Pergamon

Bioorganic & Medicinal Chemistry 9 (2001) 1957–1965

BIOORGANIC & MEDICINAL CHEMISTRY

Effects of a 3-Alkyl-, 4-Hydroxy- and/or 8-Aromatic-substituent on the Phenylethanolamine *N*-Methyltransferase Inhibitor Potency and α_2-Adrenoceptor Affinity of 2,3,4,5-Tetrahydro-1*H*-2-benzazepines

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Received 10 December 2000; accepted 9 February 2001

Abstract—2,3,4,5-Tetrahydro-1*H*-2-benzazepine (THBA; **1**) is nearly 100-fold more selective an inhibitor of phenylethanolamine *N*-methyltransferase (PNMT, EC 2.1.1.28) versus the α_2-adrenoceptor than is 1,2,3,4-tetrahydroisoquinoline (THIQ; **2**) (**1**: PNMT $K_i = 3.3\,\mu M$, α_2-adrenoceptor $K_i = 11\,\mu M$, selectivity [α_2 K_i/PNMT K_i] = 3.3; **2**: PNMT $K_i = 9.7\,\mu M$, α_2 $K_i = 0.35\,\mu M$, selectivity = 0.036;). Since the PNMT inhibitory activity and selectivity of THIQ were enhanced by the introduction of a hydrophilic electron-withdrawing 7-substituent and a 3-alkyl-substituent, a similar study was conducted on THBA. 8-Nitro-THBA (**3**) was found to be as potent an inhibitor of PNMT as its THIQ analogue (**21**) and to be more selective due to its reduced α_2-adrenoceptor affinity (**3**: PNMT $K_i = 0.39\,\mu M$, α_2 $K_i = 66\,\mu M$, selectivity = 170; **21**: PNMT $K_i = 0.41\,\mu M$, α_2 $K_i = 4.3\,\mu M$, selectivity = 10). Introduction of a 3-alkyl substituent on the THBA nucleus decreased both the α_2-adrenoceptor affinity and the PNMT inhibitory activity, suggesting an area of steric bulk intolerance at both sites. 4-Hydroxy-THBA (**15**), which can be considered a conformationally-restricted analogue of 3-hydroxymethyl-THIQ (**30**), exhibited poorer PNMT inhibitory activity and less selectivity than **30** (**15**: PNMT $K_i = 58\,\mu M$, α_2 $K_i = 100\,\mu M$, selectivity = 1.7; **30**: PNMT $K_i = 1.1\,\mu M$, α_2 $K_i = 6.6\,\mu M$, selectivity = 6.0). While the addition of an 8-nitro group to **15** increased the selectivity of **16** as compared to its THIQ analogue (**31**), it was not as potent at PNMT nor as selective as 8-nitro-THBA (**3**) (**16**, PNMT $K_i = 5.3\,\mu M$, α_2 $K_i = 680\,\mu M$, selectivity = 130; **31**: PNMT $K_i = 0.29\,\mu M$, α_2 $K_i = 19\,\mu M$, selectivity = 66). Compound **3** is the most selective (PNMT/α_2) and one of the more potent at PNMT compounds yet reported in the benzazepine series, and should have sufficient lipophilicity to penetrate the blood–brain barrier (CLogP = 1.8).

In our ongoing study into the development of a selective and potent inhibitor of the enzyme phenylethanolamine *N*-methyltransferase (PNMT, EC 2.1.1.28)—that catalyzes the final step in the biosynthesis of epinephrine—we report our findings in a benzazepine series of inhibitors. To elucidate the exact role of epinephrine in the central nervous system (CNS), an inhibitor of PNMT lacking activity at other pharmacologically relevant sites (especially the α_2-adrenoceptor) is highly desired.[2] In addition, such an inhibitor must have low polarity so that it can penetrate the blood–brain barrier (BBB) to exert its effect in the CNS.

The conformational restriction of benzylamine into a 2,3,4,5-tetrahydro-1*H*-2-benzazepine [THBA, **1**, PNMT $K_i = 3.3\,\mu M$, α_2 $K_i = 11\,\mu M$, selectivity (α_2 K_i/PNMT K_i) = 3.3] provided higher PNMT inhibitory potency and lower α_2-adrenoceptor affinity as compared to other conformationally-restricted benzylamine analogues.[3] 1,2,3,4-Tetrahydroisoquinoline (**2**, THIQ, PNMT $K_i = 9.7\,\mu M$, α_2 $K_i = 0.35\,\mu M$, selectivity = 0.036) was relatively less potent in inhibiting PNMT and also less selective than THBA. Subsequently, a hydrophilic electron-withdrawing 7-substituent[4] or a 3-alkyl substituent[5] was found to be an important structural feature that influenced the potency and selectivity of THIQ, and the combination of both on THIQ was found to exhibit a synergistic effect on the selectivity for PNMT versus the α_2-adrenoceptor.[6] These encouraging results from studies in the THIQ series prompted us to investigate the influence of similar substituents on the potency and selectivity of the THBA nucleus. The aromatic substituents to be studied (e.g., NO_2, SO_2Me and SO_2NH_2) were those that were found to have the largest

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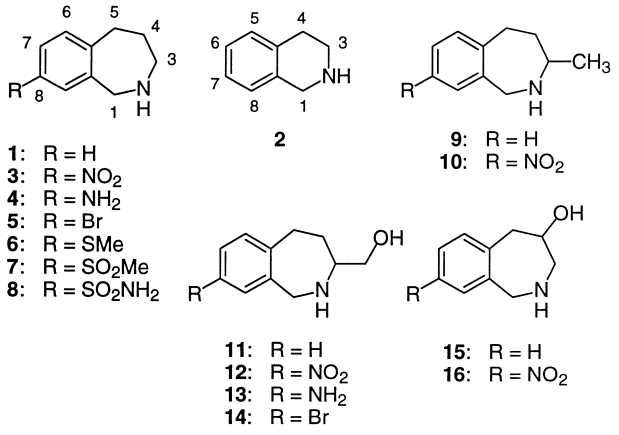
0968-0896/01/$ - see front matter
PII: S0968-0896(01)00112-2

influence on selectivity in the THIQ series.[4] Some of these 8-substituted-THBAs had been listed previously in the patent literature,[7] but the K_i values for PNMT inhibition and α_2-adrenoceptor affinity were not reported.



As proposed earlier,[3] the enhancement in PNMT inhibitory potency of **1** as compared to **2** probably arose from the puckered 3-methylene group in the bioactive conformation of **1** that interacted favorably at a spatially compact region in the PNMT active site. In contrast, the same methylene group in THBA might be involved in a negative steric interaction at the α_2-adrenoceptor. This hypothesis also explained the improved potency and selectivity of 3-methyl-THIQ[6] [**28**, PNMT $K_i = 2.1\,\mu M$, α_2 $K_i = 0.76\,\mu M$, selectivity (α_2 K_i/PNMT K_i) = 0.36] as compared to **2**. To explore the effects of the introduction of a 3-methyl substituent alone and in conjunction with an electron-withdrawing group on the THBA nucleus, analogues **9** and **10** were prepared.

The 3-hydroxymethyl substituent, with or without a hydrophilic electron-withdrawing 7-substituent, was found to be effective in enhancing the selectivity of the THIQ nucleus.[6] Hence, THBAs bearing a 3-hydroxymethyl substituent and an 8-aromatic substituent (**11**–**14**) were investigated. As a more direct comparison of the effect of the 3-hydroxymethyl substituent, 4-hydroxy-THBA (**15**)—a conformationally-constrained analogue of 3-hydroxymethyl-THIQ (**30**), where the side-chain is incorporated into the ring system—was also investigated, along with its 8-nitro analogue (**16**).

Since THBA (**1**) is more selective for PNMT versus the α_2-adrenoceptor than is THIQ (**2**), and the addition of a 3-alkyl or a 7-substituent on the THIQ nucleus improved selectivity for PNMT,[4,6] would 3-alkyl or judicious 8-substitution on the THBA nucleus improve selectivity for PNMT, and thus provide a viable pharmacological tool for the purpose of studying the function of epinephrine in the brain?

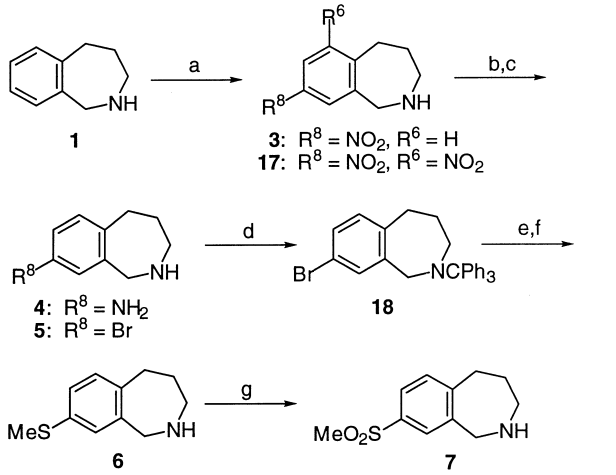
Chemistry

The chemistry used in the synthesis of 8-substituted-THBAs is similar to that developed earlier for the THIQ system[4] (Scheme 1). Nitration of THBA (**1**) was carried out by addition of potassium nitrate to an ice-cold solution of **1** in concentrated sulfuric acid. 8-Nitro-THBA (**3**) was isolated in 60% yield along with a minor quantity (7%) of 6,8-dinitro-THBA (**17**). Catalytic reduction of **3** to **4**, followed by Sandmeyer bromination gave **5**, which was protected and subjected to a halogen-metal exchange reaction. The lithiated species was trapped at low temperature with methyl disulfide and the trityl protecting group was cleaved to yield **6**. The thiomethyl ether **6** was readily oxidized under acidic conditions to yield sulfone **7** (Scheme 1).

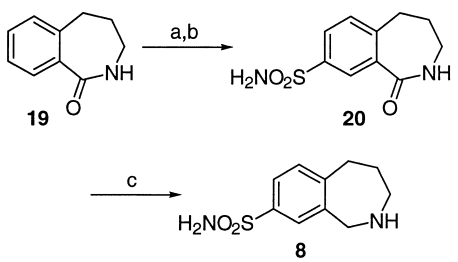
8-Aminosulfonyl-THBA (**8**) was prepared from amide **19**,[8,9] the product of a Schmidt reaction on 1-tetralone. Due to the meta-directing effect of the amido group, only a single regioisomer was obtained from the chlorosulfonation of **19**, which was converted to sulfonamide **20** (Scheme 2). Borane reduction of **20** was slow due to its low solubility in THF. An acidic work up permitted isolation of the amphoteric product (**8**) as its hydrochloride salt (Scheme 2).

The synthesis of other THBAs was developed in our laboratory using the Schmidt reaction (analogues **9**–**14**)[8] and a lactone to lactam rearrangement (analogues **15** and **16**),[9] that has been reported previously.

Biochemistry. All the compounds were evaluated as their hydrochloride or oxalate salts. In vitro PNMT activity was assessed by use of a standard radiochemical assay—using three different inhibitor concentrations



Scheme 1. Reagents and conditions: (a) KNO_3, H_2SO_4; (b) H_2, PtO_2, HCl; (c) $NaNO_2$, HBr, CuBr; (d) PH_3CCl, Et_3N, DMAP; (e) *n*-BuLi, THF −78 °C; (f) CH_3SSCH_3, 3 N HCl, Acetone; (g) CF_3CO_3H (2 equiv), CF_3CO_2H.



Scheme 2. Reagents and conditions: (a) $ClSO_3H$; (b) NH_4OH; (c) BH_3THF, reflux.

with phenylethanolamine as the variable substrate—that has been described previously.[10] Bovine adrenal PNMT used for the in vitro assay was purified according to the procedure of Connett and Kirshner[11] through the isoelectric precipitation step.

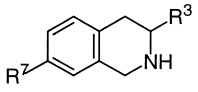
α_2-Adrenergic receptor binding assays were performed using cortex obtained from male Sprague–Dawley rats.[12] [^{3}H]Clonidine was used as the radioligand to define the specific binding and phentolamine was used to define the non-specific binding. Clonidine was used as the ligand to define α-adrenergic binding affinity to simplify the comparison with previous results.

Results and Discussion

The results of biochemical evaluation of the 8-substituted-THBAs are presented in Table 1 along with the results for the corresponding 7-substituted-THIQs.[4] Compounds **3**–**8** were reported as being synthesized in the patent literature,[7] but no data was reported. The results for 3-alkyl-substituted-THBAs and 4-hydroxy-THBAs are listed in Tables 2 and 3, respectively. As expected, all of these THBA derivatives exhibited competitive kinetics in binding to PNMT, and a Hill coefficient close to unity in α_2-adrenoceptor binding assays.

Examination of the data for the 8-substituted-THBAs showed that, as in the THIQ series,[4] the aromatic substituent had considerable influence on the PNMT inhibitory potency. Comparison of an 8-substituted-THBA derivative with the corresponding 7-substituted-THIQ showed that: (a) the potency of the nitro-, bromo-, and amino-derivatives at PNMT were unaffected by an increase in ring size, (b) the PNMT inhibitory activity of the sulfonyl-analogues was decreased in the benzazepine series, and (c) the THBA derivatives showed lower α_2-adrenoceptor affinity than the corresponding THIQ derivatives, except in the case of the 8-sulfonyl-substituted-THBAs, which had similar affinities.

8-Nitro-THBA (**3**) was found to be the most selective inhibitor in the THBA series, with a selectivity approximately that of SK&F 29661 (**26**). However, it had been reported that **26** did not penetrate into the CNS, possibly due to its high polarity.[13] Therefore, the higher lipophilicity of **3** may enable it to penetrate the BBB (**26**: calculated log P (CLogP) = −0.39 versus **3**: CLogP = 1.8).[14,15] It was interesting to note that **3** exhibited lower α_2-adrenoceptor affinity than 3-methyl-7-nitro-THIQ[6] (**27**: PNMT $K_i = 0.49\,\mu M$, α_2 $K_i = 31\,\mu M$, selectivity = 63), which would suggest that the extra ring methylene (corresponding to the methyl group in **27**) encounters more steric bulk intolerance at the α_2-adrenoceptor.[6]

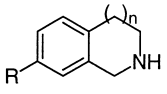


	R^3	R^7
27:	CH_3	NO_2
28:	CH_3	H
29:	CH_2CH_3	H
30:	CH_2OH	H
31:	CH_2OH	NO_2

The introduction of a 3-methyl or 3-hydroxymethyl group increased the PNMT inhibitory potency in the THIQ series,[6] but decreased it in the THBA series. The addition of an 8-substituent did not overcome the deleterious effect of the 3-alkyl group, which may be involved in negative steric interactions that prevent the optimal binding of the THBA nucleus. This result was consistent with the decreased PNMT inhibitory potency of 3-ethyl-THIQ (**29**: PNMT $K_i = 24\,\mu M$)[5] as compared to **28** (PNMT $K_i = 2.1\,\mu M$).

The trends in α_2-adrenoceptor affinity of the 3-alkyl-THBAs paralleled the results obtained in the 3-alkyl-THIQ series,[6] with the 3-hydroxymethyl substituent resulting in a greater decrease in α_2-adrenoceptor affinity than the 3-methyl substituent. However, none of these compounds were more selective than 8-nitro-THBA (**3**).

Table 1. In vitro activities of 7-substituted-1,2,3,4-tetrahydroisoquinolines and 8-substituted-2,3,4,5-tetrahydro-1*H*-2-benzazepines as inhibitors of PNMT and of the binding of [^{3}H]clonidine to the α_2-adrenoceptor

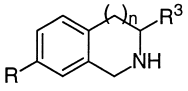


Compd	n[a]	R	PNMT $K_i \pm$ SEM (μM)	$\alpha_2 K_i \pm$ SEM (μM)	α_2/PNMT selectivity
2	1	H	9.7 ± 0.4	0.35 ± 0.1	0.036
1	2	H	3.3 ± 0.2	11 ± 1	3.3
21	1	NO_2	0.41 ± 0.05	4.3 ± 0.3	10
3	2	NO_2	0.39 ± 0.05	66 ± 3	170
22	1	NH_2	27 ± 3	3.1 ± 0.1	0.11
4	2	NH_2	24 ± 1	110 ± 10	4.6
23	1	Br	0.29 ± 0.03	0.23 ± 0.13	0.79
5	2	Br	0.29 ± 0.04	8.8 ± 0.2	30
24	1	SMe	0.61 ± 0.05	0.41 ± 0.05	0.67
6	2	SMe	1.1 ± 0.1	12 ± 1	11
25	1	SO_2Me	1.3 ± 0.06	160 ± 10	120
7	2	SO_2Me	7.7 ± 0.23	150 ± 10	19
26	1	SO_2NH_2	0.55 ± 0.04	100 ± 20	180
8	2	SO_2NH_2	1.7 ± 0.09	91 ± 3	54

[a]Data for $n = 1$ taken from ref. 4.

As both of the 8-sulfonyl-substituents reduced the PNMT inhibitory potency of THBA, these were not introduced on the 3-alkyl-THBAs. We determined the α_2-adrenoceptor affinity of a previously reported[5] PNMT inhibitor, **29** (α_2 $K_i = 0.66\,\mu M$)[6] and found that its α_2-adrenoceptor affinity was almost identical to that of **28** (α_2 $K_i = 0.76\,\mu M$), which suggested that the terminal methyl group in the ethyl side chain might be oriented in a region of space where steric bulk was tolerated. In contrast, the 3-methyl group in **9** (α_2 $K_i = 89\,\mu M$) appears to be projected into a region of steric bulk intolerance at the α_2-adrenoceptor.

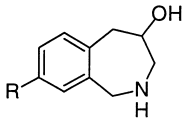
Table 2. In vitro activities of racemic 7-substituted-3-alkyl-1,2,3,4-tetrahydroisoquinolines and 8-substituted-3-alkyl-2,3,4,5-tetrahydro-1*H*-2-benzazepines as inhibitors of PNMT and of the binding of [^{3}H]clonidine to the α_2-adrenoceptor



Compd	n[a]	R	R^3	$K_i \pm$SEM (μM) PNMT	$K_i \pm$SEM (μM) α_2	Selectivity α_2/PNMT
9	2	H	Me	8.6±0.4	89±3	10
28	1	H	Me	2.1±0.1	0.76±0.08	0.36
10	2	NO_2	Me	5.5±0.3	120±10	22
27	1	NO_2	Me	0.49±0.05	31±1	63
11	2	H	CH_2OH	7.8±0.3	220±10	28
30	1	H	CH_2OH	1.1±0.1	6.6±0.6	6.0
12	2	NO_2	CH_2OH	8.1±0.4	540±10	67
31	1	NO_2	CH_2OH	0.29±0.04	19±1	66
13	2	NH_2	CH_2OH	440±30	490±10	1.1
14	2	Br	CH_2OH	6.0±0.3	58±1	9.7

[a]Data for $n = 1$ taken from ref 6.

Table 3. In vitro activities of racemic 4-hydroxy-2,3,4,5-tetrahydro-1*H*-2-benzazepines as inhibitors of PNMT and of the binding of [^{3}H]clonidine to the α_2-adrenoceptor



Compd	R_8	PNMT $K_i \pm$SEM (μM)	α_2 $K_i \pm$SEM (μM)	α_2/PNMT selectivity
15	H	58±3	100±10	1.7
16	NO_2	5.3±0.3	680±10	130

Table 4. Minimum distances between potential binding groups in the superimposition of *R*- or *S*-**15** and *R*-**30**[a]

Binding group	Distance
R-**15** vs *R*-**30**	
Oxygen lone pairs	1.17 Å
Hydroxyl hydrogens	2.86 Å
Hydroxyl oxygens	3.47 Å
S-**15** vs *R*-**30**	
Oxygen lone pairs	1.05 Å
Hydroxyl hydrogens	0.85 Å
Hydroxyl oxygens	1.62 Å

[a]Compounds were superimposed using both ends of a 2 Å long normal through the centroid of the aromatic ring and the end of the axial lone pair (2.4 Å) from the THIQ or THBA nitrogen and distances were measured using the "Analyze: Measure Distance" menu option in SYBYL.

Inclusion of the methylene group of the hydroxymethyl side chain of **30** (PNMT $K_i = 1.1\,\mu M$, α_2 $K_i = 6.6\,\mu M$, selectivity = 6.0)[6] into the ring (analogue **15**) resulted in a 50-fold loss in PNMT inhibitory activity (PNMT $K_i = 58\,\mu M$). Thus, **15** is apparently not a satisfactory conformationally-restricted analogue of the binding orientation of **30**. This result is consistent with molecular modeling studies on the (*R*)- and (*S*)-enantiomers of **15**, which show that the low energy global or local minimum conformations (not exceeding the energy of the corresponding global minimum by more than 2 kcal/mole, as determined by the grid search option in SYBYL[16]) could be fitted reasonably well [root mean square of fit = 0.240 for (*R*)-**15**), and 0.241 for (*S*)-**15**] with the more active (*R*)-enantiomer[6] of **30**. However, as shown in Table 4 and Figure 1, the minimum distances between the putative binding groups of (*R*)- or (*S*)-**15** with the more active (*R*)-enantiomer[6] of **30**, would seem to preclude these groups binding at the same region in space at the PNMT active site.

As in the case of the unsubstituted THBA (**1**), the addition of an 8-nitro substituent to **15**—compound **16**—improved the PNMT inhibitory potency by about 10-fold. However, the deleterious interaction of the 4-hydroxy group, as in **15**, was not totally overcome. The lowered α_2-adrenoceptor affinity of **16** was due to the combined effect of the 4-hydroxy and the 8-nitro groups, but while this resulted in a selectivity ratio that was higher than that of its THIQ analogue (**31**: PNMT $K_i = 0.29\,\mu M$, α_2 $K_i = 19\,\mu M$, selectivity = 66), **16** was not as potent at PNMT.

Summary and Conclusions

We have investigated the effects of an 8-substituent in the THBA system on PNMT inhibitory potency and α_2-adrenoceptor affinity. Compounds **3** and **16** were the most selective of the THBAs studied, with both displaying selectivities (α_2 K_i / PNMT K_i) greater than 100. These compounds are also more lipophilic (**3**, CLogP = 1.75; **16**, CLogP = 0.44) than SK&F 29661 (**26**, CLogP = −0.38)—which did not penetrate the BBB[13]—and may be able to penetrate into the CNS.[14] Unlike the results found in the THIQ series, the sulfonyl substituents lowered the PNMT inhibitory activity of THBA (**1**). The PNMT inhibitory potencies of the 3-alkyl- (**9**–**14**) and the 4-hydroxy-THBAs (**15**–**16**) were lower than those seen for THBA (**1**), and the introduction of an 8-substituent was unsuccessful in reducing the PNMT K_i for the 3-alkyl-THBAs. While the addition of an 8-nitro substituent to **15** increased its PNMT inhibitory potency, the deleterious effect of the 4-hydroxy group caused **16** to be less active at PNMT than unsubstituted THBA (**1**). However, the α_2-adrenoceptor affinities of these compounds were substantially lower in comparison with the corresponding THIQ derivatives, leading to overall higher

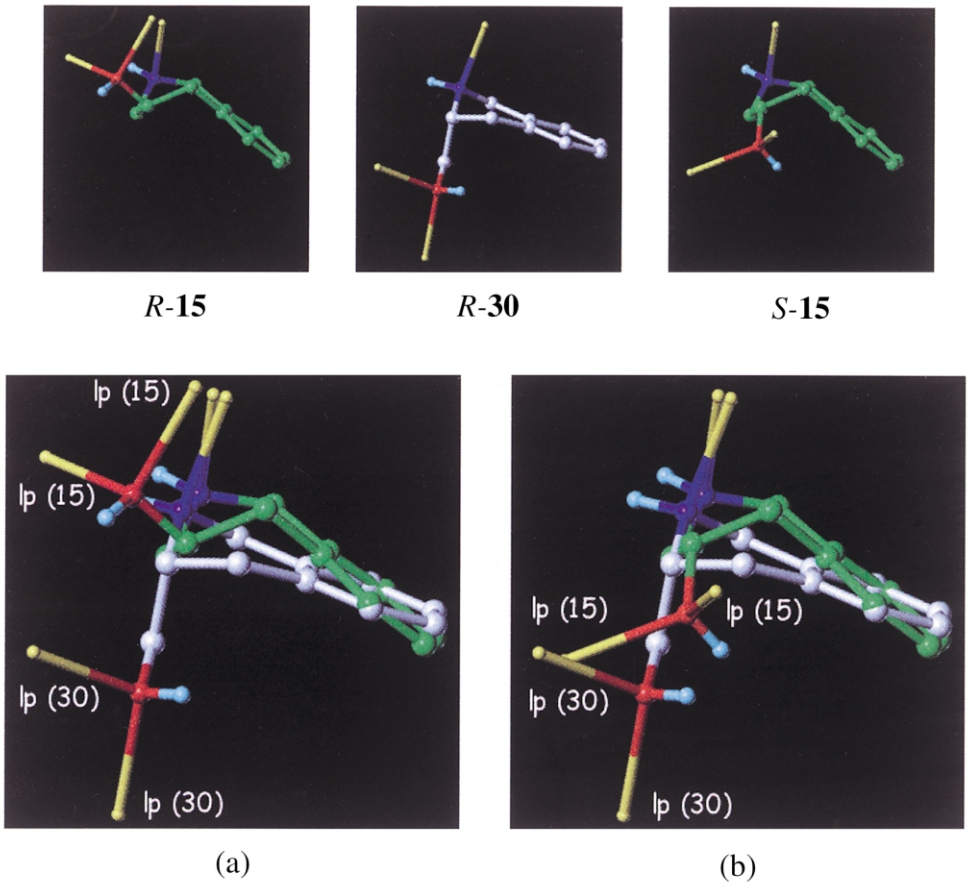


Figure 1. Superimpositions of the enantiomers of **15** (green; a: *R* and b: *S*) over the more active (at PNMT) enantiomer of **30** (white; *R*). Compounds were superimposed using both ends of a 2 Å long normal through the centroid of the aromatic ring and the end of the axial lone pair (2.4 Å) from the THIQ or THBA nitrogen. Hydroxyl oxygens are shown in red, hydroxyl hydrogens are in cyan, and lone pairs are in yellow. The hydrogens on the carbon skeleton have been deleted for clarity.

selectivity ratios. Thus, THBA—and particularly compound **3**—would provide promising leads in the development of a selective and CNS-active PNMT inhibitor.

Experimental

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 were otherwise uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Varian XL-300 or a 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). NMR spectra of hydrochloride salts were recorded in deuterated dimethylsulfoxide (DMSO-d_6) and the chemical shifts are reported relative to DMSO (2.49 ppm for ^{1}H and 39.5 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. Flash chromatography[17] was performed using silica gel 60 (230–400 mesh) supplied by Universal Adsorbents, Atlanta, Georgia. 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 inch 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. Combustion analyses were performed on a Hewlett-Packard Model 185B CHN Analyzer at the University of Kansas by Dr. Tho Ngoc Nguyen.

Unless otherwise stated, all methanol (MeOH) and ethanol (EtOH) used were anhydrous and were prepared by distillation from magnesium. Hexanes refer to the mixture of hexane isomers (bp 40–70 °C). Solvents were routinely distilled prior to use; anhydrous

tetrahydrofuran (THF) and ether (Et_2O) were obtained by distillation from sodium-benzophenone ketyl; dry methylene chloride (CH_2Cl_2) was obtained by distillation from phosphorus pentoxide. *n*-Butyl lithium was standardized by titration against 2,5-dimethoxybenzyl alcohol. All reactions requiring anhydrous conditions or an inert atmosphere were performed under a positive nitrogen (N_2) or argon (Ar) flow and all glassware was oven-dried and/or flame-dried.

Amine hydrochloride or oxalate salts were prepared by the addition of a solution of methanolic HCl (or oxalic acid) to a methanolic solution of the amine, followed by crystallization of the resulting salt from MeOH/Et_2O.

S-Adenosyl-L-methionine was obtained from Sigma Chemical Co. [*methyl*-^{3}H]-*S*-Adenosyl-L-methionine that was used in the radiochemical assay was purchased from New England Nuclear Corp. (Boston, MA). Bovine adrenal glands were obtained from Davis Meat Processing (Overbrook, KS). [^{3}H]Clonidine used in the α_2-adrenoceptor binding assay was purchased from Amersham Corporation (Arlington Heights, IL).

The syntheses of compounds **9**–**16** have been reported previously.[8]

6,8-Dinitro- and 8-nitro-2,3,4,5-tetrahydro-1*H*-2-benzazepine hydrochloride (17·HCl and 3·HCl). Compound **1**[3] (5.82 g, 39.6 mmol) was dissolved in cold concentrated H_2SO_4 (20 mL) in an ice bath, and KNO_3 (4.40 g, 43.5 mmol) was added in small portions over 1 h. The ice bath was removed and the yellow–green reaction mixture was allowed to warm to room temperature, stirred for 12 h, and carefully made alkaline (pH >10) with concentrated NH_4OH. The red–brown solution obtained was extracted with $CHCl_3$ (4×). The combined $CHCl_3$ extracts were washed with brine (once), dried over anhydrous Na_2SO_4 and evaporated to yield a yellow solid (7.60 g). Purification by flash chromatography (silica, CH_2Cl_2/MeOH/NH_4OH, 250:17:1 as the eluent) gave **3** (4.59 g, 60%) and dinitro compound **17** (0.64 g, 7%). Compound **3** was obtained as a pale yellow solid: mp 60–61 °C; IR (KBr) 3200 (NH), 2920, 1510 (NO_2), 1330 (NO_2), 1080, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.00–7.98 (m, 2H, H-7 and H-9), 7.31–7.29 (m, 1H, H-6), 4.01 (s, 2H, H-1), 3.24 (t, 2H, $J=4.9$ Hz, H-3), 3.06–3.02 (m, 2H, H-5), 1.77–1.74 (m, 2H, H-4), 1.61 (bs, e, 1H, N*H*); ^{13}C NMR ($CDCl_3$): δ 150.8, 145.8, 144.2, 129.9, 122.8, 121.9, 54.4 (C-1), 53.2 (C-3), 35.9 (C-5), 29.9 (C-4); EIMS *m*/*z* 193 ($M^+ + 1$, 18), 192 (M^+, 100), 177 (57), 145 (51), 131 (29), 116 (42), 115 (98), 103 (14), 91 (54), 77 (44), 63 (48), 51 (43), 43 (27).

The hydrochloride salt (**3**·HCl) was isolated as fluffy white needles: mp >300 °C. Anal. calcd for $C_{10}H_{12}N_2O_2$·HCl: C, 52.52; H, 5.73; N, 12.25; found: C, 52.56; H, 6.10; N, 12.18%.

Compound **17** was crystallized as yellow needles from EtOAc/hexanes: mp 111–112 °C; IR (KBr) 3350 (NH), 1530 (NO_2), 1340 (NO_2), 1135, 1080, 910, 780, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.38 (d, 1H, $J=2.3$ Hz, H-7), 8.18 (d, 1H, $J=2.3$ Hz, H-9), 4.15 (s, 2H, H-1), 3.29 (t, 2H, $J=5.3$ Hz, H-3), 3.14–3.11 (m, 2H, H-5), 1.90–1.81 (m, 2H, H-4), 1.76 (bs, e, 1H, N*H*); ^{13}C NMR ($CDCl_3$) δ 150.7, 148.0, 145.2, 143.5, 125.3, 117.5, 54.2 (C-1), 52.8 (C-3), 29.5 (C-5), 28.7 (C-4); EIMS *m*/*z* 238 ($M^+ + 1$, 5), 237 (M^+, 5), 236 (6), 208 (43), 192 (20), 191 ($M^+ - NO_2$, 20), 190 (25), 144 (25), 115 (73), 89 (44), 84 (44), 63 (50), 49 (100).

The hydrochloride salt was isolated as fine yellow needles: mp 247–249 °C. Anal. calcd for $C_{10}H_{11}N_3O_4$·HCl: C, 43.89; H, 4.42; N, 15.35; found: C, 43.55; H, 4.10; N, 14.99%.

8-Amino-2,3,4,5-tetrahydro-1*H*-2-benzazepine bisoxalate (4·2$C_2H_2O_4$). Compound **3** (4.5 g, 23 mmol) was dissolved in EtOH (50 mL) and concentrated HCl (5 mL) was added. After the addition of PtO_2 (50 mg), the pale yellow solution was hydrogenated at 50 psi until there was no further uptake of H_2 (3 h). The reaction mixture was filtered through Celite, concentrated on a rotary evaporator and chilled in an ice-bath. The cold concentrated aqueous solution was made alkaline (pH >10) with solid KOH and extracted with CH_2Cl_2 (thrice). The combined $CHCl_3$ extracts were dried over anhydrous Na_2SO_4 and evaporated to yield **4** (3.6 g, 95%) as a buff-colored solid: mp 65–75 °C, ^{1}H NMR ($CDCl_3$) δ 6.91 (d, 1H, $J=7.3$ Hz, H-6), 6.44–6.41 (m, 2H, H-7 and H-9), 3.79 (s, 2H, H-1), 3.25–2.95 (m, bs, 5H, H-3, NH_2 and N*H*, e), 2.82–2.78 (m, 2H, H-5), 1.66–1.61 (m, 2H, H-4); ^{13}C NMR ($CDCl_3$) δ 144.3, 143.1, 132.4, 129.8, 115.5, 112.9, 54.8 (C-1), 53.2 (C-3), 34.9 (C-5), 31.0 (C-4).

The bisoxalate salt (**4**·2$C_2H_2O_4$) was isolated as a white precipitate: mp 185–186 °C; EIMS *m*/*z* 163 ($M^+ + 1$, 5), 162 (M^+, 26), 145 (32), 133 (35), 132 (36), 116 (28), 106 (16), 77 (16), 45 (100). Anal. calcd for $C_{10}H_{14}N_2$·2$C_2H_2O_4$: C, 49.12; H, 5.30; N, 8.18; found: C, 48.78; H, 5.20; N, 8.00%.

8-Bromo-2,3,4,5-tetrahydro-1*H*-2-benzazepine hydrochloride (5·HCl). Amine **4** (3.20 g, 19.7 mmol) was added to a mixture of ice-cold 48% HBr (9.6 mL) and water (31.3 mL). To this stirred solution, sodium nitrite (1.50 g, 21.7 mmol) in water (19 mL) was added dropwise. The reddish colored solution turned orange. Excess HNO_2 was destroyed by the addition of urea (0.78 g) and a negative starch-iodide test was obtained. This diazotized solution was added to a well-stirred, warm (35 °C) mixture of CuBr (8.48 g, 59.1 mmol), 48% HBr (20 mL) and water (50 mL). After addition of the diazotized solution, the reaction mixture was warmed to 75–80 °C and stirred at that temperature for 1.5 h. The reaction mixture was allowed to stand overnight and was cautiously made alkaline (pH >10) with 50% KOH solution. The blue copper salts were removed by filtration and the filtrate extracted with CH_2Cl_2 (4×). The organic layers were combined, dried over anhydrous Na_2SO_4 and evaporated to yield a dark red oil (3.59 g). Bulb-to-bulb distillation (105–110 °C, 0.05 mm Hg) yielded compound **5** as a colorless solid (3.36 g, 76%): mp 68–69 °C; IR (KBr)

3200 (NH), 2990, 2910, 1480, 1140, 1110, 850, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27–7.22 (m, 2H, Ar*H*), 7.02–6.99 (m, 1H, Ar*H*), 3.87 (s, 2H, H-1), 3.20–3.17 (m, 2H, H-3), 2.90–2.86 (m, 2H, H-5), 1.72–1.60 (m, 3H, H-4 and N*H*, e); ^{13}C NMR ($CDCl_3$) δ 144.9, 141.8, 131.0, 130.8, 129.7, 119.3, 54.6 (C-1), 53.5 (C-3), 35.5 (C-5), 30.6 (C-4).

The hydrochloride salt (**5**·HCl) was isolated as colorless plates: mp >300 °C; EIMS *m*/*z* 228 (9), 227 ($M^+ + 2$, 56), 226 (27), 225 (M^+, 57), 210 (18), 130 (19), 117 (65), 116 (53), 115 (100), 102 (14), 89 (41), 77 (27), 63 (45), 51 (34). Anal. calcd for $C_{10}H_{12}BrN$·HCl: C, 45.74; H, 4.99; N, 5.33; found: C, 45.85; H, 5.00; N, 5.10%.

8-Bromo-*N*-triphenylmethyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (18). To a stirred solution of **5** (3.36 g, 14.9 mmol) in dry CH_2Cl_2 (40 mL), triethylamine (1.65 g, 2.23 mL, 16.3 mmol) was added and the solution was stirred in an ice bath. 4-Dimethylaminopyridine (0.18 g, 1.5 mmol) and triphenylmethyl chloride (6.21 g, 22.3 mmol) were added in one portion and the reaction mixture was stirred vigorously. After a few minutes a copious precipitate of triethylammonium hydrochloride was observed in the reaction mixture. The reaction was stirred at room temperature for 18 h, quenched with 1 N NaOH and extracted with CH_2Cl_2 (thrice). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated to yield a yellow–orange solid (10.1 g). The solid was passed through a silica plug using CH_2Cl_2/hexanes/MeOH/NH_4OH (150:450:10:1) as the eluent to yield a colorless foamy solid (6.26 g, 90%): mp 145–150 °C; IR (KBr) 2920, 1480, 1440, 950, 775, 745, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51–7.43 (m, 6H, Ar*H*), 7.30–7.13 (m, 11H, Ar*H*), 7.04-7.02 (m, 1H, Ar*H*), 3.45-3.15 (m, 2H, H-1), 2.72-2.60 (m, 2H, H-3), 1.95–1.85 (m, 2H, H-5), 1.59–1.50 (m, 2H, H-4); EIMS *m*/*z* 469 ($M^+ + 2$, 0.2), 467 (M^+, 0.2), 392 ($M^+ + 2 - Ph$, 1), 390 ($M^+ - Ph$, 1), 244 (31), 243 (Ph_3C^+, 100), 185 (31), 84 (23), 77 (11), 49 (57). Anal. calcd for $C_{29}H_{26}BrN$: C, 74.36; H, 5.59; N, 2.99; found: C, 74.67; H, 6.00; N, 2.99%.

8-Methylthio-2,3,4,5-tetrahydro-1*H*-2-benzazepine hydrochloride (6·HCl). In a flame dried three-neck round-bottom flask equipped with a thermometer, magnetic stirrer and a N_2 inlet was placed **18** (2.1 g, 4.5 mmol) in dry THF (20 mL). The solution was chilled to −78 °C and *n*-BuLi (2.3 M in hexanes, 2.3 mL, 5.3 mmol) was added dropwise. A dark red solution was obtained and was allowed to warm to −20 °C over 30 min. The reaction mixture was again chilled to −78 °C and a solution of methyl disulfide (0.53 g, 0.51 mL, 5.6 mmol) in dry THF (3 mL) was added. The pale yellow reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was cooled in an ice bath and acetone (8 mL) and concentrated HCl (4 mL) were added. The colorless mixture was stirred for 12 h and the organic solvents were removed under reduced pressure. The residue was diluted with water (30 mL) and washed with CH_2Cl_2 (twice). The aqueous layer was made alkaline (pH >10) with 6 N NaOH and extracted with CH_2Cl_2 (4×). The combined CH_2Cl_2 extracts were dried over anhydrous Na_2SO_4 and evaporated to yield a pale yellow oil (0.56 g). Bulb-to-bulb distillation (125–135 °C, 0.03 mm Hg) gave a colorless oil (0.43 g, 49%): mp 59–61 °C; ^1H NMR ($CDCl_3$) δ 7.10–7.00 (m, 3H, Ar*H*), 3.88 (s, 2H, H-1), 3.17 (t, 2H, $J = 5.3$ Hz, H-3), 2.91–2.87 (m, 2H, H-5), 2.45 (s, 3H, SCH_3), 1.69–1.62 (m, 3H, H-4 and N*H*, e); ^{13}C NMR ($CDCl_3$) δ 143.4, 139.9, 135.2, 129.7, 126.9, 125.3, 54.9 (C-1), 53.5 (C-3), 35.5 (C-5), 30.9 (C-4), 16.1 (SCH_3).

The hydrochloride salt was isolated as fine colorless needles: mp 268 °C (dec); IR (KBr) 2950, 2800, 2730, 1575, 1490, 1440, 1425, 1075, 820 cm^{-1}; EIMS *m*/*z* 195 ($M^+ + 2$, 7), 194 ($M^+ + 1$, 24), 193 (M^+, 100), 192 ($M^+ - 1$, 19), 178 ($M^+ - CH_3$, 19), 176 (61), 164 (83), 149 (35), 146 (14), 134 (15), 129 (30), 117 (79), 116 (50), 115 (99), 103 (16), 91 (56), 77 (52), 45 (46). Anal. calcd for $C_{11}H_{15}NS$·HCl: C, 57.50; H, 7.02; N, 6.10; found: C, 57.40; H, 7.18; N, 6.40%.

8-Methylsulfonyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine hydrochloride (7·HCl). Trifluoroacetic acid (3 mL) was added to compound **6** (0.295 g, 1.52 mmol) and the mixture was stirred in an ice bath. Trifluoroperacetic acid (8 N, 0.83 mL, 6.6 mequiv) was added in one portion and stirred for 18 h at room temperature. The acids were carefully removed under reduced pressure and residual acid was removed by addition of benzene to the residue followed by evaporation. The colorless oil obtained was made alkaline (pH >10) with 3 N NaOH and extracted with $CHCl_3$ (thrice). The combined $CHCl_3$ extracts were washed with brine, dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure to yield a pale yellow solid (0.284 g). Purification by PCTLC (silica gel, 4 mm) using CH_2Cl_2/MeOH/NH_4OH (250:17:1) as the eluent gave **7** as a pale yellow solid (0.252 g, 74%): mp 119–121 °C; IR (KBr) 3200 (NH), 2910, 1290 (SO_2), 1140 (SO_2), 1110, 1085, 960, 825, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.72–7.68 (m, 2H, H-9 and H-7), 7.34–7.32 (m, 1H, H-6), 4.00 (s, 2H, H-1), 3.25–3.21 (m, 2H, H-3), 3.04–3.01 (m, 5H, H-5 and SO_2CH_3), 1.86 (s, e, 1H, N*H*), 1.77–1.70 (m, 2H, H-4); ^{13}C NMR ($CDCl_3$) δ 149.4, 144.0, 137.8, 130.0, 126.7, 126.0, 54.5 (C-1), 53.3 (C-3), 44.3 (SO_2CH_3), 35.9 (C-5), 29.8 (C-4).

The hydrochloride salt (**7**·HCl) was isolated as fluffy white needles: mp 286−288 °C (dec); EIMS *m*/*z* 227 ($M^+ + 2$, 5), 226 ($M^+ + 1$, 17), 225 (M^+, 64), 224 ($M^+ - 1$, 41), 210 ($M^+ - CH_3$, 34), 145 (29), 131 (22), 118 (20), 117 (71), 116 (50), 115 (100), 103 (16), 102 (13), 91 (55), 77 (48), 63 (61), 42 (38). Anal. calcd for $C_{11}H_{15}NO_2S$·HCl: C, 50.47; H, 6.16; N, 5.35; found: C, 50.68; H, 6.40; N, 5.28%.

8-Aminosulfonyl-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one (20). Amide **19**[8] (0.30 g, 1.9 mmol) was added to ice-cold chlorosulfonic acid (3 mL) and the mixture was allowed to warm to room temperature. After stirring for 6 h, the brown solution was poured over ice and extracted with EtOAc (thrice). The combined EtOAc extracts were washed with 5% $NaHCO_3$ (once) and brine (once), dried over anhydrous Na_2SO_4 and the solvent removed

under reduced pressure to yield a yellow–red solid (0.50 g) which was dissolved in acetonitrile (5 mL) and concentrated NH_4OH (5 mL) and heated to reflux for 2 h. The solvent was removed under reduced pressure to yield a yellow–red solid that was crystallized from aqueous EtOH to yield a colorless solid (0.35 g, 78%): mp 215–216 °C (dec); IR (KBr) 3360 (NH_2), 3290 (NH_2), 3190 (NH), 1630 (CO), 1340 (SO_2), 1170 (SO_2) 1140, 905, 830, 800, 750 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.27 (bs, e, 1H, N*H*), 7.97 (s, 1H, H-9), 7.84 (d, 1H, $J=7.8$ Hz, H-7), 7.45–7.43 (m, 3H, H-6 and SO_2NH_2); 2.95–2.89 (m, 2H, H-3), 2.81–2.79 (t, 2H, $J=6.8$ Hz, H-5), 1.94–1.89 (m, 2H, H-4); ^{13}C NMR (DMSO-d_6) δ 170.6 (CO), 142.8, 141.9, 136.5, 129.4, 127.7, 125.6, 38.3 (C-3), 29.7, 29.6; EIMS *m*/*z* 241 ($M^+ + 1$, 17), 240 (M^+, 78), 222 (12), 212 (18), 211 (25), 159 (13), 132 (21), 131 (100), 115 (13), 103 (38), 89 (13), 77 (42), 63 (35), 51 (35). Anal. calcd for $C_{10}H_{12}N_2O_3S$: C, 49.99; H, 5.03; N, 11.66; found: C, 49.89; H, 4.80; N, 11.79%.

8-Aminosulfonyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine Hydrochloride (8·HCl). Amide **20** (0.50 g, 2.1 mmol) was suspended in dry THF (10 mL) and BH_3·THF (1M solution in THF, 5 mL, 5.0 mmol) was added. The suspension was heated to reflux under N_2 for 24 h and the resulting cloudy reaction mixture was cooled in an ice bath. Excess BH_3 was destroyed by the addition of MeOH. Evaporation of the solvent gave a colorless semisolid that was dissolved in MeOH (10 mL) and concentrated HCl (2 mL) and heated to reflux for 3 h. The solvent was removed under reduced pressure to yield a colorless solid, which was recrystallized (twice) from EtOH acidified with few drops of concentrated HCl to yield a colorless solid (0.40 g, 73%): mp 212–214 °C; IR (KBr) 3270 (NH_2), 3010, 1560, 1310 (SO_2), 1280, 1140 (SO_2), 1115, 835, 660 cm^{-1}, ^1H NMR (DMSO-d_6) δ 8.83 (bs, e, 2H, NH_2^+), 7.87 (s, 1H, H-9), 7.75 (d, 1H, $J=7.8$ Hz, H-7), 7.47 (d, 1H, $J=7.8$ Hz, H-6), 7.40 (s, e, 2H, SO_2NH_2), 4.42 (s, 2H, H-1), 3.37 (m, 2H, H-3), 3.10-3.00 (m, 2H, H-5), 1.90–1.80 (m, 2H, H-4); ^{13}C NMR (DMSO-d_6) δ 147.4, 142.4, 133.8, 130.0, 127.9, 126.4, 49.8, 49.7, 33.0, 24.6; EIMS *m*/*z* 227 ($M^+ + 1$, 14), 226 (M^+, 29), 225 ($M^+ - 1$, 19), 211 (16), 146 (7), 130 (10), 117 (31), 116 (24), 115 (46), 91 (21), 77 (13), 63 (11), 49 (100). Anal. calcd for $C_{10}H_{14}N_2O_2S$·HCl: C, 45.71; H, 5.75; N, 10.66; found: C, 45.35; H, 5.86; N, 10.48%.

Radiochemical assay for PNMT activity. The assay used in this study has been described elsewhere.[10] 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 Ci/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 1–3 by inspection of the $1/V$ versus $1/S$ plots of the data. All assays were run in duplicate with 3 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.[12] Male Sprague–Dawley rats were decapitated and the cortexes were dissected out and homogenized in 20 volumes (w/v) of ice-cold 50 mM Tris/HCl buffer (pH 7.7 at 25 °C). Homogenates were centrifuged thrice for 10 min at $50{,}000\times g$ 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 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. Non-specific binding was defined as the concentration of bound ligand in the presence of 2 μM of phentolamine. All assays were run in quadruplicate with 5 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. CLogP values were calculated[15] and molecular modeling was performed using the SYBYL software package (version 6.6, Tripos Associates, Inc., 1699 South Hanley Rd., St. Louis, MO 63144, USA) on a Silicon Graphics O2 work station.

Acknowledgements

This research was supported by USPHS Grant HL 34193.

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