Effect of Ring Size or an Additional Heteroatom on the Potency and Selectivity of Bicyclic Benzylamine-Type Inhibitors of Phenylethanolamine N-Methyltransferase[1a]

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In the search for potent and selective inhibitors of the enzyme phenylethanolamine N-methyltransferase (PNMT; EC 2.1.1.28), we examined the effect of ring size or an additional heteroatom in the conformationally-restricted benzylamine-type PNMT inhibitors. Based on semiempirical calculations (MNDO) and molecular modeling studies, PNMT-inhibitory activity of these compounds seemed to be dependent on (a) the torsion angle between the plane of the aromatic ring and the endo N atom lone pair (τ_2 angle), with the optimal value of τ_2 being about $-75°$, and (b) the amount of steric bulk about the 3-position of 1,2,3,4-tetrahydroisoquinoline (**5**, THIQ). 2,3,4,5-Tetrahydro-1*H*-2-benzazepine (**6**) was found to have the highest selectivity (PNMT K_i = 3.34 μM, α_2 K_i = 11 μM, selectivity = 3.2) as compared to other homologues of THIQ (PNMT K_i = 9.67 μM, α_2 K_i = 0.35 μM, selectivity = 0.036). The higher PNMT-inhibitory activity of **6** was attributed to favorable steric interactions of the puckered methylene groups in the putative bioactive conformation of **6** at the PNMT active site, whereas unfavorable interactions of these puckered methylene groups at the α_2-adrenoceptor were thought to be the cause of reduced α_2 affinity of **6**. No further enhancement of the selectivity of the benzazepine ring system could be obtained via introduction of a second heteroatom (N, O, S) at the 5-position in this ring system.

Epinephrine represents about 5−10% of the total brain catecholamine content,[2] and immunohistochemical techniques[3,4] have unambiguously provided evidence for the presence of epinephrine-containing neurons in the central nervous system (CNS), although their exact function is currently unknown. Based on the anatomical localization of these neurons in the CNS, it was postulated that central epinergic neurons might be involved in the regulation of α-adrenoceptors, blood pressure, respiration, and the secretion of pituitary hormones.[4−7] Epinephrine is the final product in the catecholamine biosynthetic pathway. Thus, its role in the CNS can be studied without affecting the levels of other catecholamines through the inhibition of the enzyme phenylethanolamine N-methyltransferase (PNMT; EC 2.1.1.28)[8] which catalyzes the N-methylation of norepinephrine to epinephrine using S-adenosyl-L-methionine (AdoMet) as the cofactor. It has been suggested that there is an ordered sequential binding of AdoMet followed by norepinephine[9,10] and that most inhibitors are competitive with either norepinephrine or AdoMet.[11] The suppositions regarding the role of epinephrine were later substantiated by pharmacological studies performed with PNMT inhibitors. Most notably, the ability of PNMT inhibitors to lower blood pressure in spontaneously hypertensive rats was widely investigated.[12] Reduction in the levels of central epinephrine by PNMT inhibitors was initially believed to be the cause of this antihypertensive effect. Later, it was found that most of the widely-studied PNMT inhibitors were nonselective and had α_2-adrenoceptor binding affinity,[13] which would complicate an interpretation of the effects of these compounds on blood pressure. We have undertaken the

task of designing a selective and potent inhibitor of PNMT so that the role of central epinephrine can be defined unambiguously.

1

2a: R₁=R₂=Cl
**2b**: R₁=SO₂NH₂, R₂=H

3
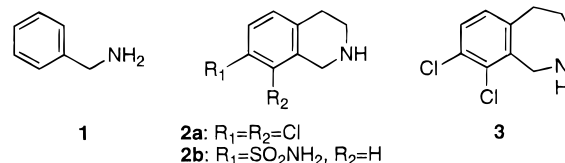
Benzylamines are a class of potent PNMT inhibitors. Conformational restriction of the aminomethyl side chain in benzylamine (**1**) in the form of 1,2,3,4-tetrahydroisoquinoline[14] (**5**) or 2,3,4,5-tetrahydro-1*H*-2-benzazepine[15] (**6**) results in increased inhibitory potency. Some well-studied inhibitors of the benzylamine class are SK&F 64139 (**2a**, 7,8-dichloro-1,2,3,4-tetrahydroisoquinoline),[16] SK&F 29661 (**2b**, 7-(aminosulfonyl)-1,2,3,4-tetrahydroisoquinoline),[17] and LY 134046 (**3**, 8,9-dichloro-2,3,4,5-tetrahydro-1*H*-2-benzazepine).[18a] Compound **3** (PNMT K_i = 0.264 μM, α_2 K_i = 4.1 μM, selectivity = 16) is more selective than **2a** (PNMT K_i = 0.202 μM, α_2 K_i = 0.022 μM, selectivity = 0.11).[18b] The 2,3-dichlorobenzylamine moiety in **2a** and **3** confers potent PNMT-inhibitory activity. Since phenylethylamines also form a class of α_2-adrenoceptor agonists,[19] it was suggested by Fuller that the α_2-adrenoceptor affinity of **2a** might result from the presence of a conformationally-restricted phenylethylamine skeleton in **2a**. Furthermore, the lack of the phenylethylamine moiety in **3** might make it a more selective inhibitor than **2a**.[13,20] Correlations of inhibitor potency with pK_a indicate that benzylamine-type inhibitors bind in the neutral form.[21,22] In addition, studies on some conformationally-restricted benzylamines from this laboratory have demonstrated the dependence of PNMT-inhibitory activity on the
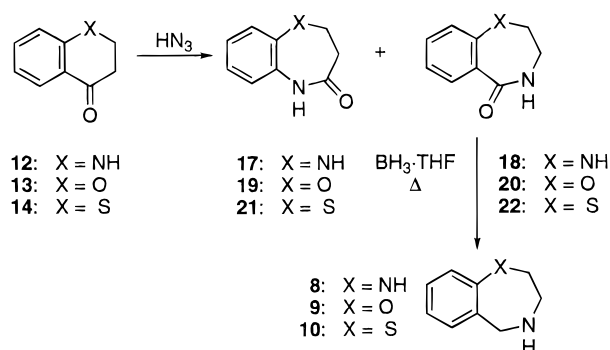
orientation of the amino group lone pair and the steric bulk at the active site.[23] It is possible that the conformational effects resulting from the increase of heterocyclic ring size from **2a** to **3** change the orientation of the amino group lone pair and the steric bulk and might be responsible for the observed increase in selectivity. Such conformational effects could be extended by further changes in the ring size (**4** and **7**) or by the addition of a second heteroatom (**8**−**10**) at the 5-position of the benzazepine ring. Such changes in conformationally-restricted benzylamines might help in the identification of a heterocycle that lacks affinity for the α_2-adrenoceptor but retains affinity for the active site of PNMT.

4: n = 1   **6:** n = 3
5: n = 2   **7:** n = 4

8: X = NH
9: X = O
10: X = S
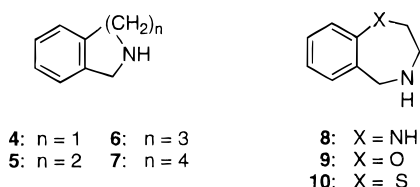
Chemistry

2,3-Dihydroisoindole (**4**) was prepared by reduction of phthalimide with borane as reported by Dubois *et al.*[24] The Schmidt reaction was used to prepare the seven-membered heterocyclic amides from the corresponding aromatic ketones. The mixture of regioisomeric amides resulting from aryl and alkyl group migration was readily separated by chromatography. Even though a mixture of regioisomers was obtained and the yields were low due to the low reactivity of these aromatic ketones, this approach provided a convenient way of synthesizing benzazepines containing a second heteroatom. The isolated amides were readily reduced with borane to yield amines **8**−**10** (Scheme 1). In the case

Scheme 1

12: X = NH   **17:** X = NH   **18:** X = NH
13: X = O   **19:** X = O   **20:** X = O
14: X = S   **21:** X = S   **22:** X = S

BH$_3$·THF
Δ

8: X = NH
9: X = O
10: X = S

of 4-chromanone (**13**), the undesired regioisomer **19** hydrolyzed faster than **20** under the reaction conditions, thus facilitating the isolation of the desired regioisomer.[25,26] With other aromatic ketones (**11**, **12**, and **14**), both regioisomers formed were stable under the reaction conditions and could be isolated.

The Schmidt reaction on 1-tetralone (**11**) under strong nonaqueous acidic conditions such as sulfuric acid[25] or polyphosphoric acid[27] produced the amide **16** from an aryl ring migration as the major product. Hjelte and Agback[28] reported the tetrazole as the major product of the Schmidt reaction on 1-tetralone in concentrated hydrochloric acid. In our laboratory, the desired **15** was obtained as the major product, while **23**, unreacted starting material (**11**), and **16** were also obtained (ratio

Scheme 2

11   **23**   **15**   **16**

LAH, THF, Δ

6   +   **24**
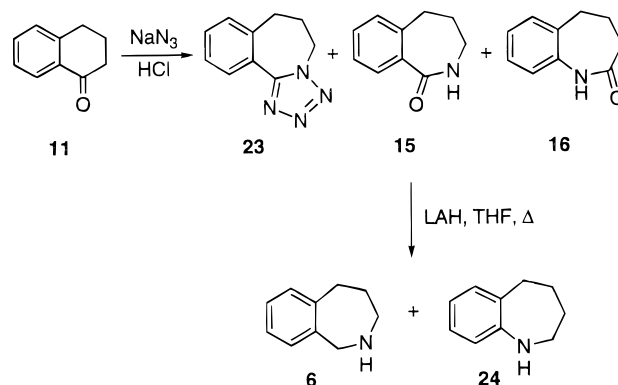
4:2:2:1) (Scheme 2).[29] Instead of separating the crude reaction mixture by chromatography,[29] it was reduced with LAH to afford a mixture of amines from which 2,3,4,5-tetrahydro-1*H*-2-benzazepine (**6**) was readily separated by taking advantage of the pK_a difference between the aliphatic and aromatic amine (1,3,4,5-tetrahydro-2*H*-1-benzazepine, **24**).

A similar approach based on the Schmidt reaction failed to provide the amide precursor to **7** from 1-benzosuberone[28] and 2-benzosuberone. Hence, *N*-methyl-1,2,3,4,5,6-hexahydro-2-benzazocine (**25**) was prepared according to the procedure described by Hauser[30] and then N-demethylated using the protocol reported by Rice.[31] Pictet−Spengler cyclocondensation[32] of either
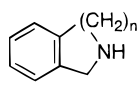

25
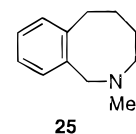
racemic or enantiomerically pure 1-phenyl-2-aminopropane[33] with formaldehyde gave **26** in an average yield of 43% (Scheme 3).

Scheme 3

R, S or (±)

CH$_2$O, HCl, Δ

R-(-)-**26**
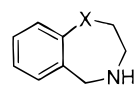
S-(+)-**26**

or (±)-**26**,
as appropriate
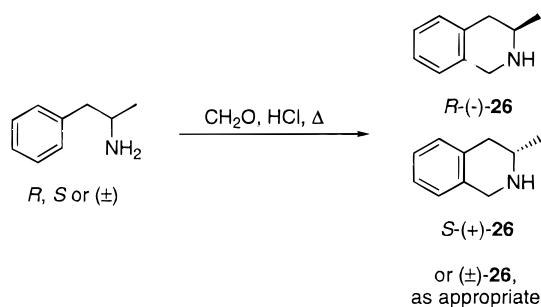
Biochemistry

All the compounds were evaluated as their hydrochloride salts for *in vitro* activity as inhibitors of PNMT. *In vitro* PNMT activity was assessed by use of a standard radiochemical assay that has been described previously for both substrates[34] and inhibitors.[35] Bovine adrenal PNMT used for the *in vitro* assay was purified according to the procedure of Connett and Kirshner[36] through the isoelectric precipitation step. Inhibition constants were determined by using three different concentrations of inhibitor, as previously described,[35] with phenylethanolamine as the variable substrate. α_2-Adrenergic receptor binding assays were performed

Table 1. *In Vitro* Activities of Benzylamine Analogues as Inhibitors of PNMT and Binding of [^{3}H]Clonidine at the α_2-Adrenoceptor

compd	n	A, PNMT $K_i \pm$ SEM, μM	B, α_2 $K_i \pm$ SEM, μM	B/A selectivity
1	0	179 ± 9	20 ± 1	0.11
4	1	231 ± 17	0.82 ± 0.11	0.0035
5	2	9.67 ± 0.37	0.35 ± 0.10	0.036
6	3	3.34 ± 0.24	11 ± 1	3.2
7	4	21.3 ± 0.8	16 ± 1	0.73

Table 2. *In Vitro* Activities of Benzylamine Analogues as Inhibitors of PNMT and Binding of [^{3}H]Clonidine at the α_2-Adrenoceptor

compd	X	A, PNMT $K_i \pm$ SEM, μM	B, α_2 $K_i \pm$ SEM, μM	B/A selectivity
6	CH_2	3.34 ± 0.24	11 ± 1	3.2
8	NH	28.0 ± 1.9	2.6 ± 0.1	0.093
9	O	21.2 ± 2.7	4.1 ± 0.2	0.19
10	S	4.10 ± 0.33	4.6 ± 0.5	1.1

(a)   (b)

$\tau_1 = \tau(C_{ortho}\text{-}C_{ipso}\text{-}C_\alpha\text{-}N)$
$\tau_2 = \tau(C_{ipso}\text{-}C_\alpha\text{-}N\text{-lp})$

$\tau_1 = 90°$
$\tau_2 = 180°$
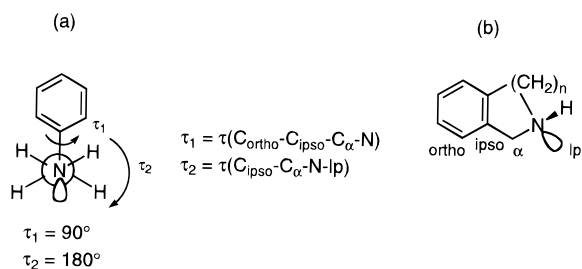
Figure 1. Conformational descriptors (τ_1 and τ_2) defined for (a) benzylamine and (b) its conformationally-restricted analogues with axial orientation of the N atom lone pair. The low-energy conformation of benzylamine has the side chain oriented perpendicular to the plane of the aromatic ring. The figure was partly adapted from ref 39.

using cortex obtained from male Sprague−Dawley rats.[37] [^{3}H]Clonidine was used as the radioligand to define the specific binding, and phentolamine was used to define the nonspecific binding.

Results and Discussion

The results of biochemical evaluation are grouped in Table 1 (effect of ring size) and Table 2 (effect of heteroatom). All the compounds evaluated exhibited competitive kinetics indicative of inhibition of the binding of phenylethanolamine (substrate) at the active site.

The moderately low activity of **1** as a PNMT inhibitor may be due to a conformational effect. Conformations of **1** have been studied using mass resolved excitation spectroscopy, and the low-energy conformation of **1** as defined in terms of conformational descriptors (torsion angles τ_1 and τ_2) is shown in Figure 1.[38,39] In this low-energy conformation the aminomethyl side chain was oriented perpendicular to the ring ($\tau_1 = 90°$), while the N-lone pair electrons were oriented away from the ring ($\tau_2 = 180°$). A slightly higher energy ($\Delta E < 0.01$ kcal/mol) conformer of **1** had $\tau_2 = 60°$. These low-energy conformers may not necessarily be the bioactive con-
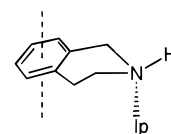
Figure 2. Three points used in generating root mean square fit illustrated for the template **5** to which the other analogues were fitted.

Table 3. Summary of Calculations for the Conformations of Benzylamine Analogues **4**−**7**

			compound			
			6		**7**	
	4	**5**	(global)[a]	(local)[a]	(global)[a,b]	(local)[a,b]
τ_1	-1.70	-15.3	-61.2	19.2	29.9	37.0
τ_2	-117	-75.1	-36.1	-75.4	-56.0	-72.2
$D_{cent-lp}$ (Å)	5.16	4.53	3.63	4.69	4.27	4.61
H_f (kcal/mol)	21.70	16.71	17.80	20.17	20.64	20.36
rms fit	0.34		0.49	0.25	0.39	0.37

[a] The global minimum was obtained by using the random search option in the Sybyl molecular modeling program, and the energies were calculated using the Tripos molecular mechanics force field. The energies of local minima were about 0.4 (**6**) and 1.4 (**7**) kcal/mol higher than the corresponding global minima. [b] The heat of formation (H_f) was calculated using the MNDO method in the semiempirical molecular orbital package (MOPAC, version 5.0 at the Sybyl interface). Based on the H_f, the local minima of **7** might actually be the global minimum conformation.

formers of **1** as evidenced by its low activity in comparison with THIQ (**5**). Conformational restriction of **1** to form a five-membered ring showed surprisingly lowered PNMT-inhibitory activity. However, other homologues of **4** were more potent than **1** itself.

To explain the effect of ring size on the biological activity, conformational analysis studies were done on ring systems using the random search option in the Sybyl molecular modeling program. The random search option in Sybyl enables one to identify the global minimum energy conformation as well as several local minima. The geometries of the supposed global minimum conformations (calculated using the Tripos molecular mechanics force field) were further optimized by using MNDO, a semiempirical quantum mechanical method implemented in MOPAC version 5.0 at the Sybyl interface. For 1,3-dihydroisoindole (**4**) and THIQ (**5**), only a single conformer was located by the random search conformational analysis. As **5** was relatively rigid and active as compared to the other homologues, it was used as a template in the rigid fitting procedure. In this three-point-fitting procedure (Figure 2), the two ends of a normal (2 Å long) passing through the centroid of the aromatic ring and an axial lone pair on the N atom (2.4 Å long, representing a possible H-bonding distance) were used. Earlier studies on tricyclic conformationally-restricted benzylamines had indicated the dependence of PNMT-inhibitory activity on the endo (axial) lone pair.[23] Better root mean square (rms) fits were produced when an axial lone pair on the N atom, instead of an equatorial lone pair, was used for the fit. The energy difference between the two forms (axial vs equatorial lone pair) was within 1 kcal/mol for analogues **5**−**7**. However, use of these global minimum conformations resulted in a poor fit for **6** and **7**. The results of the modeling studies are presented in Table 3.

Examination of the data shown in Table 3 revealed that the important factors determining the PNMT-inhibitory activity were not only the rms fit but, more
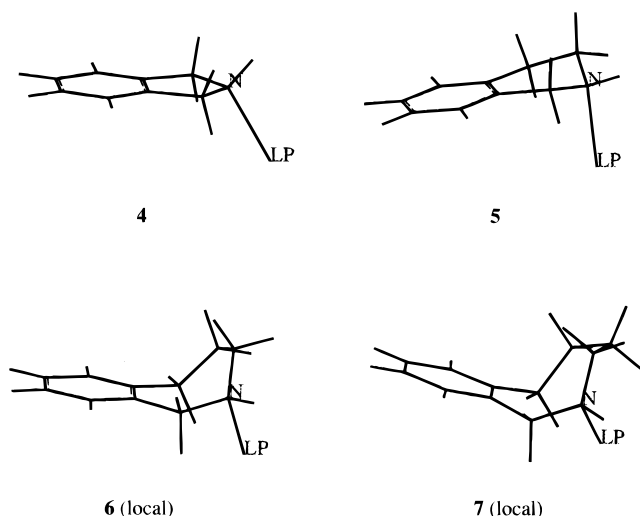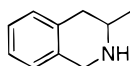
Figure 3. MNDO-optimized geometries of homologues **4**, **5**, **6** (local), and **7** (local).

Table 4. *In Vitro* Activities of Enantiomers of 3-Methyl-1,2,3,4-tetrahydroisoquinoline as Inhibitors of PNMT and Binding of [³H]Clonidine to the α_2-Adrenoceptor

compd	A, PNMT $K_i \pm$ SEM, μM	B, α_2 $K_i \pm$ SEM, μM	B/A selectivity
26 ($\pm$)	2.13 ± 0.11	0.84 ± 0.08	0.39
R-($-$)	38.3 ± 1.7	6.2 ± 0.3	0.16
S-($+$)	1.01 ± 0.05	0.52 ± 0.06	0.51

importantly, the τ_2 angle and the distance from the centroid of the aromatic ring to the N atom lone pair ($D_{cent-lp}$). The low-energy conformer of **1** had a τ_2 angle different from that of the template **5**. Thus, the low activity of **1**, as well as that of **4**, may be due to a different τ_2 angle as compared with its other analogues. This was reflected as an increased value of $D_{cent-lp}$ in **4**. At the active site the N atom lone pair in **4** may not be able to directionally interact optimally at a specific amino acid residue where the other active homologues **5**–**7** can interact. Homologues **5**–**7** have similar τ_2 angles and $D_{cent-lp}$, but they differ largely in steric bulk. While there does not appear to be a strong correlation between the τ_2 angle and PNMT activity, the optimal τ_2 angle required for binding at the PNMT active site appears to be approximately $-75°$ as this torsion angle maintains a more constant value of $D_{cent-lp}$. The putative bioactive conformations of the homologues are shown in Figure 3.

Introduction of a methyl group at the 3-position in **5** resulted in increased PNMT-inhibitory activity (**26**, see Table 4) compared to **5**.[23,40] Increased potency of the more active (S)-($+$)-**26** possibly resulted from a favorable but directional hydrophobic interaction at the PNMT active site about the 3-position of the THIQ nucleus. In the local minimum conformation of homologue **6**, the puckered methylene groups *partly* occupied the same steric region of space about the 3-position of THIQ at the PNMT active site and therefore had a K_i lower than that for **5** (Figure 4). However, this region at the PNMT active site has a limited steric bulk tolerance, and a further increase in steric bulk, such as in ($\pm$)-3-ethyl-THIQ, resulted in decreased activity ($K_i = 23.9$ μM).[40]
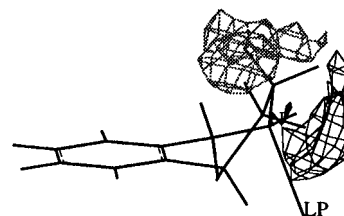

Figure 4. Computer graphics-generated intersection of the volume of the puckered methylene groups in **6** and the methyl group in enantiomers of **26** in the background of the MNDO-optimized local minimum conformation of **6**. The volume of the puckered methylene groups was obtained by subtraction (MVOL command) of the volume between **6** and modified **6** in which these two methylene groups were deleted. The MNDO-optimized conformations of **5** and PNMT active (S)-($+$)-**26** were fitted using the three-point rms-fitting procedure. Intersection of the volume occupied by the puckered methylene groups in **6** with the volume difference between **5** and (S)-($+$)-**26** (volume occupied by the methyl group) is displayed as a dotted contoured surface (upper left volume), and it represents the area of steric bulk tolerance at the PNMT active site. Thus, the puckered methylene groups in **6** *partly* occupy the same region of space corresponding to this volume difference. Favorable hydrophobic interaction about this compact region of steric bulk tolerance leads to enhanced potency (as in **6**) at the PNMT active site. Conversely, the intersection between the volume of the puckered methylene groups in **6** and the volume difference between (R)-($-$)-**26** and **5** represents the area of steric bulk intolerance at the α_2-adrenoceptor and is shown as a bold contoured surface (lower right volume). The puckered methylene groups in **6** are projected more *closely* in the region of acute steric bulk intolerance at the α_2-adrenoceptor which results in lowered affinity.

The eight-membered homologue **7** had steric bulk comparable to 3-ethyl-THIQ in the region of limited steric bulk tolerance. Negative steric interaction was the likely cause of decreased PNMT-inhibitory activity of **7** as compared to **6**.

The α_2-adrenoceptor affinity for **1** and its analogues showed a different trend. Conformational restriction of **1** as in **4** resulted in about a 25-fold increased affinity toward the α_2-adrenoceptor. Although homologues **4** and **5** have comparable affinity toward the α_2-adrenoceptor, they have very different τ_2 angles. In contrast, **5** and **6** have similar τ_2 angles but differed widely in their abilities to bind with the α_2-adrenoceptor. These results implied a nondependence of the τ_2 angle on the α_2-adrenoceptor affinity and a nonrigid interaction mode for the N atom lone pair at the α_2-adrenoceptor. The lowered affinity of (R)-($-$)-**26** probably resulted from negative steric interactions of the methyl group at the α_2-adrenoceptor. Based on the active analogue approach developed by Marshall *et al.*,[41] the volume occupied by the methyl group in (R)-($-$)-**26** represented the area of steric bulk intolerance at the α_2-adrenoceptor. The 30-fold decreased affinity of the seven-membered homologue **6** as compared to **5** can be attributed to nonfavorable interaction of the puckered extra methylene group which was projected *closer* to the region of steric bulk intolerance. The acute nature of the steric bulk intolerance was further defined by decreased affinity of the higher homologue **7**.

Lesser involvement of puckered methylene groups in **6** at the PNMT active site was reflected in a small (3-fold) gain in potency with respect to **5**. In contrast, the observed 30-fold loss in affinity of (R)-($-$)-**26** with respect to **5** at the α_2-adrenoceptor was in accordance with the proposed proximity of the puckered methylene

groups to the region of steric bulk intolerance at that site. The region about the 3-position of **26** at the PNMT active site and the α_2-adrenoceptor seemed to be complementary in terms of their steric bulk tolerance (see Figure 4).

Because the seven-membered ring showed maximum selectivity, a further improvement in selectivity was sought via the introduction of an additional heteroatom into the ring. The conformations of heterocycles having two heteroatoms would be considerably different from those containing a single heteroatom (nitrogen). The additional heteroatom could influence the overall conformation mainly through electrostatic interactions and intramolecular H-bonding.[42] A search of the Cambridge Structural Database[43] for structures similar to compounds **8**−**10** found one compound—the 7-acetyl derivative of **9**. The Sybyl-generated low-energy conformation of **9** was quite similar to the X-ray structure found.[44] Based strictly on qualitative considerations, it was observed that bioisosteric replacement of the methylene group in the benzazepine ring with electronegative and strong H-bonding heteroatoms like N and O (analogues **8** and **9**) decreased the affinity for PNMT. This effect may be the result of an altered preferred conformation due to the presence of an additional heteroatom or from a different binding mode at the PNMT active site via the interaction of the additional heteroatom with an amino acid residue. The PNMT-inhibitory activity for the heterocycle **10** bearing the S atom was comparable to that of analogue **6**. The better PNMT-inhibitory activity of the sulfur-containing analogue **10** was perhaps the consequence of the lower electronegativity (and increased lipophilicity) of the sulfur atom or its ability to form weaker H-bonds than nitrogen or oxygen atoms.[45] The α_2-adrenoceptor affinity of the analogues containing an additional heteroatom was higher (lower K_i) than for **6**. Again, as proposed above, the conformational changes induced by the other heteroatom or an altered binding mode might be responsible for this outcome.

Summary and Conclusion

The PNMT-inhibitory activity in the conformationally-restricted analogues of **1** seems to be dependent on the τ_2 angle and the amount of steric bulk. In contrast, only steric bulk was considered the main factor governing the affinity toward the α_2-adrenoceptor. Steric bulk was tolerated only to a limited extent about the 3-position of THIQ at the PNMT active site. However, the addition of steric bulk in the same region of space at the α_2-adrenoceptor resulted in significant loss of affinity. Introduction of an additional heteroatom in the benzazepine ring system failed to improve selectivity. The benzazepine ring system thus appears to be an optimal skeleton for further structural modifications to improve selectivity. This suggestion is consistent with the observed 5-fold increase in selectivity of **3** vs **6**.

Experimental Section

All reagents and solvents were reagent grade or purified by standard methods before use. Melting points were determined in open capillaries on a Thomas Hoover melting point apparatus calibrated with known compounds but are otherwise uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Varian XL-300 or a GE QE-300 spectrometer with CDCl$_3$ as the solvent, and chemical shifts

are reported in parts per million (ppm) relative to tetramethylsilane (TMS, 0.00 ppm). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a Varian XL-300 spectrometer with CDCl$_3$ as the solvent, and the chemical shifts are reported in ppm relative to CDCl$_3$ (77.0 ppm). For the hydrobromide salts of amines, NMR spectra were recorded in deuterated dimethyl sulfoxide (DMSO-d_6) and the chemical shifts are reported relative to DMSO (2.49 ppm for ^{1}H NMR and 39.5 ppm for ^{13}C NMR). 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. Flash chromatography[46] was performed using silica gel 60 (230−400 mesh) supplied by Universal Adsorbents, Atlanta, GA. Preparative centrifugal thin layer chromatography (PCTLC) was performed on a Harrison model 7924 Chromatotron (Harrison Research, Palo Alto, CA) using Merck silica gel 60 PF254/ CaSO$_4$·0.5H$_2$O binder on 1, 2, or 4 mm thickness plates. Analytical TLC was performed by using silica gel with a fluorescent indicator coated on 1 × 3 in. glass plates in 0.2 mm thickness (Whatman MKGF silica gel 200 μm). Optical rotations were recorded on a Perkin-Elmer polarimeter using the sodium D line as the source. 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. Amine hydrochloride salts were prepared by adding a solution of methanolic HCl to the methanolic solution of the amine followed by crystallization of the resulting hydrochloride from MeOH−Et$_2$O. *S*-Adenosyl-L-methionine was obtained from Sigma Chemical Co. [*methyl*-^{3}H]-*S*-Adenosyl-L-methionine used in the radiochemical assay was purchased from New England Nuclear Corp. (Boston, MA). Bovine adrenal glands were obtained from Stinson Meat Processing (Ottawa, KS). [^{3}H]Clonidine used in the α_2-adrenoceptor binding assay was purchased from Amersham Corp. (Arlington Heights, IL).

2,3,4,5-Tetrahydro-1*H*-2-benzazepine (6). The Schmidt reaction on 1-tetralone (**11**; 2.10 g, 14.1 mmol) was done according to the procedure described by Hjelte and Agback.[28] After the usual workup, the crude reaction mixture (2.30 g) was dissolved in dry THF (50 mL) and cooled in an ice bath, and LiAlH$_4$ (0.88 g, 23 mmol) was added. The suspension was heated to reflux under N$_2$ for 12 h and cooled in an ice bath, and to the suspension was cautiously added water (2.2 mL) followed by 15% NaOH (2.2 mL) and again water (6.9 mL) to quench the reaction. The reaction mixture was warmed to room temperature, stirred for 1 h, and filtered through Celite. The filter cake was washed with CH$_2$Cl$_2$ and water. The filtrate was extracted with CH$_2$Cl$_2$ (thrice), and the combined CH$_2$Cl$_2$ extracts were extracted with 2 N HCl (thrice). The acidic aqueous extract was carefully basified to pH 6.5−7 (using a pH meter to measure the pH) and washed with CH$_2$Cl$_2$ (thrice) to remove the less basic side products, which were isolated and identified previously.[29] The more basic desired amine was obtained by further basification of the aqueous layer with KOH pellets followed by extraction with CH$_2$Cl$_2$ (thrice). The combined CH$_2$Cl$_2$ extracts were dried over anhydrous K$_2$CO$_3$, evaporated to yield a yellow oil (1.44 g), and distilled bulb-to-bulb (75−80 °C, 0.25 mmHg) to afford a colorless oil (0.83 g, 41%). The hydrochloride salt was obtained as small colorless prisms: mp 220−221 °C dec (lit.[28] mp 223−225 °C; IR (KBr, HCl salt) 2940, 2800, 1570, 1445, 1070, 1020, 760 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.14−7.09 (m, 4 H, Ar*H*), 3.92 (s, 2 H, H-1), 3.19 (t, 2 H, J = 5.3 Hz, H-3), 2.95−2.91 (m, 2 H, H-5), 1.84 (bs, e, 1 H, N*H*), 1.73−1.68 (m, 2 H, H-4); ^{13}C NMR (CDCl$_3$) δ 142.6, 142.6, 128.9, 128.1, 126.8, 125.8, 54.8 (C-1), 53.4 (C-3), 35.9 (C-4), 30.7 (C-5). Anal. (C$_{10}$H$_{13}$N·HCl) C, H, N.

General Procedure for the Schmidt Reaction for the Synthesis of Compounds 15, 18, 20, and 22.[25] The ketone was dissolved in 2 times its weight of concentrated sulfuric acid, and sodium azide (1.3 mol relative to the ketone) was added in portions at ice bath temperature under a positive pressure of N$_2$. Additional concentrated sulfuric acid was

added to facilitate stirring. After stirring for 24 h at room temperature, the resulting brown-red solution was poured over ice water and cautiously basified with potassium hydroxide pellets. The solution was extracted with ether (thrice), and the combined ether extracts were dried over MgSO₄.

General Procedure for the Reduction of Schmidt Amides for the Synthesis of Compounds 6 and 8–10. To the ice-cold solution of amide (3 mmol) in dry THF (10 mL) under N₂ was added BH₃·THF complex (1 M solution in THF, 6 mL, 6 mmol). After stirring for 15 min at ice bath temperature, the reaction mixture was heated to reflux for 12 h. The reaction mixture was cooled in an ice bath, and excess borane was destroyed by careful addition of MeOH. After the removal of the solvents on a rotary evaporator, the residue was treated with methanolic HCl (15 mL) and heated to reflux for 3 h to destroy the amine–borane complex. The residue obtained after the evaporation of MeOH was suspended in water (15 mL), cooled, basified with solid KOH (pH about 12), and extracted with CH₂Cl₂ (thrice). The combined CH₂Cl₂ extracts were washed with brine (once), dried over anhydrous K₂CO₃, and evaporated to give an oil which was distilled bulb-to-bulb to furnish the amine.

2,3,4,5-Tetrahydro-5H-1,4-benzodiazepine (8). 2,3-Dihydro-1,4-benzodiazepin-5(4H)-one (18; 0.24 g, 20%) was prepared by the Schmidt reaction on 1,2,3,4-tetrahydroquinolin-4-one[47] (12; 1.1 g, 7.6 mmol). The crude product was purified by PCTLC (2 mm, silica gel; CH₂Cl₂–MeOH–NH₄OH, 250:20:1, as the eluent) and then recrystallized from EtOAc to afford small pale yellow prisms, mp 133–134 °C (lit.[48] mp 158 °C). Amide 18 (0.51 g, 3.1 mmol) was reduced to afford a colorless oil (bp 110 °C, 0.5 mmHg, 0.29 g, 63%). The dihydrochloride salt was obtained as a yellow-green crystalline solid: mp (2HCl) 238–240 °C dec (lit.[49] mp (2HCl) 243–244 °C); IR (KBr, 2HCl) 2900–2400 (b), 1570, 1465, 1400, 1310, 1170, 930, 770 cm⁻¹; ¹H NMR (DMSO-d₆) δ 10.21–9.98 (m, 4 H, 2NH₂⁺), 7.64 (d, 1 H, J = 7.8 Hz, ArH), 7.57 (d, 1 H, J = 7.6 Hz, ArH), 7.48–7.43 (m, 1 H, ArH), 7.34–7.29 (m, 1 H, ArH), 4.52 (s, 2 H, H-1), 3.59–3.53 (m, 4 H, H-3, H-4); ¹³C NMR (DMSO-d₆) δ 141.5, 132.4, 130.1, 126.6, 126.3, 122.1, 48.3, 45.6, 44.6. Anal. (C₉H₁₂N₂·2HCl) C, H, N.

2,3,4,5-Tetrahydro-5H-1,4-benzoxazepine (9). 2,3-Dihydro-1,4-benzoxazepin-5(4H)-one (20) was prepared by the Schmidt reaction on chroman-4-one (13; 5.0 g, 34 mmol) according to the above described procedure of Lockhart *et al.*[25,26] (2.0 g, 36% after crystallization from EtOAc–hexanes), mp 115–117 °C (lit.[26] mp 114–116 °C). Reduction of amide 20 (1.0 g, 6.1 mmol) by BH₃·THF followed by bulb-to-bulb distillation (75 °C, 0.10 mmHg) furnished the desired amine as a colorless oil (0.67 g, 74%). The hydrochloride crystallized to afford well-defined colorless needles: mp (HCl) 188–190 °C; IR (KBr, HCl salt) 2890, 2730, 1490, 1440, 1230, 1050, 970, 760 cm⁻¹; ¹H NMR (CDCl₃) δ 7.11–7.05 (m, 2 H, ArH), 6.99–6.93 (m, 2 H, ArH), 3.95–3.92 (m, 2 H, H-4), 3.86 (s, 2 H, H-1), 3.11 (t, 2 H, J = 4.3 Hz, H-3), 1.58 (s, e, 1 H, NH); ¹³C NMR (CDCl₃) δ 159.6, 134.7, 128.8, 127.8, 122.8, 120.5, 74.6, 52.7, 51.9. Anal. (C₉H₁₁NO·HCl) C, H, N.

2,3,4,5-Tetrahydro-5H-1,4-benzothiazepine (10). 3,4-Dihydro-1,4-benzothiazepin-5(2H)-one (22) was prepared by the Schmidt reaction on thiochroman-4-one (14; 5.0 g, 30 mmol). The crude product was subjected to flash chromatography (silica gel; EtOAc–hexanes, 2:1, as the eluent) to afford 2,3-dihydro-1,5-benzothiazepin-4(5H)-one (21; 1.1 g, 41%, mp 210–212 °C (lit.[50] mp 218–219 °C)) and the desired amide 22 (0.45 g, 16%, crystallization from EtOAc–hexanes gave colorless crystals, mp 191–192 °C (lit.[51] mp 190–191 °C)). Amide 22 (0.45 g, 2.5 mmol) was reduced by BH₃·THF, and the pure amine was obtained as a colorless oil (0.35 g, 83%) after bulb-to-bulb distillation (115 °C, 0.45 mmHg). The hydrochloride salt was crystallized to afford well-defined colorless flakes: mp 237–239 °C dec (lit.[52] 237–238 °C); IR (KBr, HCl salt) 2930, 2800, 1570, 1440, 1390, 875, 750 cm⁻¹; ¹H NMR (CDCl₃) δ 7.54 (d, 1 H, J = 7.8 Hz, H-6), 7.21–7.11 (m, 3 H, ArH), 4.10 (s, 2 H, H-1), 3.36–3.33 (m, 2 H, H-3), 2.74–2.70 (m, 2 H, H-4), 1.57 (bs, e, 1 H, NH); ¹³C NMR (CDCl₃) δ 146.5, 136.6, 132.4, 129.1, 127.5, 126.9, 55.1, 52.8, 36.3. Anal. (C₉H₁₁NS·HCl) C, H, N.

1,2,3,4,5,6-Hexahydro-2-benzazocine (7). To an ice-cold solution of N-methyl-1,2,3,4,5,6-hexahydro-2-benzazocine[30] (25; 1.20 g, 6.85 mmol) in dry toluene (10 mL) was cautiously added phenyl chloroformate (5.62 g, 4.50 mL, 36.5 mmol), and the solution was heated to reflux under N₂ for 36 h. The yellow reaction mixture was diluted with ice water and extracted with CHCl₃ (thrice). The combined CHCl₃ extracts were washed with 3 N NaOH (thrice) and brine (once) and evaporated to afford a yellow oil. Hydrazine (95%, 5 mL) and hydrazine solution in water (64%, 5 mL) were carefully added to this oil, and the solution was heated to reflux under N₂ for 6 h. After cooling, the reaction mixture was concentrated to yield a yellow-white solid that was basified with 40% NaOH and extracted with CH₂Cl₂ (thrice). The combined CH₂Cl₂ extracts were washed with brine (once), dried over anhydrous Na₂SO₂, and evaporated to give a viscous yellow oil (0.97 g). Bulb-to-bulb distillation (85–95 °C, 0.25 mmHg) gave a colorless oil (0.31 g, 28%). Because the hydrochloride salt was difficult to crystallize, the oxalate salt was prepared and crystallized from MeOH–Et₂O: mp 193–196 °C dec; ¹H NMR (CDCl₃) δ 7.22–7.19 (m, 2 H, ArH), 7.14–7.10 (m, 2 H, ArH), 3.92 (s, 2 H, H-1), 3.35 (s, e, 1 H, NH), 2.86–2.82 (m, 2 H, H-3), 2.70 (t, 2 H, J = 5.0 Hz, H-6), 1.71–1.60 (m, 2 H, H-5), 1.59–1.52 (m, 2 H, H-5); ¹³C NMR (CDCl₃) δ 141.3, 138.0, 129.5, 129.1, 127.7, 126.6, 48.8 (C-1), 45.8 (C-3), 32.0, 30.7, 28.2; EIMS m/z 162 (M + 1, 4), 161 (M⁺, 17), 160 (M⁺ − 1, 14), 146 (14), 132 (40), 118 (31), 104 (63), 91 (39), 78 (31), 77 (29), 44 (100). Anal. (C₁₁H₁₅N·C₂H₂O₄) C, H, N.

(±)-3-Methyl-1,2,3,4-tetrahydroisoquinoline (26). The procedure described by Potapov *et al.*[32] was slightly modified to improve the yield. 1-Phenyl-2-aminopropane (2.10 g, 15.5 mmol) was treated with 37% formaldehyde (2.10 mL) yielding a colorless precipitate. Concentrated HCl (12.6 mL) was added to it, and the suspension was refluxed for 6 h. The brown solution was concentrated on a rotary evaporator, and the residue obtained was taken up in water (50 mL). The aqueous solution was washed with CH₂Cl₂ (thrice) to remove brown-colored impurities. The yellow aqueous extract was cooled, basified with KOH pellets, extracted with CH₂Cl₂ (thrice), dried over anhydrous Na₂SO₂, and evaporated to provide a red viscous oil (1.58 g). Bulb-to-bulb distillation (75–80 °C, 0.5 mmHg) gave a colorless oil (1.04 g). Purification of this oil by flash chromatography using CH₂Cl₂–MeOH–NH₄OH (250:18:1) as the eluent provided the desired compound as a colorless oil (0.98 g, 43%). The hydrochloride salt was crystallized as a colorless solid from MeOH–Et₂O: mp 234–236 °C dec; IR (film) 3240 (NH), 3000, 2940, 2910, 2880, 1490, 1440, 1370, 1310, 740 cm⁻¹; ¹H NMR (CDCl₃) δ 7.12–6.98 (m, 4 H, ArH), 4.06 and 3.99 (AB q, J_AB = 16.1 Hz, H-1), 3.00–2.94 (m, 1 H, H-3), 2.75 (dd, 1 H, J = 16.1, 3.9 Hz, H-4), 2.51–2.42 (m, 1 H, H-4), 1.43 (bs, e, NH), 1.21 (d, 3 H, J = 6.3 Hz); ¹³C NMR (CDCl₃) δ 135.3, 134.8, 129.0, 125.9, 125.6, 49.1, 48.5, 37.1, 22.4. Anal. (C₁₀H₁₃N·HCl) C, H, N.

(R)-(−)-3-Methyl-1,2,3,4-tetrahydroisoquinoline ((R)-(−)-26). Using the procedure described above for the racemate, (R)-(−)-26 was synthesized from (2R)-(−)-phenyl-2-aminopropane:[33] mp (HCl) 273–275 °C dec; [α]²³_D = −75° (c = 0.40, MeOH). Anal. (C₁₀H₁₃N·HCl) C, H, N.

(S)-(+)-3-Methyl-1,2,3,4-tetrahydroisoquinoline ((S)-(+)-26). Using the procedure described above for the racemate, (S)-(+)-26 was synthesized from (2S)-(+)-phenyl-2-aminopropane: mp (HCl) 270–273 °C dec (lit.[32] mp 276–277.5 °C); [α]²³_D = 78° (c = 0.40, MeOH) (lit.[32] [α]²⁰_D = 76° (c = 0.92, EtOH)). Anal. (C₁₀H₁₃N·HCl) C, H, N.

Radiochemical Assay for PNMT Activity. The assay used in this study has been described elsewhere.[35] 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-³H]AdoMet, containing approximately 3 × 10⁵ dpm (specific activity approximately 15 mCi/mmol), 25 μL of substrate solution (phenylethanolamine), 25 μL of inhibitor solution, 25 μL of the enzyme preparation, and sufficient water to achieve a final volume of 250 μL. After the mixture was incubated for 30 min at 37 °C, the reaction was quenched by addition of 250 μL of 0.5 M borate buffer (pH 10.0), and the mixture 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, 2, and 4 by inspection of the $1/V$ vs $1/S$ plots of the data. All assays were run in duplicate with three inhibitor concentrations over a 5-fold range. K_i values were determined by a hyperbolic fit of the data.

α_2-Adrenoceptor Radioligand Binding Assay. The radioligand receptor binding was performed according to the method of U'Prichard *et al.*[37] Male Sprague–Dawley rats were decapitated, and the cortexes were dissected out and homogenized in 20 vol (w/v) of ice-cold 50 mM Tris/HCl buffer (pH 7.7 at 25 °C). Homogenates were centrifuged thrice for 10 min at $50000g$ with resuspension of the pellet in fresh buffer between spins. The final pellet was homogenized in 200 vol (w/v) of ice-cold 50 mM Tris/HCl buffer (pH 7.7 at 25 °C). Incubation tubes containing [^{3}H]clonidine (specific activity *ca.* 19.2 mCi/mmol, final concentration 4.0 nM), various concentrations of drugs, and an aliquot of freshly resuspended tissue (800 μL) in a final volume of 1 mL were used. Tubes were incubated at 25 °C for 30 min, and the incubation was terminated by rapid filtration under vacuum through GF/B glass fiber filters. The filters were rinsed with three 5 mL washes of ice-cold 50 mM Tris buffer (pH 7.7 at 25 °C). The filters were counted in vials containing premixed scintillation cocktail. Nonspecific binding was defined as the concentration of bound ligand in the presence of 2 μM phentolamine. All assays were run in quadruplicate with five inhibitor concentrations over a 16-fold range. IC$_{50}$ values were determined by a log–probit analysis of the data, and K_i values were determined by the equation $K_i = \text{IC}_{50}/(1 + [\text{clonidine}]/K_D)$, as all Hill coefficients were approximately equal to 1.

Molecular Modeling Studies. Molecular modeling was performed using the Sybyl software package (version 6.00, Tripos Assoc., Inc., St. Louis, MO) on an IBM RS/6000 (models 560 and 350) workstation. The MNDO method in the semiempirical molecular orbital package (MOPAC, version 5.0 at the Sybyl interface) and molecular mechanics (Sybyl, Tripos force field) were used in optimizing geometries. The FIT command was used in fitting the molecules to template **5**, and the MVOLUME command was used to generate the volume difference and intersection maps.

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