Iodinated Analogs of Trimetoquinol as Highly Potent and Selective β_2-Adrenoceptor Ligands

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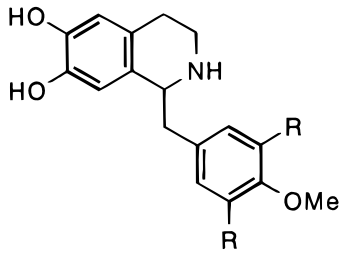
A series of trimetoquinol (**1**, TMQ) analogs were designed and synthesized based on the lead compound **2**, a diiodinated analog of trimetoquinol which exhibits improved selectivity for β_2- versus β_1-adrenoceptors (AR). To determine the influence of 1-benzyl substituents of trimetoquinol on β_2-AR binding affinity and selectivity, we replaced and/or removed the 3′-, 4′-, and 5′-methoxy substituents of trimetoquinol. Replacement of the 4′-methoxy group of **2** with an amino (**21c**) or acetamido (**15**) moiety did not significantly alter β_2-AR and thromboxane A_2/prostaglandin H_2 (TP) receptor affinity. Substitution with a 4′-hydroxy (**18**) or -iodo (**21b**) group did not significantly alter β_2-AR affinity, but greatly reduced TP receptor affinity (380- and 1200-fold, respectively). Further, the β_2-AR can accommodate larger substituents such as a benzamide at the 4′-position (**26b**). Other monoiodo derivatives (**24**, **26a**) have similar or slightly lower affinity to both β_2-AR and TP receptor compared to their diiodo analogs. Interestingly, removal of the 4′-substituent of 3′,5′-diiodo analogs increased β_2-AR affinity with little or no effect on β_1-AR and TP binding. Thus, analog **21a** displayed highly potent (pK_i 9.52) and selective (β_2/β_1 = 600) binding affinity for β_2-AR. On the other hand, trifluoromethyl substituents at the 3′- and 5′-positions (**27**) essentially abolished binding affinity at β_2-AR and TP receptors. The differential binding effects of the aforementioned trimetoquinol modifications on the receptor systems may reflect differences in the binding pocket that interacts with the benzyl portion of trimetoquinol analogs. Thus, manipulation of the 1-benzyl moiety of trimetoquinol (**1**) has resulted in analogs that exhibit potent β_2-AR binding affinity and significantly lower β_1-AR and TP receptor affinities.

Introduction

Trimetoquinol (**1**) is a potent nonspecific β-adrenoceptor (β-AR) agonist clinically used in Japan as a bronchorelaxant (Figure 1).[1] Optical resolution of trimetoquinol and subsequent evaluation of the stereoisomers revealed that the (*S*)-(−)-isomer of trimetoquinol is a potent β-AR agonist in heart and lung tissues whereas the (*R*)-(+)-isomer acts as a selective and highly stereospecific TP receptor antagonist.[2−5] Radioligand competition binding studies at β-AR and TP receptors show high stereoselective binding (>100-fold) for the (*S*)-(−)-isomer and (*R*)-(+)-isomer, respectively. This stereoselectivity is also observed in the binding of fluorinated trimetoquinol analogs at β-AR.[6]

The basic structure of catecholamines, such as norepinephrine and the β-adrenoceptor agonist isoproterenol, is incorporated within the tetrahydroisoquinoline nucleus of trimetoquinol. In studies using mutated hamster β_2-AR expressed in Chinese hamster ovary (CHO) cells, replacement of Asp113 with Asn113 abolished receptor binding of trimetoquinol and its analogs.[7] In addition, replacement of Ser204 and Ser207 with Ala204 and Ala207 decreased the binding affinity of trimetoquinol analogs in β_2-AR to a lesser extent, but greatly diminished their ability to stimulate cAMP accumulation.[7] However, both the binding and functional activities of isoproterenol are significantly reduced in the β_2-AR Asn113, Ala204, and Ala207 mutants. These results suggest that, although trimetoquinol analogs may interact with the same amino acid residues in the binding site as isoproterenol, the contribution of catechol interactions with these mutated β_2-ARs is less significant in terms of ligand binding and may well be overshadowed by the binding contributions of the trimethoxybenzyl group of trimetoquinol.



1 R = OMe
2 R = I

Figure 1.

In previous studies, substitution with fluorine or iodine on the 5- or 8-positions of trimetoquinol resulted in only a modest (~10-fold) increase in β_2-AR versus β_1-AR selectivity as compared to trimetoquinol in functional and binding studies.[6,8] In addition, we have also found that replacement of the 3′- and 5′-methoxy substituent of trimetoquinol with iodine atoms (i.e., **2**) is

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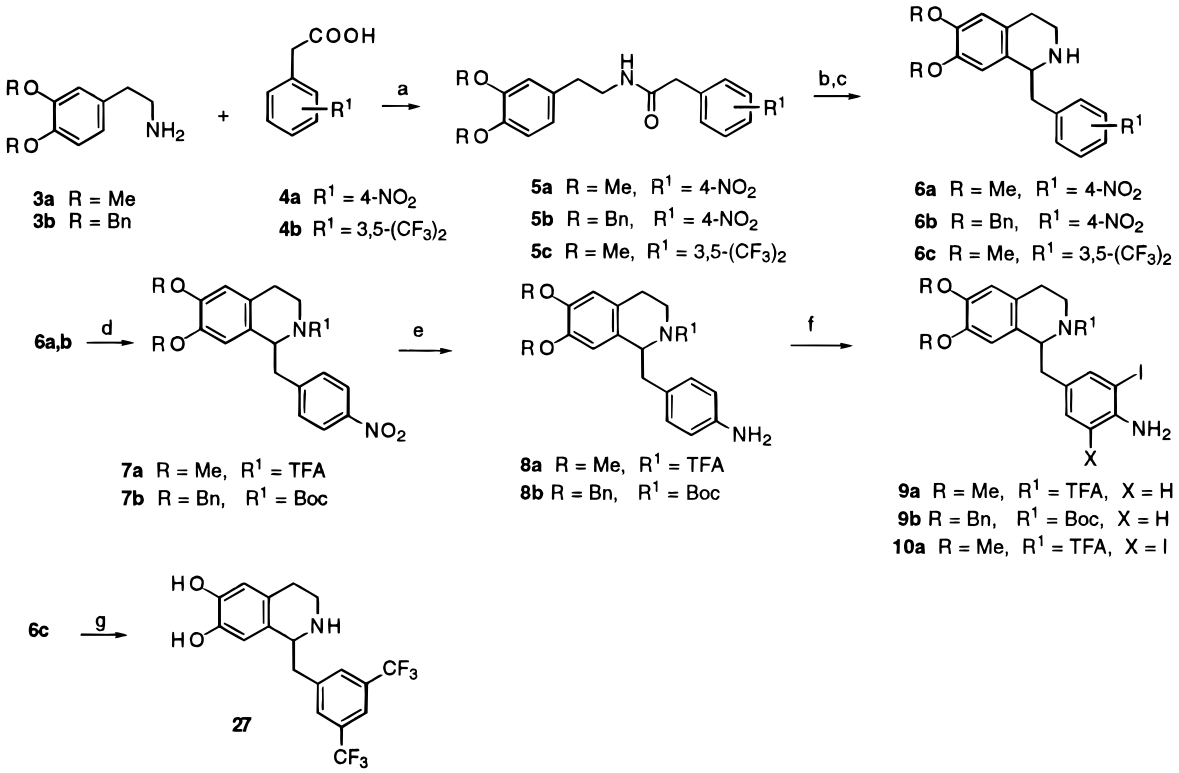
Scheme 1[a]



[a] (a) Toluene, reflux (Dean−Stark trap), 72 h; (b) $POCl_3$, MeCN, reflux; (c) $NaBH_4$, MeOH; (d) TFAA, THF (**6a**) or $(Boc)_2O$, NaOH, THF (**6b**); (e) H_2, Pd/C (**7a**) or Raney Ni (**7b**); (f) 1 equiv of $BTMACl_2I$, MeOH, CH_2Cl_2, 20 h (**8a,b**), or 4 equiv of $BTMACl_2I$, $CaCO_3$, MeOH, CH_2Cl_2, 3 days (**8a**); (g) 1. BBr_3, CH_2Cl_2, 2. MeOH.

well tolerated on both β-AR[8] and TP receptors.[9,10] Interestingly, although its binding affinity at β_1-AR is slightly better than trimetoquinol, analog **2** displays a much higher affinity than trimetoquinol for β_2-AR. These earlier findings suggest that trimetoquinol analogs interact with an auxiliary site through the substituted benzyl group in addition to the binding site shared by catecholamines. This subsite can be taken advantage of in the development of more site-selective agents. The high potency of **2** seems to suggest that this auxiliary site is hydrophobic in nature. On TP receptors, the complementary binding sites for trimetoquinol analogs are essentially unknown. However, compound **2** is a more potent TP receptor antagonist than trimetoquinol, further suggesting that 1-benzyl ring modifications are appropriate to develop agents with greater selectivity on β-AR versus TP receptors and vice versa.

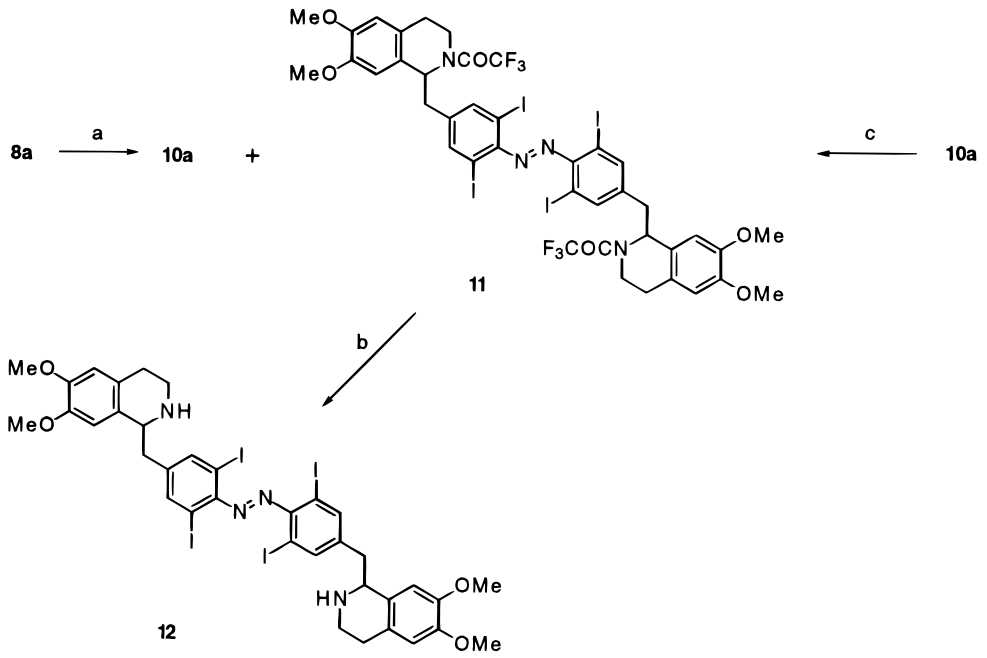
In this report, we describe the synthesis and evaluation of iodinated trimetoquinol analogs designed as probes for characterizing the receptor binding interactions associated with the benzyl substituent of trimetoquinol analogs and as site-selective β-AR and TP ligands. These chemical modifications are expected to provide us with a greater separation of the pharmacological activities for this class of compounds. Site-selective β-AR agents have potential in the treatment of cardiopulmonary diseases, non-insulin-dependent diabetes (type II), and obesity;[11] whereas highly selective TP receptor antagonists have value in the treatment of thrombolytic disorders.[5,9,12]

Chemistry

We have composed a convenient protection scheme for the synthesis of the desired trimetoquinol analogs. The triple-protected isoquinoline intermediates were synthesized as shown in Scheme 1. The tetrahydroisoquinolines **6a−c** were synthesized from the *O*-methyl- or *O*-benzyl-protected catecholamines **3a** or **3b**, respectively, and 4-nitrophenylacetic acid (**4a**) or 3,5-bis(trifluoromethyl)phenylacetic acid (**4b**) using methods described previously.[6,10,13] The amino groups of **6a** and **6b** were protected with trifluoroacetyl (TFA) and *tert*-butyloxycarbonyl (*t*-BOC), respectively. The nitro groups of **7a,b** were reduced via catalytic hydrogenation using Pd/C or Raney Nickel, respectively, to give the aniline derivatives **8a,b**. Iodination of **8a,b** with 1 equiv of benzyltrimethylammonium dichloroiodate ($BTMACl_2I$) according to Kajigaeshi et al.[14] led to the 3′-iodo analogs **9a,b**. An additional 3 equiv of $BTMACl_2I$ added in portions over a 3 day period was required to convert **8a** completely to the diiodo derivative **10a**. Interestingly, the diiodo product **10a** was often isolated as light pink to reddish crystals. We found that the minor side product **11** (Scheme 2) was responsible for the reddish coloration. TLC analysis of the reaction mixture and isolated crude product indicates that compound **11** is formed mostly during workup. Compound **11** was isolated by flash chromatography. The structure of **11** and its deacetylation product **12** was proven by ^1H and ^{13}C NMR and elemental analysis. Compound **11** was also isolated in an attempt to convert the 4′-amino of **10a** to a hydrazine group. Thus, diazotization of **10a** followed by reduction with H_2SO_3 gave compound **11** as the only isolated product in low yield.

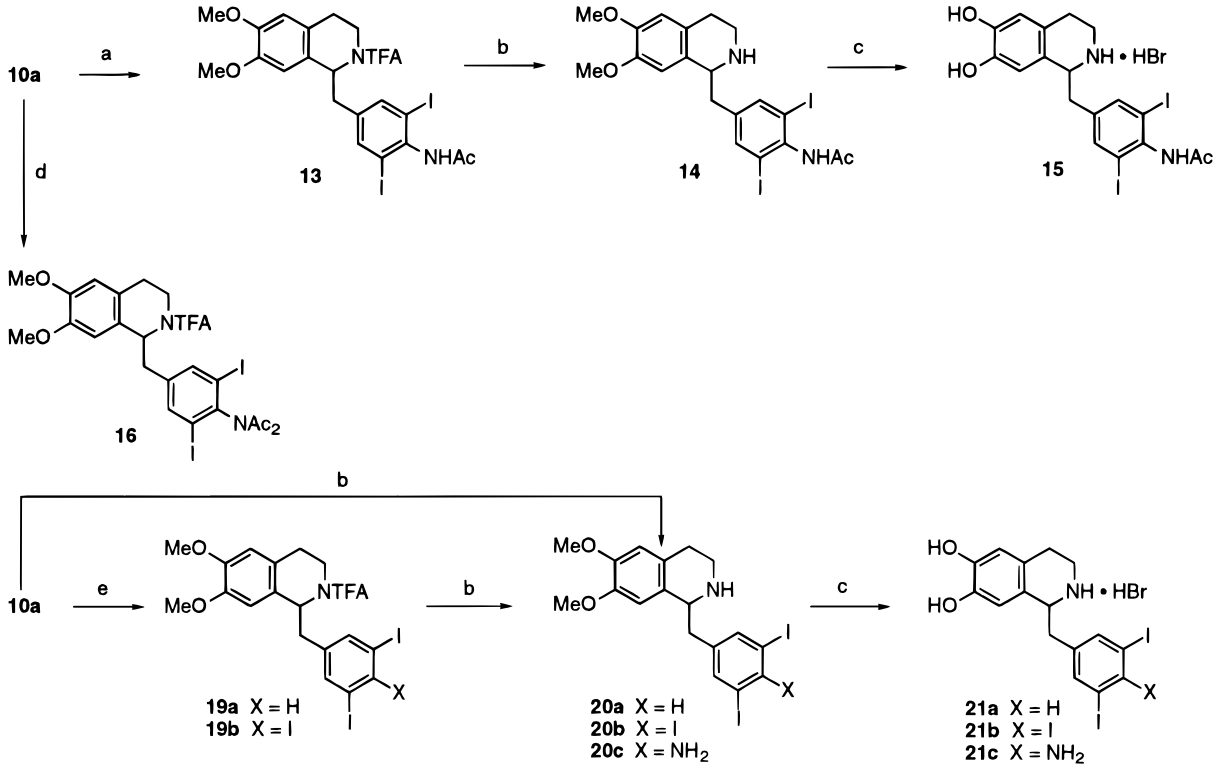
While reaction of **10a** with acetic anhydride at room temperature did not give the desired 4′-acetamido derivative **13**, heating **10a** in acetic anhydride at reflux resulted in the diacetylation product **16** (Scheme 3).

Scheme 2[a]



[a] (a) 5 equiv of $BTMACl_2I$, MeOH, CH_2Cl_2, 5 days; (b) K_2CO_3, MeOH, H_2O; (c) 1. $NaNO_2$, H_2SO_4, AcOH, 2. H_2SO_3.

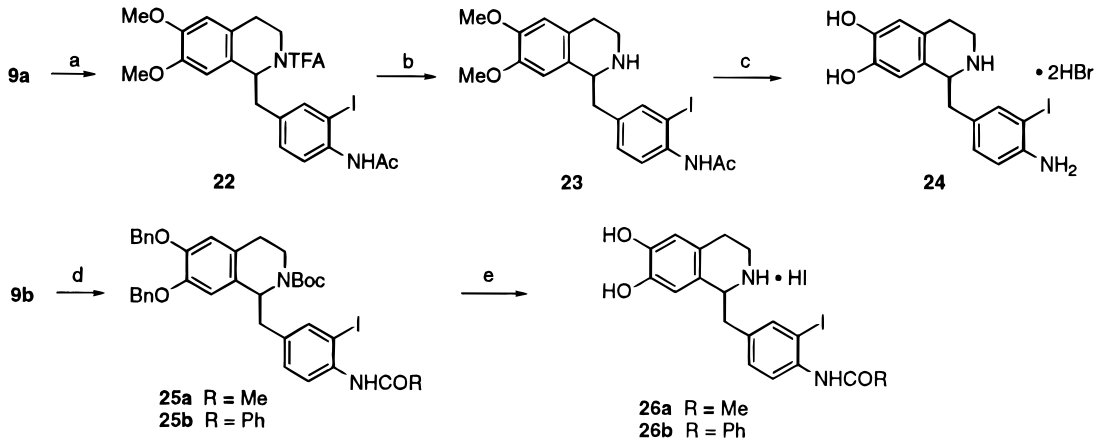
Scheme 3[a]



[a] (a) AcCl, Et_3N, DMAP; (b) K_2CO_3, MeOH, H_2O; (c) 1. BBr_3, CH_2Cl_2, 2. MeOH; (d) Ac_2O, reflux; (e) 1. $NaNO_2$, H_2SO_4, AcOH, 2. H_3PO_2 or KI.

Similar diacetylation has been reported with the reaction of 2,6-dibromo-4-toluidine with refluxing acetic anhydride while lower temperatures gave a mixture of mono- and diacetylated products.[15] With this result in mind, monoacetylation was accomplished by reacting **10a** with 5 equiv of acetyl chloride in the presence of 4-(dimethylamino)pyridine (DMAP) and triethylamine at room temperature to afford **13**. Basic hydrolysis of the trifluoroacetyl protecting group of **10a** and **13** gave **20c** and **14**, respectively. The methoxy derivatives **20c**, **14**, and **6c** were demethylated with BBr_3 to afford the desired trimetoquinol analogs **21c**, **15**, and **27**, respectively, as hydrobromide salts (Schemes 1 and 3). In a similar manner, the 6,7-bis(benzyloxy)-1-(3,5-diiodo-4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline[10] (**17**) was dealkylated with BBr_3 to give 6,7-dihydroxy-1-(3,5-diiodo-4-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**18**), the demethyl analog of **2**. Diazotization of **10a** (Scheme 3) followed by reaction of the diazonium salt with H_3PO_2 or potassium iodide (KI) gave the diiodo and triiodo

Scheme 4[a]



[a] (a) AcCl, Et_3N; (b) K_2CO_3, MeOH, H_2O; (c) 1. BBr_3, CH_2Cl_2, 2. MeOH; (d) Ac_2O, △ or PhCOCl, Et_3N; (e) 1. TMSI, MeCN, 2. MeOH.

derivatives, **19a** and **19b**, respectively. Basic hydrolysis of the trifluoroacetyl group of **19a,b** as before gave **20a,b**. Demethylation of **20a,b** with BBr_3 proceeded smoothly to give **21a,b**. Compound **9a** was acylated with acetic anhydride in refluxing benzene to give **22** which was deprotected in the same manner as **14** to give **23** (Scheme 4).

However, attempts to demethylate **23** with BBr_3 failed to give the desired product **26a**. Surprisingly, the amide bond of **23** was cleaved to give aniline **24**. This indicates the importance of both *o*-iodine atoms as a sterical hindrance toward cleavage of the acetamido group of **14** by BBr_3. Thus, we turned our attention to trimethylsilyl iodide (TMSI) as a mild reagent for ether cleavage. However, this agent was too weak to effect demethylation of **23**; therefore, the catechol *O*-methyl ether protecting groups were changed to benzyl ethers. Hence, compounds **26a** and **26b** were prepared from the *O*-benzyl and *N*-*t*-BOC protected **9b** (Scheme 4). The acylated compounds **25a** and **25b** were deblocked using TMSI. Initially, using the procedure of Lott[16] (TMSI, MeCN, 50 °C 2 h), amide **25a** gave the desired amide **26a** along with a significant amount of the deacetylation product **24**. Ordinarily, amides are stable to TMSI. To optimize the selectivity, we monitored the TMSI deprotection reaction by NMR spectroscopy at room temperature. The *O*-benzyl protecting groups were removed within 6 h, and no cleavage of the amide bond was observed at this temperature for 20 h. Thus, using the reaction conditions 4−6 equiv of TMSI, MeCN, room temperature, 6 h, we obtained **26a** and **26b** from **25a** and **25b**, respectively.

The proton NMR spectra of synthesized compounds were quite complicated, especially the 2-*t*-BOC derivatives which displayed complex splitting patterns reflecting two relatively stable conformations with ratios ranging from 5:2 to 5:4, similar to those observed for *N*-Ac- and *N*-Me-substituted tetrahydroisoquinolines.[17,18] However, the ^{13}C NMR spectra of 1-benzyltetrahydroisoquinolines can be easily used for structure identification because of their relative simplicity. Assignments of signals (final compounds) were made based on the ^{13}C NMR spectra of salsolinol,[19] effects of substituents on the benzene ring, and off-resonance spectra. For 2-TFA derivatives, the chemical shift of the C-3 atom appears as a quartet ($^4J_{C-F} \approx 3.7$ Hz) indicating its close proximity to the CF_3 group.

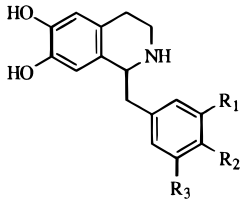
Results and Discussion

We have modified the trimethoxybenzyl portion of trimetoquinol by replacing one or more of the methoxy groups with a variety of halogenated substitutions. The effects of these modifications on the receptor binding affinity of trimetoquinol analogs (Table 1) for human β_2-AR expressed in CHO cells and human TP receptors (platelets) were determined by radioligand competition binding assays using [^{125}I]iodocyanopindolol (ICYP) and [^{3}H]-SQ 29548 as radioligands, respectively.

***β*$_2$-Adrenoceptors.** In this study, most of the modifications made on the trimethoxybenzyl portion of trimetoquinol resulted in enhancement of β_2-AR affinity. Previously, it was shown that replacement of the 3′- and 5′-methoxy groups of trimetoquinol with iodines [i.e., **1** ($pK_i = 7.36$) → **2** ($pK_i = 8.69$)] resulted in a greater than 20-fold increase in affinity.[8] In the present study, complete replacement of the 3′-, 4′-, and 5′-methoxy groups of trimetoquinol (**1**) with iodine atoms to give the triiodo analog **21b** ($pK_i = 8.82$) enhanced β_2-adrenoceptor affinity 29-fold versus trimetoquinol (**1**), but with respect to **2**, the additional iodine substituent at the 4′-position adds little to the binding affinity.

Studies on human β_2-AR indicate that 4′-position substituents reflecting varying size and chemical properties are well tolerated. Replacement of the 4′-methoxy of **2** with an amino group [i.e., **2** → **21c** ($pK_i = 8.81$)] did not significantly alter affinity, and replacement with a 4′-acetamido [i.e., **15** ($pK_i = 8.06$)] reduced affinity only 4-fold. A similar replacement with a hydroxy (i.e., **18**, $pK_i = 7.93$) reduced affinity about 5-fold as compared to **2**. The receptor binding pocket that interacts with substituents at the 4′-position seems to be sufficiently large to accommodate the 4′-benzamido moiety of **26b** ($pK_i = 8.70$). Interestingly, the diiodo analog **21a** ($pK_i = 9.52$), which lacks a 4′-substituent, exhibits the most potent affinity with a K_i value in the subnanomolar range. Thus, while a wide range of substituents at the 4′-position are accepted by the receptor binding pocket, these 4′-substituents contribute little to binding affinity. Based on the present binding data, this binding pocket is best left unoccupied for maximum binding affinity; on the other hand, we are carrying out further investigations to find the optimum substituent at the 4′-position that will take advantage of the pocket in this region for additional binding interactions.

Table 1. Human β_2-Adrenoceptors (AR) Expressed in CHO Cells and Platelet Thromboxane A_2/Prostaglandin (TP) Receptor Binding Affinities of Trimetoquinol (TMQ) Analogs



	1-benzyl substituents			human β_2-AR CHO[a]		human TP receptors[b]	
compound	R_1	R_2	R_3	pK_i ± SEM	PR[c]	pK_i ± SEM	PR[c]
1	OCH_3	OCH_3	OCH_3	7.36 ± 0.23	1.0	6.79 ± 0.09	1.00
2	I	OCH_3	I	8.69 ± 0.16	21	7.33 ± 0.07	3.5
21c	I	NH_2	I	8.81 ± 0.15	28	6.73 ± 0.12	0.87
24	I	NH_2	H	8.19 ± 0.27	6.8	6.00 ± 0.02	0.16
15	I	$NHCOCH_3$	I	8.06 ± 0.13	5.0	6.45 ± 0.11	0.46
26a	I	$NHCOCH_3$	H	8.11 ± 0.16	5.6	5.83 ± 0.14	0.11
21a	I	H	I	9.52 ± 0.13	150	6.75 ± 0.07	0.91
21b	I	I	I	8.82 ± 0.18	29	4.22 ± 0.03	0.003
26b	I	NHCOPh	H	8.70 ± 0.03	22	5.27 ± 0.13	0.03
18	I	OH	I	7.93 ± 0.03	3.7	4.72 ± 0.09	0.009
27	CF_3	H	CF_3	5.36 ± 0.32	0.01	4.08 ± 0.02	0.002

[a] Using [^{125}I]ICYP as radioligand, $N = 4-9$. [b] Using [^{3}H]-SQ 29548 as radioligand, $N = 4-9$. [c] PR = potency ratio relative to **1** (TMQ). PR = antilog [pK_i(drug) − pK_i(TMQ)].

Apparently, one *m*-iodo substituent is sufficient to retain high affinity since removing one of the iodo groups of either **21c** or **15** [i.e., **21c** → **24** (pK_i = 8.19) or **15** → **26a** (pK_i = 8.11)] resulted in only minor shifts in affinity. To determine the nature (hydrophobic or electronic) of the binding contributions of 3′- and 5′-substituents (methoxy and iodo), we synthesized the bis(trifluoromethyl) analog **27**. While the hydrophobic property (π) of the trifluoromethyl group ($\pi = 0.88$) is similar to iodine ($\pi = 1.12$), this functional group exerts a much stronger electron-withdrawing effect. The binding affinity of the bis(trifluoromethyl)analog **27** (pK_i = 5.36) was 4 orders of magnitude lower than the diiodo analog **21a**. Thus, trifluoromethyl substituents at the 3′- and 5′-positions abolish binding affinity. Since a trifluoromethyl group is similar in size to an iodine atom, the significantly stronger electron-withdrawing property of the trifluoromethyl ($\sigma_p = 0.54$ versus σ_p = 0.18 for iodine) is likely responsible for the greatly reduced binding affinity of **27**. The electron-withdrawing effect of the trifluoromethyl substituents on the π-electron system of the aromatic ring may interfere with its capability to form aromatic interactions with the receptor binding site. These aromatic interactions may be more important for binding than hydrophobic interactions.

***β*$_2$*/β*$_1$ Selectivity.** Although replacement of the 3′- and 5′-methoxy groups of trimetoquinol **1** with iodine atoms (i.e., **2**) resulted in a 21-fold increase in β_2-AR affinity, a similar increase in binding affinity was not observed for β_1-AR (Table 2). As a result, the diiodo analog **2** exhibits moderate (ca. 40-fold) selectivity for β_2-AR versus β_1-AR. More importantly, the influence of a 4′-substituent is markedly different for β_2-AR versus β_1-AR. While the absence of a 4′-substituent (i.e., **21a**) does not significantly alter β_1-AR affinity (pK_i = 6.74), the same feature increased β_2-AR affinity. Consequently, analog **21a** displays more than 600-fold selectivity for β_2-AR versus β_1-AR, and is the most selective trimetoquinol analog yet reported. These results indicate a remarkable difference in the receptor binding site or pocket of β_2- and β_1-AR that interacts with substituents at the 4′-position of trimetoquinol analogs.

Table 2. Selectivity of Trimetoquinol (TMQ) Analogs for Human β_2- and β_1-Adrenoceptors (AR) Expressed in CHO Cells

	pK_i ± SEM		
compound	human β_1 CHO[a]	human β_2 CHO[a]	β_2/β_1 selectivity[b]
1	6.49 ± 0.06	7.36 ± 0.23	7.4
2	7.10 ± 0.06	8.69 ± 0.16	39
21a	6.74 ± 0.30	9.52 ± 0.13	600

[a] Using [^{125}I]ICYP as radioligand for β_1- and β_2-AR expressed in CHO cells, $N = 4-9$. [b] β_2/β_1 selectivity = $K_i(\beta_1\text{-AR})/K_i(\beta_2\text{-AR})$.

TP Receptors. In general, replacement of the 3′- and 5′-methoxy groups of trimetoquinol (**1**, pK_i = 6.79) with iodine to give analog **2** (pK_i = 7.33) resulted in only a slight increase (3-fold) in affinity. However, replacement of all three methoxy groups of trimetoquinol with iodines to give the triiodo analog **21b** (pK_i = 4.22) practically abolished binding to TP receptors. In addition, demethylation of the 4′-methoxy substituent of **2** to give **18** (pK_i = 4.72) resulted in a similar 380-fold reduction in binding affinity. The very low binding affinity of **18** contrasts with a recent observation[20] where 6,7-dihydroxy-1-(4′-hydroxy-3′-nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline exhibited good binding affinity. By contrast, substitution of the same methoxy group with an amino moiety (i.e., **21c**, pK_i = 6.73) resulted in only a 3-fold decrease in affinity. Interestingly, removal of the 4′-substituent of **2** or **21c** to give **21a** (pK_i = 6.75) did not affect binding affinity significantly. Acetylation of the 4′-amino group of **21c** was also tolerated as **15** (pK_i = 6.45) displayed binding affinity similar to **21c**. Thus, while a primary amine, acetamide, or a methoxy group is tolerated at the 4′-position, a free hydroxy group or an iodo group is detrimental to binding affinity. Removal of one of the iodines of **21c** and **15** to give **24** (pK_i = 6.00) and **26a** (pK_i = 5.83), respectively, resulted in a 5-fold decrease in binding affinity, suggesting that hydrophobic interactions of 3′- or 5′-substituents contribute to binding. However, replacement of the 3′- and 5′-iodo groups of **21a** with similarly hydrophobic tri-

fluoromethyl substituents resulted in a drastic reduction in binding affinity. As with β_2-AR, in terms of contribution to the overall binding affinity, hydrophobic interactions appear secondary to aromatic interactions.

Conclusions

In this study, we have shown that substitution on the trimethoxybenzyl portion of trimetoquinol (**1**) has a major role in the type and potency of biological activity expressed. 3′- and 5′-diiodo substitution on the 1-benzyl moiety significantly improved binding affinity at β_2-AR, while having very little effect on β_1-AR and TP receptor binding. The role of the 4′-position is particularly interesting in that the binding pocket that interacts with this substituent is more discriminating in TP receptors, while that of the β_2-AR can accommodate more varied groups. Our studies indicate that these modifications of trimetoquinol (**1**) have provided a further separation of β_2-AR versus TP receptor affinities, and the presence of 3′,4′,5′-triiodo substitution on the 1-benzyl group (i.e., **21b**) produced 25 000-fold selectivity for β_2-AR. Moreover, the type (or the lack) of substitution at the 4-position may be key to the design of β_2-AR selective ligands based on the parent drug, trimetoquinol (**1**).

Experimental Section

Chemistry. Melting points were determined on a Thomas−Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer System 2000 FT-IR. Proton and carbon-13 magnetic resonance spectra were obtained on a Bruker AX 300 spectrometer (300 and 75 MHz for ^{1}H and ^{13}C, respectively). Chemical shift values are reported as parts per million (δ) relative to tetramethylsilane (TMS). Spectral data are consistent with assigned structures. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA, and found values are within 0.4% of the theoretical values. Routine thin-layer chromatography (TLC) was performed on silica gel GHlF plates (250 m, 2.5 × 10 cm; Analtech Inc., Newark, DE). Flash chromatography was performed on silica gel (Merck, grade 60, 230−400 mesh, 60 Å). Tetrahydrofuran (THF) was dried by distillation from sodium metal, and acetonitrile (MeCN), $CHCl_3$, and methylene chloride (CH_2Cl_2) were dried by distillation from P_2O_5. All anhydrous solvents (except anhydrous Et_2O and THF) were stored over 3- or 4-Å molecular sieves.

***N*-(3,4-Dimethoxyphenethyl)-4-nitrophenylacetamide (5a).** A solution of 3,4-dimethoxyphenethylamine (5.0 g, 27.6 mmol) and 4-nitrophenylacetic acid (7.5 g, 41.4 mmol) in toluene (150 mL) was heated at reflux for 72 h in a flask equipped with a Dean−Stark trap under an argon atmosphere. The solvent was evaporated in vacuo, and the residue was taken up in CH_2Cl_2 (200 mL). The solution was washed consecutively with H_2O (100 mL), 10% HCl (2 × 100 mL), H_2O (2 × 100 mL), 10% $NaHCO_3$ (2 × 200 mL), and H_2O (2 × 100 mL) and dried over $MgSO_4$. The solvent was evaporated, and the crude solid was recrystallized from EtOAc to give 5.49 g (58%) of the product as ivory-colored needles: mp 119−121 °C (lit.[22] 130−132 °C, ethanol−2-propanol); ^{1}H NMR ($CDCl_3$) δ 8.16 (d, J = 8.8 Hz, 2H, ArH), 7.37 (d, J = 8.8 Hz, 2H, ArH), 6.73 (d, J = 8.1 Hz, 1H, ArH), 6.65 (d, J = 1.9 Hz, 1H, ArH), 6.60 (dd, J = 8.1 & 1.9 Hz, 1H, ArH), 5.40 (m, 1H, NH), 3.86 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.59 (s, 2H, CH_2), 3.51 (q, J = 6.9 Hz, 2H, CH_2), 2.73 (t, J = 6.9 Hz, CH_2); IR (KBr) 3320 (NH), 1650 (C=O) cm^{-1}. Anal. ($C_{18}H_{20}N_2O_5$) C, H, N.

***N*-(3,4-Dimethoxyphenethyl)-3,5-bis(trifluoromethyl)-phenylacetamide (5c).** A solution of 3,4-dimethoxyphenethylamine (2.72 g, 15 mmol) and 3,5-bis(trifluoromethyl)-phenylacetic acid (2.72 g, 10 mmol) in toluene (50 mL) was heated at reflux for 80 h in a flask equipped with a Dean−Stark trap. The solvent was evaporated in vacuo, and the residue was taken up in CH_2Cl_2. The solution was washed consecutively with 0.1 N HCl (30 mL), H_2O (50 mL), 0.1 N NaOH (30 mL), and H_2O (50 mL) and dried over $MgSO_4$. The solvent was evaporated, and the crude solid was recrystallized from toluene to give 3.44 g (79%) of the product as white needles: mp 127−128 °C; ^{1}H NMR ($CDCl_3$) δ 7.79 (s, 1H, ArH), 7.72 (s, 2H, ArH), 6.75 (d, J = 8.1 Hz, 1H, ArH), 6.67 (d, J = 1.9 Hz, 1H, ArH), 6.61 (dd, J = 8.1 & 1.9 Hz, 1H, ArH), 5.55 (m, 1H, NH), 3.85 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.58 (s, 2H, CH_2), 3.52 (q, J = 6.9 Hz, 2H, CH_2N), 2.75 (t, J = 6.9 Hz, CH_2); ^{13}C NMR ($CDCl_3$) δ 168.72, 149.20, 147.87, 137.28, 131.90, 130.79, 129.47, 123.16, 121.20, 120.56, 111.72, 111.27, 55.83, 42.85, 40.90, 34.97; IR (KBr) 3323 (NH), 1651 (C=O) cm^{-1}. Anal. ($C_{20}H_{13}F_6NO_3$) C, H, N.

6,7-Dimethoxy-1-(4-nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline (6a). A mixture of **5a** (8.0 g, 23.2 mmol) and $POCl_3$ (15.6 mL, 167.4 mmol) in dry MeCN (160 mL) was heated at reflux for 4 h. The solvent was evaporated in vacuo to give a glassy residue which was taken up in methanol (250 mL) and evaporated to dryness 3 times until the residue was a solid. The solid residue was dissolved in MeOH (250 mL) and then cooled in an ice bath. Excess $NaBH_4$ (17.56 g, 167.4 mmol) was carefully added in portions. The mixture was stirred at room temperature overnight. The solvent was removed in vacuo, and the solid residue was partitioned in CH_2Cl_2 (250 mL) and H_2O (150 mL). The layers were separated, and the H_2O layer was extracted with CH_2Cl_2 (100 mL). The combined organic fraction was washed successively with H_2O (2 × 50 mL), 2 N NaOH (2 × 50 mL), and H_2O (50 mL) and dried with Na_2SO_4. The solvent was evaporated to give a reddish oil. The oil was taken up in a minimum amount of methanol. The product crystallized upon standing and was collected by filtration (3.02 g, 40%): mp 134−136 °C; ^{1}H NMR ($CDCl_3$) δ 8.18 (d, J = 8.7 Hz, 2H, ArH), 7.43 (d, J = 8.7 Hz, 2H, ArH), 6.62 (s, 1H, ArH), 6.61 (s, 1H, ArH), 4.44 (dd, J = 9.5, 4.1 Hz, ArCH−N), 3.87 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.28 (dd, J = 13.7, 4.1 Hz, 1H, $ArCH_2$), 3.23−3.15 (m, 1H, NCH), 3.04 (dd, J = 13.7, 9.5 Hz, 1H, ArCH), 3.00−2.91 (m, 1H, NCH), 2.71 (m, 2H, $ArCH_2$); IR (KBr) 3337 (NH), 1515, 1345 (NO_2) cm^{-1}. Anal. ($C_{18}H_{20}N_2O_4$) C, H, N.

6,7-Dimethoxy-1-[3,5-bis[(trifluoromethyl)benzyl]]-1,2,3,4-tetrahydroisoquinoline Hydrochloride (6c·HCl). The amide **5c** (1.31 g, 3 mmol) was cyclized in the same manner as **6a** (7 mL of 1 M HCl in ether was added to the methanolic solution of a crude product) to give **6c** (0.84 g, 60%) as a hydrochloride salt: mp 104−115 °C (MeOH−ether); ^{1}H NMR ($CDCl_3$) δ 10.34 (bs, 2H, NH), 7.82 (s, 1H, ArH), 7.75 (s, 2H, ArH), 6.61 (s, 1H, ArH), 5.87 (s, 1H, ArH), 4.77 (m, 1H, CH), 3.91 (m, 1H, CH), 3.84 (s, 3H, OMe), 3.47 (s, 3H, OMe), 3.44 (m, 2H, CH), 3.28 (m, 2H, CH), 3.02 (m, 1H, CH); ^{13}C NMR ($CDCl_3$) δ 149.29, 147.74, 138.74, 132.08, 130.39, 123.33, 123.07, 121.40, 111.71, 109.43, 55.92, 55.38, 54.94, 40.46, 38.30, 24.80; IR (KBr) 3600−2400 (NH_2), 1614, 1522 cm^{-1}. Anal. ($C_{20}H_{19}F_6NO_2$·HCl·0.5H_2O) C, H, N.

6,7-Dimethoxy-1-(4-nitrobenzyl)-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline (7a). A solution of 6,7-dimethoxy-1-(4-nitrobenzyl)-1,2,3,4-tetrahydrisoquinoline (**6a**) (3.0 g, 9.14 mmol) in dry THF (150 mL) was added to trifluoroacetic anhydride (20 mL) with stirring at 0 °C. The mixture was stirred at room temperature overnight with the flask equipped with a $CaCl_2$ drying tube. The reaction mixture was poured onto ice (200 g) and the mixture stirred for 30 min. CH_2Cl_2 (200 mL) was added, and stirring was continued for 10 min. The layers were separated, and the organic layer was washed consecutively with H_2O (50 mL), 0.2 N NaOH (100 mL), and H_2O (100 mL) and then dried with Na_2SO_4. The solvent was evaporated in vacuo to give a yellow solid. Recrystallization from EtOAc−MeOH gave 1.94 g (50%) of yellow crystals: mp 162−164 °C; ^{1}H NMR ($CDCl_3$) δ 8.14 (m, 2H, ArH), 7.28 (m, 2H, ArH), 6.62 (s, 1H, ArH), 6.34 (s, 1H, ArH), 5.64 (t, J = 6.7 Hz, ArCH−N), 3.87 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.3−3.6 (m, 2H, N−CH_2), 3.25 (d, 2H, $ArCH_2$), 2.98−2.6 (m, 2H, $ArCH_2$); IR (KBr) 1686 (C=O), 1519, 1340 (NO_2) cm^{-1}; MS *m/e* (M^+) 423 (M+H, FAB). Anal. ($C_{20}H_{19}F_3N_2O_5$) C, H, N.

6,7-Bis(benzyloxy)-2-(*tert*-butoxycarbonyl)-1-(4-nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline (7b). A solution of $(Boc)_2O$ (2.84 g, 13 mmol) in THF (10 mL) was added to a cold mixture (ice bath) of isoquinoline **6b** (6.20 g, 12 mmol) in THF (100 mL) and 1 N NaOH solution (30 mL). The ice bath was removed, and stirring was continued at room temperature overnight. THF was evaporated under reduced pressure, water was added, and the product was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and evaporated again. The oily residue was dissolved in ether and put in a refrigerator. Pink crystals were filtered and washed with ether to give 6.00 g (86%) of the title compound: mp 150−152 °C; ^{1}H NMR ($CDCl_3$) δ (the spectrum consists of two rotamers of 5:4 ratio) 8.11 and 8.06 (d, J = 8.2 Hz, 2H, ArH), 7.47−7.27 and 7.21−7.11 (m, 12H, ArH), 6.70 and 6.67 (s, 1H, H-5), 6.56 and 6.44 (s, 1H, ArH), 5.27−4.96 (m, 5H, CH_2O + CH), 4.12 and 3.74 (m, 1H, CH), 3.25−3.00 (m, 3H, CH, CH_2Ar), 2.87−2.60 (m, 1H, CH), 2.57−2.37 (m, 1H, CH), 1.38 and 1.25 (s, 9H, *t*-Bu); IR (KBr) 1688 (C=O), 1518, 1345 (NO_2) cm^{-1}. Anal. ($C_{35}H_{36}N_2O_6$) C, H, N.

1-(4-Aminobenzyl)-6,7-dimethoxy-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline (8a). A solution of **7a** (5.20 g, 12.24 mmol) in ethyl acetate (200 mL) was hydrogenated (60 psi) over 5% Pd/C (1 g) for 2 h. The catalyst was removed by filtration, and the filtrate was evaporated to dryness to give a beige solid. Recrystallization from ethyl acetate and hexane gave 4.20 g (87%) of the product as light pink to white crystals: mp 157−160 °C; ^{1}H NMR ($CDCl_3$) δ 6.88 (d, 2H, ArH), 6.59 (d, 3H, ArH), 6.32 (s, 1H, ArH), 5.53 (t, 1H, ArCH−N), 3.99 (m, 1H, CH), 3.86 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.60 (bs, 2H, NH_2), 3.42−3.56 (m, 2H, CH), 2.85−3.20 (m, 3H, CH), 2.59−2.73 (m, 1H, CH); IR (KBr) 3370 (m, NH_2), 1689 (C=O) cm^{-1}; MS *m*/*e* (M^+) 395 (M+H, FAB). Anal. ($C_{20}H_{21}F_3N_2O_3$) C, H, N.

1-(4-Aminobenzyl)-6,7-bis(benzyloxy)-2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline (8b). The nitro compound **7b** (6.00 g, 10.3 mmol) was dissolved in EtOAc (230 mL) in a Parr bottle. The solution was charged with a slurry of Raney-Ni (4 mL) and hydrogenated at 50 psi for 3 h. The solution was filtered through Celite and evaporated to give 5.10 g (90%) of the crude compound. The product was purified by flash chromatography (silica gel, hexane−EtOAc, 2:1) to give a foamy glassy solid (4.51 g, 71%); ^{1}H NMR ($CDCl_3$) δ (the spectrum consists of two rotamers of 5:2 ratio) 7.48−7.24 (m, 10H, 2×Ph), 6.82 (m, J = 8.2 Hz, ArH), 6.68 and 6.64 (s, 1H, ArH), 6.58 (m, J = 8.2 Hz, 2H, ArH), 6.49 and 6.32 (s, 1H, ArH), 5.12−4.81 (m, 5H, 2×CH_2O + CH), 4.18−4.08 and 3.81−3.71 (m, 1H, CH), 3.27−3.09 (m, 1H, CH), 3.00−2.60 (m, 3H, CH_2Ar, CH), 2.59−2.40 (m, 1H, CH), 1.43 and 1.32 (s, 9H, *t*-Bu); IR (KBr) 3451 and 3365 (NH_2), 1684 (C=O), 1624 (NH bend), 1517 (C=C Ar) cm^{-1}. Anal. ($C_{35}H_{38}N_2O_4$) C, H, N.

1-(4-Amino-3-iodobenzyl)-6,7-dimethoxy-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline (9a). A mixture of isoquinoline **8a** (6.26 g, 18 mmol), benzyltrimethylammonium dichloroiodate ($BTMAICl_2$) (8.15 g 18 mmol), and $CaCO_3$ (2.30 g, 23 mmol) in CH_2Cl_2 (200 mL) and absolute MeOH (80 mL) was stirred overnight at room temperature; then $BTMAICl_2$ (0.31 g, 0.9 mmol) was added and stirred for 1 h. The solution was filtered, washed with $Na_2S_2O_3$ solution and water, dried over $MgSO_4$, and concentrated under reduced pressure. Recrystallization of the residue from AcOEt gave the title compound (7.90 g, 84%): mp 198−200 °C (dec); ^{1}H NMR ($CDCl_3$) δ 7.34 (d, J = 2.0 Hz, 1H, ArH), 6.90 (dd, J = 2.0, 8.1 Hz, 1H, ArH), 6.66 (d, J = 8.1 Hz, 1H, ArH), 6.59 (s, 1H, ArH), 6.29 (s, 1H, ArH), 5.48 (t, J = 6.6 Hz, 1H, CH), 4.03 (s, 2H, NH_2), 3.93 (m, 1H, CH), 3.86 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.53 (ddd, J = 14.3, 10.8, 4.0 Hz, 1H, CH), 2.96 (m, 2H, CH_2-Ar), 2.90 (ddd, J = 15.9, 10.6, 5.6 Hz, 1H, CH), 2.68 (dt, J = 16.2, 4.2 Hz, 1H, CH); ^{13}C NMR ($CDCl_3$) δ 155.75 (q), 148.10, 147.41, 145.63, 139.77, 130.64, 128.46, 126.45, 124.86, 116.47 (q), 114.51, 110.96, 110.30, 83.64, 55.86, 55.79, 55.48, 40.41, 28.52; IR (KBr) 3435 and 3344 (NH_2), 1693 (C=O), 1627 (NH bend), 1521 and 1501 (C=C Ar) cm^{-1}. Anal. ($C_{20}H_{20}F_3IN_2O_3$) C, H, N.

1-(4-Amino-3-iodobenzyl)-6,7-bis(benzyloxy)-2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline (9b). A mixture of isoquinoline **8b** (1.11 g, 3.2 mmol), $BTMACl_2I$ (1.1 g, 3.2 mmol), and $CaCO_3$ (0.44 g, 4.4 mmol) in CH_2Cl_2 (50 mL) and MeOH (20 mL) was stirred overnight at room temperature. $CaCO_3$ was filtered and washed with CH_2Cl_2. The filtrate was washed with a solution of $Na_2S_2O_3$ (×2) and H_2O (×2), dissolved in $CHCl_3$ and EtOH, and concentrated till the beginning of crystallization to give 1.59 g (81%) of title compound as pink crystals: mp 169−171 °C; ^{1}H NMR ($CDCl_3$) δ (the spectrum consists of two rotamers of 2:1 ratio) 7.47−7.25 (m, 11H, ArH), 6.81 (dd, J = 8.1, 1.6 Hz, 1H, ArH), 6.70−6.59 (m, 2H, ArH), 6.49 and 6.30 (s, 1H, ArH), 5.20−5.85 (m, 5H, CH_2O + CH), 4.13 and 3.74 (m, 1H, CH), 4.01 (s, NH_2), 3.30−3.10 (m, 1H, CH), 2.96−2.59 (m, 3H, CH_2Ar + CH), 2.59−2.43 (m, 1H, CH), 1.44 and 1.32 (s, 9H, *t*-Bu); IR (KBr) 3453 and 3334 (NH_2), 1667 (C=O), 1627 (NH bend), 1520 and 1498 (C=C Ar) cm^{-1}. Anal. ($C_{35}H_{37}IN_2O_4$) C, H, N.

1-(4-Amino-3,5-diiodobenzyl)-2-(trifluoroacetyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (10a). To a solution of **8a** (0.1 g, 2.54 mmol) in CH_2Cl_2 (50 mL) and methanol (20 mL) was added $BTMACl_2I$ (2.0 g, 5.77 mmol) and $CaCO_3$ (2.0 g). The mixture was stirred overnight at room temperature. A second portion of $BTMACl_2I$ (0.97 g, 2.8 mmol) was added, and stirring was continued overnight. Analysis of the reaction indicated a mixture of mono- and diiodinated products. The reaction mixture was filtered. The filtrate was washed consecutively with aqueous 5% $Na_2S_2O_3$ (40 mL) and water (50 mL), and then dried with Na_2SO_4. Evaporation of the solvent gave a reddish glassy solid. The desired diiodinated product was purified from the crude mixture by flash chromatography (CH_2Cl_2−EtOAc, 9:1). The appropriate fractions were combined and evaporated in vacuo to give 0.72 g (44%) of the product as a white solid: mp 183−184.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.37 (s, 2H, ArH), 6.61 (s, 1H, ArH), 6.29 (s, 1H, ArH), 5.43 (m, 1H, ArH), 4.56 (bs, 2H, NH_2), 3.87 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.60 (m, 1H, CH), 2.91 (m, 4H, CH), 2.70 (m, 1H, CH); IR (KBr) 3429, 3348 (NH), 1685 (C=O) cm^{-1}. Anal. ($C_{20}H_{19}F_3I_2N_2O_3$) C, H, N.

4′,4″-Azobis[1-(4-amino-3,5-diiodobenzyl)-6,7-dimethoxy-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline] (11) was isolated from the above mixture as a bottom spot, deep purple solid: mp 229−232 °C; ^{1}H NMR ($CDCl_3$) δ 7.78 (s, 2H, ArH), 6.65 (s, 1H, ArH), 6.18 (s, 1H, ArH), 5.53 (dd, J = 7.9, 5.6 Hz, 1H, ArH), 3.99 (m, 1H, CH), 3.88 (s, 3H, OMe), 3.74 (m, 1H, CH), 3.72 (s, 3H, OMe), 3.16 (dd, J = 13.0, 5.3 Hz, 1H, CH), 2.96 (m, 2H, CH), 2.80 (dt, J = 16.2, 4.5 Hz, 1H, CH); ^{13}C NMR ($CDCl_3$) δ 156.14 (q), 148.89, 148.54, 147.59, 142.27, 141.53, 125.60, 125.05, 116.47 (q), 111.28, 110.42, 89.83, 56.15, 56.01, 55.54, 40.88 (q), 40.60, 28.45; IR (KBr) 1688 (C=O), 1520 (C=C Ar) cm^{-1}. Anal. ($C_{40}H_{34}F_6I_4N_4O_6$) C, H, N.

The same product was obtained via diazotization of **10a** (0.32 g, 0.5 mmol, see below) and stirring overnight with 20 mL of 6% H_2SO_3 at room temperature, yield 0.03 g (10%) after flash column chromatography.

4′,4″-Azobis[1-(4-amino-3,5-diiodobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline] (12). A solution of azo compound **11** (0.26 g, 0.2 mmol) in 35 mL of MeOH and 0.85 g of K_2CO_3 in 11 mL was refluxed for 4 h and evaporated. Flash chromatography on silica gel (CH_2Cl_2, CH_2Cl_2−MeOH, 50:1, 30:1) gave 0.15 g (70%) of the product: mp 176−177 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 2H, ArH), 6.62 (s, 1H, ArH), 6.61 (s, 1H, ArH), 4.20 (dd, J = 9.6, 4.0 Hz, 1H, ArH), 3.87 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.10−3.30 (m, 2H, CH), 3.00 (m, 1H, CH), 2.68−2.90 (m, 2H, CH); ^{13}C NMR ($CDCl_3$) δ 148.43, 147.75, 147.21, 144.05, 141.87, 129.76, 127.43, 112.03, 109.34, 90.43, 56.61, 56.16, 55.88, 41.65, 40.51, 29.36; IR (KBr) 1515 (C=C, Ar) cm^{-1}. Anal. ($C_{36}H_{36}I_4N_4O_4$) C, H, N.

1-(4-Acetamido-3,5-diiodobenzyl)-6,7-dimethoxy-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline (13). A solution of acetyl chloride (0.80 g, 7.8 mmol) in dry THF (2 mL) was added dropwise to a stirred solution of **10a** (1.0 g, 1.56 mmol), Et_3N (0.40 g, 7.8 mmol), and (*N*,*N*-dimethylamino)-pyridine (DMAP, at 10 mg) in dry THF (20 mL) at 0 °C under an argon atmosphere. After the addition, the reaction mixture was allowed to warm to room temperature, and stirring was continued overnight (14 h). The reaction was quenched with

H_2O (20 mL) and stirred for 30 min. The solution was extracted with Et_2OAc (3 × 75 mL). The organic extract was washed with H_2O (20 mL), dried (Na_2SO_4), and evaporated in vacuo to give a tan solid. Recrystallization of the crude product from EtOH and H_2O gave 0.93 g (87%) of the title compound as light beige needles: mp 218−219 °C; ^{1}H NMR ($CDCl_3$) δ 7.5−7.75 (bm, 2H, ArH), 6.96 (s, 1H, CONH), 6.62 (s, 1H, ArH), 6.24 (s, 1H, ArH), 5.47 (t, J = 6.7 Hz, 1H, CH), 3.98 (m, 1H, CH), 3.87 (s, 3H, OMe), 3.73 (s, 3H, OMe), 2.83−3.18 (m, 4H, CH), 2.74 (m, 1H, CH), 2.22 (s, 3H, Ac); ^{13}C NMR ($CDCl_3$) δ 168.14, 156.02 (q), 148.39, 147.68, 140.58, 140.31, 139.35, 125.71, 124.85, 116.4 (q), 98.73, 56.09, 55.93, 55.44, 40.63 (q), 40.48, 28.43, 23.62; IR (KBr) 3387 (NH), 1683 (CO). Anal. ($C_{22}H_{21}F_3I_2N_2O_4$) C, H, N.

1-(4-Acetamido-3,5-diiodobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (14·HCl). A solution of **13** (1.22 g, 1.78 mmol) in methanol (60 mL) was added to a solution of K_2CO_3 (5.6 g) in 80 mL of 1:1 methanol and water. The mixture was stirred at room temperature for 3 h. The resulting solution was concentrated and then extracted with ethyl acetate (3 × 80 mL). The organic solution was dried (Na_2SO_4) and evaporated in vacuo to give 0.79 g (75%) of the product as the free base. The free base converted to the hydrochloride salt and recrystallized from anhydrous ethanol and ethyl ether: mp 196−200 °C (dec); ^{1}H NMR (DMSO-d_6) δ 9.85 (s, 1H, CONH), 9.35 (bm, 2H, NH^+), 7.98 (s, 1H, ArH), 7.96 (s, 1H, ArH), 6.78 (s, 1H, ArH), 6.65 (s, 1H, ArH), 4.65 (bm, 1H, CH), 3.83 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.35−3.43 (m, 1H, CH), 2.8−3.2 (m, 5H, CH), 2.01 (s, 3H, Me); IR (KBr) 1677 (C═O), 1514 (C═C Ar) cm^{-1}; MS *m/e* (M^+) 592 (M−HCl, EI). Anal. ($C_{20}H_{22}I_2N_2O_3$·HCl·0.5Et_2O) C, H, N.

1-(4-Acetamido-3,5-diiodobenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrobromide (15·HBr). To a solution of **14** (0.50 g, 0.88 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C (ice bath) was added dropwise 1 M BBr_3 (4 mL, 4 mmol) in CH_2Cl_2 under an argon atmosphere. The mixture was then allowed to reach room temperature, and stirring was continued overnight. The reaction mixture was cooled with an ice bath, and methanol (20 mL) was added carefully. The solution was stirred for 10 min and then evaporated in vacuo. This was repeated 4 times to give a solid which was stirred with ether overnight. The crude product was collected by filtration and recrystallized from methanol and ethyl ether to give 0.51 g (90%) of the desired product as an off-white solid: mp 202−206 °C (dec); ^{1}H NMR (DMSO-d_6) δ 9.82 (s, 1H, CONH), 9.15 (bm, 1H, OH), 8.91 (bm, 2H, NH^+), 8.55 (bm, 1H, OH), 7.97 (s, 1H, ArH), 7.94 (s, 1H, ArH), 6.71 (s, 1H, ArH), 6.56 (s, 1H, ArH), 4.66 (bm, 1H, CH), 3.27−3.35 (m, 2H, CH), 3.10−3.16 (m, 2H, CH), 2.70−2.93 (m, 4H, CH), 2.02 (s, 3H, Me); ^{13}C NMR (CD_3OD) δ 172.51 (C═O), 147.04 and 145.89 (C-6 and C-7), 142.34 (C-4′), 141.90 and 141.73 (C-2′ and C-6′), 140.18 (C-1′), 123.67 and 123.09 (C-5a and C-8a), 116.32 (C-5), 114.11 (C-8), 100.61 and 100.46 (C-3′ and C-5′), 57.51 (C-1), 41.10 (C-3), 39.31 (CH_2Ar), 25.70 (C-4), 23.09 ($COCH_3$); IR (KBr) 1652 (CO), 1524 (C−N) cm^{-1}; MS *m/e* (M^+) 565 (M+H, FAB). Anal. ($C_{18}H_{18}N_2O_3I_2$·HBr·0.25Et_2O) C, H, N.

1-(4-Diacetamido-3,5-diiodobenzyl)-6,7-dimethoxy-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline (16). A solution of **10a** (0.70 g, 1.08 mmol) in acetic anhydride (10 mL) was heated at reflux for 2 h. The solvent was evaporated in vacuo to give an oily residue. The residue was taken up in hot ethanol. The product crystallized upon cooling to give 0.78 g (99%) of the product as white crystals: mp 190−192 °C; ^{1}H NMR ($CDCl_3$) δ 7.70 (s, 2H, ArH), 6.64 (s, 1H, ArH), 6.39 (s, 1H, ArH), 5.53 (t, J = 6.7 Hz, 1H, CH), 3.96 (m, 1H, CH), 3.87 (s, 3H, OMe), 3.79 (s, 3H, OMe), 2.68 (m, 1H, CH), 2.94−3.07 (m, 3H, CH), 2.77 (m, 1H, CH), 2.28 (s, 6H, Ac); ^{13}C NMR ($CDCl_3$) δ 171.23, 155.93 (q), 148.48, 147.86, 142.66, 141.36, 141.12, 125.65, 124.83, 116.31 (q), 111.14, 109.88, 99.21, 56.08, 55.93, 55.31, 40.58, 40.44 (q), 28.43, 26.60; IR (KBr) 1719, 1683 (C═O), 1235, 1207 (C−O) cm^{-1}. Anal. ($C_{24}H_{23}F_3I_2N_2O_5$) C, H, N.

6,7-Dihydroxy-1-(4-hydroxy-4,3,5-diiodobenzyl)-1,2,3,4-tetrahydroisoquinoline Hydrobromide (18·HBr). Hydrochloride **17**[10] (0.21 g, 0.28 mmol) was dissolved in $CHCl_3$ and washed with 1 N NaOH; the organic layer was separated, washed with water, and dried over $MgSO_4$. The solution was filtered, evaporated, and dried under vacuum. The residue was dissolved in CH_2Cl_2 (4 mL), and 1 M BBr_3 in CH_2Cl_2 (1.39 mL, 1.39 mmol) was added at −78 °C under an argon atmosphere. The mixture was stirred overnight at room temperature followed by addition of MeOH (1 mL) and stirring for 5 h. The resulting solution was evaporated with MeOH 5 times, and the residue was recrystallized from MeOH−ether to give 0.078 g (45%) of white crystals: mp 235−237 °C (dec); ^{1}H NMR (DMSO-d_6) δ 9.50 (s, 1H, OH), 9.14 (s, 1H, OH), 8.89 (s, 1H, OH), 8.78 (br s, 1H, NH^+), 8.43 (br s, 1H, NH^+), 7.76 (s, 2H, ArH), 6.64 (s, 1H, ArH), 6.55 (s, 1H, ArH), 4.55 (m, 1H, CH), 3.40−3.05 (m, 3H, CH), 2.92−2.68 (m, 3H, CH); ^{13}C NMR (CD_3OD) δ 156.59 (C-4′), 146.96 and 145.85 (C-6 and C-7), 141.69 (C-2′ and C-6′), 132.30 (C-1′), 123.71 and 123.24 (C-4a and C-8a), 116.25 (C-5), 114.14 (C-8), 85.85 (C-3′ and C-5′), 57.55 (C-1), 41.08 (C-3), 39.12 (CH_2Ar), 25.68 (C-4); IR (KBr) 3600−2600 (OH, NH), 1527 (C═C, Ar) cm^{-1}. Anal. ($C_{16}H_{15}I_2NO_3$·HBr·0.1Et_2O) C, H, N.

1-(3,5-Diiodobenzyl)-6,7-dimethoxy-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline (19a). A solution of isoquinoline **10a** (1.29 g, 2 mmol) in glacial acetic acid (30 mL) was added to a cold solution of $NaNO_2$ (0.19 g, 2.8 mmol) in concentrated (d 1.84) H_2SO_4 (3.4 mL); the temperature was kept within 0−5 °C. The solution was poured into ice−water (60 g), and H_3PO_2 (12 mL) was added in 30 min. The cooling bath was removed, and the solution was allowed to stand at room temperature for 2 days. The precipitate was filtered, dried, and chromatographed on silica gel (hexane−AcOEt, 8:1). Recrystallization from AcOEt−hexane gave 0.50 g (40%) of white crystals: mp 162−163 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (t, J = 1.5 Hz, 1H, ArH), 7.43 (d, J = 1.5 Hz, 2H, ArH), 6.62 (s, 1H, ArH), 6.24 (s, 1H, ArH), 5.48 (t, J = 6.7 Hz, 1H, CH), 3.95 (m, 1H, CH), 3.87 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.61 (m, 1H, CH), 3.06−2.86 (m, 3H, CH), 2.70 (m, 1H, CH); ^{13}C NMR ($CDCl_3$) δ 155.98 (q), 148.46, 147.67, 143.60, 141.25, 137.98, 125.86, 125.00, 116.41 (q), 111.20, 110.19, 94.58, 55.96, 55.93, 55.37, 41.13, 40.61 (q), 28.44; IR (KBr) 1686 (C═O), 1541, 1520 (C═C Ar) cm^{-1}. Anal. ($C_{18}H_{19}I_2NO_2$) C, H, N.

1-(3,4,5-Triiodobenzyl)-6,7-dimethoxy-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline (19b). Compound **10a** (1.29 g, 2 mmol) was diazotized in the usual manner. The resulting solution was poured in ice−water (60 g) followed by addition of KI (0.47 g, 2.8 mmol) in water (10 mL). The mixture was heated to 80 °C and allowed to cool. The precipitate was filtered, dried, and purified by column chromatography (silica gel, hexane−AcOEt, 3:1): yield 0.51 g (34%); mp 215−216 °C; ^{1}H NMR ($CDCl_3$) δ 7.59 (s, 2H, ArH), 6.63 (s, 1H, ArH), 6.31 (s, 1H, ArH), 5.46 (t, J = 6.7 Hz, 1H, ArH), 3.93 (m, 1H, CH), 3.88 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.61 (ddd, J = 13.8, 9.9, 4.1 Hz, 1H, CH), 3.02−2.85 (m, 3H, CH_2Ar + CH), 2.70 (dt, J = 16.2, 4.3 Hz, 1H, CH); ^{13}C NMR ($CDCl_3$) δ 156.07 (q), 148.48, 147.71, 140.45, 139.90, 125.67, 125.08, 118.91, 116.39 (q), 111.16, 110.08, 106.78, 55.97, 55.10, 40.68 (q), 40.32 28.43; IR (KBr) 1685 (C═O), 1519 (C═C Ar) cm^{-1}. Anal. ($C_{20}H_{17}F_3I_3NO_3$) C, H, N.

1-(3,5-Diiodobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (20a). A mixture of isoquinoline **19a** (0.38 g, 0.6 mmol) in MeOH (35 mL) and K_2CO_3 (0.85 g) in water (11 mL) was refluxed for 1.5 h. MeOH was evaporated, and a white precipitate was filtered and dried. The crude product was purified by flash chromatography (silica gel) using a gradient (EtOAc−hexanes, 1:2; EtOAc, EtOAc−MeOH, 30:1) and recrystallized from EtOAc−hexanes to give 0.25 g (76%) of white crystals: mp 122−124 °C; ^{1}H NMR ($CDCl_3$) δ 7.94 (t, J = 1.4 Hz, 1H, ArH), 7.60 (d, J = 1.4 Hz, 2H, ArH), 6.60 (s, 1H, ArH), 6.57 (s, 1H, ArH), 4.10 (m, 1H, CH), 3.86 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.18 (m, 1H, CH), 3.08 (dd, J = 4.1 and 13.7 Hz, 1H, CH), 2.95 (m, 1H, CH), 2.82−2.61 (m, 3H, CH); ^{13}C NMR ($CDCl_3$) δ 147.68, 147.17, 143.78, 143.15, 137.64, 129.86, 127.42, 111.98, 109.32, 94.99, 56.57, 56.06, 55.87, 42.20, 40.55, 29.39; IR (KBr) 3325 (NH), 1516 (C═C Ar) cm^{-1}. Anal. ($C_{18}H_{19}I_2NO_2$) C, H, N.

6,7-Dimethoxy-1-(3,4,5-triiodobenzyl)-1,2,3,4-tetrahydroisoquinoline (20b). A mixture of isoquinoline **19b** (0.454 g, 0.6 mmol) in MeOH (35 mL) and K_2CO_3 in water (11 mL)

was refluxed for 1.5 h. MeOH was evaporated, and a white precipitate was filtered and dried. Recrystallization from $CHCl_3$−hexane gave 0.300 g (76%) of white crystals: mp 168−170 °C (dec); ^{1}H NMR ($CDCl_3$) δ 7.79 (s, 2H, ArH), 6.60 (s, 1H, ArH), 6.58 (s, 1H, ArH), 4.09 (dd, J = 9.8, 3.8 Hz, 1H, CH), 3.86 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.17 (m, 1H, CH), 3.04−2.88 (m, 2H, CH), 2.82−2.60 (m, 3H, CH); ^{13}C NMR ($CDCl_3$) δ 147.66, 147.15, 143.00, 139.68, 129.67, 127.42, 118.18, 111.92, 109.14, 107.09, 56.35, 56.06, 55.85, 41.38, 40.56, 29.35; IR (KBr) 3312 (NH), 1516 (C=C Ar) cm^{-1}. Anal. ($C_{18}H_{18}I_3NO_2$) C, H, N.

1-(4-Amino-3,5-diiodobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (20c). A slurry of the isoquinoline **10a** (1.94 g, 3 mmol) in MeOH (260 mL) and K_2CO_3 (11.2 g) in H_2O (80 mL) was refluxed for 1 h. MeOH was evaporated under reduced pressure, and crystals were filtered, dried, and recrystallized from EtOAc−hexane to give the title compound (1.39 g, 84%): mp 169−171 °C; ^{1}H NMR ($CDCl_3$) δ 7.55 (s, 2H, ArH), 6.61 (s, 1H, ArH), 6.51 (s, 1H, ArH), 4.54 (s, 2H, NH_2), 4.04 (dd, J = 9.6, 4.0 Hz, 1H, CH), 3.86 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.18 (m, 1H, CH), 3.03 (dd, J = 13.8, 4.0 Hz, 1H, CH), 2.92 (ddd, J = 12.1, 6.8, 5.2 Hz, 1H, CH), 2.82−2.61 (m, J = 13.8, 9.6 Hz, 3H, CH); ^{13}C NMR ($CDCl_3$) δ 147.51, 147.05, 144.66, 139.97, 132.36, 130.14, 127.38, 111.88, 109.28, 81.59, 56.79, 56.01, 55.83, 40.87, 40.72, 29.47; IR (KBr) 3416 (NH), 3331 (NH), 1607 (NH bend), 1571, 1512 (C=C Ar) cm^{-1}. Anal. ($C_{18}H_{20}N_2I_2$) C, H, N.

6,7-Dihydroxy-1-(3,5-diiodobenzyl)-1,2,3,4-tetrahydroisoquinoline Hydrobromide (21a·HBr). The isoquinoline **20a** (0.19 g, 0.35 mmol) was demethylated using the same procedure as **15**. Recrystallization from MeOH−ether gave 0.20 g (96%) of the title compound: mp 157−159 °C (dec); ^{1}H NMR (DMSO-d_6) δ 9.13 (bs, 1H, OH), 8.88 (bm, 2H, NH+OH), 8.57 (bm, 1H, NH), 8.02 (t, J = 1.4 Hz, 1H, ArH), 7.80 (d, J = 1.4 Hz, 2H, ArH), 6.61 (s, 1H, ArH), 6.56 (s, 1H, ArH), 4.63 (bm, 1H, CH), 3.22−3.41 (m, 2H, CH), 3.14 (m, 1H, CH), 2.71−2.96 (m, 3H, CH); ^{13}C NMR (CD_3OD) δ 147.01 and 145.79 (C-6 and C-7), 145.69 (C-4′), 139.18 (C-2′ and C-6′), 141.15 (C-1′), 123.76 and 123.03 (C-4a and C-8a), 116.30 (C-5), 114.21 (C-8), 96.14 (C-3′ and C-5′), 57.25 (C-1), 41.02 (C-3), 40.08 (CH_2-Ar), 25.60 (C-4); IR (KBr) 3600−2700 (br OH, NH), 1617, 1521 (C=C Ar) cm^{-1}. Anal. ($C_{16}H_{15}BrI_3NO_2$) C, H, N.

6,7-Dihydroxy-1-(3,4,5-triiodobenzyl)-1,2,3,4-tetrahydroisoquinoline Hydrobromide (21b·HBr). The isoquinoline **20b** (0.23 g, 0.35 mmol) was demethylated using the same procedure as **15**. Recrystallization from MeOH−ether gave 0.24 g (97%) of the title compound: mp 210−213 °C (dec); ^{1}H NMR (MeOH-d_4) δ 7.92 (s, 2H, ArH), 6.63 (s, 1H, ArH), 6.56 (s, 1H, ArH), 4.64 (dd, J = 5.7 and 3.1 Hz, 1H, CH), 3.42−3.53 (m, 1H, CH), 3.2−3.34 (m, 2H, CH), 2.83−3.07 (m, 3H, CH); ^{13}C NMR (CD_3OD) δ 147.11 and 145.90 (C-6 and C-7), 141.06 (C-2′ and C-6′), 140.21 (C-1′), 123.70 and 122.98 (C-4a and C-8a), 120.90 (C-4′), 116.31 (C-5), 114.14 (C-8), 108.68 (C-3′ and C-5′), 57.04 (C-1), 41.01 (C-3), 39.38 (CH_2Ar), 25.62 (C-4); IR (KBr) 3600−2700 (br OH, NH), 1617, 1540 (C=C Ar) cm^{-1}. Anal. ($C_{16}H_{16}BrI_2NO_2$) C, H, N.

1-(4-Amino-3,5-diiodobenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Dihydrochloride (21c·2HCl). The isoquinoline **20c** (1.21 g, 2.2 mmol) was demethylated in the same manner as **20b** to give 1.14 g (76%) of the dihydrobromide salt: mp 155−157 °C (dec). The product was dissolved in MeOH, chromatographed (silica gel, EtOAc−NH_4OH, 100:1), and evaporated with EtOH (×5). To an ethanol solution was added a 1 N etherial solution of HCl (3 mL), concentrated, precipitated with EtOAc, and recrystallized from MeOH−*i*-PrOH: mp 176−178 °C (dec); ^{1}H NMR (DMSO-d_6) δ 9.15 (br s, 1H, OH), 8.89 (br s, 1H, NH_2^+), 7.68 (s, 2H, H-2′), 6.64 (s, 1H, H-5), 6.55 (s, 1H, H-8), 5.06 (br s, 2H, NH_2), 4.47 (m, 1H, H-1), 3.40−2.67 (m, 6H, H-3 + H-4 + CH_2Ar); ^{13}C NMR (CD_3OD) δ 147.99 (C-4′), 146.84 and 145.75 (C-6 and C-7), 141.60 (C-2′ and C-6′), 128.78 (C-1′), 123.75 and 123.33 (C-4a and C-8a), 116.24 (C-5), 114.16 (C-8), 81.86 (C-3′ and C-5′), 57.59 (C-1), 41.07 (C-3), 39.07 (CH_2Ar), 25.68 (C-4); IR (KBr) 3600−2500 (br, OH, NH), 1607 (NH bend), 1529 (C=C Ar) cm^{-1}. Anal. ($C_{16}H_{16}I_2N_2O_2$·2HCl·H_2O) C, H, N.

1-(4-Acetamido-3-iodobenzyl)-6,7-dimethoxy-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline (22). To a solution of isoquinoline **9a** (0.52 g, 1 mmol) in hot benzene (15 mL) was added Ac_2O (0.51 g, 5 mmol). The solution was refluxed for 1 h. The reaction mixture was allowed to cool. White crystals were filtered. Mother liquor was concentrated, and hexane was added. Slightly creamy crystals were filtered, total yield 0.53 g (94%). To get an analytical sample, the compound was recrystallized from EtOAc−hexane: mp 174−175 °C; ^{1}H NMR ($CDCl_3$) δ 8.11 (d, J = 8.3 Hz, 1H, H-5′), 7.52 (d, J = 1.5 Hz, 1H, H-2′), 7.36 (s, 1H, NH), 7.10 (dd, J = 8.3, 1.5 Hz, 1H, ArH), 6.60 (s, 1H, ArH), 6.32 (s, 1H, ArH), 5.23 (t, J = 6.6 Hz, CH), 3.94 (m, 1H, CH), 3.87 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.54 (ddd, OMe = 14.1, 10.4 Hz, 3.8 Hz, 1H, CH), 3.06 (m, 2H, CH), 2.90 (ddd, J = 15.9, 10.4, 5.2 Hz, 1H, CH), 2.68 (dt, J = 16.0, 4 Hz, 1H, CH), 2.23 (s, 3H, Ac); ^{13}C NMR ($CDCl_3$) δ 168.12, 155.90 (q), 148.30, 147.63, 139.63, 137.12, 134.95, 130.53, 126.19, 124.95, 121.73, 116.44 (q), 111.10, 110.17, 89.68, 55.91, 55.33, 40.75, 40.50 (q), 28.51, 24.75; IR (KBr) 3395 (NH), 1688 (C=O), 1519 (C=C Ar) cm^{-1}. Anal. ($C_{22}H_{22}F_3IN_2O_4$) C, H, N.

1-(4-Acetamido-3-iodobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (23). The title compound (0.57 g, 69%) as a glassy solid was obtained from the isoquinoline **22** (0.99 g, 1.76 mmol) in the same manner as **20c**: ^{1}H NMR ($CDCl_3$) δ 8.12 (d, J = 8.3 Hz, 1H, H-5′), 7.70 (d, J = 1.7 Hz, 1H, ArH), 7.38 (s, 1H, NH), 7.26 (dd, J = 8.3, 1.7 Hz, 1H, ArH), 6.63 (s, 1H, ArH), 6.60 (s, 1H, ArH), 4.11 (dd, J = 9.6, 3.8 Hz, 1H, CH), 3.10−3.25 (m, 2H, CH), 2.92 (m, 1H, CH), 2.63−2.86 (m, 3H, CH_2Ar, CH), 2.25 (s, 3H, Ac); ^{13}C NMR ($CDCl_3$) δ 168.19, 147.54, 147.05, 139.31, 137.30, 136.66, 130.12, 129.92, 127.28, 122.25, 111.85, 109.27, 90.50, 56.64, 55.99, 55.79, 41.63, 40.61, 29.30, 24.66; IR (KBr) 3391 (NH), 1676 (C=O), 1515 (C=C Ar) cm^{-1}. Anal. ($C_{20}H_{23}IN_2O_3$) C, H, N.

1-(4-Amino-3-iodobenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Dihydrochloride (24·2HCl). The title compound was obtained in the same manner as **21c** from the isoquinoline **23** (0.42 g, 0.90 mmol). The product was recrystallized from MeOH (twice) to give 0.32 g (64%). The compound was dissolved in $NaHCO_3$ solution and extracted with EtOAc (×5). The solution was dried ($MgSO_4$) and evaporated; 1 M HCl in ether (2 mL) was added to the methanol solution of the residue. The solution was concentrated and put in a refrigerator. The white crystals were filtered, washed with EtOAc, and dried: dec.p. 186−190 °C; ^{1}H NMR (DMSO-d_6) δ 9.05 (bs, 1H, OH), 7.68 (d, J = 1.7 Hz, 1H, ArH), 7.16 (dd, J = 8.2, 1.7 Hz, 1H, ArH), 6.94 (d, J = 8.2 Hz, 1H, ArH), 6.57 (s, 1H, ArH), 6.55 (s, 1H, ArH), 4.46 (m, 1H, CH), 3.27 (m, 1H, CH), 3.00−3.20 (m, 2H, CH), 2.80−3.00 (m, 2H, CH), 2.74 (dt, J = 16.8, 5.9 Hz, CH); ^{13}C NMR (CD_3OD) δ 147.00 and 145.76 (C-6 and C-7), 1412.68 (C-2′), 138.21 (C-4′), 136.27 (C-1′), 132.35 (C-6′), 123.82 and 123.10 (C-4a and C-8a), 116.27 (C-5), 114.33 (C-8), 124.24 (C-5′), 91.49 (C-3′), 57.27 (C-1), 40.90 (C-3), 39.87 (CH_2Ar), 25.659 (C-4); IR (KBr) 3600−2300 (br, OH, NH), 1607 (NH bend), 1526 (C=C Ar) cm^{-1}. Anal. ($C_{16}H_{17}IN_2O_2$·2HCl) C, H, N.

1-(4-Acetamido-3-iodobenzyl)-6,7-bis(benzyloxy)-2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline (25a). To a cold solution (0 °C) of isoquinoline **9b** (0.68 g, 1 mmol) and Et_3N (0.34 g, 3 mmol) in CH_2Cl_2 (10 mL) was added AcCl (0.16 g, 2 mmol). The cooling bath was removed, and the mixture was stirred overnight. The solution was washed with water (2×), dried over $MgSO_4$, filtered, and evaporated. Ether was added and evaporated again to give a glassy solid (0.65 g, 90%): mp 62−64 °C; ^{1}H NMR ($CDCl_3$) δ (the spectrum consists of two rotamers of 5:3 ratio) 8.12 and 8.06 (d, J = 8.2), 7.59−7.25 (m, 11H, ArH), 7.06 and 6.98 (m, 1H, ArH), 6.70 and 6.65 (s, 1H, ArH), 6.48 and 6.35 (s, 1H, ArH), 5.24−4.87 (m, 5H, CH_2O + CH), 4.12 and 3.73 (m, 1H, CH), 3.27−3.11 (m, 1H, CH), 2.98−2.60 (m, 3H, CH_2Ar + CH), 2.60−2.37 (m, 1H, CH), 2.22 (s, 3H, Ac), 1.43 and 1.31 (s, 9H, *t*-Bu); IR (KBr) 3389 (NH), 1688 (C=O), 1512 (C=C Ar) cm^{-1}. Anal. ($C_{37}H_{39}IN_2O_5$) C, H, N.

1-(4-(Benzoylamino)-3-iodobenzyl)-6,7-bis(benzyloxy)-2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline (25b). To a cold solution (0 °C) of isoquinoline **9b** (0.68 g, 1

mmol) and Et_3N (0.30 g, 3 mmol) in 10 mL of CH_2Cl_2 was added benzoyl chloride (0.28 g, 2 mmol). The cooling bath was removed, and the mixture was stirred overnight. CH_2Cl_2 was added (30 mL), the solution was washed with water, dried over $MgSO_4$, filtered, and evaporated till dryness. The oily residue was dissolved in ether and evaporated to give 0.60 g (76%) of a glassy solid. The compound was purified by column chromatography (silica gel, EtOAc−hexane 1:2): mp 151−153 °C; ^{1}H NMR ($CDCl_3$) δ 8.42−6.36 (m, 18H, Ar), 5.20−4.90 (m, 5H, 2 × CH_2O + H-1), 4.20−2.15 (m, 6H, aliphatic), 1.56−1.25 (m, 9H, *t*-Bu); IR (KBr) 3397 (NH), 1687 (C=O), 1513 (C=C Ar) cm^{-1}. Anal. ($C_{42}H_{41}IN_2O_5$) C, H, N.

1-(4-Acetamido-3-iodobenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydroiodide (26a·HI). To a solution of isoquinoline **25a** (0.40 g, 0.5 mmol) in anhydrous MeCN (5 mL) was added TMSI (0.40 g, 2 mmol) via a syringe in an argon atmosphere. The solution was stirred for 6 h followed by MeOH (1 mL) addition, and stirring was continued for 30 min. CH_2Cl_2 (30 mL) was added to the reaction mixture, and yellow crystals were filtered; yield 0.19 g (67%). The compound was dissolved in MeOH, AcOEt was added, and the solution was concentrated under reduced pressure. The crystals were filtered: dec.p. 172−174 °C; ^{1}H NMR (DMSO-d_6) δ 9.39 (s, 1H, NH), 8.86 (bs, 1H, OH), 8.50 (bs, 1H, OH), 7.90 (d, J = 1.7 Hz, 1H, ArH), 7.41 (d, J = 8.2 Hz, 1H, ArH), 7.35 (dd, J = 8.2, 1.7 Hz, 1H, ArH), 6.63 (s, 1H, ArH), 6.56 (s, 1H, ArH), 4.63 (m, 1H, CH), 3.43−2.70 (m, 6H, CH), 2.06 (s, 3H, Ac); ^{13}C NMR (CD_3OD) δ 172.65 (C=O), 146.98 and 145.81 (C-6 and C-7), 142.68 (C-2′), 140.11 (C-4′), 137.15 (C-1′), 131.30 (C-6′), 129.10 (C-5′), 123.63 and 123.27 (C-4a and C-8a), 116.27 (C-5), 114.15 (C-8), 91.49 (C-3′), 57.60 (C-1), 41.01 (C-3), 39.98 (CH_2Ar), 25.68 (C-4), 23.09 ($COCH_3$); IR (KBr) 3600−2400 (br, OH, NH), 1655 (C=O), 1624 (NH bend), 1522 (C=C Ar) cm^{-1}; MS *m*/*z* (M^+) 439. Anal. ($C_{18}H_{19}IN_2O_3$·HI·0.25EtOAc) C, H, N.

1-(4-(Benzoylamino)-3-iodobenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydroiodide (26b·HI). To a mixture of isoquinoline **25b** (0.16 g, 2 mmol) in MeCN (4 mL) was added TMSI (0.16 g, 0.8 mmol) under argon atmosphere, and the solution was stirred at room temperature for 7 h. MeOH (1 mL) was added and stirred for 1 h followed by ether (40 mL) addition, and the yellow precipitate was filtered to give 0.10 g (80%) of the product. The compound was dissolved in MeOH, and EtOAc was added and concentrated until the beginning of crystallization: mp 185−188 °C (dec); ^{1}H NMR (DMSO-d_6) δ 9.98 (s, 1H, N*H*COPh), 9.18 (s, 1H, NH), 8.88 (br, 2H, OH + NH), 8.54 (br, 1H, OH), 8.03−7.93 (m, 3H, ArH), 7.64−7.42 (m, 3H, ArH), 7.49 (d, J = 8.1 Hz, 1H, ArH), 7.41 (dd, J = 8.1, 1.4 Hz, 1H, ArH), 6.65 (s, 1H, ArH), 6.58 (s, 1H, ArH), 3.43−2.70 (m, 6H, CH); IR (KBr) 3500−2700 (br, NH, OH), 1649 (C=O), 1518 (C=C Ar) cm^{-1}. Anal. ($C_{23}H_{21}IN_2O_3$·HI·0.33EtOAc) C, H, N.

1-[3,5-Bis(trifluoromethyl)benzyl]-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (27·HCl). The title compound was obtained from **6c** in the same manner as **15** (85%). The product was converted to the hydrochloride salt, and recrystallization from methanol−ether gave the product as white crystals: mp 239−242 °C; ^{1}H NMR (CD_3OD-d_4) δ 7.95 (s, 3H, ArH), 6.65 (s, 1H, ArH), 6.44 (s, 1H, ArH), 4.77 (t, J = 7.7 Hz), 3.51 (dt, J = 6.88, 12.74 Hz), 3.33 (m, 2H, CH), 3.0 (m, 2H, CH); ^{13}C NMR (CD_3OD) δ 147.15 and 145.81 (C-6 and C-7), 140.21 (C-1′), 133.21 (C-3′ and C-5′), 131.61 (C-2′ and C-6′), 124.79 (CF_3), 123.79 and 122.63 (C-4a and C-8a), 122.58 (C-4′), 116.40 (C-5), 114.35 (C-8), 57.11 (C-1), 41.77 (C-3), 40.55 (CH_2Ar), 25.56 (C-4); IR (KBr) 3600−2400 (N^+H, OH), 1282 (C−O) cm^{-1}. Anal. ($C_{18}H_{16}ClF_6NO_2$) C, H, N.

Radioligand Binding Studies with β_1- and β_2-AR Expressed in CHO Cells. Competition binding experiments on β_1- and β_2-AR expressed in CHO cells were performed as described previously.[8] CHO cells expressing human β_1- and β_2-AR (provided by A. D. Strosberg, Institut Cochin de Genetique Moleculaire, Paris, France, and David Bylund, University of Nebraska, Omaha, NE, respectively) were cultured in Ham's F-12 medium supplemented with 10% fetal bovine serum, 50 units/mL−50 μg/mL penicillin−streptomycin, 2 mM L-glutamine, and 50 μg/mL Geneticin in a humidified atmosphere of 5% CO_2−95% air. CHO cells were grown to a confluence in 150-mL flasks and were detached into Ham's F-12 medium after treatment with 0.05% trypsin−0.53 mM EDTA solution. The cells were then pelleted and washed 3 times with Tris−EDTA buffer (50 mM Tris-HCl, 150 mM NaCl, 20 mM EDTA, pH 7.4) and resuspended in the same buffer. Competition binding experiments were performed in duplicate using these whole cells. Aliquots (150 μL) of cells were added to tubes containing 50 μL of [^{125}I]ICYP [(1.5−5) × 10^4 cells/20−60 pM ICYP] and varying concentrations of competing drugs. The final volume in each tube was 0.25 mL. Nonspecific binding (5−30%) was determined in the presence of 1 μM (±)-propranolol. Incubations were carried out for 60 min at 37 °C. Binding reactions were terminated by rapid filtration through Whatman GF/B glass fiber filters on a Brandel Model 12-R tissue harvester. Filters were washed twice with ice-cold Tris−EDTA buffer to remove free ICYP. The filters were dried under tissue harvester vacuum, and radioactivity was measured by gamma scintillation spectrometry (Beckman Model 8000 gamma counter; Palo Alto, CA). Specific binding to β-AR in these cells varied from 94 to 100%.

Thromboxane A_2/Prostaglandin H_2 (TP) Receptor Sites in Human Platelets. For binding experiments, human platelet-rich plasma (PRP) was centrifuged and resuspended in 50 mM Tris−saline buffer, pH 7.4.[9] Platelets were incubated with 5 nM [^{3}H]-SQ 29548 in a final volume of 0.5 mL as described by Hedberg et al.[21] Unlabeled SQ 29548 (50 μM) was used to determine nonspecific binding. Varying concentrations of each competing drug were used to quantify the inhibition of specific [^{3}H]-SQ 29548 binding. Samples were incubated 30 min at room temperature, and rapidly filtered by vacuum through Whatman GF/C glass fiber filters on a Brandel cell harvester and washed for 10 s with ice-cold Tris−saline buffer. Filters were placed in plastic scintillation vials containing 10 mL of an emulsion-type scintillation mixture, and radioactivity was measured by liquid scintillation spectrometry. Specific binding to human platelets varied between 88 and 95%.

Data Analysis. Competitive binding data were analyzed using the PC-version of the radioligand binding program LIGAND (McPherson, 1985). Inhibitory concentration-50 (IC_{50}) value of each competing drug was determined graphically from individual plots of percent radioligand bound versus log drug concentration on β-adrenoceptors and human platelets. Dissociation constants (K_i) for each competing drug were calculated using the equation: $K_i = IC_{50}/(1 + [L]/K_L)$ and the data expressed as pK_i (i.e., $-\log K_i$) values. The K_L values used in the above equation are 17 pM, 10 pM, and 3.1 nM for β_1-AR, β_2-AR, and TP receptors, respectively.

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