Inhibitors of Phenylethanolamine *N*-Methyltransferase That Are Predicted To Penetrate the Blood−Brain Barrier: Design, Synthesis, and Evaluation of 3-Fluoromethyl-7-(*N*-substituted aminosulfonyl)-1,2,3,4-tetrahydroisoquinolines That Possess Low Affinity toward the α_2-Adrenoceptor[1]

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(±)-7-Aminosulfonyl-3-fluoromethyl-1,2,3,4-tetrahydroisoquinoline (**7**) is one of the most potent and selective inhibitors of phenylethanolamine *N*-methyltransferase (PNMT) reported to date, but a blood−brain barrier (BBB) model indicates that it cannot penetrate the BBB. To increase the lipophilicity of **7** by addition of a nonpolar substituent to the sulfonamide nitrogen, a small library of (±)-3-fluoromethyl-7-(*N*-substituted aminosulfonyl)-1,2,3,4-tetrahydroisoquinolines was synthesized and evaluated as inhibitors of PNMT and for affinity at the α_2-adrenoceptor. In addition, this library probed the PNMT active site surrounding the sulfonamide nitrogen of **7**. Bulky substituents on the sulfonamide nitrogen are disfavored at the PNMT active site more so than at the α_2-adrenoceptor (thus reducing selectivity). On the other hand, alkyl chains on the sulfonamide nitrogen that contain an electron dense atom, such as a fluorine, are favored in the PNMT active site and possess little α_2-adrenoceptor affinity, thereby conferring good selectivity (>500). Several members of the library (**8**, **14**, **17**, and **18**) have excellent PNMT inhibitory potency and selectivity and are predicted, on the basis of their ClogP value (>0.5), to penetrate the BBB to a significant extent. Compounds **17** and **18** are the most potent and selective PNMT inhibitors reported to date.

Introduction

Phenylethanolamine *N*-methyltransferase (PNMT: EC 2.1.1.28) is the enzyme that catalyzes the terminal step in epinephrine (Epi, **2**) biosynthesis in which a methyl group from *S*-adenosyl-L-methionine (AdoMet, **3**) is transferred to the amino group of norepinephrine (NE, **1**) to produce Epi (**2**) and the cofactor product *S*-adenosyl-L-homocysteine (AdoHcy, **4**, Figure 1).[2] In the mid-1950s, Epi (**2**) was discovered in the central nervous system (CNS) and was found to constitute ca. 5% of the total catecholamine content in the mammalian brain.[3,4] Soon thereafter it was shown that peripheral Epi (**2**) did not cross the blood−brain barrier (BBB) but that CNS Epi was being synthesized in the brain.[5−8] CNS Epi (**2**) has been implicated in some of the neurodegeneration seen in Alzheimer's disease,[9] as well as in the regulation of blood pressure,[10] respiration,[11,12] body temperature,[11,12] and the α_2-adrenoceptor.[13,14] To help elucidate the role of CNS Epi (**2**), both a potent and selective inhibitor of PNMT is desired.

Compounds **5** and **6** are two of the most potent PNMT inhibitors yet reported (Table 1). Unfortunately, these compounds are unsuitable for the study of the observed effects from inhibiting CNS PNMT for different reasons. Compound **5** shows high affinity for the α_2-adrenoceptor (selectivity α_2 K_i/PNMT K_i = 7), which complicates biological interpretation, and **6** only inhibits peripheral PNMT because it does not cross the BBB as shown by autoradiographic[15] and BBB model studies.[16] A selectivity of >500 is desired for a PNMT inhibitor in order to properly interpret biological results. It was of interest to see if these structures could be optimized to develop an inhibitor that is both potent and selective for PNMT and is capable of penetrating the BBB.

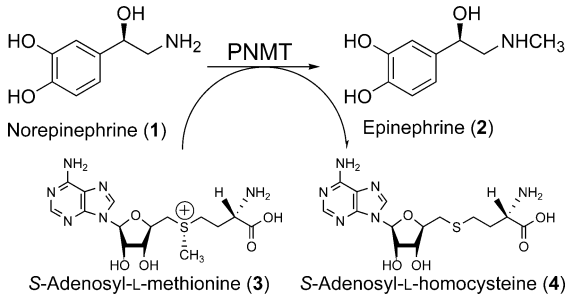

Figure 1. The terminal step in Epi (**2**) biosynthesis is catalyzed by the enzyme PNMT whereby an activated methyl group from AdoMet (**3**) is transferred to NE (**1**) to produce Epi (**2**) and AdoHcy (**4**).

Prior to the availability of the X-ray crystal structure of PNMT,[17,18] we have used molecular modeling techniques, such as quantitative structure−activity relationship studies and comparative molecular field analysis, to identify the factors that influence the binding of ligands to PNMT versus the α_2-adrenoceptor.[19,20] It was found that substitution on both the 3- and 7-positions of the 1,2,3,4-tetrahydroisoquinoline (THIQ) nucleus resulted in dramatic increases in selectivity compared to the monosubstituted analogues (e.g., **6** versus **7**).[21]

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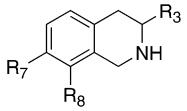
Table 1. In Vitro PNMT and α_2-Adrenoceptor Affinities of Some PNMT Inhibitors[a]



compd	R_3	R_7	R_8	hPNMT $K_i \pm$ SEM (μM)	α_2 K_i (μM)[b]	selectivity (α_2/hPNMT)	ClogP[c]
5	H	Cl	Cl	0.0031 ± 0.0006	0.021	7.0	2.75
6	H	SO_2NH_2	H	0.28 ± 0.02	100	360	−0.29
7[d]	CH_2F	SO_2NH_2	H	0.15 ± 0.01	680	4500	0.00
8[d]	CH_2F	SO_2NH-Ph-4-Cl	H	0.27 ± 0.03	140	520	3.18

[a] Biochemical data have been reported earlier for bovine PNMT. Here, we report data for recombinant human PNMT. [b] In vitro activities reported for the inhibition of binding of [^{3}H]clonidine at the α_2-adrenoceptor. [c] Calculated log *P*. [d] Reference 16.

More specifically, the addition of an electron-withdrawing group, such as a fluoromethyl substituent, to the 3-position of THIQ has led to more selective inhibitors.[16] While **7** is still too polar (ClogP = 0.00) to cross the BBB (vide infra), it provides a potential lead for increasing lipophilicity to impart CNS penetration.[16]

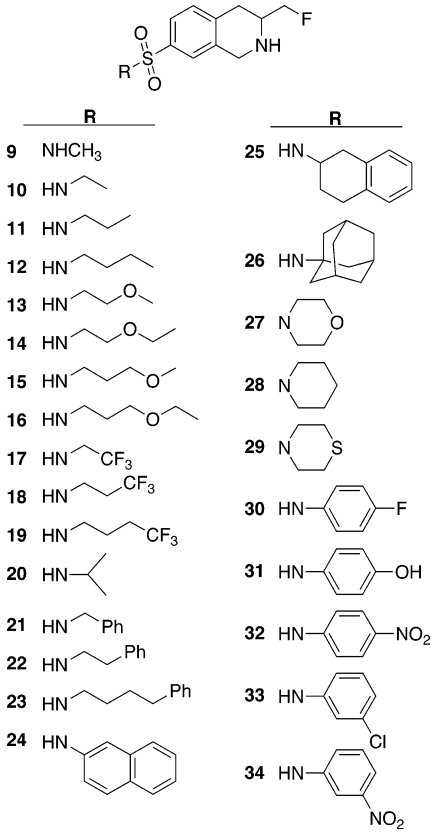
An in vitro model of BBB permeability using cultured bovine brain microendothelial cells grown on polycarbonate membranes was developed at the University of Kansas.[22,23] A study from our lab using this model on a small set of THIQs gave a good (r = 0.79) correlation between the ClogP (calculated log *P*)[24] of the compound and its permeability coefficient.[16] This correlation indicated that THIQs with a ClogP value of ca. 0.5 or greater should cross the BBB.

Previous results from our laboratory showed that **8** retained good PNMT inhibitory potency and selectivity and is predicted to penetrate the BBB (ClogP = 3.18).[16] The addition of a 4-Cl-phenyl substituent to the sulfonamide nitrogen of **7** suggested that there may be an auxiliary binding pocket in the PNMT active site surrounding the 7-position of THIQ. In this paper, we report the synthesis (**10**−**20** and **22**−**34**) and biochemical evaluation (**9**−**34**) of a small library of (±)-3-fluoromethyl-7-(*N*-substituted aminosulfonyl)-1,2,3,4-THIQs. This series of 7-*N*-substituted sulfonamides was designed to explore both the effects of steric bulk and lipophilicity on PNMT inhibitory potency and α_2-adrenoceptor affinity. Compounds **9**−**19** will provide information on increased lipophilicity and the interaction of conformationally flexible substituents within the area of the binding site surrounding the sulfonamide binding region of **7**. Compounds **20**−**29** will explore steric bulk tolerance, and **27**−**29** will also investigate conformational aspects of substituents in this binding pocket. The final series, **30**−**34**, will explore the effects of substitution on a phenyl ring in the binding pocket compared to **8**, which possesses good PNMT inhibitory potency and selectivity.

The discussion herein will use the recently published crystal structure of human PNMT[17] (hPNMT) cocrystallized with SK&F 29661 (**6**) and AdoHcy (**4**) to interpret the biochemical results obtained.

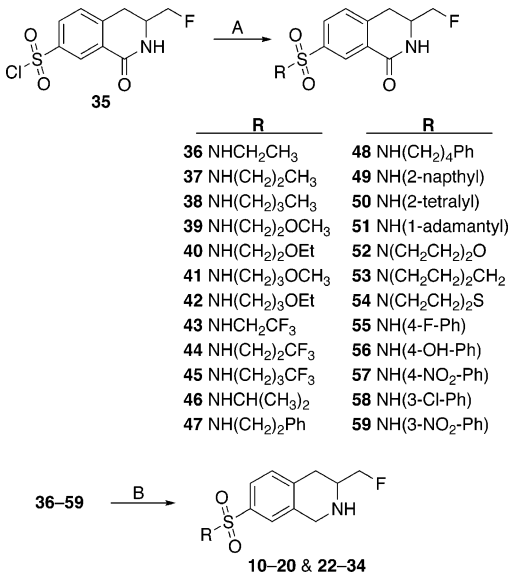
Chemistry

Compounds **9** and **21** were synthesized previously,[16] but their biochemical data for hPNMT are reported herein for the first time. Sulfonyl chloride **35**[16] was a common starting material that could be readily converted to the desired sulfonamides. By use of Schotten−Baumann reaction conditions, **35** was dissolved in a biphasic mixture of saturated sodium carbonate and ethyl acetate and treated with the requisite primary or secondary amine to produce sulfonamides **36**−**54** (Scheme 1). Use of these same reaction conditions to form the substituted *N*-phenylsulfonamides resulted in partial recovery of the starting material. It was found that when **35** was dissolved in pyridine and treated with the appropriate anilines, **55**−**59** were produced in good yield. The resulting sulfonamides (**36**−**59**) were reduced with BH_3·THF to yield the corresponding THIQs (**10**−**20** and **22**−**34**). In most cases, the intermediate lactam was isolated and characterized, but in some instances it was carried forward to the reduction reaction. Flash column chromatography was often required to purify the free amine before conversion to the HBr or HCl salt. For those salts that were hygroscopic and unable to be recrystallized, the compounds were recrystallized as the free base.



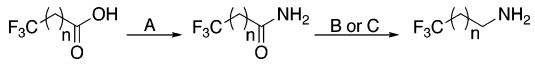
The majority of the amines were commercially available. 3,3,3-Trifluoropropylamine (**64**) and 4,4,4-trifluorobutylamine (**65**) have been reported in the literature, but because their syntheses were not practical or

Scheme 1[a]



[a] Reagents: (A) 1° or 2° amines, EtOAc/Na_2CO_3 or pyridine; (B) BH_3·THF.

Scheme 2[a]



[a] Reagents: (A) PCl_5, ether; (B) BH_3·THF; (C) $LiAlH_4$.

involved low molecular weight azides,[25,26] an alternative method was used (Scheme 2). The corresponding acid (**60** or **61**) was converted to the amide by a literature procedure.[26] The optimum conditions required the acid to be heated at reflux in ether in the presence of PCl_5 to yield the acid chloride that was then transformed in situ to the amide by saturation with ammonia gas. 4,4,4-Trifluorobutyroamide (**63**) was reduced smoothly with lithium aluminum hydride to yield 4,4,4-trifluorobutylamine (**65**). However, reduction of 3,3,3-trifluoropropionamide (**62**) with lithium aluminum hydride yielded a mixture of **64** and *n*-propylamine. 3,3,3-Trifluoropropionamide (**62**) was instead reduced with BH_3·THF to give 3,3,3-trifluoropropylamine (**64**) in good yield.

Biochemistry

All compounds were evaluated as their hydrochloride (**9**, **11**−**19**, **21**, and **26**−**30**) or hydrobromide (**20**) salts or as the free base (**10**, **22**−**25**, and **31**−**34**). Stock inhibitor solutions (10 mM) were made by dissolving the compound in H_2O (for salts) or in 0.01 N $HClO_4$ (for free amines). In the current study, hPNMT was expressed in *E. coli*[27] and purified with a C-teminal hexahistidine tag (see Experimental Section). The radiochemical assay conditions, previously reported for the bovine enzyme,[28] were modified to account for the high binding affinity of some inhibitors. Inhibition constants were determined using four concentrations of phenylethanolamine as the variable substrate and three concentrations of inhibitor.

α_2-Adrenergic receptor binding assays were performed using cortex obtained from male Sprague Dawley rats.[29] [^{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.

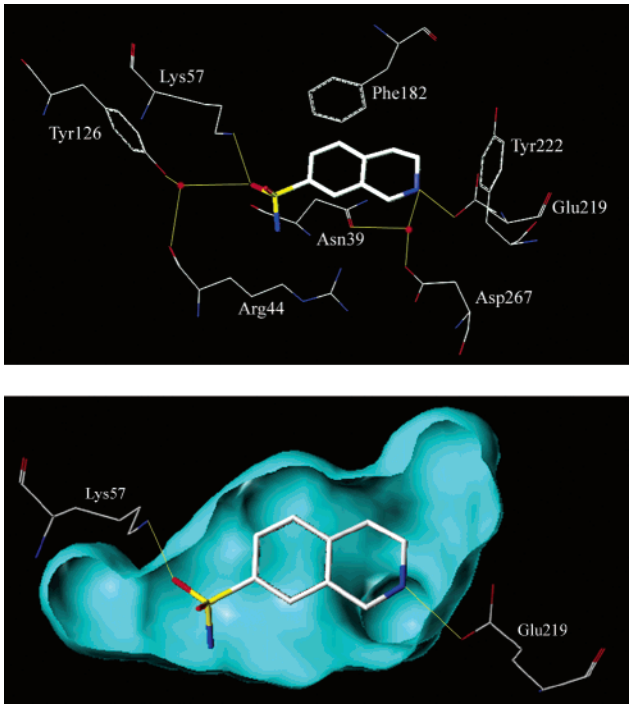


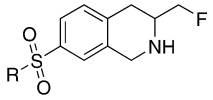
Figure 2. Part A (top) shows the amino acid residues that could interact with SK&F 29661 (**6**) within the hPNMT active site. Part B (bottom) is a Connolly (solvent accessible) surface of the active site revealing SK&F 29661 (**6**). Carbon is white, nitrogen is blue, oxygen is red, and sulfur is yellow. Hydrogens are not shown for clarity.

Results and Discussion

Figure 2A shows the interaction between SK&F 29661 (**6**) and the amino acid residues surrounding the PNMT active site.[17] A Connolly[24] (solvent accessible) surface of the active site revealing SK&F 29661 (**6**) is shown in Figure 2B. The addition of a fluoromethyl group to **6**, compound **7**, resulted in increased PNMT inhibitory potency and selectivity. Compound **7** was docked into the active site using FlexX,[30] and it appears that the 3-fluoromethyl moiety is making a hydrophobic contact to Tyr222 (picture not shown, but the same interaction can be seen with **18** in Figure 3A). We have docked the (*R*)-enantiomer into the PNMT active site because an earlier study[31] showed that (*R*)-**8** was more potent at bovine PNMT than (*S*)-**8**.[32]

The effect of straight-chain alkyl groups attached to the sulfonamide nitrogen is shown in Table 2. Figure 3B shows a Connolly surface of the hPNMT active site. The small pocket to the left of the sulfonamide moiety is where we propose substituents on the sulfonamide nitrogen are binding. Compound **11** was docked into the PNMT active site using FlexX and reveals that the side chain appears to make hydrophobic contacts with Arg44 and Val53 (picture not shown, but it is similar to **18** shown in Figure 3A). An increase in PNMT inhibitory potency is not observed with **10** or **11**, even though a hydrophobic interaction could be gained. In order for the substituent on the sulfonamide nitrogen to bind in the pocket, it must displace the water adjacent to Tyr126, resulting in the loss of the water-mediated hydrogen bond between the sulfonamide oxygen, Tyr126,

Table 2. In Vitro Activities of (±)-3-Fluoromethyl-7-(*N*-substituted aminosulfonyl)-1,2,3,4-tetrahydroisoquinolines: Alkyl Substituents



compd	R	hPNMT $K_i \pm$ SEM (μM)	α_2 $K_i \pm$ SEM (μM)	selectivity (α_2/hPNMT)	ClogP
9[a]	$NHCH_3$	3.7 ± 0.5	310 ± 10	84	0.55
10	$NHCH_2CH_3$	1.4 ± 0.1	550 ± 60	390	1.15
11	$NH(CH_2)_2CH_3$	1.7 ± 0.2	610 ± 60	360	1.60
12	$NH(CH_2)_3CH_3$	3.4 ± 0.5	260 ± 20	76	2.13
13	$NH(CH_2)_2OCH_3$	5.1 ± 0.7	430 ± 50	84	0.80
14	$NH(CH_2)_2OEt$	0.56 ± 0.05	440 ± 40	790	1.19
15	$NH(CH_2)_3OCH_3$	2.6 ± 0.2	750 ± 70	290	0.98
16	$NH(CH_2)_3OEt$	5.9 ± 0.6	350 ± 40	59	1.51
17	$NHCH_2CF_3$	0.13 ± 0.02	1200 ± 100	9200	1.41
18	$NH(CH_2)_2CF_3$	0.22 ± 0.02	660 ± 80	3000	1.39
19	$NH(CH_2)_3CF_3$	9.2 ± 1.7	350 ± 50	38	1.61

[a] Reference 16.

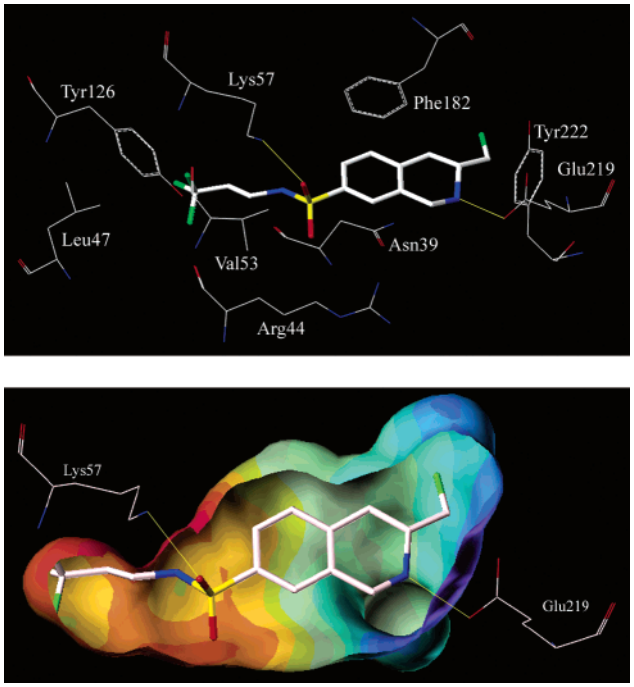


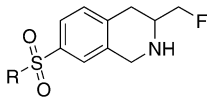
Figure 3. Part A (top) shows **18** docked into the hPNMT active site. Part B (bottom) is an electrostatic potential mapped on the Connolly surface of the hPNMT active site revealing **18**. The red-orange area indicates where electron density is favored, whereas the blue area indicates where electron density is disfavored. Green indicates neutrality. Carbon is white, nitrogen is blue, fluorine is green, oxygen is red, and sulfur is yellow. Hydrogens are not shown for clarity.

and Arg44 (Figure 2). The methyl group of **9** is not able to extend into this pocket and does not make a favorable contact in the active site. The butyl side chain of **12** may be too large to bind in this pocket, and therefore, a decrease in PNMT inhibitory potency is observed. Extending the side chain from an ethyl substituent (**10**) to a propyl substituent (**11**) lowers the α_2-adrenoceptor affinity. Substituting an oxygen at various points along the alkyl side chain (**13**−**16**) also results in decreasing α_2-adrenoceptor affinity. The ethoxyethylsulfonamide (**14**) maintains moderate PNMT inhibitory potency and selectivity. Interestingly, the sulfonamide substituent of **14** extends further than the butyl side chain of **12**, yet moderate PNMT inhibitory potency is observed. Manual docking of **14** shows that the sulfonamide substituent extends outside the auxiliary pocket (picture not shown). The longer side chain may be folding back over on itself in order to fit within the auxiliary pocket or the enzyme may be undergoing a conformational change in order to accommodate the side chain. Cocrystallization of **14** with hPNMT will be required to further address this point. The electrostatic potential of the PNMT active site surface indicates that atoms with high electron density would be favored within the auxiliary binding pocket (Figure 3B) and may lead to increased PNMT inhibitory potency. The addition of a trifluoromethyl group to the alkyl chain (**17** and **18**) resulted in a significant increase in potency and a decrease in α_2-adrenoceptor affinity, affording very selective inhibitors. Compounds **17** and **18** not only gain a hydrophobic interaction but are also highly favored because of the electron dense fluorines (Figure 3A). Extending the alkyl chain to a trifluorobutyl (**19**) results in a loss of PNMT inhibitory potency, suggesting an unfavorable contact. In this series several compounds (**14**, **17**, and **18**) have selectivities greater than 500 and, on the basis of their ClogP values, are predicted to penetrate the BBB.

To probe the width and depth of the auxiliary binding pocket, various bulky substituents (**20**−**26**) were added to the sulfonamide nitrogen (Table 3). All compounds in this series exhibited a significant loss of PNMT inhibitory potency and selectivity. This indicates that the auxiliary binding pocket of PNMT is of limited size and cannot accommodate bulky substituents.

To probe the auxiliary pocket further, we constrained some of the alkyl sulfonamide substituents to a ring (Table 4). While the data reported in Table 3 indicated that bulky substituents were not well tolerated, we obtained moderate PNMT inhibitory potency and selectivity with **29**. In this series, **27** possesses the lowest PNMT inhibitory potency. As the lipophilicity increases by substituting the oxygen with a carbon (**28**), PNMT inhibitory potency increases. Replacement of this carbon with a sulfur (**29**) leads to improved PNMT inhibitory potency; however, an increase in α_2-adrenoceptor affinity is observed resulting in only modest selectivity. It is evident from this series that the combination of a lipophilic, electron dense atom on the sulfonamide

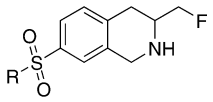
Table 3. In Vitro Activities of (±)-3-Fluoromethyl-7-(*N*-substituted aminosulfonyl)-1,2,3,4-tetrahydroisoquinolines: Bulky Substituents



compd	R	hPNMT $K_i \pm$ SEM (μM)	α_2 $K_i \pm$ SEM (μM)	selectivity (α_2/hPNMT)	ClogP
20	$NHCH(CH_3)_2$	66 ± 8	580 ± 60	8.8	1.45
21[a]	$NHCH_2Ph$	26 ± 3	110 ± 10	4.2	2.31
22	$NH(CH_2)_2Ph$	11 ± 2	58 ± 6	5.3	2.49
23	$NH(CH_2)_4Ph$	93 ± 10	6.8 ± 0.6	0.073	3.55
24	NH(2-naphthyl)	40 ± 6	12 ± 1	0.30	3.45
25[b]	NH(2-tetralyl)	33 ± 5	1.3 ± 0.1	0.039	2.94
26	NH(1-adamantyl)	88 ± 9	100 ± 10	1.1	3.12

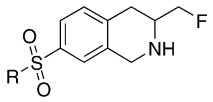
[a] Reference 16. [b] Assayed as a mixture of diastereomers.

Table 4. In Vitro Activities of (±)-3-Fluoromethyl-7-(*N*-substituted aminosulfonyl)-1,2,3,4-tetrahydroisoquinolines: Nonaromatic Rings



compd	R	hPNMT $K_i \pm$ SEM (μM)	α_2 $K_i \pm$ SEM (μM)	selectivity (α_2/hPNMT)	ClogP
27	$N(CH_2CH_2)_2O$	36 ± 4	2100 ± 200	58	0.86
28	$N(CH_2CH_2)_2CH_2$	4.6 ± 0.6	820 ± 100	180	2.15
29	$N(CH_2CH_2)_2S$	1.2 ± 0.2	190 ± 20	160	1.56

Table 5. In Vitro Activities of (±)-3-Fluoromethyl-7-(*N*-substituted aminosulfonyl)-1,2,3,4-tetrahydroisoquinolines: Substituted Phenyl Moieties



compd	R	hPNMT $K_i \pm$ SEM (μM)	α_2 $K_i \pm$ SEM (μM)	selectivity (α_2/hPNMT)	ClogP
30	NH(4-F-Ph)	1.3 ± 0.1	86 ± 10	66	2.54
31	NH(4-OH-Ph)	18 ± 2	280 ± 10	16	1.46
32	$NH(4\text{-}NO_2\text{-}Ph)$	7.7 ± 1.1	>1000[a]	>130	2.44
8[b]	NH(4-Cl-Ph)	0.27 ± 0.02	140 ± 20	520	3.18
33	NH(3-Cl-Ph)	890 ± 130	>1000[a]	>1.1	3.18
34	$NH(3\text{-}NO_2\text{-}Ph)$	250 ± 30	>1000[a]	>4.0	2.44

[a] Could not be exactly determined because of precipitation at high assay concentrations. [b] Reference 16.

nitrogen increases PNMT inhibitory potency. Compound **29** is predicted (ClogP = 1.56) to penetrate into the CNS.

Previously we have reported that adding a *p*-chlorophenyl substituent to **7** to give *N*-(*p*-chlorophenyl)-sulfonamide **8** resulted in submicromolar PNMT inhibitory potency and good selectivity, and this compound is predicted to cross the BBB.[16] To investigate this region of the binding site, several substituted *N*-phenylsulfonamides were evaluated (Table 5). Meta-substituted *N*-phenylsulfonamides (**33** and **34**) resulted in a significant decrease in PNMT inhibitory potency and α_2-adrenoceptor affinity. The auxiliary pocket of PNMT appears to be too narrow to accommodate the steric requirements of the meta substituent. In this series, good PNMT inhibitory potency is only observed with **8**. Again, having a lipophilic electron dense substituent in the auxiliary binding pocket seems to provide excellent PNMT inhibitory potency. Manual docking of **8** (picture not shown) reveals that the 4-Cl-phenyl ring is likely making hydrophobic contacts with Arg44 and Val53.

In conclusion, we have prepared a small library of (±)-3-fluoromethyl-7-(*N*-substituted aminosulfonyl)-1,2,3,4-THIQs and evaluated them for their inhibitory potency and selectivity for PNMT versus the α_2-adrenoceptor. Substituents on the sulfonamide nitrogen that are lipophilic and electron dense are highly favored within an auxiliary binding pocket of the PNMT active site. Bulky substituents are generally disfavored because of the limited size of this pocket. These conclusions are consistent with previous QSAR studies.[19] The *N*-4-Cl-phenyl (**8**), *N*-ethyl (**10**), *N*-propyl (**11**), *N*-ethoxyethyl (**14**), *N*-trifluoroethyl (**17**), *N*-trifluoropropyl (**18**), and *N*-thiomorpholino (**29**) sulfonamides represent compounds that are predicted to cross the BBB and retain moderate to excellent PNMT inhibitory potency. Four of these compounds (**8**, **14**, **17**, and **18**) exhibit selectivities greater than 500. With the addition of nonpolar substituents to the sulfonamide nitrogen of **7**, we have succeeded in producing inhibitors that are more lipophilic than **7**, that maintain PNMT inhibitory potency, and that have decreased α_2-adrenoceptor affinity. To date, **17** and **18** represent the most potent and selective inhibitors of hPNMT that, on the basis of their ClogP values, are predicted to penetrate the BBB.

Experimental Section

All of the reagents and solvents used were reagent grade or were purified by standard methods before use. Melting points were determined in open capillary tubes on a Thomas-Hoover melting point apparatus calibrated with known compounds but are otherwise uncorrected. All proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were taken on a Bruker DRX-400 or a Bruker AM-500 spectrometer. High-resolution mass spectra (HRMS) were obtained on a VG Analytical ZAB. Elemental analyses were performed by Quantitative Technologies, Inc. (Whitehouse, NJ). Flash chromatography was performed using silica gel 60 (230−400 mesh) supplied by Universal Adsorbents, Atlanta, GA. All methanol (MeOH) and ethanol (EtOH) used were anhydrous and were prepared by distillation over magnesium. Anhydrous tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl. Hexanes refers to the mixture of hexane isomers (bp 40−70 °C). All reactions that required anhydrous conditions were performed under argon, and all glassware was either oven-dried or flame-dried before use. AdoMet was obtained from Sigma-Aldrich (St. Louis, MO). [*Methyl*-^{3}H]AdoMet and [^{3}H]clonidine were obtained from PerkinElmer (Boston, MA). Compounds **37**, **40**−**42**, **51**, **52**, and **59** could not be obtained in pure form and were carried forward to the corresponding THIQ and subsequently purified.

Preparation of 6X-His-Tagged hPNMT. With pMM039[27] as the template, *Pfu* DNA polymerase and the QuikChange site-directed mutagenesis kit (Stratagene, La Jolla, CA) were employed to introduce a *Xho*I restriction site at the C-terminus of the hPNMT gene. The forward primer used for the mutagenesis, with the *Xho*I site italicized and the lower case letters indicating a base change from wild type, is as follows: 5′-GAAGGTTGGG*CTcgaG*GATCCGGCTGCTAAC-3′. The resultant plasmid was digested with *Nde*I/*Xho*I, and the 850 bp fragment ligated into *Nde*I/*Xho*I digested pET24b (Novagen, Madison, WI), resulting in a plasmid denoted pET24PNMT-his. The fidelity of the mutagenesis was confirmed by sequencing at the University of Michigan DNA sequencing facility. The vector used for protein expression, pET17PNMT-his, was prepared by ligation of a *Nde*I/*Blp*I fragment of pET24PNMT-his, containing MAH-his, into *Nde*I/*Blp*I digested pET17b (Novagen).

Expression and Purification of 6X-His-Tagged hPNMT. For expression of the his-tagged enzyme, pET17PNMT-his was transformed into *E. coli* strain BL21(DE3)pLysS. After inoculation and growth as described for wild-type hPNMT,[27] protein expression was induced by the addition of 0.5 mM IPTG. The cells were grown at 28 °C for 4 h prior to harvest, then resuspended in a buffer comprising 20 mM sodium phosphate and 300 mM NaCl, pH 7.0 (buffer A) containing 0.1 mM PMSF. After sonication and centrifugation, the cleared lysate was loaded onto a Sepharose CL-6B Ni/nitriloacetic acid (Ni−NTA) column (Qiagen, Valencia, CA) that had been equilibrated in buffer A containing 20 mM imidazole. The column was washed with the same buffer and again with buffer A containing 50 mM imidazole. Finally, the hPNMT-his was eluted with buffer A containing 250 mM imidazole. The fractions containing hPNMT-his were pooled and dialyzed against a storage buffer consisting of 20 mM Tris (pH 7.2)/15% glycerol/1 mM EDTA/0.5 mM DTT, before being concentrated and stored at 4 °C. The enzyme purified in this manner was better than 95% pure by SDS−PAGE analysis (data not shown). The kinetic constants were essentially identical (data not shown) to those obtained for the wild-type enzyme from earlier studies.[27]

Radiochemical Assay of PNMT Inhibitors. The assay used in this study has been modified from that described previously.[28] A typical assay mixture consisted of 25 μL of 0.5 M phosphate buffer (pH 8.0), 25 μL of 50 μM unlabeled AdoMet, 5 μL of [*methyl*-^{3}H]AdoMet, containing approximately 3×10^5 dpm (specific activity approximately 15 Ci/mmol), 25 μL of substrate solution (phenylethanolamine), 25 μL of inhibitor solution, 25 μL of enzyme preparation (containing 30 ng of hPNMT and 25 μg of bovine serum albumin), and sufficient water to achieve a final volume of 250 μL. After incubation for 30 min at 37 °C, the reaction mixture was quenched by addition of 250 μL of 0.5 M borate buffer (pH 10.0) and was extracted with 2 mL of toluene/isoamyl alcohol (7:3). A 1 mL portion of the organic layer was removed, transferred to a scintillation vial, and diluted with cocktail for counting. The mode of inhibition was ascertained to be competitive in all cases reported in Tables 1−5 by examination of the correlation coefficients (r^2) for the fit routines as calculated in the Enzyme Kinetics module (version 1.1) in SigmaPlot (version 7.0).[33] While all K_i values reported were calculated using competitive kinetics, it should be noted that there was not always a great difference between the r^2 values for the competitive model versus the noncompetitive model. 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 using the Single Substrate−Single Inhibitor routine in the Enzyme Kinetics module (version 1.1) in SigmaPlot (version 7.0). For inhibitors with apparent IC_{50} values less than 0.1 μM (as determined by a preliminary screen of the compounds to be assayed), the Enzyme Kinetics Tight Binding Inhibition routine was used to calculate the K_i values.

α_2-Adrenoceptor Radioligand Binding Assay. The radioligand receptor binding assay was performed according to the method of U'Prichard et al.[29] 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. 55 Ci/mmol, final concentration of 2.0 nM), various concentrations of drugs, and an aliquot of freshly resuspended tissue (800 μL) in a final volume of 1 mL were used. Tubes were incubated at 25 °C for 30 min, and the incubation was terminated by rapid filtration under vacuum through GF/B glass fiber filters. The filters were rinsed with three 5 mL washes of ice-cold 50 mM Tris buffer (pH 7.7 at 25 °C). The filters were counted in vials containing premixed scintillation cocktail. Nonspecific binding was defined as the concentration of bound ligand in the presence of 2 μM of phentolamine. All assays were run in quadruplicate with five inhibitor concentrations over a 16-fold range. IC_{50} values were determined by a log-probit analysis of the data, and K_i values were determined by the equation $K_i = IC_{50}/(1 + [\text{clonidine}]/K_D)$ because all Hill coefficients were approximately equal to 1.

Molecular Modeling. All molecular modeling was performed using the SYBYL software package on a Silicon Graphics Octane or O2 workstation.[24] The log *P* (ClogP) values were calculated with the ClogP function in SYBYL. Docking of the various inhibitors into the PNMT active site was performed using FlexX[30] with the CScore[34] scoring function. In some cases manual docking was performed. The default settings for FlexX were used. A high-scoring conformation was chosen, and the protein/ligand complex was minimized within a 6 Å radius of the inhibitor using the MMFF94 force field. Manual docking of other inhibitors involved the overlaying of the inhibitor with a FlexX docked inhibitor followed by a similar minimization of the protein/ligand complex. Connolly surfaces were generated using the MOLCAD surface function in SYBYL.

3,3,3-Trifluoropropylamine Hydrochloride (64·HCl).[26] 3,3,3-Trifluoropropionic acid (**60**, 1.77 g, 14.1 mmol) was dissolved in ether (70 mL) and was cooled in an ice−water bath. Phosphorus pentachloride (2.68 g, 21.2 mmol) was added in one portion, and the solution was heated to reflux for 2.5 h. Ether (25 mL) was added to the solution, that was cooled with an ice−water bath. $Ammonia_{(g)}$ was bubbled into the cooled solution for 30 min. The solution was concentrated, and saturated $NaHCO_3$ (25 mL) was added. The solution was extracted with EtOAc (4 × 35 mL) and dried over Na_2SO_4. The crude solid was recrystallized in EtOAc/hexanes to yield the

amide (**62**) as clear needles (1.15 g, 65%). Trifluoropropionamide (**62**, 599 mg, 4.72 mmol) was dissolved in THF (20 mL), and BH_3·THF (14.2 mL, 14.2 mmol) was added. The solution was stirred at 55 °C for 30 h. To this solution, MeOH (20 mL) and concentrated HCl (10 mL) were added, and the solution was heated to 60 °C for 4 h. The solution was then concentrated in vacuo. Water (15 mL) was added to the solution, which was cooled in an ice−water bath and made basic (pH 14) with KOH pellets, not allowing the solution to get to warm. The basic solution was extracted with ether (4 × 50 mL), and the combined organic extracts were washed with brine and dried over $NaSO_4$. The solvent was filtered, and dry $HCl_{(g)}$ was bubbled through the solution. The solvent was removed in vacuo, and the solid was recrystallized from EtOH/EtOAc to yield **64**·HCl as white crystals (426 mg, 61%): mp 125−126 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (ex s, 3H, NH), 3.03−2.99 (m, 2H), 2.78−2.73 (m, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 126.8 (q, J = 274 Hz), 33.2 (d, J = 4 Hz), 31.6 (q, J = 29 Hz); HRMS (FAB+) m/z calcd for $C_3H_6NF_3$ (MH^+) 114.0531, obsd 114.0539.

4,4,4-Trifluorobutylamine Hydrochloride (65·HCl).[25] 4,4,4-Trifluorobutyric acid (**61**, 1.08 g, 7.61 mmol) was dissolved in ether (50 mL) and was cooled in an ice−water bath. Phosphorus pentachloride (3.16 g, 9.13 mmol) was added in one portion, and the solution was heated to reflux for 3 h. Ether (25 mL) was added to the solution, which was cooled with an ice−water bath. $Ammonia_{(g)}$ was bubbled into the cooled solution for 30 min. The solution was concentrated, and saturated $NaHCO_3$ (25 mL) was added. The solution was extracted with EtOAc (4 × 35 mL) and dried over Na_2SO_4. The crude solid was recrystallized in EtOAc/hexanes to yield the amide (**63**) as clear needles (748 mg, 70%). Trifluorobutyroamide (**63**, 1.30 g, 9.22 mmol) was dissolved in ether (75 mL), and $LiAlH_4$ (723 mg, 19.0 mmol) was added. The mixture was heated to reflux for 6 h, the reaction was quenched using the Fieser and Fieser method,[35] and the mixture was stirred for 30 min. The mixture was filtered through a Celite pad and concentrated in vacuo to yield the crude amine. The amine was dissolved in ether, dry $HCl_{(g)}$ was bubbled through the solution, and the solvent was removed under reduced pressure. The solid was recrystallized from EtOAc to yield **65**·HCl as white crystals (1.11 g, 74%): mp 130−131 °C; ^{1}H NMR (DMSO-d_6) δ 8.32 (ex s, 3H, NH), 2.89−2.82 (m, 2H), 2.47−2.34 (m, 2H), 1.85−1.77 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 128.2 (q, J = 275 Hz), 38.4, 30.7 (q, J = 28 Hz), 31.6 (d, J = 3 Hz); HRMS (FAB+) m/z calcd for $C_4H_8NF_3$ (MH^+) 128.0687, obsd 128.0698.

General Procedure for the Preparation of Compounds 36−59. Sulfonyl chloride **35**[16] (200 mg, 0.721 mmol) was dissolved in a biphasic mixture of EtOAc (15 mL) and saturated Na_2CO_3 (10 mL). The requisite amine (3 equiv) was added to the reaction, and the mixture was stirred for 4 h. For compounds **43**−**45**, pyridine (2 equiv) was also added to the reaction mixture. The organic phase was removed, washed with 3 N HCl (3 × 50 mL) and brine (30 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure to yield an off-white solid, which was purified by recrystallization or column chromatography.

(±)-3-Fluoromethyl-7-(*N*-ethylaminosulfonyl)-3,4-dihydroisoquinolin-1-(2*H*)-one (36). Recrystallization from EtOAc/hexanes yielded **36** as white crystals (156 mg, 76%): mp 188−189 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (ex s, 1H, NH), 8.25 (s, 1H), 7.88−7.86 (m, 1H), 7.65 (ex s, 1H, NH), 7.56 (d, J = 8.0 Hz, 1H), 4.54−4.47 (m, 1H, CH_2F), 4.41−4.36 (m, 1H, CH_2F), 3.96−3.91 (m, 1H, H-3), 3.23−3.18 (m, 1H, H-4), 3.06−3.00 (m, 1H, H-4), 2.77 (q, J = 7.2 Hz, 2H), 0.97 (t, J = 7.2 Hz, 3H); HRMS (FAB+) m/z calcd for $C_{12}H_{16}N_2O_3FS$ (MH^+) 287.0866, obsd 287.0846.

(±)-3-Fluoromethyl-7-(*N*-butylaminosulfonyl)-3,4-dihydroisoquinolin-1-(2*H*)-one (38). Recrystallization from EtOAc/hexanes yielded **38** as white crystals (188 mg, 83%): mp 201−202 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (ex s, 1H, NH), 8.24 (s, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.68−7.65 (ex m, 1H, NH), 7.56 (d, J = 8.0 Hz, 1H), 4.54−4.47 (m, 1H, CH_2F), 4.42−4.35 (m, 1H, CH_2F), 3.96−3.90 (m, 1H, H-3), 3.24−3.18 (m, 1H, H-4), 3.06−3.00 (m, 1H, H-4), 2.72 (q, J = 6.2 Hz, 2H), 1.34 (quintet, J = 6.8 Hz, 2H), 1.22 (sextet, J = 7.2 Hz, 2H), 0.79 (t, J = 7.3 Hz, 3H); HRMS (FAB+) m/z calcd for $C_{14}H_{20}N_2O_3FS$ (MH^+) 315.1179, obsd 315.1160.

(±)-3-Fluoromethyl-7-(*N*-3-methoxypropylaminosulfonyl)-3,4-dihydroisoquinolin-1-(2*H*)-one (41). Recrystallization from EtOH/hexanes yielded **41** as white crystals (152 mg, 64%): mp 161−162 °C; ^{1}H NMR (DMSO-d_6) δ 8.39 (ex s, 1H, NH), 8.24 (m, 1H), 7.88−7.85 (m, 1H), 7.71−7.68 (ex m, 1H), 7.56 (d, J = 8.0 Hz, 1H), 4.54−4.47 (m, 1H, CH_2F), 4.42−4.36 (m, 1H, CH_2F), 3.96−3.91 (m, 1H, H-3), 3.28−3.18 (m, 3H), 3.15 (s, 3H), 3.05−3.00 (m, 1H, H-4), 2.78 (q, J = 6.7 Hz, 2H), 1.59 (quintet, J = 6.6 Hz, 2H); HRMS (FAB+) m/z calcd for $C_{14}H_{20}N_2O_4FS$ (MH^+) 331.1128, obsd 331.1141.

(±)-3-Fluoromethyl-7-(*N*-2,2,2-trifluoroethylaminosulfonyl)-3,4-dihydroisoquinolin-1-(2*H*)-one (43). Recrystallization from EtOH/hexanes yielded **43** as white crystals (107 mg, 42%): mp 230−231 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (ex s, 1H, NH), 8.40 (ex s, 1H, NH), 8.26 (s, 1H), 7.91 (m, 1H), 7.56 (d, J = 8.1 Hz, 1H), 4.51−4.49 (m, 1H, CH_2F), 4.39−4.37 (m, 1H, CH_2F), 3.95−3.86 (m, 1H, H-3), 3.66 (m, 2H), 3.21 (m, 1H, H-4), 3.03 (m, 1H, H-4); HRMS (FAB+) m/z calcd for $C_{12}H_{13}N_2O_3F_4S$ (MH^+) 341.0583, obsd 341.0574.

(±)-3-Fluoromethyl-7-(*N*-3,3,3-trifluoropropylaminosulfonyl)-3,4-dihydroisoquinolin-1-(2*H*)-one (44). Recrystallization from EtOH/hexanes yielded **44** as white crystals (100 mg, 39%): mp 140−141 °C; ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.42 (d, J = 9.6 Hz, 1H), 7.99 (m, 1H), 7.59 (m, 1H), 4.58−4.54 (m, 1H, CH_2F), 4.46−4.42 (m, 1H, CH_2F), 4.19−4.13 (m, 1H, H-3), 3.33−3.24 (m, 2H), 3.18−3.10 (m, 2H), 2.44−2.38 (m, 2H); HRMS (FAB+) m/z calcd for $C_{13}H_{15}N_2O_3F_4S$ (MH^+) 355.0740, obsd 355.0734.

(±)-3-Fluoromethyl-7-(*N*-4,4,4-trifluorobutylaminosulfonyl)-3,4-dihydroisoquinolin-1-(2*H*)-one (45). Recrystallization from EtOH/hexanes yielded **45** as white crystals (189 mg, 71%): mp 197−198 °C; ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.41 (s, 1H), 7.97 (d, J = 7.7 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 4.56−4.53 (m, 1H, CH_2F), 4.45−4.42 (m, 1H, CH_2F), 4.04−4.00 (m, 1H, H-3), 3.33−3.24 (m, 1H, H-4), 3.15−3.09 (m, 1H, H-4), 2.97−2.94 (m, 2H), 2.23−2.14 (m, 2H), 1.73−1.69 (m, 2H); HRMS (FAB+) m/z calcd for $C_{14}H_{17}N_2O_3F_4S$ (MH^+) 369.0896, obsd 369.0901.

(±)-3-Fluoromethyl-7-(*N*-1-methylethylaminosulfonyl)-3,4-dihydroisoquinolin-1-(2*H*)-one (46). Recrystallization from EtOH/hexanes yielded **46** as white crystals (116 mg, 74%): mp 186−187 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (ex s, 1H, NH), 8.27 (ex s, 1H, NH), 7.89 (d, J = 6.5 Hz, 1H), 7.69 (d, J = 7.2 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 4.51−4.49 (m, 1H, CH_2F), 4.39−4.38 (m, 1H, CH_2F), 3.96−3.90 (m, 1H, H-3), 3.28−3.18 (m, 2H), 3.03 (m, 1H, H-4), 0.95 (d, J = 6.5 Hz, 6H); HRMS (FAB+) m/z calcd for $C_{13}H_{18}N_2O_3FS$ (MH^+) 301.1022, obsd 301.1028.

(±)-3-Fluoromethyl-7-(*N*-2-phenylethylaminosulfonyl)-3,4-dihydroisoquinolin-1-(2*H*)-one (47). Recrystallization from EtOAc/hexanes yielded **47** as white crystals (209 mg, 80%): mp 162−163 °C; ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.37 (s, 1H), 7.93−7.91 (m, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.25−7.11 (m, 5H), 4.55 (m, 1H, CH_2F), 4.44 (m, 1H, CH_2F), 4.06−3.98 (m, 1H, H-3), 3.26−3.22 (m, 1H, H-4), 3.14−3.06 (m, 3H), 2.76−2.72 (m, 2H); HRMS (FAB+) m/z calcd for $C_{18}H_{20}N_2O_3FS$ (MH^+) 363.1179, obsd 363.1176.

(±)-3-Fluoromethyl-7-(*N*-4-phenylbutylaminosulfonyl)-3,4-dihydroisoquinolin-1-(2*H*)-one (48). Recrystallization from EtOAc/hexanes yielded **48** as white crystals (188 mg, 81%): mp 159−160 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (ex s, 1H, NH), 8.25 (s, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.70−7.68 (ex m, 1H, NH), 7.55 (d, J = 7.9 Hz, 1H), 7.26 (m, 2H), 7.17−7.12 (m, 3H), 4.54−4.49 (m, 1H, CH_2F), 4.42−4.35 (m, 1H, CH_2F), 3.95−3.89 (m, 1H, H-3), 3.20 (m, 1H, H-4), 3.02 (m, 1H, H-4), 2.76 (q, J = 6.2 Hz, 2H), 2.50−2.47 (m, 2H), 1.51 (quintet, J = 7.9 Hz, 2H), 1.38 (q, J = 7.1 Hz, 2H); HRMS (FAB+) m/z calcd for $C_{20}H_{24}N_2O_3FS$ (MH^+) 391.1492, obsd 391.1507.

(±)-3-Fluoromethyl-7-(*N*-2-naphthylaminosulfonyl)-3,4-dihydroisoquinolin-1-(2*H*)-one (49). The crude residue was purified by flash chromatography eluting with CH_2Cl_2/MeCN (2.5:1) to yield an off-white solid. Recrystallization from EtOAc/hexanes yielded **49** as white crystals (164 mg, 59%): mp 209−210 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.60 (ex s, 1H, NH), 8.34 (ex s, 1H, NH), 8.30 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.82−7.76 (m, 3H), 7.58 (s, 1H), 7.48−7.29 (m, 4H), 4.48−4.41 (m, 1H, CH_2F), 4.34−4.29 (m, 1H, CH_2F), 3.89−3.76 (m, 1H, H-3), 3.12 (m, 1H, H-4), 2.94 (m, 1H, H-4); HRMS (FAB+) m/z calcd for $C_{20}H_{18}N_2O_3FS$ (MH^+) 385.1022, obsd 385.1040.

(±)-3-Fluoromethyl-7-(*N*-2-tetralylaminosulfonyl)-3,4-dihydroisoquinolin-1-(2*H*)-one (50). Compound **50** is reported as a mixture of diastereomers. Recrystallization from EtOAc/hexanes yielded **50** as white crystals (251 mg, 85%): mp 158−159 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H, NH), 8.32 (s, 1H), 7.95−7.93 (m, 2H), 7.56 (d, J = 8.0 Hz, 1H), 7.05−7.03 (m, 3H), 6.94 (d, J = 6.5 Hz, 1H), 4.53−4.51 (m, 1H, CH_2F), 4.41−4.39 (m, 1H, CH_2F), 3.97−3.91 (m, 1H, H-3), 3.34−3.32 (m, 1H), 3.22 (m, 1H, H-4), 3.04 (m, 1H, H-4), 2.79−2.61 (m, 4H), 1.83−1.80 (m, 1H), 1.65−1.57 (m, 1H); HRMS (FAB+) m/z calcd for $C_{20}H_{22}N_2O_3FS$ (MH^+) 389.1335, obsd 389.1351.

(±)-3-Fluoromethyl-7-(*N*-piperidinosulfonyl)-3,4-dihydroisoquinolin-1-(2*H*)-one (53). Recrystallization from EtOAc/hexanes yielded **53** as white crystals (202 mg, 86%): mp 189−190 °C; ^{1}H NMR (400 MHZ, DMSO-d_6) δ 8.44 (ex s, 1H, NH), 8.11 (d, J = 1.7 Hz, 1H), 7.83 (m, 1H), 7.61 (d, J = 8.0 Hz, 1H), 4.53−4.50 (m, 1H, CH_2F), 4.41−4.39 (m, 1H, CH_2F), 3.98−3.92 (m, 1H, H-3), 3.23 (m, 1H, H-4), 3.05 (m, 1H, H-4), 2.91−2.85 (m, 4H), 1.55−1.54 (m, 4H), 1.37−1.36 (m, 2H); HRMS (FAB+) m/z calcd for $C_{12}H_{20}N_2O_3FS$ (MH^+) 327.1179, obsd 327.1104.

(±)-3-Fluoromethyl-7-(*N*-thiomorpholinosulfonyl)-3,4-dihydroisoquinolin-1-(2*H*)-one (54). Recrystallization from EtOAc/hexanes yielded **54** as white crystals (181 mg, 73%): mp 210−211 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (ex s, 1H, NH), 8.12 (d, J = 1.7 Hz, 1H), 7.85 (m, 1H), 7.63 (d, J = 8.0 Hz, 1H), 4.55−4.48 (m, 1H, CH_2F), 4.44−4.36 (m, 1H, CH_2F), 3.99−3.93 (m, 1H, H-3), 3.27−3.20 (m, 5H), 3.06 (m, 1H, H-4), 2.68 (t, J = 5.1 Hz, 4H); HRMS (FAB+) m/z calcd for $C_{14}H_{18}N_2O_3FS_2$ (MH^+) 345.0743, obsd 345.0740.

General Procedure for the Preparation of 55−59. Sulfonyl chloride **35** (200 mg, 0.721 mmol) was dissolved in pyridine (5 mL), treated with the requisite aniline (4 equivalents), and stirred for 4 h. A majority of the pyridine was removed under reduced pressure, and the resulting residue was dissolved in EtOAc (25 mL). The organic phase was washed with 6 N HCl (3 × 50 mL), washed with brine (30 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure to yield a crude solid, which was purified by recrystallization or column chromatography.

(±)-3-Fluoromethyl-7-(*N*-4-fluorophenylaminosulfonyl)-3,4-dihydroisoquinolin-1-(2*H*)-one (55). Recrystallization from EtOH/hexanes yielded **55** as white crystals (102 mg, 40%): mp 188−189 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (ex br s, 1H, NH), 8.37 (ex s, 1H, NH), 8.21 (s, 1H), 7.76 (m, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.12−7.08 (m, 4H), 4.49−4.46 (m, 1H, CH_2F), 4.37−4.35 (m, 1H, CH_2F), 3.92−3.87 (m, 1H, H-3), 3.18 (m, 1H, H-4), 3.03 (m, 1H, H-4); HRMS (FAB+) m/z calcd for $C_{16}H_{15}N_2O_3FS$ (MH^+) 353.0771, obsd 353.0763.

(±)-3-Fluoromethyl-7-(*N*-4-hydroxyphenylaminosulfonyl)-3,4-dihydroisoquinolin-1-(2*H*)-one (56). Recrystallization from EtOH/hexanes yielded **56** as light-brown crystals (132 mg, 52%): mp 205−206 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.80 (s, 1H, NH), 9.33 (ex s, 1H, OH), 8.35 (s, 1H, NH), 8.17 (s, 1H), 7.68 (m, 1H), 7.47 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.7 Hz, 2H), 6.60 (d, J = 8.7 Hz, 2H), 4.49−4.45 (m, 1H, CH_2F), 4.38−4.33 (m, 1H, CH_2F), 3.93−3.87 (m, 1H, H-3), 3.16 (m, 1H, H-4), 2.97 (m, 1H, H-4); HRMS (FAB+) m/z calcd for $C_{16}H_{16}N_2O_4FS$ (MH^+) 351.0815, obsd 351.0793.

(±)-3-Fluoromethyl-7-(*N*-4-nitrophenylaminosulfonyl)-3,4-dihydroisoquinolin-1-(2*H*)-one (57). Recrystallization from MeOH/ether yielded **57** as light-yellow crystals (91 mg, 33%): mp 235−236 °C; ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.45 (s, 1H), 8.21 (d, J = 9.1 Hz, 2H), 8.01 (m, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 9.2 Hz, 2H), 4.55−4.47 (m, 1H, CH_2F), 4.43−4.35 (m, 1H, CH_2F), 4.02−3.94 (m, 1H, H-3), 3.21 (m, 1H, H-4), 3.03 (m, 1H, H-4); HRMS (FAB+) m/z calcd for $C_{16}H_{15}N_3O_5FS$ (MH^+) 380.0716, obsd 380.0701.

(±)-3-Fluoromethyl-7-*N*-(3-chlorophenylaminosulfonyl)-3,4-dihydroisoquinolin-1-(2*H*)-one (58). Recrystallization from EtOAc/hexanes yielded **58** as white crystals (218 mg, 82%): mp 114−115 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.66 (ex s, 1H, NH), 8.39 (ex s, 1H, NH), 8.24 (s, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.27 (t, J = 8.1 Hz, 1H), 7.11−7.06 (m, 3H), 4.50−4.43 (m, 1H, CH_2F), 4.39−4.31 (m, 1H, CH_2F), 3.92−3.87 (m, 1H, H-3), 3.16 (m, 1H, H-4), 2.98 (m, 1H, H-4); HRMS (FAB+) m/z calcd for$C_{16}H_{15}N_2O_3ClFS$ (MH+) 369.0476, obsd 369.0491.

General Procedure for the Preparation of 10−20 and 22−34. The appropriate dihydroisoquinolone (**36**−**59**, 100−250 mg) was dissolved in THF (25 mL), and 1 M BH_3·THF (3 equiv) was added. The solution was heated at reflux for 12 h. The solution was cooled in an ice−water bath, and MeOH (10 mL) was carefully added dropwise until bubbling ceased. The solvent was removed under reduced pressure. A solution of 6 N HCl (5 mL) and MeOH (20 mL) was added slowly to the remaining reaction residue. The mixture was heated to reflux for 3 h. The solution was concentrated under reduced pressure, made basic with 15% KOH, and extracted with EtOAc (4 × 50 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to yield a crude solid, which often required chromatography. The purified solid was dissolved in EtOH, and $HBr_{(g)}$ or $HCl_{(g)}$ was bubbled through the solution. The solvent was removed under reduced pressure, and the HBr or HCl salt was purified by recrystallization.

(±)-3-Fluoromethyl-7-(*N*-ethylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline (10). Recrystallization of the free amine from EtOAc/hexanes yielded **10** as white crystals (106 mg, 76%): mp 139−140 °C; IR (Teflon film) 3296, 3048, 1600, 1471, 1379, 1348, 1041 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (br ex s, 1H, NH), 7.73 (s, 1H), 7.68−7.66 (m, 2H), 7.48 (d, J = 8.0 Hz, 1H), 4.99−4.68 (m, 2H, CH_2F), 4.48 (s, 2H, H-1), 3.87−3.22 (m, 1H, H-3), 3.15−3.07 (m, 2H, H-4), 2.79−2.74 (m, 2H), 0.99 (t, J = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 139.8, 136.8, 130.7, 130.7, 126.2, 125.8, 83.0 (d, J = 168 Hz, CH_2F), 52.7 (d, J = 19 Hz, C-3), 44.6, 38.4, 27.0, 15.6; HRMS (FAB+) m/z calcd for $C_{12}H_{18}N_2O_2FS$ (MH^+) 273.1073, obsd 273.1060. Anal. ($C_{12}H_{17}N_2O_2FS$) C, H, N.

(±)-3-Fluoromethyl-7-(*N*-propylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (11·HCl). Compound **37** was synthesized as described in the general procedure (150 mg of crude). After reduction, recrystallization from EtOH/hexanes yielded **11**·HCl as white crystals (70 mg, 60% from **35**): mp 204−205 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 (br ex s, 2H, NH_2^+), 7.73 (s, 1H), 7.69−7.64 (m, 2H), 7.48 (d, J = 8.1 Hz, 1H), 4.68−4.97 (m, 2H, CH_2F), 4.45 (s, 2H, H-1), 3.92−3.82 (m, 1H, H-3), 3.17−3.06 (m, 2H, H-4), 2.69 (q, J = 6.5 Hz, 2H), 1.39 (sextet, J = 7.2 Hz, 2H), 0.81 (t, J = 7.3 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 139.9, 136.7, 130.7, 130.6, 126.2, 125.8, 83.5 (d, J = 169 Hz, CH_2F), 52.8 (d, J = 18 Hz, C-3), 45.2, 44.7, 26.9, 23.3, 12.0; HRMS (FAB+) m/z calcd for $C_{13}H_{20}N_2O_2FS$ (MH^+) 287.1229, obsd 287.1227. Anal. ($C_{13}H_{19}N_2O_2FS$·HCl) C, H, N.

(±)-3-Fluoromethyl-7-(*N*-butylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (12·HCl). Recrystallization from EtOH/hexanes yielded **12**·HCl as white crystals (115 mg, 75%): mp 118−119 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (br ex s, 2H, NH_2^+), 7.73 (s, 1H), 7.66 (s, 2H), 7.48 (d, J = 6.8 Hz, 1H), 5.04−4.70 (m, 2H, CH_2F), 4.45 (s, 2H, H-1), 3.92−3.88 (m, 1H, H-3), 3.16−3.02 (m, 2H, H-4), 2.72 (d, J = 4.9 Hz, 2H), 1.36 (s, 2H), 1.25 (d, J = 5.6 Hz, 2H), 0.81 (s, 3H); ^{13}C NMR (500 MHz, DMSO-d_6) 139.4, 136.2, 130.2, 130.1, 125.6, 125.3, 82.5 (d, J = 168 Hz, CH_2F), 52.2 (d, J = 19 Hz, C-3), 44.1, 42.6, 31.5, 26.5, 19.6, 13.9; HRMS

(FAB+) *m/z* calcd for $C_{14}H_{22}N_2O_2FS$ (MH^+) 301.1386, obsd 301.1377. Anal. ($C_{14}H_{21}N_2O_2FS$·HCl) C, H, N.

(±)-3-Fluoromethyl-7-(*N*-2-methoxyethylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (13·HCl). Compound **39** was synthesized as described in the general procedure (116 mg crude). After reduction, the crude free amine was purified by flash chromatography eluting with CH_2Cl_2/MeCN (5:1) to yield a clear residue. Recrystallization of the HCl salt from EtOH/hexanes yielded **13**·HCl as white crystals (99 mg, 27% from **35**): mp 174−175 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43−9.95 (br ex m, 2H, NH_2^+), 7.81 (s, 1H), 7.74 (s, 1H, NH), 7.68 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 8 Hz, 1H), 4.98−4.69 (m, 2H, CH_2F), 4.44 (s, 2H, H-1), 3.90 (br m, 1H, H-3), 3.31 (m, 2H), 3.18−2.97 (m, 5H), 2.90 (m, 2H); ^{13}C NMR (500 MHz, DMSO-d_6) δ 139.5, 136.2, 130.2, 130.1, 125.7, 125.3, 82.5 (d, J = 168 Hz, CH_2F), 70.9, 58.3, 52.2 (d, J = 19 Hz, C-3), 44.1, 42.5, 26.5; HRMS (FAB+) *m/z* calcd for $C_{13}H_{20}N_2O_3FS$ (MH^+) 303.1179, obsd 303.1167. Anal. ($C_{13}H_{19}N_2O_3FS$·HCl) C, H, N.

(±)-3-Fluoromethyl-7-(*N*-2-ethoxyethylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (14·HCl). Compound **40** was synthesized as described in the general procedure (234 mg crude). After reduction, the crude free amine was purified by flash chromatography, eluting with CH_2Cl_2/MeCN (1:1) to yield a clear residue. Recrystallization of the HCl salt from EtOH/hexanes yielded **14**·HCl as white crystals (88 mg, 23% from **35**): mp 168−169 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (br ex s, 2H, NH_2^+), 7.93 (m, 1H), 7.74 (s, 1H, NH), 7.69 (d, J = 7.9 Hz, 1H), 7.47 (d, J = 8 Hz, 1H), 4.98−4.68 (m, 2H, CH_2F), 4.43 (s, 2H, H-1), 3.89 (br m, 1H, H-3), 3.37 (m, 4H), 3.16−3.02 (m, 2H, H-4), 2.90 (m, 2H), 1.06 (t, J = 7.0 Hz, 3H); ^{13}C NMR (500 MHz, DMSO-d_6) δ 139.5, 136.3, 130.2, 130.1, 125.7, 125.3, 82.5 (d, J = 168 Hz, CH_2F), 68.9, 65.8, 52.2 (d, J = 19 Hz, C-3), 44.1, 42.7, 26.5, 15.4; HRMS (FAB+) *m/z* calcd for $C_{14}H_{22}N_2O_3FS$ (MH^+) 317.1335, obsd 317.1336. Anal. ($C_{14}H_{21}N_2O_3FS$·HCl) C, H, N.

(±)-3-Fluoromethyl-7-(*N*-3-methoxypropylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (15·HCl). The crude free amine was chromatographed, eluting with CH_2Cl_2/MeCN (2:1) to yield a clear residue that solidified upon standing. Recrystallization of the HCl salt from EtOH/hexanes yielded **15**·HCl as white crystals (150 mg, 60%): mp 166−167 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (br ex s, 2H, NH_2^+), 7.73−7.67 (m, 3H), 7.48 (d, J = 7.1 Hz, 1H), 4.98−4.70 (m, 2H, CH_2F), 4.45 (s, 2H, H-1), 4.00−3.88 (m, 1H, H-3), 3.28 (s, 2H), 3.17−3.02 (m, 5H), 2.77 (s, 2H), 1.60 (s, 2H); ^{13}C NMR (500 MHz, DMSO-d_6) δ 139.3, 136.3, 130.2, 130.1, 125.7, 125.3, 82.5 (d, J = 169 Hz, CH_2F), 69.3, 58.2, 52.2 (d, J = 19 Hz, C-3), 44.1, 29.6, 26.52, 26.47; HRMS (FAB+) *m/z* calcd for $C_{14}H_{22}N_2O_3FS$ (MH^+) 317.1335, obsd 317.1328. Anal. ($C_{14}H_{21}N_2O_3FS$·HCl) C, H, N.

(±)-3-Fluoromethyl-7-(*N*-2-ethoxypropylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (16·HCl). Compound **42** was synthesized as described in the general procedure (303 mg crude). After reduction, the crude free amine was purified by flash chromatography, eluting with CH_2Cl_2/MeCN (1:1) to yield a clear residue. Recrystallization of the HCl salt from EtOH/hexanes yielded **16**·HCl as white crystals (147 mg, 37% from **35**): mp 175−176 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (br ex s, 2H, NH_2^+), 7.76−7.66 (m, 3H), 7.48 (d, J = 8 Hz, 1H), 4.98−4.62 (m, 2H, CH_2F), 4.44 (s, 2H, H-1), 3.89 (br m, 1H, H-3), 3.16−3.06 (m, 2H, H-4), 2.78 (m, 2H), 2.09 (br s, 4H), 1.60 (t, J = 6.1 Hz, 2H), 1.06 (t, J = 7.0 Hz, 3H); ^{13}C NMR (500 MHz, DMSO-d_6) δ 139.3, 136.3, 130.23, 130.18, 125.7, 125.3, 82.5 (d, J = 168 Hz, CH_2F), 67.1, 65.6, 52.2 (d, J = 19 Hz, C-3), 44.2, 31.1, 29.8, 26.5, 15.5; HRMS (FAB+) *m/z* calcd for $C_{15}H_{24}N_2O_3FS$ (MH^+) 331.1492, obsd 331.1495. Anal. ($C_{15}H_{23}N_2O_3FS$·HCl) C, H, N.

(±)-3-Fluoromethyl-7-(*N*-2,2,2-trifluoroethylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (17·HCl). Recrystallization from EtOH/hexanes yielded **17**·HCl as white crystals (67 mg, 63%): mp 120−130 °C (dec); ^{1}H NMR (400 MHZ, DMSO-d_6) δ 10.21 (br ex s, 2H, NH_2^+), 8.75 (t, J = 6.6 Hz, 1H), 7.79 (s, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.49 (d, J = 8.2 Hz, 1H), 4.99−4.68 (m, 2H, CH_2F), 4.44 (s, 2H, H-1), 3.93−3.87 (m, 1H, H-3), 3.74−3.66 (m, 2H, CF_3CH_2), 3.17−3.03 (m, 2H, H-4); ^{13}C NMR (500 MHz, DMSO-d_6) δ 139.1, 136.4, 129.93, 129.86, 125.2, 124.9, 124.3 (q, J = 279 Hz, CF_3), 82.1 (d, J = 539 Hz, CH_2F), 51.8 (d, J = 61 Hz, C-3), 43.7, 43.4 (q, J = 108 Hz, CF_3CH_2), 26.1; HRMS (FAB+) *m/z* calcd for $C_{12}H_{15}N_2O_2F_4S$ (MH^+) 327.0790, obsd 327.0787. Anal. ($C_{12}H_{14}N_2O_2F_4S$·HCl) C, H, N.

(±)-3-Fluoromethyl-7-(*N*-3,3,3-trifluoropropylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (18·HCl). Recrystallization from EtOH/hexanes yielded **18**·HCl as white crystals (80 mg, 76%): mp 111−117 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.69 (br ex s, 2H, NH_2^+), 7.98 (ex m, 1H, NH), 7.75 (s, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 4.93−4.63 (m, 2H, CH_2F), 4.44 (s, 2H, H-1), 3.92−3.85 (m, 1H, H-3), 3.16−2.93 (m, 4H), 2.49−2.40 (m, 2H, CF_3CH_2); ^{13}C NMR (400 MHz, DMSO-d_6) δ 139.1, 137.3, 131.2, 130.9, 128.3 (q, J = 276 Hz, CF_3), 126.1, 125.9, 83.2 (d, J = 168 Hz, CH_2F), 52.8 (d, J = 19 Hz, C-3), 44.9, 36.9, 34.1 (q, J = 27 Hz, CF_3CH_2), 27.2; HRMS (FAB+) *m/z* calcd for $C_{13}H_{17}N_2O_2F_4S$ (MH^+) 340.0947, obsd 340.0937. Anal. ($C_{13}H_{16}N_2O_2F_4S$·HCl) C, H, N.

(±)-3-Fluoromethyl-7-(*N*-4,4,4-trifluorobutylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (19·HCl). Recrystallization from EtOH/hexanes yielded **19**·HCl as white crystals (126 mg, 63%): mp 212−222 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.75 (br ex s, 2H, NH_2^+), 7.98 (ex m, 1H, NH), 7.74 (s, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 4.96−4.65 (m, 2H, CH_2F), 4.45 (m, 2H, H-1), 3.92 (br m, 1H, H-3), 3.16−3.00 (m, 2H, H-4), 2.84−2.81 (m, 2H), 2.27−2.20 (m, 2H), 1.65−1.60 (m, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 139.6, 137.0, 130.8, 130.7, 128.3 (q, J = 275 Hz, CF_3), 126.1, 125.8, 83.4 (d, J = 168 Hz, CH_2F), 52.8 (d, J = 19 Hz, C-3), 44.7, 42.1, 30.6 (q, J = 27 Hz, CF_3CH_2), 26.9, 22.9; HRMS (FAB+) *m/z* calcd for $C_{14}H_{19}N_2O_2F_4S$ (MH^+) 355.1103, obsd 355.1103. Anal. ($C_{14}H_{18}N_2O_2F_4S$·HCl) C, H, N.

(±)-3-Fluoromethyl-7-(*N*-1-methylethylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline Hydrobromide (20·HBr). Recrystallization from EtOH/hexanes yielded **20**·HBr as white crystals (116 mg, 73%): mp 205−206 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (br ex s, 2H, NH_2^+), 7.75 (s, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.64 (ex d, J = 7.1 Hz, 1H, NH), 7.48 (d, J = 8.1 Hz, 1H), 4.94−4.65 (m, 2H, CH_2F), 4.50 (s, 2H, H-1), 3.99−3.93 (m, 1H, H-3), 3.26−3.00 (m, 3H), 0.96 (m, 6H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 141.3, 136.4, 130.7, 130.3, 126.2, 125.7, 83.1 (d, J = 169 Hz, CH_2F), 52.9 (d, J = 19 Hz, C-3), 46.1, 44.9, 26.9, 24.1; HRMS (FAB+) *m/z* calcd for $C_{13}H_{20}N_2O_2FS$ (MH^+) 287.1229, obsd 287.1249. Anal. ($C_{13}H_{19}N_2O_2FS$·HBr) C, H, N.

(±)-3-Fluoromethyl-7-(*N*-2-phenylethylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline (22). Recrystallization from EtOAc/hexanes yielded **22** as white crystals (200 mg, 60%): mp 105−106 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (br ex s, 1H, NH), 7.52 (d, J = 8.0 Hz, 1H), 7.47 (s, 1H), 7.31−7.25 (m, 3H), 7.21−7.14 (m, 3H), 4.52−4.48 (m, 1H, CH_2F), 4.41−4.36 (m, 1H, CH_2F), 4.01−3.89 (m, 2H, H-1), 3.14−3.09 (m, 1H, H-3), 2.93 (s, 2H), 2.77 (m, 1H, H-4), 2.68 (t, J = 7.5 Hz, 2H), 2.56 (m, 1H, H-4); ^{13}C NMR (500 MHz, DMSO-d_6) δ 139.1, 138.7, 137.6, 137.2, 129.9, 128.7, 128.3, 126.2, 124.1, 123.8, 86.1 (d, J = 169 Hz, CH_2F), 52.2 (d, J = 19 Hz, C-3), 47.1, 44.1, 35.2, 29.7; HRMS (FAB+) *m/z* calcd for $C_{18}H_{22}N_2O_2FS$ (MH^+) 349.1386, obsd 349.1411. Anal. ($C_{18}H_{21}N_2O_2FS$·0.25H_2O) C, H. N.

(±)-3-Fluoromethyl-7-(*N*-4-phenylbutylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline (23). Recrystallization from EtOAc/hexanes and yielded **23** as white crystals (188 mg, 89%): mp 122−123 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53−7.48 (m, 3H), 7.34−7.24 (m, 3H), 7.18−7.13 (m, 3H), 4.53−4.48 (m, 1H, CH_2F), 4.41−4.36 (m, 1H, CH_2F), 4.02−3.89 (m, 2H, H-1), 3.13−3.08 (m, 1H, H-3), 2.79−2.71 (m, 3H), 2.59−2.47 (m, 3H), 1.51 (quintet, J = 7.0 Hz, 2H), 1.38 (quintet, J = 7.0 Hz, 2H); ^{13}C NMR (500 MHz, DMSO-d_6) δ 142.0, 138.9, 137.9, 137.2, 129.9, 128.24, 128.20, 125.6, 124.0, 123.8, 86.1 (d, J = 166 Hz, CH_2F), 52.3 (d, J = 19 Hz, C-3), 47.2, 42.3,

34.6, 29.7, 28.7, 28.0; HRMS (FAB+) *m/z* calcd for $C_{20}H_{26}N_2O_2FS$ (MH^+) 377.1699, obsd 377.1676. Anal. ($C_{20}H_{25}N_2O_2FS \cdot 0.25H_2O$) C, H, N.

(±)-3-Fluoromethyl-7-(*N*-2-naphthylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline (24). The crude free amine was purified by flash chromatography, eluting with CH_2Cl_2/MeCN (1:2). The white solid was recrystallized from EtOAc/hexanes and yielded **24** as white crystals (105 mg, 75%): mp 169−170 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80−7.76 (m, 3H), 7.58−7.55 (m, 3H), 7.46−7.30 (m, 3H), 7.23 (d, J = 8.6 Hz, 1H), 4.46−4.42 (m, 1H, CH_2F), 4.34−4.29 (m, 1H, CH_2F), 3.94−3.82 (m, 2H, H-1), 3.07−3.00 (m, 1H, H-3), 2.68 (m, 1H, H-4), 2.47 (m, 1H, H-4); ^{13}C NMR (500 MHz, DMSO-d_6) δ 139.8, 137.3, 136.8, 135.5, 133.3, 130.0, 129.9, 129.0, 127.5, 127.1, 126.6, 124.9, 124.3, 124.0, 120.1, 115.5, 86.0 (d, J = 166 Hz, CH_2F), 52.1 (d, J = 19 Hz, C-3), 47.0, 29.5; HRMS (FAB+)-*m/z* calcd for $C_{20}H_{20}N_2O_2FS$ (MH^+) 371.1230, obsd 371.1219. Anal. ($C_{20}H_{19}N_2O_2FS \cdot 0.25H_2O$) C, H, N.

(±)-3-Fluoromethyl-7-(*N*-2-tetralylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline (25). Recrystallization from EtOAc/hexanes yielded **25** as white crystals (173 mg, 75%): mp 173−174 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (d, J = 6.3 Hz, 1H, NH), 7.60 (d, J = 8.0 Hz, 1H), 7.55 (s, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.08−7.01 (m, 3H), 6.96 (d, J = 6.5 Hz, 1H), 4.53−4.49 (m, 1H, CH_2F), 4.41−4.37 (m, 1H, CH_2F), 3.97 (m, 2H, H-1), 3.34−3.30 (m, 1H), 3.12−3.09 (m, 1H, H-3), 2.81−2.51 (m, 6H), 1.82−1.79 (m, 1H), 1.64−1.57 (m, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 139.8, 139.7, 138.0, 136.1, 135.0, 130.8, 129.8, 129.3, 126.7, 126.5, 125.2, 124.9, 87.0 (d, J = 166 Hz, CH_2F), 53.1 (d, J = 18 Hz, C-3), 50.0, 48.0, 36.6, 30.5, 30.2, 27.9; HRMS (FAB+) *m/z* calcd for $C_{20}H_{24}N_2O_2FS$ (MH^+) 375.1543, obsd 375.1526. Anal. ($C_{20}H_{23}N_2O_2FS$) C, H, N.

(±)-3-Fluoromethyl-7-(*N*-1-adamantanaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (26·HCl). Compound **51** was synthesized as described in the general procedure (205 mg of crude). After reduction, recrystallization from EtOH/hexanes yielded **26**·HCl as white crystals (141 mg, 47%, from **35**): mp 175−183 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (br ex s, 2H, NH_2^+), 7.75−7.72 (m, 2H), 7.59 (s, 1H), 7.44 (d, J = 8.0 Hz, 1H), 5.00−4.68 (m, 2H, CH_2F), 3.92−3.87 (m, 1H, H-3), 3.44 (m, 2H, H-1), 3.16−3.01 (m, 2H, H-4), 1.93 (s, 3H), 1.71 (s, 6H), 1.51 (q, J = 12.1 Hz, 6H); ^{13}C NMR (500 MHz, DMSO-d_6) 143.8, 135.6, 129.97, 129.86, 125.5, 124.6, 82.5 (d, J = 539 Hz, CH_2F), 56.4, 54.2, 52.2 (d, J = 60 Hz, C-3), 44.2, 42.8, 35.9, 29.3, 26.5, 18.9; HRMS (FAB+) *m/z* calcd for $C_{20}H_{28}N_2O_2FS$ (MH^+) 379.1856, obsd 379.1841. Anal. ($C_{20}H_{27}N_2O_2FS \cdot HCl$) C, H, N.

(±)-3-Fluoromethyl-7-(*N*-morpholinosulfonyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (27·HCl). Compound **52** was synthesized as described in the general procedure (100 mg of crude). After reduction, recrystallization from EtOH/hexanes yielded **27**·HCl as white crystals (40 mg, 32%, from compound **35**): mp 230−233 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (br ex s, 2H, NH_2^+), 7.72 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 4.99−4.71 (m, 2H, CH_2F), 4.48 (s, 2H, H-1), 3.92−3.89 (m, 1H, H-3), 3.64 (s, 4H), 3.20−2.99 (m, 2H, H-4), 2.87 (s, 4H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 138.0, 133.6, 131.3, 130.9, 127.4, 127.0, 85.0 (d, J = 169 Hz, CH_2F), 66.1, 52.7 (d, J = 19 Hz, C-3), 46.7, 44.7, 27.1; HRMS (FAB+) *m/z* calcd for $C_{14}H_{20}N_2O_3FS$ (MH^+) 315.1179, obsd 315.1178. Anal. ($C_{14}H_{19}N_2O_3FS \cdot HCl \cdot 0.67H_2O$) C, H, N.

(±)-3-Fluoromethyl-7-(*N*-piperidinosulfonyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (28·HCl). The crude free amine was purified by flash chromatography, eluting with CH_2Cl_2/MeCN (1:1). Recrystallization of the HCl salt from EtOH/hexanes yielded **28**·HCl as white crystals (150 mg, 72%): mp 220−221 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (br ex s, 2H, NH_2^+), 7.71 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 4.94−4.64 (m, 2H, CH_2F), 4.55−4.45 (m, 2H, H-1), 3.94−3.90 (m, 1H, H-3), 3.18 (m, 1H, H-4), 3.05 (m, 1H, H-4), 2.89 (t, J = 5.2 Hz, 4H), 1.55 (s, 4H), 1.36 (s, 2H); ^{13}C NMR (500 MHz, DMSO-d_6) δ 137.1, 134.4, 130.5, 130.3, 126.6, 126.3, 82.5 (d, J = 166 Hz, CH_2F), 52.1 (d, J = 18 Hz, C-3), 47.0, 44.0, 26.5, 25.0, 23.3; HRMS (FAB+) *m/z* calcd for $C_{15}H_{22}N_2O_2FS$ (MH^+) 313.1386, obsd 313.1359. Anal. ($C_{15}H_{21}N_2O_2FS \cdot HCl$) C, H, N.

(±)-3-Fluoromethyl-7-(*N*-thiomorpholinosulfonyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (29·HCl). Recrystallization from EtOH/hexanes yielded **29**·HCl as white crystals (120 mg, 65%): mp 220−224 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (br ex s, 2H, NH_2^+), 7.73 (s, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 4.99−4.71 (m, 2H, CH_2F), 4.52−4.42 (m, 2H, H-1), 3.95−3.88 (m, 1H, H-3), 3.21−2.97 (m, 6H), 2.68 (t, J = 4.8 Hz, 4H); ^{13}C NMR (500 MHz, DMSO-d_6) δ 137.4, 134.9, 130.8, 130.4, 126.4, 126.1, 82.5 (d, J = 166 Hz, CH_2F), 52.1 (d, J = 18 Hz, C-3), 48.2, 44.1, 26.8, 26.6; HRMS (FAB+) *m/z* calcd for $C_{14}H_{20}N_2O_2FS_2$ (MH^+) 331.0950, obsd 331.0929. Anal. ($C_{14}H_{19}N_2O_2FS_2 \cdot HCl$) C, H, N.

(±)-3-Fluoromethyl-7-(*N*-4-fluorophenylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (30·HCl). The crude free amine was chromatographed, eluting with CH_2Cl_2/MeCN (1:1) to yield a white solid. Recrystallization of the HCl salt from EtOH/hexanes yielded **30**·HCl as white crystals (97 mg, 30%): mp 125−137 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.4 (ex s, 1H, NH), 9.64 (br ex s, 2H, NH_2^+), 7.69 (s, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.14−7.10 (m, 4H), 4.89−4.59 (m, 2H, CH_2F), 3.91−3.85 (m, 1H, H-3), 3.46−3.43 (m, 2H, H-1), 3.11 (m, 1H, H-4), 2.96 (m, 1H, H-4); ^{13}C NMR (500 MHz, DMSO-d_6) δ 159.0 (d, J = 242 Hz, F−Ph), 137.8, 136.6, 133.8, 129.9, 125.4, 125.2, 122.64, 122.58, 115.9 (d, J = 23 Hz, F−Ph), 82.6 (d, J = 166 Hz, CH_2F), 51.7 (d, J = 19 Hz, C-3), 43.7, 26.1; HRMS (FAB+) *m/z* calcd for $C_{16}H_{17}N_2O_2F_2S$ (MH^+) 339.0979, obsd 339.0975. Anal. ($C_{16}H_{16}N_2O_2F_2S \cdot HCl$) C, H, N.

(±)-3-Fluoromethyl-7-(*N*-4-hydroxyphenylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline (31). The crude solid was purified by flash chromatography, eluting with CH_2Cl_2/MeCN (1:1). This solid was recrystallized from EtOH/hexanes and yielded **31** as off-white crystals (38 mg, 32%): mp 115−116 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (br ex s, 1H, NH), 9.31 (ex s, 1H, OH), 7.40−7.37 (m, 2H), 7.24 (d, J = 7.9 Hz, 1H), 6.97 (d, J = 9.9 Hz, 2H), 6.60 (d, J = 8.7 Hz, 2H), 4.51−4.45 (m, 1H, CH_2F), 4.40−4.31 (m, 1H, CH_2F), 3.94−3.83 (m, 2H, H-1), 3.14−3.06 (m, 1H, H-3), 2.73 (m, 1H, H-4), 2.52 (m, 1H, H-4); ^{13}C NMR (500 MHz, DMSO-d_6) 155.1, 139.7, 137.4, 137.3, 130.1, 129.0, 124.6, 124.4, 124.1, 115.9, 86.4 (d, J = 166 Hz, CH_2F), 52.5 (d, J = 18 Hz, C-3), 47.4, 29.9; HRMS (FAB+)*m/z* calcd for $C_{16}H_{18}N_2O_3FS$ (MH^+) 337.1022, obsd 337.1020. Anal. ($C_{16}H_{17}N_2O_3FS$) C, H, N.

(±)-3-Fluoromethyl-7-(*N*-4-nitrophenylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline (32). The crude oil was chromatographed, eluting with CH_2Cl_2/MeCN (1:2) to yield a yellow solid. Recrystallization from EtOH/hexanes yielded **32** as yellow crystals (57 mg, 40%): mp 205−206 °C; ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.11 (d, J = 9.2 Hz, 2H), 7.69 (s, 1H), 7.67 (s, 1H), 7.33−7.27 (m, 3H), 4.65−4.35 (m, 2H, CH_2F), 4.13−4.03 (m, 2H, H-1), 3.27−3.19 (m, 1H, H-3), 2.86 (m, 1H, H-4), 2.72 (m, 1H, H-4); ^{13}C NMR (500 MHz, DMSO-d_6) δ 147.6, 140.8, 138.8, 138.1, 135.6, 130.0, 125.3, 124.4, 124.3, 118.0, 85.2 (d, J = 166 Hz, CH_2F), 52.1 (d, J = 18 Hz, C-3), 46.4, 28.8; HRMS (FAB+) *m/z* calcd for $C_{16}H_{17}N_3O_4FS$ (MH^+) 366.0924, obsd 366.0935. Anal. ($C_{16}H_{16}N_3O_4FS$) C, H, N.

(±)-3-Fluoromethyl-7-(*N*-3-chlorophenylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline (33). The crude residue was purified by flash chromatography, eluting with CH_2Cl_2/MeCN (3:1) to yield a light-yellow solid. Recrystallization from EtOAc/hexanes yielded **33** as light-yellow crystals (96 mg, 48%): mp 166−167 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53−7.51 (m, 2H), 7.29−7.23 (m, 2H), 7.12−7.04 (m, 3H), 4.52−4.43 (m, 1H, CH_2F), 4.39−4.35 (m, 1H, CH_2F), 3.98−3.85 (m, 2H, H-1), 3.45 (br ex s, 1H, NH), 3.12−3.06 (m, 1H, H-3), 2.76−2.72 (m, 1H, H-4), 2.56−2.49 (m, 1H, H-4); ^{13}C NMR (500 MHz, DMSO-d_6) 140.3, 140.2, 137.8, 137.1, 133.7, 131.3, 130.5, 124.6, 124.3, 123.6, 119.1, 118.1, 86.4 (d, J = 166 Hz, CH_2F), 52.5 (d, J = 18 Hz, C-3), 47.4, 29.9; HRMS (FAB+) *m/z* calcd for $C_{16}H_{17}N_2O_2ClFS$ (MH^+) 355.0683, obsd 355.0671. Anal. ($C_{16}H_{16}N_2O_2ClFS$) C, H, N.

(±)-3-Fluoromethyl-7-(*N*-3-nitrophenylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline (34). Compound **59** was synthesized as described in the general procedure (140 mg of crude). After reduction, the crude residue was purified by flash chromatography, eluting with CH_2Cl_2/MeCN (1:1) to yield a yellow solid. Recrystallization from acetone/hexanes yielded **34** as yellow crystals (76 mg, 42%): mp 215−220 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (s, 1H), 7.84−7.83 (m, 1H), 7.56−7.51 (m, 4H), 7.30 (d, J = 8.2, 1H), 4.53−4.44 (m, 1H, CH_2F), 4.41−4.32 (m, 1H, CH_2F), 4.00−3.87 (m, 2H, H-1), 3.45 (br ex s, 2H, NH), 3.15−3.07 (m, 1H, H-3), 2.76−2.72 (m, 1H, H-4), 2.57−2.51 (m, 1H, H-4); ^{13}C NMR (400 MHz, DMSO-d_6) 149.0, 140.9, 140.7, 138.1, 137.5, 131.6, 131.1, 126.0, 125.1, 124.8, 118.7, 113.9, 86.7 (d, J = 166 Hz, CH_2F), 52.9 (d, J = 18 Hz, C-3), 47.8, 30.3; HRMS (FAB+) *m/z* calcd for $C_{16}H_{17}N_3O_4FS$ (MH^+) 366.0924, obsd 366.0919. Anal. ($C_{16}H_{16}N_3O_4FS$) C, H, N.

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Supporting Information Available: Results from elemental analysis (C, H, N) for assayed compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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