Synthesis, Biochemical Evaluation, and Classical and Three-Dimensional Quantitative Structure−Activity Relationship Studies of 7-Substituted-1,2,3,4-tetrahydroisoquinolines and Their Relative Affinities toward Phenylethanolamine *N*-Methyltransferase and the α_2-Adrenoceptor[†,1]

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7-Substituted-1,2,3,4-tetrahydroisoquinolines (7-substituted-THIQs) are potent inhibitors of phenylethanolamine *N*-methyltransferase (PNMT, EC 2.1.1.28), the enzyme involved in the biosynthesis of epinephrine. Unfortunately, most of these compounds also exhibit strong affinity for the α_2-adrenoceptor. To design a selective (PNMT vs α_2-adrenoceptor affinity) inhibitor of PNMT, the steric and electrostatic factors responsible for PNMT inhibitory activity and α_2-adrenoceptor affinity were investigated by evaluating a number of 7-substituted-THIQs. A classical quantitative structure−activity relationship (QSAR) study resulted in a three-parameter equation for PNMT (PNMT $pK_i = 0.599\pi - 0.0725MR + 1.55\sigma_m + 5.80$; $n = 27$, $r = 0.885$, $s = 0.573$) and a three-parameter equation for the α_2-adrenoceptor (α_2 $pK_i = 0.599\pi - 0.0542MR - 0.951\sigma_m + 6.45$; $n = 27$, $r = 0.917$, $s = 0.397$). These equations indicated that steric effects and lipophilicity play a similar role at either active site but that electronic effects play opposite roles at either active site. Two binding orientations for the THIQs were postulated such that lipophilic and hydrophilic 7-substituents would not occupy the same region of space at either binding site. Using these two binding orientations, based on the lipophilicity of the 7-substituent, comparative molecular field analysis (CoMFA) models were developed that showed that the steric and electrostatic interactions at both sites were similar to those previously elaborated in the QSAR analyses. Both the QSAR and the CoMFA analyses showed that the steric interactions are similar at the PNMT active site and at the α_2-adrenoceptor and that the electrostatic interactions were different at the two sites. This difference in electrostatic interactions might be responsible for the selectivity of THIQs bearing a nonlipophilic electron-withdrawing group at the 7-position. These QSAR and CoMFA results will be useful in the design of potent and selective (PNMT vs α_2-adrenoceptor affinity) inhibitors of PNMT.

Introduction

In the biosynthesis of epinephrine, phenylethanolamine *N*-methyltransferase (PNMT, EC 2.1.1.28) catalyzes the conversion of norepinephrine to epinephrine using *S*-adenosyl-L-methionine as the cofactor.[2] Epinephrine accounts for 5−10% of the total catecholamine content of the central nervous system (CNS),[3] and it has been proposed, based on the anatomical localization of epinephrine neurons in the CNS, to control vital functions such as blood pressure, respiration, and secretion of pituitary hormones.[4] Studies—using the desoxycorticosterone salt-type hypertension model in rats—with the PNMT inhibitor SK&F 64139 (**1**, 7,8-dichloro-1,2,3,4-tetrahydroisoquinoline) showed a decrease in blood pressure and heart rate.[5] However, no acute blood pressure changes were noted with the peripherally active PNMT inhibitor SK&F 29661 (**2**, 7-aminosulfonyl-1,2,3,4-tetrahydroisoquinoline),[5] implying the role of only central epinephrine in regulating baroreceptor reflex activity.[5,6] This observation provided an impetus to develop a potent PNMT inhibitor which can be utilized as a novel antihypertensive agent. Unfortunately, most of the well-studied PNMT inhibitors, such as **1**, exhibit strong affinity for the α_2-adrenoceptor.[7] Thus, a potent PNMT inhibitor, which exhibits minimal α_2-adrenoceptor affinity, would be an important pharmacological tool to delineate the role of epinephrine in the CNS.

The PNMT inhibitory activity and the α_2-adrenoceptor affinity of 1,2,3,4-tetrahydroisoquinolines (THIQs) are largely a function of the aromatic substitution. For example, SK&F 72223 (**3**, 5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline) possesses high affinity for the α_2-adrenoceptor but is virtually devoid of PNMT inhibitory activity,[8] while **2** is a potent PNMT inhibitor that possesses low α_2-adrenoceptor affinity.[8,9] Thus, depending on the aromatic substituent and the substitution pattern, the THIQ (**4**, 1,2,3,4-tetrahydroisoquinoline) nucleus can exhibit high PNMT inhibitory activity, high α_2-adrenoceptor affinity, or both.

Fuller et al.[10] have studied the effect of aromatic substituents on PNMT inhibition in a series of benzylamines. An excellent correlation of the PNMT inhibitory

† This paper is dedicated to the memory of Ray W. Fuller (deceased 1996), noted neuropharmacologist of Eli Lilly and one of the leading scientists in the initial studies on the importance of PNMT in the central nervous system. Ray was a strong supporter of our initial studies in this area, as well as a friend. He is deeply missed.

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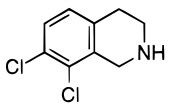

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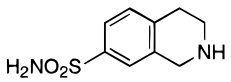

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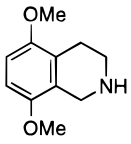

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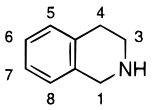


4

activity with the Hammett σ and the hydrophobic constant π was observed. Benzylamines bearing a meta-substituent were generally more potent than the corresponding ortho- or para-substituted benzylamines. In this quantitative structure−activity relationship (QSAR) study, only a narrow range of lipophilic substituents, such as chloro, bromo, iodo, fluoro, trifluoromethyl, and methyl, were used. The effect of the aromatic substituent on the pI_{50} indicated that lowering the pK_a increased the potency of benzylamines, and it was proposed that benzylamines bind to the active site of PNMT in the nonprotonated form.[10] Using quantum chemical indices derived from semiempirical molecular orbital calculations, Otto et al.[11] examined the same data set of benzylamines studied earlier by Fuller. This study indicated a good correlation between the PNMT inhibitory activity of benzylamines and the composite variable that accounts for the electrostatic interaction between the enzyme and the inhibitor. The pI_{50} values for nine new mono- and disubstituted-benzylamines were predicted with the derived QSAR equation. Subsequently, Lukovits[12] applied the method of principal component analysis to the QSAR of benzylamines using the quantum chemical indices derived by Otto. Results from Lukovits' analysis suggested that the PNMT inhibitory activity of benzylamines was dependent on charge-transfer phenomena, as well as on electrostatic forces. Studies by Mercier et al.[13] utilized molecular topology and molecular electronic structure-based QSAR methods to correlate a set of 22 of the benzylamines which had been previously evaluated by Fuller. Excellent correlations were obtained with these methods, and the PNMT inhibitory activity of putatively more active benzylamines was predicted using their QSAR equation.

THIQs contain a constrained benzylamine moiety, and such constraint has been shown to increase affinity for the PNMT active site.[14] We therefore decided to extend these studies on benzylamines with a series of carefully designed THIQ analogues.

For aromatic chloro-substituted THIQs, it was established by Kaiser et al.[15] that a chlorine at the 7-position is optimal as compared to the 5-, 6-, or 8-position and that the 7,8-dichloro substitution pattern (as in **1**) resulted in maximum inhibition of PNMT. The effect of THIQ with aromatic chloro substituents on PNMT inhibitory activity was quantified with the Fujita−Ban approach by Singh,[16] using data published by the SK&F group.[15] The QSAR analysis indicated a negative contribution from a chloro substituent at the 6-position on the THIQ nucleus. The 7-chloro substituent had the highest positive contribution to potency in comparison with chlorine atoms at the 5- or 8-position, which appear to contribute equally. A number of 7- and/or 8-sulfur-substituted THIQs were reported in the patent literature, but no detailed PNMT inhibitory or α_2-adrenoceptor affinities were reported.[17] A preliminary comparative molecular field analysis (CoMFA) study on PNMT-active ligands has been reported by our laboratory.[18] On the basis of an active site model for PNMT, 30 benzylamine-type PNMT inhibitors were aligned and subjected to the CoMFA technique. A reasonably predictive model was established by the statistics of the analysis. Several examples[19,20] have been reported in which a combined approach of traditional QSAR and CoMFA techniques has led to the development of a meaningful QSAR.

Based on these literature SAR results, it appeared that optimal potency and selectivity for the PNMT active site, as opposed to the α_2-adrenoceptor, is associated, at least in part, with the 7-substituent on the THIQ ring. Hence, an investigation of the dependence of PNMT inhibitory activity and α_2-adrenoceptor affinity on the 7-substituent on THIQ (**4**) was undertaken. Some 7-substituted-THIQs (such as **5**−**7**) had been previously evaluated,[21] and additional 7-substituents were chosen for the variation in their electronic and steric properties (**8**−**33**). Results from previous studies[21] indicated that the acidity of the aminosulfonyl group in **2** is not responsible for the observed selectivity for PNMT vs the α_2-adrenoceptor of this compound but that some other factor, possibly having to do with the presence of the sulfonyl group when attached to the aromatic ring, might be responsible. The possibility of the dependence of potency and selectivity on the sulfonyl moiety in the aminosulfonyl group[21] prompted the inclusion of **17**−**19** and **21**−**23**.

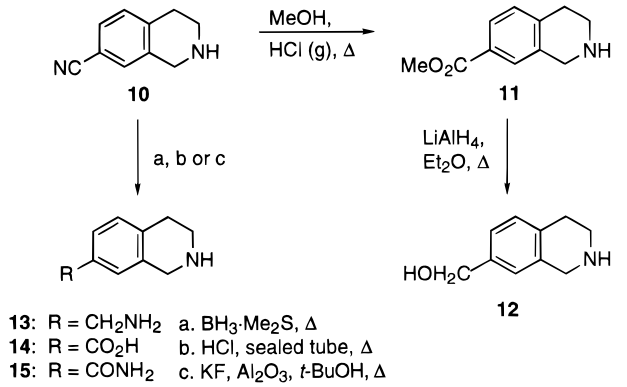
A classical regression analysis and a three-dimensional QSAR using the CoMFA technique were employed to sort out the differences in binding requirements for 7-substituted-THIQs at the PNMT active site and the α_2-adrenoceptor. The CoMFA technique can accommodate variation in the basic skeleton and is independent of steric, electronic, and hydrophobic parameters for substituents. Therefore, in contrast to a traditional QSAR, there are no restrictions in the choice of substituents in a CoMFA.[22] Such a study may lead to the identification and characterization of the steric and electronic factors on which biological activity and selectivity (PNMT vs α_2-adrenoceptor affinity) are based.

Chemistry

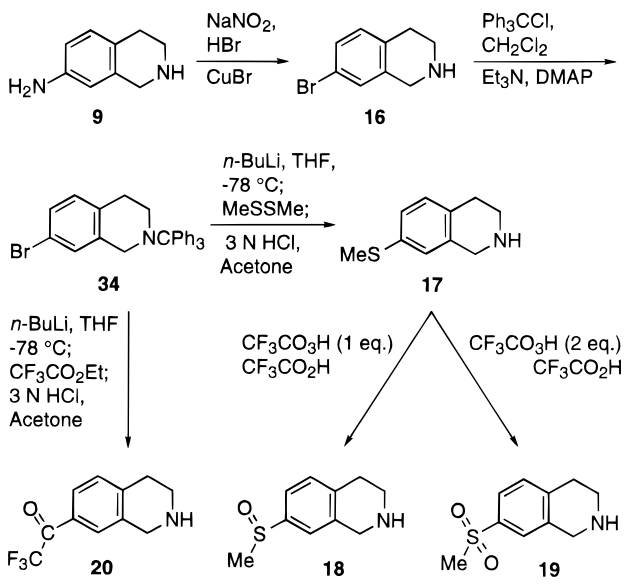
The chemistry used in the synthesis of 7-substituted-THIQs was developed with the aim of synthesizing most of the desired analogues from a key intermediate. Electrophilic substitution reactions on THIQ occur mostly at the 7-position. Nitration,[23,24] chlorosulfonation,[9,25] and Friedel−Crafts acetylation[26] are some of the known literature examples of electrophilic substitution reactions on THIQ. In acidic media, the protonated amine of THIQ directs the electrophile to the 5- or 7-position—meta with respect to the protonated benzylamine moiety.[27] More of the 7-substituted product is obtained, probably due to peri hydrogen interaction at the 5-position which disfavors electrophilic substitution at that position.

A key intermediate, 7-nitro-THIQ (**8**),[23] was obtained by nitration of **4** and was converted to another central

Scheme 1



Scheme 2

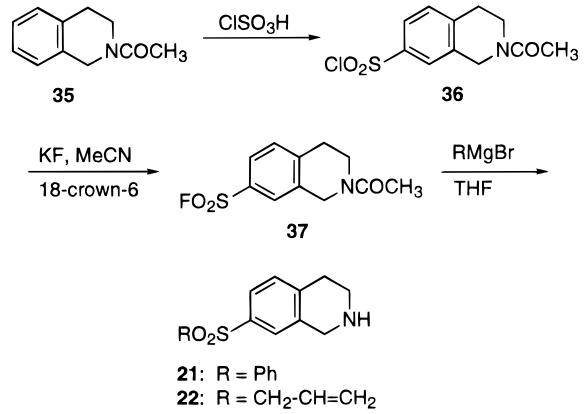


intermediate, 7-cyano-THIQ (**10**), by reduction followed by diazotization.[21] Nitrile **10** was readily converted to methoxycarbonyl **11**, hydroxymethyl **12**, aminomethyl **13**, carboxylic acid **14**, and carboxamide **15** (Scheme 1). The conversion of nitrile **10** to the carboxamide derivative **15** without protection of the THIQ nitrogen necessitated the use of potassium fluoride supported on alumina.[28]

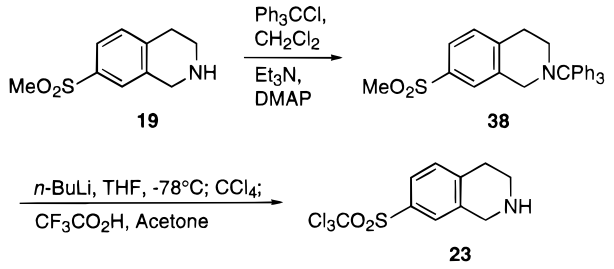
Halogen−metal exchange on 7-bromo-THIQ (**16**) provided an easy access to a variety of aromatic substituents which could not be prepared by direct electrophilic substitution. The Sandmeyer bromination reaction was used to synthesize **16** from the aromatic amine **9**. Because the Sandmeyer bromination is performed under acidic conditions, the secondary aliphatic amine in **9** does not require protection as it will be protonated and thus be unreactive.[29] Using a modified procedure for the Sandmeyer bromination of 7-amino-3,4-dihydroisoquinoline,[30] a 73% yield of **16** was obtained after Kugelrohr distillation (Scheme 2).

In the attempted halogen−metal exchange reaction on **16** to produce **17**, an additional equivalent of *n*-BuLi was used to remove the acidic hydrogen from the secondary amine and the resulting 7-lithiated species was trapped with methyl disulfide.[31] The N-butyl-7-thiomethyl-THIQ isolated after the workup resulted from the reaction of butyl bromide formed in the halogen−metal exchange reaction with the *N*-lithiated

Scheme 3



Scheme 4



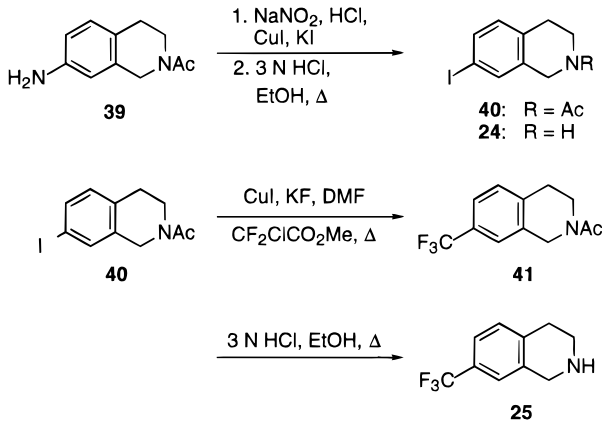
species. Synthesis of **17** from **16** required that the THIQ nitrogen be protected with a triphenylmethyl (trityl) group to yield **34**. Metalation of **34** followed by overnight treatment with methyl disulfide and then with 3 N HCl resulted in **17**. Oxidation of **17** to sulfoxide **18** and sulfone **19** was accomplished with trifluoroperacetic acid in trifluoroacetic acid.[32] Acidic conditions avoided N-oxidation of the secondary aliphatic amine to the *N*-oxide. Similarly, using a halogen−metal exchange reaction, followed by trapping the lithiated species with ethyl trifluoroacetate,[33] resulted in the formation of the trifluoroacetyl derivative **20**. This compound was characterized as its hydrochloride salt because the free base underwent rapid polymerization. The infrared spectrum and elemental analysis data of **20** indicated the presence of the hydrated form of the ketone.

The syntheses of other sulfones were based on the addition of a Grignard reagent to a sulfonyl fluoride.[34] Chlorosulfonation of *N*-acetyl-THIQ (**35**)[9] gave the 7-chlorosulfonyl derivative **36**[9] which was converted to fluorosulfonyl **37** under phase-transfer conditions[35] in the presence of potassium fluoride and 18-crown-6 ether (Scheme 3). Reaction of the fluorosulfonyl with an excess of the desired Grignard reagent gave the corresponding sulfone (**21** or **22**) with concomitant removal of the acetyl group.

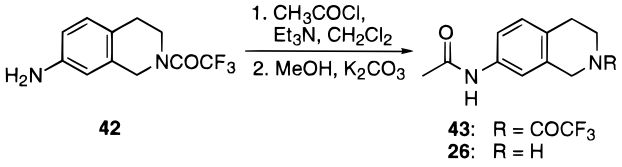
Trichloromethylsulfonyl-THIQ (**23**) was prepared from **38** (Scheme 4). Deprotonation of the acidic methanesulfonyl group with 1 equiv of *n*-BuLi resulted in a monoanion which was treated with an excess of carbon tetrachloride.[36] The resulting monochlorosulfone—being more acidic than the trichloromethyl anion—was deprotonated and chlorinated. This sequence was repeated until all the acidic hydrogen atoms were replaced by chlorine atoms.

7-Iodo-THIQ (**24**) was required to synthesize 7-trifluoromethyl-THIQ (**25**). Iodination of THIQ with I_2/Ag_2-

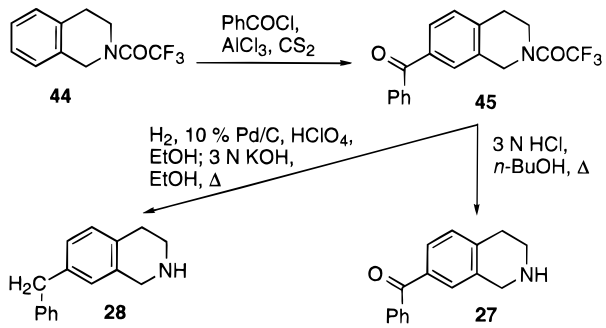
Scheme 5



Scheme 6



Scheme 7



SO_4/H_2SO_4 was reported to give mainly a mixture of 6- and 7-iodo-THIQ and a minor amount of 8-iodo-THIQ.[37] Diazotization of 7-amino-THIQ (**9**), followed by addition to aqueous KI, gave rise to multiple products and black tar. Use of biphasic conditions[38] to reduce tar formation failed to provide reasonable yields of **24**. Hence, 7-amino-*N*-acetyl-THIQ (**39**) was prepared in an analogous manner to the corresponding *N*-trifluoroacetyl derivative.[21] Diazotization and subsequent treatment with KI and a catalytic amount of CuI under biphasic conditions ($CHCl_3/H_2O$) gave **40** in 74% yield (Scheme 5). Trifluoromethylation of **40** was accomplished by a novel procedure[39] which used methyl chlorodifluoroacetate in the presence of CuI and KF as the trifluoromethylating reagent.

7-Acetamido-THIQ (**26**) was made in a straightforward manner from **42**, which was synthesized as described previously.[21] The greater hydrolytic susceptibility of the aliphatic trifluoroacetamide as compared to the aromatic acetamide led to the formation of **26** on treatment of **43** with K_2CO_3 in MeOH (Scheme 6).

The synthesis of 7-benzoyl-THIQ (**27**) (Scheme 7) was based on the literature precedence of Friedel–Crafts acetylation of *N*-trifluoroacetyl-THIQ (**44**) to afford a single regioisomer, 7-acetyl-THIQ (**29**).[26] A complex is probably formed between $AlCl_3$ and the trifluoroacetyl group which directs the acylation at the 7-position. Benzoylation under identical conditions provided a single regioisomer (**45**), the regiochemistry of which was confirmed by a one-dimensional difference nuclear Overhauser effect (NOE) experiment. Compound **45** was deprotected under acidic conditions to obtain benzoyl derivative **27**, and **45** was also hydrogenated at 50 psi under acidic conditions, followed by the removal of the trifluoroacetyl group, to afford benzyl derivative **28**.

Three additional derivatives—7-acetyl-THIQ[26] (**29**), 7-methyl-THIQ[40] (**30**), and 7-*N*-(*p*-chlorophenyl)-7-aminosulfonyl-THIQ[41] (**31**)—were prepared according to literature procedures. 7-Hydroxy-THIQ (**32**) and 7-methoxy-THIQ (**33**) were available from an earlier study conducted in our laboratory.[42]

Biochemistry

All compounds were evaluated as their hydrochloride or oxalate salts for their activity as PNMT inhibitors. Bovine adrenal PNMT,[43] which had been purified according to the method of Connett and Kirshner through the isoelectric precipitation step,[44] was used. In vitro activity was assessed by use of a standard radiochemical assay that has been previously described.[45] Inhibition constants in this investigation were determined by using three different concentrations of the inhibitor with phenylethanolamine as the substrate.

α_2-Adrenoceptor binding assays were performed using cortex obtained from male Sprague–Dawley rats.[46] [^{3}H]-Clonidine was used as the radioligand to define the specific binding and phentolamine was used to define the nonspecific binding. Clonidine was used as the ligand to define α-adrenergic binding affinity to simplify the comparison with previous results.

Results and Discussion

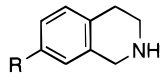
The results of in vitro biochemical evaluation of the compounds in this study are presented in Table 1. For comparison purposes, those THIQ derivatives which had been reported earlier[21,42] are also included. All THIQs competitively inhibited the binding of the substrate (phenylethanolamine), which was indicative of binding at the PNMT active site. For an inhibitor to be highly selective, it should have high PNMT inhibitory affinity but low α_2-adrenoceptor affinity.

A. Qualitative Considerations. Examination of Tables 1 and 2 revealed the following trends in SAR in 7-substituted-THIQs:

(1) There is no obvious correlation between substituent lipophilicity and PNMT affinity (compare **24** and **2**). However, as the electron-withdrawing ability of the substituent increased, the PNMT potency also increased. This was evident from the trifluoromethyl analogue **25** which was about 15-fold more active than the methyl analogue **30**, and this trend is further supported by other examples in the table (e.g., **27** as compared to **28**).

(2) A precipitous drop in the PNMT inhibitory activity of the aminomethyl derivative **13** as compared to the hydroxymethyl analogue **12** is noted. This molecule actually contains two benzylamine moieties: the conformationally restricted benzylamine of the THIQ nucleus and the conformationally flexible benzylamine comprising the 7-aminomethyl substituent. Thus, it is not clear how this molecule would bind at the active site of

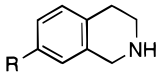
Table 1. In Vitro Activities of 7-Substituted-1,2,3,4-tetrahydroisoquinolines as Inhibitors of PNMT and Binding of [^{3}H]Clonidine at the α_2-Adrenoceptor



compd	R	(A) PNMT K_i ± SEM (μM)	(B) α_2 K_i ± SEM (μM)	B/A selectivity
2	SO_2NH_2	0.55 ± 0.04[a]	100 ± 20[a]	180
4	H	9.7 ± 0.4[b]	0.35 ± 0.11[b]	0.036
5	$NHSO_2Me$[a]	48 ± 2[a]	11 ± 0.1[a]	0.23
6	$N(SO_2Me)_2$[a]	~4500[a]	190 ± 10[a]	0.042
7	CH_2NHSO_2Me[a]	330 ± 10[a]	18 ± 1[a]	0.055
8	NO_2[c]	0.41 ± 0.05	4.3 ± 0.3	10
9	NH_2[c]	27 ± 3	3.1 ± 0.1	0.11
10	CN	1.4 ± 0.1	7.3 ± 0.2	5.2
11	CO_2Me	6.7 ± 0.3	4.6 ± 0.2	0.68
12	CH_2OH	11 ± 1	2.3 ± 0.3	0.21
13	$CH_2NH_3^+$[d]	1900 ± 100	12 ± 1	0.0063
14	CO_2^-[d]	470 ± 30	470 ± 10	1.0
15	$CONH_2$	64 ± 3	23 ± 1	0.36
16	Br	0.29 ± 0.03	0.23 ± 0.13	0.79
17	SMe	0.61 ± 0.05	0.41 ± 0.05	0.67
18	SOMe	45 ± 2	51 ± 1	1.1
19	SO_2Me	1.3 ± 0.1	160 ± 10	120
20	$COCF_3$	5.7 ± 0.3	32 ± 1	5.6
21	SO_2Ph	14 ± 1	21 ± 1	1.5
22	$SO_2CH_2CH{=}CH_2$	9.8 ± 1.0	95 ± 2	9.7
23	SO_2CCl_3	1.3 ± 0.1	34 ± 1	26
24	I	0.37 ± 0.04	0.22 ± 0.04	0.59
25	CF_3	0.18 ± 0.03	1.3 ± 0.1	7.2
26	NHCOMe	190 ± 10	9.1 ± 0.3	0.48
27	COPh	2.9 ± 0.1	27 ± 2	9.3
28	CH_2Ph	61 ± 3	4.7 ± 0.4	0.077
29	COMe[e]	4.9 ± 0.2	6.1 ± 0.2	1.2
30	Me[f]	2.7 ± 0.1	0.36 ± 0.06	0.13
31	SO_2NH-C_6H_4-p-Cl[g]	2.6 ± 0.2	6.3 ± 0.5	2.4
32	OH[h]	2.6 ± 0.1[h]	2.2 ± 0.2	0.85
33	OMe[h]	21 ± 2[h]	0.47 ± 0.04	0.022

[a] Reference 21. [b] Reference 47. [c] Reference 23. [d] The moiety is ionized at the pH of the assay [pH = 8.0 (PNMT) or 7.7 (α_2)]. [e] Reference 26. [f] Reference 40. [g] Reference 41. [h] Reference 42.

Table 2. Parameters for 7-Substituted-THIQs Used in the QSAR Study



compd	R	PNMT pK_i	α_2 pK_i	π	σ_m	MR
2	SO_2NH_2	6.26	4.00	−1.82	0.53	12.28
4	H	5.01	6.45	0.00	0.00	1.03
5	$NHSO_2Me$	4.32	4.96	−1.18	0.20	18.17
6	$N(SO_2Me)_2$	2.35	3.72	−1.51	0.47	31.20
7	CH_2NHSO_2Me	3.48	4.74	−1.23[a]	−0.10[a]	22.60[a]
8	NO_2	6.38	5.37	−0.28	0.71	7.36
9	NH_2	4.57	5.51	−1.23	−0.16	5.42
10	CN	5.87	5.14	−0.57	0.56	6.33
11	CO_2Me	5.17	5.34	−0.01	0.36	12.87
12	CH_2OH	4.97	5.64	−1.03	0.00	7.19
13	$CH_2NH_3^+$	2.72	4.92	−4.09	0.32	10.10[a]
14	CO_2^-	3.33	3.33	−4.36	−0.10	6.05
15	$CONH_2$	4.19	4.64	−1.49	0.28	9.81
16	Br	6.53	6.64	0.86	0.39	8.88
17	SMe	6.21	6.39	0.61	0.15	13.82
18	SOMe	4.35	4.29	−1.58	0.52	13.70
19	SO_2Me	5.87	3.79	−1.63	0.60	13.49
20	$COCF_3$	5.24	4.49	0.02	0.63	11.20
21	SO_2Ph	4.85	4.67	0.27	0.62	33.2
24	I	6.43	6.66	1.12	0.35	13.94
25	CF_3	6.74	5.89	0.88	0.43	5.02
26	NHCOMe	3.73	5.04	−0.97	0.21	14.93
27	COPh	5.54	4.57	1.05	0.34	30.33
28	CH_2Ph	4.21	5.33	2.01	−0.08	30.01
29	$COCH_3$	5.31	5.21	−0.55	0.38	11.18
30	CH_3	5.57	6.44	0.56	−0.07	5.65
32	OH	5.58	5.65	−0.67	0.12	2.85
33	OMe	4.70	6.33	−0.02	0.12	7.87

[a] Values obtained from the Pomona College Medicinal Chemistry database.

PNMT. On the other hand, the binding requirements at the α_2-adrenoceptor seemed to be less restrictive than those at the PNMT active site, since **12** and **13** have comparable α_2-adrenoceptor affinities.

(3) The affinity toward the α_2-adrenoceptor increased as the lipophilicity of the 7-substituent increased. Thus, 7-halo-substituted-THIQs **16** and **24** had high affinity toward the α_2-adrenoceptor. A 13-fold loss of affinity of the benzyl analogue **28** with respect to the methyl analogue **30** suggested the presence of a region of limited steric bulk tolerance around the 7-position of lipophilic THIQs at the α_2-adrenoceptor. Introduction of electron-withdrawing substituents such as NO_2, CN, and CF_3 resulted in lowered affinity toward the α_2-adrenoceptor and therefore increased selectivity toward PNMT vs the α_2-adrenoceptor.

(4) Enhancement of the electron-withdrawing capability of the 7-sulfur substituent on THIQ diminished the affinity toward the α_2-adrenoceptor. Changing the oxidation state of the thiomethyl group in **17** to the methyl sulfoxide **18** led to a 125-fold loss in binding affinity. Because compound **18** was tested as a racemate, the stereoselectivity in binding of the methylsulfinyl group in **18** was not probed. The sulfonyl group in the aminosulfonyl moiety of **2** seemed to be responsible for its lowered affinity toward the α_2-adrenoceptor.[21] In contrast to the methylsulfonyl **19**, the increased selectivity of **2** was the consequence of its higher potency at PNMT. It was interesting to note that the α_2-adrenoceptor affinity of **19** was lower than that of **2**. This might be a reflection of the better electron-withdrawing capability of the methylsulfonyl group in comparison with the aminosulfonyl group (see Table 2 for σ_m values). The good selectivity (PNMT vs the α_2-adrenoceptor) of **19** prompted us to synthesize and evaluate more THIQ 7-sulfones. Changing the substituent from methyl to phenyl, allyl, or trichloromethyl, as in **21**, **22**, or **23**, resulted in a drop in selectivity. For phenylsulfonyl **21**, the PNMT K_i increased and the α_2-adrenoceptor K_i decreased. In the case of allylsulfonyl **22**, the low selectivity resulted from a reduction in PNMT inhibitory potency. The PNMT inhibitory activity of **19** was retained by trichloromethylsulfonyl **23**, but the α_2-adrenoceptor affinity increased by about 5-fold. Anilinosulfonyl **31** was reported to be as potent as **2** in inhibiting PNMT, but no α_2-adrenoceptor affinity was reported.[41] In our assays, **31** proved to be 5-fold less potent at PNMT and had enhanced α_2-adrenoceptor affinity as compared to **2**.

B. Development of an Active Site Binding Model. A binding model for 7-substituted-THIQs at the PNMT active site and the α_2-adrenoceptor was developed based on the SAR data discussed above and on previous SAR studies on benzylamines.[18,48] As both lipophilic and hydrophilic substituents are acceptable at both the PNMT and the α_2-adrenoceptor binding sites, it is unlikely that they bind in the same orientation. If the aromatic ring and the lone pair on the nitrogen form the essential interacting points of the THIQ pharmacophore at the two binding sites, then the THIQ nucleus

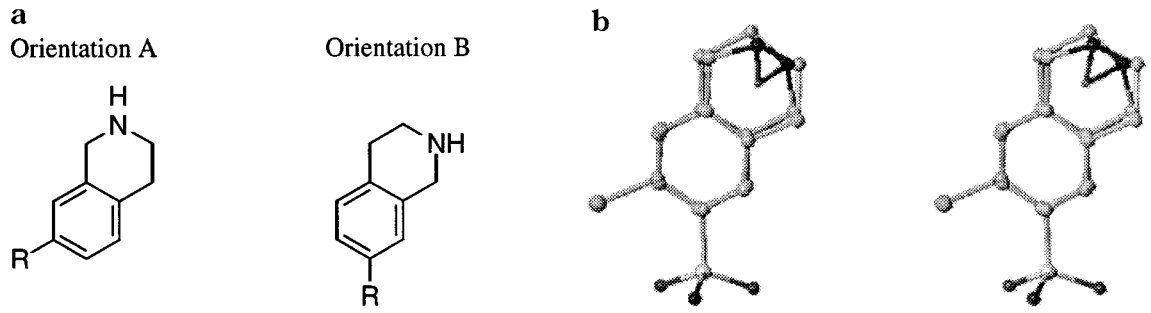


Figure 1. (a) Two possible orientations of 7-substituted-THIQs in which optimal interaction of the aromatic ring and lone pair on the nitrogen can occur. Orientation A is proposed for lipophilic ($+\pi$) substituents, while hydrophilic ($-\pi$) substituents are proposed to bind in orientation B. (b) SYBYL-generated stereoview of 7-bromo-THIQ (**16**) in orientation A, superimposed on **2** in orientation B, showing that the THIQ ring nitrogen lone pairs can reach the same area. Lipophilic and hydrophilic substituents occupy different regions of space when fitted according to this hypothesis. The optimized geometries (Tripos force field) of **2** and **16** were fitted using three points: both ends of a normal (2 Å long) passing through the centroid of the THIQ aromatic ring and the end of the axial lone pair (2.4 Å long) on the THIQ nitrogen. Hydrogens were omitted for clarity.

Table 3. One-, Two-, and Three-Parameter Equations for the QSAR of PNMT (Eq 1)

equations[a]	r	s	F_{calc}	F_{tab}
one parameter			$F_{(1,26)}$	$F_{(1,26,0.01)}$
$0.480(\pm0.266)\pi + 5.27(\pm0.41)$[b]	0.589	0.957	13.78	7.72
$-0.0444(\pm0.0499)$MR $+ 5.56(\pm0.78)$	0.337	1.11	3.34	7.72
$1.54(\pm1.71)\sigma_m + 4.55(\pm0.64)$	0.341	1.11	3.41	7.72
two parameter			$F_{(2,25)}$	$F_{(2,25,0.01)}$
$0.567(\pm0.224)\pi - 0.0643(\pm0.0362)$MR $+ 6.16(\pm0.60)$	0.758	0.787	16.87	5.57
$0.466(\pm0.251)\pi + 1.40(\pm1.39)\sigma_m + 4.87(\pm0.55)$	0.665	0.901	9.93	5.57
$1.84(\pm1.60)\sigma_m - 0.0.534(\pm0.0468)$MR $+ 5.17(\pm0.80)$	0.526	1.03	4.77	5.57
three parameter			$F_{(3,24)}$	$F_{(3,24,0.01)}$
$0.561(\pm0.183)\pi - 0.0729(\pm0.0300)$MR $+ 1.79(\pm1.01)\sigma_m + 5.77(\pm0.54)$	0.853	0.642	21.43	4.72

[a] $n = 28$. [b] Numbers in parentheses are 95% confidence intervals.

can be oriented in two possible ways as shown in Figure 1. This model would allow the binding of both lipophilic and hydrophilic substituents in different regions of space at either active site, and as shown in Figure 1b, the axial lone pairs from the THIQ nitrogen in either orientation could reach a common region of space. [See Development of the CoMFA Models (in section D) below.]

The qualitative examination of data presented on the α_2-adrenoceptor affinity of 7-substituted-THIQs, as well as limited SAR studies on THIQ-type PNMT inhibitors, has indicated that an identical binding model may hold true for these ligands at the α_2-adrenoceptor. As shown in the sections below, such a simplistic unified model can be used to explain the literature QSAR results and can provide a guideline for the alignment of these molecules for a CoMFA study.

C. Development of the QSAR Equations. A classical Hansch multivariate regression analysis was used to derive QSAR equations for our data set. The following substituents from Table 1 were not included in the Hansch analysis as their physicochemical parameters were unavailable: $SO_2CH_2CH{=}CH_2$ (**22**), SO_2CCl_3 (**23**), and $SO_2NH{-}C_6H_4$-*p*-Cl (**31**). Parameter values for compound **20** ($COCF_3$) were included in both analyses, although the experimental evidence indicated the presence of the hydrated form of the ketone. Under the assay conditions (phosphate buffer at pH 8 or Tris buffer at pH 7.7), the carboxylic acid **14** is expected to be ionized and the amine of **13** protonated. Thus, the parameters for the ionized states of those groups were used in the QSAR analyses.[49] Methyl ester **11** was determined to be stable under the assay conditions by NMR analysis (see Experimental Section). All of the compounds listed in Table 2 were used in the initial regression analysis with a number of QSAR parameters.[50a] Regression analyses and statistical calculations were done using the computer program QSAR-PC.[50b] Table 2 lists the PNMT pK_i [experimental ($-\log K_i$) value for PNMT inhibition] and the α_2 pK_i [experimental ($-\log K_i$) for the α_2-adrenoceptor affinity] values along with the substituent parameters[51] for the 7-substituted-THIQs used in the development of eqs 1 and 3.

QSAR of PNMT Ligands. Of the nine variables surveyed,[50a] the most significant single-variable equations for hydrophobic, steric, or electronic effects were those involving π, MR, or σ_m, respectively. As shown in Table 3, the most significant single-variable equation contained the π term. Stepwise analysis showed that the best (statistically significant) two-parameter equation was obtained with π and MR (F-test for the difference between equations: $F_{(1,25)} = 13.45$ vs $F_{(1,25,0.01)} = 7.77$) and the best three-parameter equation with π, MR, and σ_m ($F_{(1,24)} = 13.57$ vs $F_{(1,24,0.01)} = 7.82$), with the statistical significance after addition of a new parameter assessed by the F-test at the 99% confidence level. Thus, eq 1 was derived:

$$pK_i = 0.561(\pm0.183)\pi - 0.0729(\pm0.0300)\text{MR} + 1.79(\pm1.01)\sigma_m + 5.77(\pm0.54) \quad (1)$$

$$n = 28,\ r = 0.853,\ s = 0.642,\ F_{(3,24)} = 21.43,\ F_{(3,24,0.01)} = 4.72$$

In Table 3, all single-parameter (π, MR, and σ_m) and all combinations of two-parameter equations used in the development of the three-parameter equation (eq 1) are provided.

Table 4. Correlation Matrix for the Parameters of the 28 Compounds Used in Developing QSAR Eqs 1 and 3

PNMT	π	σ_m	MR
π	1		
σ_m	0.038	1	
MR	0.217	0.177	1

A correlation matrix (Table 4) showed that no strong correlations exist between the parameters. While π is orthogonal with respect to σ_m, some correlation between π and MR for the substituents chosen was observed. Most of the bulk parameters (including MR) show some correlation with hydrophobicity.[52] Analysis of the calculated pK_i values indicated that aminosulfonyl **2** had a residual greater than 2 standard deviations (residual = 1.45). Thus, **2** was dropped from the regression, and eq 2 was derived:

$$pK_i = 0.599(\pm0.167)\pi - 0.0725(\pm0.0268)MR + 1.55(\pm0.917)\sigma_m + 5.80(\pm0.48) \quad (2)$$

$$n = 27,\ r = 0.885,\ s = 0.573,\ F_{(3,23)} = 27.61,\ F_{(3,23,0.01)} = 4.76$$

In Table 5, all single-parameter (π, MR, and σ_m) and all combinations of two-parameter equations, along with the three-parameter equation (eq 2), are provided.[53a] The stepwise development of eq 2 showed that the best two-parameter equation contained π and MR (*F*-test for the difference between equations: $F_{(1,24)} = 17.69$ vs $F_{(1,24,0.01)} = 7.82$) and the best three-parameter equation contained π, MR, and σ_m ($F_{(1,23)} = 12.26$ vs $F_{(1,23,0.01)} = 7.88$). Values of PNMT pK_i were calculated according to eq 2, and the residuals are presented in Table 6.

Equation 2 was in general agreement with the hydrophobic and electronic effects inferred from qualitative considerations and accounted for about 75% of the variance in the data. It is surprising that the equation underpredicted the more active aminosulfonyl (**2**) and methylsulfonyl (**19**) compounds, although the latter was predicted within 2 standard deviations. However, previous studies[21] had indicated that there was some type of interaction that might be responsible for the enhanced potency of these compounds.

Equation 2 was quite similar to that obtained by Fuller et al.[10] for meta-substituted benzylamines in terms of the positive contributions of π and σ to PNMT inhibitory activity. The large positive coefficient associated with σ_m indicates that electron withdrawal by the substituent leads to a favorable interaction, probably via formation of a charge-transfer complex as suggested by Lukovits,[12] between an electron-rich region at the PNMT active site and the electron-deficient benzene ring in THIQ. A negative correlation with MR suggests that steric hindrance was experienced by the 7-substituent in binding at the PNMT active site or that repulsive van der Waals forces dominate[52] in the region around the 7-substituent at the PNMT active site.

QSAR of the α_2-Adrenoceptor Ligands. An approach identical to that used in the development of the QSAR for PNMT inhibitors was applied to the development of a QSAR for the same ligands at the α_2-adrenoceptor. However, among π, MR, and σ_m, only π and MR were significant in the initial equation (Table 7):

$$\alpha_2\ pK_i = 0.482(\pm0.154)\pi - 0.0573(\pm0.0248)MR + 6.22(\pm0.41) \quad (3)$$

$$n = 28,\ r = 0.826,\ s = 0.539,\ F_{(2,25)} = 26.77,\ F_{(2,25,0.01)} = 5.57$$

In Table 7, all single-parameter (π, MR, and σ_m) and all combinations of two-parameter equations, along with the equation containing all three parameters, are provided. The single-parameter equation in π was found to be most significant, explaining 39% of the variance in the data. The stepwise development of eq 3 showed that only the two-parameter equation derived by the addition of the MR parameter was statistically justified (*F*-test for the difference between equations: $F_{(1,25)} = 22.69$ vs $F_{(1,25,0.01)} = 7.77$), and it was surprising to note that σ_m was not statistically significant in eq 3.

The residual for the aminomethyl compound **13** was greater than 2 standard deviations (residual = 1.24). Thus, **13** was dropped from the regression, and eq 4 was derived:

$$\alpha_2\ pK_i = 0.599(\pm0.129)\pi - 0.0542(\pm0.0186)MR - 0.951(\pm0.623)\sigma_m + 6.45(\pm0.34) \quad (4)$$

$$n = 27,\ r = 0.917,\ s = 0.397,\ F_{(3,23)} = 40.53,\ F_{(3,23,0.01)} = 4.76$$

In Table 8, all single-parameter (π, MR, and σ_m) and all combinations of two-parameter equations, along with the three-parameter equation (eq 4), are provided.[53b] The hydrophobic constant (π) was the most important, as its single-parameter equation explained 47% of the variance in the data. The stepwise development of eq 4 showed that the best two-parameter equation contained π and MR (*F*-test for the difference between equations: $F_{(1,24)} = 31.85$ vs $F_{(1,24,0.01)} = 7.82$) and the best three-parameter equation contained π, MR, and σ_m ($F_{(1,23)} = 9.93$ vs $F_{(1,23,0.01)} = 7.88$). It is interesting to note that with the removal of compound **13** from the regression, σ_m became a statistically significant term in the new equation. The α_2-adrenoceptor pK_i values were calculated according to eq 4, and the residuals are presented in Table 6.

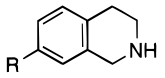
Comparison of QSAR Equations. The QSAR equations of PNMT (eq 2) and the α_2-adrenoceptor (eq 4) for 7-substituted-THIQs differed mainly in terms of the sign of the coefficient of the electronic parameter σ_m (+1.55 for PNMT vs −0.951 for the α_2-adrenoceptor). The coefficient of π in both eqs 2 and 4 (0.599 vs 0.599) was the same and suggested that hydrophobic interactions play a similar role in increasing affinity at both sites. The coefficient of MR in the α_2-adrenoceptor equation (0.0542, eq 4) was less than that in the PNMT equation (0.0725), which would indicate a somewhat greater amount of steric bulk tolerance at the α_2-adrenoceptor site. The opposite signs on the coefficients of σ_m (+1.55 for PNMT, −0.951 for α_2) indicate the principal difference between the binding requirements at the PNMT active site and at the α_2-adrenoceptor. Thus, THIQs which are more selective for PNMT vs the α_2-adrenoceptor would require a 7-substituent with a large positive σ_m value, of which aminosulfonyl **2** is one such

Table 5. One-, Two-, and Three-Parameter Equations for the QSAR of PNMT (Eq 2)

equations[a]	r	s	F_{calc}	F_{tab}
one parameter			$F_{(1,25)}$	$F_{(1,25,0.01)}$
$0.524(\pm0.253)\pi + 5.23(\pm0.38)$[b]	0.649	0.897	18.19	7.77
$-0.0439(\pm0.0497)$MR $+ 5.51(\pm0.79)$	0.342	1.11	3.31	7.77
$1.40(\pm1.76)\sigma_m + 4.56(\pm0.65)$	0.312	1.12	2.70	7.77
two parameter			$F_{(2,24)}$	$F_{(2,24,0.01)}$
$0.613(\pm0.201)\pi - 0.0652(\pm0.0320)$MR $+ 6.13\ (\pm0.53)$	0.817	0.694	24.01	5.61
$0.506(\pm0.244)\pi + 1.16(\pm1.36)\sigma_m + 4.91(\pm0.53)$	0.698	0.861	11.40	5.61
$1.72(\pm1.65)\sigma_m - 0.0525(\pm0.0473)$MR $+ 5.16(\pm0.81)$	0.509	1.03	4.21	5.61
three parameter			$F_{(3,23)}$	$F_{(3,23,0.01)}$
$0.599(\pm0.167)\pi - 0.0725(\pm0.0268)$MR $+ 1.55(\pm0.917)\sigma_m + 5.80(\pm0.48)$	0.885	0.573	27.61	4.76

[a] $n = 27$. [b] Numbers in parentheses are 95% confidence intervals.

Table 6. Experimental and Calculated PNMT pK_i (Eq 2) and α_2 pK_i (Eq 4) Values of 7-Substituted-THIQs



		PNMT pK_i			α_2 pKi		
compd	R	exptl	calcd	ΔpK_i	exptl	calcd	ΔpK_i
2	SO_2NH_2	6.26	4.64[a]	1.62	4.00	4.19	−0.19
4	H	5.01	5.73	−0.72	6.45	6.40	0.05
5	$NHSO_2Me$	4.32	4.09	0.23	4.96	4.57	0.39
6	$N(SO_2Me)_2$	2.35	3.36	−1.01	3.72	3.41	0.31
7	CH_2NHSO_2Me	3.48	3.27	0.21	4.74	4.59	0.15
8	NO_2	6.38	6.20	0.18	5.37	5.21	0.16
9	NH_2	4.57	4.42	0.15	5.51	5.58	−0.07
10	CN	5.87	5.87	0.00	5.14	5.24	−0.10
11	CO_2Me	5.17	5.42	−0.25	5.34	5.41	−0.07
12	CH_2OH	4.97	4.66	0.31	5.64	5.45	0.19
13	$CH_2NH_3^+$	2.72	3.12	−0.40	4.92	3.15[a]	1.77
14	CO_2^-	3.33	2.60	0.73	3.33	3.61	−0.28
15	$CONH_2$	4.19	4.63	−0.44	4.64	4.76	−0.12
16	Br	6.53	6.28	0.25	6.64	6.12	0.52
17	SMe	6.21	5.40	0.81	6.39	5.93	0.46
18	SOMe	4.35	4.67	−0.32	4.29	4.27	0.02
19	SO_2Me	5.87	4.78	1.09	3.79	4.18	−0.39
20	$COCF_3$	5.24	5.98	−0.74	4.49	5.26	−0.77
21	SO_2Ph	4.85	4.52	0.33	4.67	4.23	0.44
24	I	6.43	6.01	0.42	6.66	6.04	0.62
25	CF_3	6.74	6.63	0.11	5.89	6.30	−0.41
26	NHCOMe	3.73	4.47	−0.74	5.04	4.87	0.17
27	COPh	5.54	4.76	0.78	4.57	5.12	−0.55
28	CH_2Ph	4.21	4.71	−0.50	5.33	6.11	−0.78
29	COMe	5.31	5.25	0.06	5.21	5.16	0.05
30	Me	5.57	5.62	−0.05	6.44	6.55	−0.11
32	OH	5.58	5.38	0.20	5.65	5.79	−0.14
33	OMe	4.70	5.40	−0.70	6.33	5.90	0.43

[a] Compounds not included in the regression.

example.[54] Increasing selectivity by manipulating π or MR would have much less impact, given the similarity of lipophilic effects in both QSAR equations and the increased steric bulk tolerance at the α_2-adrenoceptor.

D. Comparative Molecular Field Analysis (CoMFA). CoMFA[22] is a molecular modeling based three-dimensional QSAR technique that can calculate noncovalent molecular (steric and electronic) interactions around a set of aligned ligands and correlate variations in these interactions with observed properties.

Development of the CoMFA Models. Geometry optimization and charge calculations for all of the compounds used in the development of these CoMFA models were done as detailed in the Experimental Section.

The alignment of ligands is extremely important in a CoMFA. In the absence of an alignment rule (i.e., when all 7-substituted-THIQs were aligned in the same fashion, with the THIQ nucleus superimposed and all 7-substituents in the same region of space), significantly lower cross-validated r^2 values were obtained for either the PNMT or the α_2-adrenoceptor models than when the molecules were aligned in orientations A or B, as described in the legend for Figure 1a. The orientations of the 30 compounds used in the PNMT and the α_2-adrenoceptor CoMFA are listed in Table 9. Individual consideration of either steric or electrostatic fields in either the PNMT or α_2 CoMFA resulted in almost 50% lower cross-validated r^2 values as compared to the analyses when both steric and electrostatic fields were used.

As sulfoxide **18** was synthesized and evaluated as a racemate, it was excluded from the data set to avoid any ambiguities in the input of data and the interpretation of the model. As was mentioned previously, experimental data indicated the presence of the hydrated form of the ketone of trifluoroacetyl analogue **20**, and so this structure was used in the CoMFA.

CoMFA of 7-Substituted-THIQs for PNMT. As was done in the PNMT QSAR (eq 1), **13** and **14** (charged forms) were included in the analysis; however, this resulted in a negative cross-validated r^2 for the CoMFA. Surprisingly, when the neutral forms of analogues **13** and **14** were used in the analysis, the cross-validated r^2 improved to 0.477. As analogue **13** contains two benzylamine moieties, either of which could theoretically bind at the active site, a check was made with the compound "flipped" (Figure 2) so that the 7-position benzylamine was in the area of space occupied by the THIQ nitrogen. While this only improved the cross-validated r^2 slightly to 0.546, the nonvalidated r^2 was improved from 0.851 to 0.904 (Table 10) with three components, with an increase in the F-test value from 49.64 to 81.84. Thus, the flipped orientation of analogue **13** was used in the development of the PNMT models.[55] The residuals of the nonvalidated analysis are presented in Table 9, and all activity predictions were within the 95% confidence interval. In this model, the relative contributions of electrostatic and steric potential to the CoMFA regression equation indicated that electrostatic forces dominate (Table 11). The CoMFA steric and electrostatic contour maps for PNMT are shown in Figure 3a,b, respectively.

CoMFA of 7-Substituted-THIQs for the α_2-Adrenoceptor. The alignment rule for compounds used in the development of the α_2 CoMFA model was the same as that used in the PNMT model. It is a rather simplistic hypothesis that 7-substituted-THIQs bind in a similar fashion at both the PNMT active site and the α_2-adrenoceptor. Nevertheless, a higher cross-validated r^2 was obtained when the molecules were aligned in

Table 7. One-, Two-, and Three-Parameter Equations for the QSAR of the α_2-Adrenoceptor (Eq 3)

equations[a]	r	s	F_{calc}	F_{tab}
one parameter			$F_{(1,26)}$	$F_{(1,26,0.01)}$
$0.404(\pm0.203)\pi + 5.43(\pm0.31)$[b]	0.627	0.730	16.84	7.72
$-0.0404(\pm0.0387)$MR $+ 5.71(\pm0.61)$	0.387	0.864	4.59	7.72
$-1.05(\pm1.38)\sigma_m + 5.48(\pm0.52)$	0.294	0.896	2.45	7.72
two parameter			$F_{(2,25)}$	$F_{(2,25,0.01)}$
$0.482(\pm0.154)\pi - 0.0573(\pm0.0248)$MR $+ 6.22(\pm0.41)$	0.826	0.539	26.77	5.57
$0.416(\pm0.188)\pi - 1.17(\pm1.04)\sigma_m + 5.76(\pm0.41)$	0.707	0.676	12.50	5.57
$-0.840(\pm1.33)\sigma_m - 0.0362(\pm0.0388)$MR $+ 5.89(\pm0.67)$	0.452	0.853	3.20	5.57
three parameter			$F_{(3,24)}$	$F_{(3,24,0.01)}$
$0.485(\pm0.142)\pi - 0.0531(\pm0.0232)$MR $- 0.883(\pm0.777)\sigma_m + 6.42(\pm0.42)$	0.861	0.496	22.89	4.72

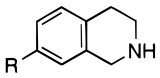
[a] $n = 28$. [b] Numbers in parentheses are 95% confidence intervals.

Table 8. One-, Two-, and Three-Parameter Equations for the QSAR of the α_2-Adrenoceptor (Eq 4)

equations[a]	r	s	F_{calc}	F_{tab}
one parameter			$F_{(1,25)}$	$F_{(1,25,0.01)}$
$0.503(\pm0.220)\pi + 5.43(\pm0.30)$[b]	0.685	0.695	22.09	7.77
$-0.0410(\pm0.0395)$MR $+ 5.73(\pm0.63)$	0.393	0.878	4.56	7.77
$-1.04(\pm1.41)\sigma_m + 5.48(\pm0.53)$	0.293	0.913	2.34	7.77
two parameter			$F_{(2,24)}$	$F_{(2,24,0.01)}$
$0.591(\pm0.151)\pi - 0.0587(\pm0.0215)$MR $+ 6.25(\pm0.36)$	0.879	0.465	40.65	5.61
$0.523(\pm0.199)\pi - 1.24(\pm0.966)\sigma_m + 5.78(\pm0.38)$	0.767	0.624	17.20	5.61
$-0.828(\pm1.36)\sigma_m - 0.0368(\pm0.0397)$MR $+ 5.91(\pm0.68)$	0.455	0.868	3.13	5.61
three parameter			$F_{(3,23)}$	$F_{(3,23,0.01)}$
$0.599(\pm0.129)\pi - 0.0542(\pm0.0186)$MR $- 0.951(\pm0.623)\sigma_m + 6.45(\pm0.34)$	0.917	0.397	40.53	4.76

[a] $n = 27$. [b] Numbers in parentheses are 95% confidence intervals.

Table 9. CoMFA Alignment Rule and Residual Values for 7-Substituted-1,2,3,4-tetrahydroisoquinolines Calculated According to the CoMFA Model at the Active Site of PNMT and at the α_2-Adrenoceptor



compd	7-substituent R	CoMFA orientation	residuals[a] PNMT	residuals[a] α_2
2	SO_2NH_2	B	0.32	−0.11
4	H	B	−0.63	0.25
5	$NHSO_2Me$	B	0.44	−0.05
6	$N(SO_2Me)_2$	B	0.28	0.25
7	CH_2NHSO_2Me	B	−0.28	0.17
8	NO_2	B	0.57	−0.26
9	NH_2	B	−0.44	−0.44
10	CN	B	−0.28	−0.07
11	CO_2Me	B	0.07	0.21
12	CH_2OH	B	−0.12	−0.24
13	CH_2NH_2	B	−0.73	−0.35
14	CO_2H	B	−0.18	−0.07
15	$CONH_2$	B	−0.62	−0.21
16	Br	A	0.38	0.23
17	SMe	A	0.03	−0.13
19	SO_2Me	B	0.25	−0.31
20	$COCF_3$[b]	B	−0.12	−0.09
21	SO_2Ph	A	−0.01	0.28
22	$SO_2CH_2CH{=}CH_2$	B	−0.05	0.16
23	SO_2CCl_3	A	0.09	−0.34
24	I	A	0.27	0.29
25	CF_3	A	−0.45	−0.23
26	NHCOMe	B	0.51	−0.08
27	COPh	A	0.04	−0.13
28	CH_2Ph	A	−0.29	−0.05
29	COMe	B	0.28	0.12
30	Me	A	0.01	0.13
31	SO_2NH-C_6H_4−*p*−Cl	A	0.26	0.41
32	OH	B	0.37	−0.06
33	OMe	B	0.04	0.74

[a] Negative logarithm of the difference between actual and predicted values. [b] Hydrated form of the ketone was used.

orientation A or B (Table 9), as opposed to a single orientation in which all of the 7-substituents were superimposed. As in the PNMT model, when the neutral

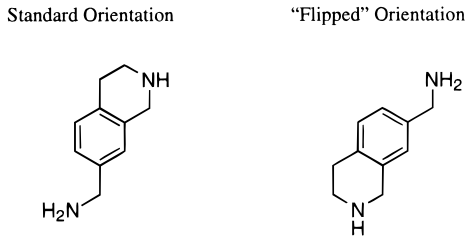


Figure 2. Dual orientations of 7-aminomethyl-THIQ (**13**) showing the molecule in the standard and "flipped" orientations.

Table 10. Selected Statistical Results of the CoMFAs (Cross-Validated Runs)

analysis	n	no. of components	r^2	press s
PNMT	30	1	0.260	0.989
PNMT	30	2	0.413	0.897
PNMT	30	3	0.546	0.804
α_2	30	1	0.598	0.585
α_2	30	2	0.682	0.530
α_2	30	3	0.694	0.530

Table 11. Statistical Results of the CoMFAs (Nonvalidated Runs, Three Components)

		conventional			contributions	
analysis	n	r^2	s	F value[a]	steric	electrostatic
PNMT	30	0.904	0.369	81.84	0.396	0.604
α_2	30	0.915	0.279	93.70	0.428	0.572

[a] The table F-value for $F_{(3,26,0.01)} = 4.64$.

forms of analogues **13** and **14** were used in the analysis, the cross-validated r^2 improved to 0.686. The "flipped" orientation (Figure 2) of compound **13** was also used, which improved the cross-validated r^2 slightly to 0.694 and improved the nonvalidated r^2 from 0.852 to 0.915 (Table 10) with three components, with an increase in the F-test value from 77.73 to 93.70.

The predictive power of this CoMFA model was better (cross-validated $r^2 = 0.694$, "press s" = 0.530, optimal number of components = 3) than that of the PNMT

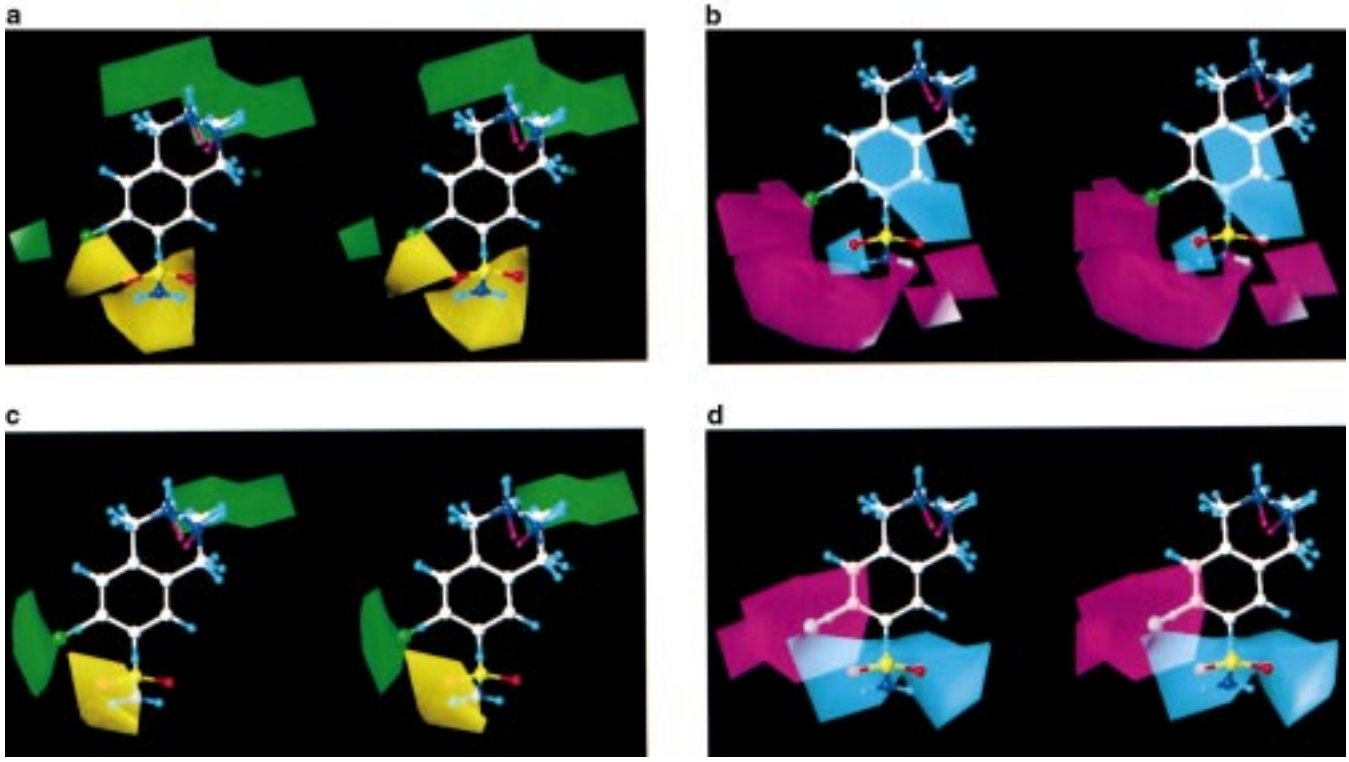


Figure 3. Contour maps for the PNMT and the α_2-adrenoceptor CoMFAs of 7-substituted-THIQs. SK&F 29661 (**2**) and compound **16** are superimposed in their proposed alignments as the reference molecules. For the steric maps, the contours where steric bulk is positively correlated with activity are shown in green, while the contours where steric bulk is negatively correlated with activity are shown in yellow. For the electrostatic maps, the contours where electron deficiency is correlated with activity are shown in cyan, while the contours where electron density is correlated with activity are shown in magenta. (a) PNMT steric: the contours are drawn at the contribution levels (positive:negative) of 85:30. (b) PNMT electrostatic: the contours are drawn at the contribution levels (positive:negative) of 85:25. (c) α_2 steric: the contours are drawn at the contribution levels (positive:negative) of 90:30. (d) α_2 electrostatic: the contours are drawn at the contribution levels (positive:negative) of 70:5.

CoMFA model (cross-validated $r^2 = 0.546$, "press s" = 0.804, optimal number of components = 3). The CoMFA contour maps, generated after a nonvalidated analysis using three components, are presented in Figure 3c,d. In contrast to the PNMT CoMFA, in which all activities were predicted within the 95% confidence interval, the predicted activity of methoxy analogue **33** was outside the 95% confidence interval (residual = 0.74).

E. Comparison of Classical QSAR and CoMFA Results. The traditional QSAR analysis of 7-substituted-THIQs for the active site of PNMT and for the α_2-adrenoceptor has established the importance of lipophilicity (π) and size (MR) of the 7-substituent. From comparison of QSAR eqs 2 and 4, it appears that at both the PNMT active site and at the α_2-adrenoceptor, the hydrophobic and steric interactions of 7-substituted-THIQs were similar. When the steric field contours for PNMT and α_2-adrenoceptor ligands from the CoMFA were compared, they seemed to overlap with each other quite well (Figure 3a,c). MR is a rough steric index of the substituent, and though it lacks directionality, it can be used to account for steric interactions at a given position. In a CoMFA, the steric contours represent critical van der Waals interactions of the molecule with probe atoms, and these interactions are correlated with biological activity. The outcome of the CoMFA not only confirmed the QSAR analysis but also confirmed the three-dimensional location of the steric bulk tolerance regions in space with respect to the THIQ skeleton. Examination of Figure 3a,c revealed a few positive contours associated with the region where bulky lipophilic substituents were projected. There appeared to be more steric bulk intolerance in the region of the nonlipophilic 7-substituents (orientation B).

The sign of the coefficient of the electronic parameter (σ_m) was the only significant difference between QSAR eqs 2 and 4. This difference in the electronic requirements at the PNMT active site and at the α_2-adrenoceptor can be readily seen in the electrostatic contour maps for the ligands in the PNMT and the α_2-adrenoceptor CoMFAs (Figure 3b,d). Large contours representing an area where electron density is favored were associated with nonlipophilic substituents in the CoMFA for PNMT, and indicated that an increase in negative charge in this region was positively correlated with PNMT inhibitory potency. Electron-deficient substituents will pull—via induction or by resonance—the aromatic π electron cloud to increase their negative charge. This was consistent with the QSAR result for PNMT ligands, which indicated that an increase in the electron-withdrawing ability of the 7-substituent should increase the PNMT inhibitory potency. On the other hand, large contours representing an area where electron deficiency is favored were associated with nonlipophilic substituents in the CoMFA electrostatic map for the α_2-adrenoceptor. As implied above, the electron-withdrawing substituents will have more electron density around them and will experience electrostatic repulsion in this area. Hence, THIQs bearing an electron-withdrawing group were predicted to have lower affinity toward the α_2-adrenoceptor, as would be expected given the sign

of the coefficient of σ_m in the QSAR equation (eq 4) for the α_2-adrenoceptor.

Summary and Conclusion

A series of 7-substituted-THIQs were synthesized and evaluated for PNMT inhibitory activity and α_2-adrenoceptor affinity. Both qualitative and quantitative treatments of the data (see section B above) required a binding model in which two different binding modes were assigned to 7-substituted-THIQs based on the lipophilicity of the 7-substituent. A classical QSAR and CoMFA were successfully developed to determine the influence of the steric and electrostatic interactions involved in binding of 7-substituted-THIQs at the PNMT active site and at the α_2-adrenoceptor. The results from these two different techniques were in general agreement with each other. The CoMFA model provided a hypothetical "receptor map" which indicated a degree of similarity in the steric interactions at the PNMT active site and the α_2-adrenoceptor. However, major differences were found in the electrostatic interactions, and a strong nonlipophilic, electron-withdrawing substituent was determined to be optimal for imparting PNMT over α_2-adrenoceptor selectivity to the THIQ nucleus. Since these models were calculated from a limited set of data on 7-substituted-THIQs, they should not be overinterpreted. However, they can provide an important tool for future drug design of selective inhibitors of PNMT.

Experimental Section

All reagents and solvents were reagent grade or were purified by standard methods before use. Melting points were determined in open capillaries on a Thomas-Hoover melting point apparatus calibrated with known compounds but are otherwise uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Varian XL-300 or a GE QE Plus spectrometer with $CDCl_3$ as the solvent, and chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS, 0.00 ppm). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a Varian XL-300 spectrometer with $CDCl_3$ as the solvent, and the chemical shifts are reported in ppm relative to $CDCl_3$ (77.00 ppm). For the hydrobromide salts of the phenolic amines, NMR spectra were recorded in deuterated dimethyl sulfoxide (DMSO-d_6) and the chemical shifts are reported relative to DMSO (2.49 ppm for ^{1}H and 39.50 ppm for ^{13}C). Multiplicity abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet; e, exchangeable. Infrared spectra were obtained on a Perkin-Elmer 1420 infrared spectrophotometer. Electron-impact mass spectra (EIMS) were obtained on Ribermag R10-10 mass spectrometer. The relative intensities of the mass spectrum peaks are listed in parentheses. Flash chromatography[56] was performed using silica gel 60 (230−400 mesh) supplied by Universal Adsorbents, Atlanta, GA. Preparative centrifugal thin-layer chromatography (PCTLC) was performed on a Harrison model 7924 Chromatotron (Harrison Research, Palo Alto, CA) using Merck silica gel 60 PF254/$CaSO_4 \cdot 0.5H_2O$ binder on 1-, 2-, or 4-mm thickness plates. Analytical TLC was performed by using silica gel with a fluorescent indicator coated on 1- × 3-in. glass plates in 0.2-mm thickness (Whatman MKGF silica gel 200μ). Bulb-to-bulb distillations were carried out on a Kugelrohr distillation apparatus (Aldrich Chemical Co., Milwaukee, WI), and oven temperatures were recorded. Combustion analyses were performed on a Hewlett-Packard model 185B CHN analyzer at the University of Kansas by Dr. Tho Ngoc Nguyen.

Unless otherwise stated, all methanol (MeOH) and ethanol (EtOH) used were anhydrous and were prepared by distillation from magnesium. Hexanes refer to the mixture of hexane isomers (bp 40−70 °C). Solvents were routinely distilled prior to use; anhydrous tetrahydrofuran (THF), ether (Et_2O), and benzene were obtained by distillation from sodium−benzophenone ketyl; dry methylene chloride (CH_2Cl_2) was obtained by distillation from phosphorus pentoxide. *n*-Butyllithium was standardized by titration against 2,5-dimethoxybenzyl alcohol. All reactions requiring anhydrous conditions and/or an inert atmosphere were performed under a positive nitrogen (N_2) or argon (Ar) flow, and all glassware was oven-dried and/or flame-dried.

Amine hydrochloride salts were prepared by the addition of a solution of methanolic HCl to a methanolic solution of the amine, followed by crystallization of the resulting hydrochloride from MeOH−Et_2O.

The compounds SK&F 64139 (**1**), SK&F 29661 (**2**), and SK&F 72223 (**3**) were kindly provided by Smith Kline and French Laboratories, Smith Kline Corp., Philadelphia, PA. *S*-Adenosyl-L-methionine was obtained from Sigma Chemical Co. [*methyl*-^{3}H]-*S*-Adenosyl-L-methionine that was used in the radiochemical assay was purchased from New England Nuclear Corp. (Boston, MA). Bovine adrenal glands were obtained from Davis Meat Processing (Overbrook, KS). [^{3}H]Clonidine used in the α_2-adrenoceptor binding assay was purchased from Amersham Corp. (Arlington Heights, IL).

7-Methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (11·HCl). Nitrile **10**[21] (0.205 g, 1.29 mmol) was added to a saturated methanolic HCl solution (20 mL, prepared by bubbling HCl in dry MeOH), and to the resulting suspension was added water (0.03 mL). The mixture was heated to reflux for 18 h. The solution was cooled, and solvent was removed on a rotary evaporator to yield a colorless solid which was treated with 5% $NaHCO_3$. The solution was extracted with CH_2Cl_2 (thrice), dried over anhydrous Na_2SO_4, and evaporated to give a colorless semisolid (0.243 g, 98.0%). Recrystallization of the semisolid from CH_2Cl_2−hexanes produced white fluffy needles: mp 216−218 °C dec; IR (KBr) 3390 (NH), 2949, 2730, 1700 (CO), 1585, 1430, 1290, 1270, 1200, 1100, 805 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.78−7.68 (m, 2 H, H-6 and H-8), 7.12 (d, 1 H, J = 8 Hz, H-5), 4.02 (s, 2 H, H-1), 3.88 (s, 3 H, CO_2CH_3), 3.13 (t, 2 H, J = 5.9 Hz, H-3), 2.83 (t, 2 H, J = 5.9 Hz), 2.46 (bs, e, 1 H, N*H*); ^{13}C NMR ($CDCl_3$) δ 166.9 (CO_2Me), 140.1, 135.6, 129.2, 127.4, 126.9, 51.7 (OCH_3), 47.8 (C-1), 43.2 (C-3), 29.1 (C-4).

The hydrochloride salt was recrystallized from MeOH−Et_2O as colorless needles: mp 222−223 °C dec; EIMS *m*/*z* 192 (M + 1, 6), 191 (M^+, 33), 190 ($M^+ - 1$, 100), 176 (15), 162 (46), 131 (73), 103 (48), 77 (50), 51 (35). Anal. ($C_{11}H_{13}NO_2 \cdot$HCl) C, H, N.

The stability of the methyl ester to hydrolysis in the assay conditions was determined by an NMR experiment, using a procedure described previously.[57] Compound **11**·HCl in pD 9.03 0.5 M phosphate buffer was monitored by NMR and showed no evidence of hydrolysis over a period of 60 min (twice the standard PNMT or α_2-adrenoceptor assay incubation time).

7-Hydroxymethyl-1,2,3,4-tetrahydroisoquinoline Oxalate (12). To dry ether (20 mL) under N_2 was added $LiAlH_4$ (0.30 g, 7.8 mmol), and the suspension was heated to reflux for 1 h. After cooling to room temperature, compound **11** (0.50 g, 2.6 mmol) was added as a solution in dry THF (5 mL), and the mixture was allowed to stir at room temperature for 12 h. The reaction mixture was cooled in an ice bath and quenched carefully with water (0.2 mL) and 10% KOH (0.2 mL). The resulting suspension was filtered and extracted with CH_2Cl_2 (four times), dried over anhydrous Na_2SO_4, and evaporated to give a colorless solid (0.38 g, 88%) which was crystallized from CH_2Cl_2−hexanes: mp 132−134 °C; IR (KBr) 3260, 3050, 1450, 1360, 1340, 1120, 1060, 970, 905, 805 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.10−6.97 (m, 3 H, Ar*H*), 4.53 (s, 2 H, ArCH_2O), 3.93 (s, 2 H, H-1), 3.45−3.15 (m, b, e, 2 H, N*H* and O*H*), 3.07 (t, 2 H, J = 6 Hz, H-3), 2.75 (t, 2 H, J = 5.9 Hz, H-4); ^{13}C NMR ($CDCl_3$) δ 138.7, 134.9, 132.8, 128.5, 124.0, 63.3, 47.4, 43.0, 28.1.

As the hydrochloride salt was difficult to crystallize, the oxalate salt of the amine was prepared. A saturated solution

of anhydrous oxalic acid in dry Et_2O was added to a methanolic solution of the amine **12**, and the oxalate salt obtained was crystallized from MeOH−Et_2O: mp 155−156 °C; EIMS *m/z* 164 (M + 1, 5), 163 (M^+, 46), 162 ($M^+ - 1$, 100), 134 (70), 132 (60), 130 (20), 117 (24), 105 (94), 91 (85), 77 (68), 51 (36), 44 (28). Anal. ($C_{10}H_{13}NO \cdot C_2H_2O_4$) C, H, N.

7-Aminomethyl-1,2,3,4-tetrahydroisoquinoline Dihydrochloride (13·2HCl). Nitrile **10**[21] (0.30 g, 1.9 mmol) was dissolved in dry THF (10 mL), and $BH_3 \cdot Me_2S$ complex (2.0 M in THF, 2 mL, 4 mmol) was added dropwise. The solution was heated to reflux for 14 h under N_2 followed by removal of the THF by distillation. The semisolid obtained was treated with saturated methanolic HCl (10 mL) and heated to reflux for 5 h. After cooling the solvent was removed on a rotary evaporator to give a colorless solid which was made alkaline with 10% KOH solution and extracted with CH_2Cl_2 (four times). The combined CH_2Cl_2 extracts were washed with brine (once), dried (anhydrous K_2CO_3), and evaporated to produce a colorless thick oil (0.30 g) which was distilled bulb-to-bulb (120−130 °C, 0.1 mmHg) to give a colorless oil (0.14 g, 44%): ^{1}H NMR ($CDCl_3$) δ 7.10−7.04 (m, 2 H, Ar*H*), 6.95 (m, 1 H, Ar*H*), 3.97 (s, 2 H, H-1), 3.78 (s, 2 H, ArCH_2NH_2), 3.09 (t, 2 H, J = 5.9 Hz, H-3), 2.74 (t, 2 H, J = 5.9 Hz, H-4), 1.51 (s, e, 3 H, NH_2 and N*H*); ^{13}C NMR ($CDCl_3$) δ 140.5, 135.8, 133.0, 129.1, 124.5, 124.5, 48.1 (C-1), 45.9 (ArCH_2NH_2), 43.7 (C-3), 28.7 (C-4).

The dihydrochloride salt was crystallized from MeOH−Et_2O as fine colorless crystals: mp 324−325 °C dec; IR (KBr) 3180, 2900, 2800, 1585, 1500, 1365, 1060, 820 cm^{-1}; EIMS *m/z* 162 (M^+, 47), 161 ($M^+ - 1$, 93), 145 (57), 133 (54), 132 (100), 130 (23), 118 (29), 115 (29), 105 (29), 103 (24), 91 (61), 77 (49), 51 (21). Anal. ($C_{10}H_{14}N_2 \cdot 2HCl$) C, H, N.

1,2,3,4-Tetrahydroisoquinoline-7-carboxylic Acid Hydrochloride (14·HCl). In a thick-walled tube with a sidearm was placed nitrile **10**[21] (0.25 g, 1.6 mmol), and to it concentrated HCl (1.9 mL) was added. The reaction mixture was cooled in a dry ice−acetone bath, and vacuum was applied to the sidearm to evacuate the tube. The reaction mixture was evacuated thrice and then heated in the sealed tube at 150 °C for 9 h. After cooling to room temperature, the colorless solid which formed was collected by filtration and crystallized from water (0.32 g, 93%): mp 338−340 °C dec; IR (KBr) 3140, 1690, 1590, 1570, 1400, 1270, 1235, 1130, 870 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.88 (bs, e, 2 H, NH_2^+), 7.82−7.78 (m, 2 H, H-6 and H-8), 7.33 (d, 1 H, J = 7.8 Hz, H-5), 4.3 (s, 2 H, H-1), 3.34 (t, 2 H, J = 5.6 Hz, H-3), 3.08 (t, 2 H, J = 5.6 Hz, H-4); ^{13}C NMR (DMSO-d_6) δ 166.9 (CO_2H), 137.3, 129.5, 129.0, 128.0, 43.2 (C-1), 40.1 (C-3), 24.8 (C-4); EIMS *m/z* 177 (M^+, 30), 176 ($M^+ - 1$, 100), 149 (40), 148 (64), 132 (21), 131 (33), 103 (26), 91 (14), 77 (44), 51 (26), 45 (39) 44 (17), 43 (30), 42 (19). Anal. ($C_{10}H_{11}NO_2 \cdot HCl$) C, H, N.

7-Aminocarbonyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (15·HCl). To a suspension of KF−Al_2O_3[28] (1.0 g) and *t*-BuOH (10 mL) was added nitrile **10**[21] (0.300 g, 1.89 mmol), and the mixture was heated to reflux under N_2 for 24 h. The suspension was filtered to remove the alumina, and the solid was washed with $CHCl_3$ and water. The filtrate was extracted with $CHCl_3$ (thrice), dried (anhydrous Na_2SO_4), and evaporated to yield a pale-yellow-colored oil (0.095 g, 28.4%). (The low yield could be avoided by just filtering and evaporating the reaction mixture. The amide had very low solubility in organic solvents.) The pale-yellow solid was crystallized from CH_2Cl_2−hexanes to afford a colorless solid: mp 173−175 °C dec; ^{1}H NMR (DMSO-d_6) δ 7.97 (s, 2 H, Ar$CONH_2$), 7.64−7.56 (m, 2 H, H-6 and H-8), 7.11 (d, 1 H, J = 7.9 Hz, H-5), 3.94 (s, 3 H, H-1 and N*H*, e), 3.03 (t, 2 H, J = 5.9 Hz, H-3), 2.78 (t, 2 H, J = 5.9 Hz, H-4); ^{13}C NMR (DMSO-d_6) δ 168.3, 138.3, 135.7, 131.0, 128.5, 125.2, 124.5, 47.6, 42.9, 28.6.

The hydrochloride salt was crystallized from MeOH−Et_2O: mp 260−262 °C; IR (KBr) 3460 (NH_2), 3340 (NH_2), 3100, 1650 ($CONH_2$), 1600, 1400, 1380, 770 cm^{-1}; MS (CI, NH_3) *m/z* 177 (M + 1, 100), 175 ($M^+ - 1$, 11). Anal. ($C_{10}H_{12}N_2O \cdot HCl$) C, H, N.

7-Bromo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (16·HCl). Amine **9** (0.75 g, 5.06 mmol) was added to ice-cold 48% HBr (2.4 mL) in water 8.1 mL). To this stirred solution was added sodium nitrite (0.38 g, 5.6 mmol) dropwise as a solution in water (4.5 mL). The reddish-colored solution turned orange, and the presence of excess HNO_2 was checked by starch−iodide paper. Excess HNO_2 was destroyed by adding urea (0.20 g) to the reaction mixture (a negative starch−iodide test was obtained at this point). This diazotized solution was added to a well-stirred, warm (35 °C) mixture of CuBr (2.17 g, 15.1 mmol), 48% HBr (5.1 mL), and water (12.6 mL). After the completion of the addition of the diazotized solution, the reaction mixture was warmed to 75−80 °C and stirred at that temperature for 1.5 h. The reaction mixture was allowed to stand overnight and then cautiously made alkaline with 50% KOH solution. The blue copper salts were filtered, and the filtrate was extracted with CH_2Cl_2 (four times), dried over anhydrous Na_2SO_4, and evaporated to get a dark-red oil (0.88 g). Bulb-to-bulb distillation (110−115 °C, 0.15 mmHg) yielded compound **16** as a clean colorless oil (0.75 g, 73%): ^{1}H NMR ($CDCl_3$) δ 7.21 (dd, 1 H, J = 1.6, 8.1 Hz, Ar*H*), 7.13 (m, 1 H, Ar*H*), 6.92 (d, 1 H, J = 8.1 Hz, Ar*H*), 3.94 (s, 2 H, H-1), 3.09 (t, 2 H, J = 6 Hz, H-3), 2.70 (t, 2 H, J = 5.9 Hz, H-4), 2.33 (bs, e, 1 H, N*H*); ^{13}C NMR ($CDCl_3$) δ 137.8, 133.5, 130.8, 128.8, 119.0, 119.0, 47.7 (C-1), 43.4 (C-3), 28.4 (C-4).

The colorless needles of the hydrochloride salt were obtained by crystallization from MeOH−Et_2O: mp 245−247 °C dec; IR (KBr) 2940, 2710, 1580, 1400, 1195, 840, 810 cm^{-1}; EIMS *m/z* 214 (M + 3, 17), 213 (M + 2, 59), 212 (M + 1, 100), 211 (M^+, 59), 184 (72), 182 (72), 132 (39), 130 (33), 103 (84), 77 (64), 51 (61). Anal. ($C_9H_{10}BrN \cdot HCl$) C, H, N.

7-Bromo-*N*-triphenylmethyl-1,2,3,4-tetrahydroisoquinoline (34). To a stirred solution of **16** (0.564 g, 2.66 mmol) in CH_2Cl_2 (10 mL) was added triethylamine (0.296 g, 0.410 mL, 2.92 mmol), and the solution was stirred in an ice bath. 4-(Dimethylamino)pyridine (0.033 g, 0.27 mmol) and triphenylmethyl chloride (1.115 g, 4.00 mmol) were added in one portion, and the reaction mixture was stirred vigorously. After a few minutes a copious precipitate of triethylammonium hydrochloride was observed in the reaction mixture. The reaction was stirred at room temperature for 18 h, quenched with 1 N NaOH, and extracted with CH_2Cl_2 (thrice), and the combined organic extracts were dried over anhydrous Na_2SO_4. Evaporation gave a yellow-orange-colored solid (1.705 g). The solid was passed through a silica plug using hexanes/EtOAc (3:1) as eluent. The pale-yellow solid thus obtained was subjected to PCTLC (silica, 4 mm; CH_2Cl_2/hexanes/MeOH/NH_4OH, 150:450:10:1, as the eluent) to yield a colorless foamy solid (1.147 g, 94.90%): mp 170−177 °C (smears on melting); IR (KBr) 1590, 1480, 1440, 1030, 740, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.54−7.52 (m, 6 H, Ar*H*), 7.28−6.94 (m, 12 H, Ar*H*), 3.45−3.35 (m, 2 H, H-1), 2.94−2.90 (m, 2 H, H-3), 2.55−2.45 (m, 2 H, H-4); ^{13}C NMR ($CDCl_3$) δ 142.1, 138.2, 133.7, 130.1, 129.2, 129.0, 128.8, 127.4, 126.0, 118.6, 76.4 (CPh_3), 50.38 (C-1), 45.98 (C-3), 29.24 (C-4); MS *m/z* (CI, NH_3) 454 (M + 1, 0.1), 378 (0.2), 376 (0.2), 243 (Ph_3C^+, 100), 165 (10). Anal. ($C_{28}H_{24}BrN$) C, H, N.

7-Methylthio-1,2,3,4-tetrahydroisoquinoline Hydrochloride (17·HCl). In a flame-dried three-neck round-bottom flask equipped with a thermometer, magnetic stir bar, and a N_2 inlet was placed **34** (1.08 g, 2.37 mmol) in dry THF (15 mL). The solution was chilled to −78 °C, and *n*-BuLi (1.95 M in hexanes, 1.34 mL, 2.62 mmol) was added dropwise. A dark-red-colored solution was obtained and was allowed to warm to −10 °C, over a period of 1 h. The reaction mixture was again chilled to −78 °C and a solution of methyl disulfide (0.27 g, 0.26 mL, 2.8 mmol) in dry THF (3 mL) was added. The reaction mixture was stirred overnight, then cooled in an ice bath, and treated with acetone (4 mL) and concentrated HCl (2 mL). The pale-yellow colorless mixture was stirred overnight, and then the organic solvents were removed on a rotary evaporator. The residue obtained was diluted with water (15 mL) and washed with CH_2Cl_2 (twice). The aqueous layer was made alkaline with 6 N NaOH and extracted with CH_2Cl_2 (four times). The combined CH_2Cl_2 extracts were dried over anhydrous Na_2SO_4 and evaporated to yield a colorless oil (0.27 g). Bulb-to-bulb

distillation (95−100 °C, 0.05 mmHg) gave a colorless oil (0.24 g, 56%): IR (film) 3300 (NH), 2920, 1595, 1425, 1255, 1190, 950, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.04−6.92 (m, 3 H, Ar*H*), 3.96 (s, 2 H, H-1), 3.10 (t, 2 H, J = 6 Hz, H-3), 2.72 (t, 2 H, J = 5.9 Hz, H-4), 2.44 (s, 3 H, SCH_3), 1.69 (bs, e, 1 H, N*H*); ^{13}C NMR ($CDCl_3$) δ 136.6, 135.0, 132.0, 129.7, 124.9, 124.7, 48.2 (C-1), 43.8 (C-3), 28.7 (C-4), 16.3 (S*C*H_3).

The hydrochloride salt was crystallized from MeOH−Et_2O: mp 249−251 °C dec (lit.[17] mp 247−248 °C); EIMS *m*/*z* 181 (M + 2, 4), 180 (M + 1, 10), 179 (M^+, 66), 178 (27), 150 (100), 135 (16), 117 (13), 91 (15). Anal. ($C_{10}H_{13}NS$·HCl) C, H, N.

(±)-7-Methylsulfinyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (18·HCl). To compound **17** (0.255 g, 1.42 mmol) was added trifluoroacetic acid (3 mL), and the mixture was stirred in an ice bath. Trifluoroperacetic acid (6.37 N, 0.250 mL, 1.59 mequiv) was added in one portion, and the mixture was stirred for 14 h at room temperature. At this stage TLC showed little starting material and a slight positive starch−iodide test. The trifluoroacetic acid was carefully removed on a rotary evaporator. Traces of trifluoroacetic acid were removed by adding benzene to the residue followed by evaporation. The colorless oil was made alkaline with 3 N NaOH and extracted with $CHCl_3$ (thrice). After washing the $CHCl_3$ extracts with brine and drying over anhydrous Na_2SO_4, evaporation of the combined $CHCl_3$ extracts yielded a pale-orange-red oil (0.211 g). The oil was purified by PCTLC (silica gel, 4 mm) using CH_2Cl_2/MeOH/NH_4OH (250:20:1) as the eluent to give **18** as a viscous colorless liquid (0.117 g, 44.8%): IR (KBr) 3460 (NH), 2900, 2780, 1420, 1015 (SO), 950, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37−7.34 (m, 2 H), 7.25−7.22 (m, 1 H), 4.08 (s, 2 H, H-1), 3.17 (t, 2 H, J = 5.8 Hz, H-3), 3.12 (b, e, 1 H, N*H*), 2.87 (t, 2 H, J = 5.8 Hz, H-4), 2.70 (s, 3 H, SOCH_3); ^{13}C NMR ($CDCl_3$) δ 142.6, 138.0, 136.7, 130.1, 121.1, 120.9, 47.7, 43.8, 43.1, 28.7.

The hydrochloride salt was crystallized from MeOH−Et_2O as a colorless solid: mp 225 °C dec (lit.[17] mp 200−202 °C); EIMS *m*/*z* 196 (M + 1, 11), 195 (M^+, 54), 194 (M^+ − 1, 65), 180 (38), 179 (57), 178 (46), 166 (10), 151 (100), 150 (36), 130 (38), 117 (20), 102 (27), 91 (69), 77 (75), 51 (49), 45 (45). Anal. ($C_{10}H_{13}NOS$·HCl) C, H, N.

7-Methylsulfonyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (19·HCl). Amine **17** (0.281 g, 1.57 mmol) was dissolved in trifluoroacetic acid (3 mL), the pale-yellow-colored solution was chilled in an ice bath, and trifluoroperacetic acid (4 M, 0.81 mL, 3.2 mmol) was added. The reaction mixture was allowed to stir for 24 h at room temperature. After workup as for compound **18**, followed by evaporation of the organic layer, a pale-yellow-colored solid was obtained (single spot on TLC, 0.281 g, 84.9%): mp 124−126 °C; IR (KBr) 3320 (NH), 2900, 1410, 1290 (SO_2), 1130 (SO_2), 960, 810, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68−7.60 (m, 2 H, H-6 and H-8), 7.27 (d, 1 H, J = 8.0 Hz, H-5), 4.07 (s, 2 H, H-1), 3.16 (t, 2 H, J = 5.9 Hz, H-3), 3.03 (s, 3 H, SO_2CH_3), 2.88 (t, 2 H, J = 5.9 Hz, H-4), 1.88 (bs, e, 1 H, N*H*); ^{13}C NMR ($CDCl_3$) δ 141.6, 137.7, 137.4, 130.3, 125.2, 124.6, 48.1, 44.5, 43.2, 29.3.

The hydrochloride salt was crystallized from MeOH−Et_2O as small colorless needles: mp 262−264 °C dec (lit.[17] mp 258−260 °C); EIMS *m*/*z* 212 (M + 1, 9), 211 (M^+, 29), 210 (M^+ − 1, 100), 182 (22), 131 (59), 103 (34), 91 (73), 77 (62), 51 (33). Anal. ($C_{10}H_{13}NO_2S$·HCl) C, H, N.

7-Trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (20·HCl). Compound **34** (2.9 g, 6.4 mmol) was dissolved in dry THF (20 mL) and treated with *n*-BuLi (1.4 M, 5 mL, 7 mmol) at −78 °C under a positive pressure of N_2. After stirring for 1 h at −78 °C, the reaction mixture was transferred via a double-tipped needle to a three-neck flask containing a solution of trifluoroethyl acetate (1.0 g, 0.83 mL, 7.0 mmol) in dry THF (10 mL) at −78 °C. The reaction mixture was allowed to warm to room temperature over a period of 12 h and then quenched with saturated Na_2CO_3. The reaction mixture was extracted with EtOAc (thrice); the combined extracts were dried over anhydrous Na_2SO_4 and evaporated to afford a yellow solid (3.0 g). Purification of the crude product by column chromatography (silica gel; CH_2Cl_2/hexanes/MeOH/NH_4OH, 150:450:10:1, as the eluent) gave a yellow solid (1.5 g, 50%) which was identified as 7-trifluoroacetyl-*N*-triphenylmethyl-THIQ: IR (KBr) 1705 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.82 (d, 1 H, J = 7.8 Hz, H-6), 7.65 (bs, 1 H-8), 7.56−7.50 (m, 6 H), 7.30−7.15 (m, 10 H), 3.52 (bs, 2 H, H-1), 3.08−3.06 (m, 2 H, H-3), 2.57 (bs, 2 H, H-4). This compound (0.68 g, 1.4 mmol) was dissolved in a mixture of acetone (10 mL) and 3 N HCl (5 mL). After stirring for 1 h at room temperature, the colorless reaction mixture was concentrated (4 mL) on a rotary evaporator and washed with CH_2Cl_2 (thrice) to remove triphenylmethanol. Evaporation of the aqueous layer gave a colorless solid (0.36 g) which was crystallized from MeOH−Et_2O to give **20**·HCl as a white crystalline solid (0.34 g, 89% or 44% from **34**): mp 240 °C dec; IR (KBr) 3290, 2940, 2790, 1580, 1170, 1050, 940, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.84 (bs, 2 H, NH_2^+), 7.40−7.30 (m, 2 H), 7.27 (m, 1 H), 4.27 (s, 2 H, H-1), 3.36−3.30 (m, 2 H, H-3), 3.05−3.01 (m, 2 H, H-4); EIMS *m*/*z* 229 (M^+, 31), 228 (M^+ − 1, 75), 200 (13), 132 (25), 131 (100), 130 (20), 103 (39), 77 (60), 51 (32). Anal. ($C_{11}H_{10}F_3NO$·HCl·0.5H_2O) C, H, N.

7-Fluorosulfonyl-*N*-acetyl-1,2,3,4-tetrahydroisoquinoline (37). 7-Chlorosulfonyl-*N*-acetyl-1,2,3,4-tetrahydroisoquinoline[9] (**36**; 6.63 g, 24.2 mmol) was dissolved in dry acetonitrile (20 mL), and to it were added anhydrous KF (2.72 g, 48.4 mmol) and 18-crown-6 ether (0.06 g, 0.2 mmol). The suspension was stirred under N_2 for 14 h, and a thick slurry resulted which was diluted with water (100 mL). The emulsion was extracted with EtOAc (thrice); the combined EtOAc extracts were dried over anhydrous Na_2SO_4 and evaporated. The yellow oil (4.8 g) thus obtained was passed through a silica plug (hexanes/EtOAc, 1:1, as the initial eluent to remove nonpolar impurities and then acetone as the final eluent) to afford a pale-yellow syrup (3.83 g). Bulb-to-bulb distillation (165 °C, 0.05 mmHg) yielded a pale-yellow oil (3.60 g, 57.2%) that solidified on standing: mp 80−90 °C; IR (film) 1650 (CO), 1450, 1390 (SO_2), 1210 (SO_2), 1090, 860, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.84−7.79 (m, 2 H, H-6 and H-8), 7.46−7.42 (m, 1 H, H-5), 4.85−4.75 (m, 2 H, H-1), 3.87 and 3.76 (t, 2 H, J = 5.9 Hz, H-3, conformers), 2.07−2.96 (m, 2 H, H-4), 2.22−2.21 (m, 3 H, COCH_3); EIMS *m*/*z* 258 (M + 1, 5), 257 (M^+, 31), 214 (M^+ − $COCH_3$, 34), 200 (12), 186 (10), 130 (8), 116 (13), 103 (10), 77 (11), 43 (100). Anal. ($C_{11}H_{12}FNO_3S$) C, H, N.

7-Phenylsulfonyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (21·HCl). Sulfonyl fluoride **37** (0.26 g, 1.0 mmol) was dissolved in dry THF (20 mL) and cooled to −78 °C. Dropwise addition of phenylmagnesium bromide (3 M solution in Et_2O) to the stirred solution under N_2 produced a yellow-red reaction mixture. The mixture was allowed to warm to room temperature and stirred for 14 h. The red solution was cooled in an ice bath and quenched with saturated NH_4Cl solution followed by 3 N HCl (10 mL). The resulting yellow solution was washed with CH_2Cl_2 (thrice) to remove nonbasic impurities. The aqueous layer was made alkaline with solid KOH and filtered through Celite to remove $Mg(OH)_2$, and the Celite layer was washed with CH_2Cl_2 (thrice). The filtrate was extracted with CH_2Cl_2 (thrice), the organic washes and extracts were combined and dried (anhydrous K_2CO_3), and the solvent was removed by rotary evaporation to yield a yellow oil (0.14 g, 51%): ^1H NMR ($CDCl_3$) δ 7.91 (d, 2 H, J = 7.2 Hz, Ar*H*), 7.66 (d, 1 H, J = 7.8 Hz, Ar*H*), 7.60−7.46 (m, 4 H, Ar*H*), 7.20 (d, 1 H, J = 7.9 Hz, Ar*H*), 4.02 (s, 2 H, H-1), 3.10 (t, 2 H, J = 5.9 Hz, H-3), 2.80 (m, 3 H, H-4 and N*H*).

The hydrochloride salt was crystallized as a pale-yellow solid from MeOH−Et_2O: mp 135−137 °C; IR (KBr) 3400, 1440, 1300 (SO_2), 1150 (SO_2), 1130, 1090, 880, 720, 680 cm^{-1}; EIMS *m*/*z* 274 (M + 1, 10), 273 (M^+, 33), 272 (M^+ − 1, 100), 244 (21), 132 (M^+ − SO_2Ph, 29), 131 (67), 130 (26), 125 (60), 103 (17), 91 (44), 77 (94), 65 (18), 51 (36). Anal. ($C_{15}H_{15}NO_2S$·HCl·H_2O) C, H, N.

7-Allylsulfonyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (22·HCl). Treatment of allylmagnesium bromide (1 M solution in THF, 18 mL, 18 mmol) with sulfonyl fluoride **37** (0.78 g, 3.0 mmol) in dry THF (50 mL) in a similar manner as described above gave a pale-yellow oil (0.71 g). Purification

by PCTLC (silica, 2 mm) using CH_2Cl_2/MeOH /NH_4OH (250:17:1) as the eluent furnished a pale-yellow oil (0.46 g, 65%): IR (film) 3310, 1420, 1300 (SO_2), 1130 (SO_2), 1080, 800, 630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60−7.53 (m, 2 H, H-6 and H-8), 7.27−7.25 (m, 1 H, H-5), 5.83−5.72 (m, 1 H, C*H*=CH_2), 5.36−5.30 (m, 1 H), 5.17 (d, 1 H, J = 17 Hz), 4.07 (s, 2 H, H-1), 3.79 (d, 2 H, J = 7.3 Hz, CH_2CH=CH_2), 3.16 (t, 2 H, J = 5.9 Hz, H-3), 2.88 (t, 2 H, J = 5.9 Hz, H-4), 1.92 (bs, e, 1 H, N*H*).

The hydrochloride salt was obtained as a pale-yellow crystalline solid: mp 188−190 °C; EIMS m/z 238 (M + 1, 10), 237 (M^+, 31), 236 (M^+ − 1, 100), 196 (20), 132 (40), 131 (M^+ − $SO_2C_3H_5$, 59), 130 (21), 129 (19), 103 (34), 91 (10), 77 (40). Anal. ($C_{12}H_{15}NO_2S$·HCl) C, H, N.

7-Methylsulfonyl-*N*-triphenylmethyl-1,2,3,4-tetrahydroisoquinoline (38). Compound **19** (0.72 g, 3.4 mmol) was subjected to the same procedure as described for compound **34**, to afford a pale-yellow solid (1.0 g, 66%): mp 145−150 °C; IR (KBr) 2920, 1480, 1440, 1305 (SO_2), 1140 (SO_2), 960, 760, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55−7.52 (m, 6 H), 7.31−7.15 (m, 12 H), 3.52 (bs, 2 H, H-1), 3.08−3.06 (m, 2 H, H-3), 2.98 (s, 3 H, SO_2CH_3), 2.57 (bs, 2 H, H-4); ^{13}C NMR ($CDCl_3$) δ 141.75, 137.76, 129.68, 129.11, 127.86, 127.68, 127.19, 126.27, 125.60, 124.67, 77.18 (*C*Ph_3), 50.74 (C-1), 45.77, 44.50, 30.13 (C-4); MS (CI NH_3) m/z 376 (M^+ − Ph, 2), 244 (21), 243 (Ph_3C^+, 100), 165 (28). Anal. ($C_{29}H_{27}NO_2S$) C, H, N.

7-Trichloromethylsulfonyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (23·HCl). Compound **38** (0.48 g, 1.1 mmol) was dissolved in dry THF (10 mL) and treated with *n*-BuLi (2.0 M, 0.6 mL, 1.2 mmol) at −78 °C under a positive pressure of N_2. The resulting dark-yellow-orange reaction mixture was stirred at −78 °C for 45 min, CCl_4 (1.0 mL) was added, and the reaction mixture was allowed to warm to room temperature. After stirring for 14 h, the dark-red reaction mixture was quenched with a mixture of acetone and HCl (2:1, 6 mL). After an identical workup as described for compound **17**, a red-orange oil was isolated. Purification by PCTLC (silica, 2 mm) using CH_2Cl_2/MeOH/NH_4OH (250:20:1) as the eluent gave a pale-orange oil (0.13 g, 39%): ^1H NMR ($CDCl_3$) δ 7.89−7.80 (m, 2 H, H-6 and H-8), 7.35 (d, 1 H, J = 8.2 Hz, H-5), 4.14 (s, 2 H, H-1), 3.21 (t, 2 H, J = 6.0 Hz, H-3), 2.96 (t, 2 H, J = 6.0 Hz, H-4).

The hydrochloride salt was crystallized from MeOH−Et_2O: mp 243−244 °C dec; IR (KBr) 2920, 2760, 1575, 1420, 1345 (SO_2), 1155 (SO_2), 820 cm^{-1}; EIMS m/z 317 (M + 4, 2), 315 (M + 2, 4), 313 (M^+, 6), 312 (M^+ − 1, 16), 196 (32), 167 (15), 132 (100), 131 (58), 130 (43), 117 (42), 103 (50), 84 (18), 77 (69), 47 (29). Anal. ($C_{10}H_{10}Cl_3NO_2S$·HCl) C, H, N.

7-Iodo-*N*-acetyl-1,2,3,4-tetrahydroisoquinoline (40). 7-Amino-*N*-acetyl-1,2,3,4-tetrahydroisoquinoline (**39**) was prepared from **8** in the same manner as described for **42**.[21] To the aromatic amine **39** (7.00 g, 36.8 mmol) was added concentrated HCl (13.6 mL) in water (45 mL), and the solution was cooled in an ice bath. Sodium nitrite (2.64 g, 40.6 mmol) was added dropwise as a solution in water (15 mL). The diazotized amine was stirred in the ice bath for 30 min and then transferred in small portions to a vigorously stirred biphasic mixture consisting of $CHCl_3$ (150 mL), potassium iodide solution (12.2 g, 73.6 mmol of KI in 45 mL water), and copper(I) iodide (0.50 g). After stirring for 7 h at room temperature, the brown suspension was diluted with $CHCl_3$ (100 mL), transferred to a separatory funnel, and washed with 10% $Na_2S_2O_3$ solution (thrice). The organic layer was dried over anhydrous Na_2SO_4 followed by evaporation to yield a yellow oil (11.4 g) which was passed through a silica plug ($CHCl_3$/THF, 20:1, as the eluent) to afford a relatively pure pale-yellow oil (8.21 g, 74.1%). Analytically pure pale-yellow oil was obtained by bulb-to-bulb (150−160 °C, 0.01 mmHg) distillation: IR (film) 3450, 1630 (CO), 1430, 1240, 1225, 1025, 750, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50−7.46 (m, 2 H, Ar*H*), 6.92−6.87 (m, 1 H, Ar*H*), 4.67 and 4.57 (s, 2 H, H-1), 3.79 and 3.66 (t, 2 H, J = 5.9 Hz, H-3, conformers), 2.86−2.78 (m, 2 H, H-4), 2.17 (s, 3 H, COCH_3); EIMS m/z 302 (M + 1, 21), 301 (M^+, 46), 286 (M^+ − CH_3, 10), 258 (M^+ − $COCH_3$, 25), 244 (16), 230 (49), 130 (11), 115 (29), 103 (38), 77 (51), 43 (100). Anal. ($C_{11}H_{12}INO$) C, H, N.

7-Iodo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (24·HCl). Iodoamide **40** (0.60 g, 2.0 mmol) was dissolved in EtOH (5 mL) and heated to reflux with 3 N HCl (5 mL) for 4 h. A thick suspension resulted on cooling, and on removal of the solvent a solid was obtained. The solid was treated with 20% KOH and extracted with CH_2Cl_2 (four times). The organic layers were combined, dried (anhydrous Na_2SO_4), and evaporated to yield a buff-colored solid (0.50 g). Purification by PCTLC (silica, 2 mm) using CH_2Cl_2/MeOH/NH_4OH (250:17:1) as the eluent gave a buff-colored solid (0.45 g, 87%), mp 83−85 °C. The hydrochloride salt was crystallized from MeOH−Et_2O: mp 243−244 °C dec; IR (KBr, HCl salt) 2920, 2760, 1575, 1420, 1345 (SO_2), 1155 (SO_2), 820 cm^{-1}; IR (KBr) 3300 (NH), 2940, 1475, 1125, 800, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43−7.35 (m, 2 H, H-6 and H-8), 6.82 (d, 1 H, J = 8.2 Hz, H-5), 3.94 (s, 2 H, H-1), 3.10 (t, 2 H, J = 5.9 Hz, H-3), 2.71 (t, 2 H, J = 5.9 Hz, H-4), 1.85 (s, e, 1 H, N*H*); ^{13}C ($CDCl_3$) δ 138.3, 134.9, 134.8, 134.4, 131.1, 90.6 (C-7), 47.6 (C-1), 43.5 (C-3), 28.6 (C-4).

The hydrochloride salt was crystallized from MeOH−Et_2O: mp 243−244 °C dec; IR (KBr, HCl salt) 2920, 2760, 1575, 1420, 1345 (SO_2), 1155 (SO_2), 820 cm^{-1}; EIMS m/z 260 (M + 1, 6), 259 (M^+, 49), 258 (M^+ − 1, 75), 231 (10), 230 (76), 132 (M^+ − I, 27), 103 (77), 77 (100). Anal. ($C_9H_{10}IN$·HCl) C, H, N.

7-Trifluoromethyl-*N*-acetyl-1,2,3,4-tetrahydroisoquinoline (41). To a solution of iodoacetamide **40** (1.5 g, 5.0 mmol) in anhydrous DMF were added copper(I) iodide (0.95 g, 5.0 mmol), dry potassium fluoride (0.29 g, 5.0 mmol), and methyl chlorodifluoroacetate (1.4 g, 1.1 mL, 10 mmol). Effervescence was observed after the reaction mixture was heated to reflux, and a dark-brown solution resulted. After heating to reflux for 8 h under N_2, the dark-brown solution was diluted with water (20 mL) and filtered through Celite to remove precipitated solids. The Celite bed was washed with CH_2Cl_2 (thrice), and the combined filtrate was extracted with CH_2Cl_2 (thrice). The organic washes and extracts were combined and evaporated to yield a dark-brown oil (1.26 g) which was passed through a silica plug ($CHCl_3$/THF, 20:1 as the eluent) to afford a brown oil (1.1 g). Further purification by PCTLC (silica, 4 mm; $CHCl_3$/THF, 20:1, as the eluent) gave a brown oil (0.94 g, 78%). A small amount of this product was distilled bulb-to-bulb (120 °C, 0.1 mmHg) to get an analytically pure sample: IR (film) 3460, 1640 (CO), 1325, 1230, 1160, 1070, 825, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44−7.12 (m, 3 H, Ar*H*), 4.77−4.62 (m, 2 H, H-1), 3.84−3.60 (m, 2 H, H-3), 2.98−2.85 (m, 2 H, H-4), 2.20−2.11 (m, 3 H, COCH_3); MS EIMS m/z 243 (M^+, 43), 200 (M^+ − $COCH_3$, 24), 186 (12), 185 (18), 172 (26), 103 (17), 91 (18), 77 (13), 43 (100). Anal. ($C_{12}H_{12}F_3NO$) C, H, N.

7-Trifluoromethyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (25·HCl). Acidic hydrolysis of the trifluoroacetamide **41** (0.89 g, 3.7 mmol) as described for the iodo derivative yielded a colorless oil (0.49 g, 67%): ^1H NMR ($CDCl_3$) δ 7.38−7.17 (m, 3 H, Ar*H*), 4.04 (s, 2 H, H-1), 3.15 (t, 2 H, J = 5.9 Hz, H-3), 2.84 (t, 2 H, J = 5.9 Hz, H-4), 1.88 (bs, e, 1 H, N*H*).

The hydrochloride salt was obtained as colorless flakes: mp 242−244 °C dec; IR (KBr, HCl salt) 2775, 1580, 1340, 1170, 1110, 1075, 820 cm^{-1}; EIMS m/z 202 (M + 1, 6), 201 (M^+, 36), 200 (M^+ − 1, 100), 182 (10), 172 (56), 151 (16), 132 (M^+ − CF_3, 15), 103 (34). Anal. ($C_{10}H_{10}F_3N$·HCl) C, H, N.

7-Acetamido-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (43). To a solution of the amine **42**[21] (1.38 g, 5.65 mmol) in CH_2Cl_2 (10 mL) were added triethylamine (1.14 g, 1.57 mL, 11.3 mmol) and acetyl chloride (0.66 g, 0.60 mL, 8.5 mmol). The reaction mixture was stirred at room temperature for 6 h and then quenched with ice water. After extraction of the reaction mixture with CH_2Cl_2 (thrice), the combined extracts were washed with 1 N HCl (thrice). Drying (anhydrous Na_2SO_4), followed by the removal of the solvent, gave a yellow solid which was crystallized from EtOAc−hexanes to afford small pale-yellow crystals (1.19 g, 73.5%): mp 167−168 °C; IR (KBr) 3320 (NH), 1690−1670 (CO), 1595, 1535,

1500, 1410, 1180, 1145, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.96−8.93 (m, e, 1 H, N*H*), 7.61−7.25 (m, 2 H, H-6 and H-8), 7.11−7.07 (m, 1 H, H-5), 4.76 and 4.72 (s, 2 H, H-1, conformers), 3.89−3.91 (m, 2 H, H-3), 2.93−2.87 (m, 2 H, H-4), 2.15 (s, 3 H, COC*H*$_3$); EIMS *m/z* 287 (M+1, 9), 286 (M^+, 50), 245 (14), 244 (100), 243 ($M^+ - COCH_3$, 13), 229 (69), 217 (11), 147 (15), 131 (21), 119 (42), 91 (20), 43 (56). Anal. ($C_{13}H_{13}F_3N_2O_2$) C, H, N.

7-Acetamido-1,2,3,4-tetrahydroisoquinoline Hydrochloride (26·HCl). Acetamide **43** (0.55 g, 1.9 mmol) was dissolved in 20% aqueous MeOH (12 mL) and treated with K_2CO_3 (0.34 g, 2.4 mmol). After stirring at room temperature for 14 h, the reaction mixture was evaporated to dryness, and the residue was suspended in water (15 mL) and extracted with EtOAc (thrice). The combined EtOAc extracts were dried (anhydrous Na_2SO_4) and evaporated to yield a yellow solid (0.33 g). PCTLC (silica, 2 mm) was performed on the crude product (CH_2Cl_2/MeOH/NH_4OH, 250:17:1, as the initial eluent and then CH_2Cl_2/MeOH/NH_4OH, 250:34:1, as the final eluent) to afford a pale-yellow solid (0.22 g, 61%): mp 130−132 °C; IR (KBr) 3280 (NH), 3220 (N*H*COCH$_3$), 1665 (CO), 1590, 1540, 1410, 1250, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.15 (s, e, 1 H, N*H*COCH$_3$), 7.30−7.26 (m, 2 H, H-6 and H-8), 6.98 (d, 1 H, J = 7.9 Hz, H-5), 3.94 (s, 2 H, H-1), 3.32 (bs, e, N*H*), 3.11 (t, 2 H, J = 6.0 Hz, H-3), 2.75 (t, 2 H, J = 5.8 Hz, H-4), 2.11 (s, 3 H, COC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 168.3 (CO), 136.1, 134.6, 129.2, 128.9, 117.9, 117.2, 47.2 (C-1), 43.0 (C-3), 27.6 (C-4), 23.8 (CO*C*H$_3$).

The hydrochloride salt was obtained as a yellow solid: mp 235 °C dec; EIMS *m/z* 190 (M^+, 17), 189 ($M^+ - 1$, 12), 161 (19), 148 (32), 120 (17), 119 (100), 118 (23), 91 (18), 57 (11). Anal. ($C_{11}H_{14}N_2O$·HCl·0.3H_2O) C, H, N.

7-Benzoyl-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (45). The compound was prepared from **44** according to the procedure described[26] for the synthesis of 7-acetyl-1,2,3,4-tetrahydroisoquinoline in which benzoyl chloride was used instead of acetyl chloride. The yellow-orange crude product was subjected to flash chromatography (silica; $CHCl_3$/THF, 20:1, as the eluent) to yield an orange solid (70%) which was crystallized to afford a colorless crystalline light flakes from hexanes−EtOAc (17%): mp 116−117 °C; IR (KBr) 1685 (NCOCF_3), 1650 (COPh), 1410, 1280, 1190, 1170, 1150, 1130, 910, 700 cm^{-1}; ^1H NMR ($CDCl_3$) 7.82−7.74 (m, 2 H, Ar*H*), 7.68−7.58 (m, 3 H, Ar*H*), 7.52−7.45 (m, 2 H, Ar*H*), 7.32−7.22 (m, 1 H, Ar*H*), 4.78−4.89 (m, 2 H, H-1), 3.96−3.84 (m, 2 H, H-3), 3.10−3.00 (m, 2 H, H-4); EIMS *m/z* 334 (M + 1, 13), 333 (M^+, 53), 256 (16), 208 (16), 131 (15), 115 (11), 105 ($PhCO^+$, 100), 77 (78), 69 (11), 51 (22). Anal. ($C_{18}H_{14}F_3NO_2$) C, H, N.

The regiochemistry of the product was confirmed by a one-dimensional difference nuclear Overhauser effect (NOE) experiment. When the protons at approximately 4.83 ppm were irradiated (corresponding to the 1-position on the THIQ nucleus), a positive NOE response was detected at 7.62 ppm (corresponding to the 8-position on the THIQ nucleus). This singlet was the only NOE enhancement observed.

7-Benzoyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (27·HCl). The hydrolysis procedure as described[26] for the preparation of 7-acetyl-1,2,3,4-tetrahydroisoquinoline was performed on **45** (0.35 g, 1.0 mmol) to yield **27** (0.25 g, 86%) as a colorless solid: mp 244−246 °C dec; IR (KBr) 1640 (CO), 1600, 1580, 1270, 1250, 720 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.90 (bs, e, 2 H, NH_2^+), 7.75−7.55 (m, 7 H, Ar*H*), 7.41 (d, 1 H, J = 8.1 Hz, Ar*H*), 4.34 (s, 2 H, H-1), 3.39−3.37 (m, 2 H, H-3), 3.14−3.12 (m, 2 H, H-4); ^{13}C NMR (DMSO-d_6) δ 195.2 (CO), 137.3, 136.9, 135.2, 132.8, 129.6, 129.0, 128.6, 128.5, 128.2, 43.3 (C-1), 40.1 (C-3), 24.9 (C-4); EIMS *m/z* 238 (M + 1, 8), 237 (M^+, 44), 236 ($M^+ - 1$, 78), 208 (26), 132 (20), 131 (36), 015 ($PhCO^+$, 34), 77 (100), 51 (30). Anal. ($C_{16}H_{15}NO$·HCl) C, H, N.

7-Benzyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (28·HCl). Amide **45** (0.22 g, 0.66 mmol) was dissolved in EtOH (10 mL), and to this solution were added Pd/C (10%, 0.5 g) and $HClO_4$ (70%, 0.2 mL). The suspension was hydrogenated at 50 psi for 8 h at room temperature. The reaction mixture was filtered through Celite and evaporated to dryness. The resultant pale-yellow semisolid was dissolved in EtOH (5 mL) and heated to reflux with 3 N KOH (3 mL) under N_2 for 3 h. The solvent was removed on a rotary evaporator to afford a solid which was suspended in water (15 mL). Extraction with CH_2Cl_2 (thrice), drying (K_2CO_3), and evaporation yielded a pale-yellow oil (0.15 g). Purification by PCTLC (silica, 1 mm) using CH_2Cl_2/MeOH/NH_4OH (250:17:1) as the eluent yielded **28** as a pale-yellow oil (0.12 g, 80%): ^1H NMR ($CDCl_3$) δ 7.30−7.10 (m, 5 H, Ar*H*), 6.99−6.91 (m, 2 H, Ar*H*), 6.82−6.80 (m, 1 H, Ar*H*), 4.00−3.88 (m, 4 H, H-1, PhCH_2Ar), 3.08 (t, 2 H, J = 5.9 Hz, H-3), 2.74 (t, 2 H, J = 5.8 Hz, H-4), 2.11 (bs, e, 1 H, N*H*).

The free base was converted to the hydrochloride salt and crystallized as shiny flakes from MeOH−Et_2O: mp (HCl) 215−216 °C dec; IR (KBr) 2940, 2780, 1580, 1490, 1450, 1420, 1060, 960, 790, 710, 690 cm^{-1}; EIMS *m/z* 224 (M + 1, 12), 223 (M^+, 60), 222 ($M^+ - 1$, 100), 194 (70), 179 (32), 178 (31), 165 (19), 132 (45), 115 (21), 91 ($PhCH_2^+$, 48), 77 (14), 65 (14), 51 (18). Anal. ($C_{16}H_{17}N$·HCl·0.3H_2O) C, H, N.

Radiochemical Assay for PNMT Activity. The assay used in this study has been described elsewhere.[45] Briefly, a typical assay mixture consisted of 50 μL of 0.5 M phosphate buffer (pH 8.0), 25 μL of 10 mM unlabeled AdoMet, 5 μL of [*methyl*-^{3}H]AdoMet, containing approximately 3×10^5 dpm (specific activity approximately 15 mCi/mmol), 25 μL of substrate solution (phenylethanolamine), 25 μL of inhibitor solution, 25 μL of the enzyme preparation, and sufficient water to achieve a final volume of 250 μL. After incubation for 30 min at 37 °C, the reaction mixture was quenched by addition of 250 μL of 0.5 M borate buffer (pH 10.0) and was extracted with 2 mL of toluene/isoamyl alcohol (7:3). A 1-mL portion of the organic layer was removed, transferred to a scintillation vial, and diluted with cocktail for counting. The mode of inhibition was ascertained to be competitive in all cases reported in Table 1 by inspection of the 1/*V* vs 1/*S* plots of the data. All assays were run in duplicate with three inhibitor concentrations over a 5-fold range. K_i values were determined by a hyperbolic fit of the data.

α_2-Adrenoceptor Radioligand Binding Assay. The radioligand receptor binding was performed according to the method of U'Prichard et al.[46] Male Sprague−Dawley rats were decapitated, and the cortexes were dissected out and homogenized in 20 volumes (w/v) of ice-cold 50 mM Tris/HCl buffer (pH 7.7 at 25 °C). Homogenates were centrifuged thrice for 10 min at 50 000*g* with resuspension of the pellet in fresh buffer between spins. The final pellet was homogenized in 200 volumes (w/v) of ice-cold 50 mM Tris/HCl buffer (pH 7.7 at 25 °C). Incubation tubes containing [^{3}H]clonidine (specific activity ca. 19.2 mCi/mmol, final concentration 4.0 nM), various concentrations of drugs, and an aliquot of freshly resuspended tissue (800 μL) in a final volume of 1 mL were used. Tubes were incubated at 25 °C for 30 min, and the incubation was terminated by rapid filtration under vacuum through GF/B glass fiber filters. The filters were rinsed with three 5-mL washes of ice-cold 50 mM Tris buffer (pH 7.7 at 25 °C). The filters were counted in vials containing premixed scintillation cocktail. Nonspecific binding was defined as the concentration of bound ligand in the presence of 2 μM phentolamine. All assays were run in quadruplicate with five inhibitor concentrations over a 16-fold range. IC_{50} values were determined by a log−probit analysis of the data, and K_i values were determined by the equation $K_i = IC_{50}/(1 + [\text{clonidine}]/K_D)$, as all Hill coefficients were approximately equal to 1.

Comparative Molecular Field Analysis (CoMFA) Modeling. For all of the compounds in this study, with the exception of those containing SO_2NHR substructures, the minimum energy conformations were calculated without electrostatics using the Tripos force field, followed by reminimization with charges calculated by the AM1 method in MOPAC (SYBYL 6.2 implementation). The semiempirical AM1 option in MOPAC was used for the geometry optimization and charge calculation of compounds with SO_2NHR substructures, as torsion parameters for such were not available in the Tripos force field. The conformations of compounds bearing side

chains were calculated by the "systematic search" option in SYBYL to locate the global minimum energy conformation. If possible, side chains were oriented such that they occupied the same region of space, even though this necessitated the use of a local minimum energy conformation (within 2 kcal/mol of the corresponding global minimum.)

Molecules were aligned in orientations A (lipophilic) or B (hydrophilic) and fit using three points: both ends of a normal (2 Å long) passing through the centroid of the THIQ aromatic ring and the end of the axial lone pair (2.4 Å long) on the THIQ nitrogen. The CoMFA procedure was then implemented by defining a three-dimensional lattice around the superimposed molecules which had a grid spacing of 2 Å and extended beyond the shape of all the molecules by a distance of at least 4 Å. The electrostatic (Coulombic) and steric (van der Waals) interactions were then sampled—using an sp^3-hybridized carbon containing a unit positive charge as a probe atom—at each intersection point of the lattice, except at those points where the steric interaction energy indicated that the probe atom was "inside" the aligned molecules (i.e., energy greater than 30 kcal/mol). The CoMFA model was developed using a partial least-squares (PLS) analysis, as implemented in SYBYL 6.2. Cross-validated (leave-one-out) runs were used to refine the model and evaluate the number of components that yielded the best r^2.

Molecular Graphics Studies. Molecular modeling was performed using the SYBYL software package (version 6.2, Tripos Associates, Inc., St. Louis, MO) on a Silicon Graphics Indigo^2 workstation.

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(49) As will be noted later in the CoMFA section, the best CoMFA models were obtained by using the parameters for the neutral forms of compounds **13** and **14**. However, in the QSAR, the r values showed significant reduction if the neutral forms were used (eq 1, $r = 0.853$ vs $r = 0.730$ if neutral forms used; eq 3, $r = 0.826$ vs $r = 0.800$ if neutral forms used).
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(53) (a) An increase in the correlation coefficient of eq 2 (PNMT) ($r = 0.912$ vs $r = 0.885$) could be obtained through the inclusion of an indicator variable (I) to account for the higher activity of lipophilic compounds that could bind in orientation A. As shown in Figure 1, all 7-substituted-THIQs bearing a lipophilic ($+\pi$) substituent which may bind in orientation A were given a value of $I = 1$, while those bearing hydrophilic ($-\pi$) substituents which may bind in orientation B were given a value of $I = 0$. However, the inclusion of I was not justified statistically ($F_{(1,22)} = 6.36$ vs $F_{(1,22,0.01)} = 7.94$). (b) Addition of an indicator variable in the α_2-adrenoceptor equation (eq 4) did not increase the correlation (0.917 vs 0.917) and was therefore not included in the derivation.
(54) Attempts at using the selectivity (α_2 K_i/PNMT K_i) as the dependent variable with the parameters π, σ_m, and MR showed that only the single-variable equation with σ_m was statistically significant [log(selectivity) $= 2.05(\pm 1.48)\sigma_m - 0.686(\pm 0.552)$; $n = 28$, $r = 0.487$, $s = 0.955$, $F_{(1,26)} = 8.10$, $F_{(1,26,0.01)} = 7.72$]. This equation explains only 24% of the variance in the data and would indicate that both sites cannot be described by a single equation.
(55) This suggests that the use of the flipped orientation might have been of value in the QSAR analyses. However, there is only one such compound in the data set, and using an indicator variable for it would be of limited usefulness in the QSAR analyses.
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