Enantiospecific Synthesis of 3-Fluoromethyl-, 3-Hydroxymethyl-, and 3-Chloromethyl-1,2,3,4-tetrahydroisoquinolines as Selective Inhibitors of Phenylethanolamine *N*-Methyltransferase versus the α_2-Adrenoceptor[1]

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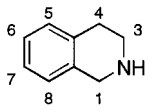
An enantiospecific method was developed for the synthesis of 3-fluoromethyl-, 3-hydroxymethyl-, and 3-chloromethyl-7-substituted-1,2,3,4-tetrahydroisoquinolines (THIQs) from phenylalanine. Biochemical evaluation of the enantiomers of these compounds at both PNMT and the α_2-adrenoceptor indicates that both sites display similar stereoselectivity. Overall the *R*-enantiomer was usually the more potent enantiomer at both PNMT and the α_2-adrenoceptor for these 3-fluoromethyl-, 3-hydroxymethyl-, and 3-chloromethyl-THIQs. The one exception is 3-hydroxymethyl-7-nitro-THIQ (**9**), which was found to display the opposite stereoselectivity at the α_2-adrenoceptor. A comparison of the PNMT inhibitory potency of the enantiomers of these 3-fluoromethyl-, 3-hydroxymethyl-, and 3-chloromethyl-THIQs indicates that all of the 3-substituted-THIQs displayed similar inhibitory potency for PNMT. However, the nature of the 3-substituent was found to have a major effect on the α_2-adrenoceptor affinity of these compounds with the 3-hydroxymethyl- and 3-fluoromethyl-THIQs having the highest affinity and THIQs containing the 3-chloromethyl moiety the least. Compounds *R*-3-fluoromethyl-7-cyano-THIQ (*R*-**12**) and *R*-3-fluoromethyl-7-*N*-(4-chlorophenyl)aminosulfonyl-THIQ (*R*-**13**) and both enantiomers of 3-chloromethyl-7-nitro-THIQ (*R*- and *S*-**30**) are the most selective inhibitors in this study and display selectivities (α_2-adrenoceptor K_i/PNMT K_i) greater than 200. These compounds give important insight into the steric and stereochemical preferences of both PNMT and the α_2-adrenoceptor, which should assist in the development of new PNMT inhibitors.

Introduction

Phenylethanolamine *N*-methyltransferase (PNMT; EC 2.1.1.28) catalyzes the final step in the biosynthesis of the catecholamine epinephrine (Epi).[2] Epi has been determined to make up 5−10% of the catecholamines found in the central nervous system (CNS).[3] Epi and PNMT are co-localized in the CNS[4] and found in very specific areas of the brain (e.g., the C1 and C2 regions of the medulla).[5] Although the presence of Epi in the CNS is well-documented, its function is not very well-understood. Therefore, primarily on the basis of the location of these Epi-containing neurons and from inhibition studies of PNMT, Epi has been postulated to be involved in the regulation of a number of physiological processes in the CNS—regulation of blood pressure and respiration,[5,6] secretion of hormones from the pituitary gland,[4,7] regulation of the α_2-adrenoceptor,[8] and some of the neurodegeneration seen in Alzheimer's disease.[9] However, the inhibitors used in these studies have been shown to display considerable affinity for the α_2-adrenoceptor, which complicates the interpretation of these data.[10] Therefore, to ascertain the role of Epi in these processes, our laboratory is attempting to develop highly selective inhibitors of PNMT versus the α_2-adrenoceptor that will have the ability to penetrate the blood−brain barrier (BBB).



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1,2,3,4-Tetrahydroisoquinoline (THIQ, **1**) is an inhibitor of PNMT (Table 1).[11] SK&F 64139 (**2**) is a THIQ-type inhibitor and is one of the most potent inhibitors of PNMT known (Table 1). However, **2** also displays considerable affinity for the α_2-adrenoceptor (Table 1).[12] SK&F 29661 (**3**) is a highly potent THIQ-type inhibitor of PNMT but displays very poor affinity for the α_2-adrenoceptor (Table 1). Unfortunately, autoradiographic studies have shown that **3** is unable to penetrate the BBB,[13] presumably due to the high polarity of the sulfonamide, making it a poor candidate for physiological studies.

Later studies investigating the structure−activity relationships of THIQs have shown that substitution at the 7-position was found to be the most important factor influencing PNMT potency.[14,15] To gain some understanding of the differences between the PNMT active site and α_2-adrenoceptor, we performed a comparative molecular field analysis (CoMFA),[16] a type of three-dimensional QSAR study, for a set of 30 7-substituted-THIQs for the α_2-adrenoceptor and the PNMT active site.[17] In this study we proposed that THIQs could bind in one of two different orientations at the PNMT active site and at the α_2-adrenoceptor, depending on the

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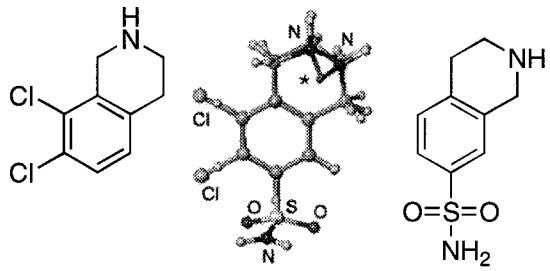
Table 1. In Vitro Activity of Several PNMT Inhibitors at PNMT and Inhibition of [^{3}H]Clonidine Binding at the α_2-Adrenoceptor[a]

compd		K_i, μM PNMT (A)	K_i, μM α_2 (B)	B/A selectivity
1[b]		10 ± 1	0.35 ±0.10	0.35
2[b]		0.22 ± 0.05	0.021 ± 0.005	0.095
3[c]		0.56 ± 0.04	100 ± 20	180
4[d]		2.1 ± 0.1	0.76 ± 0.08	0.36
5[d]		1.1 ± 0.1	6.6 ± 6.6	6.0
6[e]		1.5 ± 0.1	3.8 ± 0.1	2.5
7[d]		24 ± 1	0.67 ± 0.3	0.028
8[d]	(±)	0.34 ± 0.06	1400 ± 30	4100
9[d]	*R*-(+)	0.24 ± 0.03	38 ± 1	160
9[d]	*S*-(−)	0.90 ± 0.05	13 ± 1	14
10[e]	(±)	0.66 ± 0.10	680 ± 10	1000
11[e]	(±)	0.54 ± 0.06	76 ± 6	140
12[e]	(±)	1.1 ± 0.1	460 ± 10	420
13[e]	(±)	0.74 ± 0.07	160 ± 10	220
15[e]	(±)	0.64 ± 0.1	6.4 ± 0.2	10

[a] PNMT and α_2-adrenoceptor K_i values for literature compounds were determined in our laboratory for consistent internal comparison. [b] Reference 11. [c] Reference 32. [d] Reference 19. [e] Reference 20.

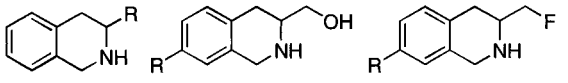


SK&F 64139: **2** SK&F 29661: **3**

Figure 1. Two proposed orientations of 7-substituted-THIQs at PNMT and the α_2-adrenoceptor, showing orientation A for lipophilic ($+\pi$) 7-substituents and orientation B for hydrophilic ($-\pi$) 7-substituents. Between the structures of **2** and **3** is a SYBYL-generated view of the superimposition of **2** in orientation A on **3** in orientation B. The asterisk marks the area in space where the lone pairs of both compounds may overlap. (This figure was adapted from ref 31, copyright 1999, with permission from Elsevier Science.)

lipophilicity of the 7-substituent (Figure 1). Thus, THIQs containing a hydrophilic ($-\pi$) substituent are thought to bind differently than THIQs possessing a lipophilic ($+\pi$) substituent. Also, THIQs containing a hydrophilic ($-\pi$) electron-withdrawing 7-substituent were usually found to be selective for PNMT, while THIQs possessing a lipophilic ($+\pi$) electron-withdrawing 7-substituent were usually found to be nonselective inhibitors of PNMT.

Further studies examining substitution on the THIQ nucleus found that substitution of a (±)-3-methyl (**4**) or a (±)-3-hydroxymethyl moiety (**5**) increased both potency and selectivity relative to THIQ (**1**) (Table 1).[18,19] However, it was also found that the area around the 3-position of THIQ at PNMT was found to exhibit limited steric bulk tolerance with only a (±)-3-methyl (**4**), (±)-3-hydroxymethyl (**5**),[19] or (±)-3-fluoromethyl (**6**)[20] moiety displaying good inhibitory potency (Table 1). Substitution of larger groups [e.g., (±)-3-ethyl (**7**)][18] caused a significant decrease in PNMT inhibitory potency (Table 1), which may be a result of an area of steric bulk intolerance at the PNMT active site or the lack of a group (e.g., OH) that can participate in hydrogen-bonding interactions with the PNMT active site.



4 R = CH_3
5 R = CH_2OH
6 R = CH_2F
7 R = CH_2CH_3

8 R = SO_2NH_2
9 R = NO_2

10 R = SO_2NH_2
11 R = NO_2
12 R = CN
13 R = SO_2NHPh-4-Cl

Later studies from this laboratory discovered that the combination of a 3-substituent (i.e., 3-methyl or 3-hydroxymethyl) and a hydrophilic electron-withdrawing 7-substituent (i.e., 7-SO_2NH_2, 7-NO_2) resulted in synergistic increases in selectivity for PNMT versus the α_2-adrenoceptor. Compound **8** is an example of this type of inhibitor and is the most selective inhibitor of PNMT yet reported (Table 1). However, studies have indicated that **8** was too polar to penetrate the BBB.[20]

To decrease the polarity of the 3-hydroxymethyl-THIQs (e.g., **8** and **9**) to increase the possibility that these compounds may penetrate the BBB, a series of 3-fluoromethyl-THIQs (**10**−**13**) were synthesized and evaluated.[20] A similar trend of increased selectivity was found for THIQs in this study that combined a 3-fluoromethyl moiety and hydrophilic electron-withdrawing 7-substituents (**10**−**13**; Table 1), and these compounds are some of the most selective inhibitors of PNMT known.

To determine the BBB permeability of some of these inhibitors, we performed an in vitro study[20] using a model developed by Borchardt and Audus.[21,22] The results of this study indicated that there was a good correlation between lipophilicity and BBB penetration for THIQ-type inhibitors and that THIQs possessing calculated partition coefficients (Clog *P*) in the range of 0.13−0.57 or greater should be able to gain some penetration into the brain. Compounds **8**−**10** were included in this study, and on the basis of the results of this model, it was determined that **9** (Clog $P = +0.57$) should be able to penetrate the BBB, whereas **8** (Clog $P = -1.01$) and **10** (Clog $P = -0.07$) probably would not. 3-Fluoromethyl-THIQs, **11** (Clog $P = +1.51$), **12** (Clog $P = +1.20$), and **13** (Clog $P = +2.79$), possess calculated partition coefficients greater than 0.57 and according to this model should be able to penetrate the BBB. These compounds are also very selective inhibitors of PNMT (Table 1) and represent promising new leads in the development of selective PNMT inhibitors with the ability to penetrate into the CNS.

However, most of these THIQs (**8**, **10**−**13**) were evaluated as racemates. Therefore, the influence of the chirality of the 3-substituent of these compounds at both the PNMT active site and the α_2-adrenoceptor was unknown. Due to the small amount of information known about the effects of chirality on the potency and selectivity of these 3-hydroxymethyl- and 3-fluoromethyl-THIQs for PNMT, we deemed it necessary to evaluate the enantiomers of **8** and **11**−**13**.

The enantiomers of **14** and **15** were also proposed for synthesis, as in our previous studies of 3,7-disubstituted-THIQs[19,20] the effects of chirality of the 3-substituent of THIQ in combination with a lipophilic electron-

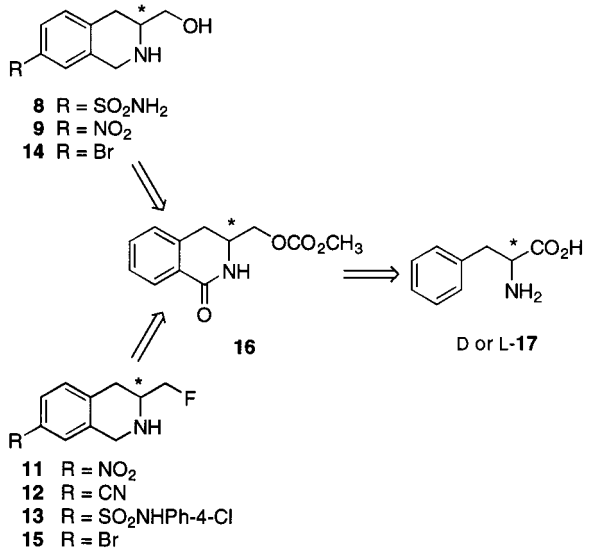
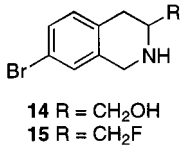


Figure 2. Retrosynthetic analysis of target compounds *R*- or *S*-3-hydroxymethyl-THIQs (**8**, **9**, **14**) and *R*- or *S*-3-fluoromethyl-THIQs (**11**−**13**, **15**) formed from either D- or L-phenylalanine (**17**), respectively. The asterisk denotes the chiral center that is fixed by the chiral starting material.

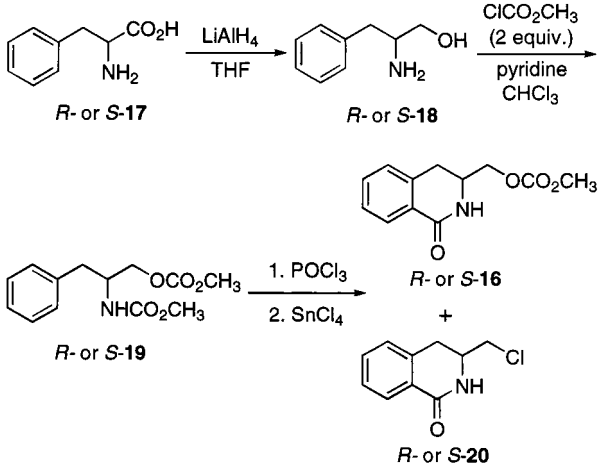
withdrawing group (e.g., Br) had not been investigated. Compound **15** had been evaluated previously as a racemate (Table 1) and was found to be a nonselective inhibitor of PNMT.[20] This lack of selectivity was believed to be due to its ability to bind in the proposed lipophilic orientation at the α_2-adrenoceptor (see Figure 1). However, the influence of chirality on the activity of this compound has not been investigated. Therefore, if **14** and **15** are bound differently at either the PNMT active site or the α_2-adrenoceptor (due to the lipophilicity of the 7-substituent), these compounds may display a different rank order of potency based on their chirality as compared to THIQs that contain hydrophilic 7-substituents.



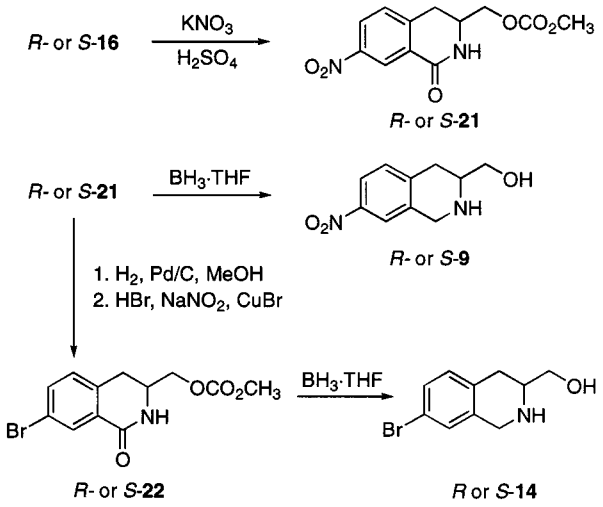
The previous synthesis used for the preparation of 3-hydroxymethyl-THIQs (**8** and the enantiomers of **9**) possessed several limitations (racemization of a key intermediate, multiple fractional recrystallizations, difficult separations of regioisomers, and low yields),[19] while the synthesis used for the preparation of 3-fluoromethyl-THIQs (**10**−**13**, **15**) could only produce these products as racemic mixtures.[20]

Therefore, a new enantiospecific synthesis for the production of both 3-hydroxymethyl- and 3-fluoromethyl-THIQs was proposed. Retrosynthetic analysis of *R*- or *S*-3-hydroxymethyl-THIQs (**8**, **9**, **14**) and 3-fluoromethyl-THIQs (**11**−**13**, **15**) indicates that both series of compounds could be derived from a common intermediate (**16**), which could be synthesized in enantiomerically pure form from either D- or L-phenylalanine (**17**) (Figure 2). This synthesis has several advantages over those previously used. Most importantly, the absolute configuration of the final product is set with a starting material of known chirality. Second, the carbonyl of lactam intermediate **16** can act as a directing group for electrophilic aromatic substitution reactions. Hence, the 7-position of these THIQs can be readily functionalized without the formation of other regioisomers. Finally, a large number of chiral 3-hydroxymethyl- and 3-fluoromethyl-7-substituted-THIQs can be made using the same synthesis.

Scheme 1



Scheme 2

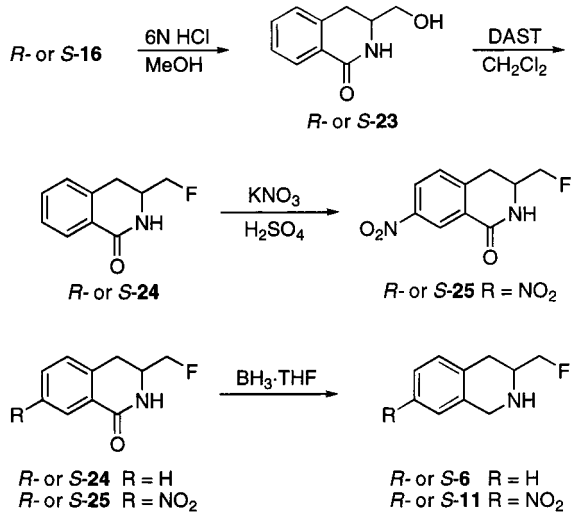


Chemistry

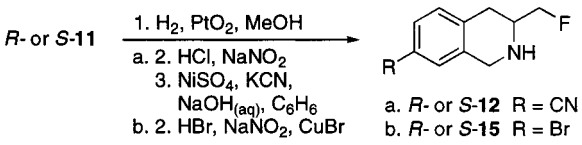
Beginning with either D- or L-phenylalanine (**17**), reduction with $LiAlH_4$ formed *R*- or *S*-**18**, respectively.[23] Treatment of *R*- or *S*-**18** with 2 equiv of methyl chloroformate yielded *R*- or *S*-**19**. Carbamate **19** was cyclized by treatment with phosphorus oxychloride at reflux followed by the addition of $SnCl_4$[24] at 0 °C to produce a mixture of lactams *R*- or *S*-**16** and *R*- or *S*-**20** (3:1) (Scheme 1), which were easily separated by flash column chromatography (silica gel). It was noted that if the $SnCl_4$ was added to the phosphorus oxychloride and carbamate **19** mixture while the mixture was still hot, lactam **20** was obtained as the sole product.

Nitration of lactam *R*- or *S*-**16** with KNO_3 in H_2SO_4 formed *R*- or *S*-**21**. Reduction of the lactam and deprotection of the alcohol was accomplished in one step by treatment with BH_3·THF to yield *R*- or *S*-**9** (Scheme 2). Treatment of lactam **16** with chlorosulfonic acid to add a 7-chlorosulfonyl moiety to form an intermediate in the

Scheme 3



Scheme 4



synthesis of **8** was unsuccessful and led only to decomposition products. On the basis of our in vitro BBB model studies, which indicated that **8** would not be able to penetrate the CNS, we decided not to pursue the synthesis of the enantiomers of **8**. *R*- or *S*-3-Hydroxymethyl-7-bromo-THIQ (**14**) was synthesized using the conditions outlined in Scheme 2. Hydrogenation of the 7-nitro substituent of *R*- or *S*-**21** to the amine followed by a Sandmeyer bromination formed *R*- or *S*-**22**.[25] Reduction of the lactam and deprotection of the alcohol was accomplished by treatment with BH_3·THF to yield *R*- or *S*-**14**.

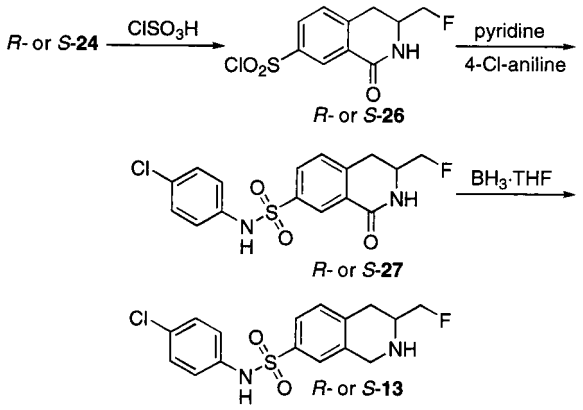
Beginning with lactam *R*- or *S*-**16**, hydrolysis of the carbonate ester to the primary alcohol afforded *R*- or *S*-**23**, which was treated with diethylaminosulfur trifluoride (DAST) to yield *R*- or *S*-**24**.[26] Reduction of the lactam with BH_3·THF produced *R*- or *S*-**6**. Nitration of *R*- or *S*-**24** with KNO_3 and H_2SO_4 yielded lactam *R*- or *S*-**25**, which was reduced with BH_3·THF to form *R*- or *S*-**11** (Scheme 3).

The enantiomers of 3-fluoromethyl-THIQs **12** and **15** were synthesized using the procedures outlined in Scheme 4. The hydrogenation of the nitro group of *R*- or *S*-**11** to the amine followed by a modified Sandmeyer reaction yielded *R*- or *S*-**12**.[27] A similar procedure was used for the production of *R*- or *S*-**15**. Hydrogenation of *R*- or *S*-**11** followed by a Sandmeyer bromination gave *R*- or *S*-**15**.[25]

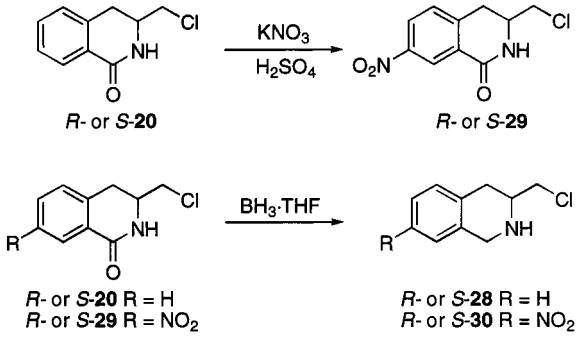
We decided not to pursue the synthesis of the enantiomers of **10** due to our in vitro BBB model studies,[20] which had indicated that **10** would not be able to penetrate into the CNS. However, *R*- or *S*-**13** was synthesized using the conditions shown in Scheme 5. Chlorosulfonylation of *R*- or *S*-**24** with chlorosulfonic acid (neat) yielded *R*- or *S*-**26**. Treatment of *R*- or *S*-**26** with 4-chloroaniline in pyridine formed *R*- or *S*-**27**, which was reduced with BH_3·THF to produce *R*- or *S*-**13**.

Considering that chloromethyl lactam *R*- or *S*-**20**

Scheme 5



Scheme 6



could be isolated from the cyclization reaction that formed key intermediate **16**, it was decided to synthesize several 3-chloromethyl-THIQs in order to determine how these compounds would compare to similarly substituted 3-hydroxymethyl- and 3-fluoromethyl-THIQs. Reduction of lactam *R*- or *S*-**20** with BH_3·THF yielded *R*- or *S*-**28** (Scheme 6). Nitration of *R*- or *S*-**20** with KNO_3 and H_2SO_4 formed *R*- or *S*-**29**, which was reduced with BH_3·THF to yield *R*- or *S*-**30** (Scheme 6). Attempts to synthesize a 7-bromo-3-chloromethyl-THIQ were unsuccessful using the standard Sandmeyer bromination conditions.

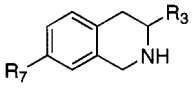
Enantiomeric excess (ee) was determined for all final compounds and was found to be greater than 95% by chiral HPLC.

Biochemistry

All compounds were evaluated as their hydrochloride or hydrobromide salts for their activity as inhibitors of PNMT and inhibitors of the binding of [^{3}H]clonidine to the α_2-adrenoceptor. Bovine adrenal PNMT was prepared using the method of Connett and Kirshner through the isoelectric precipitation step.[28] The in vitro activity of these compounds was determined using a standard radiochemical assay that has been described previously.[29] Inhibition constants were determined by using three different concentrations of the inhibitor using phenylethanolamine as the substrate.

α_2-Adrenoceptor binding assays were performed using a standard radiochemical assay developed by U'Prichard et al.[30] that uses [^{3}H]clonidine as the radioligand to define specific binding and phentolamine to determine the nonspecific binding affinity in order to simplify the comparison with previous results.

Table 2. Biochemical Evaluation of 3,7-Disubstituted-1,2,3,4-tetrahydroisoquinolines



compd	R_3	R_7	K_i, μM PNMT (A)	K_i, μM α_2 (B)	B/A selectivity
5[a]	*R*-CH_2OH	H	0.56 ± 0.05	4.4 ± 0.3	7.9
	S-CH_2OH	H	15 ± 2	17 ± 1	1.1
9	*R*-CH_2OH	NO_2	0.24 ± 0.03	38 ± 1	160
	S-CH_2OH	NO_2	0.90 ± 0.05	13 ± 1	14
14	*R*-CH_2OH	Br	0.38 ± 0.05	1.2 ± 0.1	3.2
	S-CH_2OH	Br	0.48 ± 0.05	0.97 ± 0.20	2.0
6	*R*-CH_2F	H	0.69 ± 0.06	2.9 ± 0.4	4.2
	S-CH_2F	H	9.9 ± 0.4	37 ± 5	3.7
11	*R*-CH_2F	NO_2	0.52 ± 0.07	47 ± 3	90
	S-CH_2F	NO_2	0.88 ± 0.06	140 ± 10	160
12	*R*-CH_2F	CN	0.97 ± 0.08	360 ± 30	370
	S-CH_2F	CN	3.5 ± 0.2	580 ± 50	170
13	*R*-CH_2F	SO_2NHPh-4-Cl	0.28 ± 0.04	97 ± 10	350
	S-CH_2F	SO_2NHPh-4-Cl	1.9 ± 0.1	101 ± 10	53
15	*R*-CH_2F	Br	0.51 ± 0.06	3.1 ± 0.1	6.1
	S-CH_2F	Br	0.47 ± 0.05	17 ± 1	36
28	*R*-CH_2Cl	H	3.5 ± 0.2	2.3 ± 0.2	0.66
	S-CH_2Cl	H	12 ± 1	6.6 ± 0.4	0.55
30	*R*-CH_2Cl	NO_2	0.47 ± 0.03	100 ± 10	210
	S-CH_2Cl	NO_2	0.66 ± 0.04	270 ± 10	410
4[a]	*S*-CH_3	H	1.0 ± 0.1	0.49 ± 0.05	0.49
	R-CH_3	H	38 ± 2.0	5.7 ± 0.3	0.15
31[a]	*S*-CH_3	NO_2	0.25 ± 0.02	19 ±. 1	76
	R-CH_3	NO_2	1.3 ± 0.1	53 ± 2	41

[a] Reference 19.

Results and Discussion

The results of the biochemical evaluation of compounds from this study are shown in Table 2. *R*- and *S*-3-Hydroxymethyl-THIQ (**5**), *R*- and *S*-3-methyl-THIQ (**4**), and *R*- and *S*-3-methyl-7-nitro-THIQ (**32**) have been synthesized previously[19] and were included in the table for comparison purposes. It should be noted that although the absolute configurations of *S*-**31** and *R*-**9** are opposite—due to the Cahn−Ingold−Prelog rules for assigning priority—the area of space in which the 3-substituent of these compounds is aligned is identical.

Direct comparison of all the PNMT inhibitory potencies of these compounds (3-fluoromethyl-, 3-hydroxymethyl-, and 3-chloromethyl-THIQs) indicates that PNMT displays the same stereoselectivity for all 3-substituted-THIQs, with the *R*-enantiomer being the more potent. However, the amount of differentiation between enantiomers seems to be dependent on the 7-substituent. PNMT seems to display very little stereoselectivity for THIQs containing lipophilic 7-substituents (**14** and **15**), whereas the degree of differentiation between the enantiomers is much larger for THIQs that either are unsubstituted at the 7-posititon (e.g., **4**−**6** and **28**) or contain hydrophilic electron-withdrawing 7-substituents (e.g., **9**−**13**, **30**, and **31**). This supports the hypothesis that THIQs containing lipophilic 7-substituents may be bound differently than THIQs that are unsubstituted or contain hydrophilic 7-substituents as proposed previously for PNMT (Figure 1).[17,20]

A similar trend in stereoselectivity was found for the α_2-adrenoceptor where the *R*-enantiomer is the more potent for the majority of these 3-fluoromethyl-, 3-hydroxymethyl-, and 3-chloromethyl-THIQs. This trend is similar to that found previously for 3-methyl-THIQs **4** and **31**.[19] The only exception is 3-hydroxymethyl-THIQ (**9**), where the *S*-enantiomer was found to be the more potent. This may be an indication that the *S*-3-hydroxymethyl substituent of **9** may be participating in a type of hydrogen bond interaction with the α_2-adrenoceptor that the *R*-enantiomer of 3-methyl-, *S*-enantiomer of 3-fluoromethyl-, or *S*-enantiomer of 3-chloromethyl-THIQs cannot. Examination of the α_2-adrenoceptor affinities of **14** and **15** indicates that **14** shows little stereoselectivity, whereas **15** displays a 6-fold difference in affinity between the *R*- and *S*-enantiomers. This also may be an indication that a hydrogen-bonding interaction may be taking place with the *S*-enantiomer of **14** increasing its affinity in a similar manner as that found for *S*-**9**.

Examination of the PNMT inhibitory potencies of the 7-nitro-THIQs **9**, **11**, **30**, and **31** indicates that both enantiomers of these compounds display similar activities. However, examination of their α_2-adrenoceptor affinities reveals that the 3-substituent has a large effect on the potency of these compounds with *S*-**31** > *R*-**9** > *R*-**11** > *R*-**30** and *S*-**9** > *R*-**31** > *S*-**11** > *S*-**30**. Except for 3-hydroxymethyl-THIQ **9** which displays a reversal in potency of the enantiomers, the overall trend for these compounds indicates that as the 3-substituent gets larger (methyl < fluoromethyl < chloromethyl), the α_2-adrenoceptor affinity decreases for both enantiomers. This result would seem to confirm previous data that had suggested that an area of limited steric bulk tolerance surrounds the 3-position of THIQs possessing hydrophilic 7-substituents at the α_2-adrenoceptor.[19,31]

Conclusions

An enantiospecific synthesis was developed for the production of 3-hydroxymethyl-, 3-fluoromethyl-, and 3-chloromethyl-THIQs. Biochemical evaluation of the

enantiomers of these compounds at both PNMT and the α_2-adrenoceptor indicates that both of these sites display similar stereoselectivity where the *R*-enantiomer was consistently the more potent. The one exception is 3-hydroxymethyl-7-nitro-THIQ (**9**), which displayed the opposite stereoselectivity at the α_2-adrenoceptor. The amount of stereoselectivity displayed by the α_2-adrenoceptor for these compounds is relatively the same for all compounds, whereas the amount of stereoselectivity for PNMT seems to be dependent on the lipophilicity of the 7-substituent. Compounds containing hydrophilic 7-substituents display a fairly large degree of stereoselectivity, whereas compounds containing lipophilic 7-substituents display very little stereoselectivity. This may be an indication that these two types of compounds are binding differently at the PNMT active site. A comparison of 3-methyl, 3-fluoromethyl, 3-hydroxymethyl, and 3-chloromethyl substituents indicates that all of the 3-substituted-THIQs displayed similar inhibitory potency for PNMT, whereas for the α_2-adrenoceptor the order of affinity from the highest to the least was found to be 3-methyl > 3-hydroxymethyl ≅ 3-fluoromethyl > 3-chloromethyl, which suggests that the α_2-adrenoceptor has a limited amount of steric bulk tolerance in the area surrounding the 3-position of THIQ. Furthermore, compounds *R*-3-fluoromethyl-7-cyano-THIQ (*R*-**12**; Clog P = 1.20), *R*-3-fluoromethyl-7-*N*-(4-chlorophenyl)aminosulfonyl-THIQ (*R*-**13**; Clog P = 2.63), and both enantiomers of 3-chloromethyl-7-nitro-THIQ (*R*- and *S*-**30**; Clog P = 1.85) display selectivity ratios (α_2-adrenoceptor K_i/PNMT K_i) greater than 200 and according to our previous BBB model study[20] may be able to penetrate into the CNS. These compounds give important insight into the steric and stereochemical factors that determine potency and selectivity for PNMT and are important leads in the development of new, more selective inhibitors of PNMT that should have the ability to penetrate into the brain.

Experimental Section

All reactions that required inert atmospheric conditions were performed under positive pressure of nitrogen in glassware that was either flame-dried or oven-dried. All chemicals used were of reagent grade unless stated otherwise. Solvents were routinely distilled prior to use according to standard methods. In some cases solvents were used directly from Aldrich Sure Seal bottles. Hexanes refers to a mixture of isomeric hexanes (bp 68−70 °C), and brine refers to a saturated solution of NaCl. Melting points were determined in open capillaries on a Thomas-Hoover melting point apparatus and are otherwise uncorrected. Flash column chromatography was carried out using silica gel 60 (230−400 mesh) purchased from Universal Adsorbents, Atlanta, GA. Bulb-to-bulb distillations were carried out using a Kugelrohr distillation apparatus (Aldrich Chemical Co., Milwaukee, WI), and the boiling range noted indicates the internal oven temperature. Proton nuclear magnetic resonance spectra (^{1}H NMR) and carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a Varian XL-300, a GE QE-300, or a Bruker DRX-400 spectrophotometer, with $CDCl_3$ as the solvent unless otherwise noted. Proton chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS, 0.00 ppm). Carbon chemical shifts are reported in ppm relative to $CDCl_3$ (77.0 ppm). For the hydrochloride and hydrobromide salts of these THIQs, NMR spectra were recorded in either deuterated dimethyl sulfoxide (DMSO-d_6) and the chemical shifts reported relative to DMSO (2.49 ppm for ^{1}H and 39.5 ppm for ^{13}C) or deteurated methanol (CD_3OD) (3.31 ppm for ^{1}H and 49.2 ppm for ^{13}C). Coupling constants (J) are reported in hertz (Hz), and s, d, t, q, m, br, and ex refer to singlet, doublet, triplet, quartet, multiplet, broad, and exchangeable, respectively. Infrared spectra (IR) were recorded on a Perkin-Elmer IR 727 spectrophotometer. Chemical-ionization mass spectra (CIMS) were obtained on a Varian Atlas CH-5 or a Ribermag R 10-10 mass spectrophotometer. The intensity of each peak in the spectrum is reported relative to the base peak in parentheses. Microanalyses were performed on a Hewlett-Packard model 185B CHN analyzer at the University of Kansas. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter using the sodium D line. Chiral high-performance liquid chromatography (HPLC) was performed on a Shimadzu LC 6A system. The Chiralcel OJ column (0.46 × 25 cm) was purchased from Daicel Inc., New York, NY.

S-Adenosyl-L-methionine used in the radiochemical assays was obtained from Sigma Chemical Co. [^{3}H]-*S*-Adenosyl-L-methionine was purchased from American Radiolabeled Chemicals (St. Louis, MO). [^{3}H]Clonidine used in the α_2-adrenoceptor assays was purchased from New England Nuclear Corp. (Boston, MA). Bovine adrenal glands were obtained from Davis Meat Processing (Overbrook, KS).

***R*-(+)-2-Amino-3-phenylpropanol (*R*-18).** A solution of lithium aluminum hydride (3.0 g, 78.9 mmol) in dry THF (150 mL) was stirred and cooled in an ice bath. D-(*R*)-Phenylalanine (**17**) (9.00 g, 55.0 mmol) was added over 30 min. The mixture was stirred at 0 °C for 2 h, warmed to room temperature, and stirred an additional 2 h. The reaction mixture was heated at reflux for 16 h. The solution was cooled in an ice bath and diluted slowly with ether (100 mL). Water (4.5 mL), 15% NaOH (4.5 mL), and water (12 mL) were added dropwise to the solution in succession. The mixture was filtered through Celite to remove the aluminum salts. The Celite was washed with ether (200 mL). The filtrate was collected and the solvent was removed under reduced pressure to yield a yellow solid. Bulb-to-bulb distillation (120 °C, 0.1 mmHg) gave *R*-**18** as a white solid (6.67 g, 82%): mp 91−93 °C (lit.[23] mp 90−91 °C); $[\alpha]_D^{22}$ = +23.2° (*c* 1.0, EtOH) [lit.[23] $[\alpha]_D^{22}$ = +23.8° (*c* 1.0, EtOH)]; ^{1}H NMR ($CDCl_3$) δ 7.34−7.18 (m, 5H, ArH), 3.66−3.62 (m, 1H, CH_2O), 3.41−3.35 (m, 1H, CH_2O), 3.14−2.98 (m, 1H, CHN), 2.83−2.77 (m, 1H, ArCH), 2.56−2.48 (m, 1H, ArCH), 2.30−2.00 (ex br m, 3H, OH and NH_2); ^{13}C NMR ($CDCl_3$) δ 138.7, 129.2, 128.6, 126.4, 66.2, 54.2, 40.8. Anal. ($C_9H_{13}NO$) C, H, N.

***S*-(−)-2-Amino-3-phenylpropanol (*S*-18).** Compound *S*-**18** was prepared in the same manner as *R*-**18** using L-phenylalanine (*S*-**17**) as the starting material: mp 92−94 °C (lit.[23] mp 90−91 °C); $[\alpha]_D^{20}$ = −23.1° (*c* 1.0, EtOH) [lit.[23] $[\alpha]_D^{25}$ = −25.4° (*c* 1.22, EtOH)]. Anal. ($C_9H_{13}NO$) C, H, N.

***R*-(+)-*N*,*O*-Bis(methoxycarbonyl)-2-amino-3-phenylpropanol (*R*-19).** A solution of *R*-**18** (5.60 g, 37.0 mmol) in dry $CHCl_3$ (75 mL) and pyridine (15 mL) was cooled to 0 °C. Methyl chloroformate (5.80 mL, 74.0 mmol) was added dropwise via an addition funnel. After the addition, the solution was stirred at room temperature for 14 h. Ice water (50 mL) was added slowly to the reaction mixture and the mixture was stirred for 15 min. The organic phase was extracted and the aqueous phase was extracted with $CHCl_3$ (2 × 50 mL). The organic extracts were combined and washed with 3 N HCl (2 × 50 mL), 5% $NaHCO_3$ (50 mL), and brine (50 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. Bulb-to-bulb distillation (140−150 °C, 0.5 mmHg) yielded *R*-**19** as a white solid (14.3 g, 99%): mp 83−84 °C; $[\alpha]_D^{20}$ = +3.9° (*c* 0.38, EtOH); IR (KBr) 3350, 3080−2950, 1740, 1680, 975, 950, 790, 755, 700 cm^{-1}; ^{1}H NMR δ 7.65−7.18 (m, 5H, ArH), 4.80 (br ex s, 1H, NH), 4.20−4.05 (m, 3H, CH(N)CH_2O), 3.81 (s, 3H, CH_3), 3.63 (s, 3H, CH_3), 2.93−2.81 (m, 2H, $ArCH_2C$); ^{13}C NMR ($CDCl_3$) δ 156.3, 155.5, 136.8, 129.1, 128.6, 126.7, 68.0, 54.9, 52.1, 51.2, 37.4; CIMS *m*/*z* (relative intensity) 285 (M + NH_4^+, 18), 268 (MH^+, 11), 236 (57), 195 (12), 193 (12), 192 (86), 178 (27), 176 (15), 117 (10), 116 (13), 100 (100), 92 (11), 91 (60), 65 (12). Anal. ($C_{13}H_{17}NO_5$) C, H, N.

***S*-(−)-*N*,*O*-Bis(methoxycarbonyl)-2-amino-3-phenylpropanol (*S*-19).** Using the same procedures as for *R*-**19**, *S*-**18** was treated with methyl chloroformate to form *S*-**19**: mp 83−84 °C; $[\alpha]_D^{20} = -3.4°$ (*c* 0.50, EtOH). Anal. ($C_{13}H_{17}NO_5$) C, H, N.

***R*-(−)-*O*-Methoxycarbonyl-3-hydroxymethyl-3,4-dihydroisoquinolin-1-2*H*-one (*R*-16) and *R*-(−)-3-Chloromethyl-3,4-dihydroisoquiolin-1-2*H*-one (*R*-20).** Freshly distilled $POCl_3$ (60 mL) was added to *R*-**19** (9.01 g, 38.4 mmol). The solution was heated at reflux (120 °C) for 24 h. The solution was cooled in an ice bath and $SnCl_4$ (7.0 mL, 60 mmol) was added dropwise. The solution was stirred for 3 h at 0 °C. The solution was warmed to room temperature and stirred for another 2 h. The reaction mixture was poured onto ice (200 g) and the solution stirred for 30 min. The solution was extracted with CH_2Cl_2 (4 × 100 mL). The organic extracts were combined, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to yield a brown oil. The product was purified by flash column chromatography (silica gel) with EtOAc/hexanes (1:1) to yield *R*-**16** (3.18 g, 43%) and *R*-**20** (1.05 g, 16%).

***R*-16:** mp 125−126 °C; $[\alpha]_D^{20} = -27°$ (*c* 0.29, EtOH); IR (KBr) 3400, 3080, 2950, 1750, 1668, 1600, 1455, 1445, 1270, 1260, 1040, 970, 940, 785, 750 cm^{-1}; ^1H NMR δ 8.09−8.06 (d, $J = 7.4$ Hz, 1H, ArH-8), 7.70−7.45 (m, 1H, ArH-6), 7.40−7.33 (m, 1H, ArH-7), 7.23−7.21 (d, $J = 7.3$ Hz, 1H, ArH-5), 6.35−6.20 (br ex s, 1H, CONH), 4.31−4.25 (m, 1H, CH_2O), 4.19−4.15 (m, 1H, CH_2O), 4.09−4.00 (m, 1H, H-3), 3.81 (s, 3H, OCH_3), 3.13−3.03 (m, 1H, H-4), 2.98−2.89 (m, 1H, H-4); ^{13}C NMR δ 165.7, 155.3, 136.4, 132.4, 128.1, 127.9, 127.6, 127.2, 68.7, 55.0, 49.6, 29.9; CIMS *m*/*z* (relative intensity) 236 (MH^+, 53), 221 (23), 204 (100), 146 (25), 118 (30). Anal. ($C_{12}H_{13}NO_4$) C, H, N.

***R*-20:** mp 86−87 °C; $[\alpha]_D^{20} = -21°$ (*c* 0.99, EtOH); IR (KBr) 3180, 3050, 2940, 1650, 1600, 1570, 1450, 1385, 1325, 775, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05 (d, $J = 8.0$ Hz, 1H, ArH-8), 7.51−7.47 (m, 1H, ArH-6), 7.41−7.34 (m, 1H, ArH-7), 7.24 (d, $J = 7.5$ Hz, 1H, ArH-5), 6.38 (br ex s, 1H, NH), 4.02−3.94 (m, 1H, H-3), 3.66−3.58 (m, 2H, CH_2Cl), 3.18−3.03 (m, 2H, H-4); ^{13}C NMR ($CDCl_3$) δ 166.1, 136.7, 133.1, 128.6, 128.5, 128.2, 127.9, 52.6, 46.6, 31.6; CIMS *m*/*z* (relative intensity) 196 (MH^+, 60), 146 (100). Anal. ($C_{10}H_{10}ClNO$) C, H, N.

***S*-(+)-*O*-Methoxycarbonyl-3-hydroxymethyl-3,4-dihydroisoquinolin-1-2*H*-one (*S*-16) and *S*-(+)-3-Chloromethyl-3,4-dihydroisoquinolin-1-2*H*-one (*S*-20).** Compounds *S*-**16** and *S*-**20** were prepared using the identical procedure as for *R*-**16** and *R*-**20** using *S*-**19** as the starting material.

***S*-16:** mp 125−126 °C; $[\alpha]_D^{20} = +28°$ (*c* 0.18, EtOH). Anal. ($C_{12}H_{13}NO_4$) C, H, N.

***S*-20:** mp 85−86 °C; $[\alpha]_D^{20} = +21°$ (*c* 0.98, EtOH). Anal. ($C_{10}H_{10}ClNO$) C, H, N.

***R*-(−)-O-Methoxycarbonyl-3-hydroxymethyl-7-nitro-3,4-dihydroisoquinolin-1-2*H*-one (*R*-21).** Lactam *R*-**16** (614 mg, 2.61 mmol) was dissolved in H_2SO_4 (10 mL) and cooled to 0 °C. KNO_3 (257 mg, 2.54 mmol) was added in three portions over 30 min. The mixture was warmed to room temperature and stirred overnight. The mixture was poured onto ice and stirred for 15 min as a white precipitate formed. The precipitate was collected by filtration and dried. The aqueous filtrate was extracted with EtOAc (4 × 50 mL). The combined organic extractions were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed and the residue combined with the dried precipitate. The off-white solid was recrystallized from acetone/hexanes to yield *R*-**21** as fluffy white crystals (580 mg, 79%): mp 209−210 °C; $[\alpha]_D^{20} = -17°$ (*c* 0.56, acetonitrile); IR (KBr) 3190, 3090, 2980, 1740, 1680, 1610, 1520, 1430, 1345, 1260, 920, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.93 (d, $J = 2.3$ Hz, 1H, ArH-8), 8.34 (dd, $J = 2.3$, 8.3 Hz, 1H, ArH-6), 7.44 (d, $J = 8.3$ Hz, 1H, ArH-5), 6.40 (br ex s, 1H, CONH), 4.40−4.15 (m, 2H, CH_2O), 4.14−4.08 (m, 1H, H-3), 3.83 (s, 3H, OCH_3), 3.21−3.05 (m, 2H, H-4); ^{13}C NMR (DMSO-d_6) δ 162.7, 155.3, 147.1, 145.4, 130.4, 130.3, 126.7, 122.0, 68.9, 55.2, 48.8, 29.8; CIMS *m*/*z* (relative intensity) 281 (MH^+, 100), 249 (75), 163 (50). Anal. ($C_{12}H_{12}N_2O_6$) C, H, N.

***S*-(+)-*O*-Methoxycarbonyl-3-hydroxymethyl-7-nitro-3,4-dihydroisoquinolin-1-2*H*-one (*S*-21).** Compound *S*-**21** was prepared using the identical procedure as for *R*-**21** using *S*-**16** as the starting material: mp 209−210 °C; $[\alpha]_D^{20} = +17°$ (*c* 0.63, acetonitrile). Anal. ($C_{12}H_{12}N_2O_6$) C, H, N.

***R*-(+)-3-Hydroxymethyl-7-nitro-1,2,3,4-tetrahydroisoquinoline Hydrochloride (*R*-9·HCl).** Lactam *R*-**21** (207 mg, 0.661 mmol) was suspended in a solution of anhydrous THF (35 mL). 1 M BH_3·THF (4.0 mL) was added to the suspension dropwise and the solution was heated at reflux for 16 h. It was cooled in an ice bath and MeOH (5 mL) was added dropwise. The solvent was removed under reduced pressure to yield a white residue. This residue was dissolved in MeOH (10 mL) and 12 M HCl (5 mL) and heated at reflux for 3 h. The solution was concentrated to ca. 5 mL and the pH of the solution was adjusted to 10 with 15% KOH. The solution was extracted with EtOAc (3 × 50 mL). The organic extracts were combined and dried over K_2CO_3. The solvent was removed to yield a white solid, which was dissolved in dry EtOH, and dry HCl(g) was used to form the hydrochloride salt. The solvent was removed under reduced pressure and the residue was recrystallized from EtOH to yield *R*-**9**·HCl as off-white needles (80.2 mg, 50%). This compound has been prepared previously using different methodology and all spectral data were identical to those reported previously:[19] mp 268 °C dec (lit.[19] mp 270 °C dec); $[\alpha]_D^{20} = +68°$ (*c* 0.31, MeOH) [lit.[19] $[\alpha]_D^{20} = +62°$ (*c* 0.28, MeOH)]. Anal. ($C_{10}H_{12}N_2O_3$·HCl) C, H, N.

***S*-(−)-3-Hydroxymethyl-7-nitro-1,2,3,4-tetrahydroisoquinoline Hydrochloride (*S*-9·HCl).** Compound *S*-**9**·HCl was prepared in the same manner as *R*-**9**·HCl using *S*-**21** as the starting material: mp 268 °C dec (lit.[19] mp 270 °C dec); $[\alpha]_D^{20} = -62°$ (*c* 0.31, MeOH) [lit.[19] $[\alpha]_D^{20} = -69°$ (*c* 0.28, MeOH)]. Anal. ($C_{10}H_{12}N_2O_3$·HCl) C, H, N.

***R*-(+)-*O*-Methoxycarbonyl-3-hydroxymethyl-7-bromo-3,4-dihydroisoquinolin-1-2*H*-one (*R*-22).** Compound *R*-**21** (160 mg, 0.572 mmol) was dissolved in MeOH (50 mL) and Pd/C (10 mg) was added. The mixture was hydrogenated for 3 h at 50 psi. The solution was filtered through Celite and the Celite bed rinsed with MeOH (50 mL). The solvent was removed and the residue was dissolved in H_2O (2.5 mL) and 48% HBr(aq) and cooled to 0 °C. KNO_2 (40.4 mg, 0.580 mmol) was dissolved in H_2O (1 mL), added dropwise to the reaction mixture, and stirred for 30 min. Excess HNO_2 was destroyed by the addition of urea (20 mg). This reaction mixture was added dropwise to a warm (35 °C) solution of CuBr (252 mg, 1.76 mmol), 48% HBr (1.5 mL), and H_2O (2 mL). After completion of the addition, the resulting solution was warmed to 75−80 °C and stirred for 1.5 h. The solution was cooled to room temperature and stirred overnight. The solution was made basic (pH > 10) with 50% KOH. The blue copper salts were removed by filtration and rinsed with CH_2Cl_2 (30 mL). The filtrate was extracted with CH_2Cl_2 (3 × 30 mL). The organic rinse and extracts were combined and dried over anhydrous Na_2SO_4 and the solvent was removed. The residue was purified by flash chromatography (silica gel) eluting with hexanes/EtOAc (4:1) to yield a white solid, which was recrystallized from EtOAc/hexanes to yield *R*-**22** as white needles (85.2 mg, 48%): mp 139−141 °C; $[\alpha]_D^{20} = -27°$ (*c* 0.23, EtOH); ^1H NMR ($CDCl_3$) δ 8.23 (d, $J = 2.1$ Hz, 1H, ArH-8), 7.61 (dd, $J = 2.1$, 8.1 Hz, 1H, ArH-6), 7.20 (d, $J = 8.1$ Hz, 1H, ArH-5), 6.55 (br ex s, 1H, NH), 4.31−4.15 (m, 2H, CH_2O), 4.07−4.03 (m, 1H, H-3), 3.83 (s, 3H, OCH_3), 3.07−2.87 (m, 2H, H-4); ^{13}C NMR ($CDCl_3$) δ 164.6, 155.5, 135.8, 135.6, 131.5, 130.2, 129.8, 121.7, 69.2, 55.6, 50.2, 30.0; CIMS *m*/*z* (relative intensity) 316 ($MH^+ + 2$, 100), 314 (MH^+, 100), 301 (50), 299 (50), 284 (75), 282 (75). Anal. ($C_{12}H_{12}NO_4Br$) C, H, N.

***S*-(+)-O-Methoxycarbonyl-3-hydroxymethyl-7-bromo-3,4-dihydroisoquinolin-1-2*H*-one (*S*-22).** Compound *S*-**22** was prepared in the same manner as *R*-**22** using *S*-**21** as the starting material: mp 139−141 °C; $[\alpha]_D^{20} = +26°$ (*c* 0.22, EtOH). Anal. ($C_{12}H_{12}NO_4Br$) C, H, N.

***R*-(+)-3-Hydroxymethyl-7-bromo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (*R*-14·HCl).** Compound *R*-**22** (49.2 mg, 0.157 mmol) was dissolved in THF (15 mL) and 1 M

BH_3·THF (1.5 mL, 1.5 mmol) was added dropwise. The solution was heated at reflux for 6 h and cooled in an ice bath. MeOH (5 mL) was added to the reaction mixture. The solvent was removed under reduced pressure and the residue dissolved in MeOH (10 mL) and 6 N HCl (10 mL). The reaction mixture was heated at reflux for 3 h. The solution was concentrated (ca. 10 mL) and made basic (pH > 10) with 10% NaOH. This basic solution was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were combined and dried over anhydrous Na_2SO_4. The solvent was removed and the residue purified by flash chromatography (silica gel) eluting with EtOAC/hexanes (3:1) to yield a white solid. The solid was dissolved in CH_2Cl_2 and dry HCl(g) was used to form the hydrochloride salt. The salt was recrystallized from EtOH/hexanes to yield *R*-**14**·HCl as white needles (25.9 mg, 57%): mp 250 °C dec; $[\alpha]_D^{20} = +48°$ (*c* 0.15, MeOH); ^{1}H NMR (CD_3OD) δ 7.34−7.33 (m, 2H, ArH-6,8), 7.07 (d, J = 8.7 Hz, 1H, ArH-5), 4.27−4.26 (m, 2H, CH_2OH), 3.85−3.80 (m, 1H, H-4), 3.60−3.54 (m, 1H, H-4), 3.52−3.45 (m, 1H, H-3), 2.91−2.88 (m, 2H, H-1); CIMS *m*/*z* (relative intensity) 244 (MH^+ + 2, 100), 242 (MH^+, 100), 212 (45), 210 (45). Anal. ($C_{10}H_{12}NOBr$·HCl) C, H, N.

***S*-(−)-3-Hydroxymethyl-7-bromo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (*S*-14·HCl).** The same procedure used for the synthesis of *R*-**14** was used for *S*-**14** with *S*-**22** as the starting material: mp 250 °C dec; $[\alpha]_D^{20} = -49°$ (*c* 0.12, MeOH). Anal. ($C_{10}H_{12}NOBr$·HCl) C, H, N.

***R*-(−)-3-Hydroxymethyl-3,4-dihydroisoquinolin-1-2*H*-one (*R*-23).** A solution of *R*-**16** (541 mg, 2.30 mmol) in MeOH (20 mL) and 6 N HCl (20 mL) was heated at reflux overnight. The MeOH was removed under reduced pressure. The solution was neutralized with 6 N NaOH and extracted with EtOAc (4 × 50 mL). The extracts were combined, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was purified by a flash column chromatography (silica gel) with EtOAc as the eluent to yield *R*-**23** as a white solid (365 mg, 90%): mp 141−142 °C; $[\alpha]_D^{20}$= +14° (*c* 1.1, EtOH); ^{1}H NMR (DMSO-d_6) δ 7.78 (d, J = 6.9 Hz, 1H, ArH-8), 7.67 (br ex s, 1H, NH), 7.43−7.38 (m, 1H, ArH-7), 7.25 (m, 2H, ArH-5,6), 4.9 (br ex s, 1H, OH), 3.51−3.50 (m, 1H, H-3), 3.49−3.25 (m, 2H, CH_2O), 2.96−2.76 (m, 2H, H-4); ^{13}C NMR (DMSO-d_6) δ 164.8, 138.3, 132.3, 129.3, 128.4, 127.3, 127.0, 63.5, 52.4, 30.0; CIMS *m*/*z* (relative intensity) 178 (MH^+, 60), 146 (100), 128 (20), 89 (15). Anal. ($C_{10}H_{11}NO_2$) C, H, N.

***S*-(−)-3-Hydroxymethyl-3,4-dihydroisoquinolin-1-2*H*-one (*S*-23).** Compound *S*-**23** was prepared in the same manner as *R*-**23** using *S*-**16** as the starting material: mp 141−142 °C; $[\alpha]_D^{20} = -14°$ (*c* 1.1, EtOH). Anal. ($C_{10}H_{11}NO_2$) C, H, N.

***R*-(−)-3-Fluoromethyl-3,4-dihydroisoquinolin-1-2*H*-one (*R*-24).** Compound *R*-**23** (600 mg, 3.38 mmol) was added to dry CH_2Cl_2 (10 mL) and cooled to −78 °C. Diethylaminosulfur trifluoride (DAST; 0.90 mL, 6.8 mmol) was added dropwise to the suspension. The mixture was slowly warmed to room temperature and stirred for 16 h. Ice water (10 mL) was added and the reaction mixture was stirred for 15 min. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The organic phase and extracts were combined and washed with 3 N HCl (50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with hexane/EtOAc (1:1) to yield a white solid that was recrystallized from hexanes to yield *R*-**24** as white needles (281 mg, 46%). This compound has been synthesized in racemic form[20] and all spectral data were identical to those reported previously: mp 120−121 °C; $[\alpha]_D^{20} = -22°$ (*c* 0.36, EtOH). Anal. ($C_{10}H_{10}NOF$) C, H, N.

***S*-(+)-3-Fluoromethyl-3,4-dihydroisoquinolin-1-2*H*-one (*S*-24).** Lactam *S*-**24** was prepared in the same manner as racemic **24**[20] using *S*-**23** as the starting material: mp 119−120 °C; $[\alpha]_D^{20} = +21°$ (*c* 0.30, EtOH). Anal. ($C_{10}H_{10}NOF$) C, H, N.

***R*-(+)-3-Fluoromethyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (*R*-6·HCl).** Lactam *R*-**24** (43.3 mg, 0.241 mmol) was reduced using the same procedures as for the synthesis of racemic **6**[20] to yield *R*-**6**·HCl as white needles (32.0 mg, 66%). All spectral data were identical to those reported previously: mp 241 °C; $[\alpha]_D^{20} = +54°$ (*c* 0.20, MeOH). Anal. ($C_{10}H_{12}NF$·HCl) C, H, N.

***S*-(−)-3-Fluoromethyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (*S*-6·HCl).** Compound *S*-**6** was prepared in the same manner as racemic **6**[20] using *S*-**24** as the starting material: mp 241 °C; $[\alpha]_D^{20} = -52°$ (*c* 0.28, MeOH). Anal. ($C_{10}H_{12}NF$·HCl) C, H, N.

***R*-(−)-3-Fluoromethyl-7-nitro-3,4-dihydroisoquinolin-1-2*H*-one (*R*-25).** Lactam *R*-**24** (200 mg, 1.12 mmol) was nitrated using the same procedures used for the synthesis of racemic **25**[20] to yield *R*-**25** as light yellow needles (132 mg, 53%). All spectral data were identical to those reported previously: mp 209 °C; $[\alpha]_D^{20} = -3.4°$ (*c* 0.53, acetone). Anal. ($C_{10}H_9NO_3F$) C, H, N.

***S*-(+)-3-Fluoromethyl-7-nitro-3,4-dihydroisoquinolin-1-2*H*-one (*S*-25).** Compound *S*-**25** was prepared in the same manner as racemic **25**[20] using *S*-**24** as the starting material: mp 209 °C; $[\alpha]_D^{20} = +3.7°$ (*c* 0.43, acetone). Anal. ($C_{10}H_9NO_3$-F) C, H, N.

***R*-(+)-3-Fluoromethyl-7-nitro-1,2,3,4-tetrahydroisoquinoline Hydrochloride (*R*-11·HCl).** Lactam *R*-**25** (141 mg, 0.629 mmol) was reduced in the same manner as used for the synthesis of racemic **11**[20] to yield *S*-**11**·HCl as off-white crystals (75.0 mg, 48%). All spectral data were identical to those reported previously: mp 260 °C dec; $[\alpha]_D^{20} = +72°$ (*c* 0.52, EtOH). Anal. ($C_{10}H_{11}N_2O_2F$·HCl) C, H, N.

***S*-(−)-3-Fluoromethyl-7-nitro-1,2,3,4-tetrahydroisoquinoline Hydrochloride (*S*-11·HCl).** Compound *S*-**11** was prepared in the same manner as racemic **11**[20] using *S*-**25** as the starting material: mp 260 °C dec; $[\alpha]_D^{20} = -66°$ (*c* 0.55, EtOH). Anal. ($C_{10}H_{11}N_2O_2F$·HCl) C, H, N.

***R*-(+)-3-Fluoromethyl-7-cyano-1,2,3,4-tetrahydroisoquinoline Hydrochloride (*R*-12·HCl).** THIQ *R*-**11**·HCl (1.23 g, 4.99 mmol) was converted to nitrile *R*-**12** using the same procedures reported for the synthesis of racemic **12**[20] to yield *R*-**12** (256 mg, 27%) as a pale brown solid. The hydrochloride salt was formed in MeOH using dry HCl(g). The solvent was removed under reduced pressure and the crude hydrochloride salt was recrystallized from MeOH/EtOAc to yield *R*-**12**·HCl (267 mg, 100%). All spectral data were identical to those reported previously: mp 240 °C dec; (free base) $[\alpha]_D^{20} = +110°$ (*c* 0.14, $CHCl_3$). Anal. ($C_{11}H_{11}N_2F$·HCl) C, H, N.

***S*-(−)-3-Fluoromethyl-7-cyano-1,2,3,4-tetrahydroisoquinoline Hydrochloride (*S*-12·HCl).** Compound *S*-**12** was prepared using the same methods as racemic **12**[20] using *S*-**11** as the starting material: mp 240 °C dec; (free base) $[\alpha]_D^{20} = -110°$ (*c* 0.15, $CHCl_3$). Anal. ($C_{11}H_{11}N_2F$·HCl) C, H, N.

***R*-(+)-3-Fluoromethyl-7-bromo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (*R*-15·HCl).** THIQ *R*-**11**·HCl (804 mg, 3.26 mmol) was converted to *R*-**15** using the same methods reported for the synthesis of racemic **15**[20] to yield *R*-**15** as a white solid (527 mg, 67%): mp 91−92 °C. The hydrochloride salt was formed in MeOH using dry HCl(g). The solvent was removed and the crude hydrochloride salt recrystallized from MeOH and ether to yield *R*-**15**·HCl as white needles (604 mg, 100%). This compound was synthesized in racemic form[20] and all spectral data were identical to those reported previously: mp 258 °C dec; $[\alpha]_D^{20} = +56°$ (*c* 0.50, MeOH). Anal. ($C_{10}H_{11}$-NFBr·HCl) C, H, N.

***S*-(−)-3-Fluoromethyl-7-bromo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (*S*-15·HCl).** Compound *S*-**15** was prepared using the same methods as for racemic **15**[20] using *S*-**11**·HCl as the starting material: mp 258 °C dec; $[\alpha]_D^{20} = -52°$ (*c* 0.62, MeOH). Anal. ($C_{10}H_{11}NFBr$·HCl) C, H, N.

***R*-(−)-3-Fluoromethyl-7-chlorosulfonyl-3,4-dihydroisoquinolin-1-2*H*-one (*R*-26).** Lactam *R*-**24** (338 mg, 1.89 mmol) was chlorosulfonylated using the procedures reported for the synthesis of racemic **26**[20] to yield *R*-**26** as white crystals (342 mg, 65%). All spectral data were identical to those reported previously: mp 183 °C; $[\alpha]_D^{20} = -13°$ (*c* 0.20, acetonitrile). Anal. ($C_{10}H_9NO_3FClS$) C, H, N.

***S*-(+)-3-Fluoromethyl-7-chlorosulfonyl-3,4-dihydroisoquinolin-1-2*H*-one (*S*-26).** Compound *S*-**26** was prepared using the same methods as for racemic **26**[20] using *S*-**24** as the starting material: mp 183 °C; $[\alpha]_D^{20} = +13°$ (*c* 0.16, acetonitrile). Anal. ($C_{10}H_9NO_3FClS$) C, H, N.

***R*-(+)-3-Fluoromethyl-7-*N*-(4-chlorophenyl)aminosulfonyl-3,4-dihydroisoquinolin-1-2*H*-one (*R*-27).** Compound *R*-**26** (500 mg, 1.80 mmol) was transformed into sulfonamide *R*-**27** using the same procedures reported[20] for the production of racemic **27** to yield compound *R*-**27** as light orange crystals (639 mg, 1.74 mmol, 97%). All spectral data were identical to those reported previously: mp 197−198 °C; $[\alpha]_D^{20} = +13°$ (*c* 0.55, acetone). Anal. ($C_{16}H_{14}N_2O_3FClS$) C, H, N.

***S*-(−)-3-Fluoromethyl-7-*N*-(4-chlorophenyl)aminosulfonyl-3,4-dihydroisoquinolin-1-2*H*-one (*S*-27).** Compound *S*-**27** was prepared using the same methods as for racemic **27**[20] using *S*-**26** as the starting material: mp 197−198 °C; $[\alpha]_D^{20} = -13°$ (*c* 0.55, acetone). Anal. ($C_{16}H_{14}N_2O_3FClS$) C, H, N.

***R*-(+)-3-Fluoromethyl-7-*N*-(4-chlorophenyl)aminosulfonyl-1,2,3,4-tetrahydroisoquinoline (*R*-13).** Lactam *R*-**27** (639 mg, 1.74 mmol) was reduced using the same procedures reported previously for the synthesis of racemic **27**[20] to yield *R*-**13** as white crystals (248 mg, 36%). It should be noted that *R*-**13** was isolated and characterized as its free base. All spectral data were identical to those reported previously: mp 178−179 °C; $[\alpha]_D^{20} = +50°$ (*c* 0.29, MeOH). Anal. ($C_{16}H_{16}N_2O_2FClS$) C, H, N.

***S*-(−)-3-Fluoromethyl-7-*N*-(4-chlorophenyl)aminosulfonyl-1,2,3,4-tetrahydroisoquinoline (*S*-13).** Compound *S*-**13** was prepared using the same methods as for racemic **13**[20] using *S*-**27** as the starting material: mp 178−179 °C; $[\alpha]_D^{20} = -56°$ (*c* 0.23, MeOH). Anal. ($C_{16}H_{16}N_2O_2FClS$) C, H, N.

***R*-(+)-3-Chloromethyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (*R*-28·HCl).** Lactam *R*-**20** (310 mg, 1.58 mmol) was dissolved in dry THF (20 mL) and 1 M BH_3·THF (5 mL) was added dropwise to the solution. The mixture was heated at reflux for 15 h. It was cooled in an ice bath and MeOH (5 mL) was added dropwise. The solvent was removed under reduced pressure to yield a white residue. This residue was dissolved in MeOH (10 mL) and concentrated HCl (5 mL) and heated at reflux for 3 h. The MeOH was removed under reduced pressure and 15% KOH was added until the solution was at pH > 10. The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (50 mL) and dried over anhydrous K_2CO_3. The solvent was removed under reduced pressure to yield *R*-**28** as a white solid, from which the hydrochloride salt was formed in MeOH using HCl(g). The solvent was removed and the residue recrystallized from EtOH/hexanes to yield *R*-**28**·HCl as white crystals (286 mg, 83%): mp 226−228 °C; $[\alpha]_D^{20} = +38°$ (*c* 1.0, MeOH); IR (KBr) 3380, 2880, 2580, 2480, 2400, 1575, 1495, 1430, 1395, 1000, 750, 690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.23 (br ex s, 2H, NH_2^+), 7.26−7.24 (m, 4H, Ar−H), 4.34 (m, 2H, H-1), 4.11−4.01 (m, 2H, CH_2Cl), 3.88 (m, 1H, H-3), 3.17−3.08 (m, 2H, H-4); ^{13}C NMR (DMSO-d_6) δ 131.9, 129.6, 129.3, 128.3, 127.5, 127.4, 53.9, 45.1, 45.0, 29.3; CIMS *m*/*z* (relative intensity) 182 (MH^+, 85), 132 (100), 104 (45), 78 (20). Anal. ($C_{10}H_{12}ClN$·HCl) C, H, N.

***S*-(−)-3-Chloromethyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (*S*-28·HCl).** This compound was prepared in the same manner as *R*-**28**·HCl using lactam *S*-**20** as the starting material: mp 226−228 °C; $[\alpha]_D^{20} = -40°$ (*c* 1.0, MeOH). Anal. ($C_{10}H_{12}ClN$·HCl) C, H, N.

***R*-(+)-3-Chloromethyl-7-nitro-3,4-dihydroisoquinolin-1-2*H*-one (*R*-29).** Lactam *R*-**20** (620 mg, 3.17 mmol) was dissolved in concentrated H_2SO_4 (12 mL) at 0 °C and KNO_3 (385 mg, 8.80 mmol) was added to the solution in one portion. The reaction mixture was stirred overnight at room temperature. The reaction solution was poured onto ice carefully and the resulting solution was extracted with EtOAc (4 × 50 mL). The combined organic extractions were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed to yield a yellow solid, which was recrystallized with EtOAc/hexanes to yield *R*-**29** as pale yellow needles (641 mg, 84%); mp 180−182 °C; $[\alpha]_D^{20} = +4.8°$ (*c* 1.0, acetone); IR (KBr) 3200, 3080, 2950, 1670, 1600, 1500, 1430, 1340, 740 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.54 (d, *J* = 2.5 Hz, 1H, H-8), 8.50 (ex s, 1H, NH), 8.33 (dd, *J* = 2.5, 8.3 Hz, 1H, H-6), 7.41 (d, *J* = 8.3 Hz, 1H, H-5), 4.08−3.99 (m, 1H, H-3), 3.75−3.68 (m, 2H, CH_2Cl), 3.32−3.13 (m, 2H, H-4); ^{13}C NMR (DMSO-d_6) δ 163.1, 147.6, 145.7, 130.8, 130.6, 127.3, 122.4, 51.3, 47.6, 30.8; CIMS *m*/*z* (relative intensity) 241 (MH^+, 100), 191 (45), 145 (15). Anal. ($C_{10}H_9ClN_2O_3$) C, H, N.

***S*-(−)-3-Chloromethyl-7-nitro-3,4-dihydroisoquinolin-1-2*H*-one (*S*-29).** This compound was prepared in the same manner as *R*-**29** using lactam *S*-**20** as the starting material: mp 180−182 °C; $[\alpha]_D^{20} = -4.9°$ (*c* 1.0, acetone). Anal. ($C_{10}H_9ClN_2O_3$) C, H, N.

***R*-(+)-3-Chloromethyl-7-nitro-1,2,3,4-tetrahydroisoquinoline Hydrochloride (*R*-30·HCl).** Lactam *R*-**29** (616 mg, 2.56 mmol) was dissolved in dry THF (30 mL) and 1 M BH_3·THF (7.7 mL, 7.7 mmol) was added dropwise to the solution. The mixture was heated at reflux for 15 h. It was cooled in an ice bath and MeOH (5 mL) was added dropwise. The solvent was removed under reduced pressure to yield a white residue. This residue was dissolved in MeOH (10 mL) and 6 N HCl (10 mL) and heated to reflux for 3 h. The MeOH was removed under vacuum and the solution was made basic (pH > 10) with 15% NaOH. The aqueous solution was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (50 mL) and dried over anhydrous K_2CO_3. The solvent was removed under reduced pressure to yield *R*-**30** as a white solid, from which the hydrochloride salt was formed in using dry HCl(g). The solvent was removed and the residue recrystallized from EtOH/hexanes to yield *R*-**30**·HCl as white needles (524 mg, 78%): mp 258−260 °C; $[\alpha]_D^{20} = +53°$ (*c* 1.0, MeOH); IR (KBr) 3000−2600 (broad), 2480, 1575, 1510, 1495, 1435, 1345, 1330, 770, 735 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.43 (br ex s, 2H, NH_2^+), 8.23 (br s, 1H, ArH-6), 8.09 (br s, 1H, ArH-8), 7.55 (br s, 1H, H-5), 4.49 (s, 2H, H-1), 4.14 (m, 2H, CH_2Cl), 3.96 (m, 1H, H-3), 3.24 (m, 2H, H-4); ^{13}C NMR (DMSO-d_6) δ 146.9, 140.3, 131.5, 137.2, 122.9, 122.7, 53.3, 44.7, 44.7, 29.5; CIMS *m*/*z* (relative intensity) 227 (MH^+, 100), 177 (75). Anal. ($C_{10}H_{11}ClN_2O_2$·HCl) C, H, N.

***S*-(−)-3-Chloromethyl-7-nitro-1,2,3,4-tetrahydroisoquinoline Hydrochloride (*S*-30·HCl).** Compound *S*-**30**·HCl was prepared using the same methods as for *R*-**30**·HCl using *S*-**29** as the starting material: mp 258−260 °C; $[\alpha]_D^{20} = -54°$ (*c* 1.0, MeOH). Anal. ($C_{10}H_{11}ClN_2O_2$·HCl) C, H, N.

Determination of Enantiomeric Excess. Enantiomeric excess (ee) was determined for every compound to be greater than 95% and was assessed in the following manner. Using Chiral HPLC analysis (Chiralcel OJ) eluting with hexanes/isopropyl alcohol/$NH(Et)_2$, all compounds appeared as a single distinct peak. However, for the racemic mixtures of these compounds, baseline separation could not be obtained due to tailing caused by the THIQ amine. Several solutions of each isolated enantiomer (2.0 mg in 5 mL of isopropyl alcohol) were prepared and mixed in the following proportions (95:5, 97.5:2.5, and 98.75:1.25). These solutions were analyzed, and it was found each enantiomer could easily be detected as a shoulder in the 97.5:2.5 mixture but not in the 98.75:1.25 mixture, which implied that the ee of each of these compounds was at a minimum greater than 95%.

Radiochemical Assay for PNMT Activity. The assay used for this study has been described previously.[29] A normal assay tube mixture consisted of 50 μL of 0.5 M phosphate buffer (pH 8.0), 25 μL of 10 mM AdoMet, 5 μL of [^{3}H]AdoMet that contains 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 water to achieve a total volume of 250 μL. The mixture was incubated for 30 min at 37 °C, quenched by the addition of 250 μL of 0.5 M borate buffer (pH 10), and extracted with 2 mL of toluene/isoamyl alcohol (7:3). A 1-mL aliquot of the organic layer was removed, transferred to a scintillation vial, and diluted with cocktail for counting. The mode of inhibition for all of the inhibitors assayed was determined to be competi-

tive by inspection of the 1/*V* versus 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 binding assay was performed using the methods developed by U′Prichard et al.[30] Male Sprague−Dawley rats were decapitated and the cortexes removed and homogenized with 20 volumes (w/v) of ice-cold 50 mM Tris/HCl buffer (pH 7.7 at 25 °C). Homogenates were centrifuged three times for 10 min at 50000*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 2.0 nM), various concentrations of the inhibitors, and an aliquot of freshly suspended tissue (800 μL) to 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 50 mM Tris/HCl buffer (pH 7.7 at 25°C). The filters were counted in vials containing premixed scintillation cocktail. Nonspecific binding was determined as the concentration of ligand bound in the presence of 2 μM phentolamine. All assays were examined by a log−probit analysis of the data to determine the IC_{50} values, 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.

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