3,7-Disubstituted-1,2,3,4-tetrahydroisoquinolines Display Remarkable Potency and Selectivity as Inhibitors of Phenylethanolamine *N*-Methyltransferase versus the α_2-Adrenoceptor[1a]

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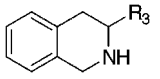
3-Hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (**4**) is a more selective inhibitor (PNMT K_i = 1.1 μM, α_2 K_i = 6.6 μM, selectivity (α_2 K_i/PNMT K_i) = 6.0) of phenylethanolamine *N*-methyltransferase (PNMT, EC 2.1.1.28), with respect to its α_2-adrenoceptor affinity, than is 3-methyl-1,2,3,4-tetrahydroisoquinoline (**2**; PNMT K_i = 2.1 μM, α_2 K_i = 0.76 μM, selectivity = 0.36) or 1,2,3,4-tetrahydroisoquinoline (**1**, THIQ; PNMT K_i = 9.7 μM, α_2 K_i = 0.35 μM, selectivity = 0.036). Evaluation of the *O*-methyl ether derivative of **4** suggested that the 3-hydroxymethyl substituent might be involved in a hydrogen-bond donor-type of interaction at a sterically compact region in the PNMT active site. The directionality of the steric bulk tolerance at both the PNMT active site and the α_2-adrenoceptor appears to be the same. Since the presence of a hydrophilic electron-withdrawing substituent (such as NO_2, SO_2CH_3, or SO_2NH_2) at the 7-position of THIQ reduced the binding affinity toward the α_2-adrenoceptor, we investigated the combination of both a hydrophilic electron-withdrawing 7-substituent and a 3-alkyl substituent on a THIQ nucleus. A synergistic effect in increasing the PNMT-inhibitory potency of the THIQ nucleus and reducing the affinity toward the α_2-adrenoceptor was observed with this 3,7-disubstitution. Remarkably, 7-aminosulfonyl-3-hydroxymethyl-THIQ (**12**; PNMT K_i = 0.34 μM, α_2 K_i = 1400 μM, selectivity = 4100) displayed a 23−680-fold enhanced selectivity over the parent compounds **27** (SK&F 29661; PNMT K_i = 0.55 μM, α_2 K_i = 100 μM, selectivity = 180) and **4** (selectivity = 6.0) and is thus the most selective PNMT inhibitor yet reported.

Introduction

We have targeted the enzyme phenylethanolamine *N*-methyltransferase (PNMT, EC 2.1.1.28), the enzyme involved in the biosynthesis of epinephrine, to define the role of epinephrine in the central nervous system (CNS). Inhibition of PNMT offers a unique way of studying the pharmacology of central epinephrine without significantly affecting the levels of other brain catecholamines.[2,3] On the basis of the innervation of various brain nuclei, epinephrine is speculated to be involved in the control of oxytocin secretion, food and water intake, gonadotrophin secretion, blood pressure, and respiration, along with sleep and wakefulness.[4] Also, more recent studies have implied that PNMT may play a role in the degeneration of epinephrine-containing neurons in the progression of Alzheimer's and Parkinson's diseases.[5,6] Unfortunately, the high affinity of most of the well-studied PNMT inhibitors toward the α_2-adrenoceptor has been the major barrier in unambiguously defining the role of epinephrine in the central nervous system.[7]

A number of potent inhibitors of PNMT contain the 1,2,3,4-tetrahydroisoquinoline (THIQ, **1**) nucleus.[8] It was established by Kaiser et al.[8] that a chlorine at the 7-position on the THIQ nucleus is optimal as compared to the 5-, 6-, or 8-position in regard to PNMT inhibition. Subsequently, we reported that the 3-position was best for an alkyl substituent as compared to position 1 or 4 on the THIQ nucleus.[9] Introduction of a methyl substituent at position 1 or 4 led to a 10−20-fold reduction in PNMT-inhibitory activity as compared to 3-methyl-THIQ (**2**). The increased potency of **2** (K_i = 3.0 μM, molar refractivity (MR) for CH_3 = 5.65) over **1** (K_i = 10 μM) was attributed to a favorable steric interaction at the PNMT active site.[10] Previously, a variety of substituents at the 3-position on THIQ had been synthesized[11] to probe this site and the nature of the interaction that enhanced PNMT-inhibitory potency (Table 1). An ethyl substituent is not very sterically demanding (MR = 10.3) relative to a hydroxymethyl substituent (MR = 7.19), but **3** (3-ethyl-THIQ) was found to be 10 times less active (K_i = 24 μM) at inhibiting PNMT than **4** (3-hydroxymethyl-THIQ; K_i = 2.4 μM). This result

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



compd	R_3	PNMT K_i ± SEM[b]	α_2 K_i ± SEM[c]
1	H	10 ± 1	0.35 ± 0.10[d]
2	CH_3	3.0 ± 0.2	0.76 ± 0.08
3	CH_2CH_3	24 ± 1	0.66 ± 0.11
4	CH_2OH	2.4 ± 0.2	6.6 ± 0.3
5	CO_2H	>2000	
6	CO_2CH_3	70 ± 6	11 ± 1
7	$CONH_2$	41 ± 2	250 ± 20

[a] All values are μM. [b] Reference 11. [c] Determined in our laboratory. [d] Reference 10.

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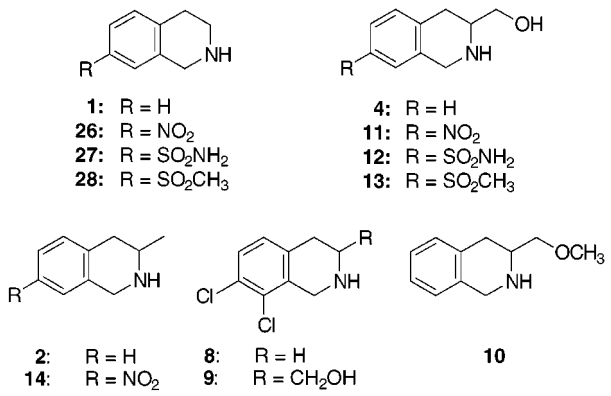
argued for a hydrogen-bonding-type of interaction that overcomes steric bulk intolerance and increases PNMT-inhibitory activity. Evaluation of THIQs bearing carbonyl substituents, such as CO_2CH_3 and $CONH_2$, indicated that not only the amount of steric bulk but also the spatial orientation of the steric bulk was important. Linear chains of limited steric bulk were tolerated better than the bent carbonyl chains.

Introduction of a 3-hydroxymethyl substituent onto the potent PNMT inhibitor SK&F 64139 (**8**) to produce 3-hydroxymethyl-7,8-dichloro-THIQ (**9**) was expected to further enhance the PNMT-inhibitory activity. However, **9** ($K_i = 0.38\ \mu M$)[11] was found to exhibit similar potency as a PNMT inhibitor compared to **8** ($K_i = 0.20\ \mu M$),[10] while the α_2-adrenoceptor affinity of **9** (α_2 $K_i = 0.15\ \mu M$)[12] was found to be about 7 times lower than that of **8** (α_2 $K_i = 0.022\ \mu M$),[10] resulting in an overall gain in selectivity (**8**, selectivity (α_2 K_i/PNMT K_i) = 0.11 vs **9**, selectivity = 0.39). In light of our previous study on 7-substituted-THIQs,[13] it seemed of interest to probe the effect of the 3-hydroxymethyl substituent on THIQs bearing a hydrophilic electron-withdrawing substituent at the 7-position that previously had been shown to confer enhanced selectivity (e.g., NO_2, SO_2NH_2, or SO_2CH_3).

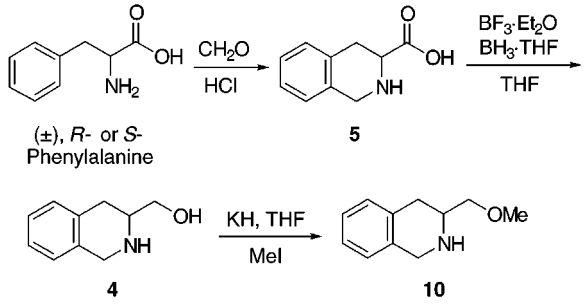


The 3-substituted-THIQs evaluated above were racemates, and thus stereoselectivity in binding remained undetermined. On the basis of these considerations, the enantiomers resulting from the combination of a 3-methyl or a 3-hydroxymethyl substituent with a 7-substituent on THIQ were investigated. Also, the *O*-methyl ether derivative of **4** (compound **10**) was synthesized to probe the nature of the hydrogen-bonding interaction.

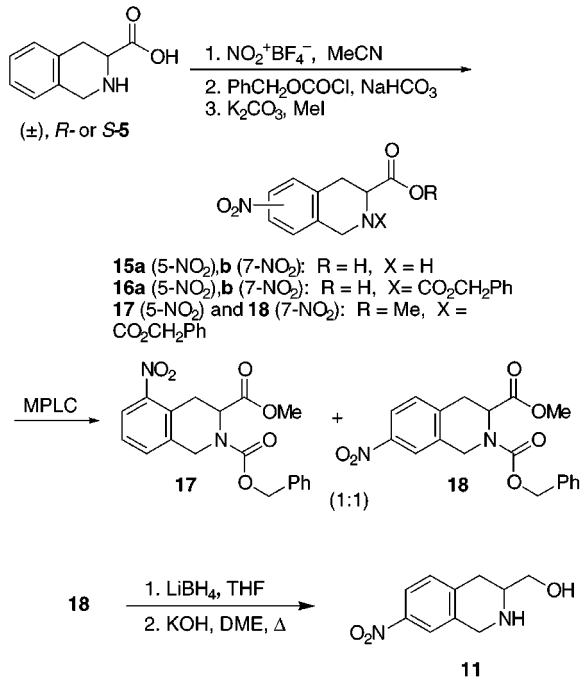
Chemistry

Compound **5** was prepared from phenylalanine by treatment with formaldehyde and concentrated hydrochloric acid (Scheme 1), according to literature procedure.[14] However, with enantiopure phenylalanine, partial racemization of **5** was reported to occur under the acidic reaction conditions.[14b] Repeated crystallization of **5** from aqueous ethanol (to constant optical rotation) permitted the isolation of the enantiomers in enantiomerically pure form, albeit in modest yields. The borane-mediated reduction of amino acid **5** was facilitated by the addition of $BF_3{\cdot}Et_2O$[15] which formed a THF-soluble complex with **5**. Preferential *O*-methylation of **4** to yield **10** was accomplished quantitatively using the reaction conditions described by Meyers et al.[16]

Scheme 1

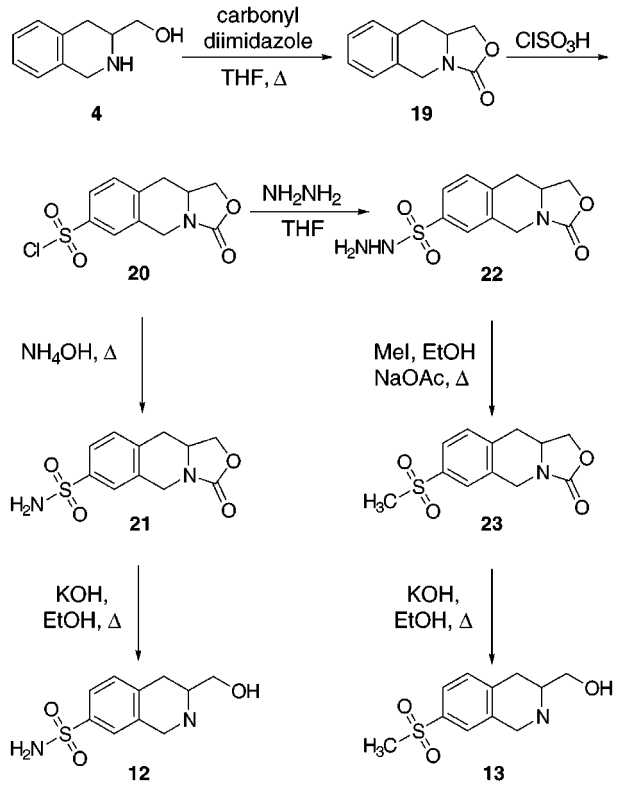


Scheme 2



Most of the classical methods for the preparation of THIQs (e.g., Pictet−Spengler, Bischler−Napieralski, and Pomeranz−Fritsch reactions) involve the participation of the aromatic ring π electrons in the cyclization step. Therefore, these methods cannot be used in the synthesis of THIQs bearing strong electron-withdrawing substituents on the aromatic ring. In the synthesis of **11**, a direct approach based on electrophilic aromatic nitration of **5** was undertaken (Scheme 2). Electrophilic substitution reactions such as nitration,[17,18] chlorosulfonation,[19] and Friedel−Crafts acylation[20] have been quite successful in introducing a substituent at the 7-position on THIQ. To minimize racemization of **5**, an unconventional nitration was carried out with commercially available nitronium tetrafluoroborate[21] using nonaqueous and nonacidic conditions. The mixture of 5- and 7-nitro amino alcohols **15a**,**b** obtained could not be separated by column chromatography. Thus, the mixture was converted to the *N*-benzyloxycarbonyl derivatives **16a**,**b**, followed by esterification to the methyl esters **17** and **18**, which enabled the successful separation of the regioisomers by medium-pressure liquid chromatography (MPLC).[22] (It was interesting to note that the *N*-*tert*-butyloxycarbonyl methyl ester derivative of **5** could not be cleanly separated by MPLC.) The regiochemistry of the isolated products was unambiguously established only after their conversion to the

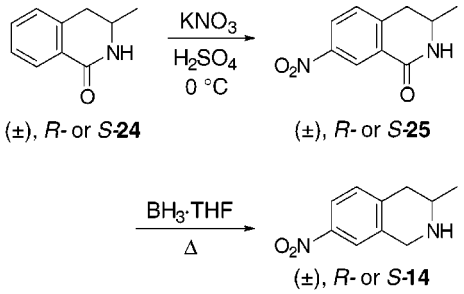
Scheme 3



corresponding amino alcohols. Reduction of the ester group in **18** followed by cleavage of the benzyloxycarbonyl group under basic conditions[23] gave the desired compound **11**. On the basis of the aromatic splitting pattern in the ^{1}H NMR spectrum and the results of a one-dimensional difference nuclear Overhauser effect (NOE) experiment on **11**, the nitro group was assigned to the 7-position (see Experimental Section).

Chlorosulfonation of the aromatic nucleus provided a convenient way of introducing a sulfur substituent. The reaction of **4** with carbonyldiimidazole[24] gave oxazolidinone **19**—the key intermediate for the synthesis of 7-sulfur-substituted 3-hydroxymethyl-THIQs (Scheme 3). The protection of **4** as an oxazolidinone avoided any side reactions in the subsequent chlorosulfonation process. Unlike the chlorosulfonation of *N*-acetyl-THIQ, which gave only the 7-regioisomer,[13] oxazolidinone **19** gave a mixture of regioisomers after treatment with chlorosulfonic acid. Fortunately, the desired 7-chlorosulfonyl regioisomer **20** could be purified by fractional crystallization from ethyl acetate in a low yield of 16%. The regiochemistry of **20** was confirmed by a one-dimensional difference NOE experiment (see Experimental Section). Formation of sulfonamide **21** from **20**, followed by basic hydrolysis of the oxazolidinone, furnished the desired aminosulfonyl alcohol **12**. The transformation of the sulfonyl hydrazide derivative **22** to the methanesulfonyl oxazolidinone **23** was conveniently achieved by heating an ethanolic suspension of **22** with methyl iodide and sodium acetate. In this general method,[25] the initially formed *N*-methylsulfonyl hydrazide is thought to undergo an acetate anion-mediated elimination to the sulfinate anion which is then alkylated by methyl iodide to afford the methyl sulfone. Removal of the oxazolidinone protecting group from **23** gave sulfone **13**.

Scheme 4



As mentioned earlier, electrophilic substitution reactions such as chlorosulfonation and Friedel–Crafts acylation on *N*-acetyl-THIQ are known to produce the desired 7-regioisomer. However, nitration of **2** or its *N*-acetyl derivative gave an inseparable mixture of regioisomers. Nitration of 3,4-dihydro-2*H*-isoquinolin-1-one has been reported[26] to produce only the 7-nitro product in excellent yields. Racemic 3-methylisoquinolone **24** and its enantiomers were readily prepared by a literature method[27] and nitrated cleanly to yield a single regioisomer **25** and its enantiomers (Scheme 4). The presence of the most downfield doublet at 8.55 ppm (due to H-8 which is ortho to both the nitro and the amido group) in the ^{1}H NMR spectrum of **25** is in accordance with the assigned regiochemistry. Borane reduction of amide **25** gave **14**, with no competing reduction of the nitro group noted.

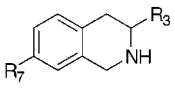
Biochemistry. All the compounds were evaluated as their hydrochloride salts. In vitro PNMT activity was assessed by use of a standard radiochemical assay that has been described previously for both substrates[28] and inhibitors.[29] Bovine adrenal PNMT used for the in vitro assay was purified according to the procedure of Connett and Kirshner[30] through the isoelectric precipitation step. Inhibition constants were determined by using at least three different concentrations of inhibitor, as previously described,[29] with phenylethanolamine as the variable substrate. α_2-Adrenergic receptor binding assays were performed using cortex obtained from male Sprague–Dawley rats.[31] [^{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 the biochemical evaluations are reported in Table 2. For comparison, the PNMT K_i values for the enantiomers of **2**[10] are included. For internal consistency, the PNMT K_i values given in Table 2 for racemic **2** and **4** were determined in assays done simultaneously with their enantiomers, rather than those reported previously.[9,11] Also, the PNMT K_i value reported for **1** was determined in an assay run concurrently with its α_2 assay,[10] rather than that reported previously.[11]

In comparison with unsubstituted THIQ (**1**; PNMT K_i = 9.7 μM, α_2 K_i = 0.35 μM, selectivity (α_2 K_i/PNMT K_i) = 0.036),[10] racemic **2** and **4** were more potent at PNMT and were also more selective (PNMT vs α_2-adrenoceptor affinity). Although the absolute configu-

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



compd	R_3	R_7	stereo	PNMT K_i (A) ± SEM (μM)	α_2 K_i (B) ± SEM (μM)	B/A selectivity
2	CH_3	H	(±)	2.1 ± 0.1	0.76 ± 0.08	0.36
			R-(−)	38 ± 2	5.7 ± 0.3	0.15
			S-(+)	1.0 ± 0.1	0.49 ± 0.05	0.49
14	CH_3	NO_2	(±)	0.49 ± 0.05	31 ± 1	63
			R-(−)	1.3 ± 0.1	53 ± 2	41
			S-(+)	0.25 ± 0.02	19 ± 1	76
4	CH_2OH	H	(±)	1.1 ± 0.1	6.6 ± 0.3	6.0
			R-(+)	0.56 ± 0.05	4.4 ± 0.3	7.9
			S-(−)	15 ± 2	17 ± 1	1.1
11	CH_2OH	NO_2	(±)	0.29 ± 0.04	19 ± 1	66
			R-(+)	0.24 ± 0.03	38 ± 1	160
			S-(−)	0.90 ± 0.05	13 ± 1	14
12	CH_2OH	SO_2NH_2	(±)	0.34 ± 0.06	1400 ± 30	4100
13	CH_2OH	SO_2CH_3	(±)	0.64 ± 0.04	660 ± 10	1000
10	CH_2OCH_3	H	(±)	9.2 ± 0.4	2.8 ± 0.1	0.30

ration of the more active enantiomer was the opposite in the case of **2** and **4** (due to the Cahn−Ingold−Prelog priority rule), the side chains are oriented in the same region of space. As such, the more active enantiomer in each case at PNMT was the (+)-enantiomer. Unfortunately, in the case of both **2** and **4**, the enantiomer that was more active at PNMT also had the higher α_2-adrenoceptor affinity (lower α_2 K_i) and, therefore, lower overall selectivity. It can be inferred that the directionality of steric bulk tolerance of the 3-substituted-THIQs at the PNMT active site and at the α_2-adrenoceptor appeared to be the same. Higher selectivity (PNMT vs α_2-adrenoceptor affinity) of (*R*)-(+)-**4** over (*S*)-(+)-**2** might be attributed to two factors: (1) higher potency at PNMT due to a hydrogen-bonding-type of interaction of the 3-hydroxymethyl substituent of **4** and (2) lower affinity at the α_2-adrenoceptor due to unfavorable steric interactions of the 3-substituent (the hydroxymethyl group is larger than the methyl group).

To probe the nature of hydrogen-bonding interactions (i.e., a hydrogen bond acceptor-type or donor-type of interaction), the *O*-methyl ether derivative **10** was prepared in racemic form. In comparison with (±)-**4**, (±)-**10** (PNMT K_i = 9.2 μM, α_2 K_i = 2.8, selectivity = 0.30) was less potent at PNMT and had a 2-fold higher affinity toward the α_2-adrenoceptor. On the basis of these results, it appeared that, at the PNMT active site, there is either a limited amount of steric bulk tolerance at the 3-position, as in the case of the 3-ethyl compound **3**, or a hydrogen bond donor-type of interaction that might be responsible for the increase in potency, as in the case of the 3-methoxymethyl compound **10**. The 2-fold enhancement in affinity of **10** toward the α_2-adrenoceptor might result from the increased lipophilicity of the CH_2OCH_3 ($\pi = -0.78$)[32] substituent over the CH_2OH substituent ($\pi = -1.03$).[32] This hypothesis was consistent with the observed higher α_2-adrenoceptor affinity of (±)-**2**, wherein the 3-substituent was more lipophilic (π for CH_3 = 0.56).[32]

The combination of a nitro group at the 7-position and a 3-alkyl substituent on THIQ enhanced selectivity (PNMT vs α_2-adrenoceptor affinity) as compared to 3-alkyl-THIQs or 7-nitro-THIQ (**26**; PNMT K_i = 0.41 μM, α_2 K_i = 4.3 μM, selectivity = 10)[13] alone. This synergistic effect was not observed for **9**. We have proposed that THIQs bind in two different orientations—lipophilic (orientation A) and nonlipophilic (orientation B), depending on the lipophilicity of the 7-substituent on the aromatic ring.[13] Thus, the lack of synergism is not surprising, given that **9** (π = 0.71 for 7-Cl) is proposed to bind in orientation A, which would place the 3-hydroxymethyl substituent in a different region of space (Figure 1a).

Accordingly, the hydrophilicity of the 7-nitro group will direct the binding of the THIQ in orientation B (Figure 1b). The effect of adding a 7-nitro substituent to **2** (compound **14**) in reducing the α_2-adrenoceptor affinity was more pronounced than adding a 7-nitro substituent to **4** (compound **11**). As shown by the stereoselectivity ratios (as measured by the ratio of the K_i values of the two enantiomers) in Table 3, the general trend seen in this series was that the enantiomer which was more active in inhibiting PNMT also had the higher affinity toward the α_2-adrenoceptor, although this did not hold true for (*R*)-(+)-**11**.

Sulfonyl substituents (such as the methylsulfonyl and aminosulfonyl groups) markedly affect the potency and selectivity of the THIQ nucleus, and a remarkable synergism is displayed when a 3-hydroxymethyl substituent is combined with a 7-sulfonyl substituent. The 3-hydroxymethyl analogue (**12**; PNMT K_i = 0.34 μM) of SK&F 29661 (**27**) was about 1.6 times more potent than **27** (PNMT K_i = 0.55 μM)[13] in inhibiting PNMT. More importantly, its affinity toward the α_2-adrenoceptor was significantly decreased (**12**, α_2 K_i = 1400 μM vs **27**, α_2 K_i = 100 μM), resulting in a tremendous gain in selectivity (**12**, α_2/PNMT = 4100 vs **27**, α_2/PNMT = 180). Compound **12** is thus the most selective inhibitor of PNMT yet reported.

The synergistic effect was less dramatic in the case of the 3-hydroxymethyl analogue (**13**) of 7-methylsulfonyl-THIQ (**28**). In comparison with **28** (PNMT K_i = 1.34 μM, α_2 K_i = 160 μM, selectivity = 120),[13] a 2-fold enhancement in PNMT-inhibitory activity and a 4-fold loss in affinity toward the α_2-adrenoceptor were observed for **13** (PNMT K_i = 0.64 μM, α_2 K_i = 660 μM, selectivity = 1000). It previously had been shown that the 7-methylsulfonyl group was more effective than the

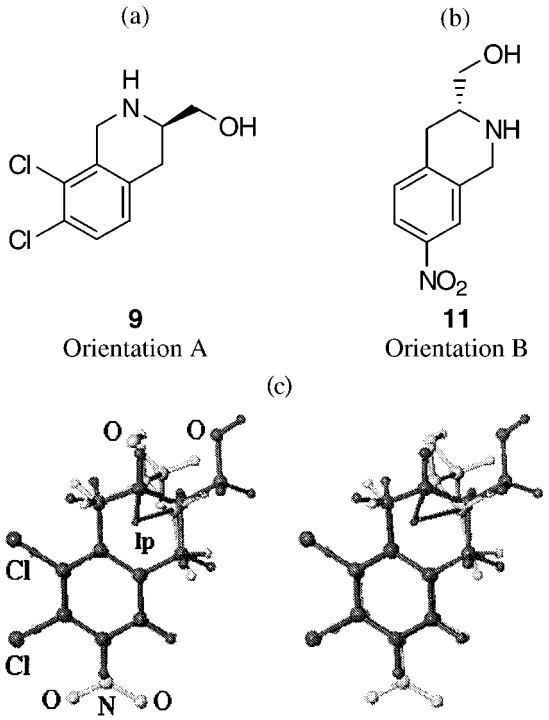


Figure 1. (a) Putatively more active *R* enantiomer of **9**, in orientation A, wherein it cannot approach the hydrogen-bonding site and was therefore unable to exhibit a synergistic effect at the PNMT active site. (b) More active *R* enantiomer of **11**, in orientation B, in which the side chain can participate in a hydrogen-bonding interaction and enhance the PNMT-inhibitory potency in a synergistic manner. (c) SYBYL-generated stereoview of (*R*)-**9** (orientation A: dark) superimposed on (*R*)-**11** (orientation B: light). The optimized geometries (Tripos force field) of **9** and **11** 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.

Table 3. Stereoselectivity Ratios[a] for PNMT and α_2-Adrenoceptor Activities

compd	PNMT (−)/(+)	α_2 (−)/(+)
2	38	12
4	27	3.9
11	3.8	0.34
14	5.2	2.8

[a] Ratios of the K_i values of the enantiomers.

7-aminosulfonyl group in reducing the α_2-adrenoceptor affinity of the THIQ nucleus (compare **27** and **28**).[13] In contrast, the reverse was found to be true in the case of the 3-hydroxymethyl-THIQs. The cause of further reduction in the binding affinity of **12** was not readily understood. It might be possible that **12** is binding in a different fashion or at some other allosteric site at the α_2-adrenoceptor.

Summary and Conclusion

It appears that the α_2-adrenoceptor displays more stereoselectivity in the binding of ligands than does the active site of PNMT. The directionality of steric bulk tolerance at the PNMT active site and at the α_2-adrenoceptor appears to be the same. The 3-hydroxymethyl substituent was more effective in increasing the PNMT-inhibitory activity of THIQ as well as reducing the α_2-adrenoceptor affinity, as compared to the 3-methyl-THIQs. At the PNMT active site, the hydroxymethyl substituent may be involved in a hydrogen bond donor-type of interaction. The combination of a 7-electron-withdrawing substituent and a 3-alkyl substituent on the THIQ ring not only enhanced PNMT-inhibitory potency but also reduced the α_2-adrenoceptor affinity. In general, the trend in stereoselectivity in binding of 7-nitro-3-alkyl-THIQs at the PNMT active site remained the same as observed for the 3-alkyl-THIQs. A tremendous gain in selectivity was observed when a hydroxymethyl substituent was introduced on **27**, resulting in the most selective (PNMT vs α_2-adrenoceptor affinity) compound (**12**) yet reported. Unfortunately, previous studies have shown that **27** is unable to penetrate the blood−brain barrier (BBB),[33] presumably due to its high polarity. Therefore, it is also likely that **12** would be unable to penetrate the BBB, which would make it an unsuitable pharmacological tool to define the role of epinephrine in the CNS. It is hoped that other combinations of 3,7-disubstitution on THIQ will produce a selective inhibitor with sufficient lipophilicity to penetrate the BBB.

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 GE QE-300 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 $CDCl_3$ (77.0 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 a Ribermag R10-10 mass spectrometer. The relative intensities of the mass spectrum peaks are listed in parentheses. Medium-pressure liquid chromatography (MPLC), using an adaptation of the apparatus of Meyers and co-workers,[22] 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/$CaSO_4$·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 200 μm). Bulb-to-bulb distillations were carried out on a Kugelrohr distillation apparatus (Aldrich Chemical Co., Milwaukee, WI), and oven temperatures were recorded. High-performance liquid chromatography was performed on a Shimadzu LC 6A system. The Chiralcel OJ column (0.46 × 25 cm) was purchased from Diacel Inc., New York. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter using the sodium D line as the light source. Combustion analyses were performed on a Hewlett-Packard model 185B CHN analyzer at the University of Kansas by Dr. Tho Ngoc Nguyen.

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

The compounds SK&F 64139 (**8**) and SK&F 29661 (**27**) were kindly provided by Smith Kline and French Laboratories, Smith Kline Corp., Philadelphia, PA. *S*-Adenosyl-L-methionine (AdoMet) 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).

(±)-3-Hydroxymethyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (4·HCl). A suspension of **5**[14a] (1.10 g, 5.64 mmol) in dry THF (15 mL) was stirred under N_2, and BF_3·Et_2O (1.0 mL, 8.1 mmol) was added to it via syringe. After the mixture stirred for 30 min, BH_3·THF complex (1 M in THF, 11 mL, 11 mmol) was added and the mixture was stirred overnight. The clear solution was cooled in an ice bath, and MeOH (5 mL) was added dropwise. After the effervescence ceased the solvent was removed on a rotary evaporator to afford a pale-yellow viscous oil that was heated with 6 N NaOH (10 mL) to reflux under N_2 for 6 h. The reaction mixture was cooled and extracted with ether (four times). The ether layers were combined, washed with brine, and dried over anhydrous $MgSO_4$. Evaporation of the etheral extract afforded a viscous yellow oil (1.10 g) that was distilled bulb-to-bulb (115−120 °C, 0.3 mmHg) to obtain a pale-yellow oil that solidified on cooling (0.64 g, 69%): mp 84−86 °C; IR (KBr) 3240 (NH), 3150−3050 (OH), 2900, 2820, 1450, 1320, 1060, 1040, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.13−6.98 (m, 4 H, Ar*H*), 3.98 (s, 2 H, H-1), 3.68 (dd, 1 H, J = 11.0, 3.7 Hz, OCH_2), 3.48 (dd, 1 H, J = 11.0, 7.5 Hz, OCH_2), 3.02−2.95 (m, 1 H, H-3), 2.62−2.55 (m, 2 H, H-4); the two exchangeable protons NH and OH were not observed and might be rapidly exchanged; ^{13}C NMR ($CDCl_3$) δ 135.2, 133.9, 129.2, 126.1, 126.0, 125.7, 65.3 (*C*H_2O), 55.0 (C-3), 47.8 (C-1), 30.8 (C-4). The free base was converted to the hydrochloride salt and recrystallized from MeOH−Et_2O: mp 196−198 °C, lit.[11] mp 195−196 °C.

(*R*)-(+)-3-Hydroxymethyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (4·HCl). Similarly (*R*)-(+)-**5**[14b] (0.40 g, 2.2 mmol) gave (*R*)-(+)-**4** (0.22 g, 60%): mp 113−114 °C (recrystallized from PhH), lit.[34] mp 116 °C. The free base was converted to its HCl salt: mp 240−241 °C dec; $[\alpha]^{24}_D$ = 56° (*c* 0.23, EtOH). Anal. ($C_{10}H_{13}NO$·HCl) C, H, N.

(*S*)-(−)-3-Hydroxymethyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (4·HCl). Similarly (*S*)-(−)-**5**[14b] (0.5 g, 2.8 mmol) gave (*S*)-(−)-**4** (0.33 g, 72%): mp 115−116 °C (recrystallized from PhH), lit.[35] mp 118−119 °C (recrystallized from PhH). The free base was converted to its HCl salt: mp 240−241 °C dec; $[\alpha]^{24}_D$ = −56° (*c* 0.23, MeOH). Anal. ($C_{10}H_{13}NO$·HCl) C, H, N.

(±)-3-Methoxymethyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10·HCl). The amino alcohol **4** (1.00 g, 6.16 mmol) was methylated according to the procedure described by Meyers et al.[16] for the *O*-methylation of amino alcohols with methyl iodide. After bulb-to-bulb distillation (100−105 °C, 0.25 mmHg) of the crude product, a colorless oil was obtained (1.00 g, 91.7%): IR (film) 3320 (NH), 2910, 2880, 1450, 1320, 1100, 790, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.11−6.98 (m, 4 H, Ar*H*), 4.06 and 4.01 (AB q, 2 H, J_{AB} = 15.6 Hz, H-1), 3.49 (dd, 1 H, J = 9.28, 3.8 Hz, CH_2O), 3.38−3.33 (m, 4 H, OCH_3 and CH_2O), 3.14−3.08 (m, 1 H, H-3), 2.78−2.50 (m, 2 H, H-4), 2.05 (bs, e, 1 H, N*H*); ^{13}C ($CDCl_3$) δ 135.4, 133.8, 129.0, 125.9, 125.8, 125.5, 76.4 (*C*H_2O), 58.8 (O*C*H_3), 52.9 (C-3), 47.9 (C-1), 31.2 (C-4). The hydrochloride salt was crystallized as colorless small crystals: mp 214−215 °C dec; EIMS m/z 178 (M^+ + 1, 1), 177 (M^+, 1), 133 (11), 144 (4), 134 (100), 117 (11), 115 (12), 104 (14), 77 (11), 45 (14). Anal. ($C_{11}H_{15}NO$·HCl) C, H, N.

(±)-5- and (±)-7-Nitro-*N*-benzyloxycarbonyl-3-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (17 and 18). To an ice-cold suspension of (±)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**5**)[14a] (2.50 g, 14.1 mmol) in dry acetonitrile (20 mL) was added nitronium tetrafluoroborate (2.43 g of 85% $NO_2^+BF_4^-$, 15.5 mmol) in one portion under N_2 with rapid stirring. After stirring for 1 h the reaction mixture was poured onto ice, and 10% NH_4OH was added dropwise until Congo red paper no longer turned blue. The solid was collected by suction filtration and was successively washed with water, EtOH, and ether. After air-drying **15a**,**b** was obtained as a pale-yellow solid (3.09 g, 98.6%): mp > 300 °C dec; IR (KBr) 2940, 2760, 2640, 2500, 1620 (CO), 1530 (NO_2), 1450, 1390, 1350 (NO_2), 1310, 1080, 860, 830, 780, 730 cm^{-1}.

To a rapidly stirred suspension of **15a**,**b** (0.50 g, 2.2 mmol) and $NaHCO_3$ (0.51 g, 6.1 mmol) in water (10 mL) was added benzyl chloroformate (0.48 g, 2.8 mmol) in small portions. The reaction mixture was stirred for 2 h at room temperature, and then the reaction mixture was washed with ether (thrice). The aqueous layer was adjusted to pH 2 with 1 N HCl, and the aqueous layer was extracted with EtOAc (thrice). The combined EtOAc layers were washed with brine and dried and the solvent removed by rotary evaporation to yield **16a**,**b** (0.53 g, 69%) as a thick red oil: IR (film) 3300−2800, 1700 (CO), 1660 (NCO), 1520 (NO_2), 1345 (NO_2), 1225, 1105, 1000, 730 cm^{-1}; MS (CI, NH_3), m/z 374 (M + NH_4^+, 97), 357 (M^+ + 1, 19), 313 (27), 221 (15), 177 (34), 145 (100), 106 (75), 91 (10), 52 (52).

A solution of **16a**,**b** (2.08 g, 5.83 mmol), K_2CO_3 (1.61 g, 11.7 mmol), and MeI (2.48 g, 1.09 mL, 17.5 mmol) in dry acetone (100 mL) was heated at reflux for 30 min under N_2. After cooling to room temperature the solvent was removed by rotary evaporation, water was added, and the mixture was extracted with CH_2Cl_2 (thrice). The combined CH_2Cl_2 layers were dried and evaporated to afford a mixture of **17** and **18** as an orange oil (2.59 g). The separation of the regioisomers was accomplished by MPLC using hexane/EtOAc (3:1) as the eluent, yielding **17** (0.810 g, 37.5%) and **18** (1.09 g, 50.6%).

(±)-17 was obtained as a thick yellow oil: IR (film) 2950, 1740 (CO_2Me), 1700 (CON), 1520 (NO_2), 1340 (NO_2), 1300, 1200, 1100, 1010, 730, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.08−8.05 (m, 2 H, H-6 and H-8), 7.41−7.24 (m, 6 H, H-7 and C_6H_5), 5.33−5.20 (m, 2 H, OCH_2Ph), 5.16−5.10 (m, 1 H, H-3), 4.91 and 4.71 (d, 2 H, J = 18.0 Hz, H-1, conformers), 3.64 and 3.58 (s, 3 H, OCH_3, conformers), 3.45−3.22 (m, 2 H, H-4); MS (CI, NH_3) m/z 388 (M + NH_4^+, 11), 371 (M^+ + 1, 16), 341 (9), 279 (49), 205 (11), 190 (24), 164 (53), 157 (100), 129 (26), 126 (13), 110 (26), 102 (13), 85 (32), 79 (63), 49 (98). Anal. ($C_{19}H_{18}N_2O_6$) C, H, N.

(±)-18 was crystallized from EtOAc−hexanes as a pale-yellow solid: mp 135−136 °C; IR (KBr) 3060, 2960, 1730 (CO_2Me), 1700 (CON), 1520 (NO_2), 1410, 1340 (NO_2), 1320, 1240, 1200, 1100, 1010, 900, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.04−7.99 (m, 2 H, H-6 and H-8), 7.41−7.31 (m, 6 H, H-5 and C_6H_5), 5.31−5.19 (m, 2 H, OCH_2Ph), 5.10−5.07 (m, 1 H, H-3), 4.93 and 4.69 (d, 2 H, J = 17 0.0 Hz, H-1, conformers), 3.64 and 3.57 (s, 3 H, OCH_3, conformers), 3.44−3.20 (m, 2 H, H-4); MS (CI, NH_3) m/z 388 (M + NH_4^+, 13), 371 (M^+ + 1, 6), 341 (10), 279 (11), 207 (24), 145 (11), 108 (13), 91 (13), 52 (100). Anal. ($C_{19}H_{18}N_2O_6$) C, H, N.

(*R*)-(−)-7-Nitro-*N*-benzyloxycarbonyl-3-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (18). Using an identical procedure as for the racemic compound, (*R*)-(+)-**5**[14b] yielded (*R*)-(−)-**18** as a thick yellow oil: $[\alpha]^{22}_D$ = −46° (*c* 0.20, $CHCl_3$). Anal. ($C_{19}H_{18}N_2O_6$) C, H, N.

(*S*)-(+)-7-Nitro-*N*-benzyloxycarbonyl-3-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (18). Using an identical procedure as for the racemic compound, (*S*)-(−)-**5**[14b] yielded (*S*)-(+)-**18** as a thick yellow oil: $[\alpha]_D^{22}$ = 52° (*c* 0.20, $CHCl_3$). Anal. ($C_{19}H_{18}N_2O_6$) C, H, N.

(±)-3-Hydroxymethyl-7-nitro-1,2,3,4-tetrahydroisoquinoline Hydrochloride (11·HCl). To a rapidly stirred ice-cold solution of (±)-**18** (1.10 g, 2.97 mmol) in dry THF (30 mL) was added $LiBH_4$ solution (2.0 M solution in THF, 5.9 mL, 12 mmol) dropwise under a positive pressure of N_2. The reaction mixture was allowed to stir at room temperature for 3 h and quenched with MeOH and 1 N HCl. Evaporation of the reaction mixture gave a yellow oil which was treated with water and extracted with CH_2Cl_2 (thrice). Drying followed by evaporation of the combined CH_2Cl_2 extracts furnished a yellow semisolid (0.84 g, 82%).

In a thick-walled tube the yellow semisolid (0.70 g, 2.0 mmol) was dissolved in DME (7 mL), and to it KOH (0.34 g, 6.1 mmol) was added as a solution in water (3 mL). The tube was flushed with N_2, and the orange-colored reaction mixture was heated at about 100 °C for 12 h. The resulting black-brown solution was cooled, made acidic with 6 N HCl, and extracted with CH_2Cl_2 (thrice) to remove color impurities. The aqueous solution was cooled, made alkaline with KOH pellets, and extracted with EtOAc (thrice). The combined EtOAc extracts were washed with brine (once), dried, and evaporated to yield a yellow-brown solid (0.25 g, 58%), which was crystallized from EtOAc−hexanes: mp 172−174 °C; IR (KBr) 3230 (NH), 3100 (OH), 2880, 2820, 1540 (NO_2), 1345 (NO_2), 1080, 1060, 1040, 830, 740 cm^{-1}; ^1H NMR (DMSO-d_6 and $CDCl_3$) δ 7.94 (m, 2 H, H-6 and H-8), 7.27 (d, 1 H, J = 8.5 Hz, H-6), 4.17 and 4.12 (AB q, 2 H, J_{AB} = 16.2 Hz, H-1), 3.73 (dd, 1 H, J = 10.7, 3.8 Hz, OCH_2), 3.60−3.36 (m, 2 H, OCH_2 and NH), 3.09−3.00 (m, 1 H, H-3), 2.85−2.62 (m, 2 H, H-4); ^{13}C NMR (DMSO-d_6 and $CDCl_3$) δ 145.0, 142.1, 136.4, 129.4, 120.4, 120.1, 64.4 (OCH_2), 53.9 (C-3), 47.1 (C-1), 30.7 (C-4); MS (CI, NH_3) m/z 209 (M^+ + 1), 169 (43), 104 (15), 102 (100), 85 (98).

The regiochemistry of the product was confirmed by a one-dimensional difference NOE experiment. When the protons at approximately 4.00 ppm were irradiated (corresponding to the 1-position on the THIQ nucleus), a positive NOE response was detected at 7.94 ppm (corresponding to the 8-position on the THIQ nucleus). This singlet was the only NOE enhancement observed. The hydrochloride salt was obtained as a pale-brown solid: mp 253−268 °C dec. Anal. ($C_{10}H_{12}N_2O_3$·HCl) C, H, N.

(*R*)-(+)-3-Hydroxymethyl-7-nitro-1,2,3,4-tetrahydroisoquinoline Hydrochloride (11·HCl). Application of the above procedure to (*R*)-(−)-**18** gave (*R*)-(+)-**11**: mp 171−173 °C dec, mp (HCl) > 270 °C dec; $[\alpha]^{22}_D$ = 62° (*c* 0.28, $CHCl_3$). Anal. ($C_{10}H_{12}N_2O_3$·HCl) C, H, N.

(*S*)-(−)-3-Hydroxymethyl-7-nitro-1,2,3,4-tetrahydroisoquinoline Hydrochloride (11·HCl). Application of the above procedure to (*S*)-(+)-**18** gave (*S*)-(−)-**11**: mp 174−176 °C dec, mp (HCl) > 270 °C dec; $[\alpha]^{22}_D$ = −69° (*c* 0.28, $CHCl_3$). Anal. ($C_{10}H_{12}N_2O_3$·HCl) C, H, N.

(±)-3,4-Dihydro-3-methyl-7-nitroisoquinolin-1-(2*H*)-one (25). The amide 3,4-dihydro-3-methylisoquinolin-1-(2*H*)-one[27b] (**24**; 0.90 g, 5.6 mmol) was dissolved in concentrated H_2SO_4 (4 mL) and cooled in an ice bath. Potassium nitrate (0.63 g, 6.2 mmol) was added in three portions to the stirred ice-cold reaction mixture. After stirring for 4 h at room temperature, the reaction mixture was poured onto ice to yield a yellow solid which was filtered, dried, and crystallized (with charcoal treatment) from aqueous EtOH to yield a golden-yellow crystalline solid (0.83 g, 72%): mp 242−243 °C; IR (KBr) 3180 (NH), 3070, 2960, 1660 (CO), 1510 (NO_2), 1335 (NO_2), 1060, 920, 850, 805, 740 cm^{-1}; ^1H NMR (DMS0-d_6) δ 8.55 (d, 1 H, J = 2.4 Hz, H-8), 8.35−8.30 (m, 2 H, H-7 and NH), 7.63 (d, 1 H, J = 8.4 Hz, H-5), 3.81−3.74 (m, 1 H, H-3), 3.14 (dd, 1 H, J = 16.5, 4.3 Hz, H-4), 2.82 (dd, 1 H, J = 16.4, 9.9 Hz, H-4), 1.22 (d, 3 H, J = 6.4 Hz, CH_3); ^{13}C NMR (DMSO-d_6) δ 162.6 (CO), 146.6, 146.0, 130.1, 129.6. 126.2, 121.5, 45.8 (C-3), 35.1 (C-4), 20.8 (*C*H_3); EIMS m/z 207 (M^+ + 1, 3), 206 (M^+, 8), 192 (13), 191 (100), 163 (52), 145 (26), 135 (12), 89 (37), 77 (15), 69 (11). Anal. ($C_{10}H_{10}N_2O_3$) C, H, N.

(*R*)-(−)-3,4-Dihydro-3-methyl-7-nitroisoquinolin-1-(2*H*)-one (25). Nitration as described above on (*R*)-(−)-**24** {mp 145−146 °C; $[\alpha]_D^{23}$ = −91° (*c* 0.20, MeOH)} gave a golden-yellow crystalline solid: mp 232−233 °C dec; $[\alpha]_D^{23}$ = −106° (*c* 0.20, MeOH). Anal. ($C_{10}H_{10}N_2O_3$) C, H, N.

(*S*)-(+)-3,4-Dihydro-3-methyl-7-nitroisoquinolin-1-(2*H*)-one (25). Nitration as described above on (*S*)-(+)-**24** {mp 143−144 °C, lit.[27b] mp 147 °C; $[\alpha]_D^{23}$ = 91° (*c* 0.22, MeOH)} gave a golden-yellow crystalline solid: mp 232−233 °C dec; $[\alpha]_D^{23}$ = 100° (*c* 0.20, MeOH). Anal. ($C_{10}H_{10}N_2O_3$) C, H, N.

(±)-3-Methyl-7-nitro-1,2,3,4-tetrahydroisoquinoline Hydrochloride (14·HCl). The suspension of amide (±)-**25** (0.40 g, 1.9 mmol) in dry THF (5 mL) was heated to reflux with BH_3·THF complex (1 M solution in THF, 6 mL, 6 mmol) under N_2 for 14 h. The resulting yellow solution was cooled in an ice bath, and the excess BH_3 was quenched carefully by dropwise addition of MeOH. The reaction mixture was evaporated to dryness, then methanolic HCl (15 mL) was added, and the reaction mixture was heated to reflux for 6 h. The solvent was removed on a rotary evaporator, and the solid obtained was suspended in water, made alkaline with solid Na_2CO_3, and extracted with $CHCl_3$ (four times). The organic layers were combined and dried (K_2CO_3), and the solvent was removed by rotary evaporation to yield a yellow-red solid. Purification by PCTLC (silica, 2 mm) using CH_2Cl_2/MeOH/NH_4OH (250:17:1) as the eluent gave a pale-yellow solid (0.34 g, 92%) which was recrystallized from EtOAc−hexanes as pale-buff needles: mp 96−98 °C; IR (KBr) 3200 (NH), 2950, 2910, 1520 (NO_2), 1335 (NO_2), 1090, 810, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.99−7.92 (m, 2 H, H-6 and H-8), 7.21 (d, 1 H, J = 8.3 Hz, H-5), 4.15 (s, 2 H, H-1), 3.08−3.01 (m, 1 H, H-3), 2.88 (dd, 1 H, J = 17.1, 3.9 Hz, H-4), 2.57 (dd, 1 H, J = 17.1, 10.7 Hz, H-4), 1.66 (bs, e, 1 H, NH), 1.28 (d, 3 H, J = 6.3 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 146.0, 142.9, 136.8, 129.9, 121.2, 121.0, 48.7 (C-1), 48.4 (C-3), 37.3 (C-4), 22.2 (*C*H_3). The hydrochloride salt was obtained as a colorless solid: mp 284−286 °C dec; EIMS m/z 193 (M^+ + 1, 4), 192 (M^+, 7), 178 (11), 177 (100), 149 (16), 131 (16), 130 (16), 103 (18), 91 (20), 77 (16). Anal. ($C_{10}H_{12}N_2O_2$·HCl) C, H, N.

(*R*)-(−)-3-Methyl-7-nitro-1,2,3,4-tetrahydroisoquinoline Hydrochloride (14·HCl). Using the same procedure as above, (*R*)-(−)-**25** was reduced to the desired amine (−)-**14**: mp 99−100 °C, mp (HCl) 283 °C dec; $[\alpha]_D^{22}$ = −91° (*c* 0.20, MeOH). Anal. ($C_{10}H_{12}N_2O_2$·HCl) C, H, N.

(*S*)-(+)-3-Methyl-7-nitro-1,2,3,4-tetrahydroisoquinoline Hydrochloride (14·HCl). Using the same procedure as above, (*S*)-(+)-**25** was reduced to the desired amine (+)-**14**: mp 98−99 °C, mp (HCl) 278−279 °C dec; $[\alpha]_D^{22}$ = 89° (*c* 0.20, MeOH). Anal. ($C_{10}H_{12}N_2O_2$·HCl) C, H, N.

(±)-1,4,9,9a-Tetrahydro-2-oxa-3a-azacyclopenta[*b*]naphthalen-3-one (19). To a solution of (±)-**4** (9.40 g, 57.6 mmol) in dry THF (100 mL) was added 1,1′-carbonyldiimidazole (11.2 g, 69.1 mmol), and the mixture was heated to reflux under N_2 overnight. The reaction mixture was cooled, and 1 N HCl (100 mL) was added. The acidic aqueous layer was extracted with CH_2Cl_2 (thrice). The organic layers were combined, washed with brine, and dried, and the solvent was removed by rotary evaporation to yield a pale-yellow solid (9.87 g). Recrystallization of this solid from EtOAc gave **19** as a colorless crystalline solid (8.36 g, 77.2%): mp 120−122 °C; IR (KBr) 2940, 1735 (CO), 1430, 1265, 1080, 1000, 950, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27−7.13 (m, 4 H, ArH), 4.81 (d, 1 H, J = 16.7 Hz, H-4), 4.57 (t, 1 H, J = 8.3 Hz, CH_2O), 4.35 (d, 1 H, J = 16.5 Hz, H-4), 4.15−4.10 (m, 1 H, CH_2O), 3.99−3.92 (m, 1 H, H-9a), 2.97−2.80 (m, 2 H, H-9); ^{13}C NMR ($CDCl_3$) δ 157.3 (CO), 131.6, 131.2, 129.3, 126.9, 126.7, 126.3, 68.3 (*C*H_2O), 51.0 (C-3), 42.9 (C-1), 33.9 (C-4); EIMS m/z 190 (M^+ + 1, 18), 189 (M^+, 52), 188 (M^+ − 1, 10), 144 (9), 128 (14), 116 (19), 105 (12), 104 (100), 78 (20), 51 (11). Anal. ($C_{11}H_{11}NO_2$) C, H, N.

(±)-6-Chlorosulfonyl-1,4,9,9a-tetrahydro-2-oxa-3a-azacyclopenta[*b*]naphthalen-3-one (20). Compound **19** (2.0 g, 11 mmol) was dissolved in $CHCl_3$ (30 mL), and the solution was chilled in a dry ice−acetone bath. Chlorosulfonic acid (8.5 g, 4.8 mL, 73 mmol) was added dropwise, and the reaction mixture was allowed to warm and stir at room temperature for 14 h. The reaction mixture was poured carefully onto ice and extracted with $CHCl_3$ (four times). The combined $CHCl_3$ extracts were washed with brine, dried, and evaporated to yield a yellow oil (2.82 g). Fractional crystallization from EtOAc gave a single regioisomer **20** as a colorless crystalline solid (0.50 g, 16%): mp 190−192 °C dec; IR (KBr) 3180, 3160, 1720 (CO), 1460, 1410, 1365 (SO_2), 1160 (SO_2), 1070, 1020, 950, 900, 820, 760, 710 cm^{-1}; ^1H NMR ($CDCl_3$) 7.88−7.85 (m, 2 H, H-5 and H-7), 7.43 (d, 1 H, J = 7.8 Hz, H-8), 4.98 (d, 1 H, J = 17.5 Hz, H-4), 4.64 (t, 1 H, J = 8.3 Hz, CH_2O), 4.47 (d, 1 H, J = 17.6 Hz, H-4), 4.24−4.19 (m, 1 H, CH_2O), 4.06−4.00 (m, 1 H, H-9a), 3.15−2.94 (m, 2 H, H-9); ^{13}C NMR ($CDCl_3$) 157.0 (CO), 143.1, 140.2, 133.7, 131.0, 125.2, 125.1, 68.1, 50.3, 43.0, 34.0; EIMS m/z 289 (M^+ + 2, 15), 287 (M^+, 39), 272 (10),

252 (M^+ − Cl, 13), 204 (30), 202 (73), 188 (M^+ − SO_2Cl, 15), 167 (12), 143 (13), 127 (12), 115 (46), 103 (86), 102 (34), 91 (20), 86 (28), 77 (100), 63 (34), 51 (70), 49 (94). Anal. ($C_{11}H_{10}ClNO_4S$) C, H, N.

The regiochemistry of the product was confirmed by a one-dimensional difference NOE experiment. When the protons at approximately 4.47 and 4.98 ppm (corresponding to the two protons at H-4) were irradiated, a positive NOE response was detected at 7.84 ppm (singlet; corresponding to the proton at H-5).

(±)-6-Aminosulfonyl-1,4,9,9a-tetrahydro-2-oxa-3a-azacyclopenta[*b*]naphthalen-3-one (21). Compound **20** (1.30 g, 4.52 mmol) was suspended in acetonitrile (20 mL) and heated to reflux with concentrated NH_4OH (20 mL) overnight. The solvent was removed by rotary evaporation to yield a colorless solid. The solid was filtered, washed thoroughly with MeOH and water, and dried in vacuo (1.20 g, 86.3%): mp 228−230 °C dec; IR (KBr) 3220 (NH_2), 1710 (CO), 1320 (SO_2), 1270, 1160 (SO_2), 1080, 760 cm^{-1}; ^1H NMR (DMSO-d_6) 7.70−7.63 (m, 2 H, H-5 and H-7), 7.38 (d, 1 H, J = 7.9 Hz, H-8), 7.34 (s, 2 H, SO_2NH_2), 4.69 (d, 1 H, J = 17.5 Hz, H-4), 4.55 (t, 1 H, J = 8.2 Hz, CH_2O), 4.40 (d, 1 H, J = 17.5 Hz, H-4), 4.18−4.13 (m, 1 H, CH_2O), 4.02−3.99 (m, 1 H, H-9a), 3.04 (dd, 1 H, J = 16.1, 3.9 Hz, H-9), 2.87−2.75 (m, 1 H, H-9); ^{13}C NMR (DMSO-d_6) 157.7 (CO), 151.3, 143.3, 137.6, 133.3, 130.9, 124.6, 68.9 (CH_2O), 51.0 (C-3), 43.4 (C-1), 33.8 (C-4); EIMS m/z 269 (M^+ + 1, 14), 268 (59), 253 (11), 224 (15), 195 (23), 183 (100), 115 (14), 103 (10), 91 (10), 77 (10). Anal. ($C_{11}H_{12}N_2O_4S$) C, H, N.

(±)-7-Aminosulfonyl-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (12·HCl). A solution of KOH (0.17 g, 3.0 mmol) in water (3 mL) was added to a suspension of oxazolidinone **21** (0.33 g, 1.2 mmol) in EtOH (5 mL). The resulting pale-yellow solution was heated to reflux under N_2 for 10 h. The reaction mixture was cooled and made acidic with concentrated HCl. Loss of CO_2 occurred, and the reaction mixture was concentrated to yield a solid which was heated in absolute EtOH, cooled, and filtered to remove KCl. The filtrate was evaporated to dryness and crystallized from 90% EtOH−Et_2O to afford colorless needles (0.15 g, 44%): mp 218−220 °C dec; IR (KBr) 3480, 3200, 2930, 1335, 1150, 1025, 800, 720 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.95−9.60 (m, 2 H, NH_2^+), 7.73−7.65 (m, 2 H, H-6 and H-8), 7.45−7.39 (m, 3 H, H-5 and SO_2NH_2), 5.60 (bs, 1 H, O*H*), 4.34 (s, 2 H, H-1), 3.85−3.66 (m, 2 H, CH_2O), 3.52−3.42 (m, 1 H, H-3), 3.3 (d, 2 H, J = 7.2 Hz, H-4); ^{13}C NMR (DMSO-d_6) δ 142.4, 136.1, 129.7, 129.6, 124.60 123.9, 60.5 (CH_2O), 53.9 (C-3), 43.7 (C-1), 27.5 (C-4); MS (CI, NH_3) m/z 243 (M^+ + 1, 100), 211 (6), 52 (7). Anal. ($C_{10}H_{14}N_2O_3S$·HCl·0.25H_2O) C, H, N.

(±)-6-Hydrazinosulfonyl-1,4,9,9a-tetrahydro-2-oxa-3a-azacyclopenta[*b*]naphthalen-3-one (22). To an ice-cold solution of sulfonyl chloride **20** (0.50 g, 1.7 mmol) in THF (10 mL) was added hydrazine (0.15 mL, 4.8 mmol), and the mixture was stirred at room temperature for 8 h. The solvent was removed, and the resulting semisolid was crystallized from aqueous MeOH as a colorless crystalline solid (0.26 g, 53%): mp 178−179 °C; IR (KBr) 3420, 3380, 3300 (NH), 2900, 1750 (CO), 1620, 1430, 1330 (SO_2), 1280, 1150 (SO_2), 940, 730, 700, 670 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.39 (bs, 1 H, N*H*), 7.69−7.60 (m, 2 H, H-5 and H-7), 7.41 (d, 1 H, J = 7.9 Hz, H-8), 4.73 (d, 1 H, J = 17.5 Hz, H-4), 4.55 (t, 1 H, J = 8.2 Hz, CH_2O), 4.42 (d, 1 H, J = 17.2 Hz, H-4), 4.19−3.99 (m, 3 H, CH_2O, H-9a and N*H*), 3.36 (bs, 1 H, N*H*), 3.15−3.04 (m, 1 H, H-9), 2.88−2.79 (m, 1 H, H-9); ^{13}C NMR (DMSO-d_6) δ 156.8 (CO), 137.6, 136.4, 132.6, 130.1, 125.9, 125.5, 68.0 (CH_2O), 50.1 (C-3), 42.5 (C-1), 33.0 (C-4). Anal. ($C_{11}H_{13}N_3O_4S$) C, H, N.

(±)-6-Methylsulfonyl-1,4,9,9a-tetrahydro-2-oxa-3a-azacyclopenta[*b*]naphthalen-3-one (23). To a suspension of sulfonylhydrazide **22** (0.25 g, 0.88 mmol) in EtOH (5 mL) were added NaOAc (0.48 g, 5.85 mmol) and MeI (0.62 g, 0.27 mL, 4.8 mmol). The resulting suspension was heated to reflux for 14 h yielding a yellow solution which was cooled and concentrated to yield a semisolid. Water (15 mL) was added to the semisolid, and the mixture was extracted with EtOAc (four times). The organic layers were combined and dried, and the solvent was removed on a rotary evaporator to yield a yellow solid. Recrystallization of this solid from EtOH−water gave a pale-yellow crystalline solid (0.20 g, 83%): mp 212−213 °C; IR (KBr) 3000, 2920, 1750 (CO), 1440, 1290 (SO_2), 1150 (SO_2), 1070, 775 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.77−7.72 (m, 2 H, H-5 and H-7), 7.41 (d, 1 H, J = 7.8 Hz, H-8), 4.88 (d, 1 H, J = 17.1 Hz, H-4), 4.62 (t, 1 H, J = 8.3 Hz, CH_2O), 4.46 (d, 1 H, J = 17.6 Hz, H-4), 4.24−4.19 (m, 1 H, CH_2O), 4.08−4.02 (m, 1 H, H-9a), 3.14−2.88 (m, 5 H, H-9 and SO_2CH_3); ^{13}C NMR (DMSO-d_6) δ 156.8 (CO), 139.0, 138.9, 133.2, 130.5, 125.3, 124.8, 68.1 (CH_2O), 50.0 (C-3), 43.6, 42.5, 33.1 (C-4); EIMS m/z 268 (M^++1, 4), 267 (M^+, 24), 252 (M^+-CH_3, 5), 223 (11), 208 (5), 194 (21), 182 (57), 143 (23), 115 (51), 103 (27), 102 (23), 91 (100), 77 (82), 65 (33), 63 (61), 51 (33). Anal. ($C_{12}H_{13}NO_4S$) C, H, N.

(±)-7-Methylsulfonyl-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (13·HCl). The oxazolidinone **23** (0.20 g, 0.74 mmol) was hydrolyzed with KOH (0.2 g) by using the procedure as described for compound **12**·HCl. The hydrochloride salt was isolated as colorless crystals (0.11 g, 52%): mp 225−226 °C dec; IR (KBr) 3360 (OH), 2980, 2920, 2760, 1320, 1305 (SO_2), 1150 (SO_2), 1130, 1080, 1050, 960, 770 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.93 (bs, 2 H, NH_2^+), 7.86−7.76 (m, 2 H, H-6 and H-8), 7.48 (d, 1 H, J = 7.8 Hz, H-6), 5.60 (bs, 1 H, O*H*), 4.35 (s, 2 H, H-1), 3.77−3.67 (m, 2 H, CH_2O), 3.50−3.32 (m, 1 H, H-3), 3.19 (s, 3 H, SO_2CH_3), 3.19−3.05 (m, 2 H, H-4); ^{13}C NMR (DMSO-d_6) δ 139.0, 138.2, 130.4, 130.0, 125.6, 125.4, 60.4 (CH_2O), 53.7 (C-1), 43.5, 27.6 (C-4); MS (CI, NH_3) m/z 242 (M^+ + 1, 35), 211 (12), 210 (100), 131 (17), 130 (29), 129 (12). Anal. ($C_{11}H_{15}NO_3S$·HCl) C, H, N.

Radiochemical Assay for PNMT Activity. The assay used in this study has been described elsewhere.[29] 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 Tables 1 and 2 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.[31] 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 50000g 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 of 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.

Molecular Modeling Studies. Molecular modeling was performed using SYBYL software package (version 6.4, Tripos Associates, Inc., 1699 South Hanley Rd, St. Louis, MO 63144) on an Silicon Graphics Indigo^2 work station.

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