Articles

Examination of the Role of the Acidic Hydrogen in Imparting Selectivity of 7-(Aminosulfonyl)-1,2,3,4-tetrahydroisoquinoline (SK&F 29661) Toward Inhibition of Phenylethanolamine *N*-Methyltransferase *vs* the α_2-Adrenoceptor[1a]

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7-(Aminosulfonyl)-1,2,3,4-tetrahydroisoquinoline (SK&F 29661, **1**) is a potent inhibitor of the enzyme phenylethanolamine *N*-methyltransferase (PNMT, EC 2.1.1.28). In contrast to other inhibitors of PNMT, it is also highly selective toward PNMT in comparison with its affinity toward the α_2-adrenoceptor (PNMT $K_i = 0.55$ μM, α_2 $K_i = 100$ μM, selectivity [α_2 K_i/PNMT K_i] = 180). A diverse set of compounds was synthesized and evaluated to probe the role of the acidic hydrogen of the aminosulfonyl group of **1** in imparting this selectivity. Compounds were designed to investigate the effect on selectivity of the acidity of the NH group [the 7-*N*-methyl (compound **5**) and 7-*N*-(*p*-chlorophenyl) (compound **4**) derivatives of **1**], the relative spatial position of the acidic hydrogen [7-(*N*-(methylsulfonyl)amino)-1,2,3,4-tetrahydroisoquinoline (**6**) and 7-((*N*-(methylsulfonyl)amino)methyl)-1,2,3,4-tetrahydroisoquinoline (**8**)], or the effect of the substitution of an acidic phenolic group for the aminosulfonyl moiety [1-(aminomethyl)-6-hydroxynaphthalene (**23**) and 8-hydroxy-1,2,3,4-tetrahydrobenz[*h*]isoquinoline (**9**)]. All of the compounds studied displayed lower affinity for PNMT than **1**, and nine of the eleven compounds studied showed increased, rather than the desired decreased, affinity for the α_2-adrenoceptor. Specifically, compound **4**, in which the aminosulfonyl NH group is more acidic than that in **1**, showed greatly reduced selectivity on account of increased α_2-adrenoceptor affinity as compared to **1** (PNMT $K_i = 2.6$ μM, α_2 $K_i = 6.3$ μM, selectivity = 2.4). Compound **8**, in which the acidic NH group is in the same region of space as that in **1**, although the aminosulfonyl group is reversed with respect to the aromatic ring, showed poor PNMT affinity and modest α_2-adrenoceptor affinity (PNMT $K_i = 330$ μM, α_2 $K_i = 18$ μM, selectivity = 0.055). Compound **9**, in which a phenolic group is in the same region of space as the acidic NH of **1**, exhibited the best α_2-adrenoceptor affinity of any of the compounds studied (PNMT $K_i = 0.98$ μM, α_2 K_i = 0.078 μM, selectivity = 0.080). Results from this study suggest that the selectivity of **1** is not solely due to the presence of an acidic hydrogen on the 7-aminosulfonyl group of **1** but is likely also dependent on some other property (e.g. electron-withdrawing character) of the aminosulfonyl group.

Phenylethanolamine *N*-methyltransferase (PNMT, EC 2.1.1.28) catalyzes the conversion of the neurotransmitter norepinephrine to epinephrine. The role of brain epinephrine, which constitutes about 5−10% of the total catecholamine content of the central nervous system (CNS), is poorly understood due to the lack of a selective PNMT inhibitor.[2] Central epinephrine has been postulated to be involved in the control of blood pressure and heart rate,[3] control of the secretion of pituitary hormones,[3,4] control of exercise tolerance,[5] and ethanol intoxication.[6] Demonstration of the antihypertensive effect of PNMT inhibitors in spontaneously hypertensive rats[7] stimulated the interest to develop a potent inhibitor of PNMT as a novel antihypertensive drug. However, most well-studied PNMT inhibitors exhibit high affinity toward the α_2-adrenoceptor.[8] An exception was SK&F 29661 (**1**), which exhibited high affinity for PNMT and good selectivity for PNMT over the α_2-adrenoceptor (PNMT $K_i = 0.55$ μM, α_2 $K_i = 100$ μM, selectivity [α_2 K_i/PNMT K_i] = 180). In vivo administration of **1** decreased adrenal epinephrine levels, but central epinephrine pools were unaffected. Autoradiographic studies showed that **1** did not cross the blood−brain barrier (bbb),[9] presumably due to its low lipophilicity. As compared to **1**, SK&F 64139 (**2**) was less selective (PNMT $K_i = 0.20$ μM, α_2 $K_i = 0.021$ μM, selectivity = 0.10), but was able to penetrate the bbb.[10] A number of more lipophilic 1,2,3,4-tetrahydroisoquinoline-7-sulfonanilides (**3**) were prepared and evaluated by Blank et al.[11] From that study it was concluded that an acidic NH, rather than an acidic hydrogen such as in $SO_2CH_2(C{=}O)Ar$, is essential for PNMT-inhibitory activity. However, no data on these compounds for their α_2-adrenoceptor affinity were reported, and thus the actual role of an acidic hydrogen, or an acidic NH of the aminosulfonyl group, in imparting selectivity remained to be evaluated. Because of the high potency of **1** toward the inhibition of PNMT and its low affinity for the α_2-adrenoceptor, it seemed important to determine the reason for the selectivity of **1**—is it the presence of an acidic hydrogen, is it more specifically the presence of an acidic NH as part of an aminosulfonyl

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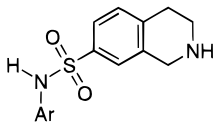
Table 1. In Vitro Activities of Inhibitors of PNMT and Binding of [^{3}H]Clonidine at the α_2-Adrenoceptor

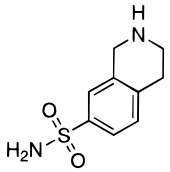
compd	pK_a[a]	A PNMT $K_i \pm$ SEM (μM)	B α_2 $K_i \pm$ SEM (μM)	B/A selectivity
1	10.0	0.55 ± 0.04	100 ± 20	180
4	7.8[b]	2.6 ± 0.2	6.3 ± 0.5	2.4
5	11.4	4.6 ± 0.3	130 ± 10	28
6	9.0	48 ± 2	11 ± 1	0.23
7		~4500	190 ± 10	0.042
8	11.9[c]	330 ± 10	18 ± 1	0.055
9	10.0	0.98 ± 0.06	0.078 ± 0.002	0.080
21		4.7 ± 0.2	1.6 ± 0.1	0.34
22		15 ± 2	4.6 ± 0.1	0.31
23	10.0	8.4 ± 0.8	2.1 ± 0.1	0.25
27		1.4 ± 0.1	0.84 ± 0.03	0.60
28	10.0	2.6 ± 0.1	2.2 ± 0.2	0.85

[a] pK_a values were based on literature data for the benzene analogues,[14] as the values for the substituted THIQ's were unavailable. For example, the pK_a of **1** was based on $PhSO_2NH_2$, which has a value of 10. Thus, while the pK_a values listed will not be exact, the relative values listed in the table should be correct. [b] The pK_a value was estimated based on known compounds and substituent effects. The value for compound **4** was based on $PhSO_2NHPh$, which has a reported pK_a of 8.4.[14] A *p*-chloro substituent lowers the pK_a by approximately 0.6 (e.g. the pK_a of *p*-chloroaniline is 4.07,[33a] as compared to 4.69 for aniline[33b] and the pK_a of *p*-chlorophenol is 9.4,[34] as compared to 10.0 for phenol), and so the pK_a for **4** was estimated as 7.8. [c] The value for compound **8** was based on $PhSO_2NHCH_2Ph$, which has a reported pK_a of 11.25.[14] Substitution of a methyl group for the phenyl attached to the sulfonyl increases the pK_a by approximately 0.7, and so the pK_a for **8** was estimated as 11.9 (e.g. the pK_a of $CH_3SO_2NH_2$ is 10.7 [pK_a value of 10.8 at 25 °C corrected to 20 °C], as compared to 10.0 for $PhSO_2NH_2$).[14]

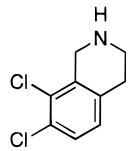
group, or is some other factor responsible? We have designed a diverse set of compounds to address these points.



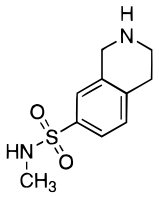
3: THIQ-7-sulfonanilides
4: Ar = *p*-chlorophenyl



SK&F 29661 (**1**)



SK&F 64139 (**2**)



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Compounds **4** and **5**, which had been previously synthesized,[11] were chosen to explore the relative importance of the acidity of the NH of **1**. Addition of a *p*-chlorophenyl moiety (**4**) to the aminosulfonyl group of **1** greatly increased the acidity of the aminosulfonyl group, while the addition of a methyl group (**5**) decreased the acidity as compared to **1**. (See Table 1 for pK_a values of this and the other compounds presented in this study.) Although either addition increased the steric bulk near the aminosulfonyl group, both **4** and **5** exhibited good PNMT affinity,[11] although no data for their α_2-adrenoceptor affinity were reported.

Compound **6** possesses a reversed aminosulfonyl [(methylsulfonyl)amino] group and differs from **1** in several respects: (1) it is more acidic than **1**, (2) the acidic NH is closer to the aromatic ring of the tetrahydroisoquinoline (THIQ) nucleus, and (3) the electron-withdrawing effect of the (methylsulfonyl)amino group is less than that of the aminosulfonyl group (σ_p = 0.03 and 0.57, respectively). Because of the good PNMT inhibition by **4**,[11] it was thought that there was some steric bulk tolerance at this region of the active site of PNMT, and so compound **7**, which possesses no acidic hydrogen, was included for comparison purposes. The addition of a methylene spacer at the 7-position of **6** (compound **8**) restores the acidic hydrogen to the same region of space as that of **1**. However, this also reduces the acidity of **8** as compared to **1**.

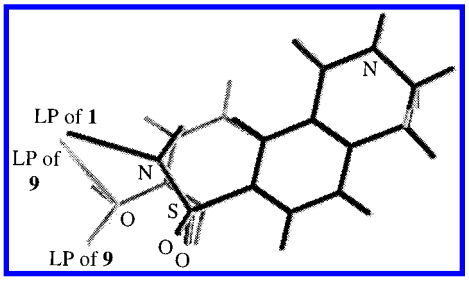
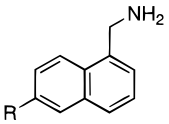
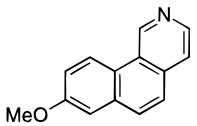


Figure 1. Alignment of compound **9** (gray) with SK&F 29661 (**1**, bold) showing the proximity of the lone pair (2.4 Å long) on the oxygen of the phenolic hydroxy group of **9** with that on the nitrogen of the aminosulfonyl group of **1**. MNDO-optimized geometries of **1** and **9** were fitted using the THIQ nitrogen and two ends of a 2 Å long normal passing through the centroid of the aromatic ring in the tetrahydroisoquinoline nucleus. The closest distance between these lone pairs was about 0.23 Å. Free rotation about the C−O bond in **9** and the SO_2−N bond in **1** was presumed to arrive at this distance.

Compounds **9** and **23** (a less conformationally constrained analogue of **9**) were proposed because relatively flat substituents are tolerated at the 7- and 8-positions of THIQ at the PNMT active site[12,13] and the hydroxyl group in phenol has about the same pK_a as that of the aminosulfonyl group as in **1**.[14] In addition, the lone pair on the oxygen of **9** is in a position in space near that occupied by the lone pair on the aminosulfonyl nitrogen in **1** (see Figure 1). Thus, **9** and **23** will allow assessment of the effect of the acidic hydrogen, independent of the aminosulfonyl group. Compound **21** is the nonphenolic analogue of **23** and is included for comparison purposes, as are the methoxy intermediates of **23** (compound **22**) and **9** (compound **27**). Compound **28** was previously evaluated in our laboratory[15] and is included for comparison purposes as the 7-OH group is in the same region of space as the acidic NH of **6**.



21: R = H
22: R = OMe
23: R = OH



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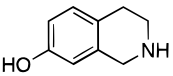

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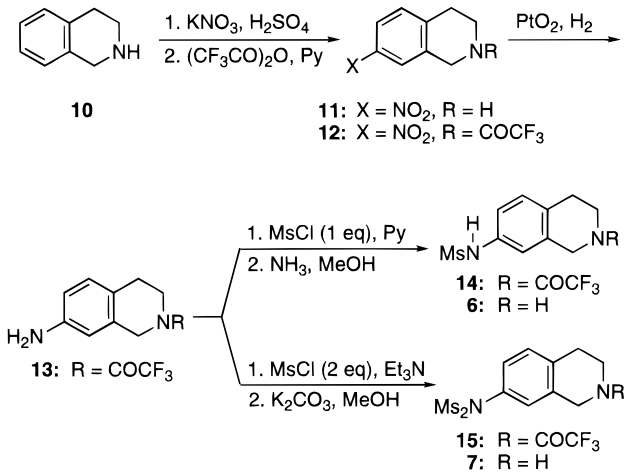
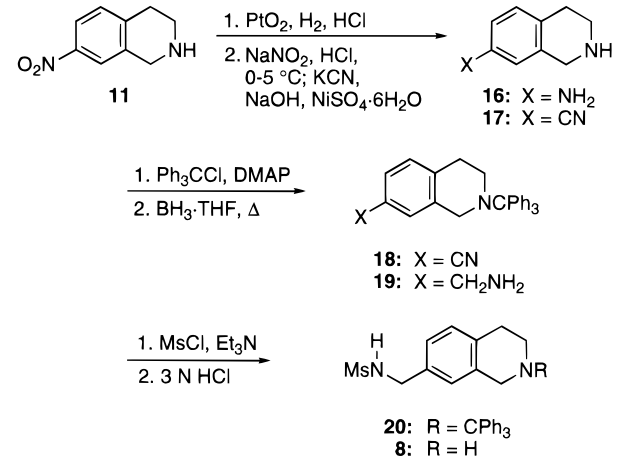
Chemistry

Compound **4** was prepared by the method of Blank et al.[11] Compound **5** was synthesized according to a general literature procedure.[11,16] Compound **6** was synthesized from the readily available 1,2,3,4-tetrahydroisoquinoline (**10**) as outlined in Scheme 1. Nitration of **10** according to the literature procedure[17,18] afforded a mixture of two regioisomers with the desired com-

Scheme 1



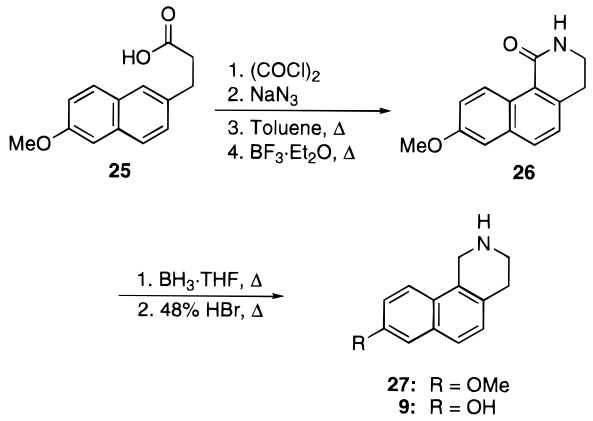
Scheme 2



pound **11** purified by fractional crystallization in 29% yield. The aromatic proton splitting pattern in the ^{1}H NMR spectrum was in accordance for the 7-substitution, and this was further ascertained by a one-dimensional difference nuclear Overhauser experiment, wherein the irradiation of H-1 led to increased intensity of the downfield aromatic proton (H-8). Protection of the secondary amine as the trifluoroacetamide (**12**) followed by catalytic reduction gave **13**. Treatment of thearomatic amine with 1 equiv of mesyl chloride in the presence of pyridine as the base led to monomesylation, whereas in the presence of 2 equiv of mesyl chloride bismesylation occurred. Removal of the trifluoroacetyl group under mild conditions[19,20] provided the desired compounds **6** and **7**.

In the attempted synthesis of the ((methylsulfonyl)-amino)methyl compound **8** (Scheme 2), when the diamine **16** was diazotized under normal Sandmeyer conditions, it failed to provide the nitrile **17**. Addition of the diazotized solution of **16** to a basic solution (pH 8−9) of KCN/CuCN resulted in decomposition and resin formation. As a basic pH is required to avoid the formation of HCN, a biphasic cyanation procedure[21] using nickel(II) sulfate instead of cuprous cyanide was employed and a 34% yield of **17** could be obtained after column chromatography. Protection of the secondary amine as its trityl derivative followed by reduction of the nitrile yielded **19**. Mesylation and subsequent deprotection under acidic conditions provided compound **8**.

Scheme 3



Compounds **22** and **23** were readily synthesized from 6-methoxynaphthalene-1-carbonitrile.[22] Attempts to synthesize the benz[*h*]isoquinoline compound **27** by a modified Pomeranz−Fritsch reaction[23] on 6-methoxy-1-naphthaldehyde (prepared by reduction of 6-methoxynaphthalene-1-carbonitrile with DIBAL-H) yielded the tricyclic product **24** in poor yields (10 to 15% after extensive purification). The difficulty in cyclization at the β-position on naphthalene is due to its low reactivity.[24] Hence, another approach based on the synthesis of azasteroids was adopted.[25] Commercially available 6′-methoxy-2′-propiononaphthone was converted to the 6′-methoxy-2′-naphthylpropionic acid (**25**) by the Willgerodt reaction.[26] This acid was subjected to the Curtius reaction protocol (Scheme 3), and the intermediate isocyanate was cyclized to **26** by heating with BF_3·Et_2O.[27] The α-position on the naphthalene nucleus is more reactive than the β-position,[24] and hence only **26** was obtained. It is interesting to note that failure to form a seven-membered ring in the intramolecular cyclization of isocyanate in the same ring system has been observed.[28] An alternate lengthy method has been reported for the synthesis of **26**.[28] Protons H-5 and H-6 showed *ortho* coupling in the aromatic region of the proton NMR spectrum of **26**, confirming the assignment of the structure. Such a coupling would be absent if the intermediate isocyanate had cyclized in the alternate mode at the β-position. Reduction followed by demethylation gave the desired naphthol compound **9**.

Biochemistry

All the compounds were evaluated as their hydrochloride or hydrobromide salts for in vitro activity as inhibitors of PNMT. In vitro PNMT affinity was assessed by use of a standard radiochemical assay that has been described previously for inhibitors.[29] Bovine adrenal PNMT used for the in vitro assay was purified according to the procedure of Connett and Kirshner[30] through the isoelectric precipitation step. Inhibition constants were determined by using three different concentrations of inhibitor, as previously described,[29] with phenylethanolamine as the variable substrate. α_2-Adrenergic receptor binding assays were performed using cortex obtained from male Sprague−Dawley rats.[31] [^{3}H]Clonidine was used as the radioligand to define the specific binding and phentolamine was used to define the nonspecific binding. Clonidine was used as the ligand to define α-adrenergic binding affinity to simplify the comparison with previous results.

Results and Discussion

The results of biochemical evaluations of the compounds are presented in Table 1. We have expressed selectivity as a ratio of the α_2 K_i versus the PNMT K_i.

The exact binding mode of **1** at either the PNMT active site or the α_2-adrenoceptor is unknown. All of the compounds in this study exhibited competitive kinetics when binding to PNMT. If we assume that they bind in a similar fashion at the PNMT active site, then the acidic hydrogen of compounds **4**, **5**, **8**, **9**, and **23** will be located in the same region of space as that in **1**, while the acidic hydrogen of compounds **6** and **28** will lie closer to the THIQ aromatic ring. With regard to acidity, the pK_a of the acidic hydrogen in compounds **9**, **23**, and **28** is equivalent to that of **1**, while for compounds **4** and **6** it is lower and for compounds **5** and **8**, it is higher.[14] Compounds **7**, **21**, **22**, and **27** do not possess an acidic hydrogen. As probes for the effect of the sulfonyl group, compounds **4** and **5** are derivatives of **1**, compounds **6**−**8** have the amine of the aminosulfonyl group reversed with regard to the aromatic ring (i.e. the electron-withdrawing effect of the (methylsulfonyl)amino group is less than that of the aminosulfonyl group of **1**), and compounds **9**, **22**, **23**, **27**, and **28** possess electron-donating hydroxy or methoxy groups.

In general, all compounds showed reduced affinity toward PNMT and, with the exceptions of **5** and **7**, showed increased α_2-adrenergic affinity as compared to **1** (Table 1). For compounds **1**, **4**, and **5**, the PNMT affinity did not correlate with pK_a (which would have been the case if acidity was the determining factor); however, both compounds **4** and **5** do possess additional steric bulk which could complicate this interpretation. It was noted that the α_2-adrenoceptor affinity did correlate with acidity for compounds **1**, **4** and **5**. The pK_a of compound **8** is comparable to that of **5**, and the acidic hydrogen occupies a similar region of space in both molecules. However, the potency of **8** at PNMT is considerably less and its α_2-adrenoceptor affinity is much greater, which would seem to indicate little importance of the acidic hydrogen in determining affinity for PNMT or selectivity. However, as noted above, there are significant differences in the electron-withdrawing properties of the 7-substituents of compounds **1** and **8**.

When the THIQ portions of the low-energy conformations of **1** and **9** were superimposed, the lone pair on the oxygen atom in **9** and the lone pair on the aminosulfonyl nitrogen of **1** were only 0.23 Å apart (Figure 1). If the unfavorable interaction responsible for the low potency of **1** at the α_2-adrenoceptor was occurring through the acidic hydrogen or the lone pair, then **9** should also be a selective inhibitor. It was found that **9** was actually one of the least selective inhibitors of those studied. Compound **23**, a less conformationally constrained analogue of **9**, displayed a similar lack of selectivity. Substitution of the phenolic hydrogen in **9** and **23** by a methyl group was found to reduce both PNMT potency (as expected[15]) and α_2-adrenoceptor affinity slightly, as in compounds **27** and **22**. Also, compound **21**, which does not possess a polar functional group in the area of interest, has a higher affinity for both PNMT and the α_2-adrenoceptor than do **22** or **23**. Again, there is no apparent correlation of PNMT affinity or selectivity with the presence of an acidic hydrogen in the region of space being studied.

Reversing the aminosulfonyl group, as in compound **6**, moves the acidic hydrogen closer to the aromatic ring. This increases the acidity of the hydrogen, but **6** displays reduced selectivity as a result of decreased PNMT affinity and increased α_2-adrenoceptor affinity. The acidic hydrogen of **28** is in a similar region of space as that of **6**, and **28** also displays a lack of selectivity, although it possesses good PNMT inhibitor activity. Again, there is no correlation with the presence of an acidic hydrogen in the given region of space with PNMT affinity or selectivity.

Removal of the aminosulfonyl acidic hydrogen, as in compound **7**, reduces selectivity even more, primarily due to greatly reduced PNMT potency, but this is likely a result of steric interference with binding at the PNMT active site, as **7** also showed the lowest α_2-adrenoceptor affinity of all the compounds in this study.

Summary and Conclusion

The results from this study indicate that the presence of an acidic hydrogen of the aminosulfonyl group of **1** does not impart selectivity for PNMT over the α_2-adrenoceptor. The results also indicate that the acidic NH group was not essential for the high PNMT-inhibitory activity in THIQ-type inhibitors. However, the interpretation of these data is dependent on all of the compounds binding in a similar manner at the PNMT active site and in a similar manner (although not necessarily the same manner as for PNMT) at the α_2-adrenoceptor.[32] Thus, in the case of **1**, it is likely some other factor (such as the presence of the sulfonyl group on the aromatic ring) which plays a major role in imparting selectivity between the PNMT active site and the α_2-adrenoceptor, and not its pK_a.

Experimental Section

All reagents and solvents were reagent grade or were purified by standard methods before use. Melting points were determined in open capillaries on a Thomas-Hoover melting point apparatus calibrated with known compounds but are otherwise uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Varian XL-300, a GE QE-300 or a Bruker DRX-400 spectrometer with $CDCl_3$ as the solvent unless noted in the text, 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 or a Bruker DRX-400 spectrometer with $CDCl_3$ as the solvent, and the chemical shifts are reported in ppm relative to $CDCl_3$ (77.0 ppm). For the hydrobromide salts of the phenolic amines, NMR spectra were recorded in deuterated dimethyl sulfoxide (DMSO-d_6), and the chemical shifts are reported relative to DMSO (2.49 ppm for ^{1}H and 39.5 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. Preparative centrifugal thin-layer chromatography (PCTLC) was performed on a Harrison Model 7924 Chromatotron (Harrison Research, Palo Alto, CA) using Merck silica gel 60 PF254/$CaSO_4$·0.5H_2O binder on 1, 2, or 4 mm thickness plates. Analytical TLC was performed by using silica gel with a fluorescent indicator coated on 1 × 3 in. glass plates in 0.2 mm thickness (Whatman MKGF silica gel 200 μm). Bulb to bulb distillations were carried out on a Kugelrohr distillation apparatus (Aldrich Chemical Co., Milwaukee, WI), and oven

temperatures were recorded. Combustion analyses were performed on a Hewlett-Packard Model 185B CHN analyzer at the University of Kansas by Dr. Tho Ngoc Nguyen.

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

Compounds **1** and **2** were kindly provided by Smith Kline and French Laboratories, Smith Kline Beecham Corp., Philadelphia, PA. *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).

7-((*N*-Methylamino)sulfonyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (5·HCl). Compound **1** (58.1 mg, 0.274 mmol) was dissolved in dry THF (2 mL) and added to a suspension of NaH (60% in mineral oil, 11.0 mg, 0.274 mmol) in THF (2 mL) at 0 °C. The solution was stirred for 10 min. A solution of MeI (13.0 μL, 0.206 mmol) in dry THF (1 mL) was then added, and the solution was stirred for an additional 30 min. The reaction was quenched by the addition of water (2 mL). The resulting solution was extracted with EtOAc (three times), and the combined extracts were washed with 10% Na_2CO_3(aq) and brine. The organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure to yield an off-white solid. Flash chromatography (flash silica gel 32−63 μm, EtOAc as the eluent), followed by removal of the solvent under reduced pressure yielded a colorless solid, which was dissolved in methanol and converted to the hydrochloride salt. The solvent was removed and the residue recrystallized from EtOH/hexane to yield **5**·HCl as white needles (28.2 mg, 39.1%): mp (HCl) 243−244 °C; IR (KBr) 3150 (NH), 2900, 2800, 1410, 1320 (SO_2), 1160 (SO_2), 1130, 1050, 895, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.77 (bs, e, 2 H, NH_2^+), 7.68 (s, 1 H, Ar*H*), 7.65 (d, 1 H, J = 8 Hz, Ar*H*), 7.54 (brs, ex, 1 H, N*H*), 7.46 (d, 1 H, J = 8 Hz, Ar*H*), 4.34 (s, 2 H, H-1), 3.37 (s, 3 H, NCH_3), 3.10 (t, 2 H, J = 6 Hz, H-3), 2.55 (t, 2 H, J = 6 Hz, H-4); ^{13}C NMR (DMSO-d_6) δ 138.4, 137.8, 131.1, 130.6, 130.6, 126.2, 44.1(C-1), 40.9 (C-3), 29.5 (NCH_3), 25.6 (C-4); CIMS *m*/*z* (relative intensity) 217 (M^+ + 1, 100), 132 (10), 131 (15). Anal. ($C_{10}H_{14}N_2O_2S$·HCl) C, H, N.

7-Nitro-1,2,3,4-tetrahydroisoquinoline Hydrochloride (11·HCl). 1,2,3,4-Tetrahydroisoquinoline (11.6 g, 84.8 mmol) was added dropwise with care to stirred ice-cold concentrated H_2SO_4 (42.0 mL). Potassium nitrate (9.40 g, 93.0 mmol) was then added in small portions, taking care that the temperature of the reaction mixture did not rise above 5 °C. After being stirred overnight at room temperature, the dark brown reaction mixture was added carefully to a stirred ice-cold concentrated NH_4OH solution. The basic red reaction mixture was extracted with $CHCl_3$ (three times), and the combined $CHCl_3$ extracts were washed with brine (once) and dried over anhydrous Na_2SO_4. Evaporation of the organic solvent gave a dark brown oil (14.6 g) which was taken up in EtOH (65 mL) and cooled in an ice bath. Treatment of this reddish solution with concentrated HCl (11 mL) yielded a viscous yellow precipitate of the hydrochloride salt which was filtered and crystallized from methanol (250 mL) to yield **11**·HCl as a buff solid (5.36 g, 29.4%). An analytically pure sample was obtained by crystallization from aqueous acetone (mp 260−262 °C; lit.[17] mp 261 °C): IR (KBr) 1585, 1520 (NO_2), 1425, 1345 (NO_2), 1090, 950, 740 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.07 (bs, 2 H, NH_2^+), 8.21 (d, J = 2.2 Hz, 1 H, H-8), 8.11 (dd, 1 H, J = 8.4, 2.4 Hz, H-6), 7.53 (d, J = 8.6 Hz, 1 H, H-5), 4.39 (s, 2 H, H-1), 3.38 (t, J = 5.9 Hz, 2 H, H-3), 3.17 (t, J = 5.9 Hz, 2 H, H-4); ^{13}C NMR (DMSO-d_6) δ 145.8, 140.4, 131.0, 130.2, 122.0, 121.9, 43.0 (C-1), 39.7 (C-3), 24.9 (C-4); EIMS *m*/*z* (relative intensity) 178 (M^+ + 1), 177 (M^+), 161, 149, 131 (M^+ − NO_2), 103, 102, 91, 77, 63, 51. Anal. ($C_9H_{10}N_2O_2$·HCl) C, H, N.

7-Nitro-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline (12). Compound **11**·HCl (5.00 g, 23.3 mmol) was suspended in CH_2Cl_2 (20 mL), and to it pyridine (9.22 g, 9.42 mL, 117 mmol) was added. The suspension was stirred in an ice bath, trifluoroacetic anhydride (7.34 g, 4.94 mL, 34.9 mmol) was added, and the mixture was allowed to stir for 24 h at room temperature. The reaction mixture was poured onto ice and extracted with CH_2Cl_2 (four times). The combined CH_2Cl_2 extracts were washed with 1 N HCl (four times) and brine (once). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to yield a yellow oil. The oil solidified on standing and was crystallized from aqueous EtOH as pale buff needles (4.95 g, 80.6%, mp 66−67 °C): IR (KBr) 1685 (CO), 1520 (NO_2), 1460, 1340 (NO_2), 1200, 1140, 890 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.15−8.05 (m, 2 H, H-7, H-8), 7.40−7.32 (m, 1 H, H-6), 4.90−4.85 (m, 2 H, H-1), 4.00−3.89 (m, 2 H, H-3), 3.10−3.06 (m, 2 H, H-4); EIMS *m*/*z* (relative intensity) 275 (M^+ + 1, 16), 274 (M^+, 100), 259 (10), 227 (25), 162 (14), 149 (35), 130 (15), 116 (26), 115 (30), 103 (28), 102 (14), 91 (31), 77 (69), 69 (45), 51 (34). Anal. ($C_{11}H_9F_3N_2O_3$) C, H, N.

7-Amino-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline (13). Compound **12** (4.95 g, 18.1 mmol) was dissolved in absolute EtOH, and PtO_2 (0.05 g) was added. The reaction mixture was hydrogenated at 50 psi until no further uptake of H_2 was seen (5 h). The suspension was filtered and evaporated to afford a red oil that solidified on standing (3.68 g, 83.4%). The compound was crystallized from CH_2Cl_2−hexanes as colorless crystals: mp 61−62 °C; IR (KBr) 3440 (NH_2), 3360 (NH_2), 1690 (CO), 1460, 1180, 1130, 820 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.96−6.90 (m, 1 H, Ar*H*), 6.58−6.53 (m, 1 H, Ar*H*), 6.45−6.40 (m, 1 H, Ar*H*), 4.67−4.62 (m, 2 H, H-1), 3.85−3.77 (m, 2 H, H-3), 3.66 (bs, e, 2 H, NH_2), 2.85−2.79 (m, 2 H, H-4); EIMS *m*/*z* (relative intensity) 245 (M^+ + 1, 14), 244 (M^+, 100), 229 (20), 147 (M^+ − $COCF_3$, 11), 132 (12), 131 (19), 130 (23), 119 (85), 91 (27), 69 (45). Anal. ($C_{11}H_{11}F_3N_2O$) C, H, N.

7-(*N*-(Methylsulfonyl)amino)-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline (14). Amine **13** (1.25 g, 5.12 mmol) was dissolved in CH_2Cl_2 (15 mL), and pyridine (0.81 g, 0.83 mL, 10 mmol) was added, followed by mesyl chloride (0.71 g, 0.83 mL, 10 mmol). The orange reaction mixture was stirred overnight, and the reaction was then quenched by the addition of 1 N HCl. Extraction by CH_2Cl_2 (four times) followed by drying and evaporation of the solvent yielded an orange-red semisolid which was passed through a silica plug ($CHCl_3$−THF, 20:1, as the eluent). The yellow oil (1.26 g, 76.4%) obtained was crystallized from CH_2Cl_2−hexanes to yield the desired compound **14** as white plates: mp 109−111 °C; IR (KBr) 3240 (NH), 1690 (CO), 1310 (SO_2), 1180 (SO_2), 1140, 1110, 970, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.44 (m, b, e, 1 H, N*H*), 7.15−7.09 (m, 3 H, Ar*H*), 4.77−4.70 (m, 2 H, H-1), 3.90−3.80 (m, 2 H, H-3), 3.02 (s, 3 H, SO_2CH_3), 3.00−2.90 (m, 2 H, H-4); EIMS *m*/*z* (relative intensity) 324 (M^+ + 2, 5), 323 (M^+ + 1, 15), 322 (M^+, 63), 243 (M^+ − SO_2Me, 72), 197 (34), 146 (13), 145 (13), 130 (68), 118 (29), 103 (27), 91 (100), 84 (18), 69 (31), 49 (41). Anal. ($C_{12}H_{13}F_3N_2O_3S$) C, H, N.

7-(*N*-(Methylsulfonyl)amino)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (6·HCl). Trifluoroacetamide **14** (0.64 g, 2.0 mmol) was added to dry saturated methanolic ammonia and stirred for 14 h at room temperature. The solvent was removed under reduced pressure to yield a pale yellow oil (0.47 g, 83%) which solidified on addition of CH_2Cl_2. Recrystallization from CH_2Cl_2−hexanes gave **6** as a colorless solid: mp 180−181 °C dec; IR (KBr) 3300 (NH), 1310 (SO_2), 1140 (SO_2), 980, 820 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 6.99 (s, 2 H, H-6, H-8), 6.88 (s, 1 H, H-7), 5.21 (bs, e, 2 H, N*H*, N*H*SO_2Me), 3.89 (s, 2 H, H-1), 3.02 (t, J = 5.8 Hz, 2 H, H-3), 2.88 (s, 3 H, SO_2CH_3), 2.69 (t, J = 5.7 Hz, 2 H, H-4); ^{13}C NMR (DMSO-d_6) δ 136.6, 135.3, 130.7, 129.5, 118.2, 117.8, 47.7, 43.2, 38.3, 28.0.

The hydrochloride salt was crystallized from aqueous MeOH: mp 263−264 °C dec; EIMS *m*/*z* (relative intensity) 226 (M^+, 14), 225 (M^+ − 1, 9), 197 (36), 147 (M^+ − SO_2Me, 12), 118 (22), 91 (88), 79 (13), 65 (100). Anal. ($C_{10}H_{14}N_2O_2S$·HCl) C, H, N.

7-(*N*,*N*-Bis(methylsulfonyl)amino)-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline (15). Amine **13** (1.25 g, 5.12 mmol) was dissolved in CH_2Cl_2 (20 mL), and triethylamine (2.59 g, 3.56 mL, 25.6 mmol) was added. The pale yellow solution was stirred in an ice bath, and mesyl chloride (1.76

g, 1.21 mL, 15.4 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 48 h. The orange-red reaction mixture was diluted with 1 N HCl and extracted with CH_2Cl_2 (four times). The combined CH_2Cl_2 layers were washed with 1 N HCl (four times) and brine (once). Evaporation of the solvent after drying over Na_2SO_4 yielded a red foam (1.80 g). Purification by PCTLC (silica, 4 mm) using $CHCl_3$−THF (20:1) as the eluent yielded **15** as a pale yellow foam (1.58 g, 77.3%). The compound was crystallized from CH_2Cl_2 as pink plates: mp 149−150 °C; IR (KBr) 1690 (CO), 1360 (SO_2), 1190, 1170, 1155, 1130, 970, 930, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30−7.15 (m, 3 H, Ar*H*), 4.83−4.75 (m, 2 H, H-1), 3.89−3.85 (m, 2 H, H-3), 3.35 (s, 6 H, SO_2CH_3), 3.00−2.90 (m, 2 H, H-4); EIMS *m/z* (relative intensity) 402 ($M^+ + 2$, 3), 401 ($M^+ + 1$, 6), 400 (M^+, 27), 321 ($M^+ - SO_2Me$, 10), 289 (6), 259 (7), 243 (16), 242 (20), 241 (74), 130 (10), 116 (18), 84 (52), 79 (23), 49 (100). Anal. ($C_{13}H_{15}F_3N_2O_5S_2$) C, H, N.

7-(*N*,*N*-Bis(methylsulfonyl)amino)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (7·HCl). Trifluoroacetamide **15** (0.75 g, 1.9 mmol) was dissolved in 20% aqueous MeOH (12 mL). To that solution was added K_2CO_3 (0.28 g, 2.1 mmol), and the solution was stirred for 10 h at room temperature. The solvent was removed under reduced pressure, and the yellow residue was suspended in water and extracted with CH_2Cl_2 (three times). The combined CH_2Cl_2 extracts were dried over Na_2SO_4 and evaporated to yield a yellow foam. This compound was purified by PCTLC (silica, 2 mm) using CH_2Cl_2−MeOH−NH_4OH (250:20:1) as the eluent. Compound **7** was isolated as a colorless solid (0.26 g, 46%): mp 170−171 °C dec; ^1H NMR ($CDCl_3$) δ 7.27−7.00 (m, 3 H), 3.96 (s, 2 H, H-1), 3.38 (s, 6 H, SO_2CH_3), 3.16−3.12 (m, 2 H, H-3), 2.83−2.75 (m, 2 H, H-4), 1.98 (bs, e, 1 H, N*H*); ^{13}C NMR ($CDCl_3$) δ 137.9, 137.8, 130.8, 130.6, 128.2, 127.9, 48.0 (C-1), 43.3, 42.6, 28.9 (C-4).

The hydrochloride salt was crystallized from aqueous methanol: mp 263−264 °C dec; IR (KBr) 1360 (SO_2), 1335, 1150 (SO_2), 950, 920, 760 cm^{-1}; EIMS *m/z* (relative intensity) 305 ($M^+ + 1$, 5), 304 (M^+, 15), 303 (26), 275 (11), 225 ($M^+ - SO_2Me$, 100), 209 (17), 146 (85), 119 (19), 118 (36), 116 (38), 91 (98), 79 (52), 65 (36), 43(32). Anal. ($C_{11}H_{16}N_2O_4S_2$·HCl) C, H, N.

7-Amino-1,2,3,4-tetrahydroisoquinoline Dihydrochloride (16·2HCl). In a Parr shaker bottle was placed **11**·HCl (15.0 g, 69.9 mmol) dissolved in 95% EtOH (100 mL), and concentrated HCl (10 mL), water (25 mL), and PtO_2 (0.5 g) were added. The mixture was hydrogenated at 50 psi until no drop in pressure was observed (4 h). The yellowish suspension was filtered through Celite and evaporated to dryness to afford a yellowish solid which was made basic with 10% NaOH solution. Extraction of the basic solution with $CHCl_3$ (three times), followed by drying over anhydrous Na_2SO_4 and evaporation of the solvent, yielded a reddish yellow solid (9.54 g, 92.2%): mp 110−112 °C (lit.[17] mp 120−121 °C); IR (KBr) 3400 (NH_2), 3320 (NH_2), 1500, 1440, 1300, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.86 (d, J = 7.8 Hz, 1 H, H-6), 6.51−6.47 (m, 1 H, H-8), 6.39−6.30 (bs, 1 H, H-5), 3.90 (s, 2 H, H-1), 3.08 (t, J = 5.9 Hz, 2 H, H-3), 2.66 (t, J = 5.9 Hz, 2 H, H-4); ^{13}C NMR ($CDCl_3$) δ 144.0, 136.6, 129.8, 124.5, 113.4, 112.1, 48.2 (C-1), 44.1 (C-3), 28.2 (C-4).

The dihydrochloride salt was recrystallized from aqueous MeOH as buff-colored needles: mp 290 °C dec; EIMS *m/z* (relative intensity) 149 ($M^+ + 1$, 5), 148 (M^+, 38), 119 (100), 118 (29), 91 (19), 51 (11). Anal. ($C_9H_{12}N_2$·2HCl) C, H, N.

7-Cyano-1,2,3,4-tetrahydroisoquinoline Hydrochloride (17·HCl). The diamine **16** (0.75 g, 5.1 mmol) was dissolved in concentrated HCl (1.75 mL) and water (2 mL) and stirred in an ice bath, giving a red solution. To this solution was added dropwise $NaNO_2$ (0.35 g, 5.1 mmol) dissolved in water (2 mL). After 15 min of stirring, a positive starch−iodide test was obtained and the excess HNO_2 was destroyed by the addition of urea (0.10 g).

In another flask, a solution of NaOH (0.50 g in 1.5 mL water) and KCN (1.63 g in 5 mL water) was prepared, and benzene (5 mL) was added. This suspension was chilled in an ice bath, and to it was added a solution of Ni_2SO_4·$6H_2O$ (1.3 g, 5 mmol in 2.5 mL water). The color of the resulting mixture changed to yellow-brown. To this mixture was added dropwise with vigorous stirring the diazotized solution. Brisk evolution of N_2 was observed, and the reaction mixture was allowed to warm to room temperature over a period of 2 h. The mixture was warmed to 50 °C in an oil bath for 1 h, cooled to room temperature, made basic with 1 N NaOH, and filtered through Celite. The Celite bed was washed with CH_2Cl_2, the filtrate was extracted with CH_2Cl_2 (three times), and the combined organic layers were washed with brine (once). Removal of the solvent after drying gave a dark black oil (0.60 g) which was distilled bulb to bulb (100−105 °C, 0.15 mmHg) to afford a colorless oil (0.30 g) which solidified on cooling. The compound was further purified by PCTLC (silica, 2 mm) using CH_2Cl_2−MeOH−NH_4OH (250:20:1) as the eluent. Compound **17** was obtained as a colorless solid (0.27 g, 33%, mp 92−94 °C): IR (KBr) 3300 (NH), 2220 (CN), 1490, 1420, 950, 860, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37 (d, J = 7.8 Hz, 1 H), 7.31−7.29 (m, 1 H), 7.17 (d, J = 8 Hz, 1 H), 4.00 (s, 2 H, H-1), 3.12 (t, J = 5.9 Hz, 2 H, H-3), 2.84 (d, J = 5.9 Hz, 2 H, H-4), 1.8 (s, e, 1 H, N*H*); ^{13}C NMR ($CDCl_3$) δ 140.6, 137.2, 130.0, 129.8, 129.3, 118.9, 109.2 (*C*N), 47.7 (C-1), 43.1 (C-3), 29.3 (C-4).

The hydrochloride salt was crystallized from MeOH−Et_2O as a colorless solid: mp 298−300 °C dec; EIMS *m/z* (relative intensity) 159 ($M^+ + 1$, 3), 158 (M^+, 34), 157 ($M^+ - 1$, 100), 129 (95), 102 (21), 77 (11) 51 (16). Anal. ($C_{10}H_{10}N_2$·HCl) C, H, N.

7-Cyano-2-(triphenylmethyl)-1,2,3,4-tetrahydroisoquinoline (18). Triethylamine (1.12 g, 1.55 mL, 11.1 mmol) was added to a solution of nitrile **17** (1.58 g, 10.0 mmol) in CH_2Cl_2 (15 mL). The solution was chilled in an ice bath, and 4-(dimethylamino)pyridine (0.12 g, 1.0 mmol) and triphenylmethyl chloride (4.18 g, 15.0 mmol) were added. After 14 h of stirring, the reaction was quenched by the addition of water. The reaction mixture was extracted with CH_2Cl_2 (three times), and the combined CH_2Cl_2 extracts were dried and evaporated to yield a yellow foam (4.93 g). The foam was purified by chromatography (silica gel, CH_2Cl_2−hexanes−MeOH−NH_4OH, 150:450:10:1, as the eluent) to yield **18** as a colorless fluffy solid (3.47 g, 86.7%). Crystallization of the solid from CH_2Cl_2−hexanes gave colorless needles (mp softens at 195 °C and melts completely at 202 °C): IR (KBr) 2210 (CN), 1480, 1440, 1070, 1035, 935, 740, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.54−7.51 (m, 6 H), 7.39−7.14 (m, 12 H), 3.44 (bs, 2 H, H-1), 3.06−3.02 (m, 2 H, H-3), 2.55 (bs, 2 H, H-4); ^{13}C NMR ($CDCl_3$) δ 142.1, 140.9, 137.6, 130.3, 129.5, 129.1, 127.9, 127.7, 126.3, 119.1 (*C*N), 109.1, 77.2 (*C*Ph_3), 50.5 (C-1), 45.8 (C-3), 30.2 (C-4); EIMS *m/z* (relative intensity) 400 (0.1), 323 ($M^+ - Ph$, 3), 243 (Ph_3C^+, 100), 165 (52), 105 (15), 91 (13), 51 (11). Anal. ($C_{29}H_{24}N_2$) C, H, N.

7-(Aminomethyl)-2-(triphenylmethyl)-1,2,3,4-tetrahydroisoquinoline (19). To a solution of nitrile **18** (3.05 g, 7.61 mmol) in dry THF (20 mL) was added BH_3·THF complex (1 M solution in THF, 10 mL, 10 mmol) dropwise. After addition was complete, the mixture was refluxed under N_2 for 18 h. The reaction mixture was cooled, and MeOH was added to quench excess borane. The solvent was removed under reduced pressure and the residue was heated under N_2 with 6 N NaOH (50 mL) for 3 h. The reaction mixture was extracted with CH_2Cl_2 (four times) and evaporated to yield a foamy solid (3.39 g). Purification by PCTLC (silica gel, 4 mm) using CH_2Cl_2−MeOH−NH_4OH (250:17:1) as the eluent yielded compound **19** as a colorless foam (2.37 g, 76.9%). Crystallization of this foam from CH_2Cl_2−hexanes afforded pale yellow crystals: mp 109−110 °C; IR (KBr) 3430 (NH_2), 3360 (NH_2), 1480, 1440, 1030, 740, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.56−7.54 (m, 6 H, Ar*H*), 7.27−7.05 (m, 12 H, Ar*H*), 3.73 (s, 2 H, H-1), 3.45 (bs, 2 H, ArCH_2NH_2), 2.98−2.96 (m, 2 H, H-3), 2.52 (bs, 2 H, H-4), 1.49 (bs, e, 2 H, NH_2); ^{13}C NMR ($CDCl_3$) δ 142.2, 140.1, 136.1, 133.2, 129.0, 128.6, 127.3, 125.8, 125.0, 124.6, 76.4 (*C*Ph_3), 50.6 (C-1), 46.2, 45.9, 29.4 (C-4); EIMS *m/z* (relative intensity) 404 (M^+, 0.3), 327 ($M^+ - Ph$, 4), 243 (Ph_3C^+, 91), 165 (100), 132 (25), 115 (26), 91 (56), 77 (35), 51 (27). Anal. ($C_{29}H_{28}N_2$) C, H, N.

7-((*N*-(Methylsulfonyl)amino)methyl)-2-(triphenylmethyl)-1,2,3,4-tetrahydroisoquinoline (20). A solution of amine **19** (2.10 g, 5.19 mmol) in dry CH_2Cl_2 (20 mL) was chilled

in an ice bath, and triethylamine (0.58 g, 0.79 mL, 5.7 mmol) was added. After addition of mesyl chloride (0.65 g, 0.45 mL, 5.4 mmol), the mixture was stirred at room temperature for 16 h. The reaction was quenched with 1 N NaOH and extracted with CH_2Cl_2 (four times). The combined CH_2Cl_2 layers were dried and evaporated to yield a white foam (2.59 g) which was passed through a silica gel plug ($CHCl_3$−THF, 20:1, as the eluent) to yield a colorless solid (2.21 g, 88.4%): mp 185−187 °C dec; IR (KBr) 3270 (NH), 1320 (SO_2), 1145 (SO_2), 1130, 1070, 740, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55−7.52 (m, 6 H, Ar*H*), 7.28−7.09 (m, 12 H, Ar*H*), 4.69 (bs, e, 1 H, N*H*), 4.20−4.18 (m, 2 H, H-1), 3.43 (bs, 2 H, CH_2NH), 2.98−2.96 (m, 2 H, H-3), 2.82 (s, 3 H, SO_2CH_3), 2.56−2.45 (m, 2 H, H-4); ^{13}C NMR ($CDCl_3$) δ 142.4, 142.3, 136.9, 135.0, 133.6, 129.2, 127.6, 126.1, 125.5, 77.4 (*C*Ph$_3$), 50.9 (C-1), 46.9, 46.3, 40.9 (SO_2CH_3), 29.6 (C-4); EIMS *m/z* (relative intensity) 482 (M^+, 0.1), 405 (M^+ − Ph, 2), 244 (26), 243 (Ph_3C^+, 100), 165 (64), 91 (15). Anal. ($C_{30}H_{30}N_2O_2S$) C, H, N.

7-((*N*-(Methylsulfonyl)amino)methyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (8·HCl). To a solution of compound **20** (2.0 g, 4.1 mmol) in acetone (25 mL) was added 3 N HCl (10 mL). The solution was stirred for 12 h at room temperature, and the acetone was removed under reduced pressure. The aqueous layer was washed with CH_2Cl_2 (four times) and evaporated to yield a colorless solid (1.04 g, 75.9%). Crystallization from aqueous MeOH yielded colorless needles: mp 224−226 °C dec; EIMS *m/z* (relative intensity) 241 ($M^+ + 1$, 4), 240 (M^+, 17), 239 ($M^+ - 1$, 53), 211 (19), 159 (15), 145 (22), 132 (74), 131 (100), 117 (18), 115 (17), 103 (18), 77 (41), 51 (15). Anal. ($C_{11}H_{16}N_2O_2S$·HCl) C, H, N.

A small amount of the hydrochloride salt was neutralized with 5% NH_4OH, and the solution was extracted with CH_2Cl_2 (four times). The colorless solid obtained by evaporation of the CH_2Cl_2 extracts was crystallized from CH_2Cl_2−hexanes as small colorless crystals: mp 144−145 °C; IR (KBr) 3300 (NH), 1500, 1300 (SO_2), 1140 (SO_2), 1070, 980, 850, 800 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.4 (bs, e, 1 H, N*H*), 7.11−6.98 (m, 3 H, Ar*H*), 4.12 (s, 2 H, CH_2NHSO$_2$Me), 3.93 (s, 2 H, H-1), 3.05 (t, 2 H, J = 5.8 Hz, H-3), 2.77 (s, 3 H, SO_2CH_3), 2.73 (t, 2 H, J = 5.8 Hz, H-4); ^{13}C NMR (DMSO-d_6) δ 134.8, 133.7, 132.8, 127.9, 124.2, 124.0, 46.8, 45.0, 42.3, 39.1, 27.4.

1-(Aminomethyl)-6-methoxynaphthalene Hydrochloride (22·HCl). 6-Methoxynaphthalene-1-carbonitrile[22] (2.00 g, 10.9 mmol) was dissolved in dry THF (10 mL), and BH_3·Me_2S complex (2 M solution in THF, 6 mL, 12.0 mmol) was added dropwise to this red-brown solution. After heating to reflux for 3 h, the solvent was removed by evaporation, and the resulting red-yellow residue was carefully acidified with methanolic HCl (20 mL). After the mixture was heated to reflux for 12 h, a suspension was obtained which was cooled to room temperature, and the solvent was evaporated to yield a yellow solid. The solid was dissolved in 10% HCl (30 mL), and the solution was washed with Et_2O (four times). The aqueous layer was cooled and made basic with KOH pellets. Extraction of the aqueous layer with Et_2O (four times) followed by evaporation of the Et_2O extracts yielded a yellow solid (1.69 g). Purification by PCTLC (silica, 4 mm) using CH_2Cl_2−MeOH−NH_4OH (250:25:1) as the eluent yielded a yellowish-white solid (1.42 g, 69.6%, mp 58−60 °C): ^1H NMR ($CDCl_3$) δ 7.92 (d, 1 H, J = 9.1 Hz), 7.62 (d, 1 H, J = 8.2 Hz), 7.36 (t, 1 H, J = 7.6 Hz), 7.26 (d, 1 H, J = 7 Hz), 7.14−7.12 (m, 2 H), 4.21 (s, 2 H), 3.86 (s, 3 H), 1.59 (s, e, 2 H); ^{13}C NMR ($CDCl_3$) δ 157.2, 138.8, 135.0, 126.4, 126.3, 126.1, 124.7, 122.1, 118.5, 106.6, 55.1, 43.9.

The hydrochloride salt was crystallized from MeOH−Et_2O as colorless shiny fluffy needles: mp 268−270 °C dec; IR (KBr) 3030, 1615, 1600, 1510, 1260, 1230, 1020, 830, 810 cm^{-1}; EIMS, *m/z* (relative intensity) 188 ($M^+ + 1$, 14), 187 (M^+, 100), 171 ($M^+ - CH_3$, 25), 144 (33), 127 (27), 128 (29), 115 (100), 114 (27), 102 (12), 89 (19), 77 (22), 63 (43). Anal. ($C_{12}H_{13}NO$·HCl) C, H, N.

1-(Aminomethyl)-6-hydroxynaphthalene Hydrobromide (23·HBr). Amine **22** (0.50 g, 2.7 mmol) was heated to reflux with 48% HBr (10.5 mL) for 3 h. The reaction mixture was cooled and concentrated *in vacuo* to give a reddish brown solid which was crystallized from MeOH−Et_2O as pale reddish brown needles (0.56 g, 82%): mp 256−258 °C dec; IR (KBr) 3270 (OH), 1610, 1600, 1580, 1240, 1210, 870, 800 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.85 (bs, e, 1 H, O*H*), 8.35 (bs, e, 3 H, NH_3^+), 8.01 (d, J = 9.2 Hz, 1 H), 7.75 (d, J = 7.7 Hz, 1 H), 7.46−7.38 (m, 2 H), 7.23−7.14 (m, 2 H), 4.47 (s, 2 H, CH_2); ^{13}C NMR (DMSO-d_6) δ 155.5, 135.1, 129.8, 127.5, 125.7, 125.2, 125.2, 124.1, 119.1, 109.7, 39.4 (*C*H$_2$); EIMS *m/z* (relative intensity) 174 ($M^+ + 1$, 10), 173 (M^+, 100), 172 ($M^+ - 1$, 93), 157 (25), 145 (26), 144 (20), 128 (31), 127 (48), 115 (74). Anal. ($C_{11}H_{11}$-NO·HBr) C, H, N.

3,4-Dihydro-8-methoxy-benz[*h*]isoquinolin-1(2*H*)-one (26). (6′-Methoxy-2′-naphthyl)-3-propionic acid[26] (1.00 g, 4.34 mmol) was treated with oxalyl chloride (3.4 mL, 39.1 mmol) for 2 h at room temperature, and the dark brown-red reaction mixture was evaporated to dryness. Dry benzene was added to the residue and evaporated to remove the traces of oxalyl chloride. The acid chloride was dissolved in acetone (5 mL) and chilled in an ice bath, and sodium azide (0.61 g, 9.3 mmol), dissolved in a minimum amount of water, was added. After the completion of the addition the reaction mixture was allowed to warm to room temperature and was stirred for 1 h. The biphasic reaction mixture was quenched with ice and extracted with toluene (three times), and the combined organic extracts were dried over anhydrous Na_2SO_4. The dark brown toluene extract was heated to reflux for 3 h. The solvent was removed to afford a dark brown oil which showed a characteristic band for the isocyanate group in the IR at 2300 cm^{-1}. The oil was refluxed under nitrogen for 14 h with BF_3·Et_2O (5 mL), the reaction mixture was quenched with ice and extracted with CH_2Cl_2 (three times). The combined extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated to yield a dark brown solid (0.98 g), which was purified by flash chromatography (hexanes−EtOAc, 1:1, as the eluent) to yield a pale brown solid (0.75 g, 76%). The compound was crystallized from EtOAc−hexanes as a pale pink shiny crystalline solid: mp 171−172 °C (lit.[28] mp 170−172 °C); IR (KBr) 3190 (NH), 1660 (CO), 1620, 1475, 1235, 1165, 1025, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.34 (d, 1 H, J = 9.6 Hz, H-6), 7.78 (d, 1 H, J = 8.4 Hz, H-5), 7.28−7.24 (m, 2 H, H-7 and H-9), 7.16 (bs, e, 1 H, N*H*), 7.13−7.10 (m, 1 H, H-10), 3.91 (s, 3 H, OCH_3), 3.56−3.50 (m, 2 H, H-3), 3.05 (t, 2 H, J = 6.6 Hz, H-4); ^{13}C NMR ($CDCl_3$) δ 167.3 (CO), 157.1, 137.4, 134.6, 131.4, 128.3, 127.1, 125.9, 123.8, 120.0, 106.3, 55.2 (O*C*H$_3$), 39.3 (C-3), 30.0 (C-4); EIMS *m/z* (relative intensity) 228 ($M^+ + 1$, 18), 227 (M^+, 100), 199 (8), 198 (40), 170 (74), 155 (36), 139 (15), 128 (18), 127 (47), 126 (18), 99 (13), 77 (18), 63 (13). Anal. ($C_{14}H_{13}NO_2$) C, H, N.

8-Methoxy-1,2,3,4-tetrahydrobenz[*h*]isoquinoline Hydrochloride (27·HCl). Amide **26** (1.26 g, 5.54 mmol) was dissolved in dry THF (10 mL) and refluxed under N_2 with BH_3·Me_2S complex (2 M solution in THF, 8.3 mL, 16.6 mmol) for 14 h. The excess borane was destroyed with methanol, and the solvent was removed to yield a semisolid. The semisolid was refluxed with concentrated HCl (2 mL) and MeOH (10 mL) for 4 h. The resulting white suspension was cooled, made basic with KOH pellets, and extracted with CH_2Cl_2 (three times). The combined extracts were dried over anhydrous Na_2SO_4, and the solvent was evaporated to yield a yellow solid (1.30 g). PCTLC (4 mm, silica gel; CH_2Cl_2−MeOH−NH_4OH, 250:17:1, as the eluent) yielded a colorless solid (1.01 g, 85.6%): mp 84−86 °C; mp (HCl) 228−229 °C dec; IR (KBr) 3250 (NH), 1620, 1600, 1240, 1160, 1120, 1030, 850, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.64 (d, 1 H, J = 9.1 Hz, H-6), 7.51 (d, 1 H, J = 8.4 Hz, H-5), 7.14−7.08 (m, 3 H, H-7, H-9 and H-10), 4.32 (s, 2 H, H-1), 3.88 (s, 3 H, OCH_3), 3.15 (t, 2 H, J = 5.8 Hz, H-3), 2.85 (t, 2 H, J = 5.8 Hz, H-4), 2.12 (s, e, 1 H, N*H*); ^{13}C NMR ($CDCl_3$) δ 156.8, 133.1, 130.3, 129.8, 128.5, 125.8, 125.1, 123.3, 118.2, 106.7, 55.1 (O*C*H$_3$), 45.4 (C-1), 43.4 (C-4), 29.6 (C-3).

The hydrochloride salt was crystallized from *i*-PrOH−MeOH as a colorless fluffy solid: mp 228−229 °C; EIMS *m/z* (relative intensity) 214 ($M^+ + 1$, 16), 213 (M^+, 88), 212 ($M^+ - 1$, 63), 198 ($M^+ - CH_3$, 8), 185 (22), 184 (100), 169 (19), 141 (36), 139 (15), 115 (33), 86 (17), 84 (25), 49 (35). Anal. ($C_{14}H_{15}NO$·HCl·0.75H_2O) C, H, N.

8-Hydroxy-1,2,3,4-tetrahydrobenz[*h*]isoquinoline Hy-

drobromide (9·HBr). Compound **27** (0.50 g, 2.3 mmol) was refluxed with 48% HBr (9.4 mL) under N_2 for 5 h to yield a pink suspension which was evaporated to remove excess HBr. The resulting pale red solid was crystallized from aqueous MeOH and ether to yield the pale pink crystalline hydrobromide (0.45 g, 68%): mp 295−296 °C dec; IR (KBr) 3310 (OH), 2940, 2820, 1510, 1260, 1245, 950, 800 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.81 (bs, e, 1 H, O*H*), 9.34 (bs, e, 2 H, NH_2^+), 7.73 (d, 1 H, J = 9.8 Hz, H-6), 7.63 (d, 1 H, J = 8.3 Hz, H-5), 7.24−7.15 (m, 3 H, H-7, H-9 and H-10); 4.62 (s, 2 H, H-1), 3.46−3.30 (m, 2 H, H-3), 3.15−3.01 (m, 2 H, H-4); ^{13}C NMR (DMSO-d_6) δ 155.2, 133.4, 127.3, 126.4, 126.1, 124.0, 123.6, 123.4, 118.9, 109.0, 41.7 (C-1), 40.4 (C-3), 25.0 (C-4); EIMS *m/z* (relative intensity) 200 (M^+ + 1, 14), 199 (M^+, 85), 198 (M^+ − 1, 77), 171 (21), 170 (100), 169 (26), 141 (20), 115 (25). Anal. ($C_{13}H_{13}NO$·HBr) C, H, N.

Radiochemical Assay for PNMT Affinity. The assay used in this study has been described elsewhere.[29] Briefly, a typical assay mixture consisted of 50 μL of 0.5 M phosphate buffer (pH 8.0), 25 μL of 10 mM unlabeled *S*-adenosyl-L-methionine (AdoMet), 5 μL of [*methyl*-^{3}H]AdoMet, containing approximately 3 × 10^5 dpm (specific activity approximately 15 mCi/mmol), 25 μL of substrate solution (phenylethanolamine), 25 μL of inhibitor solution, 25 μL of the enzyme preparation, and sufficient water to achieve a final volume of 250 μL. After incubation for 30 min at 37 °C, the reaction mixture was quenched by addition of 250 μL of 0.5 M borate buffer (pH 10.0) and was extracted with 2 mL of toluene−isoamyl alcohol (7:3). A 1 mL portion of the organic layer was removed and transferred to a scintillation vial and diluted with cocktail for counting. The mode of inhibition was ascertained to be competitive in all cases reported in Table 1 by inspection of the 1/*V* vs 1/*S* plots of the data. All assays were run in duplicate with three inhibitor concentrations over a 5-fold range. K_i values were determined by a hyperbolic fit of the data.

α_2-Adrenoceptor Radioligand Binding Assay. The radioligand receptor binding was performed according to the method of U'Prichard et al.[31] Male Sprague−Dawley rats were decapitated, and the cortexes were dissected out and homogenized in 20 volumes (w/v) of ice-cold 50 mM Tris·HCl buffer (pH 7.7 at 25 °C). Homogenates were centrifuged thrice for 10 min at 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 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 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. Molecular modeling was performed using the Sybyl software package (version 6.00, Tripos Associates, Inc., St. Louis, MO) on an IBM RS/6000 (Models 560 and 350) work station. The MNDO method in the semiempirical molecular orbital package (MOPAC, version 5.0 at the Sybyl interface) was used. The FIT command was used in fitting **9** with **1**.

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References

(1) (a) Presented at the 206th American Chemical Society National Meeting, Chicago, IL, August 22−27, 1993, Abstract MEDI 168. (b) Taken in large part from the Ph. D. dissertation of V.H.D., University of Kansas, 1994.

(2) Fuller, R. W. Overview and Concluding Remarks. In *Epinephrine in the Central Nervous System. Proceedings of the International Symposium on Brain Epinephrine*; Stolk, J., U'Prichard, D., Fuxe, K., Eds.; Oxford Press: London, 1987; pp 366−369.

(3) Hökfelt, T.; Fuxe, K.; Goldstein, M.; Johansson, G. Immunohistochemical Evidence for the Existence of Adrenaline Neurons in the Rat Brain. *Brain Res.* **1974**, *66*, 235−251.

(4) Crowley, W. R.; Terry, L. C.; Johnson, M. D. Evidence for the Involvement of Central Epinephrine Systems in the Regulation of Luteinizing Hormone, Prolactin, and Growth Hormone Release in Female Rats. *Endocrinology* **1982**, *110*, 1102−1107.

(5) Trudeau, F.; Brisson, G. R.; Péronnet, F. PNMT Inhibition Decrease Exercise Tolerance in the Rat. *Physiol. Behav.* **1992**, *52*, 389−392.

(6) Mefford, I. N.; Lister, R. G.; Ota, M.; Linnoila, M. Antagonism of Ethanol Intoxication in Rats by Inhibitors of Phenylethanolamine *N*-Methyltransferase. *Alcoholism* **1990**, *14*, 53−57.

(7) Saavedra, J. M. Adrenaline Levels in Brain Stem Nuclei and Effects of a PNMT Inhibitor on Spontaneously Hypertensive Rats. *Brain Res.* **1976**, *166*, 283−292.

(8) Toomey, R. E.; Horng, J. S.; Hemrick-Luecke, S. K.; Fuller, R. W. α_2-Adrenoceptor Affinity of Some Inhibitors of Norepinephrine *N*-Methyltransferase. *Life Sci.* **1981**, *29*, 2467−2472.

(9) Pendleton, R. G.; Gessner, G.; Weiner, G.; Jenkins, B.; Sawyer, J.; Bondinell, W.; Intoccia, A. Studies on SK&F 29661, an Organ Specific Inhibitor of Phenylethanolamine *N*-Methyltransferase. *J. Pharmacol. Exp. Ther.* **1979**, *208*, 24−30.

(10) Sauter, A. M.; Lew, J. Y.; Baba, Y.; Goldstein, M. Effect of Phenylethanolamine *N*-Methyltransferase and Dopamine β-hydroxylase Inhibition on Epinephrine Levels in the Brain. *Life Sci.* **1977**, *21*, 261−266.

(11) Blank, B.; Krog, A. J.; Weiner, G.; Pendleton, R. G. Inhibitors of Phenylethanolamine *N*-Methyltransferase and Epinephrine Biosynthesis. 2. 1,2,3,4-Tetrahydroisoquinoline-7-sulfonanilides. *J. Med. Chem.* **1980**, *23*, 837−840.

(12) Rafferty, M. F.; Borchardt, R. T.; Grunewald, G. L. Directional Probes of the Hydrophobic Component of the Aromatic Ring Binding Site of Norepinephrine *N*-Methyltransferase. *J. Med. Chem.* **1982**, *25*, 1204−1208.

(13) Grunewald, G. L.; Carter, A. E.; Sall, D. J.; Monn, J. A. Conformational Preference for the Binding of Biaryl Substrates and Inhibitors to the Active Site of Phenylethanolamine *N*-Methyltransferase. *J. Med. Chem.* **1988**, *31*, 60−65.

(14) King, J. F. Chapter 6: Acidity. In *The Chemistry of Sulphonic Acids, Esters and Their Derivatives*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons, Ltd.: West Sussex, 1991; pp 252−253.

(15) Sall, D. J.; Grunewald, G. L. Inhibition of Phenylethanolamine *N*-Methyltransferase (PNMT) by Aromatic Hydroxy-Substituted 1,2,3,4-Tetrahydroisoquinolines: Further Studies on the Hydrophilic Pocket of the Aromatic Ring Binding Region of the Active Site. *J. Med. Chem.* **1987**, *30*, 2208−2216.

(16) Jung, M. E.; Kaas, S. M. Facile Synthesis of a Substituted Bicyclo[4.2.1]nonane via an Anionic [1,3]-Sigmatropic Shift: Use of Long Range 2D HETCOR and Difference NOE in Structure Determination. *Tetrahedron Lett.* **1989**, *30*, 641−644.

(17) McCoubrey, A.; Mathieson, D. W. Isoquinolines. Part III. The Nitration of 3,4-Dihydro and 1,2,3,4-Tetrahydroisoquinolines. *J. Chem. Soc.* **1951**, 2851−2853.

(18) Ajao, A. F.; Bird, C. W. The Preparation and Oxidative Dimerization of 2-Acetyl-7-hydroxy-1,2,3,4-tetrahydroisoquinoline. A New Approach to Tetrahydroisoquinoline Synthesis. *J. Heterocycl. Chem.* **1985**, *22*, 329−331.

(19) Bergeron, R. J.; McManis, J. S. Reagents for the Stepwise Functionalization of Spermine. *J. Org. Chem.* **1988**, *53*, 3108−3111.

(20) Imazawa, M.; Eckstein F. Facile Synthesis of 2′Amino-2′deoxyribofuranosyl Purines. *J. Org. Chem.* **1979**, *44*, 2039−2041.

(21) McRae, J. A. The Preparation of 1-Naphthoic Nitrile from 1-Naphthylamine. *J. Am. Chem. Soc.* **1930**, *52*, 4550−4552.

(22) Jacobs, S. A.; Harvey, R. G. Synthesis of Conjugated Nitrile from a Benzylic Ketone via a Cyanotrimethylsilane Adduct: 3,4-Dihydro-6-methoxynaphthalene-1-carbonitrile. *J. Org. Chem.* **1983**, *48*, 5134−5135.

(23) Bevis, M. J.; Forbes, E. J.; Naik, N. N.; Uff, B. C. The Synthesis of Isoquinolines, Indoles and Benzthiophen by an Improved Pomeranz-Fritsch Reaction, Using Boron Trifluoride in Trifluoroacetic Anhydride. *Tetrahedron* **1971**, *27*, 1253−1259.

(24) Stock, L. M. *Aromatic Substitution Reactions*; Prentice-Hall: Inc.: Englewood Cliffs, NJ, 1968; pp 73−76.

(25) Kessar, S. V.; Sobti, A. K.; Joshi, G. S. Azasteroids. Part VII. Synthesis of 7-Hydroxy-2-methoxy-7, 8, 9, 10-tetrahydrobenzo-[*j*]phenanthridine. *J. Chem. Soc. C* **1971**, 259−261.

(26) Grunewald, G. L.; Borchardt, R. T.; Rafferty, M. F.; Krass, P. Conformationally Defined Adrenergic Agents. 5. Conformational Preferences of Amphetamine Analogues for Inhibition of Phenylethanolamine *N*-Methyltransferase. *Mol. Pharmacol.* **1981**, *20*, 377−381.

(27) Jacques, J.; Horeau, A. Nᵉ 149.- Structure Moléculaire et activité Œstrogène. (VI). Préparation de Quelques dérivés L'acide Amphihydroxynaphtyl β-propionique (Acide Allénolique). (No. 149.—Molecular Structure and Estrogenic Activity. (VI). Preparation of Some Derivatives of Amphihydroxynaphthyl β-Propionic Acid (Allenolic Acid).) *Bull. Soc. Chim. Fr.* **1948**, *15*, 711−716.

(28) Davies, R. V.; Iddon, B.; Suschitzky, H.; Gitos, M. W. Intramolecular Cyclization of 2-Phenethylisocyanates. *J. Chem. Soc., Perkin Trans. 1* **1978**, 180−184.

(29) Wrobel, J.; Dietrich, A.; Gorham, B. J.; Sestanj, K. Conformationally Rigid Analogues of Aldose Reductase Inhibitor, Tolrestat. Novel Syntheses of Naphthalene-Fused γ-, δ-, and ϵ-Lactams. *J. Org. Chem.* **1990**, *55*, 2694−2702.

(30) Connett, R. J.; Kirshner, N. Purification and Properties of Bovine Phenylethanolamine *N*-Methyltransferase. *J. Biol. Chem.* **1970**, *245*, 329−334.

(31) U'Prichard, D. C.; Greenberg, D. A.; Synder, S. H. Binding Characteristics of Radiolabeled Agonists and Antagonists at Central Nervous System *Alpha* Noradrenergic Receptors. *Mol. Pharmacol.* **1977**, *13*, 454−473.

(32) A comparative molecular field analysis (CoMFA) study in our laboratory of 72 compounds for PNMT and 74 compounds for the α_2-adrenoceptor has indicated that there may be two binding modes which are dependent on the lipophilicity of the aromatic substituent. Unpublished results with V. Dahanukar and R. Jalluri.

(33) (a) Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solutions*; Butterworth: London, 1965; p 68. (b) *Ibid.*; p 58.

(34) Kortüm, G.; Vogel, W.; Andrussow, K. *Dissociation Constants of Organic Acids in Aqueous Solutions*; Butterworth: London, 1961; p 445.

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