U46619-Induced Contraction of Rat Thoracic Aorta by N-Substituted TMQ Analogues in the Presence of Indomethacin[a]

compound	pD_2 (control)	pD_2 (+ drug, 100 μM)	pK_B	K_B, μM
(±)-TMQ	8.17 ± 0.07	6.78 ± 0.12	5.37 ± 0.13	4.26
3	8.11 ± 0.05	7.86 ± 0.07	3.86 ± 0.10	138.03
6	8.05 ± 0.06	7.58 ± 0.07	4.26 ± 0.17	54.95
7	8.10 ± 0.05	8.09 ± 0.07		
8	8.07 ± 0.04	7.64 ± 0.10	4.16 ± 0.18	69.18
9	8.21 ± 0.03	7.84 ± 0.10	4.05 ± 0.16	89.12
10	8.12 ± 0.05	8.22 ± 0.02		
11	8.26 ± 0.06	8.03 ± 0.05	3.79 ± 0.08	162.00

[a] pD_2 and pK_B values represent the mean ± SEM of data from at least four different preparations.

In separate experiments, compounds **6–11** were evaluated for their ability to inhibit the contractile effect of U46619 in rat thoracic aorta (Table III). Again, the values for (±)-TMQ and *N*-benzyl-TMQ are also shown for comparison. In contrast to the findings in platelet systems, there was no apparent correlation between U46619 antagonist activity and electron density of the *N*-benzyl ring. The 4-amino analogue **11**, the most potent compound in platelet systems, was one of the least potent compounds in inhibiting contractile responses, while the 4-nitro analogue **9**, the least active compound in platelet systems, was actually more potent than *N*-benzyl-TMQ in this system. The 4-methyl analogue **6** was the most potent inhibitor of U46619-mediated contraction of rat thoracic aorta, while the two chloro analogues **7** and **10** were completely inactive. Schild plot analysis of **6** as an inhibitor of U46619-induced contraction in rat aorta revealed a pA_2 of 4.52 and a slope of −1.69 (95% confidence limits = −0.91 to −2.27), a value that was not significantly different from unity (n = 3–5). Similar to the results presented earlier with **11** in platelet systems, these results are consistent with a competitive antagonism of U46619. Previously, Shtacher et al.[13] and Mayo et al.[14] demonstrated that TMQ is a competitive reversibly acting antagonist of U46619 in human platelets; an effect that was independent of α- or β-adrenergic activation. Thus, like TMQ, these *N*-benzyl analogues are proposed to mediate their actions by inhibition of TXA_2 at the receptor level. The results also show that the electronic nature of substituents on the *N*-benzyl group of TMQ influence binding to the TXA_2/PGH_2 α receptors to a greater extent than to the TXA_2/PGH_2 τ receptor. This is in agreement with the current theory[7] that the platelet and vascular TXA_2/PGH_2 receptors are distinct entities and that these compounds provide the basis for the development of selective nonprostanoid TXA_2/PGH_2 receptor antagonists.

Experimental Section

Melting points (uncorrected) were determined on a Thomas-Hoover melting point apparatus. NMR spectral data was obtained with either a Bruker HX-90E NMR spectrometer (90 MHz), a Bruker WP-80DS NMR spectrometer (80 MHz), or an IBM AF/270 spectrometer (270 MHz) in the pulse mode. Chemical

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shifts are expressed in parts per million (ppm) on the δ scale relative to tetramethylsilane. IR spectral data was obtained with a Beckman 4230 infrared spectrophotometer. Mass spectra were obtained with a Kratos MS25RFA double-focusing mass spectrometer or at The Ohio State University Chemical Instrumentation Center by use of a Kratos MS-30 mass spectrometer. The spectroscopic data for all new compounds was consistent with the assigned structures. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, and were within ±0.4% of the theoretical values for the elements indicated. ADP was obtained from Sigma Chemical Co. (St. Louis, MO). [^{14}C]-Serotonin (57 mCi/mmol) was supplied by Amersham (Arlington Heights, IL). U46619 (15(*S*)-hydroxy-11α,9α-(epoxymethano)-prosta-5(*Z*),13(*E*)-dienoic acid) was kindly provided by Peter Chelune of Upjohn Laboratories (Kalamazoo, MI).

1-(3,4,5-Trimethoxybenzyl)-2-(4-methylbenzyl)-6,7-bis(benzyloxy)-1,2,3,4-tetrahydroisoquinoline Oxalate (22). Tetrahydroisoquinoline **16**[21] (2.00 g, 3.56 mmol) was dissolved in chloroform (40 mL) and was converted to the free base by washing with saturated $NaHCO_3$ (3 × 40 mL) and water (2 × 40 mL). The chloroform layer was dried (Na_2SO_4) and concentrated to an oil. The oil was dissolved in ethanol (40 mL), and NaI (catalytic), $NaHCO_3$ (400 mg, 4.76 mmol), and α-bromo-*p*-xylene (658 mg, 3.56 mmol) was added to the resulting solution. The reaction mixture was stirred under reflux for 4 h. The solution was allowed to cool to room temperature, and water (40 mL) was added. This resulted in the formation of a cloudy solution, which was extracted twice with chloroform (40 mL). The chloroform extracts were pooled, washed with saturated $NaHCO_3$ (2 × 80 mL) and water (2 × 80 mL), dried (Na_2SO_4), and evaporated to afford a yellow oil. This oil was dissolved in a minimal amount of toluene (ca. 5 mL), and a solution of oxalic acid dihydrate (450 mg, 3.56 mmol) in methanol (ca. 5 mL) was added. Upon addition of diethyl ether, the product crystallized as the oxalate salt. Filtration of the white solid provided 1.70 g (66.7%) of tetrahydroisoquinoline **22**: mp 189–192 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 7.48–7.19 (m, 14 H, benzyl ArH), 6.76 (s, 1 H, ArH), 6.14 (s, 2 H, ArH ortho to OCH_3), 5.77 (s, 1 H, ArH), 5.15 (s, 2 H, $PhCH_2OAr$), 4.84 (d, J = 12.6 Hz, 1 H, $PhCH_2OAr$), 4.60 (d, J = 12.6 Hz, 1 H, $PhCH_2OAr$), 4.28 (m, 3 H, ArCHRN and $ArCH_2N$), 3.81 (s, 3 H, OCH_3), 3.71 (s, 6 H, OCH_3), 3.55–2.60 (m, 6 H, alkyl), 2.35 (s, 3 H, $ArCH_3$); mass spectrum, m/z 448 (M^+ – trimethoxybenzyl, base), 181, 105, 91. Anal. ($C_{41}H_{43}NO_5 \cdot C_2H_2O_4$) C, H, N.

1-(3,4,5-Trimethoxybenzyl)-2-(4-methylbenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (6). The oxalate salt of tetrahydroisoquinoline **22** (500 mg, 0.695 mmol) was dissolved in chloroform (20 mL), washed with 10% NaOH (2 × 20 mL) and water (1 × 20 mL), dried ($MgSO_4$), and concentrated to an oil. This oil was dissolved in a 1:1 mixture of concentrated HCl/methanol (30 mL) and refluxed under argon for 27 h. The solvent and excess HCl were removed in vacuo. The residue was washed with methanol, and the methanol was removed in vacuo. This step was repeated a total of three times. The residue was dried on a vacuum pump for 2 h and then recrystallized from ethanol/diethyl ether to provide 222 mg (66.0%) of a white solid: mp 148–151 °C dec; ^{1}H NMR (D_2O, 90 MHz) δ 7.28–7.02 (m, 4 H, *N*-benzyl ArH), 6.75 (s, 1 H, ArH), 6.16 (s, 3 H, ArH), 4.38–4.19 (m, 3 H, ArCHRN and $ArCH_2N$), 3.67 (s, 3 H, OCH_3), 3.59 (s, 6 H, OCH_3), 3.50–2.96 (m, 6 H, alkyl), 2.28 (s, 3 H, $ArCH_3$); IR (KBr, cm^{-1}) 3200 (OH). Mass spectrum, m/z 268 (M^+ – trimethoxybenzyl), 181, 105 (base). Anal. ($C_{27}H_{31}NO_5 \cdot HCl$) C, H, N.

1-(3,4,5-Trimethoxybenzyl)-2-(4-chlorobenzyl)-6,7-bis(benzyloxy)-1,2,3,4-tetrahydroisoquinoline Oxalate (23). Tetrahydroisoquinoline **16**[21] (1.00 g, 1.78 mmol) was converted to the free base and reacted with 4-chlorobenzyl chloride (286 mg, 1.78 mmol), $NaHCO_3$ (154 mg, 1.78 mmol), and NaI (catalytic) in ethanol (25 mL) according to the procedure previously described for the synthesis of tetrahydroisoquinoline **22**. The resulting oil was dissolved in toluene and converted to the oxalate salt by the addition of a solution of oxalic acid dihydrate (225 mg, 1.78 mmol) in methanol. Addition of diethyl ether resulted in the formation of a white solid, which was filtered and dried to give 752 mg (58.4%) of tetrahydroisoquinoline **23**: mp 180–181 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 7.49–7.16 (m, 14 H, benzyl ArH), 6.76 (s, 1 H, ArH), 6.12 (s, 2 H, ArH ortho to OCH_3), 5.73 (s, 1 H, ArH), 5.16 (s, 2 H, $PhCH_2OAr$), 4.88 (d, J = 12.6 Hz, 1 H, $PhCH_2OAr$), 4.57 (d, J = 12.6 Hz, 1 H, $PhCH_2OAr$), 4.25 (m, 3 H, ArCHRN and $ArCH_2N$), 3.82 (s, 3 H, OCH_3), 3.72 (s, 6 H, OCH_3), 3.47–2.75 (m, 6 H, alkyl); mass spectrum, m/z 470 (M^+ – trimethoxybenzyl, ^{37}Cl), 4.68 (M^+ – trimethoxybenzyl, ^{35}Cl, base), 181, 127 (^{37}Cl), 125 (^{35}Cl), 91. Anal. ($C_{40}H_{40}NO_5Cl \cdot C_2H_2O_4$) C, H, N.

1-(3,4,5-Trimethoxybenzyl)-2-(4-chlorobenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (7). Tetrahydroisoquinoline **7** was synthesized by the procedure previously described for tetrahydroisoquinoline **6**. Thus, bis(benzyloxy)-protected tetrahydroisoquinoline **23** (500 mg, 0.985 mmol) was converted to the free base and refluxed in methanol/concentrated HCl (30 mL) for 24 h under argon. The resulting oil was washed with methanol, dried under vacuum, and recrystallized from ethanol/diethyl ether to give 247 mg (73.0%) of the desired catechol: mp 149–153 °C dec; ^{1}H NMR (D_2O, 90 MHz) δ 7.45–7.13 (m, 4 H, *N*-benzyl ArH), 6.75 (s, 1 H, ArH), 6.19 (s, 3 H, ArH), 4.29 (m, 3 H, ArCHRN and $ArCH_2N$), 3.68 (s, 3 H, OCH_3), 3.61 (s, 6 H, OCH_3), 3.53–2.98 (m, 6 H, alkyl); IR (KBr) cm^{-1} 3220 (br, OH); mass spectrum, m/z 290 (M^+ – trimethoxybenzyl, ^{37}Cl), 288 (M^+ – trimethoxybenzyl, ^{35}Cl), 181, 127 (^{37}Cl), 125 (^{35}Cl, base). Anal. ($C_{28}H_{28}NO_5Cl \cdot HCl$) C, H, N.

1-(3,4,5-Trimethoxybenzyl)-2-(4-methoxybenzyl)-6,7-bis(benzyloxy)-1,2,3,4-tetrahydroisoquinoline Oxalate (24). Tetrahydroisoquinoline **16**[21] (1.00 g, 1.78 mmol) was dissolved in chloroform (20 mL) and converted to the free base by washing with saturated $NaHCO_3$ (3 × 20 mL) and water (2 × 20 mL). The chloroform layer was dried (Na_2SO_4) and concentrated to an oil. The oil was dissolved in acetone (20 mL), and NaI (catalytic), $NaHCO_3$ (500 mg, 5.95 mmol), and 4-methoxybenzyl chloride (0.25 mL, 1.85 mmol) were added. The reaction mixture was stirred at room temperature for 24 h at which time an additional equivalent of 4-methoxybenzyl chloride was added. The reaction mixture was stirred at room temperature for an additional 24 h. Water (20 mL) was then added to the reaction mixture, resulting in the formation of a cloudy solution, which was extracted twice with chloroform (2 × 20 mL). The chloroform layers were pooled, washed with saturated $NaHCO_3$ (2 × 40 mL) and water (2 × 40 mL), dried (Na_2SO_4), and concentrated to an oil. The oil was dissolved in toluene (ca. 3 mL), and a solution of oxalic acid dihydrate (225 mg, 1.78 mmol) in methanol (ca. 3 mL) was added. Addition of diethyl ether resulted in the formation of a yellow solid, which was recrystallized from methanol/diethyl ether to afford 724 mg (55.3%) of the desired compound: mp 185–188 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 7.50–7.20 (m, 12 H, ArH), 6.85 (d, J = 8.58 Hz, 2 H, ArH ortho to 4-OCH_3), 6.76 (s, 1 H, ArH), 6.13 (s, 2 H, ArH ortho to 3- and 5-OCH_3), 5.76 (s, 1 H, ArH), 5.15 (s, 2 H, $PhCH_2OAr$), 4.85 (d, J = 12.6 Hz, 1 H, $PhCH_2OAr$), 4.60 (d, J = 12.6 Hz, 1 H, $PhCH_2OAr$), 4.38–4.02 (m, 3 H, ArCHRN and $ArCH_2N$), 3.81 (s, 6 H, OCH_3), 3.71 (s, 6 H, OCH_3), 3.51–2.60 (m, 6 H, alkyl); mass spectrum, m/z 523 (M^+ – *N*-benzyl), 464 (M^+ – trimethoxybenzyl), 344, 181, 121 (base), 91. Anal. ($C_{41}H_{43}NO_6 \cdot C_2H_2O_4$) C, H, N.

1-(3,4,5-Trimethoxybenzyl)-2-(4-methoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (8). Tetrahydroisoquinoline **8** was synthesized by the procedure previously described for tetrahydroisoquinoline **6**. Thus, bis(benzyloxy)-protected tetrahydroisoquinoline **24** (770 mg, 1.05 mmol) was converted to the free base and refluxed in methanol/concentrated HCl (40 mL) for 3 h under argon. The resulting yellow oil was washed with methanol, dried under vacuum, and recrystallized from ethanol/diethyl ether to provide 413 mg (78.6%) of catechol **8** as white crystals: mp 159–163 °C dec; ^{1}H NMR (MeOH-d_4, 90 MHz) δ 7.42–7.30 (m, 2 H, *N*-benzyl ArH), 7.06–6.97 (m, 2 H, *N*-benzyl ArH ortho to OCH_3), 6.71 (s, 1 H, ArH), 6.23 (s, 3 H, ArH), 4.32 (m, 3 H, ArCHRN and $ArCH_2N$), 3.84 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 3.70 (s, 6 H, OCH_3), 3.64–3.03 (m, 6 H, alkyl); IR (KBr, cm^{-1}) 3210 (br, OH); mass spectrum, m/z 465 (M^+), 284, 181, 121 (base). Anal. ($C_{27}H_{31}NO_6 \cdot HCl$) C, H, N.

1-(3,4,5-Trimethoxybenzyl)-2-(4-nitrobenzyl)-6,7-bis(benzyloxy)-1,2,3,4-tetrahydroisoquinoline Oxalate (25). Tetrahydroisoquinoline **16**[21] (6.00 g, 10.7 mmol) was converted to the free base, dissolved in ethanol (100 mL), and reacted with 4-nitrobenzyl bromide (2.33 g, 10.7 mmol), $NaHCO_3$ (1.20 g, 14.3 mmol), and NaI (catalytic) according to the procedure previously

described for the synthesis of tetrahydroisoquinoline **22**. The resulting oil was dissolved in toluene and converted to the oxalate salt by the addition of a solution of oxalic acid dihydrate (1.35 g, 10.7 mmol) in methanol. Addition of diethyl ether resulted in the formation of a pale yellow solid, which was filtered and dried H, give 6.21 g (77.3%) of tetrahydroisoquinoline **25**: mp 156–159 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.13 (d, J = 8.6 Hz, 2 H, ArH ortho to NO_2), 7.52 (d, J = 8.6 Hz, 2 H, ArH), 7.45–7.21 (m, 10 H, $C_6H_5CH_2OAr$), 6.76 (s, 1 H, ArH), 6.12 (s, 2 H, ArH ortho to OCH_3), 5.75 (s, 1 H, ArH), 5.14 (s, 2 H, $PhCH_2OAr$), 4.86 (d, J = 12.4 Hz, 1 H, $PhCH_2OAr$), 4.57 (d, J = 12.4 Hz, 1 H, $PhCH_2OAr$), 4.44–4.24 (m, 3 H, ArCHRN and $ArCH_2N$), 3.78 (s, 3 H, OCH_3), 3.68 (s, 6 H, OCH_3), 3.65–3.34 (m, 3 H, alkyl), 3.12–2.73 (m, 3 H, alkyl); IR (KBr, cm^{-1}) 1510 and 1355 (NO_2); mass spectrum, m/z 523 (M^+ – N-benzyl), 479 (M^+ – trimethoxybenzyl), 344, 181, 91 (base). Anal. ($C_{40}H_{40}N_2O_7 \cdot C_2H_2O_4$) C, H, N.

1-(3,4,5-Trimethoxybenzyl)-2-(4-nitrobenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (9). Tetrahydroisoquinoline **9** was synthesized by the procedure previously described for tetrahydroisoquinoline **6**. Thus, bis(benzyloxy)-protected tetrahydroisoquinoline **25** (5.00 g, 6.66 mmol) was converted to the free base and reacted with methanol/concentrated HCl (100 mL) for 4 h under argon. The residue was washed with methanol, dried under vacuum, and recrystallized from ethanol/diethyl ether to give 3.17 g (92.1%) of the desired catechol as yellow crystals: mp 150–153 °C dec; ^{1}H NMR (D_2O, 90 MHz) δ 8.17 (d, J = 8.58 Hz, 2 H, ArH ortho to NO_2), 7.44 (d, J = 8.26 Hz, 2 H, ArH), 6.73 (s, 1 H, ArH), 6.17 (s, 3 H, ArH), 4.37–4.20 (m, 3 H, ArCHRN and $ArCH_2N$), 3.64 (s, 3 H, OCH_3), 3.56 (s, 6 H, OCH_3), 3.70–2.98 (m, 6 H, alkyl); IR (KBr, cm^{-1}) 3300 (br, OH), 1525, and 1350 (NO_2); mass spectrum, m/z 299 (M^+ – trimethoxybenzyl), 181, 164, 136 (base). Anal. ($C_{26}H_{28}N_2O_7 \cdot HCl \cdot CH_3CH_2OH$) C, H, N.

1-(3,4,5-Trimethoxybenzyl)-2-(3,4-dichlorobenzyl)-6,7-bis(benzyloxy)-1,2,3,4-tetrahydroisoquinoline Oxalate (26). Tetrahydroisoquinoline **16**[21] (1.00 g, 1.78 mmol) was converted to the free base and was reacted with α,3,4-trichlorotoluene (0.254 mL, 1.78 mmol), $NaHCO_3$ (200 mg, 2.38 mmol), and NaI (catalytic) in ethanol (20 mL) according to the procedure previously reported for the synthesis of tetrahydroisoquinoline **22**. A solution of oxalic acid dihydrate (225 mg, 1.78 mmol) in methanol was added to a solution of the resulting oil in toluene. Addition of diethyl ether resulted in the formation of a white solid. Filtration of this solid gave 930 mg (67.5%) of tetrahydroisoquinoline **26** as the oxalate salt: mp 178–180 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 7.50–7.20 (m, 13 H, benzyl ArH), 6.77 (s, 1 H, ArH), 6.15 (s, 2 H, ArH ortho to OCH_3), 5.82 (s, 1 H, ArH), 5.16 (s, 2 H, $PhCH_2OAr$), 4.85 (d, J = 12.6 Hz, 1 H, $PhCH_2OAr$), 4.63 (d, J = 12.6 Hz, 1 H, $PhCH_2OAr$), 4.40–3.95 (m, 3 H, ArCHRN and $ArCH_2N$), 3.82 (s, 3 H, OCH_3), 3.72 (s, 6 H, OCH_3), 3.65–2.62 (m, 6 H, alkyl); mass spectrum, m/z 504 (M^+ – trimethoxybenzyl, ^{35}Cl, ^{37}Cl), 502 (M^+ – trimethoxybenzyl, $^{35}Cl_2$), 181, 91 (base). Anal. ($C_{40}H_{39}Cl_2NO_5 \cdot C_2H_2O_4$) C, H, N.

1-(3,4,5-Trimethoxybenzyl)-2-(3,4-dichlorobenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10). Tetrahydroisoquinoline **10** was synthesized by the procedure previously described for tetrahydroisoquinoline **6**. Thus, bis(benzyloxy)-protected tetrahydroisoquinoline **26** (500 mg, 0.645 mmol) was converted to the free base and treated with methanol/concentrated HCl (30 mL) for 4 h under argon. The white solid that was obtained was washed with methanol, dried under vacuum, and recrystallized from ethanol/diethyl ether to give 260 mg (74.5%) of the desired catechol as white crystals: mp 137–140 °C dec; ^{1}H NMR (D_2O, 90 MHz) δ 7.51–7.01 (m, 3 H, N-benzyl ArH), 6.71 (s, 1 H, ArH), 6.19 (s, 3 H, ArH), 4.23 (m, 3 H, ArCHRN and $ArCH_2N$), 3.63 (s, 3 H, OCH_3), 3.58 (s, 6 H, OCH_3), 3.47–2.79 (m, 6 H, alkyl); IR (KBr, cm^{-1}) 3300 (br, OH); mass spectrum, m/z 324 (M^+ – trimethoxybenzyl, ^{37}Cl, ^{35}Cl), 322 (M^+ – trimethoxybenzyl, $^{35}Cl_2$, base), 181, 161 (^{37}Cl, ^{35}Cl), 159 ($^{35}Cl_2$). Anal. ($C_{26}H_{27}NO_5Cl_2 \cdot HCl \cdot CH_3CH_2OH$) C, H, N.

1-(3,4,5-Trimethoxybenzyl)-2-(4-aminobenzyl)-6,7-bis(benzyloxy)-1,2,3,4-tetrahydroisoquinoline Oxalate (27). Tetrahydroisoquinoline **25** (6.00 g, 7.99 mmol) and stannous chloride dihydrate (24.0 g, 106 mmol) were dissolved in a solution of ethanol (100 mL) and concentrated HCl (24 mL). The reaction mixture was stirred under reflux for 45 min and then was allowed to cool to room temperature. Water (100 mL) was added, and the solution was extracted once with dichloromethane (100 mL). The dichloromethane solution was washed with 10% NaOH (2 × 100 mL) and water (2 × 100 mL), dried ($MgSO_4$), and concentrated to an oil. The oil was dissolved in toluene (5–10 mL), and a solution of oxalic acid dihydrate (2.00 g, 15.9 mmol) in methanol (ca. 5 mL) was added. Following the addition of diethyl ether, the desired amine crystallized from the solution. Filtration of the solution provided 4.62 g (80.2%) of a white solid: mp 141–144 °C; ^{1}H NMR (free base, $CDCl_3$, 270 MHz) δ 7.47–7.26 (m, 10 H, $C_6H_5CH_2OAr$), 6.98 (d, J = 8.27 Hz, 2 H, ArH), 6.68 (s, 1 H, ArH), 6.57 (d, J = 8.42 Hz, 2 H, ArH ortho to NH_2), 6.26 (s, 1 H, ArH), 6.21 (s, 2 H, ArH ortho to OCH_3), 5.11 (s, 2 H, $PhCH_2OAr$), 4.95 (d, J = 12.4 Hz, 1 H, $PhCH_2OAr$), 4.87 (d, J = 12.4 Hz, 1 H, $PhCH_2OAr$), 3.85–3.59 (m, 5 H, ArCHRN, $ArCH_2N$ and NH_2), 3.83 (s, 3 H, OCH_3), 3.75 (s, 6 H, OCH_3), 3.27–2.63 (m, 5 H, alkyl), 2.40 (m, 1 H, alkyl); IR (free base, neat, cm^{-1}) 3450 and 3370 (NH_2); mass spectrum, m/z 523 (M^+ – N- benzyl), 449 (M^+ – trimethoxybenzyl), 344, 181, 106, 91 (base). Anal. ($C_{40}H_{42}N_2O_5 \cdot C_2H_2O_4 \cdot 0.25H_2O$) C, H, N.

1-(3,4,5-Trimethoxybenzyl)-2-(4-aminobenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Dihydrochloride (11). Tetrahydroisoquinoline **11** was synthesized by the procedure previously described for tetrahydroisoquinoline **6**. Thus, bis(benzyloxy)-protected tetrahydroisoquinoline **27** (4.53 g, 6.28 mmol) was converted to the free base and reacted with methanol/concentrated HCl (100 mL) for 3.5 h under argon. The resulting oil was washed with methanol, dried under vacuum, and recrystallized from ethanol/diethyl ether to afford 2.71 g (82.4%) of an off-white solid: mp 162–164 °C dec; ^{1}H NMR (MeOH-d_4, 270 MHz) δ 7.69 (d, J = 8.42 Hz, 2 H, ArH ortho to NH_2), 7.48 (d, J = 8.42 Hz, 2 H, ArH), 6.73 (s, 1 H, ArH), 6.36 (s, 2 H, ArH ortho to OCH_3), 6.08 (s, 1 H, ArH), 4.41 (m, 3 H, ArCHRN and $ArCH_2N$), 3.74 (s, 3 H, OCH_3), 3.72 (s, 6 H, OCH_3), 3.88–2.97 (m, 6 H, alkyl); IR (KBr, cm^{-1}) 3400 (br, OH); mass spectrum, m/z 164 (M^+ – both benzyl groups, base), 181, 106. Anal. ($C_{26}H_{30}N_2O_5 \cdot 2HCl \cdot CH_3CH_2OH$) C, H, N.

Inhibitory Activities in Rat Aorta. Thoracic aorta were isolated from male Sprague–Dawley rats, and spirally cut strips were prepared and mounted in a muscle chamber containing physiological salt solution as described previously.[24] U46619-induced isometric contractions of rat aortic strips were recorded on a polygraph. In experiments where TMQ analogues (100 μM) were tested as inhibitors of U46619-induced contractions, aortic strips were equilibrated for 1 h in Krebs–Heinseleit solution containing 3 × 10^{-6} M indomethacin. Cumulative concentration–response curves (CRC's) of U46619 were obtained by the method of van Rossum.[25] In experiments designed to assess the nature of inhibition, shifts in the CRC's of U46619-induced contraction of rat aorta by varying concentrations (3 × 10^{-5}, 7 × 10^{-5}, and 10^{-4} M) of **6** were evaluated.

Platelet Antiaggregatory Activities. Blood was collected from normal human volunteers who reported to be free of medication for at least 10 days prior to blood collection. Platelet-rich plasma was prepared as described previously[14] and used for all studies. Platelet aggregation studies were performed according to the turbidometric method of Born[26] in a Payton Model 600 dual-channel aggregometer interfaced to an Apple microcomputer for acquisition, quantitation, presentation, and management of platelet aggregation data.[27] Both inducers were used at the minimum concentrations required to stimulate maximal aggregation. Inhibitors were added 1 min prior to induction of platelet activation, and inhibitory concentration-50 (IC_{50}) values for each inhibitor were determined from changes in the amplitude of light transmittance after 6 min for ADP and 4 min for U46619. Secretion of the contents of platelet-dense granules was measured by monitoring the release of radioactivity from platelets prelabeled

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with [^{14}C]serotonin.[28] In experiments designed to assess the nature of inhibition, the shifts in the CRC's of U46619-induced aggregation and serotonin secretion by varying concentrations (10^{-5}, 3×10^{-5}, 7×10^{-5}, and 10^{-4} M) of **11** were evaluated.

Data Analyses. Effective concentration-50 (EC_{50}) values of U46619 on rat aorta were determined graphically from individual plots of percent response vs log concentration and expressed as a pD_2 value. Antagonists of U46619 responses were also quantified by calculating their K_B or pA_2 values according to the methods of Furchgott and Bursztyn[29] and Arunlakshana and Schild.[30] A 5% level of significance was used to determine differences between control and drug-treated groups of data. Schild plots were analyzed by computer according to the method of Tallarida and Murray.[31]

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Registry No. (±)-**1**, 21650-42-0; (±)-**3**, 108925-23-1; (±)-**6**, 114185-24-9; (±)-**6**·HCl, 114185-17-0; (±)-**7**, 114185-25-0; (±)-**7**·HCl, 114185-18-1; (±)-**8**, 114185-26-1; (±)-**8**·HCl, 114185-19-2; (±)-**9**, 114185-27-2; (±)-**9**·HCl, 114185-20-5; (±)-**10**, 114185-28-3; (±)-**10**·HCl, 114185-21-6; (±)-**11**, 114185-30-7; (±)-**11**·2HCl, 114185-22-7; (±)-**16**, 114248-27-0; (±)-**16**·HCl, 114248-26-9; **17**, 104-81-4; **18**, 104-83-6; **19**, 824-94-2; **20**, 100-14-1; **21**, 102-47-6; (±)-**22**, 114185-12-5; (±)-**22**·oxalate, 114185-23-8; (±)-**23**, 114185-13-6; (±)-**23**·oxalate, 114197-85-2; (±)-**24**, 114185-14-7; (±)-**24**·oxalate, 114197-86-3; (±)-**25**, 114185-15-8; (±)-**25**·oxalate, 114197-87-4; (±)-**26**, 114185-16-9; (±)-**26**·oxalate, 114197-88-5; (±)-**27**, 114185-29-4; (±)-**27**·oxalate, 114197-89-6.

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Ergolines as Selective 5-HT$_1$ Agonists

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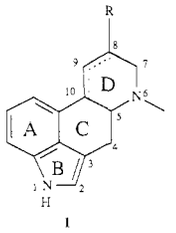
The synthesis and serotonin receptor subtype affinity of a series of ergolines are described. High selectivity for the 5-HT$_1$ subtype was found with a number of 8-substituted (3β,5β)-9,10-didehydro-6-methylergolines. The more potent and selective of these compounds increased the concentration of serotonin and decreased the concentration of 5-HIAA in rat brain and increased corticosterone concentration in rat serum. Oral administration of **13**, (3β)-2,3-dihydrolysergine, produced long-lasting decreases in serotonin turnover. Compound **13** lacked substantial dopaminergic activity as measured by its effects on dopamine turnover in whole brain or striatum and its affinity for α-adrenergic binding sites was significantly less than for 5-HT$_1$ binding sites. The increases in serum corticosterone concentrations produced by **13** were not blocked by the serotonin uptake inhibitor fluoxetine or by the serotonin synthesis inhibitor *p*-chlorophenylalanine, suggesting that **13** exerts its effects through direct stimulation of serotonin receptors.

Drugs that enhance central serotonergic function, such as serotonin-uptake inhibitors, monoamine oxidase (MAO) inhibitors, and direct acting serotonin agonists, have been shown to affect memory, depression, anxiety, pain, appetite, and other important centrally mediated functions in humans and animals.[1-5] Because serotonin-uptake and MAO inhibitors enhance serotonin function by increasing the availability of endogenous serotonin, these agents do not reveal if these effects are mediated through single or multiple serotonin receptor subtypes. The development of compounds that are selective agonists at a single serotonin receptor subtype could lead to the discovery of the role of these subtypes in central nervous system function and disease.

The receptors for serotonin in the central nervous system have been divided into two major subtypes, 5-HT$_1$ and 5-HT$_2$, on the basis of their relative affinities for [^{3}H]-serotonin and [^{3}H]spiperone, respectively.[6] Recently, the 5-HT$_1$ receptor has been subdivided into the 5-HT$_{1A}$,[7] 5-HT$_{1B}$,[7] 5-HT$_{1C}$,[8] and 5-HT$_{1D}$[9] subtypes on the basis of various biochemical evidence. The functional significance of these serotonin receptor subtypes and their possible roles in human disease is the subject of intensive current research and speculation.[1]

The tetracyclic structure of the ergolines, **1**, contains the essential features of the monoamine neurotransmitters dopamine, noradrenaline, and serotonin. Many naturally



1

occurring and synthetic ergolines have been shown to bind

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