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# Exploring the active site of phenylethanolamine *N*-methyltransferase: 3-alkyl-7-substituted-1,2,3,4-tetrahydroisoquinoline inhibitors☆

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**Abstract**—A series of 3-alkyl-7-substituted-1,2,3,4-tetrahydroisoquinolines was synthesized and these compounds were evaluated for their PNMT inhibitory potency and affinity for the $\alpha_2$-adrenoceptor. 7-Nitro-, 7-bromo-, 7-aminosulfonyl-, or 7-*N*-2,2,2-trifluoroethylaminosulfonyl-THIQs that possess a 3-alkyl substituent that is longer than a methyl group showed decreased PNMT inhibitory potency, except for 3-propyl-7-aminosulfonyl-THIQ, which displayed excellent PNMT inhibitory potency. The rank order for selectivity (PNMT vs the $\alpha_2$-adrenoceptor) is 3-alkyl-7-aminosulfonyl-THIQs ≅ 3-alkyl-7-*N*-2,2,2-trifluoroethylaminosulfonyl-THIQs > 3-alkyl-7-nitro-THIQs > 3-alkyl-7-bromo-THIQs.


## 1. Introduction

Central nervous system (CNS) epinephrine (Epi) has been implicated in the regulation of blood pressure,[2] respiration,[3,4] body temperature,[3,4] the $\alpha_1$-adrenoceptor,[5] and the $\alpha_2$-adrenoceptor,[6,7] as well as in some of the neurodegeneration seen in Alzheimer's disease.[8,9] In order to elucidate the role of CNS Epi (**2**) we have directed our studies toward the development of an inhibitor of Epi (**2**) biosynthesis. More specifically, we have targeted phenylethanolamine *N*-methyltransferase[10] (PNMT: EC 2.1.1.28), the enzyme that catalyzes the terminal step in Epi (**2**) biosynthesis in which an activated methyl group is transferred from *S*-adenosyl-L-methionine (**3**) to the primary amine of norepinephrine (**1**) to form Epi (**2**) and the cofactor product *S*-adenosyl-L-homocysteine (AdoHcy; **4**) (Fig. 1).

Problems associated with early PNMT inhibitors limit their usefulness as pharmacological tools in the CNS.

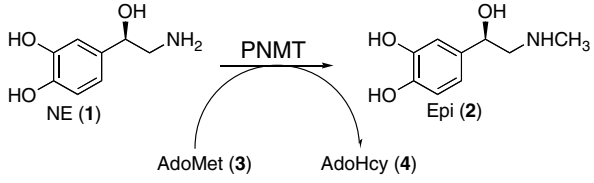


**Figure 1.** The terminal step in Epi (**2**) biosynthesis.

Some inhibitors are too polar to penetrate the blood–brain barrier (BBB), while others exhibit affinity toward other biologically relevant sites, most notably the $\alpha_2$-adrenoceptor. Studies using a BBB model on a small set of tetrahydroisoquinoline-type (THIQ-type) PNMT inhibitors indicate that a calculated log *P* (Clog *P*) value of 0.5 or greater appears to be required in order to observe significant BBB penetration.[11–13] We have undertaken a research program that is aimed at developing a PNMT inhibitor that is potent, selective (PNMT inhibitory potency vs the $\alpha_2$-adrenoceptor affinity), and capable of penetrating the BBB.

Many PNMT inhibitors contain a THIQ nucleus. We have shown that disubstitution on the THIQ nucleus at the 3- and 7-positions can result in dramatic increases

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☆See Ref. 1.
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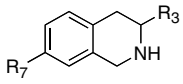
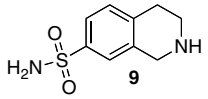
**Table 1.** In vitro activities of some (±)-THIQ-type PNMT inhibitors



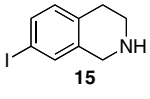

| Compd | $R_3$ | $R_7$ | PNMT[a] $K_i$ (μM) ± SEM | $\alpha_2$[b] $K_i$ (μM) ± SEM | Selectivity ($\alpha_2$/PNMT) | Clog $P$[c] |
|---|---|---|---|---|---|---|
| **5**[d] | $CH_3$ | H | 1.4 ± 0.1 | 0.76 ± 0.08 | 0.54 | 2.11 |
| **6**[e] | $CH_2F$ | H | 0.82 ± 0.04 | 3.8 ± 0.1 | 4.6 | 1.84 |
| **7**[f] | H | $NO_2$ | 0.12 ± 0.01 | 0.23 ± 0.13 | 1.9 | 1.34 |
| **8**[f] | H | Br | 0.056 ± 0.003 | 4.3 ± 0.3 | 77 | 2.46 |
| **9**[g] | H | $SO_2NH_2$ | 0.28 ± 0.02 | 100 ± 10 | 360 | −0.29 |
| **10**[h] | $CH_3$ | $NO_2$ | 0.072 ± 0.005 | 31 ± 1 | 430 | 1.86 |
| **11**[e] | $CH_2F$ | Br | 0.023 ± 0.003 | 6.4 ± 0.2 | 280 | 2.70 |
| **12**[e] | $CH_2F$ | $NO_2$ | 0.15 ± 0.01 | 76 ± 6 | 510 | 1.58 |
| **13**[e] | $CH_2F$ | $SO_2NH_2$ | 0.15 ± 0.01 | 680 ± 10 | 4500 | 0.00 |
| **14**[i] | $CH_2F$ | $SO_2NHCH_2CF_3$ | 0.13 ± 0.02 | 1200 ± 100 | 9200 | 1.41 |

[a] Reported in this table for human recombinant PNMT.
[b] In vitro activities reported for the inhibition of binding of [$^3$H]clonidine at the $\alpha_2$-adrenoceptor.
[c] Calculated log $P$.
[d] Ref. 15.
[e] Ref. 11.
[f] Ref. 16.
[g] Ref. 32.
[h] Ref. 14.
[i] Ref. 20.

in selectivity for PNMT versus the $\alpha_2$-adrenoceptor.[14] The selectivity of **10**,[14] for example, is much greater than that for mono-substituted **5**[15] or **7**[16] (Table 1). Quantitative structure–activity relationship[16] and comparative molecular field analysis[17] (CoMFA) studies on a series of PNMT inhibitors predicted that THIQs could bind in the active site in one of two different orientations, depending on the hydrophobic nature of the 7-substituent. Recently, we have published the crystal structure of human PNMT (hPNMT) cocrystallized with AdoHcy (**4**) and inhibitors containing either a lipophilic (7-iodo-THIQ **15**)[18] or hydrophilic (SK&F 29661 **9**)[19] 7-substituent. These crystal structures have shown that our proposed CoMFA-derived hypothesis regarding a change in the binding orientation of the inhibitors in the active site of PNMT was inaccurate, and that a conformational change in the enzyme active site occurs to accommodate the two classes (hydrophilic vs lipophilic aromatic substituents) of inhibitors.




**9**




**15**

It was of interest to synthesize and evaluate 3-alkyl-7-substituted-THIQs for two reasons. First, examination of the hPNMT active site region surrounding the 3-position of the cocrystallized ligands revealed that the channel between the AdoHcy (**4**) binding site and the inhibitor binding site contains lipophilic amino acids (Fig. 2). Docking studies indicated that 3-alkyl substituents on 7-substituted-THIQs that extend into this lipophilic channel may bind favorably, thus increasing PNMT inhibitory potency (Figs. 3–5). Second, our previously reported $\alpha_2$-adrenoceptor CoMFA model on a set of THIQs showed that there was steric bulk intolerance around the 3-position of THIQ,[17] and thus 3-substituents longer than a methyl group should be disfavored at the $\alpha_2$-adrenoceptor and a highly selective PNMT inhibitor should result. Initially, we wished to explore the 3-alkyl substituent on THIQs that possessed either a hydrophilic or hydrophobic 7-substituent. 7-Nitro- (**7**) and 7-bromo-THIQ (**8**) were chosen as templates because they display excellent PNMT inhibitory potency, but lack selectivity. We were also encouraged by a previous observation in which the addition of a 3-methyl substituent to **7** (**10**, 3-$CH_3$, 7-$NO_2$), led to

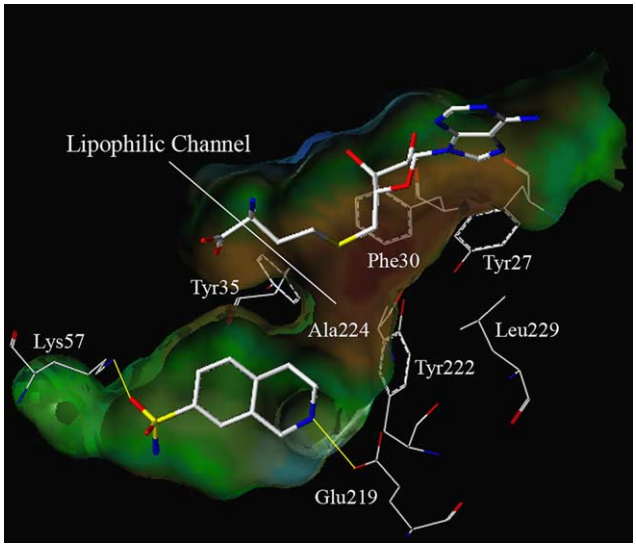



**Figure 2.** This is a Connolly (solvent accessible) surface of the active site exposing SK&F 29661 (**9**) and AdoHcy (**4**). A lipophilic potential is mapped on the Connolly surface of hPNMT whereby green is neutral, blue is hydrophilic and brown is lipophilic. Possible hydrogen bonds are indicated by yellow lines. Carbon is white, nitrogen is blue, oxygen is red and sulfur is yellow. Hydrogens are not shown for clarity.

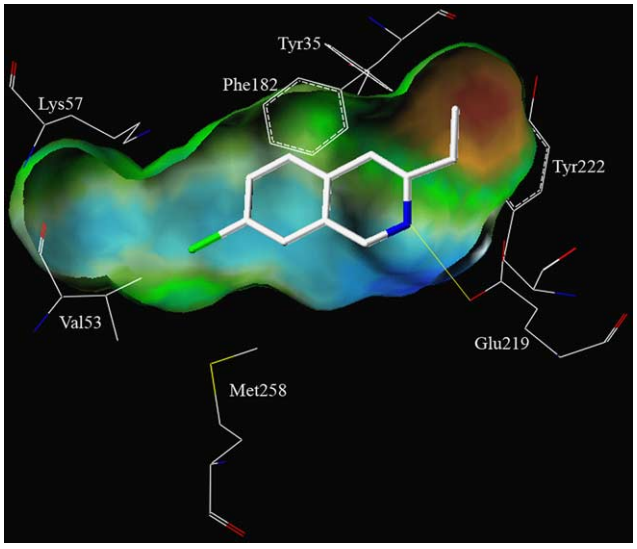



**Figure 3.** This figure shows **22b** docked into the active site of hPNMT (from the hPNMT X-ray structure cocrystallized with AdoHcy **4** and 7-iodo-THIQ **16**)[18] and the amino acid residues that could interact with **22b**. Although docking studies indicate that a 3-ethyl substituent should bind favorably, the biochemical data indicated otherwise (see text). A Connolly surface mapped with a lipophilic potential exposing **22b** is also shown. Yellow lines indicate possible hydrogen bonds. Carbon is white, nitrogen is blue and bromine is green. Hydrogens are not shown for clarity.

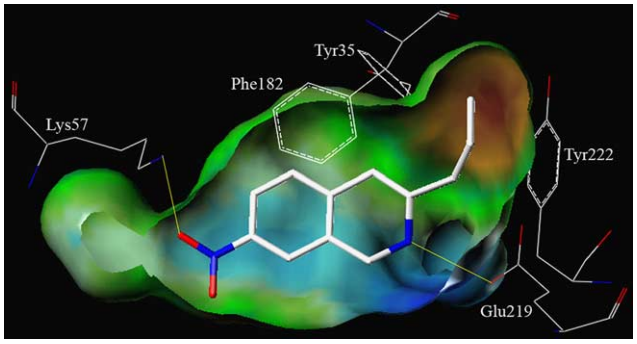



**Figure 4.** This figure shows **23c** docked into the active site of hPNMT (from the hPNMT X-ray structure cocrystallized with AdoHcy **4** and SK&F 29661 **9**)[19] and the amino acid residues that could interact with **23c**. Although docking studies indicate that a 3-ethyl substituent should bind favorably, the biochemical data indicated otherwise (see text). A Connolly surface mapped with a lipophilic potential exposing **23c** is also shown. Yellow lines indicate possible hydrogen bonds. Carbon is white, nitrogen is blue and oxygen is red. Hydrogens are not shown for clarity.

an inhibitor with better PNMT inhibitory potency and selectivity.

A previous study showed that the addition of a 7-aminosulfonyl substituent (**13**) to 3-fluoromethyl-THIQ (**6**) increased selectivity for PNMT versus the $\alpha_2$-adrenoceptor compared to a 7-nitro (**7**) or 7-bromo (**8**) substituent (e.g., **11** vs **13**; Table 1).[11] It was also observed that selectivity could be further increased with the addition of a 2,2,2-trifluoroethyl (**14**) substituent to the sulfonamide

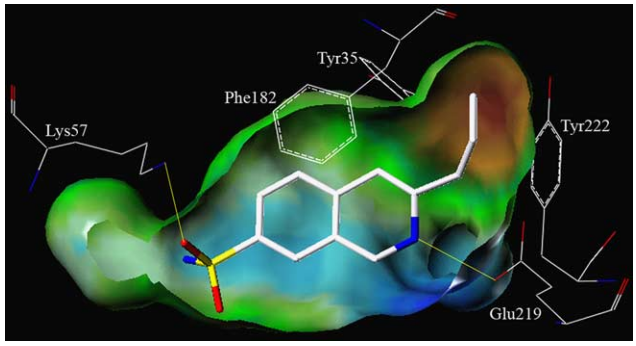


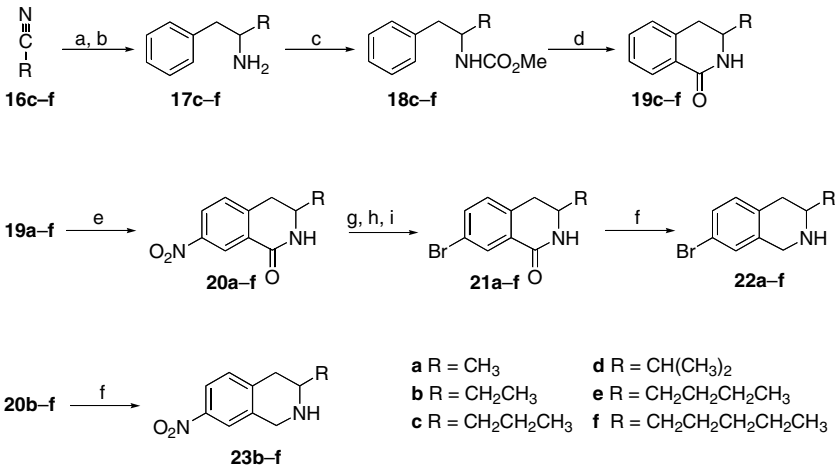

**Figure 5.** This figure shows **27c** docked into the active site of hPNMT (from the hPNMT X-ray structure cocrystallized with AdoHcy **4** and SK&F 29661 **9**)[19] and the amino acid residues that could interact with **27c** (see text). A Connolly surface mapped with a lipophilic potential exposing **27c** is also shown. Yellow lines indicate possible hydrogen bonds. Carbon is white, nitrogen is blue, oxygen is red and sulfur is yellow. Hydrogens are not shown for clarity.

nitrogen of **6**.[20] Therefore, it was also of interest to determine if a 7-aminosulfonyl or a 7-*N*-2,2,2-trifluoroethylaminosulfonyl moiety on 3-alkyl-THIQs also result in increased selectivity compared to their 7-nitro and 7-bromo analogues.

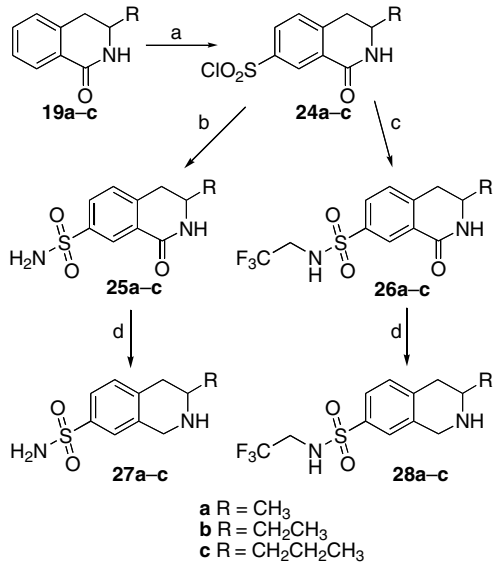
## 2. Chemistry

The synthesis of (±)-3-alkyl-7-bromo- (**22a–f**) and (±)-3-alkyl-7-nitro-THIQs (**23b–f**) is shown in Scheme 1. Compounds **19a**[21] and **19b**[15] were prepared as reported previously. The appropriate alkyl nitriles (**16c–f**) were treated with benzyl magnesium chloride and the imine salts were reduced in situ with lithium aluminum hydride to form the corresponding phenethylamines (**17c–f**).[22] Treatment of amines **17c–f** with $K_2CO_3$ and methylchloroformate yielded carbamates **18c–f**. Lactams **19c–f** were produced by the addition of carbamates **18c–f** to polyphosphoric acid. Compounds **19a–f** were nitrated in the presence of sulfuric acid and potassium nitrate to produce the 7-nitro-substituted-lactams (**20a–f**). Compounds **20b–f** were reduced with $BH_3$·THF to yield the 3-alkyl-7-nitro-THIQs (**23b–f**). The nitro moieties of **20a–f** were transformed to bromo functionalities by reduction of **20a–f** to the aniline followed by a Sandmeyer reaction to produce **21a–f**. Subsequent reduction of **21a–f** yielded the corresponding 3-alkyl-7-bromo-THIQs (**22a–f**).

The synthesis of (±)-3-alkyl-7-aminosulfonyl-THIQs (**27a–c**) and 3-alkyl-7-*N*-(2,2,2-trifluoroethylaminosulfonyl)-THIQs (**28a–c**) is shown in Scheme 2. Lactams **19a–c** were treated with chlorosulfonic acid to yield sulfonyl chlorides **24a–c**. Compounds **24a–c** were dissolved in acetonitrile and treated with ammonium hydroxide to afford sulfonamides **25a–c**. Compounds **26a–c** were produced by treatment of **24a–c** with 2,2,2-trifluoroethylamine and pyridine in a biphasic mixture of EtOAc and sodium carbonate. Reduction of **25a–c** and **26a–c** with $BH_3$·THF afforded THIQs **27a–c** and **28a–c**.




**Scheme 1.** Reagents: (a) BnMgCl, ether; (b) $LiAlH_4$, THF; (c) $K_2CO_3$, $ClCO_2Me$, THF; (d) PPA; (e) $H_2SO_4$, $KNO_3$; (f) 1 M $BH_3$·THF; (g) $PtO_2$, $H_2$; (h) HBr, $NaNO_2$; (i) CuBr, HBr.




**Scheme 2.** Reagents: (a) $ClSO_3H$; (b) ammonium hydroxide, MeCN; (c) 2,2,2-trifluoroethylamine, pyridine, EtOAc/satd $Na_2CO_3$; (d) 1 M $BH_3$·THF.

## 3. Biochemistry

In the current study, hPNMT with a C-teminal hexahistidine tag was expressed in *E. coli*.[20,23] The radiochemical assay conditions, previously reported for the bovine enzyme,[24] were modified to account for the high binding affinity of some inhibitors.[20,25] Inhibition constants were determined using four concentrations of phenylethanolamine as the variable substrate, and three concentrations of inhibitor.

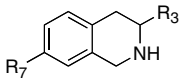
$\alpha_2$-Adrenergic receptor binding assays were performed using cortex obtained from male Sprague–Dawley rats.[26] [$^3$H]Clonidine was used as the radioligand to define the specific binding and phentolamine was used to define the nonspecific binding. Clonidine was used as the ligand to define α-adrenergic binding affinity to simplify the comparison with previous results.

## 4. Results and discussion

Compounds **10**, **22a–f**, and **23b–f** were prepared and evaluated, and their biochemical results are shown in Table 2. Three trends are noted from the biochemical data. First, similar trends in PNMT inhibitory potencies are observed for both 3-alkyl-7-nitro- and -7-bromo-THIQs (**10**, **22a–f**, and **23b–f**). Second, 3-alkyl substituents on 7-nitro- and 7-bromo-THIQs that are longer than a methyl substituent result in a significant decrease in PNMT inhibitory potency. Third, 3-alkyl-7-nitro-THIQs (**10**, **23b–f**) show less affinity for the $\alpha_2$-adrenoceptor as compared to their 7-bromo analogues (**22a–f**), and therefore are more selective. This is consistent with a previous QSAR study on 7-substituted-THIQs whereby THIQs with hydrophilic 7-substituents show less affinity for the $\alpha_2$-adrenoceptor than THIQs with hydrophobic 7-substituents.[16] The extension of the 3-methyl substituent in both 3-alkyl-7-nitro- and -7-bromo-THIQs did not lead to an increase in selectivity in part because moderate $\alpha_2$-adrenoceptor affinity was also observed.

Docking studies (AutoDock 3.0)[27] were performed to aid in the interpretation of the PNMT biochemical data of these inhibitors. The docking of inhibitors into the PNMT active site was performed on the *S*-enantiomer since a previous study on 3-methyl-7-nitro-THIQ (**10**) indicated that the *S*-enantiomer is preferred over the *R*-enantiomer in the hPNMT active site.[28] The docking studies on inhibitors that contain a 7-$NO_2$, 7-$SO_2NH_2$, and 7-$SO_2NHCH_2CF_3$ substituent used the crystal structure of PNMT cocrystallized with SK&F 29661 (**9**),[19] whereas studies on inhibitors that possess a 7-Br substituent used the crystal structure of PNMT cocrystallized with 7-iodo-THIQ (**15**).[18] Residues Lys57 and Met258 move within the PNMT active site depending on the hydrophobicity of the 7-substitutent.[18] The ami-

**Table 2.** In vitro activities of (±)-3-alkyl-7-nitro- and -7-bromo-THIQs




| Compd | $R_3$ | $R_7$ | PNMT $K_i$ (μM) ± SEM | $\alpha_2$[a] $K_i$ (μM) ± SEM | Selectivity ($\alpha_2$/PNMT) | Clog $P$[b] |
|---|---|---|---|---|---|---|
| **10**[c] | $CH_3$ | $NO_2$ | 0.072 ± 0.005 | 31 ± 1 | 430 | 1.86 |
| **23b** | $CH_2CH_3$ | $NO_2$ | 0.49 ± 0.03 | 28 ± 0.3 | 57 | 2.39 |
| **23c** | $(CH_2)_2CH_3$ | $NO_2$ | 0.53 ± 0.02 | 6.8 ± 0.2 | 13 | 2.91 |
| **23d** | $CH(CH_3)_2$ | $NO_2$ | 4.6 ± 0.3 | 36 ± 3 | 7.8 | 2.79 |
| **23e** | $(CH_2)_3CH_3$ | $NO_2$ | 6.6 ± 0.4 | 8.0 ± 0.7 | 1.2 | 3.44 |
| **23f** | $(CH_2)_4CH_3$ | $NO_2$ | 9.8 ± 0.3 | 4.3 ± 0.2 | 0.44 | 3.97 |
| **22a** | $CH_3$ | Br | 0.017 ± 0.005 | 1.1 ± 0.1 | 65 | 2.98 |
| **22b** | $CH_2CH_3$ | Br | 0.48 ± 0.02 | 1.2 ± 0.1 | 2.5 | 3.51 |
| **22c** | $(CH_2)_2CH_3$ | Br | 0.48 ± 0.02 | 1.1 ± 0.1 | 2.3 | 4.03 |
| **22d** | $CH(CH_3)_2$ | Br | 4.4 ± 0.3 | 3.9 ± 0.3 | 0.89 | 3.90 |
| **22e** | $(CH_2)_3CH_3$ | Br | 7.6 ± 0.2 | 0.93 ± 0.09 | 0.12 | 4.56 |
| **22f** | $(CH_2)_4CH_3$ | Br | 11 ± 1 | 2.2 ± 0.2 | 0.20 | 5.09 |

[a] In vitro activities reported for the inhibition of binding of [$^3$H]clonidine at the $\alpha_2$-adrenoceptor.
[b] Calculated log $P$.
[c] Ref. 14.

no acid residues surrounding the 3-position of the cocrystallized ligands SK&F 29661 (**9**) and 7-iodo-THIQ (**15**) remain in similar positions for both crystal structures.

Several observations are made from the docking studies of 3-alkyl-7-nitro- and -7-bromo-THIQs in the PNMT active site: (1) a 3-methyl, 3-ethyl, or 3-propyl substituent appears to make a hydrophobic contact with Tyr222 (Fig. 3 shows a 3-ethyl), (2) a 3-propyl substituent appears to make an additional hydrophobic contact with Tyr35 (Fig. 4), (3) THIQs that possess larger 3-alkyl substituents, such as an isopropyl, butyl, or pentyl substituent, do not fit within the PNMT active site (based on docking studies), which is consistent with their significant loss in PNMT inhibitory potency, (4) the 7-nitro moiety of 3-alkyl-THIQs appears to mimic the sulfonamide moiety of SK&F 29661 (**9**) and may form a hydrogen bond to Lys57 (Fig. 4), and (5) the 7-bromo substituent of 3-alkyl-THIQs appears to mimic the iodo group of 7-iodo-THIQ (**2**) and appears to make hydrophobic contacts with Met258 and Val53 (Fig. 3). We have previously reported studies on the binding of a 3-fluoromethyl substituent[20] and it appears to make a similar hydrophobic contact as the 3-methyl or 3-ethyl substituent. It is not clear from the modeling why the 3-ethyl-(**25b**, **24b**) or 3-propyl-(**25c**, **24c**)-7-nitro- and -7-bromo-THIQs are equipotent at PNMT nor why they are less potent than their methyl analogues.

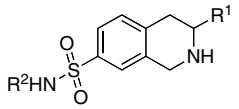
It was observed in previous studies that a 7-aminosulfonyl[11] or a 7-*N*-2,2,2-trifluoroethylaminosulfonyl[20] substituent on 3-fluoromethyl-THIQ (**6**) increased selectivity for PNMT versus the $\alpha_2$-adrenoceptor compared to a 7-nitro (**11**) or 7-bromo (**12**) substituent. Since a 3-methyl, 3-ethyl, or 3-propyl substituent on 7-nitro and 7-bromo-THIQs (Table 2) resulted in compounds that retained submicromolar PNMT inhibitory potency, it was of interest to explore the effect of a 7-sulfonamide substituent on these 3-alkyl-THIQs. The biochemical results for **27a**–**c** and **28a**–**c** are shown in Table 3.

Generally, a comparison of **27a**–**c** and **28a**–**c** with their 7-nitro (**23c**) and 7-bromo (**22c**) analogues showed a similar trend, whereby lengthening the 3-alkyl chain also results in a loss of PNMT inhibitory potency. 3-Methyl analogues **27a** (7-$SO_2NH_2$) and **28a** (7-$SO_2NHCH_2CF_3$) display excellent PNMT inhibitory potency and moderate selectivity. Surprisingly, **27c** (3-Pr, 7-$SO_2NH_2$) displayed a 5-fold improvement in PNMT inhibitory potency compared to its 7-nitro and 7-bromo analogues. Docking of **27c** into the PNMT active site reveals that this inhibitor could bind favorably, which is consistent with its PNMT $K_i$ (Fig. 5). While docking studies show that compounds **22c** (3-Pr, 7-Br) and **23c** (3-Pr, 7-$NO_2$, Fig. 4) should bind similarly to **27c**, both compounds show a loss in PNMT inhibitory potency.

An interesting and currently inexplicable trend in PNMT inhibitory potency is observed for **27a**–**c**. It is not readily apparent from modeling why a dramatic decrease in PNMT inhibitory potency is observed for **27b** (3-Et, 7-$SO_2NH_2$) nor why **27c** (3-Pr, 7-$SO_2NH_2$) is able to regain PNMT inhibitory potency. An X-ray crystal structure of PNMT cocrystallized with **27c** may be required to explain this anomalous result.

Both **28a** (3-$CH_3$, 7-$SO_2NHCH_2CF_3$) and **28b** (3-Et, 7-$SO_2NHCH_2CF_3$) are more potent at PNMT than their 7-unsubstituted-sulfonamide analogues (**27a**, **27b**). It was expected that the addition of a 2,2,2-trifluoroethyl substituent to **27c** (3-Pr, 7-$SO_2NH_2$) would also result in increased PNMT inhibitory potency; however, a dramatic decrease in PNMT inhibitory potency was observed for **28c** (3-Pr, 7-$SO_2NHCH_2CF_3$). Figure 6 shows the docking of **28a** and it appears that the 2,2,2-trifluoroethyl substituent binds in an auxiliary pocket, with possible hydrophobic contacts made between the sulfonamide substituent, and Val53 and Arg44. These interactions are similar to those previously reported for the binding of **14** (3-$CH_2F$, 7-$SO_2NHCH_2CF_3$).[20] Although it is not clear from modeling, the biochemical data suggest that the PNMT active

**Table 3.** In vitro activities of (±)-3-alkyl-7-aminosulfonyl-and -7-*N*-(2,2,2-trifluoroethylaminosulfonyl)-THIQs




| Compd | $R^1$ | $R^2$ | PNMT $K_i$ (μM) ± SEM | $\alpha_2$[a] $K_i$ (μM) ± SEM | Selectivity ($\alpha_2$/PNMT) | Clog *P*[b] |
|---|---|---|---|---|---|---|
| **27a** | $CH_3$ | H | 0.077 ± 0.003 | 61 ± 9 | 790 | 0.28 |
| **27b** | $CH_2CH_3$ | H | 1.8 ± 0.1 | 120 ± 20 | 67 | 0.81 |
| **27c** | $(CH_2)_2CH_3$ | H | 0.12 ± 0.01 | 37 ± 5 | 310 | 1.33 |
| **28a** | $CH_3$ | $CH_2CF_3$ | 0.034 ± 0.003 | 23 ± 4 | 680 | 1.69 |
| **28b** | $CH_2CH_3$ | $CH_2CF_3$ | 0.51 ± 0.02 | 20 ± 3 | 39 | 2.21 |
| **28c** | $(CH_2)_2CH_3$ | $CH_2CF_3$ | 0.92 ± 0.06 | 14 ± 2 | 15 | 2.74 |

[a] In vitro activities reported for the inhibition of binding of [$^3$H]clonidine at the $\alpha_2$-adrenoceptor.
[b] Calculated log *P*.

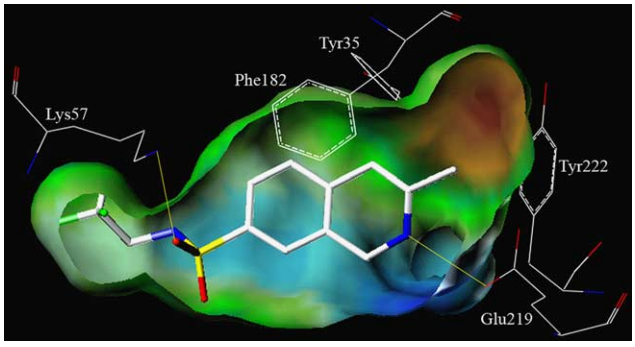



**Figure 6.** This figure shows **28a** docked into the active site of hPNMT (from the hPNMT X-ray structure cocrystallized with AdoHcy **4** and SK&F 29661 **9**)[19] and the amino acid residues that could interact with **28a**. A Connolly surface mapped with a lipophilic potential exposing **28a** is also shown. Yellow lines indicate possible hydrogen bonds. Carbon is white, nitrogen is blue, oxygen is red, fluorine is green and sulfur is yellow. Hydrogens are not shown for clarity.

site cannot simultaneously accommodate both the favorable binding of the 3-propyl substituent and the 7-*N*-2,2,2-trifuoroethylaminosulfonyl substituent of **28c**. As predicted, better selectivity is observed for **27a–c** and **28a–c** compared to their 7-nitro or 7-bromo analogues. However, an increase in selectivity was not observed for **28a–c** compared to **27a–c**, which is a different trend that we had previously observed for the addition of a 2,2,2-trifluroethyl substituent to the sulfonamide nitrogen of **13** (3-$CH_2F$, 7-$SO_2NH_2$).[20]

In summary, 3-methyl-THIQs that possess a 7-nitro (**10**), 7-bromo (**22a**), 7-aminosulfonyl (**27a**), or a 7-*N*-2,2,2-trifluoroethylaminosulfonyl (**28a**) substituent display excellent PNMT inhibitory potency. 7-Nitro and 7-bromo-THIQs that possess a 3-alkyl substituent that is longer than a methyl group (**23b–f**, **22b–f**) showed decreased PNMT inhibitory potency. The same general trend is also observed for 7-aminosulfonyl- and 7-(*N*-2,2,2-trifluoroethylaminosulfonyl)-THIQs (**27a**,**b**, **28a–c**), with the exception of 3-propyl-7-aminosulfonyl (**27c**), which displayed excellent PNMT inhibitory potency. As predicted, the rank order for selectivity (PNMT inhibitory potency vs the $\alpha_2$-adrenoceptor affinity) is 3-alkyl-7-aminosulfonyl-THIQs (**27a–c**) > 3-alkyl-7-nitro-THIQs (**10**, **23b–f**) > 3-alkyl-7-bromo-THIQs (**22a–f**). It was predicted that 3-alkyl-7-(*N*-2,2,2-trifluoroethylaminosulfonyl)-THIQs (**28a–c**) would display the highest selectivity, but it was observed that these inhibitors were no more selective than their 7-unsubstituted-sulfonamide analogues (**27a–c**). 3-Methyl-7-(*N*-2,2,2-trifluoroethylaminosulfonyl)-THIQ (**28a**) is one of the most potent PNMT inhibitors that displays good selectivity.

## 5. Experimental

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, New Jersey). Flash chromatography was performed using silica gel 60 (230–400 mesh) supplied by Universal Adsorbents, Atlanta, Georgia. 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).

### 5.1. Radiochemical assay of PNMT inhibitors

The assay used in this study has been modified from that described previously.[24] 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 $3 \times 10^5$ 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 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 1–3 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).[29] 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.

### 5.2. $\alpha_2$-Adrenoceptor radioligand binding assay

The radioligand receptor binding assay was performed according to the method of U'Prichard et al.[26] Male Sprague–Dawley rats were decapitated, and the cortexes were dissected out and homogenized in 20 vol (w/v) of ice-cold 50 mM Tris/HCl buffer (pH 7.7 at 25 °C). Homogenates were centrifuged thrice for 10 min at 50,000*g* with resuspension of the pellet in fresh buffer between spins. The final pellet was homogenized in 200 vol (w/v) of ice-cold 50 mM Tris/HCl buffer (pH 7.7 at 25 °C). Incubation tubes containing [$^3$H]clonidine (specific activity approximately 55 Ci/mmol, final concentration 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 $K_i = IC_{50}/(1 + [\text{Clonidine}]/K_D)$, as all Hill coefficients were approximately equal to 1.

### 5.3. Molecular modeling

Calculated log *P* (Clog *P*) values and Connolly surfaces were generated in SYBYL® on a Silicon Graphics Octane workstation.[30] Docking of the inhibitors into the PNMT active site was performed using AutoDock 3.0.[27] The default settings for AutoDock were used. The docking of inhibitors that contain a 7-$NO_2$, 7-$SO_2NH_2$, or 7-$SO_2NHCH_2CF_3$ substituent used the crystal structure of PNMT cocrystallized with SK&F 29661 (**9**), whereas inhibitors that contain a 7-Br substituent used the crystal structure of PNMT cocrystallized with 7-iodo-THIQ (**15**). The inhibitor to be docked was initially overlayed with either cocrystallized ligand **9** or **15**, and minimized with the Tripos force field.

### 5.4. General procedure for 18c–d (selected procedure for 18c)

Butyronitrile (**16c**, 6.29 mL, 72.3 mmol) was diluted with 20 mL of ether and added dropwise to a 1 M benzyl magnesium chloride solution in ether (86.8 mL, 86.8 mmol) under an argon atmosphere. The mixture was heated to reflux for 2.5 h, THF (30 mL) was added to the reaction flask, and the mixture was cooled to 0 °C. Lithium aluminum hydride (3.29 g, 86.7 mmol) was added cautiously and the solution was heated to reflux overnight. The reaction was quenched using the Fieser and Fieser method.[31] For *n* g of LAH, *n* mL of $H_2O$, *n* mL of 15% NaOH, and 3*n* mL of $H_2O$ were added consecutively to the solution and the mixture was stirred for 0.5 h. The solution was filtered through a Celite pad and concentrated in vacuo to yield the crude amine **17c**[22] (8.13 g, 49.9 mmol). The amine was dissolved in THF (50 mL) and $K_2CO_3$ was added. The solution was cooled to 0 °C and methylchloroformate (4.62 mL, 59.8 mmol) was added slowly by syringe. The reaction was stirred under argon for 5 h. Upon completion, the solution was filtered through a Celite pad and concentrated in vacuo to yield the crude carbamate.

**5.4.1. (±)-*N*-(Methoxycarbonyl)-1-phenyl-2-aminopentane (18c).** The crude carbamate (**18c**) was purified by Kugelrohr distillation (0.62 mmHg, 92 °C) to yield a clear oil that solidified on standing (4.63 g, 29%): mp 53–54 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.32–7.29 (m, 2H), 7.25–7.19 (m, 3H), 4.73 (br ex s, 1H, NH), 3.91 (m, 1H), 3.63 (s, 3H), 2.89–2.75 (m, 2H), 1.51–1.31 (m, 4H), 0.91 (t, $J$ = 6.7 Hz, 3H); HRMS (FAB+) *m*/*z* calcd for $C_{13}H_{20}NO_2$ ($MH^+$) 222.1494 obsd 222.1483.

**5.4.2. (±)-*N*-(Methoxycarbonyl)-3-methyl-1-phenyl-2-aminobutane (18d).** Isobutyronitrile (6.30 mL, 72.3 mmol) was used to form **17d**. The crude carbamate was purified by Kugelrohr distillation (0.62 mmHg, 92 °C) to yield **18d** as a white solid (5.78 g, 36%): mp 63–64 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.36–7.20 (m, 5H), 4.50 (br ex s, 1H, NH), 3.82 (m, 1H), 3.62 (s, 3H), 2.85–2.68 (m, 2H), 1.81–1.76 (m, 1H), 1.00–0.94 (m, 6H); HRMS (FAB+) *m*/*z* calcd for $C_{13}H_{20}NO_2$ ($MH^+$) 222.1494 obsd 222.1494.

**5.4.3. (±)-*N*-(Methoxycarbonyl)-1-phenyl-2-aminohexane (18e).** Valeronitrile (18.9 mL, 180.7 mmol) was used to form **17e**. The crude carbamate was purified by Kugelrohr distillation (0.3 mmHg, 124 °C) to yield **18e** as a white solid (15.4 g, 16%): mp 56–58 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.31–7.27 (m, 2H), 7.23–7.19 (m, 3H), 4.73 (br ex s, 1H, NH), 3.89 (m, 1H), 3.62 (s,

3H), 2.81–2.74 (m, 2H), 1.51–1.32 (m, 6H), 0.90 (t, $J = 6.7$ Hz, 3H); HRMS (FAB+) *m/z* calcd for $C_{14}H_{22}NO_2$ ($MH^+$) 236.1651 obsd 236.1626.

**5.4.4. (±)-*N*-(Methoxycarbonyl)-1-phenyl-2-aminoheptane (18f).** Hexanenitrile (2.48 mL, 20.6 mmol) was used to form **17f**. The crude carbamate was purified by Kugelrohr distillation (0.7 mmHg, 120 °C) to yield **18f** as a white solid (2.34 g, 46%): mp 61–62 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37–7.29 (m, 5H), 4.67 (br ex s, 1H, NH), 4.03 (m, 1H), 3.63 (s, 3H), 2.79 (m, 2H), 1.59–1.29 (m, 8H), 0.88 (t, $J = 6.7$ Hz, 3H); HRMS (FAB+) *m/z* calcd for $C_{15}H_{24}NO_2$ ($MH^+$) 250.1807 obsd 250.1798.

### 5.5. General procedure for 19c–f (selected procedure for 19c)

Polyphosporic acid (PPA, 20 g) was heated in a flask to 140 °C and carbamate **18c** (900 mg, 4.07 mmol) was added. After stirring for 15 min, the mixture was poured onto ice. The mixture was extracted with DCM ($3 \times 75$ mL). The organic layers were combined, washed with brine, and dried over $Na_2SO_4$. The solvent was removed in vacuo to yield the crude lactam.

**5.5.1. (±)-3-Propyl-3,4-dihydroisoquinolin-1-(2*H*)-one (19c).** The crude lactam was purified by recystalliztion in ether/hexanes to yield **19c** as white crystals (613 mg, 76%): mp 97–98 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.03 (d, $J = 7.2$ Hz, 1H), 7.80 (br ex s, 1H, NH), 7.38–7.35 (m, 1H), 7.29–7.26 (m, 1H), 7.13 (d, $J = 7.0$ Hz, 1H), 3.64 (m, 1H), 2.91 (m, 1H), 2.75–2.68 (m, 1H), 1.64–1.41 (m, 4H), 0.91 (t, $J = 6.8$ Hz, 3H); HRMS (FAB+) *m/z* calcd for $C_{12}H_{16}NO$ ($MH^+$) 190.1232 obsd 190.1233.

**5.5.2. (±)-3-(1-Methyl)ethyl-3,4-dihydroisoquinolin-1-(2*H*)-one (19d).** Carbamate **18d** (1.02 g, 4.59 mmol) was dissolved in PPA (20 g). The crude lactam was purified by flash chromatography (3:1 EtOAc/hexanes) to yield **19d** as a white solid (5.63 g, 63%): mp 124–126 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.07 (d, $J = 7.6$ Hz, 1H), 7.47–7.21 (m, 3H), 6.16 (s, 1H, NH), 3.52–3.47 (m, 1H), 2.91 (m, 2H), 1.90–1.83 (m, 1H), 1.05–1.02 (m, 6H); HRMS (FAB+) *m/z* calcd for $C_{12}H_{16}NO$ ($MH^+$) 190.1232 obsd 190.1241.

**5.5.3. (±)-3-Butyl-3,4-dihydroisoquinolin-1-(2*H*)-one (19e).** Carbamate **18e** (1.2 g, 5.11 mmol) was dissolved in PPA (22 g). The crude lactam was recrystallized in ether/hexane to yield **19e** as white crystals (606 mg, 61%): mp 92–93 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.02 (d, $J = 7.2$ Hz, 1H), 7.84 (br ex s, 1H, NH), 7.35–7.34 (m, 1H), 7.28–7.27 (m, 1H), 7.12 (d, $J = 7.0$ Hz, 1H), 3.61 (m, 1H), 2.93–2.89 (m, 1H), 2.74–2.68 (m, 1H), 1.63–1.53 (m, 2H), 1.37–1.31 (m, 4H), 0.87 (t, $J = 6.8$ Hz, 3H); HRMS (FAB+) *m/z* calcd for $C_{13}H_{18}NO$ ($MH^+$) 204.1388 obsd 204.1401.

**5.5.4. (±)-3-Pentyl-3,4-dihydroisoquinolin-1-(2*H*)-one (19f).** Carbamate **18f** (1.0 g, 4.02 mmol) was dissolved in PPA (22 g). The crude lactam was purified by flash chromatography (2:1 hexanes/EtOAc) to yield **19f** as a white solid (711 mg, 82%): mp 80–81 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.05 (s, 1H), 7.38–7.31 (m, 3H), 7.17 (s, 1H), 3.66 (m, 1H), 2.97–2.94 (m, 1H), 2.80–2.77 (m, 1H), 1.64–1.57 (m, 2H), 1.41–1.30 (m, 6H), 0.87 (s, 3H); HRMS (FAB+) *m/z* calcd for $C_{14}H_{20}NO$ ($MH^+$) 218.1545 obsd 218.1539.

### 5.6. General procedure for 20b–f (selected procedure for 20c)

Lactam **19c** (200 mg, 1.06 mmol) was dissolved in $H_2SO_4$ (5 mL) and cooled to 0 °C. Potassium nitrate (128 mg, 1.27 mmol) was added in small portions to the solution, which was stirred overnight. The reaction mixture was poured onto ice and extracted with EtOAc ($3 \times 75$ mL). The organic layers were combined, washed with saturated $NaHCO_3$, washed with brine, and dried over $Na_2SO_4$. The solvent was removed in vacuo to yield the crude nitro lactam.

**5.6.1. (±)-3-Ethyl-7-nitro-3,4-dihydroisoquinolin-1-(2*H*)-one (20b).** Lactam **19b** (200 mg, 1.79 mmol) and $KNO_3$ (138 mg, 1.93 mmol) were used. The crude nitro lactam was recrystallized in $CHCl_3$/hexanes to yield **20b** as yellow crystals (181 mg, 72%): mp 199–200 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.93 (s, 1H), 8.32 (d, $J = 8.4$ Hz, 1H), 7.43 (d, $J = 8.3$ Hz, 1H), 6.09 (br ex s, 1H), 3.72–3.69 (m, 1H), 3.17–3.12 (m, 1H), 2.98–2.91 (m, 1H), 1.75–1.68 (m, 2H), 1.07 (t, $J = 7.4$ Hz, 3H); HRMS (FAB+) *m/z* calcd for $C_{11}H_{13}N_2O_3$ ($MH^+$) 221.0926 obsd 221.0921.

**5.6.2. (±)-7-Nitro-3-propyl-3,4-dihydroisoquinolin-1-(2*H*)-one (20c).** The crude nitro lactam was recyrstallized in EtOH/hexanes to yield **20c** as light yellow crystals (212 mg, 85%): mp 205–206 °C; $^1$H NMR (400 MHz, MeOH-$d_4$) $\delta$ 8.74 (s, 1H), 8.37 (d, $J = 2.5$ Hz, 1H), 7.59 (d, $J = 8.4$ Hz, 1H), 3.76–3.75 (m, 1H), 3.28–3.23 (m, 1H), 2.99–2.93 (m, 1H), 1.65–1.45 (m, 4H), 0.99 (t, $J = 7.3$ Hz, 3H); HRMS (FAB+) *m/z* calcd for $C_{12}H_{15}N_2O_3$ ($MH^+$) 235.1083 obsd 235.1083.

**5.6.3. (±)-3-(1-Methyl)ethyl-7-nitro-3,4-dihydroisoquinolin-1-(2*H*)-one (20d).** Lactam **19d** (1.00 g, 5.29 mmol) and $KNO_3$ (641 mg, 6.35 mmol) were used. The crude nitro lactam was recrystallized in EtOH to yield **20d** as yellow crystals (960 mg, 77%): mp 200–201 °C; $^1$H NMR (400 MHz, MeOH-$d_4$) $\delta$ 8.74 (s, 1H), 8.36 (d, $J = 8.3$ Hz, 1H), 7.60 (d, $J = 8.4$ Hz, 1H), 3.57–3.52 (m, 1H), 3.21–3.04 (m, 2H), 1.90–1.85 (m, 1H), 1.03–1.00 (m, 6H); HRMS (FAB+) *m/z* calcd for $C_{14}H_{15}N_2O_3$ ($MH^+$) 235.1083 obsd 235.1077.

**5.6.4. (±)-3-Butyl-7-nitro-3,4-dihydroisoquinolin-1-(2*H*)-one (20e).** Lactam **19e** (200 mg, 0.985 mmol) and $KNO_3$ (119 mg, 1.18 mmol) were used. The crude nitro lactam was recrystallized in EtOH/hexanes to yield **20e** as yellow crystals (163 mg, 67%): mp 196–197 °C; $^1$H NMR (400 MHz, acetone-$d_6$) $\delta$ 8.71 (s, 1H), 8.35–8.33 (m, 1H), 7.66 (d, $J = 8.0$ Hz, 1H), 7.33 (br ex s, 1H, NH), 3.79 (m, 1H), 3.32–3.28 (m, 1H), 3.02–2.96 (m, 1H), 1.72–1.64 (m, 2H), 1.47–1.36 (m, 4H), 0.92 (t,

$J = 7.3$ Hz, 3H); HRMS (FAB+) *m/z* calcd for $C_{13}H_{17}N_2O_3$ ($MH^+$) 249.1239 obsd 249.1236.

**5.6.5. (±)-7-Nitro-3-pentyl-3,4-dihydroisoquinolin-1-(2*H*)-one (20f).** Lactam **19f** (350 mg, 1.14 mmol) and $KNO_3$ (195 mg, 1.37 mmol) were used. The crude nitro lactam was recrystallized in EtOH/hexanes to yield **20f** as yellow crystals (363 mg, 85%): mp 188–189 °C; $^1$H NMR (400 MHz, MeOH-$d_4$) $\delta$ 8.74 (s, 1H), 8.37 (s, 1H), 7.60 (s, 1H), 3.73 (m, 1H), 3.3–3.24 (m, 1H), 2.99–2.95 (m, 1H), 1.66–1.59 (m, 2H), 1.46–1.36 (m, 6H), 0.94 (s, 3H); HRMS (FAB+) *m/z* calcd for $C_{14}H_{19}N_2O_3$ ($MH^+$) 263.1396 obsd 263.1409.

### 5.7. General procedure for 23b–f (selected procedure for 23c)

Compound **20c** (207 mg, 0.885 mmol) was dissolved in THF (25 mL) and 1 M $BH_3$·THF (3.54 mL, 3.54 mmol) was added. The solution was heated to reflux overnight, was cooled to 0 °C, and MeOH (10 mL) was added dropwise. The solvent was removed in vacuo and to the remaining residue a solution of 6 N HCl (6 mL) and MeOH (25 mL) was added. The mixture was heated to reflux for 3 h and the MeOH was removed in vacuo. Water (25 mL) was added to the mixture, and the mixture was cooled in ice and made basic with KOH pellets. The basic solution was extracted with EtOAc ($4 \times 50$ mL) and the combined organic extracts were washed with brine and dried over $Na_2SO_4$. The solvent was removed in vacuo to yield a crude orange residue, which was purified by flash chromatography (2:1 MeCN/DCM). The free amine was dissolved in EtOH and dry $HCl_{(g)}$ was bubbled through the solution.

**5.7.1. (±)-3-Ethyl-7-nitro-1,2,3,4-tetrahydroisoquinoline hydrobromide (23b·HBr).** Compound **20b** (166 mg, 0.76 mmol) and 1 M $BH_3$·THF (3.02 mL, 3.02 mmol) were used. After workup, the solvent was removed in vacuo to yield a crude residue that was purified by flash chromatography (3:1 hexanes/acetone). The free amine was dissolved in EtOH and dry $HBr_{(g)}$ was bubbled through it. The solvent was removed and the solid was recrystallized from EtOH/hexanes to yield **23b**·HBr as white crystals (159 mg, 73%): mp 255–256 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.90 (br ex s, 2H, $NH_2^+$), 8.23 (s, 1H), 8.13 (d, $J = 8.5$ Hz, 1H), 7.53 (d, $J = 8.6$ Hz, 1H), 4.53–4.40 (m, 2H), 3.32 (m, 1H), 2.90–2.83 (m, 1H), 1.81–1.77 (m, 1H), 1.67–1.60 (m, 1H), 1.04–1.00 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (500 MHz, DMSO-$d_6$) $\delta$ 146.0, 140.1, 130.9, 130.4, 122.2, 121.8, 53.4, 43.9, 30.5, 25.5, 9.3; HRMS (FAB+) *m/z* calcd for $C_{11}H_{15}N_2O_2$ ($MH^+$) 207.1134 obsd 207.1137; Anal. Calcd for $C_{11}H_{14}N_2O_2$·HBr: C, 46.01; H, 5.27; N, 9.76. Found: C, 45.87; H, 5.28; N, 9.54.

**5.7.2. (±)-7-Nitro-3-propyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (23c·HCl).** The hydrochloride salt was recrystallized from EtOH/hexanes to yield **23c**·HCl as white crystals (173 mg, 77%): mp 265–295 °C (dec); IR (film) 2960, 2919, 2852, 1670, 1614, 1521, 1455, 1342; $^1$H NMR (400 MHz, DMSO-$d_6$) 9.75 (br ex s, 2H, $NH_2^+$), 8.24 (s, 1H), 8.12 (d, $J = 8.5$ Hz, 1H), 7.51 (d, $J = 8.5$ Hz, 1H), 4.49–4.37 (m, 2H), 3.47 (m, 1H), 3.28–3.23 (m, 1H), 2.98–2.91 (m, 1H), 1.85–1.78 (m, 1H), 1.67–1.58 (m, 1H), 1.52–1.42 (m, 2H), 0.93 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (400 MHz, DMSO-$d_6$) $\delta$ 146.9, 141.1, 131.7, 131.1, 123.0, 122.8, 52.6, 44.3, 35.0, 31.6, 18.6, 14.6; HRMS (FAB+) *m/z* calcd for $C_{12}H_{17}N_2O_2$ ($MH^+$) 221.1290 obsd 221.1264; Anal. Calcd for $C_{12}H_{16}N_2O_2$·HCl·0.25$H_2O$: C, 55.17; H, 6.77; N, 10.73. Found: C, 55.34; H, 6.69; N, 10.69.

**5.7.3. (±)-3-(1-Methyl)ethyl-7-nitro-1,2,3,4-tetrahydroisoquinoline hydrochloride (23d·HCl).** Compound **20d** (251 mg, 1.07 mmol) and 1 M $BH_3$·THF (4.29 mL, 4.29 mmol) were used. The crude residue was purified by flash chromatography (5:1 hexanes/acetone). The hydrochloride salt was recrystallized from EtOH/hexanes to yield **23d**·HCl as white crystals (200 mg, 73%): mp > 300 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.64 (br ex s, 2H, $NH_2^+$), 8.24 (s, 1H), 8.13–8.11 (m, 1H), 7.52 (d, $J = 8.5$ Hz, 1H), 4.49–4.38 (m, 2H), 3.37 (m, 1H), 3.17–3.12 (m, 1H), 3.02–2.95 (m, 1H), 2.16–2.11 (m, 1H), 1.07–1.03 (m, 6H); $^{13}$C NMR (400 MHz, DMSO-$d_6$) $\delta$ 146.9, 141.4, 131.7, 131.1, 123.0, 122.7, 58.3, 45.4, 30.5, 28.2, 19.5, 17.8; HRMS (FAB+) *m/z* calcd for $C_{12}H_{17}N_2O_2$ ($MH^+$) 221.1290 obsd 221.1288; Anal. Calcd for $C_{12}H_{16}N_2O_2$·HCl: C, 56.14; H, 6.67; N, 10.91. Found: C, 56.17; H, 6.49; N, 10.67.

**5.7.4. (±)-3-Butyl-7-nitro-1,2,3,4-tetrahydroisoquinoline hydrochloride (23e·HCl).** Compound **20e** (155 mg, 0.625 mmol) and 1 M $BH_3$·THF (2.50 mL, 2.50 mmol) were used. The crude orange residue was purified by flash chromatography (2:1 MeCN/DCM). The hydrochloride salt was recrystallized from EtOH/hexanes to yield **23e**·HCl as white crystals (100 mg, 59%): mp 290–293 °C (dec); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.65 (br ex s, 2H, $NH_2^+$), 8.23 (s, 1H), 8.12 (d, $J = 7.9$ Hz, 1H), 7.51 (d, $J = 8.2$ Hz, 1H), 4.49–4.37 (m, 2H), 3.47 (m, 1H), 3.28–3.23 (m, 1H), 2.97–2.90 (m, 1H), 1.84 (m, 1H), 1.62 (m, 1H), 1.43–1.34 (m, 4H), 0.92 (t, $J = 6.9$ Hz, 3H); $^{13}$C NMR (400 MHz, DMSO-$d_6$) $\delta$ 146.9, 141.1, 131.7, 131.2, 122.9, 122.7, 52.9, 44.4, 32.6, 31.7, 27.3, 22.7, 14.6; HRMS (FAB+) *m/z* calcd for $C_{13}H_{19}N_2O_2$ ($MH^+$) 235.1447 obsd 235.1444; Anal. Calcd for $C_{13}H_{18}N_2O_2$·HCl: C, 57.67; H, 7.07; N, 10.35. Found: C, 57.46; H, 7.06; N, 10.16.

**5.7.5. (±)-7-Nitro-3-pentyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (23f·HCl).** Compound **20f** (320 mg, 1.22 mmol) and 1 M $BH_3$·THF (4.89 mL, 4.89 mmol) were used. The crude orange residue was purified by flash chromatography (3:1 EtOAc/hexanes). The hydrochloride salt was recrystallized from EtOH/hexanes to yield **23f**·HCl as white crystals (204 mg, 67%): mp 271–275 °C (dec); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.68 (br ex s, 2H, $NH_2^+$), 8.23 (s, 1H), 8.12 (d, $J = 7.9$ Hz, 1H), 7.51 (d, $J = 8.2$ Hz, 1H), 4.49–4.37 (m, 2H), 3.48 (m, 1H), 3.29–3.24 (m, 1H), 2.97–2.90 (m, 1H), 1.85 (m, 1H), 1.63 (m, 1H), 1.44 (m, 2H), 1.31 (s, 4H), 0.89 (m, 3H); $^{13}$C NMR (400 MHz, DMSO-$d_6$) $\delta$ 146.9, 141.0, 131.7, 131.2, 123.0, 122.7, 52.9, 44.4, 32.9, 31.8, 31.6, 24.9, 22.8, 14.7; HRMS (FAB+) *m/z* calcd for

$C_{14}H_{21}N_2O_2$ ($MH^+$) 249.1603 obsd 249.1607; Anal. Calcd for $C_{14}H_{20}N_2O_2$·HCl: C, 59.05; H, 7.43; N, 9.84. Found: C, 59.19; H, 7.43; N, 9.76.

### 5.8. General procedure for 21a and 21c–f (selected procedure for 21c)

Platinum oxide (186 mg, 0.794 mmol) was placed in a Parr shaker bottle. Methanol (30 mL) and concentrated HCl (3 mL) were cautiously added. Compound **20c** (54 mg, 0.238 mmol) was added and the mixture was hydrogenated at 50 psi for 5 h. The reaction mixture was filtered over a Celite pad and washed with MeOH. The solution was concentrated in vacuo. The crude aniline hydrochloride salt (191 mg, 0.793 mmol) was dissolved in HBr (5 mL) and water (12 mL) and the solution was cooled in an ice-water bath. Sodium nitrite (60 mg, 0.870 mmol) in water (10 mL) was added dropwise. Excess $HNO_2$ was destroyed by the addition of a small portion of urea. Copper(I) bromide (126 mg, 0.875 mmol), HBr (10 mL), and water (20 mL) were combined, added dropwise to the diazonium salt solution, and the reaction mixture was stirred overnight at room temperature. Ethyl acetate (30 mL) was added and stirred for 20 min. The mixture was filtered over a Celite pad, which was washed with EtOAc. The organic phase was separated and the aqueous phase was extracted with EtOAc ($3 \times 50$ mL). The combined organic layers were washed with saturated sodium bicarbonate and brine, and dried over sodium sulfate. The solvent was removed in vacuo to yield the crude lactam.

**5.8.1. (±)-7-Bromo-3-methyl-3,4-dihydroisoquinolin-1-(2*H*)-one (21a).** Lactam **20a** (200 mg, 0.962 mmol), $PtO_2$ (65 mg, 0.026 mmol), $NaNO_2$ (73 mg, 1.06 mmol), and CuBr (415 mg, 2.88 mmol) were used. Compound **21a** was purified by flash chromatography eluting with 3:1 hexanes/EtOAc (115 mg, 50%): mp 135–136 °C; $^1$H NMR (400 MHz, MeOH-$d_4$) $\delta$ 8.05 (s, 1H), 7.66–7.64 (m, 1H), 7.24 (d, $J = 8.1$ Hz, 1H), 3.86–3.77 (m, 1H), 3.03–2.99 (m, 1H), 2.77–2.70 (m, 1H), 1.31 (m, 3H); HRMS (FAB+) *m*/*z* calcd for $C_{10}H_{11}BrNO$ ($MH^+$) 240.0024 obsd 240.0019.

**5.8.2. (±)-7-Bromo-3-propyl-3,4-dihydroisoquinolin-1-(2*H*)-one (21c).** Compound **21c** was purified by flash chromatography eluting with 3:1 hexanes/EtOAc (160 mg, 75%): mp 132–133 °C; $^1$H NMR (400 MHz, MeOH-$d_4$) $\delta$ 8.04 (s, 1H), 7.66–7.64 (m, 1H), 7.25 (d, $J = 8.1$ Hz, 1H), 3.69–3.64 (m, 1H), 3.10–3.05 (m, 1H), 2.81–2.75 (m, 1H), 1.62–1.43 (m, 4H), 0.97 (t, $J = 6.6$ Hz, 3H); HRMS (FAB+) *m*/*z* calcd for $C_{12}H_{15}BrNO$ ($MH^+$) 268.0337 obsd 268.0355.

**5.8.3. (±)-7-Bromo-3-(1-methyl)ethyl-3,4-dihydroisoquinolin-1-(2*H*)-one (21d).** Lactam **20d** (500 mg, 2.14 mmol), $PtO_2$ (146 mg, 0.643 mmol), $NaNO_2$ (162 mg, 2.35 mmol), and CuBr (923 mg, 6.41 mmol) were used. Compound **21d** was purified by flash chromatography eluting with 3:1 hexanes/EtOAc (300 mg, 52%): mp 119–120 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.28 (s, 1H), 7.68 (d, $J = 8.0$ Hz, 1H), 7.11 (d, $J = 8.0$ Hz, 1H), 5.90 (ex s, 1H, NH), 3.51–3.46 (br m, 1H), 2.86 (m, 2H), 1.82 (m, 1H), 0.95 (m, 6H); HRMS (FAB+) *m*/*z* calcd for $C_{12}H_{15}BrNO$ ($MH^+$) 268.0337 obsd 268.0329.

**5.8.4. (±)-7-Bromo-3-butyl-3,4-dihydroisoquinolin-1-(2*H*)-one (21e).** Lactam **20e** (500 mg, 2.02 mmol), $PtO_2$ (137 mg, 0.604 mmol), $NaNO_2$ (153 mg, 2.22 mmol), and CuBr (871 mg, 6.05 mmolmol) were used. Compound **21e** was purified by flash chromatography eluting with 3:1 hexanes/EtOAc → 2:1 hexanes/EtOAc (423 mg, 74%): mp 135–136 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.15 (s, 1H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.40 (ex s, 1H, NH), 6.86 (d, $J = 8.0$ Hz, 1H), 3.91–3.88 (br m, 1H), 2.93 (m, 1H), 2.71 (m, 1H), 1.64–1.54 (m, 2H), 1.36 (m, 4H), 0.90 (t, $J = 6.6$ Hz, 3H); HRMS (FAB+) *m*/*z* calcd for $C_{13}H_{17}BrNO$ ($MH^+$) 282.0494 obsd 282.0487.

**5.8.5. (±)-7-Bromo-3-pentyl-3,4-dihydroisoquinolin-1-(2*H*)-one (21f).** Lactam **20f** (500 mg, 1.91 mmol), $PtO_2$ (130 mg, 0.573 mmol), $NaNO_2$ (145 mg, 2.16 mmol), and CuBr (824 mg, 5.72 mmol) were used. Compound **21f** was purified by flash chromatography eluting with 3:1 hexanes/EtOAc (124 mg, 22%): mp 134–135 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.20 (s, 1H), 7.56 (d, $J = 8.0$ Hz, 1H), 7.10 (d, $J = 8.0$ Hz, 1H), 6.54 (ex s, 1H, NH), 3.69 (br m, 1H), 2.98–2.93 (m, 1H), 2.79–2.72 (m, 1H), 1.65–1.55 (m, 2H), 1.43–1.34 (m, 6H), 0.92 (t, $J = 6.4$ Hz, 3H); HRMS (FAB+) *m*/*z* calcd for $C_{13}H_{19}BrNO$ ($MH^+$) 296.0632 obsd 296.0650.

**5.8.6. (±)-7-Bromo-3-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (22a·HCl).** Compound **21a** (100 mg, 0.416 mmol) was reduced with 1 M $BH_3$·THF (1.67 mL, 1.67 mmol) as described in the general procedure for **23b–f**. The free amine was purified by flash chromatography eluting with 5:95 MeOH/EtOAc → 20:80 MeOH/EtOAc. The hydrochloride salt was recrystallized in EtOH/hexanes to yield **22a**·HCl as white crystals (62 mg, 57%): mp dec 273–290 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.84 (ex br s, 2H, $NH_2^+$), 7.50 (s, 1H), 7.45 (d, $J = 8.2$ Hz, 1H), 7.17 (d, $J = 8.3$ Hz, 1H), 4.28 (m, 2H), 3.54–3.47 (m, 1H), 3.04–2.98 (m, 1H), 2.81–2.74 (m, 1H), 1.37 (m, 3H); $^{13}$C NMR (400 MHz, DMSO-$d_6$) $\delta$ 132.2, 132.0, 131.7, 131.1, 130.1, 120.1, 49.3, 43.8, 32.9, 18.9; HRMS (FAB+) *m*/*z* calcd for $C_{10}H_{13}BrN$ ($MH^+$) 226.0231 obsd 226.0225; Anal. Calcd for $C_{10}H_{12}NBr$·HCl: C, 45.74; H, 4.99; N, 5.33. Found: C, 45.72; H, 4.67; N, 5.20.

**5.8.7. (±)-7-Bromo-3-ethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (22b·HCl).** Compound **20b** (75 mg, 0.261 mmol), Pd/C (55 mg, 0.103 mmol), $NaNO_2$ (20 mg, 0.288 mmol), and CuBr (114 mg, 0.792 mmol) were used to synthesize **21b** as described in the general procedure for **21a** and **21c–f**. Crude **21b** was carried forward to the reduction reaction with 1 M $BH_3$·THF as described in the general procedure for **23b–f**. The free amine was purified by flash chromatography eluting with EtOAc. The hydrochloride salt was recrystallized in MeOH/ether to yield **22b**·HCl as white crystals (23 mg, 33%): mp > 300 °C; $^1$H NMR (400 MHz, MeOH-$d_4$) $\delta$ 7.56–7.48 (m, 2H), 7.21 (d, $J = 8.9$ Hz, 1H), 4.40 (m, 2H), 3.46–3.44 (m, 1H), 3.22–3.17 (m, 1H), 2.88–2.81 (m, 1H), 1.90–1.76 (m, 2H), 1.16–1.12

(m, 3H); $^{13}$C NMR (500 MHz, MeOH-$d_4$) $\delta$ 132.4, 132.3, 132.2, 131.8, 130.6, 121.7, 56.5, 45.8, 31.6, 27.4, 9.8; HRMS (FAB+) *m/z* calcd for $C_{11}H_{15}BrN$ ($MH^+$) 240.0388 obsd 240.0398; Anal. Calcd for $C_{11}H_{14}NBr{\cdot}HCl$: C, 47.76; H, 5.47; N, 5.06. Found: C, 47.40; H, 5.44; N, 4.92.

**5.8.8. (±)-7-Bromo-3-propy1-1,2,3,4-tetrahydroisoquinoline hydrochloride (22c·HCl).** Compound **21c** (634 mg, 2.36 mmol) was reduced with 1 M $BH_3$·THF (7.09 mL, 7.09 mmol) as described in the general procedure for **23b–f**. The free amine was purified by flash chromatography eluting with 2:1 EtOAc/hexanes. The hydrochloride salt was recrystallized in EtOH/hexanes to yield **22c**·HCl as white crystals (229 mg, 35%): mp 224–225 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.81 (ex m, 2H, $NH_2^+$), 7.51 (s, 1H), 7.44 (d, $J$ = 8.3 Hz, 1H), 7.17 (d, $J$ = 8.3 Hz, 1H), 4.26 (s, 2H), 3.46–3.38 (m, 3H), 3.05 (m, 1H), 2.79 (m, 1H), 1.86–1.79 (m, 1H), 1.65–1.56 (m, 1H), 0.93 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (400 MHz, DMSO-$d_6$) $\delta$ 132.31, 132.26, 131.8, 131.3, 130.0, 120.1, 52.9, 44.0, 35.0, 30.9, 18.7, 14.6; HRMS (FAB+) *m/z* calcd for $C_{12}H_{17}BrN$ ($MH^+$) 254.0544 obsd 254.0538; Anal. Calcd for $C_{12}H_{16}NBr{\cdot}HCl$: C, 49.59; H, 5.90; N, 4.82. Found: C, 49.56; H, 5.77; N, 4.66.

**5.8.9. (±)-7-Bromo-3-(1-methyl)ethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (22d·HCl).** Compound **21d** (290 mg, 1.08 mmol) was reduced with 1 M $BH_3$·THF (4.33 mL, 4.33 mmol) as described in the general procedure for **23b–f**. The free amine was purified by flash chromatography eluting with 2:1 EtOAc/hexanes. The hydrochloride salt was recrystallized in EtOH/hexanes to yield **22d**·HCl as white crystals (219 mg, 76%): mp dec 305–308 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.53 (ex br s, 2H, $NH_2^+$), 7.54 (s, 1H), 7.45 (d, $J$ = 8.3 Hz, 1H) 7.20 (d, $J$ = 8.3 Hz, 1H), 4.30 (m, 2H), 3.33 (m, 1H), 2.95 (m, 1H), 2.85 (m, 1H), 2.13 (m, 1H), 1.03 (m, 6H); $^{13}$C NMR (500 MHz, DMSO-$d_6$) $\delta$ 132.1, 131.9, 131.4, 130.5, 129.5, 119.6, 58.2, 44.7, 30.0, 27.0, 19.1, 17.3; HRMS (FAB+) *m/z* calcd for $C_{12}H_{17}BrN$ ($MH^+$) 254.0544 obsd 254.0539; Anal. Calcd for $C_{12}H_{16}NBr{\cdot}HCl$: C, 49.59; H, 5.90; N, 4.82. Found: C, 49.61; H, 5.80; N, 4.68.

**5.8.10. (±)-7-Bromo-3-butyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (22e·HCl).** Compound **21e** (415 mg, 1.47 mmol) was reduced with 1 M $BH_3$·THF (5.89 mL, 5.89 mmol) as described in the general procedure for **23b–f**. The free amine was purified by flash chromatography eluting with 2:1 EtOAc/hexanes. The hydrochloride salt was recrystallized in EtOH/hexanes to yield **22e**·HCl as white crystals (331 mg, 74%): mp 229–230 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.77 (ex m, 2H, $NH_2^+$), 7.51 (s, 1H), 7.44 (d, $J$ = 8.3 Hz, 1H), 7.17 (d, $J$ = 8.3 Hz, 1H), 4.27 (s, 2H), 3.39 (m, 1H), 3.05 (m, 1H), 2.79 (m, 1H), 1.86 (m, 1H), 1.61 (m, 1H), 1.41–1.32 (m, 4H) 0.92 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (500 MHz, DMSO-$d_6$) $\delta$ 131.8, 131.8, 131.3, 130.5, 129.5, 119.6, 52.6, 43.5, 32.1, 30.5, 26.9, 22.3, 14.1; HRMS (FAB+) *m/z* calcd for $C_{13}H_{19}BrN$ ($MH^+$) 268.0701 obsd 268.0695; Anal. Calcd for $C_{13}H_{18}NBr{\cdot}HCl$: C, 51.25; H, 6.29; N, 4.60. Found: C, 51.27; H, 6.33; N, 4.45.

**5.8.11. (±)-7-Bromo-3-pentyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (22f·HCl).** Compound **21f** (120 mg, 0.405 mmol) was reduced with 1 M $BH_3$·THF (1.62 mL, 1.62 mmol) as described in the general procedure for **23b–f**. The free amine was purified by flash chromatography eluting with 3:2 EtOAc/hexanes. The hydrochloride salt was recrystallized in EtOH/hexanes to yield **22f**·HCl as white crystals (60 mg, 47%): mp 219–220 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.59 (ex br s, 2H, $NH_2^+$), 7.51 (s, 1H), 7.45 (d, $J$ = 8.3 Hz, 1H), 7.19 (d, $J$ = 8.3 Hz, 1H), 4.29 (s, 2H), 3.42 (m, 1H), 3.07 (m, 1H), 2.78 (m, 1H), 1.82 (m, 1H), 1.61 (m, 1H), 1.43–1.31 (m, 6H) 0.90 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (500 MHz, DMSO-$d_6$) $\delta$ 131.7, 131.7, 131.3, 130.6, 129.5, 119.6, 52.7, 43.6, 32.4, 31.3, 30.5, 24.4, 22.3, 14.2; HRMS (FAB+) *m/z* calcd for $C_{14}H_{21}BrN$ ($MH^+$) 282.0857 obsd 282.0864; Anal. Calcd for $C_{14}H_{20}NBr{\cdot}HCl$: C, 52.76; H, 6.64; N, 4.40. Found: C, 52.47; H, 6.65; N, 4.16.

### 5.9. General procedure for 24a–c (selected procedure for 24c)

Lactam **19c** (500 mg, 2.64 mmol) was treated with $ClSO_3H$ (5 mL) and stirred at 50 °C for 8 h. The mixture was pipetted cautiously onto ice (50 mL). The aqueous mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated sodium bicarbonate and brine, and dried over sodium sulfate. The solvent was removed in vacuo to yield sulfonyl chloride **24c**, which required no further purification.

**5.9.1. (±)-3-Methyl-7-chlorosulfonyl-3,4-dihydroisoquinolin-1-(2*H*)-one (24a).** Lactam **19a** (696 mg, 4.32 mmol) was treated with chlorosulfonic acid (7 mL) to yield **24a** (313 mg, 28%): mp 109–110 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.76 (s, 1H), 8.12 (m, 1H), 7.50 (m, 1H), 6.42 (ex s, 1H), 3.95 (m, 1H), 3.11–2.95 (m, 2H), 1.42 (m, 3H);HRMS (FAB+) *m/z* calcd for $C_{10}H_{11}NO_3SCl$ ($MH^+$) 260.0148 obsd 260.0145.

**5.9.2. (±)-3-Ethyl-7-chlorosulfonyl-3,4-dihydroisoquinolin-1-(2*H*)-one (24b).** Lactam **19b** (1.18 g, 6.73 mmol) was treated with chlorosulfonic acid (10 mL) to yield **24b** (345 mg, 19%): mp 169–170 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.76 (s, 1H), 8.11 (m, 1H), 7.50 (d, $J$ = 8.1 Hz, 1H), 6.46 (ex s, 1H), 3.74–3.69 (m, 1H), 3.19–3.14 (m, 1H), 2.99–2.93 (m, 1H), 1.80–1.67 (m, 2H), 1.08 (t, $J$ = 7.4 Hz, 3H); HRMS (FAB+) *m/z* calcd for $C_{11}H_{13}NO_3SCl$ ($MH^+$) 274.0305 obsd 274.0314.

**5.9.3. (±)-3-Propyl-7-chlorosulfonyl-3,4-dihydroisoquinolin-1-(2*H*)-one (24c).** Lactam **19c** (500 mg, 2.64 mmol) was treated with chlorosulfonic acid (5 mL) to yield **24c** (608 mg, 80%): mp 159–160 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.76 (s, 1H), 8.11 (s, 1H), 7.50 (s, 1H), 6.23 (ex s, 1H), 3.86 (m, 1H), 3.17–3.14 (m, 1H), 2.98–2.93 (m, 1H), 1.66–1.49 (m, 4H), 0.95 (m, 3H); HRMS (FAB+) *m/z* calcd for $C_{12}H_{15}NO_3SCl$ ($MH^+$) 288.0461 obsd 288.0469.

### 5.10. General procedure for 27a–c (selected procedure for 27c)

Sulfonyl chloride **24c** (390 mg, 1.36 mmol) was dissolved in acetonitrile (6 mL), ammonium hydroxide (6 mL) was added, and the reaction stirred overnight. The acetonitrile was removed in vacuo and water (10 mL) was added. The aqueous mixture was extracted with EtOAc ($3 \times 25$ mL). The combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was evaporated in vacuo to yield sulfonamide **25c** (326 mg), which required no further purification. Sulfonamide **25c** was reduced with 1 M $BH_3$·THF (4.53 mL, 4.53 mmol) as described in the general procedure for **23b–f** except the free amine was extracted from the aqueous layer at pH 10. The free amine was purified by column chromatography eluting with 10:1 DCM/MeOH.

**5.10.1. (±)-7-Aminosulfonyl-3-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (27a·HCl).** Sulfonyl chloride **24a** (150 mg, 0.578 mmol) was used to produce sulfonamide **25a** (122 mg), which was subsequently reduced with 1 M $BH_3$·THF (2.31 mL, 2.31 mmol). The free amine was purified by flash chromatography eluting with 20:1 DCM/MeOH. The hydrochloride salt was recrystallized in EtOH/hexanes to yield **27a**·HCl (69 mg, 45%): mp 221–222 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.63 (br ex s, 2H), 7.71–7.69 (m, 2H), 7.41–7.40 (m, 3H), 4.39–4.29 (m, 2H), 3.60–3.55 (m, 1H), 3.15–3.09 (m, 1H), 2.93–2.86 (m, 1H), 1.40–1.38 (m, 3H); $^{13}$C NMR (400 MHz, DMSO-$d_6$) $\delta$ 143.3, 136.8, 130.3, 130.2, 125.4, 124.7, 49.2, 44.2, 33.3, 18.9; HRMS (FAB+) *m/z* calcd for $C_{10}H_{15}N_2O_2S$ ($MH^+$) 227.0854 obsd 227.0869; Anal. Calcd for $C_{10}H_{14}N_2O_2S$·HCl: C, 45.71; H, 5.75; N, 10.66. Found: C, 45.74; H, 5.80; N, 10.46.

**5.10.2. (±)-7-Aminosulfonyl-3-ethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (27b·HCl).** Sulfonyl chloride **24b** (150 mg, 0.548 mmol) was used to produce sulfonamide **25b** (130 mg), which was subsequently reduced with 1 M $BH_3$·THF (2.19 mL, 2.19 mmol). The free amine was purified by flash chromatography eluting with 20:1 DCM/MeOH → 10:1 DCM/MeOH. The hydrochloride salt was recrystallized in EtOH/hexanes to yield **27b**·HCl (79 mg, 52%): mp 244–245 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.65 (br ex s, 2H), 7.72–7.69 (m, 2H), 7.43–7.40 (m, 3H), 4.38 (m, 2H), 3.43–3.36 (m, 1H), 3.19–3.14 (m, 1H), 2.92–2.85 (m, 1H), 1.90–1.87 (m, 1H), 1.67–1.64 (m, 1H) 1.04–1.00 (m, 3H); $^{13}$C NMR (400 MHz, DMSO-$d_6$) $\delta$ 143.3, 136.8, 130.4, 130.4, 125.4, 124.7, 54.4, 44.5, 31.0, 26.1, 10.2; HRMS (FAB+) *m/z* calcd for $C_{11}H_{17}N_2O_2S$ ($MH^+$) 241.1011 obsd 241.1016; Anal. Calcd for $C_{11}H_{16}N_2O_2S$·HCl: C, 47.73; H, 6.19; N, 10.12. Found: C, 47.94; H, 6.13; N, 10.00.

**5.10.3. (±)-7-Aminosulfonyl-3-propyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (27c·HCl).** The hydrochloride salt was recrystallized in EtOH/hexanes to yield **27c**·HCl (220 mg, 54%): mp 205–206 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 9.72 (br ex s, 2H), 7.71–7.69 (m, 2H), 7.42–7.39 (m, 3H), 4.39–4.36 (m, 2H), 3.50–3.41 (m, 1H), 3.19–3.13 (m, 1H), 2.93–2.86 (m, 1H), 1.86–1.79 (m, 1H), 1.64–1.58 (m, 1H), 1.50–1.43 (m, 2H), 0.93 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 143.2, 136.9, 130.5, 130.4, 125.4, 124.7, 52.8, 44.4, 35.0, 31.4, 18.6, 14.6; HRMS (FAB+) *m/z* calcd for $C_{12}H_{19}N_2O_2S$ ($MH^+$) 255.1167 obsd 255.1175; Anal. Calcd for $C_{12}H_{18}N_2O_2$·HCl: C, 49.56; H, 6.59; N, 9.63. Found: C, 49.34; H, 6.37; N, 9.40.

### 5.11. General procedure for 28a–c (selected procedure for 28c)

Sulfonyl chloride **24c** (200 mg, 0.695 mmol) was dissolved in a biphasic mixture of EtOAc (25 mL) and saturated sodium carbonate (12 mL). Pyridine (3 mL) and 2,2,2-trifluoroethylamine (0.166 mL, 2.09 mmol) were added and the reaction stirred overnight. The organic layer was separated and washed with 3 N HCl ($2 \times 15$ mL), saturated sodium bicarbonate, and brine. The organic layer was dried over sodium sulfate and evaporated in vacuo to yield sulfonamide **26c** (216 mg), which required no further purification. Sulfonamide **26c** was reduced with 1 M $BH_3$·THF (1.85 mL, 1.85 mmol) as described in the general procedure for **23b–f**, except the free amine was extracted from the aqueous layer at pH 10. The free amine was purified by flash chromatography eluting with 20:1 DCM/MeOH → 10:1 DCM/MeOH.

**5.11.1. (±)-3-Methyl-7-*N*-(2,2,2-trifluoroethylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (28a·HCl).** Sulfonyl chloride **24a** (145 mg, 0.558 mmol) and 2,2,2-trifluoroethylamine (0.133 mL, 1.67 mmol) were used to produce sulfonamide **26a** (146 mg), which was reduced with 1 M $BH_3$·THF (1.81 mL, 1.81 mmol). The free amine was purified by flash chromatography eluting with 20:1 DCM/MeOH. The hydrochloride salt was recrystallized in EtOH/hexanes to yield **28a**·HCl (65 mg, 34%): mp 270–271 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.65 (br ex s, 2H), 8.70 (ex s, 1H), 7.75–7.70 (m, 2H), 7.44 (d, $J = 8.1$ Hz, 1H), 4.44–4.33 (m, 2H), 3.71–3.65 (m, 2H), 3.60–3.55 (m, 1H), 3.17–2.94 (m, 1H), 2.94–2.87 (m, 1H), 1.39 (m, 3H); $^{13}$C NMR (500 MHz, DMSO-$d_6$) $\delta$ 139.3, 137.5, 130.2, 130.1, 125.5, 125.2, 124.7 (q, $J = 279$ Hz, $CF_3$), 48.6, 43.7 (q, $J = 31$ Hz, $CF_3CH_2$), 43.6, 32.9, 18.4; HRMS (FAB+) *m/z* calcd for $C_{12}H_{16}N_2O_2SF_3$ ($MH^+$) 309.0885 obsd 309.0878; Anal. Calcd for $C_{12}H_{15}N_2O_2SF_3$·HCl: C, 41.80; H, 4.68; N, 8.12. Found: C, 42.06; H, 4.67; N, 7.93.

**5.11.2. (±)-3-Ethyl-7-*N*-(2,2,2-trifluoroethylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (28b·HCl).** Sulfonyl chloride **24b** (150 mg, 0.548 mmol) and 2,2,2-trifluoroethylamine (0.131 mL, 1.64 mmol) were used to produce sulfonamide **26b** (154 mg), which was subsequently reduced with 1 M $BH_3$·THF (1.83 mL, 1.83 mmol). The free amine was purified by flash chromatography eluting with 3:1 MeCN/DCM. The hydrochloride salt was recrystallized in EtOH/hexanes to yield **28b**·HCl (97 mg, 49%): mp 259–260 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.73 (br ex s, 2H), 8.70 (ex s,

1H), 7.77–7.70 (m, 2H), 7.46 (d, $J = 8.1$ Hz, 1H), 4.45–4.34 (m, 2H), 3.74–3.65 (m, 2H), 3.42 (m, 1H), 3.22–3.17 (m, 1H), 2.92–2.85 (m, 1H), 1.90–1.84 (m, 1H), 1.71–1.60 (m, 1H), 1.02 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (500 MHz, DMSO-$d_6$) 139.4, 137.4, 130.3, 130.3, 125.5, 125.2, 124.7 (q, $J = 277$ Hz, $CF_3$), 53.9, 44.0, 43.7 (q, $J = 34$ Hz, $CF_3CH_2$), 30.6, 25.6, 9.7; HRMS (FAB+) *m/z* calcd for $C_{13}H_{18}N_2O_2SF_3$ ($MH^+$) 323.1041 obsd 323.1041; Anal. Calcd for $C_{13}H_{17}N_2O_2SF_3$·HCl: C, 43.52; H, 5.06; N, 7.81. Found: C, 43.53; H, 4.98; N, 7.62.

**5.11.3. (±)-3-Propyl-7-*N*-(2,2,2-trifluoroethylaminosulfonyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (28c·HCl).** The hydrochloride salt was recrystallized in EtOH/hexanes to yield **28c**·HCl (51 mg, 20%): mp 224–225 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.49 (br ex s, 2H), 8.70 (ex s, 1H), 7.76–7.70 (m, 2H), 7.45 (d, $J = 8.0$ Hz, 1H), 4.45–4.35 (m, 2H), 3.71–3.65 (m, 2H), 3.50 (m, 1H), 3.23–3.17 (m, 1H), 2.92–2.82 (m, 1H), 1.78 (m. 1H), 1.65–1.39 (m, 3H), 0.94 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (400 MHz, DMSO-$d_6$) $\delta$ 139.8, 137.9, 130.8. 130.8, 126.0, 125.7, 125.2 (q, $J = 277$ Hz, $CF_3$), 52.8, 44.4, 44.2 (q, $J = 34$ Hz, $CF_3CH_2$), 35.1, 31.4, 18.6, 14.5; HRMS (FAB+) *m/z* calcd for $C_{14}H_{20}N_2O_2SF_3$ ($MH^+$) 337.1198 obsd 337.1202; Anal. Calcd for $C_{14}H_{19}N_2O_2SF_3$·HCl: C, 45.10; H, 5.41; N, 7.51. Found: C, 44.95; H, 5.26; N, 7.52.

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