Discovery and Optimization of Anthranilic Acid Sulfonamides as Inhibitors of Methionine Aminopeptidase-2: A Structural Basis for the Reduction of Albumin Binding

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Methionine aminopeptidase-2 (MetAP2) is a novel target for cancer therapy. As part of an effort to discover orally active reversible inhibitors of MetAP2, a series of anthranilic acid sulfonamides with micromolar affinities for human MetAP2 were identified using affinity selection by mass spectrometry (ASMS) screening. These micromolar hits were rapidly improved to nanomolar leads on the basis of insights from protein crystallography; however, the compounds displayed extensive binding to human serum albumin and had limited activity in cellular assays. Modifications based on structural information on the binding of lead compounds to both MetAP2 and domain III of albumin allowed the identification of compounds with significant improvements in both parameters, which showed good cellular activity in both proliferation and methionine processing assays.

Introduction

Methionine aminopeptidases are metalloenzymes responsible for the removal of the *N*-terminal initiator methionine residue of nascent proteins. Humans have multiple methionine aminopeptidases. MetAP1 and MetAP2 represent related but distinct enzymes found in the cytosol;[1] in addition, a mitochondrial aminopeptidase of uncertain function, structurally related to MetAP1, has recently been reported.[2] The type I and type II methionine aminopeptidases seem to show similar substrate preferences; however, they are not fully redundant because the siRNA depletion of either enzyme is reported to inhibit the proliferation of human cells.[3] Although one article has questioned the conclusion based on siRNA knockdown studies,[4] multiple studies have demonstrated that MetAP2 is the molecular target of the antiangiogenic natural product fumagillin[5] (**1a,** Chart 1) and its semisynthetic analogue **1b** (TNP-470),[6] which irreversibly inactivate the enzyme by a covalent modification of a histidine residue in the active site.[7] Fumagillin derivatives, such as **1b**,[8] **1c** (PPI-2458),[9] and **1d** (CKD-732)[10] display inhibitory activity in animal models of angiogenesis and tumor growth, supporting the potential of MetAP2 inhibition as an approach to the treatment of cancer and other diseases with an angiogenic component. Reversible inhibitors of MetAP2 such as **2** (A-357300)[11] have also demonstrated activity in animal models of angiogenesis and tumor growth, as have nonselective inhibitors of both MetAP1 and MetAP2 such as **3** (LAF-389).[12]

Efforts to identify reversible selective MetAP2 inhibitors with characteristics suitable for oral administration in humans by affinity selection by mass spectrometry (ASMS) screening[13] of Mn^{2+} MetAP2[14] led to the identification of anthranilic acid sulfonamides such as **4** and **5**.[15] As indicated in Table 1, compound **5** showed potent inhibition in a MetAP2 enzyme assay (IC_{50} = 10 nM); however, it was only moderately active in inhibiting the proliferation of the human fibrosarcoma-derived cell line HT-1080 (EC_{50} = 2.4 μM). The addition of physiological concentrations (40 mg/mL)[16] of human serum albumin (HSA) produced significant shifts in potency in both assays (Table 1), indicating that protein binding in general and HSA binding in particular were potentially problematic issues for this structure class. Compounds **4** and **5** were measured to be 99.7% and 99.8%, respectively, protein bound in rat plasma.

Compound Design. HSA is a highly abundant plasma protein that plays a central role in drug distribution and pharmacokinetics. Albumin represents around 60% of the total plasma protein with a typical concentration of 0.6 mM. HSA possesses several binding sites and is capable of binding a wide range of endogenous and exogenous molecules.[16] To characterize the nature and kinetics of binding, an NMR study was undertaken on **4** using domain III of albumin, which is reported to have a high affinity for anionic aromatic compounds.[17] Initial studies indicated high affinity binding to a specific site. A structure of the complex was then obtained, shown in Figure 1, indicating the binding to what is termed site II of albumin.[17] Compound **4** binds to the hydrophobic cavity of domain III formed by helices 1, 2, 3, 4, and 6. The aromatic rings of the ligand point deep into the pocket and make multiple contacts with residues I388 and N391 on alpha helix 1, F403, L407 R410, and Y411 on alpha helix 2, V433 on alpha helix 3, and A449 and L453 on alpha helix 4. As seen in Figure 1, these constraints bury the ortho position of the benzene sulfonyl ring of the ligand in a hydrophobic pocket of the protein. The carboxyl group of the ligand is in close proximity to R410 and Y411 of the protein and, thus, sits in a position analogous to the carboxyl group of myristic acid and diflunisal in their HSA domain III ligand complexes.[18,19] This high affinity binding appears to be restrictive,[20] that is, kinetically limiting to the amount of drug available for distribution into cells. We, therefore, sought to modify our lead structures to reduce the extent of binding to HSA.

A comparison of the NMR structure of **4** bound to domain III of albumin with the X-ray crystal structures of **4** and **5** bound to MetAP2 (Figure 2) suggested a strategy for the disruption

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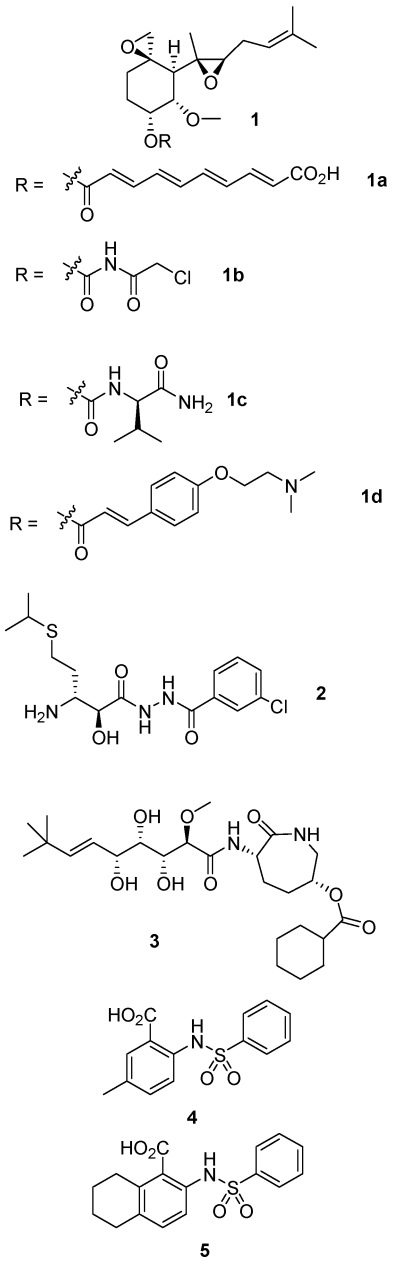
Chart 1. MetAP2 Inhibitor Structures

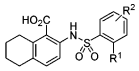


of the high affinity binding to HSA. Substitution at the ortho position of the arylsulfonamide moiety would project away from the MetAP2 protein into solvent and should, therefore, be accommodated, whereas the corresponding space in the albumin complex is occupied by hydrophobic residues. We, therefore, reasoned that the addition of a positively charged functional group such as a tertiary amine tethered to the ortho position on the benzenesulfonyl portion of **5** would afford potent MetAP2 inhibitors with reduced affinity for HSA. Because albumin is able to undergo shifts to accommodate a variety of structures, the simple addition of steric bulk at this position was less likely to disrupt binding. This approach of rational design using structural data on drug−HSA complexes has been previously employed successfully for the reduction of protein binding to diflunisal derivatives[18] and Bcl-2 inhibitors.[21]

Results and Discussion

As an initial approach, the addition of various amines through an aminoalkyl tether was examined. Compounds **10** were prepared by the routes shown in Scheme 1. The hydrogenation of commercially available methyl 2-hydroxy-1-naphthoate, followed by triflate formation provided intermediate **6**. The desired amino functionality was introduced using benzophenone imine as an ammonia synthon under the palladium-catalyzed conditions developed by Buchwald[22] to provide **7**, which was treated with HCl in wet THF to provide hydrochloride salt **8**. Sulfonylation with 2-fluorobenzenesulfonyl chloride provided

Table 1. Structure and Biological Activity of Anthranilic Acid Sulfonamide MetAP2 Inhibitors



Compd	R^1	R^2	Enzyme Inhibition[a] IC_{50} (μM)	Enzyme Inhibition[a] IC_{50} with HSA[c] (μM)	HT1080 Prolif.[b] EC_{50} (μM)	HT1080 Prolif.[b] EC_{50} with HSA[c] (μM)
4			1.4	>100	7.2	>100
5	H	H	0.010	4.2	2.4	89
10a	$NHCH_2CH_2N(CH_3)_2$	H	0.048	0.56	1.3	15.
10b	$NHCH_2CH_2N(CH_2CH_3)_2$	H	0.031	0.48	0.54	3.4
10c	$NHCH_2CH_2N[CH(CH_3)_2]_2$	H	0.031	0.41	0.64	1.8
10d		H	0.069	1.5	2.2	7.8
10e	$NH(CH_2)_3N(CH_3)_2$	H	0.014	0.47	0.19	1.7
10f	$NH(CH_2)_3N(CH_2CH_3)_2$	H	0.025	0.95	0.14	1.7
10g	$NH(CH_2)_3N[(CH_2)_3CH_3]_2$	H	0.052	1.9	0.29	5.7
10h	$NHCH_2C(CH_3)_2CH_2N(CH_3)_2$	H	0.018	0.78	0.61	2.0
10i	$NH(CH_2)_3N(CH_2CH_2OH)_2$	H	0.026	0.49	1.0	2.2
10j	$NH(CH_2)_3NHCH_2CH_3$	H	0.012	0.40	0.11	2.2
10k	$NH(CH_2)_3NHCH_2CH_2OH$	H	0.015	0.49	0.28	4.4
10l	$NH(CH_2)_3NHBOC$	H	0.077	26.	4.9	>100
10m	$NH(CH_2)_3NCH_3BOC$	H	0.11	37.	4.3	>100
10n	$NH(CH_2)_3NH_2$	H	0.013	0.36	0.16	2.2
10o		H	0.026	2.1	0.41	13.
10p		H	0.020	1.2	0.51	3.9
10q		H	0.022	5.9	0.32	98.
10r		H	0.017	0.49	0.085	1.9
10s		H	0.017	0.56	0.096	1.2
10t		H	0.020	4.5	1.6	86
10u		H	0.091	4.6	15	NT
10v		H	0.035	1.6	0.29	7.1
10w		H	0.034	0.79	0.38	8.0
10x		H	0.017	1.2	0.46	5.3
10y		H	0.022	0.55	0.14	NT
10z		H	0.058	1.4	1.1	NT
10aa		H	0.010	3.3	2.9	NT
10ab		H	0.035	11	17.	NT
10ac		H	0.053	12	2.0	NT
10ad		H	0.016	5.7	8.5	NT
10ae		H	0.040	11	1.4	26.
10af	$NH(CH_2)_3N(CH_2CH_3)_2$	6-F	0.019	0.41	14.	NT
10ag	$NH(CH_2)_3N(CH_2CH_3)_2$	5-F	0.18	3.0	8.3	NT
10ah	$NH(CH_2)_3N(CH_2CH_3)_2$	3-Cl	0.015	0.19	0.37	NT
10ai	$NH(CH_2)_3N(CH_2CH_3)_2$	5-Cl	0.056	1.7	10.	NT
10aj	$NH(CH_2)_3N(CH_2CH_3)_2$	4-Cl 5-F	0.79	7.7	13	NT
10ak	$NH(CH_2)_3N(CH_2CH_3)_2$	5-CH_3	0.066	2.3	0.66	NT
10al	$NH(CH_2)_3N(CH_2CH_3)_2$	4-Cl	0.11	1.4	3.1	NT
10am	$NH(CH_2)_3N(CH_2CH_3)_2$	4-CH_3	0.15	3.2	2.1	NT
10an	$NH(CH_2)_3N(CH_2CH_3)_2$	5-CF_3	0.69	13.	100	NT
10ao	$NH(CH_2)_2N(CH_3)_2$	H	0.012	0.63	0.46	1.4
10ap	$NHCH(CH_3)(CH_2)_2N(CH_2CH_3)_2$	H	0.13	66.	0.21	1.9
11a	NH_2	H	0.013	7.3	6.2	NT
13a		H	0.046	3.6	0.95	7.6
13b		H	0.15	23	1.5	NT
13c		H	0.070	0.42	0.50	5.1
13d		H	0.069	9.1	1.3	NT
13e		H	0.062	0.68	0.35	3.2
13f		H	0.015	1.2	0.13	2.1
13g		H	0.055	2.5	0.37	8.7

[a] Inhibition of the Mn^{2+} form of human MetAP2 as described in ref 14. [b] Inhibition of the proliferation of HT-1080 cells as described in ref 23. [c] The measurements were carried out in the presence of 40 mg/mL of human serum albumin.

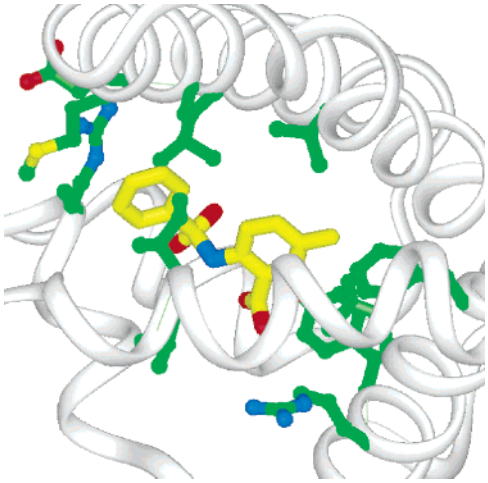


Figure 1. Binding mode of **4** to domain III of human serum albumin determined by NMR spectroscopy. The protein side chains showing NOE interactions with the ligand are shown in green.

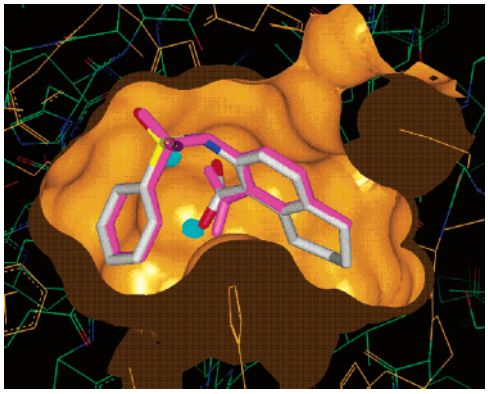


Figure 2. Binding mode of **4** and **5** to the active site of MetAP2 determined by protein crystallography. The atomic coordinates have been deposited with the Protein Data Bank (1YW7, 1YW8).

9a, which was subjected to microwave-assisted nucleophilic aromatic substitution with concomitant ester hydrolysis under the reaction conditions to provide compounds **10a**−**10ae**. A series of analogues of **10f**, bearing additional substitution on the benzenesulfonamide (**10af**−**10an**), were prepared by the same route using the respective substituted arylsulfonyl chlorides. Alternatively, the sulfonylation of **8** with 2-nitrophenylsulfonyl chloride followed by the reduction to provide **11b** allowed the synthesis of **10y**. Additional examples of tethered tertiary amines **13** were accessed from the corresponding secondary amines by reductive amination, followed by ester hydrolysis. The compounds were tested for the inhibition of the MetAP2 enzyme, with and without the addition of 40 mg/mL of HSA to the assay buffer, as well as the inhibition of the proliferation of the human fibrosarcoma-derived cell line HT-1080 (Table 1).

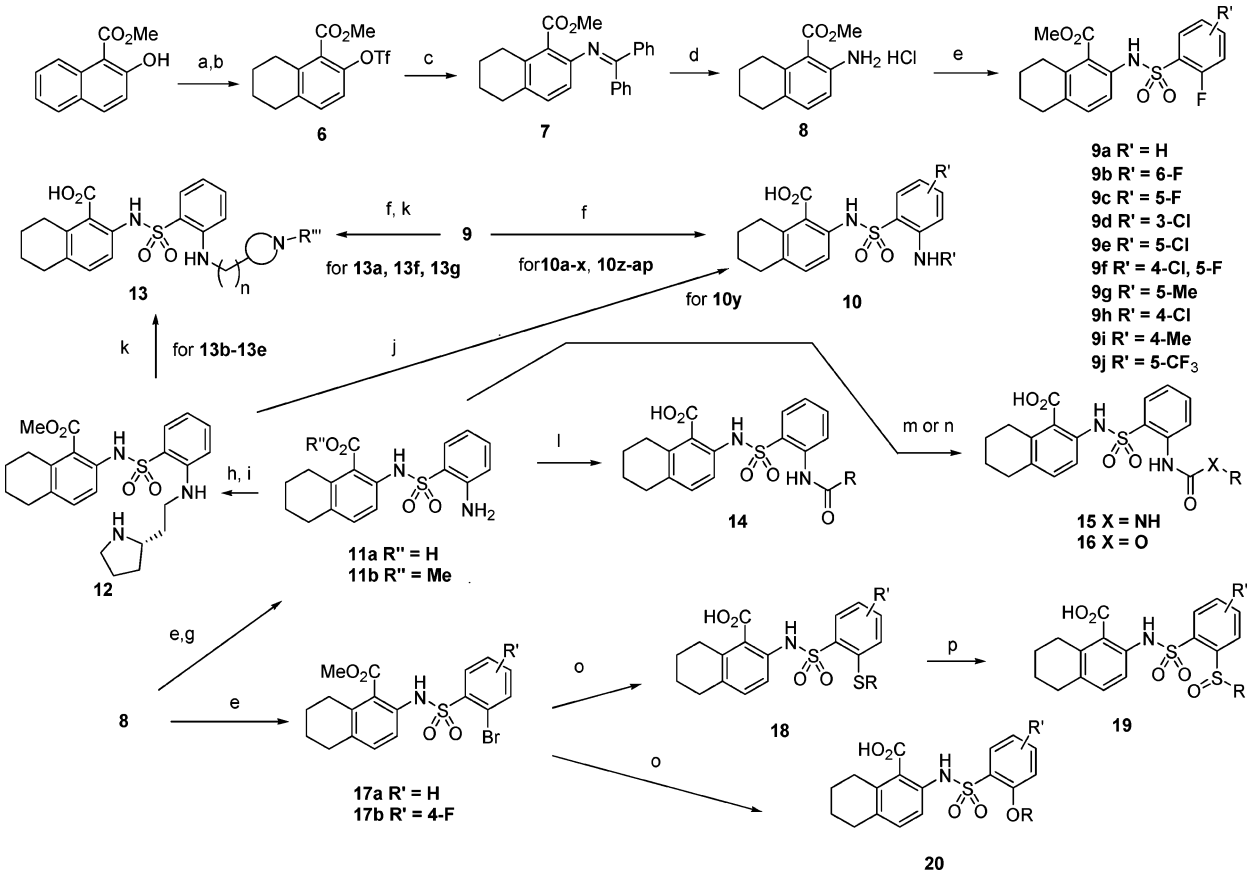
As anticipated on the basis of the structural analysis discussed above, the compounds generally retained enzyme inhibitory values comparable to that of **5**. Although the introduction of the amines led to 2−10-fold decreases in activity against the enzyme, the compounds linked to protonatable amines displayed a reduced shift in potency upon the addition of HSA to the assay. Activities in the proliferation assay were also improved relative to that of **5** in most of the examples, in both the standard assay format (containing 10% fetal bovine serum) and with the addition of HSA. The importance of the amine protonation is illustrated by the large HSA shifts for Boc derivatives **10l** and **m**, pyrrolidinone analogue **10ae**, and the less basic heteroaromatic analogues **10aa**−**10ad**. The introduction of larger hydrophobic groups surrounding the distal amine (e.g., **10t**, **10u, 13b**, and **13d**) led to larger potency shifts. Smaller alkyl groups, such as dimethyl and diethylamino, gave the best results. Tether length had only a modest effect, and 3−4 carbon atoms between the nitrogen attached to the benzenesulfonyl moiety and the tertiary amine was optimal. Branching and cyclization into the tether was well tolerated with the exception of the branching adjacent to the anilino nitrogen (e.g., **10ap**). Substitution at other positions of the benzenesulfonyl (**10af**−**10an**) led to decreased activity.

Having validated the approach of tethering a tertiary amine to reduce HSA binding, we turned our attention to other tethering strategies. Amide (**14**), urea (**15**), and carbamate (**16**) variants of the alkylamino tether were prepared from intermediate **11b** (Scheme 1). Analogues linked via sulfide (**18**)-, sulfoxide (**19**)-, and alkoxide (**20**)-containing tethers were prepared from *ortho*-bromo intermediate **17** (Scheme 1). Analogues tethered via carbon linkages were prepared as shown in Scheme 2. Analogues linked through an amide carbonyl were accessible through either coupling to acid **22** followed by ester hydrolysis, or through the aminocarbonylation of aryl bromide **17**. Intermediate **17** also provided access to analogues linked via alkenyl (**24** and **25**) and alkyl (**28**) linkers via palladium-catalyzed coupling reactions. Analogues **24** could be prepared through coupling with the appropriate aminoalkylalkenyl stannanes or from allylic alcohol intermediates **27**. In the latter sequence, the protection of the sulfonamide nitrogen was required to prevent intramolecular alkylation upon the activation of the alcohol. A similar sequence (Scheme 3) was used to prepare the cyclopropylmethyl-linked analogue **32**.

As indicated in Table 2, *Z*-alkenyl linked analogues **24** provided the compounds with the best activity. The X-ray structure of analogue **24n** bound to MetAP2 (Figure 3) when overlaid with that of **5** illustrates that, as planned, the addition of the tethered amine group did not alter the mode of binding with the target. The addition of a 4-fluoro substituent on the benzenesulfonyl group had no effect on MetAP2 inhibition but led to slight reductions in the HSA shift and improved the activity in the proliferation assay. A *Z*-propenyl link combined with a diethylamino group provided the best activity in the proliferation assay, with **24b** showing the best activity.

Most analogues in the study had similar activity against the isolated enzyme, yet a range of activities in cellular assays spanning approximately 1000-fold was observed. The increased potencies achieved in cellular assays are attributed primarily to reduced protein binding (the assay medium contains 10% fetal bovine serum) and improved cell permeability, providing higher effective concentrations at the intracellular target. A comparison of the enzyme potencies in the presence of HSA does not completely explain the difference in antiproliferative values, suggesting additional influences on the cellular activities. Although cell permeability was not routinely measured, compounds bearing the tethered amine were observed to achieve higher concentrations in cells. For example, the relative cytosolic to extracellular concentrations of **5** measured in rat erythrocytes after equilibration with 10 μM compound was 1.29, whereas the corresponding value for **10f** was 2.81. Enhanced cell permeability may, therefore, account for some of the enhanced activity in the cellular assays. Other factors such as additional protein binding partners or differences in subcellular localization may also be involved. Although it is unlikely to be of physiological relevance,[14] the enzyme activity of key analogues

Scheme 1[a]



[a] (a) H_2 1500 psi, Pd/C, MeOH/H_2O, 60 °C; (b) Tf_2O, pyridine, CH_2Cl_2, −20 °C; (c) $Ph_2C{=}NH$, Cs_2CO_3, $PdOAc_2$, Xantphos, dioxane, 100 °C; (d) HCl, THF/H_2O; (e) $ArSO_2Cl$, pyridine (method A); (f) diamine, Et_3N, CH_3CN, microwave, 200 °C (method B); (g) H_2, RaNi, MeOH/EtOAc; (h) Boc-homoprolinal, HOAc, $PSCNBH_3$, CH_2Cl_2/MeOH, 70 °C; (i) TFA, CH_2Cl_2; (j) LiOH, dioxane/H_2O, microwave, 160 °C; (k) carbonyl compound, HOAc, $PSCNBH_3$, DMF; LiOH, dioxane/H_2O, microwave, 160 °C (method C); (l) $ClCH_2COCl$, pyridine, CH_2Cl_2; amine (method D); (m) triphosgene, pyridine, diamine, 70 °C; (n) carbonyldiimidazole, THF, diamine; LiI, pyridine, microwave, 150 °C (method E); (o) RSH or ROH, NaH, DMF; LiI, pyridine, microwave, 150 °C (method F); (p) 30% aq H_2O_2, HOAc (method G).

against the Co^{2+} form of MetAP2 was examined and showed that the analogues were again of similar potency to each other but 100-fold weaker than the values measured against the Mn^{2+} form (data not shown).

To confirm that the compounds were showing better activity in the proliferation assay because of the more effective inhibition of intracellular MetAP2 rather than the addition of an off-target effect, 46 compounds with a range of potencies from 15 to 0.006 μM in the HT-1080 proliferation assay were evaluated for their ability to inhibit methionine processing in HT-1080 cells by MetAP2, using a previously described protocol (Table 3).[14] As shown in Figure 4, the correlation between potency in the two assays was good, with an R^2 value of 0.821. An analysis of a larger and more structurally diverse set of compounds within the anthranilic acid sulfonamide series provided an even higher correlation ($R^2 = 0.927$, data not shown), strongly supporting the view that improvements in proliferation inhibition were achieved by the inhibition of MetAP2 enzyme activity in cells.

In summary, the use of detailed structural data on the binding of lead compounds to both the MetAP2 target and an anti-target, HSA, allowed the achievement of a greater than 100-fold gain of activity in cellular assays and substantial improvements in compound accessibility in the presence of HSA, as measured by potency shifts from the added protein in enzyme and cellular assays. The in vivo evaluation of these improved compounds in animal models of angiogenesis and tumor growth will be reported in a separate publication.

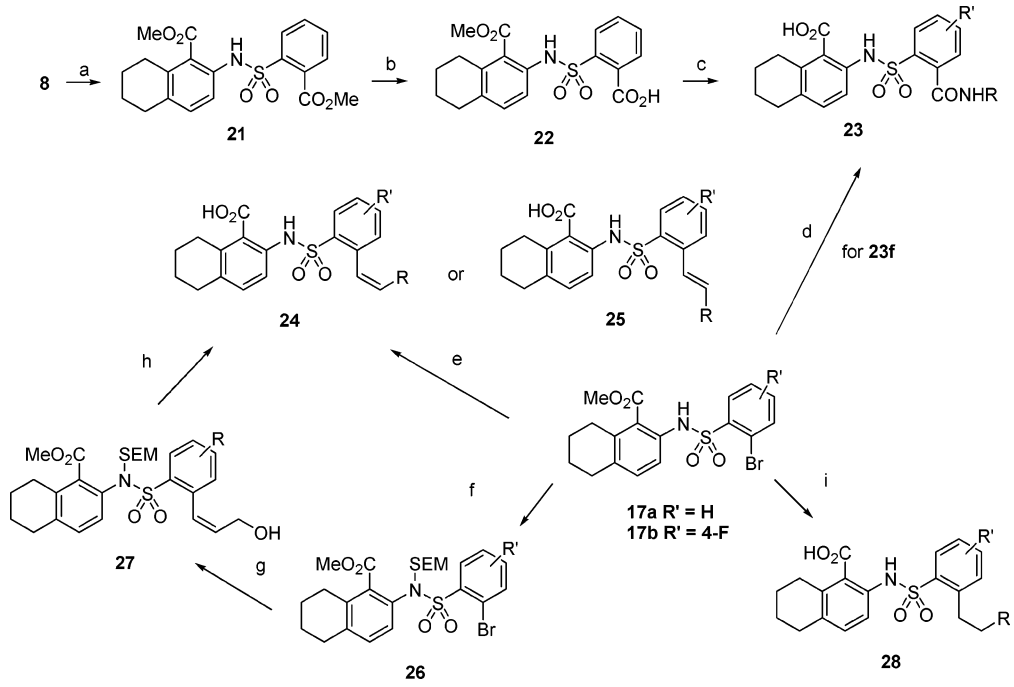
Experimental Section

Biological Assays. MetAP2 enzyme inhibition experiments,[14] HT-1080 proliferation assays,[23] and methionine processing measurements[11] were carried out as reported in previous publications from these laboratories and are described in the Supporting Information.

Protein Structure Determinations. NMR Structure of HSA Domain III. HSA domain III (residues 381−585) was expressed in *Escherichia coli* and purified as previously described.[24] Uniformly ^{15}N,^{13}C-labeled samples were prepared with media containing $^{15}NH_4Cl$ and [U-^{13}C]glucose. NMR samples contained 1.0 mM of HSA domain III and 1.1 mM ligand in 50 mM phosphate buffer (pH 7.5) in 100% D_2O. Spectra were acquired at 310 K on a Bruker DRX600 or DRX800 NMR spectrometer. Protein resonance assignments were made using earlier assignments[18] and $^{13}C/^{1}H$ TOCSY and NOESY spectra.[25,26] NOE distance restraints were obtained from 3D ^{15}N- and ^{13}C-edited NOESY or 3D ^{13}C-edited/filtered NOESY spectra acquired with a mixing time of 80 ms.

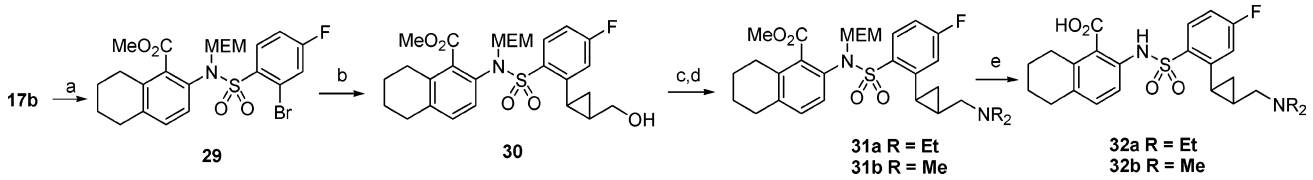
Structure Calculations. A total of 36 intermolecular NOEs were assigned between compound **1** and resonances of HSA domain III. The structures were calculated using this NOE data to dock the ligand into the crystal structure of the HSA−myristate complex[19] using the program CNX (MSI, San Diego).[27] During docking, the coordinates of the protein backbone were fixed. A square-well potential ($F_{NOE} = 50$ kcal mol^{-1}) was employed to constrain NOE-derived distances. There were no NOE violations greater than 0.2 Å in the final structures. Only covalent geometry, NOE, torsion, and repulsive terms were included in structure refinement.

Scheme 2[a]



[a] (a) $ArSO_2Cl$, pyridine (method A); (b) LiOH, MeOH/H_2O, 60 °C; (c) diamine, HATU, NMM, DMF (method H); (d) CO 450 psi, diamine, $PdCl_2$dppf, Et_3N, THF, 120 °C; LiI, pyridine, microwave, 160 °C; (e) RCH═CHSnBu_3, Pd(P*t*Bu_3)$_2$, toluene, 90 °C; LiI, pyridine, microwave, 150 °C (method I); (f) SEMCl, NaH, THF; (g) $HOCH_2CH$═CHSnBu_3, Pd(P*t*Bu_3)$_2$, toluene, 50 °C; (h) MsCl, *i*Pr_2NEt, CH_2Cl_2; amine; LiI, pyridine, microwave, 150 °C (method J); (i) RCH═CHSnBu_3, Pd(P*t*Bu_3)$_2$, toluene, 90 °C; H_2, Pd/C, MeOH; LiI, pyridine, microwave, 150 °C (method K).

Scheme 3[a]



[a] (a) MEMCl, NaH, THF; (b) tributyl-(2-(hydroxymethyl)cyclopropyl)stannane, Pd(P*t*Bu_3)$_2$, Pd_2dba_3, toluene, 90 °C; (c) MsCl, pyridine; (d) R_2NH, reflux; (e) LiI, pyridine, microwave, 160 °C.

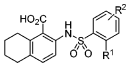
General Chemical Procedures. Unless otherwise indicated, all reagents and solvents were obtained commercially and used as received. Microwave-assisted chemical reactions were carried out using either a Smith Synthesizer single mode instrument purchased from Personal Chemistry or a Milestone MicroSYNTH multimode instrument from Milestone, Inc.; comparable results were obtained with both systems. NMR spectra were generally obtained on General Electric QE 300 or Varian Unity spectrometers with chemical shifts (δ) reported relative to that of tetramethylsilane as an internal standard. Mass spectra were obtained on Finnigan SSQ7000 instruments using desorptive chemical ionization (DCI), atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI). Elemental analyses were performed by Robertson Microlit Laboratories or Quantitative Technologies Incorporated. Preparative HPLC purifications were typically performed using a Waters Symmetry C8 column (40 mm × 100 mm, 7 μm particle size) using a gradient of 10% to 100% acetonitrile/0.1% aqueous TFA over 12min (15min run time) at a flow rate of 70 mL/min.

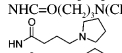
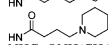
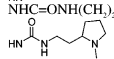
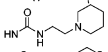
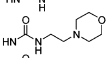
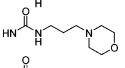
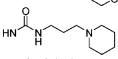
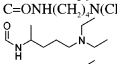
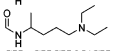
2-Hydroxy-5,6,7,8-tetrahydronaphthalene-1-carboxylic Acid Methyl Ester. A steel autoclave was charged with 2-hydroxy-naphthalene-1-carboxylic acid methyl ester (50.0 g, 248 mmol), 1000 mL of methanol, 100 mL of water, and 25.0 mg of 50 wt %/wt Pd/C. The reaction vessel was pressurized with hydrogen to 1500 psi and stirred at 60 °C for 2.5 h. The slurry was filtered to remove the palladium catalyst. Concentration of the solution in vacuo provided an emulsion. Toluene (500 mL) was added, and the mixture further concentrated in vacuo. Toluene (500 mL) was added, the aqueous layer was drained off, and the mixture was concentrated and then chase distilled with 2 × 500 mL of toluene. The crude product was then purified by silica gel chromatography (hexanes/ethyl acetate) to provide 35.8 g of the desired product (70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.87 (s, 1 H), 7.13 (d, J = 8.56 Hz, 1 H), 6.79 (d, J = 8.56 Hz, 1 H), 3.96 (s, 3 H), 2.99 (m, 2 H), 2.73 (m, 2 H), 1.75 (m, 4 H).

2-Trifluoromethanesulfonyloxy-5,6,7,8-tetrahydronaphthalene-1-carboxylic Acid Methyl Ester (6). A 2 L round-bottomed flask was charged with 35.0 g (169.7 mmol) of 2-hydroxy-5,6,7,8-tetrahydronaphthalene-1-carboxylic acid methyl ester, dichloromethane (500 mL), and pyridine (35.6 mL, 441.2 mmol). The mixture was cooled to an internal temperature of −20 °C. Trifluoromethanesulfonic anhydride (35.0 mL, 203.6 mmol) was added dropwise over approximately 20 min. The mixture was maintained at −20 °C for 15 min and warmed to ambient temperature over 1 h. Methyl-*tert*-butyl ether (1 L) was added, and the reaction mixture was stirred 10 min and then filtered. The filtrate was washed with 2 × 300 mL of 2 N HCl, 300 mL of water, and 300 mL of saturated aqueous sodium chloride solution. The organics were dried over $MgSO_4$ and concentrated in vacuo to a pink oil (55.02 g, 96% yield). The product was used directly in the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.64 Hz, 1 H), 7.07 (d, J = 8.51 Hz, 1 H), 3.95 (s, 3 H), 2.81 (m, 4 H), 1.83−1.79 (m, 4H).

2-(Benzhydrylidene-amino)-5,6,7,8-tetrahydronaphthalene-1-carboxylic Acid Methyl Ester (7). A 2 L round-bottomed flask

Table 2. Structure and Biological Activity of Anthranilic Acid Sulfonamide MetAP2 Inhibitors



Compd	R_1	R_2	Enzyme Inhibition[a] IC_{50} (μM)	Enzyme Inhibition[a] IC_{50} with HSA[c] (μM)	HT1080 Prolif.[b] EC_{50} (μM)	HT1080 Prolif.[b] EC_{50} with HSA[c] (μM)
14a	$NHC{=}OCH_2N(CH_2CH_3)_2$	H	0.038	1.4	6.9	85
14b	$NHC{=}OCH_2CH_2N(CH_2CH_3)_2$	H	0.059	0.56	0.79	7.8
14c	$NHC{=}O(CH_2)_2N(CH_2CH_3)_2$	H	0.059	0.34	0.84	2.6
14d		H	0.042	0.21	0.43	2.8
14e		H	0.032	0.21	0.48	2.4
15a	$NHC{=}ONH(CH_2)_2N(CH_2CH_3)_2$	H	0.017	0.15	0.37	4.6
15b		H	0.072	0.50	2.8	NT
15c		H	0.082	0.44	0.97	NT
15d		H	0.11	0.85	3.1	NT
15e		H	0.055	0.68	2.5	NT
15f		H	0.042	0.41	0.77	5.0
16	$NHC{=}OO(CH_2)_2N(CH_2CH_3)_2$	H	0.051	0.49	0.83	5.1
18a	$S(CH_2)_2N(CH_2CH_3)_2$	H	0.046	0.71	0.69	8.8
18b	$S(CH_2)_3N(CH_2CH_3)_2$	H	0.043	1.2	0.52	3.1
18c	$S(CH_2)_2N(CH_2CH_3)_2$	4-F	0.037	0.31	0.33	3.1
18d	$S(CH_2)_2N(CH_3)_2$	4-F	0.030	0.35	0.70	6.3
18e	$S(CH_2)_2N(CH_3)_2$	H	0.052	0.90	0.92	6.3
19a	$SO(CH_2)_2N(CH_2CH_3)_2$	H	0.039	0.19	0.27	2.7
19b	$SO(CH_2)_2N(CH_2CH_3)_2$	4-F	0.055	0.23	0.11	0.60
19c	$SO(CH_2)_2N(CH_3)_2$	4-F	0.062	0.30	0.25	2.1
19d	$SO(CH_2)_2N(CH_3)_2$	H	0.054	0.26	0.85	9.3
20a	$O(CH_2)_2N(CH_2CH_3)_2$	H	0.18	3.0	5.1	82
20b		H	0.43	8.2	6.2	NT
23a	$C{=}ONH(CH_2)_2N(CH_2CH_3)_2$	H	0.031	0.16	0.52	1.2
23b		H	0.037	0.17	2.1	NT
23c		H	0.050	0.19	1.1	NT
23d	$C{=}ONH(CH_2)_3N(CH_2CH_3)_2$	H	0.025	0.20	0.55	1.2
23e	$C{=}ONH(CH_2)_3N(CH_2CH_3)_2$	H	0.044	0.41	1.2	2.8
23f		4-F	0.067	0.34	0.12	0.36
23g		H	0.17	1.0	2.6	10.6
24a	$CH{=}CHCH_2N(CH_2CH_3)_2$	H	0.012	0.13	0.019	0.26
24b	$CH{=}CHCH_2N(CH_2CH_3)_2$	4-F	0.011	0.079	0.006	0.056
24c	$CH{=}CH(CH_2)_2N(CH_2CH_3)_2$	H	0.016	0.47	0.049	0.95
24d	$CH{=}CH(CH_2)_3N(CH_2CH_3)_2$	H	0.028	1.3	0.033	0.63
24e		H	0.030	0.56	0.29	2.9
24f		4-F	0.010	0.12	0.051	0.58
24g	$CH{=}CHCH(CH_3)N(CH_2CH_3)_2$	H	0.019	0.28	0.26	2.3
24h	$CH{=}CHCH(CH_3)N(CH_2CH_3)_2$	4-F	0.016	0.15	0.070	0.53
24i		H	0.020	0.27	0.15	1.6
24j		4-F	0.020	0.21	0.031	0.36
24k		H	0.015	0.19	0.038	0.35
24l		H	0.018	0.49	0.042	0.37
24m	$CH{=}CHCH_2N(CH_3)_2$	H	0.017	0.17	0.081	0.71
24n	$CH{=}CHCH_2N(CH_3)_2$	4-F	0.019	0.084	0.036	0.18
24o	$CH{=}CHCH_2N(CH_3)CH_2CH_3$	H	0.009	0.18	0.023	0.39
24p	$CH{=}CHCH_2N(CH_3)CH_2CH_2OH$	H	0.015	0.12	0.024	0.39
24q	$CH{=}CHCH_2N(CH_3)CH(CH_3)_2$	H	0.012	0.17	0.027	0.40
25a	$CH{=}CHCH_2N(CH_2CH_3)_2$	H	0.027	0.41	0.29	2.6
25b	$CH{=}CH(CH_2)_2N(CH_2CH_3)_2$	H	0.025	0.70	0.17	2.0
25c	$CH{=}CH(CH_2)_2N(CH_2CH_3)_2$	H	0.020	1.0	0.12	2.5
28a	$(CH_3)_2N(CH_2CH_3)_2$	H	0.009	0.44	0.073	1.1
28b	$(CH_3)_2N(CH_2CH_3)_2$	4-F	0.017	0.19	0.024	0.38
28c	$(CH_3)_2N(CH_2CH_3)_2$	H	0.019	1.0	0.068	2.4
28d	$(CH_3)_2N(CH_2CH_3)_2$	H	0.045	3.4	0.35	5.9
28e	$(CH_3)_2N(CH_3)_2$	H	0.010	0.24	0.035	1.1
32a		4-F	0.054	0.57	0.042	0.20
32b		4-F	0.055	0.51	0.088	0.43

[a] Inhibition of the Mn^{2+} form of human MetAP2 as described in ref 14. [b] Inhibition of the proliferation of HT-1080 cells as described in ref 23. [c] The measurements were carried out in the presence of 40 mg/mL of human serum albumin.

(equipped with thermocouple, overhead stirring and a nitrogen inlet) was charged with cesium carbonate (74.1 g, 227.6 mmol), palladium(II) acetate (730 mg, 3.25 mmol), and 4,5-bis-diphenylphosphanyl-9,9-dimethyl-9*H*-xanthene (Xantphos, 2.82 g, 4.88 mmol). The flask was evacuated and backfilled with nitrogen 3×. Dioxane (300 mL) was added followed by another set of three cycles of evacuation and backfilling with nitrogen. The canary-yellow slurry was stirred at room temperature for 10 min, and triethylamine (0.68 mL, 4.877 mmol) was added. Continued stirring

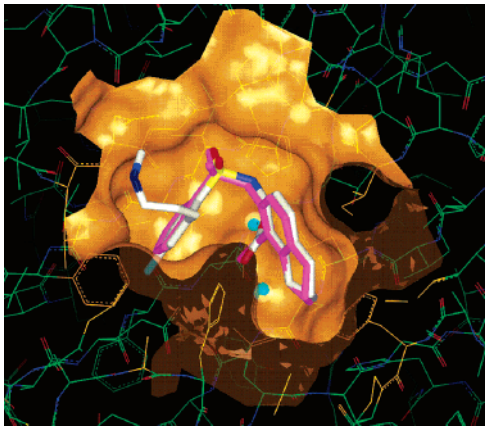


Figure 3. Binding mode of **5** and **24n** to the active site of MetAP2 determined by protein crystallography. The atomic coordinates have been deposited with the Protein Data Bank (1YW8, 1YW9).

for 10 min at room temperature gradually changed the color from yellow to red. 2-Trifluoromethanesulfonyloxy-5,6,7,8-tetrahydronaphthalene-1-carboxylic acid methyl ester (55.0 g, 162 mmol) and benzophenone imine (32.7 mL, 195.1 mmol) were added in 200 mL of dioxane via a cannula (50 mL wash). The reaction mixture was warmed to an internal temperature of 100 °C for 4 h. Cooling the reaction mixture to ambient temperature was followed by pouring the slurry into 1000 mL of ethyl acetate. The organics were washed with 2 × 500 mL of water, and the ethyl acetate solution was concentrated in vacuo. The mixture was chase distilled with 3 × 600 mL of methanol and adjusted to a final methanol volume of 600 mL. The red slurry was warmed to reflux for 30 min and then cooled to ambient temperature. Subsequent stirring for 2 h was followed by filtration and washing of the yellow crystals with 2 × 100 mL of methanol. The solid was dried in vacuo (>30 mmHg, 60 °C, 12 h) to provide the title compound as bright yellow crystals (54.06 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (m, 2 H), 7.35 (m, 8 H), 6.75 (d, J = 8.10 Hz, 1 H), 6.14 (d, J = 8.10 Hz, 1 H), 3.82 (s, 3 H), 2.69 (m, 4 H), 1.75 (m, 4 H).

2-Amino-5,6,7,8-tetrahydronaphthalene-1-carboxylic Acid Methyl Ester Hydrochloride (8). A 2 L three-necked round-bottomed flask was charged with 2-(benzhydrylidene-amino)-5,6,7,8-tetrahydronaphthalene-1-carboxylic acid methyl ester (54.0, 146.2 mmol) and 550 mL of tetrahydrofuran. Aqueous hydrochloric acid (2.0 N, 225 mL) was added, and the reaction mixture was stirred at ambient temperature for 1 h. The mixture was neutralized with saturated aqueous potassium carbonate solution (until >pH 10) and then poured into 500 mL of ethyl acetate. A thick slurry formed, whereupon 100 mL of saturated potassium carbonate was added to form two distinct layers. The layers were separated, and the aqueous solution was back-extracted with ethyl acetate (200 mL). The combined extracts were washed with 250 mL of saturated aqueous sodium chloride solution (250 mL) and dried over anhydrous sodium sulfate. The organics were filtered and concentrated in vacuo to a dark yellow oil. The oil was diluted with isopropyl acetate (1.1 L) and transferred to a 2 L three-necked round-bottomed flask (equipped with an addition funnel, overhead stirrer, and nitrogen line). A hydrogen chloride solution in dioxane (4.0 M, 40.2 mL, 160.8 mmol) was added slowly via an addition funnel over a period of 30 min whereupon a thick colorless slurry formed. The mixture was stirred for additional period of 1 h and then filtered, washed with 2 × 300 mL of isopropyl acetate, and dried in vacuo (>30 mmHg, 50 °C, 12 h) to provide **5** as a white solid (36.0 g, 100%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.0−9.0 (br s 3H), 7.15 (m, 1 H), 6.99 (d, J = 8.31 Hz, 1 H), 3.82 (s, 3 H), 2.68 (m, 4 H), 1.67 (m, 4 H).

Method A. Methyl 2-{[(2-Fluorophenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylate (9a). A solution of **8** (6.2 g, 25.7 mmol) in pyridine (70 mL) was treated with 2-fluorobenzenesulfonyl chloride (5.09 g, 26.2 mmol), stirred overnight at room temperature, concentrated by rotary evaporation,

Table 3. Proliferation and Methionine Processing Inhibition in HT-1080 Cells by Sulfonamide MetAP2 Inhibitors

compd	proliferation EC_{50} (μM)[a]	cellular MetAP2 EC_{50} (μM)[b]
5	2.4	9.6
10a	1.3	1.9
10b	0.54	0.62
10c	0.64	0.27
10d	2.2	1.5
10e	0.19	0.46
10f	0.14	0.15
10h	0.61	0.13
10n	0.16	0.21
10o	0.41	0.4
10p	0.51	0.098
10r	0.085	0.091
10s	0.096	0.065
10t	1.6	0.51
10u	15	18
10v	0.29	0.069
10w	0.38	0.11
10x	0.46	0.052
10y	0.14	0.11
10ao	0.46	0.066
10ap	0.21	0.12
13a	0.95	1
13c	0.5	0.095
13e	0.35	0.27
13f	0.13	0.22
14d	0.43	0.8
14e	0.48	0.24
15b	2.8	1.9
15e	2.5	2.2
15f	0.77	0.38
16	0.83	0.68
18b	0.52	0.66
19a	0.27	0.36
19b	0.11	0.023
20b	6.2	5.1
23a	0.52	0.35
23e	1.2	1.1
23f	0.12	0.26
23g	2.6	6.4
24a	0.019	0.023
24b	0.006	0.0053
24c	0.049	0.056
24d	0.033	0.12
25a	0.29	3
25b	0.17	0.39
28c	0.068	0.12

[a] Inhibition of the proliferation of HT-1080 cells as described in ref 23. [b] Inhibition of methionine processing by MetAP2 in HT-1080 cells as described in ref 11.

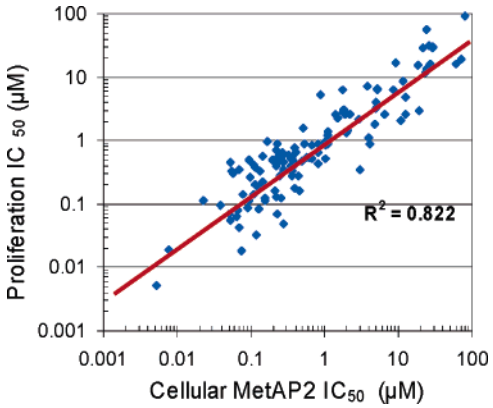


Figure 4. MetAP2 inhibitors have similar IC_{50} values in inhibiting proliferation and cellular MetAP2 activity in HT-1080 cells. The cellular MetAP2 activity was assessed by the ^{35}S methionine labeling of cells in the presence of inhibitors, binding the proteins to a Fast Red column and eluting the ^{35}S methionine cleaved with exogenous MetAP2. Cell proliferation was assessed using standard MTS reagents.

and the residues shaken in a separatory funnel with 1 N HCl and EtOAc. The organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated to give 8.56 g of the crude product, which was slurried in 25 mL of hot EtOAc. Hexanes (75 mL) were added and the mixture cooled and filtered to provide 8.03 g (86%) of the title compound as orange needles. MS (ESI(+)) *m/e* 364 $(M + H)^+$; (ESI(−)) *m/e* 362 $(M - H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 7.64 (m, 2H), 7.38 (dt, 1H), 7.28 (dt, 1H), 7.02 (d, 1H), 6.90 (d, 1H), 3.64 (s, 3H), 2.65 (br s, 2H), 2.51 (br s, 2H), 1.67 (br s, 4H).

Methyl 2-{[(2,6-Difluorophenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylate (9b). The title compound was prepared from **8** and 2,6-difluorophenylsulfonyl chloride using method A. MS (ESI(+)) *m/e* 382 $(M + H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 10.30 (s, 1H), 7.70 (m, 1H), 7.25 (m, 2H), 7.13 (d, 1H), 6.97 (d, 1H), 3.64 (s, 3 H), 2.70 (m, 2 H), 2.50 (m, 2H), 1.67 (m, 4 H).

Methyl 2-{[(2,5-Difluorophenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylate (9c). The title compound was prepared from **8** and 2,5-difluorophenylsulfonyl chloride using method A. MS (ESI(+)) *m/e* 382 $(M + H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 10.21 (s, 1H), 7.56 (m, 2H), 7.41 (m, 1H), 7.12 (d, 1H), 6.92 (d, 1H), 3.65 (s, 3 H), 2.69 (m, 2 H), 2.50 (m, 2H), 1.66 (m, 4 H).

Methyl 2-{[(3-Chloro-2-fluorophenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylate (9d). The title compound was prepared from **8** and 3-chloro-2-fluorophenylsulfonyl chloride using method A. MS [(−)-ESI] *m/z* 395.9 $[M - H]^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 10.28 (s, 1 H), 7.89 (ddd, J = 8.2, 6.7, 1.7 Hz, 1 H), 7.58 (ddd, J = 7.9, 6.4, 1.7 Hz, 1 H), 7.33 (dt, J = 8.1, 1.0 Hz, 1 H), 7.12 (d, J = 8.1 Hz, 1 H), 6.96 (d, J = 8.1 Hz, 1 H), 3.65 (s, 3 H), 2.73−2.66 (m, 2 H), 2.55−2.49 (m, 2H), 1.70−1.61 (m, 4 H); Anal. ($C_{18}H_{17}ClFNO_4S$) C, H, N.

Methyl 2-{[(5-Chloro-2-fluorophenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylate (9e). The title compound was prepared from **8** and 5-chloro-2-fluorophenylsulfonyl chloride using method A. MS (ESI(+)) *m/e* 398 $(M + H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 10.25 (s, 1H), 7.78 (m, 1H), 7.58 (dd, 1H), 7.52 (t, 1H), 7.13 (d, 1H), 6.93 (d, 1H), 3.64 (s, 3 H), 2.70 (m, 2 H), 2.53 (m, 2H), 1.67 (m, 4 H).

Methyl 2-{[(4-Chloro-2,5-difluorophenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylate (9f). The title compound was prepared from **8** and 4-chloro-2,5-difluorophenylsulfonyl chloride using method A. MS (ESI(+)) *m/e* 416 $(M + H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 10.35 (s, 1H), 7.97 (dd, 1H), 7.62 (dd, 1H), 7.12 (d, 1H), 6.94 (d, 1H), 3.66 (s, 3 H), 2.70 (m, 2 H), 2.50 (m, 2H), 1.67 (m, 4 H).

Methyl 2-{[(2-Fluoro-5-methylphenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylate (9g). The title compound was prepared from **8** and 2-fluoro-5-methylphenylsulfonyl chloride using method A. MS (ESI(+)) *m/e* 378 $(M + H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.90 (s, 1H), 7.46 (m, 2H), 7.31 (dd, 1H), 7.08 (d, 1H), 6.90 (d, 1H), 3.66 (s, 3 H), 2.68 (m, 2 H), 2.50 (m, 2H), 1.66 (m, 4 H).

Methyl 2-{[(4-Chloro-2-fluorophenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylate (9h). The title compound was prepared from **8** and 4-chloro-2-fluorophenylsulfonyl chloride using method A. MS (ESI(+)) *m/e* 398 $(M + H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 10.15 (s, 1H), 7.73 (dd, 1H), 7.63 (t, 1H), 7.42 (dd, 1H), 7.11 (d, 1H), 6.93 (d, 1H), 3.65 (s, 3 H), 2.69 (m, 2 H), 2.50 (m, 2H), 1.66 (m, 4 H).

Methyl 2-{[(2-Fluoro-4-methylphenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylate (9i). The title compound was prepared from **8** and 2-fluoro-4-methylphenylsulfonyl chloride using method A. MS (ESI(+)) *m/e* 378 $(M + H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.85 (s, 1H), 7.51 (t, 1H), 7.26 (d, 1H), 7.12 (d, 1H), 7.07 (d, 1H), 6.90 (d, 1H), 3.66 (s, 3 H), 2.67 (m, 2 H), 2.50 (m, 2H), 1.66 (m, 4 H).

Methyl 2-{[(2-Fluoro-5-(trifluoromethyl)phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylate (9j). The title compound was prepared from **8** and 2-fluoro-5-(trifluoromethyl)phenylsulfonyl chloride using method A. MS (ESI(+)) *m/e* 432 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.37 (s, 1H), 8.15 (m, 1H), 7.87 (dd, 1H), 7.72 (t, 1H), 7.13 (d, 1H), 6.96 (d, 1H), 3.59 (s, 3 H), 2.70 (m, 2 H), 2.51 (m, 2H), 1.66 (m, 4 H).

Method B. 2-{[(2-{[3-(Dimethylamino)propyl]amino}phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10e). A mixture of **9a** (0.20 g, 0.57 mmol), triethylamine (0.21 mL, 1.5 mmol), acetonitrile (2.0 mL), and *N,N*-dimethyl-1,3-propanediamine (0.35 mL, 3.2 mmol) was sealed in a 5 mL vessel and heated in a microwave reactor for 1500 s at 200 °C. The solution was cooled and adjusted to pH 4 with 1 N HCl. The aqueous layer was extracted with ethyl acetate (3×), and the combined organic fractions were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by preparative RP HPLC to provide the desired product as a TFA salt (59%). MS (ESI(+)) *m/e* 460 $(M + H)^+$; (ESI(−)) *m/e* 458 $(M - H)^-$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.15 (br s, 1H), 9.54 (s, 1H), 9.02 (br s, 1H), 7.51 (dd, 1H), 7.41 (dt, 1H), 6.96 (2, 1H), 6.86 (d, 1H), 6.64 (m, 2H), 6.00 (t, 1H), 3.29 (q, 2H), 3.09 (m, 7H), 2.65 (br s, 4H), 1.89 (m, 2H), 1.67 (br s, 4H), 1.14 (t, 6H). Anal. ($C_{22}H_{29}N_3O_4S$·TFA) C, H, N.

2-{[(2-{[2-(Dimethylamino)ethyl]amino}phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10a). The title compound was prepared from **9a** and *N,N*-dimethylethylenediamine using method B. MS (DCI) *m/e* 418 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.12 (br s, 1H), 9.52 (br s, 1H), 7.40 (m, 2H), 6.95 (d, 1H), 6.90 (d, 1H), 6.88 (br s, 1H), 6.65 (t, 1H), 6.07 (t, 1H), 3.60 (q, 2H), 3.27 (t, 2H), 2.86 (s, 6H), 2.64 (m, 4H), 1.63 (br s, 4H). Anal. ($C_{21}H_{27}N_3O_4S$·TFA) C, H, N.

2-{[(2-{[2-(Diethylamino)ethyl]amino}phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10b). The title compound was prepared from **9a** and *N,N*-diethylethylenediamine using method B. MS (DCI) *m/e* 446 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.18 (br s, 1H), 9.52 (br s, 1H), 7.42 (m, 2H), 6.94 (d, 1H), 6.89 (d, 1H), 6.79 (br s, 1H), 6.67 (m, 1H), 6.05 (br s, 1H), 3.59 (q, 2H), 3.23 (m, 6H), 2.64 (m, 4H), 1.64 (br s, 4H), 1.20 (t, 6H). Anal. ($C_{23}H_{31}N_3O_4S$·2 TFA) C, H, N.

2-{[(2-{[2-(Diisopropylamino)ethyl]amino}phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10c). The title compound was prepared from **9a** and 2-(*N,N*-diisopropylamino)ethylamine using method B. MS (DCI) *m/e* 474 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.15 (br s, 1H), 9.45 (br s, 1H), 7.53 (d, 1H), 7.45 (t, 1H), 6.95 (d, 1H), 6.84 (d, 1H), 6.71 (m, 2H), 6.11 (br s, 1H), 1.80 (m, 2H), 3.55 (m, 2H), 3.25 (m, 2H), 2.65 (m, 4H), 1.65 (br s, 4H), 1.28 (d, 12H). Anal. ($C_{25}H_{35}N_3O_4S$·1.2 TFA) C, H, N.

2-{[(2-{[2-(1-Pyrrolidinyl)ethyl]amino}phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10d). The title compound was prepared from **9a** and 1-(2-aminoethyl)pyrrolidine using method B. MS (DCI) *m/e* 444 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.85 (br s, 1H), 7.40 (m, 2H), 6.96 (d, 1H), 6.89 (m, 2H), 6.65 (t, 1H), 6.10 (t, 1H), 3.58 (m, 4H), 3.30 (m, 4H), 2.64 (br s, 4H), 1.94 (br s, 4H), 1.63 (br s, 4H). Anal. ($C_{23}H_{29}N_3O_4S$·1.1 TFA) C, H, N.

2-{[(2-{[3-(Diethylamino)propyl]amino}phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10f). The title compound was prepared from **9a** and *N,N*-diethyl-1,3-propanediamine using method B and converted to the hydrochloride salt by treatment with HCl/dioxane. MS (ESI(+)) *m/e* 460 $(M + H)^+$; (ESI(−)) *m/e* 458 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.15 (br s, 1H), 9.54 (s, 1H), 9.02 (br s, 1H), 7.51 (dd, 1H), 7.41 (dt, 1H), 6.96 (2, 1H), 6.86 (d, 1H), 6.64 (m, 2H), 6.00 (t, 1H), 3.29 (q, 2H), 3.09 (m, 7H), 2.65 (br s, 4H), 1.89 (m, 2H), 1.67 (br s, 4H), 1.14 (t, 6H). Anal. ($C_{24}H_{33}N_3O_4S$·HCl·H_2O) C, H, N.

2-{[(2-{[3-(Dibutylamino)propyl]amino}phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10g). The title compound was prepared from **9a** and *N,N*-dibutyl-1,3-propanediamine using method B. MS (DCI) *m/e* 516 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.22 (br s, 1H), 9.59 (br s, 1H), 7.51 (d, 1H), 7.40 (t, 1H), 6.93 (d, 1H), 6.84 (d, 1H), 6.71 (br s, 1H), 6.63 (t, 1H), 6.05 (br s, 1H), 3.16 (br s, 3H), 2.99 (m, 5H), 2.68 (br s, 2H), 2.64 (br s, 2H), 1.88 (m, 2H), 1.65 (br s, 4H), 1.52 (m, 4H), 1.28 (m, 4H), 0.86 (t, 6H). Anal. ($C_{28}H_{41}N_3O_4S$·TFA) C, H, N.

2-{[(2-{[3-(Dimethylamino)-2,2-dimethylpropyl]amino}phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10h). The title compound was prepared from **9a** and 3-*N,N*-(dimethylamino)-2,2-dimethylpropylamine using method B. MS (ESI(+)) *m/e* 460 $(M + H)^+$; (ESI(−)) *m/e* 458 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.53 (dd, 1H), 7.40 (dt, 1H), 6.97 (d, 1H), 6.92 (d, 1H), 6.68 (t, 1H), 6.58 (d, 1H), 3.09 (s, 2H), 3.06 (m, 2H), 2.83 (s, 6H), 2.66 (m, 4H), 1.67 (m, 4H), 1.01 (s, 6H). Anal. ($C_{24}H_{33}N_3O_4S$·1.2 TFA) C, H, N.

2-({[2-({3-[Bis(2-hydroxyethyl)amino]propyl}amino)phenyl]sulfonyl}amino)-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10i). The title compound was prepared from **9a** and 2-[(3-aminopropyl)(2-hydroxyethyl)amino]ethanol using method B. MS (ESI(+)) *m/e* 492 $(M + H)^+$; (ESI(−)) *m/e* 490 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.50 (dd, 1H), 7.41 (dt, 1H), 6.96 (d, 1H), 6.85 (d, 1H), 6.64 (m, 2H), 5.99 (m, 1H), 3.73 (t, 4H), 3.24 (m, 8H), 2.65 (m, 4H), 1.96 (m, 2H), 1.67 (m, 4H). Anal. ($C_{24}H_{33}N_3O_6S$·1.6 TFA) C, H, N.

2-{[(2-{[3-(Ethylamino)propyl]amino}phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10j). The title compound was prepared from **9a** and 3-ethylaminopropylamine using method B. MS (ESI(+)) *m/e* 432 $(M + H)^+$; (ESI(−)) *m/e* 430 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51 (dd, 1H), 7.40 (dt, 1H), 6.94 (d, 1H), 6.84 (d, 1H), 6.63 (m, 2H), 6.01 (m, 1H), 3.31 (m, 2H), 2.95 (m, 4H), 2.65 (m, 4H), 1.85 (m, 2H), 1.66 (m, 4H), 1.15 (t, 3H). Anal. ($C_{22}H_{29}N_3O_4S$·1.25 TFA) C, H, N.

2-({[2-({3-[(2-Hydroxyethyl)amino]propyl}amino)phenyl]sulfonyl}amino)-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10k). The title compound was prepared from **9a** and 2-[(3-aminopropyl)amino]ethanol using method B. MS (ESI(+)) *m/e* 448 $(M + H)^+$; (ESI(−)) *m/e* 446 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51 (dd, 1H), 7.41 (dt, 1H), 6.95 (d, 1H), 6.84 (d, 1H), 6.64 (m, 2H), 6.00 (m, 1H), 3.63 (t, 2H), 3.28 (m, 2H), 2.96 (m, 4H), 2.65 (m, 4H), 1.89 (m, 2H), 1.67 (m, 4H). Anal. ($C_{22}H_{29}N_3O_5S$·1.4 TFA) C, H, N.

2-({[2-({3-[(*tert*-Butoxycarbonyl)amino]propyl}amino)phenyl]sulfonyl}amino)-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10l). The title compound was prepared from **9a** and *tert*-butyl 3-aminopropylcarbamate using method B and purified by RP HPLC with an ammonium acetate buffer. MS (ESI(+)) *m/e* 504 $(M + H)^+$, 526 $(M + Na)^+$; (ESI(−)) *m/e* 502 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.47 (dd, 1H), 7.37 (dt, 1H), 6.95 (d, 1H), 6.76 (d, 1H), 6.60 (m, 2H), 5.90 (m, 1H), 3.14 (m, 2H), 2.97 (q, 2H), 2.65 (m, 4H), 1.66 (m, 4H), 1.64 (m, 2H), 1.38 (s, 9H). Anal. ($C_{25}H_{33}N_3O_6S$) C, H, N.

2-({[2-({3-[(*tert*-Butoxycarbonyl)(methyl)amino]propyl}amino)phenyl]sulfonyl}-amino)-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10m). The title compound was prepared from **9a** and *tert*-butyl 3-aminopropyl(methyl)carbamate using method B and purified by RP HPLC with an ammonium acetate buffer. MS (ESI(+)) *m/e* 518 $(M + H)^+$, 540 $(M + Na)^+$; (ESI(−)) *m/e* 516 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.49 (dd, 1H), 7.38 (dt, 1H), 6.94 (d, 1H), 6.75 (d, 1H), 6.60 (m, 2H), 5.89 (m, 1H), 3.19 (m, 2H), 3.10 (m, 2H), 2.76 (s, 3H), 2.65 (m, 4H), 1.71 (m, 2H), 1.66 (m, 4H), 1.36 (s, 9H). Anal. ($C_{26}H_{35}N_3O_6S$) C, H, N.

2-[({2-[(3-Aminopropyl)amino]phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10n). Compound **10q** (0.035 g, 0.070 mmol) was dissolved in saturated HCl/dioxane (2 mL), stirred for 1 h, concentrated, treated with diethyl ether, and then concentrated to provide the desired product. MS (ESI(+)) *m/e* 404 $(M + H)^+$, 426 $(M + Na)^+$; (ESI(−)) *m/e* 402 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.48 (dd, 1H), 7.41 (dt, 1H), 6.95 (d, 1H), 6.84 (d, 1H), 6.60 (m, 2H), 5.98 (m, 1H), 3.28 (m, 2H), 2.85 (m, 2H), 2.65 (m, 4H), 1.84 (m, 2H), 1.67 (m, 4H). Anal. ($C_{20}H_{25}N_3O_4S$·HCl·H_2O) C, H, N.

2-{[(2-{[3-(4-Methyl-1-piperazinyl)propyl]amino}phenyl)-sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10o). The title compound was prepared from **9a** and 3-(4-methyl-1-piperazinyl)-1-propanamine using method B. MS (DCI) *m/e* 487 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.56 (br s, 1H), 7.50 (dd, 1H), 7.39 (m, 1H), 6.96 (d, 1H), 6.80 (d, 1H), 6.66 (d, 1H), 6.62 (t, 1H), 6.02 (br s, 1H), 3.30 (t, 4H), 3.20 (m, 4H), 2.73 (br s, 3H), 2.65 (m, 4H), 1.66 (m, 4H). Anal. ($C_{25}H_{34}N_4O_4S\cdot 3$ TFA$\cdot H_2O$) C, H, N.

2-{[(2-{[3-(1-Piperidinyl)propyl]amino}phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10p). The title compound was prepared from **9a** and 1-(3-aminopropyl)piperidine using method B. MS (DCI) *m/e* 472 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.22 (br s, 1H), 9.54 (br s, 1H), 7.51 (d, 1H), 7.40 (t, 1H), 6.94 (d, 1H), 6.82 (d, 1H), 6.63 (m, 1H), 6.05 (br s, 1H), 3.27 (m, 4H), 3.10 (m, 2H), 2.67−2.64 (m, 4H), 1.89 (m, 2H), 1.78 (br s, 2H), 1.58 (br s, 2H), 1.65 (br s, 6H). Anal. ($C_{25}H_{33}N_3O_4S\cdot$TFA) C, H, N.

2-{[(2-{[3-(4-Morpholinyl)propyl]amino}phenyl)sulfonyl]-amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10q). The title compound was prepared from **9a** and 1-(3-aminopropyl)-morpholine using method B. MS (DCI) *m/e* 474 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.44 (d, 1H), 7.33 (t, 1H), 7.08 (br s, 1H), 6.92 (d, 1H), 6.76 (d, 1H), 6.54 (t, 1H), 6.18 (br s, 1H), 3.79 (br s, 4H), 3.26−3.17 (m, 8H), 2.73 (br s, 2H), 2.62 (br s, 2H), 1.81 (br s, 2H), 1.62 (br s, 4H). Anal. ($C_{24}H_{31}N_3O_5S\cdot 0.67$ TFA) C, H, N.

2-{[(2-{[3-(1-Pyrrolidinyl)propyl]amino}phenyl)sulfonyl]-amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10r). The title compound was prepared from **9a** and 1-(3-aminopropyl)-pyrrolidine using method B. MS (DCI) *m/e* 458 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.14 (br s, 1H), 9.72 (br s, 1H), 7.51 (dd, 1H), 7.40 (m, 1H), 6.95 (d, 1H), 6.83 (d, 1H), 6.72 (br s, 1H), 6.64 (t, 1H), 6.01 (br s, 1H), 3.27 (m, 4H), 3.18 (m, 4H), 2.67−2.64 (m, 4H), 1.89 (m, 6H), 1.65 (br s, 4H). Anal. ($C_{24}H_{31}N_3O_4S\cdot$TFA) C, H, N.

2-({[2-({2-[1-Methyl-2-pyrrolidinyl]ethyl}amino)phenyl]-sulfonyl}amino)-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10s). The title compound was prepared from **9a** and 2-(2-aminoethyl)-1-methylpyrrolidine using method B. MS (ESI(+)) *m/e* 458 $(M + H)^+$, 480 $(M + Na)^+$; (ESI(−)) *m/e* 456 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.20 (br s, 1H), 10.02 (br s, 1H), 9.54 (s, 1H), 7.52 (dd, 1H), 7.42 (dt, 1H), 6.96 (d, 1H), 6.86 (d, 1H), 6.65 (t, 1H), 6.60 (d, 1H), 5.97 (br s, 1H), 3.26 (m, 4H), 2.98 (quint, 1H), 2.72 (d, 3H), 2.65 (br s, 4H), 2.33−2.13 (m, 2H), 2.00−1.75 (m, 2H), 1.67 (br s, 5H). Anal. ($C_{24}H_{31}N_3O_4S\cdot 1.33$ TFA) C, H, N.

2-[({2-[(1-Benzyl-4-piperidinyl)amino]phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10t). The title compound was prepared from **9a** and 4-amino-1-benzylpiperidine using method B. MS (ESI(+)) *m/e* 520 $(M + H)^+$; MS (ESI(−)) *m/e* 518 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.63 (s, 1H), 7.51 (m, 6H), 7.37 (m, 1H), 6.93 (d, 1H), 6.89 (d, 1H), 6.65 (m, 1H), 6.55 (d, 1H), 5.72 (d, 1H), 4.33 (m, 1H), 3.96 (s, 2H), 3.44 (m, 2H), 3.06 (m, 2H), 2.65 (m, 4H), 211 (m, 2H), 1.96 (m, 2H), 1.65 (m, 4H). Anal. ($C_{29}H_{33}N_3O_4S\cdot 1$ TFA) C, H, N.

2-[({2-[(1,2,2,6,6-Pentamethyl-4-piperidinyl)amino]phenyl}-sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10u). The title compound was prepared from **9a** and 4-amino-1,2,2,6,6-pentamethylpiperidine using method B. MS (ESI(+)) *m/e* 500 $(M + H)^+$; MS (ESI(−)) *m/e* 498 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.68 (s, 1H), 8.45 (s, 1H), 7.52 (dd, 1H), 7.42 (ddd, 1H), 6.94 (d, 1H), 6.68 (t, 1H), 6.50 (d, 1H), 5.70 (d, 1H), 3.99 (m, 1H), 2.75 (s, 3H), 2.67 (m, 4H), 2.10 (m, 2H), 1.68 (m, 4H), 1.57 (t, 2H), 1.46 (s, 6H), 1.40 (s, 6H). Anal. ($C_{27}H_{37}N_3O_4S\cdot$ 1.25 TFA) C, H, N.

2-{[(2-{[3-Piperidinylmethyl]amino}phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10v). The title compound was prepared from **9a** and 1-*tert*-butoxycarbonyl-3-(aminomethyl)piperidine using method B and deprotected with saturated HCl/dioxane. MS (ESI(+)) *m/e* 444 $(M + H)^+$, 461 $(M+NH_4)^+$, 466 $(M + Na)^+$; (ESI(−)) *m/e* 442 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51 (dd, 1H), 7.38 (dt, 1H), 6.96 (d, 1H), 6.82 (d, 1H), 6.63 (m, 2H), 6.04 (m, 1H), 3.69 (m, 1H), 3.49 (m, 1H), 3.08 (m, 2H), 2.83 (m, 2H), 2.65 (m, 4H), 1.83 (m, 3H), 1.67 (m, 4H), 1.29 (m, 2H). Anal. ($C_{23}H_{29}N_3O_4S\cdot 1$ TFA) C, H, N.

2-{[(2-{[3-Pyrrolidinylmethyl]amino}phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10w). The title compound was prepared from **9a** and 1-*tert*-butoxycarbonyl-3-(aminomethyl)pyrrolidine using method B and deprotected with saturated HCl/dioxane. MS (ESI(+)) *m/e* 430 $(M + H)^+$; (ESI(−)) *m/e* 428 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51 (dd, 1H), 7.40 (dt, 1H), 6.95 (d, 1H), 6.87 (d, 1H), 6.65 (t, 1H), 6.59 (d, 1H), 6.01 (m, 1H), 3.11 (m, 4H), 3.02 (m, 2H), 2.65 (m, 4H), 2.02 (m, 1H), 1.67 (m, 4H) 1.28 (m, 2H). Anal. ($C_{22}H_{27}N_3O_4S\cdot 1.33$ TFA) C, H, N.

2-[({2-[(4-Piperidinylmethyl)amino]phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10x). The title compound was prepared from **9a** and 1-*tert*-butoxycarbonyl-4-(aminomethyl)piperidine using method B and deprotected with saturated HCl/dioxane. MS (ESI(+)) *m/e* 444 $(M + H)^+$, 466 $(M + Na)^+$; (ESI(−)) *m/e* 442 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51 (dd, 1H), 7.38 (dt, 1H), 6.95 (d, 1H), 6.82 (d, 1H), 6.63 (m, 2H), 3.26 (d, 2H), 3.06 (m, 2H), 2.81, (m, 2H), 2.66 (m, 4H), 1.83 (m, 3H), 1.67 (m, 4H), 1.33 (m, 2H). Anal. ($C_{23}H_{29}N_3O_4S\cdot 1$ TFA) C, H, N.

2-({[2-({2-[(2*S*)-2-Pyrrolidinyl]ethyl}amino)phenyl]sulfonyl}-amino)-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10y). Compound **12** (0.13 g, 0.3 mmol), lithium hydroxide (0,127 g, 3.0 mmol), dioxane (3 mL), and water (1.5 mL) were sealed in a vial and microwaved at 160 °C for 15 min. The reaction mixture was concentrated and the residues purified by C_{18} reverse-phase HPLC using acetonitrile/water/0.1% TFA to provide the desired product. MS (DCI) *m/e* 444 $(M + H)^+$; ^{1}H NMR (500 MHz, CD_3OD) 7.54 (dd, 1H), 7.38 (m, 1H), 7.13 (d, 1H), 7.02 (d, 1H), 6.80 (d, 1H), 6.65 (m, 1H), 3.71 (m, 1H), 3.44 (t, 1H), 2.72 (br m, 4H), 2.38−2.27 (m, 2H), 2.14−2.00 (m, 4H), 1.72 (m, 4H). Anal. ($C_{23}H_{29}N_3O_4S\cdot$ 1.25 TFA) C, H, N.

2-[2-(3-(4-(1-Piperidinyl)1-piperidinyl)propylamino)-benzenesulfonylamino]-5,6,7,8-tetrahydronaphthalene-1-carboxylic Acid (10z). The title compound was prepared from **9a** and *N*-(3-diethylaminopropyl)-4-(1-piperidinyl)piperidine using method B. MS (ESI(+)) *m/e* 555 $(M + H)^+$; ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.50 (dd, J = 7.96, 1.65 Hz, 1 H); 7.35 (ddd, J = 8.54, 7.10, 1.65 Hz, 1 H); 7.17 (d, J = 8.23 Hz, 1 H); 7.02 (d, J = 8.37 Hz, 1 H); 6.80 (d, J = 7.68 Hz, 1 H); 6.61 (td, J = 7.62, 0.96 Hz, 1 H); 3.81 (d, J = 12.76 Hz, 2 H); 3.45−3.60 (m, J = 11.97, 11.97, 3.57, 3.36 Hz, 3 H); 3.31−3.36 (m, 4 H); 3.03−3.14 (m, 3 H); 2.67−2.78 (m, 4 H); 2.37 (d, J = 13.86 Hz, 2 H); 2.02−2.17 (m, 4 H); 1.91−2.01 (m, 2 H); 1.76−1.89 (m, 3 H); 1.66−1.76 (m, 5 H). Anal. ($C_{30}H_{42}N_4O_4S\cdot 3$ TFA$\cdot H_2O$) C, H, N.

2-{[(2-{[3-(1*H*-Imidazol-1-yl)propyl]amino}phenyl)sulfonyl]-amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10aa). The title compound was prepared from **9a** and 1-(3-aminopropyl)-imidazole using method B. MS (DCI) *m/e* 455 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.87 (br s, 1H), 9.56 (br s, 1H), 9.03 (br s, 1H), 7.74 (s, 1H), 7.67 (s, 1H), 7.51 (dd, 1H), 7.39 (m, 1H), 6.95 (d, 1H), 6.78 (d, 1H), 6.67−6.63 (m, 2H), 5.93 (t, 1H), 3.20−3.16 (m, 4H), 2.63 (m, 4H), 2.10 (m, 2H), 1.65 (br s, 4H). Anal. ($C_{23}H_{26}N_4O_4S\cdot 1.25$ TFA) C, H, N.

2-[({2-[(4-Pyridinylmethyl)amino]phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10ab). The title compound was prepared from **9a** and 4-aminomethylpyridine using method B. MS (ESI(+)) *m/e* 438 $(M + H)^+$; (ESI(−)) *m/e* 436 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.64 (d, 2H), 7.62 (d, 2H), 7.56 (dd, 1H), 7.30 (dt, 1H), 6.97 (d, 1H), 6.65 (m, 2H), 6.57 (d, 1H), 4.66 (d, 2H), 2.67 (m, 4H), 1.68 (m, 4H). Anal. ($C_{23}H_{23}N_3O_4S\cdot 1$ TFA) C, H, N.

2-{[(2-{[2-(2-Pyridinyl)ethyl]amino}phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10ac). The title compound was prepared from **9a** and 2-(2-aminoethyl)pyridine

using method B. MS (DCI) *m/e* 452 $(M + H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (ddd, 1H), 7.70 (td, 1H), 7.54 (dd, 1H), 7.33 (d, 1H), 7.29 (ddd, 1H), 7.22 (ddd, 1H), 6.90 (d, 1H), 6.80 (d, 1H), 6.76 (d, 1H), 6.58 (m, 1H), 6.14 (br s, 1H), 3.47 (t, 2H), 3.02 (t, 2H), 2.90 (m, 2H), 2.59 (m, 2H), 1.60 (m, 4H). Anal. ($C_{24}H_{25}N_3O_4S$·1 TFA) C, H, N.

2-{[(2-{[2-(4-Pyridinyl)ethyl]amino}phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10ad). The title compound was prepared from **9a** and 4-(2-aminoethyl)pyridine using method B. MS (ESI(+)) *m/e* 452 $(M + H)^+$; MS (ESI(−)) *m/e* 450 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.48 (s, 1H), 8.63 (d, 2H), 7.66 (d, 2H), 7.49 (dd, 1H), 7.40 (t, 1H), 6.95 (d, 1H), 6.89 (d, 1H), 6.65 (d, 1H), 6.59 (d, 1H), 5.97 (bd s, 1H), 3.01 (t, 2H), 2.66 (m, 4H), 2.55 (m, 2H), 1.66 (m, 4H). Anal. ($C_{24}H_{25}N_3O_4S$·1 TFA) C, H, N.

2-{[(2-{[3-(2-Oxo-1-pyrrolidinyl)propyl]amino}phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10ae). The title compound was prepared from **9a** and 1-(3-aminopropyl)-2-pyrrolidinone using method B. MS (DCI) *m/e* 472 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.11 (br s, 1H), 9.50 (br s, 1H), 7.48 (dd, 1H), 7.37 (m, 1H), 6.94 (d, 1H), 6.76 (d, 1H), 6.60 (m, 2H), 5.91 (m, 1H), 3.32 (t, 2H), 3.22 (t, 2H), 3.11 (m, 2H), 2.65 (m, 4H), 2.23 (t, 2H), 1.92 (m, 2H), 1.71 (m, 2H), 1.66 (br s, 4H). Anal. ($C_{24}H_{29}N_3O_5S$·0.67 H_2O) C, H, N.

2-[2-(3-Diethylaminopropylamino)-6-fluorobenzenesulfonylamino]-5,6,7,8-tetrahydronaphthalene-1-carboxylic Acid (10af). The title compound was prepared from **9b** and *N,N*-diethyl-1,3-propanediamine using method B. MS [ESI] *m/z* 478 $[M + H]^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.26−7.21 (m, 2H), 6.87 (d, 1H), 6.52 (d, 1H), 6.28 (dd, 1H), 3.30 (m, 4H), 3.10 (m, 4H), 2.83 (m, 2H), 2.60 (m, 2H), 1.79 (m, 2H), 1.59 (m, 4H), 1.17 (t, 6H). Anal. ($C_{24}H_{32}FN_3O_4S$·0.75 H_2O) C, H, N.

2-[2-(3-Diethylaminopropylamino)-5-fluorobenzenesulfonylamino]-5,6,7,8-tetrahydronaphthalene-1-carboxylic Acid (10ag). The title compound was prepared from **9c** and *N,N*-diethyl-1,3-propanediamine using method B. MS [ESI] *m/z* 478 $[M + H]^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.50 (m, 1H), 7.40−7.30 (m, 2H), 7.08 (d, 1H), 6.86 (d, 1H), 3.50 (q, 4H), 3.42 (m, 2H), 3.07 (m, 2H), 2.98 (m, 4H), 2.59 (m, 2H), 1.59 (m, 4H), 1.16 (t, 6H). Anal. ($C_{24}H_{32}FN_3O_4S$·TFA) C, H, N.

2-[3-Chloro-2-(3-diethylaminopropylamino)-benzenesulfonylamino]-5,6,7,8-tetrahydronaphthalene-1-carboxylic Acid (10ah). The title compound was prepared from **9d** and *N,N*-diethyl-1,3-propanediamine using method B. MS [(−)-ESI] *m/z* 492.1 $[M - H]^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.74 (dd, J = 7.8, 1.4 Hz, 1 H), 7.51 (dd, J = 8.0, 1.2 Hz, 1 H), 7.15 (d, J = 8.5 Hz, 1 H), 6.94 (t, J = 8.0 Hz, 1 H), 6.87 (d, J = 8.5 Hz, 1 H), 3.42−3.24 (m, 4 H), 3.18−3.06 (m, 6 H), 2.93−2.85 (m, 2 H), 2.63−2.54 (m, 2 H), 2.07−1.94 (m, 2 H), 1.63−1.55 (m, 4 H), 1.21 (t, J = 7.1 Hz, 6 H). Anal. ($C_{24}H_{32}ClN_3O_4S$·0.67 H_2O) C, H, N.

2-[5-Chloro-2-(3-diethylaminopropylamino)-benzenesulfonylamino]-5,6,7,8-tetrahydronaphthalene-1-carboxylic Acid (10ai). The title compound was prepared from **9e** and *N,N*-diethyl-1,3-propanediamine using method B. MS [ESI] *m/z* 494 $[M + H]^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.35 (d, 1H), 7.32 (dd, 1H), 7.26 (d, 1H), 6.93 (d, 1H), 6.76 (d, 1H), 3.26 (m, 4H), 3.07 (m, 4H), 2.79 (m, 2H), 2.61 (m, 2H), 1.75 (m, 2H), 1.59 (m, 4H), 1.17 (t, 6H). Anal. ($C_{24}H_{32}ClN_3O_4S$·2 H_2O) C, H, N.

2-[4-Chloro-2-(3-diethylaminopropylamino)-5-fluorobenzenesulfonylamino]-5,6,7,8-tetrahydronaphthalene-1-carboxylic Acid (10aj). The title compound was prepared from **9f** and *N,N*-diethyl-1,3-propanediamine using method B. MS [ESI] *m/z* 512 $[M + H]^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.36 (d, 1H), 7.26 (d, 1H), 6.92 (d, 1H), 6.88 (d, 1H), 3.22 (m, 4H), 3.09 (m, 4H), 2.82 (m, 2H), 2.61 (m, 2H), 1.75 (m, 2H), 1.59 (m, 4H), 1.17 (t, 6H). Anal. ($C_{24}H_{31}ClFN_3O_4S$·0.5 H_2O) C, H, N.

2-[2-(3-Diethylaminopropylamino)-5-methylbenzenesulfonylamino]-5,6,7,8-tetrahydronaphthalene-1-carboxylic Acid (10ak). The title compound was prepared from **9g** and *N,N*-diethyl-1,3-propanediamine using method B. MS [ESI] *m/z* 474 $[M + H]^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.36 (m, 1H), 7.25 (d, 1H), 6.96 (d, 1H), 6.78 (d, 1H), 6.67 (m, 1H), 3.24 (m, 4H), 3.09 (m, 4H), 2.66 (m, 4H), 1.85 (m, 2H), 1.67 (m, 4H), 1.13 (t, 6H). Anal. ($C_{25}H_{35}N_3O_4S$·TFA) C, H, N.

2-[4-Chloro-2-(3-diethylaminopropylamino)benzenesulfonylamino]-5,6,7,8-tetrahydronaphthalene-1-carboxylic Acid (10al). The title compound was prepared from **9h** and *N,N*-diethyl-1,3-propanediamine using method B. MS [ESI] *m/z* 494 $[M + H]^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.47 (d, 1H), 6.97 (d, 1H), 6.87 (s, 1H), 6.65 (m, 1H), 3.34 (m, 4H), 3.11 (m, 4H), 2.66 (m, 4H), 1.84 (m, 2H), 1.66 (m, 4H), 1.15 (t, 6H). Anal. ($C_{24}H_{32}ClN_3O_4S$· TFA) C, H, N.

2-[2-(3-Diethylaminopropylamino)-4-methylbenzenesulfonylamino]-5,6,7,8-tetrahydronaphthalene-1-carboxylic Acid (10am). The title compound was prepared from **9i** and *N,N*-diethyl-1,3-propanediamine using method B. MS [ESI] *m/z* 474 $[M + H]^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.41 (d, 1H), 6.96 (d, 1H), 6.65 (s, 1H), 6.65 (m, 1H), 6.47 (d, 1H), 3.27 (m, 4H), 3.10 (m, 4H), 2.65 (m, 4H), 1.87 (m, 2H), 1.66 (m, 4H), 1.14 (t, 6H). Anal. ($C_{25}H_{35}N_3O_4S$·1.4 TFA) C, H, N.

2-[2-(3-Diethylaminopropylamino)-5-(trifluoromethyl)benzenesulfonylamino]-5,6,7,8-tetrahydronaphthalene-1-carboxylic Acid (10an). The title compound was prepared from **9j** and *N,N*-diethyl-1,3-propanediamine using method B. MS [ESI] *m/z* 528$[M + H]^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.71 (m, 2H), 7.02 (d, 1H), 6.98 (d, 1H), 6.53 (m, 1H), 3.37 (m, 4H), 3.11 (m, 4H), 2.66 (m, 4H), 1.88 (m, 2H), 1.67 (m, 4H), 1.15 (t, 6H). Anal. ($C_{25}H_{32}F_3N_3O_4S$· 1.1 TFA) C, H, N.

2-{[(2-{[4-(*N,N*-Dimethylamino)butyl]amino}phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10ao). The title compound was prepared from **9a** and 4-(*N,N*-dimethylamino)butylamine using method B. MS (DCI) *m/e* 446 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.09 (br s, 1H), 9.52 (br s, 1H), 7.51 (d, 1H), 7.38 (m, 1H), 6.95 (d, 1H), 6.79 (d, 1H), 6.68 (br s, 1H), 6.62 (t, 1H), 5.90 (br s, 1H), 3.18 (m, 2H), 3.06 (m, 2H), 2.74 (s, 6H), 2.68−2.65 (m, 4H), 1.69−1.66 (m, 6H), 1.57 (m, 2H). Anal. ($C_{23}H_{31}N_3O_4S$·1.9 TFA) C, H, N.

2-{[(2-{[4-(Diethylamino)-1-methylbutyl]amino}phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (10ap). The title compound was prepared from **9d** and 4-(*N,N*-diethylamino)-1-methylbutylamine using method B. MS (DCI) *m/e* 488 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.10 (br s, 1H), 9.66 (br s, 1H), 7.54 (d, 1H), 7.35 (t, 1H), 6.93 (d, 1H), 6.80 (d, 1H), 6.59 (t, 1H), 5.65 (d, 1H), 3.63 (m, 1H), 3.07−2.97 (br m, 6H), 2.63 (br s, 4H), 1.76−1.47 (br m, 8H), 1.16 (t, 6H), 1.10 (d, 3H). Anal. ($C_{26}H_{37}N_3O_4S$·TFA) C, H, N.

2-{[(2-Aminophenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (11a). Methyl 2-{[(2-nitrophenyl)-sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylate was prepared from **8** and 2-nitrobenzenesulfonyl chloride using method A, followed by saponification with aqueous LiOH at 160 °C for 30 min in a microwave reactor to give 2-{[(2-nitrophenyl)sulfonyl]-amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic acid. A solution thereof (1.4192 g, 3.77 mmol) in methanol (20 mL) was treated with Raney nickel (14.1 g), pressurized to 60 psi with H_2 and shaken for 5 h. The reaction was then filtered, and the filtrate was concentrated to yield **11a** (1.18 g, 90%). MS (ESI(+)) *m/e* 332 $(M + H)^+$, 364 $(M + NH_4)^+$, 369 $(M + Na)^+$; MS (ESI(−)) *m/e* 345 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.48 (d, 1H), 7.17 (t, 1H), 6.92 (d, 1H), 6.80 (d, 1H), 6.71 (d, 3H), 6.52 (t, 1H), 2.92 (m, 2H), 2.58 (m, 2H), 1.60 (m, 4H). Anal. ($C_{17}H_{18}N_2O_4S$) C, H, N.

Methyl 2-{[(2-Aminophenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylate (11b). Methyl 2-{[(2-nitrophenyl)-sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylate was prepared from **8** and 2-nitrobenzenesulfonyl chloride using method A. A solution thereof (2.0873 g, 5.35 mmol) in 4:1 methanol/ethyl acetate (120 mL) was treated with Raney nickel (4.00 g), pressurized to 60 psi with H_2 and shaken for 2 h. The reaction was then filtered, and the filtrate was concentrated to yield **11b** (1.8750 g, 97%). MS (ESI(+)) *m/e* 361 $(M + H)^+$, 383 $(M + Na)^+$; MS (ESI(−)) *m/e* 359 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.32 (dd,

1H), 7.23 (td, 1H), 7.02 (d, 1H), 6.80 (m, 2H), 6.52 (td, 1H), 3.74 (s, 3H), 2.65 (m, 2H), 2.53 (m, 2H), 1.65 (m, 4H).

Methyl 2-({[2-[(2*S*)-(*N*-*tert*-Butoxycarbonyl)-pyrrolidin-2-yl]ethyl}amino)phenyl]sulfonyl}amino)-5,6,7,8-tetrahydro-1-naphthalenecarboxylate (12). A mixture of [(2*R*)-1-(*tert*-butoxycarbonyl)-2-pyrrolidinyl]acetic acid (1.004 g, 4.4 mmol) in THF (10 mL) at −10 °C was treated with NMM (0.484 mL, 4.4 mmol) and isopropyl chloroformate (0.572 mL, 4.4 mmol), stirred for 30 min, filtered, then added dropwise to a stirred solution of sodium borohydride (0.37 g, 9.8 mmol) in water (4 mL), and stirred for 1 h. The solution was acidified to pH 4 with 0.1 M HCl, then transferred to a separatory funnel, and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$), filtered, and concentrated to provide the primary alcohol (0.546 g). MS (DCI) *m*/*e* 216 $(M + H)^+$. The intermediate alcohol (0.546 g, 2.5 mmol) in dimethylacetamide (14 mL) was treated with Dess−Martin periodinane (8.25 mL of 15 wt % solution in CH_2Cl_2, 2.1 mmol), stirred for 15 min, and filtered. The filtrate was added to a solution of **11b** (1.005 g, 2.79 mmol) in CH_2Cl_2/methanol (11 mL), and the resulting mixture was treated with acetic acid (1.65 mL) and macroporous polystyrene-bound cyanoborohydride resin (3.3 g, 7.5 mmol), shaken at 70 °C for 15 h, filtered, concentrated, and purified by flash chromatography, eluting with 30% ethyl acetate/hexanes. MS (DCI) *m*/*e* 544 $(M + H)^+$; ^{1}H NMR (300 MHZ, DMSO-d_6) δ 9.50 (br s, 1 H), 7.3−7.4 (m, 2 H), 7.00 (m, 1 H), 6.75 (m, 2 H), 6.52 (m, 1 H), 5.90 (m, 1 H), 3.80 (m, 2 H), 3.75 (s, 3 H), 3.10 (m, 2 H), 2.65 (m, 2 H), 1.60−1.95 (m, 10 H), 1.40 (s, 9 H).

The Boc-protected intermediate was dissolved in CH_2Cl_2 (100 mL), treated with TFA (20 mL), stirred for 1.5 h, and concentrated to provide **12**, which was used as is without purification or characterization.

Methyl 2-[({2-[(4-(Piperidinyl)methyl)amino]phenyl}-sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalene Carboxylate. Compound **9a** (1.80 g, 5.0 mmol) and 1-*tert*-butoxycarbonyl-4-(aminomethyl)piperidine (5.0 g, 23.4 mmol) were reacted according to method B, and the resulting crude 2-[({2-[(4-(*N*-*tert*-butoxycarbonyl-piperidinyl)methyl)amino]phenyl}-sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalene-carboxylic acid was treated with trimethylsilyldiazomethane (3.0 mL of a 2 M solution in hexanes, 6.0 mmol) in 50 mL of 4:1 benzene/methanol for 90 min. The excess reagent was quenched by the addition of acetic acid and the mixture shaken in a separatory funnel with EtOAc and aq $NaHCO_3$, and the organics were dried over $MgSO_4$. Column chromatography (25% EtOAc/hexanes) provided 0.59 g of methyl 2-[({2-[(4-(*N*-*tert*-butoxycarbonyl-piperidinyl)methyl)amino]phenyl}-sulfonyl)-amino]-5,6,7,8-tetrahydro-1-naphthalene carboxylate, which was dissolved in CH_2Cl_2 (10 mL) and treated with TFA (2 mL) for 150 min. The reaction mixture was shaken in a separatory funnel with CH_2Cl_2 and pH 7 buffer solution and the organics dried over $MgSO_4$ to provide the title compound. MS (ESI) *m*/*e* 458 $(M + H)^+$;^{1}H NMR (300 MHz, DMSO-d_6) δ 7.48 (dd, 1H), 7.29 (dt, 1H), 6.90 (d, 1H), 6.75 (m, 2H), 6.57 (t, 1H), 3.71 (s, 3H), 3.24 (m, 2H), 3.03 (m, 2H), 2.81, (m, 2H), 2.62 (m, 4H), 1.82 (m, 3H), 1.65 (m, 4H), 1.29 (m, 2H).

Method C. 2-{[(2-{[(1-Isopropyl-4-piperidinyl)methyl]amino}-phenyl)sulfonyl]-amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (13a). A mixture of methyl 2-[({2-[(4-(piperidinyl)-methyl)amino]phenyl}-sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalene carboxylate (0.080 g, 0.18 mmol) in DMF (4 mL) was treated with acetic acid (0.04 mL) and acetone (0.022 mL, 0.3 mmol). The mixture was shaken at 50 °C for 20 min, treated with macroporous polystyrene-bound cyanoborohydride resin (85 mg, 0.2 mmol), shaken at 70 °C for 5 h, and filtered. The filtrate was concentrated, dissolved in 4 mL of 2:1 dioxane/water, treated with LiOH (100 mg, 2.4 mmol), and heated to 160 °C for 30 min in a microwave reactor. The reaction mixture was concentrated and the residues purified by C_{18} reverse-phase HPLC using acetonitrile/water/0.1% TFA to provide the desired product (15 mg). MS (ESI-(+)) *m*/*e* 486 $(M + H)^+$; (ESI(−)) *m*/*e* 484 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51 (dd, 1H), 7.38 (dt, 1H), 6.95 (d, 1H), 6.84 (d, 1H), 6.62 (m, 2H), 6.09 (br t, 1H), 3.52 (m, 2H), 3.12 (m, 3H), 2.89, (m, 2H), 2.66 (m, 4H), 1.90 (m, 3H), 1.67 (m, 4H), 1.42 (m, 2H), 1.22 (d, 6H). Anal. ($C_{26}H_{35}N_3O_4S$·2 TFA) C, H, N.

2-({[2-({2-[(2*S*)-1-(Cyclohexylmethyl)-2-pyrrolidinyl]ethyl}-amino)phenyl]-sulfonyl}amino)-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (13b). The title compound was prepared from **12** and cyclohexylcarboxaldehyde using method C. MS (DCI) *m*/*e* 540 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.24 (br s, 1H), 9.58 (br s, 1H), 7.55 (m, 1H), 7.41 (m, 1H), 6.92 (d, 1H), 6.84 (d, 1H), 6.66 (br s, 2H), 6.00 (br s, 1H), 3.59 (br s, 1H), 3.05 (m, 2H), 2.93 (br s, 2H), 2.71 (br m, 2H), 2.63 (br s, 4H), 2.28 (br s, 2H), 1.96 (m, 2H), 1.79−1.60 (m, 15H), 1.13 (m, 2H). Anal. ($C_{30}H_{41}N_3O_4S$·TFA) C, H, N.

2-({[2-({2-[(2*S*)-1-(1-Methyl-4-piperidinyl)-2-pyrrolidinyl]-ethyl}amino)phenyl]-sulfonyl}amino)-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (13c). The title compound was prepared from **12** and 1-methyl-4-piperidone using method C. MS (DCI) *m*/*e* 541 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.24 (br s, 1H), 9.61 (br s, 1H), 7.54 (dd, 1H), 7.42 (m, 1H), 6.97 (d, 1H), 6.86 (d, 1H), 6.67 (m, 2H), 5.93 (br s, 1H), 3.67 (br s, 2H), 3.12−3.07 (m, 4H), 2.88 (br s, 2H), 2.76 (s, 3H), 2.67 (m, 4H), 2.18 (br s, 2H), 2.07 (m, 2H), 1.95 (m, 2H), 1.82 (br s, 4H), 1.67 (m, 4H). Anal. ($C_{29}H_{40}N_4O_4S$ ·2 TFA) C, H, N.

2-({[2-({2-[(2*S*)-1-Cyclohexyl-2-pyrrolidinyl]ethyl}amino)-phenyl]sulfonyl}amino)-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (13d). The title compound was prepared from **12** and cyclohexanone using method C. MS (DCI) *m*/*e* 526 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.20 (br s, 1H), 9.57 (br s, 1H), 7.56 (d, 1H), 7.41 (t, 1H), 6.94 (d, 1H), 6.85 (d, 1H), 6.66 (m, 2H), 5.96 (br s, 1H), 3.61 (br s, 1H), 3.18−3.08 (m, 3H), 2.68−2.64 (m, 4H), 2.17 (br s, 2H), 1.92 (br s, 2H), 1.85−1.72 (m, 4H), 1.66 (m, 6H), 1.53 (m, 1H), 1.32−1.01 (m, 5H). Anal. ($C_{29}H_{39}N_3O_4S$· 1.5 TFA) C, H, N.

2-({[2-({2-[(2*S*)-1-Isopropyl-2-pyrrolidinyl]ethyl}amino)phenyl]-sulfonyl}amino)-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (13e). The title compound was prepared from **12** and acetone using method C. MS (DCI) *m*/*e* 526 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.20 (br s, 1H), 9.57 (br s, 1H), 7.56 (d, 1H), 7.41 (t, 1H), 6.94 (d, 1H), 6.85 (d, 1H), 6.66 (m, 2H), 5.96 (br s, 1H), 3.61 (br s, 1H), 3.18−3.08 (m, 3H), 2.68−2.64 (m, 4H), 2.17 (br s, 2H), 1.92 (br s, 2H), 1.85−1.72 (m, 4H), 1.66 (m, 6H), 1.53 (m, 1H), 1.32−1.01 (m, 5H). Anal. ($C_{26}H_{35}N_3O_4S$·TFA) C, H, N.

2-{[(2-{[(1-Methyl-4-piperidinyl)methyl]amino}phenyl)sulfonyl]-amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (13f). The title compound was prepared from methyl 2-[({2-[(4-(piperidinyl)methyl)amino]phenyl}-sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalene carboxylate and 37% aqueous formaldehyde using method C. MS (ESI(+)) *m*/*e* 458 $(M + H)^+$; (ESI(−)) *m*/*e* 456 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51 (dd, 1H), 7.38 (dt, 1H), 6.94 (d, 1H), 6.83 (d, 1H), 6.62 (m, 2H), 6.05 (br t, 1H), 3.17 (s, 3H), 3.10 (m, 2H), 2.86 (m, 2H), 2.74 (m, 2H), 2.65 (m, 4H), 1.86 (m, 3H), 1.67 (m, 4H), 1.36 (m, 2H). Anal. ($C_{24}H_{31}N_3O_4S$·TFA) C, H, N.

2-{[(2-{[(1′-Methyl-1,4′-bipiperidin-4-yl)methyl]amino}phenyl)-sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (13 g). The title compound was prepared from methyl 2-[({2-[(4-(piperidinyl)methyl)amino]phenyl}-sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalene carboxylate and 1-methyl-4-piperidone using method C. MS (ESI(+)) *m*/*e* 541 $(M + H)^+$; (ESI(−)) *m*/*e* 539 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51 (dd, 1H), 7.39 (dt, 1H), 6.96 (d, 1H), 6.84 (d, 1H), 6.62 (m, 2H), 6.09 (br t, 1H), 3.58 (m, 2H), 3.51 (m, 2H), 3.34 (m, 1H), 3.12 (m, 2H), 2.97, (m, 4H), 2.78 (s, 3H), 2.66 (m, 4H), 2.25 (m, 2H), 2.00−1.82 (m, 5H), 1.67 (m, 4H), 1.42 (m, 2H). Anal. ($C_{29}H_{40}N_4O_4S$·3 TFA) C, H, N.

Method D. 2-[({2-[(*N*,*N*-Diethylglycyl)amino]phenyl}sulfonyl)-amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (14a). A solution of **11a** (0.0590 g, 0.17 mmol) in CH_2Cl_2 (3.0 mL) was treated with chloroacetyl chloride (16 μL, 0.20 mmol) and pyridine (69 μL, 0.85 mmol), stirred for 4 h at room temperature, and then quenched with 1 N HCl (10 mL). The layers were separated, and the organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated to a residue (45.0 mg). The residue was dissolved

in acetone (0.4 mL), treated with diethylamine (50 μL, 0.48 mmol), heated to 60 °C for 2 h, cooled to room temperature, diluted with EtOAc (10 mL), and washed with 1 N HCl (10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The concentrate was purified by C_{18} reverse-phase HPLC using acetonitrile/water/0.1% TFA to provide the desired product (8.7 mg, 18%). MS (ESI(+)) *m/e* 460 $(M + H)^+$; MS (ESI(−)) *m/e* 458 $(M - H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 7.79 (m, 2H), 7.56 (m, 1H), 7.23 (m, 2H), 6.90 (m, 1H), 3.30 (m, 4H), 2.80 (m, 2H), 2.73 (s, 2H), 2.59 (m, 2H), 1.61 (m, 4H), 1.06 (m, 6H). Anal. ($C_{23}H_{29}N_3O_5S$·TFA) C, H, N.

2-[({2-[(*N*,*N*-Diethyl[*b*]alanyl)amino]phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (14b). The title compound was prepared from **11a** and 3-chloropropanoyl chloride using method D. MS (ESI(+)) *m/e* 474 $(M + H)^+$; MS (ESI(−)) *m/e* 472 $(M - H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 7.65 (m, 2H), 7.55 (m, 1H), 7.22 (m, 2H), 6.89 (m, 1H), 3.38 (m, 2H), 3.17 (q, 4H), 3.08 (m, 2H), 2.80 (m, 2H), 2.57 (m, 2H), 2.55 (m, 4H), 2.43 (m, 2H), 1.75 (m, 2H), 1.57 (m, 4H), 1.27 (t, 6H). Anal. ($C_{24}H_{31}N_3O_5S$·TFA) C, H, N.

2-{[(2-{[4-(Diethylamino)butanoyl]amino}phenyl)sulfonyl]-amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (14c). The title compound was prepared from **11a** and 4-chlorobutanoyl chloride using method D. MS (ESI(+)) *m/e* 488 $(M + H)^+$; MS (ESI(−)) *m/e* 486 $(M - H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.73 (s, 1H), 8.15 (d, 1H), 7.79 (dd, 1H), 7.41 (td, 1H), 7.11 (td, 1H), 7.04 (d, 1H), 3.30 (m, 4H), 2.92 (m, 2H), 2.55 (m, 4H), 2.43 (m, 2H), 1.75 (m, 2H), 1.57 (m, 4H), 0.98 (t, 6H). Anal. ($C_{25}H_{33}N_3O_5S$·TFA) C, H, N.

2-{[(2-{[4-(1-Pyrrolidinyl)butanoyl]amino}phenyl)sulfonyl]-amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (14d). The title compound was prepared from **11a**, 4-chlorobutanoyl chloride, and pyrrolidine using method D. MS (ESI(+)) *m/e* 486 $(M + H)^+$; MS (ESI(−)) *m/e* 484 $(M - H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.18 (s, 1H), 8.15 (d, 1H), 7.71 (dd, 1H), 7.62 (ddd, 1H), 7.25 (td, 1H), 6.96 (d, 1H), 6.54 (d, 1H), 3.17 (m, 3H), 3.01 (m, 1H), 2.67 (m, 4H), 2.46 (m, 2H), 1.92 (m, 6H), 1.67 (m, 4H). Anal. ($C_{25}H_{31}N_3O_5S$·TFA) C, H, N.

2-{[(2-{[4-(1-Piperidinyl)butanoyl]amino}phenyl)sulfonyl]-amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (14e). The title compound was prepared from **11a**, 4-chlorobutanoyl chloride, and piperidine using method D. MS (ESI(+)) *m/e* 500 $(M + H)^+$; MS (ESI(−)) *m/e* 498 $(M - H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.15 (d, 1H), 7.71 (dd, 1H), 7.62 (td, 1H), 7.26 (td, 1H), 6.96 (d, 1H), 6.53 (d, 1H), 3.46 (m, 2H), 3.07 (m, 2H), 2.87 (m, 2H), 2.67 (m, 4H), 2.46 (m, 2H), 1.94 (m, 2H), 1.79 (m, 2H), 1.67 (m, 7H), 1.40 M, 1H). Anal. ($C_{26}H_{33}N_3O_5S$·TFA) C, H, N.

2-[({2-[({2-[(Diethylamino)ethyl]amino}carbonyl)amino]-phenyl}-sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (15a). A mixture of **11a** (30.2 mg, 0.09 mmol), triphosgene (8.5 mg, 0.03 mmol), and pyridine (1 mL) was stirred for 3 h at 70 °C, treated with *N*,*N*-diethylethylenediamine (61 μL, 0.44 mmol), stirred for 18 h at 70 °C, concentrated, and purified by C_{18} reverse-phase HPLC using acetonitrile/water/0.1% TFA to provide the desired product (2.0 mg, 5%). MS (ESI(+)) *m/e* 489 $(M + H)^+$; MS (ESI(−)) *m/e* 487 $(M - H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.27 (s, 1H), 8.18 (d, 1H), 7.69 (dd, 1H), 7.53 (td, 1H), 7.47 (m, 1H), 7.10 (t, 1H), 6.95 (d, 1H), 6.65 (s, 1H), 3.19 (m, 6H), 2.66 (m, 4H), 1.66 (m, 4H), 1.20 (t, 6H). Anal. ($C_{24}H_{32}N_4O_5S$·TFA) C, H, N.

Method E. 2-{[(2-{[({2-[1-Methyl-2-pyrrolidinyl]ethyl}amino)-carbonyl]amino}-phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (15b). A solution of **11b** (145.6 mg, 0.404 mmol) in THF (0.25 mL) was treated with carbonyldiimidazole (65.5 mg, 0.404 mmol), heated to 50 °C for 1.5 h, cooled to room temperature, then treated with 2-(2-aminoethyl)-1-methylpyrrolidine (58 μL, 0.404 mmol), stirred for 24 h, and concentrated. The residue was dissolved in pyridine (0.5 mL), treated with LiI (162.2 mg, 1.212 mmol), heated in a microwave reactor at 150 °C for 25 min, concentrated, and purified by C_{18} reverse-phase HPLC using acetonitrile/water/0.1% TFA to provide **15b**. (58.7 mg, 29%). MS (ESI(−)) *m/e* 499 $(M - H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.74 (s, 1H), 8.21 (m, 1H), 7.66 (dd, 1H), 7.53 (ddd, 1H), 7.32 (t, 1H), 7.07 (td, 1H), 6.96 (d, 1H), 6.53 (d, 1H), 3.18 (m, 3H), 3.01 (m, 2H), 2.78 (s, 3H), 2.66 (m, 4H), 2.30 (m, 2H), 1.92 (m, 2H), 1.67 (m, 4H), 1.28 (m, 1H), 0.87 (m, 1H). Anal. ($C_{25}H_{32}N_4O_5S$·TFA) C, H, N.

2-[({2-[({2-[(1-Piperidinyl)ethyl]amino}carbonyl)amino]-phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (15c). The title compound was prepared from **11b** and 1-aminoethylpiperidine using method E. MS (ESI(+)) *m/e* 501 $(M + H)^+$; MS (ESI(−)) *m/e* 499 $(M - H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.27 (s, 1H), 8.21 (dd, 1H), 7.68 (dd, 1H), 7.55 (ddd, 1H), 7.47 (t, 1H), 7.09 (ddd, 1H), 6.95 (d, 1H), 6.60 (d, 1H), 3.50 (m, 2H), 3.45 (g, 2H), 3.16 (m, 2H), 2.91 (m, 2H), 2.66 (m, 4H), 1.82 (m, 2H), 1.67 (m, 7H), 1.39 (m, 1H). Anal. ($C_{25}H_{32}N_4O_5S$·TFA) C, H, N.

2-[({2-[({2-[(4-Morpholinyl)ethyl]amino}carbonyl)amino]-phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (15d). The title compound was prepared from **11b** and 4-aminoethylmorpholine using method E. MS (ESI(−)) *m/e* 501 $(M - H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.21 (m, 2H), 7.68 (dd, 1H), 7.54 (m, 2H), 7.07 (ddd, 1H), 6.94 (d, 1H), 6.77 (d, 1H), 3.84 (m, 4H), 3.46 (m, 4H), 3.24 (t, 4H), 2.67 (m, 4H), 1.65 (m, 4H). Anal. ($C_{24}H_{30}N_4O_6S$·TFA) C, H, N.

2-[({2-[({[3-(4-Morpholinyl)propyl]amino}carbonyl)amino]-phenyl}sulfonyl)-amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (15e). The title compound was prepared from **11b** and 4-(3-aminopropyl)morpholine using method E. MS (ESI(+)) *m/e* 517 $(M + H)^+$; MS (ESI(−)) *m/e* 515 $(M - H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.18 (m, 2H), 7.70 (d, 1H), 7.53 (ddd, 1H), 7.37 (m, 1H), 7.08 (ddd, 1H), 6.95 (d, 1H), 6.63 (m, 1H), 3.93 (m, 2H), 3.39 (m, 2H), 3.12 (m, 6H), 2.67 (m, 4H), 1.82 (m, 4H). Anal. ($C_{25}H_{32}N_4O_6S$·TFA) C, H, N.

2-[({2-[({[3-(1-Piperidinyl)propyl]amino}carbonyl)amino]-phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (15f). The title compound was prepared from **11b** and 1-(3-aminopropyl)piperidine using method E. MS (ESI(+)) *m/e* 515 $(M + H)^+$; MS (ESI(−)) *m/e* 513 $(M - H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.18 (m, 2H), 7.69 (dd, 1H), 7.53 (ddd, 1H), 7.34 (s, 1H), 7.08 (ddd, 1H), 6.95 (d, 1H), 6.59 (m, 1H), 3.42 (d, 2H), 3.14 (q, 2H), 3.06 (m, 2H), 2.83 (m, 2H), 2.67 (m, 4H), 1.82 (m, 5H), 1.66 (m, 6H), 1.38 (m, 1H). Anal. ($C_{26}H_{34}N_4O_5S$·TFA) C, H, N.

2-({[2-({[2-(Diethylamino)ethoxy]carbonyl}amino)phenyl]-sulfonyl}amino)-5,6,7,8-tetrahydro-1-naphthalenecarboxylic acid (16). A mixture of **11a** (36.7 mg, 0.11 mmol), triphosgene (10.4 mg, 0.033 mmol), and pyridine (1 mL) was stirred for 3 h at 70 °C, treated with 2-(diethylamino)ethanol (70 μL, 0.53 mmol), stirred for 18 h at 70 °C, concentrated, and purified by C_{18} reverse-phase HPLC using acetonitrile/water/0.1% TFA to provide the desired product (4.5 mg, 9%). MS (ESI(+)) *m/e* 490 $(M + H)^+$; MS (ESI(−)) *m/e* 488 $(M - H)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ 8.80 (s, 1H), 8.04 (d, 1H), 7.74 (dd, 1H), 7.64 (m, 1H), 7.24 (t, 1H), 6.97 (d, 1H), 6.65 (m, 1H), 4.40 (t, 2H), 3.20 (q, 6H), 2.56 (m, 4H), 1.66 (m, 4H), 1.20 (t, 6H). Anal. ($C_{24}H_{31}N_3O_6S$·TFA) C, H, N.

Methyl 2-({[2-Bromophenyl]sulfonyl}amino)-5,6,7,8-tetrahydro-1-naphthalene-carboxylate (17a). The title compound was prepared from **8** and 2-bromobenzenesulfonyl chloride using method A. ^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1 H) 8.09 (m, 1 H); 7.68 (m, 1 H); 7.37 (m, 2 H); 7.25 (d, J = 8.56 Hz, 1 H); 7.00 (d, J = 8.56 Hz, 1 H); 3.88 (s, 3 H); 2.69 (m, 4 H); 1.68 (m, 4 H).

Methyl 2-({[2-Bromo-4-fluorophenyl]sulfonyl}amino)-5,6,7,8-tetrahydro-1-naphthalene-carboxylate (17b). The title compound was prepared from **8** and 2-bromo-4-fluorobenzenesulfonyl chloride using method A. ^1H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 7.89 (m, 2 H) 7.39 (td, 1 H); 7.09 (d, 1 H); 6.86 (d, 1 H); 3.70 (s, 3 H); 2.67 (m, 2 H); 2.53 (m, 2H); 1.66 (m, 4 H).

Method F. 2-{[(2-{[2-(Diethylamino)ethyl]sulfanyl}phenyl)-sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid

(18a). A suspension of 2-(diethylamino)ethanethiol hydrochloride (560 mg, 3.30 mmol) and 60% sodium hydride dispersion (224 mg, 10.18 mmol) was stirred in 3 mL of dry DMF until hydrogen evolution ceased. The mixture was treated with a solution of **17a** (200 mg, 0.55 mmol) in 1 mL of DMF, stirred at 70−75 °C overnight, concentrated, and dissolved in 2 mL of pyridine. The mixture was treated with LiI (0.221 g, 1.7 mmol), heated in a microwave reactor at 150 °C for 25 min, and concentrated. The crude material was purified by C_{18} reverse-phase HPLC using acetonitrile/water/0.1% TFA to provide the desired product (200 mg, 78.7%). MS (APCI) *m*/*e* 462.8 $(M + H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 7.89 (dd, 1H), 7.65 (dd, 1H), 7.57 (dt, 1H) 7.34 (dt, 1H), 7.18 (d, 1H), 7.00 (d, 1H), 3.34−3.51 (m, 4H), 3.29 (m, 2H), 3.25 (q, 4H), 2.65−2.77 (m, 4H), 1.70 (m, 4H), 1.28 (t, 6H). Anal. ($C_{23}H_{30}N_2O_4S_2$·TFA) C, H, N.

2-{[(2-{[3-(Diethylamino)propyl]sulfanyl}phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (18b). The title compound was prepared from **17a** and 3-(diethylamino)-propanethiol hydrochloride using method F. MS (APCI) *m*/*e* 477.3 $(M + H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 7.92 (dd, 1H), 7.59 (dd, 1H), 7.53 (dt, 1H) 7.29 (dt, 1H), 7.17 (d, 1H), 6.99 (d, 1H), 3.27−3.35 (m, 4H), 3.19 (m, 6H), 2.65−2.80 (m, 4H), 2.08 (m, 2H), 1.70 (m, 4H), 1.26 (t, 6H). Anal. ($C_{24}H_{32}N_2O_4S_2$·TFA) C, H, N.

2-{[(2-{[2-(Diethylamino)ethyl]sulfanyl}-4-fluorophenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (18c). The title compound was prepared from **17b** and 3-(diethylamino)ethanethiol hydrochloride using method F. MS (ESI) *m*/*e* 481 $(M + H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 7.91 (dd, 1H), 7.43 (dd, 1H), 7.05 (m, 2H), 7.04 (d, 1H), 3.41−3.52 (m, 4H), 3.29 (q, 4H), 2.72 (m, 4H), 1.71 (m, 4H), 1.31 (t, 6H). Anal. ($C_{23}H_{29}FN_2O_4S_2$·TFA) C, H, N.

2-{[(2-{[2-(Dimethylamino)ethyl]sulfanyl}phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (18d). The title compound was prepared from **17b** and 3-(dimethylamino)-ethanethiol hydrochloride using method F. MS (ESI) *m*/*e* 453 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.55 (m, 1H), 7.50 (dd, 1H), 7.07 (m, 2H), 6.97 (d, 1H), 3.57 (m, 2H), 3.37 (m, 2H), 2.80 (s, 6H), 2.64 (m, 4H), 1.61 (m, 4H). Anal. ($C_{21}H_{25}FN_2O_4S_2$·TFA) C, H, N.

2-{[(2-{[2-(Dimethylamino)ethyl]sulfanyl}-4-fluorophenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (18e). The title compound was prepared from **17a** and 3-(dimethylamino)ethanethiol hydrochloride using method F. MS (ESI) *m*/*e* 435 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.56 (d, 1H), 7.50 (dd, 1H), 7.44 (d, 1H), 7.24 (d, 1H), 7.14 (m, 1H), 6.92 (d, 1H), 3.57 (m, 2H), 3.32 (m, 2H), 2.77 (s, 6H), 2.63 (m, 4H), 1.58 (m, 4H). Anal. ($C_{21}H_{26}N_2O_4S_2$·TFA) C, H, N.

Method G. 2-{[(2-{[2-(Diethylamino)ethyl]sulfinyl}phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (19a). A sample of **18a** (0.091 g, 0.20 mmol) was dissolved in 2.5 mL of glacial acetic acid. To this was added 650 mg of 30% hydrogen peroxide solution. After stirring at room temperature for 8.3 h, the reaction mixture was concentrated and purified by C_{18} reverse-phase HPLC using acetonitrile/water/0.1% TFA to provide the desired product (45 mg, 47.8%). MS (APCI): *m*/*e* 479.1 $(M + H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (dd, 1H), 7.90 (dt, 1H), 7.84 (dd, 1H) 7.70 (dt, 1H), 7.09 (d, 1H), 6.98 (d, 1H), 3.60−3.73 (m, 2H), 3.42−3.50 (m, 1H), 3.23−3.32 (m, 4H), 3.01−3.10 (m, 1H), 2.66−2.78 (m, 4H), 1.65−1.80 (m, 4H), 1.31 (t, 6H). Anal. ($C_{23}H_{30}N_2O_5S_2$·1.5 TFA) C, H, N.

2-{[(2-{[2-(Diethylamino)ethyl]sulfinyl}-4-fluorophenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (19b). The title compound was prepared from **18c** using method G. MS (ESI) *m*/*e* 497 $(M + H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (m, 2H), 7.58 (m, 1H), 7.02 (d, 1H), 6.82 (d, 1H), 3.40 (m, 2H), 3.14 (m, 2H), 3.07 (q, 4H), 2.68 (m, 4H), 1.60 (m, 4H), 1.15 (t, 6H). Anal. ($C_{23}H_{29}FN_2O_5S_2$·TFA·H_2O) C, H, N.

2-{[(2-{[2-(Dimethylamino)ethyl]sulfinyl}-4-fluorophenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (19c). The title compound was prepared from **18d** using method G. MS (ESI) *m*/*e* 469 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87 (dd, 1H), 7.78 (dd, 1H), 7.64 (td, 1H), 7.06 (d, 1H), 6.69 (d, 1H), 3.54−3.44 (m, 2H), 3.24−3.04 (m, 2H), 2.77 (s, 6H), 2.70 (m, 2H), 2.62 (m, 2H), 1.68 (m, 4H). Anal. ($C_{21}H_{25}FN_2O_5S_2$·TFA) C, H, N.

2-{[(2-{[2-(Dimethylamino)ethyl]sulfinyl}phenyl)sulfonyl]amino}-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (19d). The title compound was prepared from **18e** using method G. MS (ESI) *m*/*e* 451 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.09 (dd, 1H), 7.96 (td, 1H), 7.86−7.76 (m, 2H), 7.02 (d, 1H), 6.62 (d, 1H), 3.52−3.43 (m, 2H), 3.24−3.01 (m, 2H), 2.78 (s, 6H), 2.69 (m, 2H), 2.64 (m, 2H), 1.67 (m, 4H). Anal. ($C_{21}H_{26}N_2O_5S_2$·1.5 TFA) C, H, N.

2-[({2-[3-(Diethylamino)propoxy]phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (20a). The title compound was prepared from **17a** and 3-diethylamino-1-propanol using method F. MS (APCI): *m*/*e* 461 $(M + H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 7.74 (dd, 1H), 7.54 (dt, 1H), 7.27 (d, 1H) 7.12 (d, 1H), 6.98−7.04 (m, 2H), 4.27 (t, 2H), 3.43−3.51 (m, 2H), 3.25−3.36 (m, 6H), 3.65−3.81 (m, 4H), 3.35 (m, 2H), 1.70 (m, 4H), 1.37 (t, 6H). Anal. ($C_{23}H_{30}N_2O_5S$·1.25 TFA) C, H, N.

2-[({2-[2-(1-Methylpyrrolidin-2-yl)ethoxy]phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (20b). The title compound was prepared from **17a** and 2-(2-hydroxyethyl)-1-methylpyrrolidine using method F. MS (APCI): *m*/*e* 459 $(M + H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, 1H), 7.44 (dt, 1H), 7.38 (d, 1H) 7.02−9.97 (m, 2H), 6.87 (d, 1H), 4.32 (m, 1H), 4.05−3.80 (m, 7H), 3.77 (m, 1H), 3.15 (s, 3H), 2.85 (m, 1H), 2.63 (m, 1H), 2.39 (m, 1H), 2.25−2.10 (m, 2H), 2.00 (m, 1H), 1.73 (m, 2H), 1.60 (m, 2H). Anal. ($C_{24}H_{30}N_2O_5S$·TFA) C, H, N.

Methyl 2-({[2-(Methoxycarbonyl)phenyl]sulfonyl}amino)-5,6,7,8-tetrahydro-1-naphthalenecarboxylate (21). The title compound was prepared from **8** and methyl 2-(chlorosulfonyl)benzoate using method A. MS (ESI(+)) *m*/*e* 404 $(M + H)^+$; 480 $(M + Na)^+$; (ESI(−)) *m*/*e* 402 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.14 (s, 1H), 7.77−7.65 (m, 4H), 7.12 (d, 1H), 6.98 (d, 1H), 3.01 (s, 3H), 3.63 (s, 3H), 2.68 (br s, 2H), 2.53 (br s, 2H), 1.66 (br m, 4H).

2-({[1-(Methoxycarbonyl)-5,6,7,8-tetrahydro-2-naphthalenyl]amino}sulfonyl)-benzoic Acid (22). A solution of **21** (3.04 g, 7.54 mmol) in methanol (70 mL) and distilled water (7.8 mL) was treated with lithium hydroxide monohydrate (1.58 g, 37.7 mmol), heated to 60 °C overnight, cooled to room temperature, treated with 1 N HCl, and concentrated. The aqueous layer was washed twive with dichloromethane, and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated to provide the desired product. MS (ESI(+)) *m*/*e* 388 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 14.00 (br s, 1H), 8.85 (br s, 1H), 7.83 (d, 1H), 7.73 (m, 2H), 7.64 (m, 1H), 7.13 (s, 2H), 3.63 (s, 3H), 2.67 (br s, 2H), 2.51 (br s, 2H), 1.65 (br m, 4H).

Method H. 2-({[2-({[2-(Diethylamino)ethyl]amino}carbonyl)-phenyl]sulfonyl}-amino)-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (23a). A solution of **22** (100 mg, 0.257 mmol) in dimethylformamide (2.0 mL) was treated with 4-methylmorpholine (109 μL, 0.992 mmol) and *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (188.5 mg, 0.496 mmol), stirred for 1 h at room temperature, treated with *N*,*N*-diethylethylenediamine (72 μL, 0.514 mmol), stirred overnight at room temperature, and treated with 1 N HCl. The aqueous layer was washed twice with dichloromethane, and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by preparative HPLC to provide the methyl ester. MS (ESI(+)) *m*/*e* 488 $(M + H)^+$; (ESI(−)) *m*/*e* 486 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.10 (br s, 1H), 9.06 (t, 1H), 9.84 (s, 1H), 7.77 (dt, 1H), 7.68 (dd, 2H), 7.62 (m, 1H), 7.12 (d, 1H), 7.08 (d, 1H), 3.64 (m, 2H), 3.63 (s, 3H), 3.29−3.22 (m, 6H), 2.68 (br s, 2H), 2.51 (br s, 2H), 1.65 (br m, 4H), 1.24 (t, 6H).

A sample of the intermediate ester (13.8 mg, 0.028 mmol), dioxane (0.5 mL), distilled water (0.25 mL), and lithium hydroxide monohydrate (12.0 mg, 0.283 mmol) was sealed in a 2 mL microwave reaction vessel and heated in a microwave for 1200 s

at 160 °C. The solution was cooled to room temperature, treated with 1 N HCl, and concentrated. The resulting residue was purified by preparative HPLC to provide the desired product. MS (ESI(+)) *m/e* 474 $(M + H)^+$; (ESI(−)) *m/e* 472 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.20 (br s, 1H), 9.14 (br s, 1H), 9.02 (t, 2H), 7.77 (m, 2H), 7.65 (m, 2H), 7.04 (d, 1H), 6.93 (d, 1H), 3.63 (q, 1H), 3.25 (m, 6H), 2.67 (br s, 2H), 2.61 (br s, 2H), 1.66 (br s, 4H), 1.23 (t, 6H). Anal. ($C_{24}H_{31}N_3O_5S$·TFA) C, H, N.

2-[({2-[({2-[1-Methyl-2-pyrrolidinyl]ethyl}amino)carbonyl]-phenyl}sulfonyl)-amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (23b). The title compound was prepared from **22** and 2-(2-aminoethyl)-1-methylpyrrolidine using method H. MS (ESI-(+)) *m/e* 486 $(M + H)^+$; (ESI(−)) *m/e* 484 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.15 (br s, 1H), 9.46 (br s, 1H), 9.00 (s, 1H), 8.89 (t, 1H), 7.75 (dd, 2H), 7.62 (m, 2H), 7.02 (d, 1H), 6.92 (d, 1H), 3.57 (m, 2H), 3.32 (m, 3H), 3.06 (quint, 1H), 2.81 (d, 3H), 2.65 (s, 2H), 2.60 (s, 2H), 2.37 (m, 1H), 2.16 (m, 1H), 1.99 (m, 1H), 1.90 (m, 1H), 1.70 (m, 1H) 1.65 (s, 4H). Anal. ($C_{25}H_{31}N_3O_5S$·TFA) C, H, N.

2-({[2-({[2-(1-Piperidinyl)ethyl]amino}carbonyl)phenyl]-sulfonyl}amino)-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (23c). The title compound was prepared from **22** and 1-(2-aminoethyl)piperidine using method H. MS (ESI(+)) *m/e* 486 $(M + H)^+$; (ESI(−)) *m/e* 484 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.02 (br m, 2H), 7.78 (m, 2H), 7.64 (m, 2H), 7.04 (d, 1H), 6.93 (d, 1H), 3.66 (q, 3H), 3.26 (t, 3H), 2.98 (br s, 2H), 2.67 (br s, 2H), 2.61 (br s, 2H), 1.83 (br m, 2H), 1.66 (t, 7H), 1.40 (br s, 1H). Anal. ($C_{25}H_{31}N_3O_5S$·TFA) C, H, N.

2-({[2-({[3-(Diethylamino)propyl]amino}carbonyl)phenyl]-sulfonyl}amino)-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (23d). The title compound was prepared from **22** and 3-(*N*,*N*-diethylamino)propylamine using method H. MS (ESI(+)) *m/e* 488 $(M + H)^+$, 510 $(M + Na)^+$; (ESI(−)) *m/e* 486 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.14 (br s, 1H), 9.01 (s, 2H), 8.92 (t, 1H), 7.75 (dt, 2H), 7.63 (dd, 2H), 7.03 (d, 1H), 6.92 (d, 1H), 3.39 (q, 2H), 3.14 (m, 6H), 2.66 (br s, 2H), 2.61 (br s, 2H), 1.89 (m, 2H), 1.20 (t, 6H). Anal. ($C_{25}H_{33}N_3O_5S$·1.66 TFA) C, H, N.

2-({[2-({[4-(Diethylamino)butyl]amino}carbonyl)phenyl]-sulfonyl}amino)-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (23e). The title compound was prepared from **22** and 4-(*N*,*N*-diethylamino)butylamine using method H. MS (ESI(+)) *m/e* 502 $(M + H)^+$; (ESI(−)) *m/e* 500 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.11 (br s, 1H), 9.03 (s, 1H), 8.93 (br s, 1H), 8.86 (t, 1H), 7.74 (dt, 2H), 7.62 (dd, 2H), 7.03 (d, 1H), 6.90 (d, 1H), 3.58 (m, 2H), 3.33 (q, 2H), 3.12 (m, 4H), 2.66 (br s, 2H), 2.60 (br s, 2H), 1.74−1.56 (m, 8H), 1.20 (t, 6H). Anal. ($C_{26}H_{35}N_3O_5S$·TFA) C, H, N.

2-({[2-({[(4-(Diethylamino)-1-methylbutyl]amino}carbonyl)-4-fluorophenyl]-sulfonyl}amino)-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (23f). In a high-pressure vessel was placed **17b** (1.26 g, 2.85 mmol), THF (12 mL), triethylamine (6 mL), *N*-(4-aminopentyl)-*N*,*N*-diethylamine (4.5 g, 28.4 mmol), and $PdCl_2$(dppf)·CH_2Cl_2 (233 mg). The solution was stirred at 120 °C under 450 psi carbon monoxide for 16 h, cooled to room temperature, and filtered. The filtrate was treated with 1 N HCl, and the aqueous layer was extracted twice with ethyl acetate. The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by preparative HPLC to provide methyl 2-({[2-({[4-(diethylamino)-1-methylbutyl]amino}carbonyl)-4-fluorophenyl]sulfonyl}amino)-5,6,7,8-tetrahydro-1-naphthalenecarboxylate (1.16 g, 74%). MS (ESI(+)) *m/e* 548 $(M + H)^+$; (ESI(−)) *m/e* 546 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.93 (br s, 1H), 8.87 (s, 1H), 8.82 (d, 1H), 7.70 (dd, 1H), 7.53 (dt, 1H), 7.12 (d, 1H), 7.06 (d, 1H), 4.02 (m, 2H), 3.18−3.02 (m, 6H), 2.68 (br s, 2H), 2.51 (br s, 2H), 1.75−163 (br m, 5H), 1.55 (m, 2H), 1.20 (m, 9H).

Methyl 2-({[2-({[4-(diethylamino)-1-methylbutyl]amino}carbonyl)-4-fluorophenyl]-sulfonyl}amino)-5,6,7,8-tetrahydro-1-naphthalenecarboxylate (1.16 g, 2.12 mmol), pyridine (20 mL), and lithium iodide (0.849 g, 6.34 mmol) were combined and heated in a microwave reactor for 1500 s at 160 °C. The solution was cooled to room temperature, treated with 1 N HCl, and concentrated. The resulting residue was purified by preparative HPLC to provide **23f** (0.459 g, 41%). MS (ESI(+)) *m/e* 534 $(M + H)^+$; (ESI(−)) *m/e* 532 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.13 (br s, 1H), 9.45 (br s, 1H), 8.96 (br s, 2H), 8.74 (d, 1H), 7.78 (dd, 1H), 7.50−7.42 (m, 2H), 7.04 (d, 1H), 6.92 (d, 1H), 4.02 (m, 1H), 3.18−3.02 (m, 6H), 2.67 (br s, 2H), 2.60 (br s, 2H), 1.74−163 (br m, 6H), 1.52 (m, 2H), 1.19 (m, 9H). Anal. ($C_{27}H_{36}FN_3O_5S$·TFA) C, H, N.

2-({[2-({[(4-(Diethylamino)-1-methylbutyl]amino}carbonyl)-phenyl]sulfonyl}-amino)-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (23g). The title compound was prepared from **22** and *N*-(4-aminopentyl)-*N*,*N*-diethylamine using method H. MS (ESI-(+)) *m/e* 516 $(M + H)^+$, 538 $(M + Na)^+$; (ESI(−)) *m/e* 514 $(M - H)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.18 (br s, 1H), 9.02 (br s, 1H), 8.70 (d, 1H), 7.74 (dt, 2H), 7.61 (m, 2H), 7.02 (d, 1H), 6.89 (d, 1H), 4.04 (quint, 1H), 3.17−3.00 (m, 6H), 2.66 (br s, 2H), 2.61 (br s, 2H), 1.72 (m, 2H), 1.66 (s, 4H), 1.54 (q, 2H), 1.20 (m, 9H). Anal. ($C_{27}H_{37}N_3O_5S$·TFA) C, H, N.

Method I. 2-[({2-[(1*Z*)-3-(Diethylamino)-1-propenyl]phenyl}-sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (24a). A solution of **17a** (0.212 g, 0.5 mmol), (*Z*)-tributyl-(3-(dimethylamino)-prop-1-enyl)stannane (0.245 g, 0.6 mmol), and bis-(tri-*tert*-butylphosphine)palladium (0.050 g, 0.1 mmol) in 2 mL of degassed toluene was heated under Ar at 90 °C for 90 min. The mixture was concentrated, chromatographed on silica (0:15% triethylamine/EtOAc), and the product recrystallized from hot 4:1 heptane/EtOAc to give a tan solid (0.153 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.96 Hz, 1H), 7.50 (t, J = 7.48 Hz, 1H), 7.37 (t, J = 7.62 Hz, 1H), 7.31 (d, J = 7.27 Hz, 1H), 6.97 (m, 3H), 5.97 (m, 1H), 3.83 (s, 3H), 3.01 (d, J = 6.59 Hz, 2H), 2.70 (m, 4H), 2.41 (q, J = 7.09 Hz, 4H), 1.70 (m, 4H), 0.87 (t, J = 7.14 Hz, 6H).

The intermediate methyl ester (0.116 g, 0.25 mmol) and lithium iodide (0.134 g, 1.0 mmol) in pyridine (7 mL) were heated in a microwave reactor at 150 °C for 35 min and then concentrated in vacuo. The crude product was purified by C_{18} reverse-phase HPLC using acetonitrile/water/0.1% TFA to provide the desired product (0.085 g, 77%). MS (ESI(+)) *m/e* 443 $(M + H)^+$; MS (ESI(−)) *m/e* 441 $(M - H)^-$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.75 (s, 1H), 9.53 (s, 1H), 7.81 (dd, J = 7.89, 1.17 Hz, 1H), 7.66 (td, J = 7.55, 1.10 Hz, 1H), 7.51 (t, J = 7.34 Hz, 1H), 7.33 (m, 2H), 6.97 (d, J = 8.23 Hz, 1H), 6.66 (d, J = 8.37 Hz, 1H), 5.89 (dt, J = 11.66, 6.93 Hz, 1H), 3.80 (d, J = 6.45 Hz, 2H), 3.05 (q, J = 7.23 Hz, 4H), 2.66 (m, 4H), 1.65 (m, 4H), 1.02 (t, J = 7.20 Hz, 6H). Anal. ($C_{24}H_{30}N_2O_4S$·HCl·0.25 H_2O) C, H, N.

2-[({2-[(1*Z*)-3-(Diethylamino)-1-propenyl]-4-fluorophenyl}-sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (24b). The title compound was prepared from **17b** and *N*,*N*-diethyl-*N*-[(2*Z*)-3-(tributylstannyl)-2-propenyl]amine using method I. MS (ESI(+)) *m/e* 461 $(M + H)^+$; MS (ESI(−)) *m/e* 459 $(M - H)^-$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.79 (s, 1H), 9.81 (s, 1H), 7.82 (m, 1H), 7.37−7.23 (m, 3H), 7.02 (d, 1H), 6.71 (d, 1H), 6.11 (m, 1H), 3.83 (m, 2H), 3.02 (q, 4H), 2.65 (m, 4H), 1.67 (m, 4H), 1.09 (t, 6H). Anal. ($C_{24}H_{29}FN_2O_4S$·TFA) C, H, N.

2-[({2-[(1*Z*)-4-(Diethylamino)-1-butenyl]phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (24c). The title compound was prepared from **17a** and *N*,*N*-diethyl-*N*-[(3*Z*)-4-(tributylstannyl)-3-butenyl]amine using method I. MS (ESI(+)) *m/e* 457 $(M + H)^+$; MS (ESI(−)) *m/e* 455 $(M - H)^-$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (d, J = 7.82 Hz, 1H), 7.62 (t, J = 8.16 Hz, 1H), 7.45 (t, J = 7.75 Hz, 1H), 7.39 (d, J = 7.55 Hz, 1H), 6.97 (m, 2H), 6.73 (d, J = 8.10 Hz, 1H), 5.73 (m, 1H), 3.09 (m, 2H), 3.02 (q, J = 7.18 Hz, 4H), 2.65 (m, 4H), 2.40 (m, 2H), 1.64 (m, J = 3.02, 3.02 Hz, 4H), 1.09 (t, J = 7.27 Hz, 6H). Anal. ($C_{25}H_{32}N_2O_4S$·1.4 TFA) C, H, N.

2-[({2-[(1*Z*)-5-(Diethylamino)-1-pentenyl]phenyl}sulfonyl)-amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (24d). The title compound was prepared from **17a** and *N*,*N*-diethyl-*N*-[(4*Z*)-5-(tributylstannyl)-4-pentenyl]amine using method I. MS (ESI(+)) *m/e* 471 $(M + H)^+$; MS (ESI(−)) *m/e* 469 $(M - H)^-$; ^{1}H

NMR (400 MHz, DMSO-d_6) δ 7.79 (dd, J = 7.83, 1.22 Hz, 1H), 7.48 (td, J = 7.46, 1.22 Hz, 1H), 7.32 (m, 2H), 7.12 (d, J = 8.31 Hz, 1H), 6.93 (d, J = 11.74 Hz, 1H), 6.79 (d, J = 8.31 Hz, 1H), 5.71 (dt, J = 11.55, 7.06 Hz, 1H), 2.90 (m, 2H), 2.68 (q, J = 7.09 Hz, 4H), 2.58 (m, 4H), 2.10 (m, 2H), 1.56 (m, 6H), 0.99 (t, J = 7.21 Hz, 6H). Anal. ($C_{26}H_{34}N_2O_4S$·TFA) C, H, N.

2-[({2-[(1*Z*)-3-(1-Pyrrolidino)-1-butenyl]phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (24e). The title compound was prepared from **17a** and (*Z*)-3-(1-pyrrolidinyl)-1-butenyl-tributylstannane using method I. MS (APCI) 455 (M + H)$^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (s, 2 H); 7.83 (dd, J = 7.82, 1.10 Hz, 1 H); 7.66 (td, J = 7.58, 1.30 Hz, 1 H); 7.52 (td, J = 7.72, 1.03 Hz, 1 H); 7.30 (d, J = 7.41 Hz, 1 H); 7.18 (d, J = 11.53 Hz, 1 H); 6.97 (d, J = 8.37 Hz, 1 H); 6.65 (d, J = 8.23 Hz, 1 H); 5.80 (dd, J = 11.53, 10.43 Hz, 1 H); 3.98 (s, 1 H); 2.99 (s, 1 H); 2.74 (s, 1 H); 2.65 (s, 4 H); 1.88 (s, 1 H); 1.76 (s, 3 H); 1.65 (m, 4 H); 1.43 (d, J = 6.45 Hz, 3 H). Anal. ($C_{25}H_{30}N_2O_4S$·TFA·H_2O) C, H, N.

2-[({2-[(1*Z*)-3-(1-Pyrrolidino)-1-butenyl]-4-fluorophenyl}-sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (24f). The title compound was prepared from **17b** and (*Z*)-3-(1-pyrrolidinyl)-1-butenyl-tributylstannane using method I. MS (APCI) 473 (M + H)$^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (dd, 1H), 7.20 (dt, 1H), 7.10−7.02 (m, 4H), 5.87 (t, 1H), 3.50 (m, 2H), 3.30 (m, 1H), 3.06 (m, 1H), 2.87 (m, 1H), 2.73 (m, 4H), 2.05−1.85 (m, 4H), 1.72 (m, 4H), 1.54 (d, 3H). Anal. ($C_{25}H_{29}FN_2O_4S$·TFA) C, H, N.

2-[({2-[(1*Z*)-3-(Diethylamino)-1-butenyl]phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (24g). The title compound was prepared from **17a** and (*Z*)-3-(triethylamino)-1-butenyl-tributylstannane using method I. MS (APCI) 457 (M + H)$^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1 H); 9.81 (s, 1 H); 7.81 (dd, J = 7.96, 1.10 Hz, 1 H); 7.67 (td, J = 7.55, 1.24 Hz, 1 H); 7.51 (t, J = 7.27 Hz, 1 H); 7.34 (d, J = 7.41 Hz, 1 H); 7.24 (d, J = 11.66 Hz, 1 H); 6.98 (d, J = 8.23 Hz, 1 H); 6.66 (d, J = 8.23 Hz, 1 H); 5.91 (t, J = 11.11 Hz, 1 H); 3.00 (m, 2 H); 2.85 (m, 1 H); 2.64 (m, 4 H); 1.66 (m, 4 H); 1.53 (d, J = 6.45 Hz, 3 H); 1.03 (t, J = 7.14 Hz, 3 H); 0.89 (t, J = 7.00 Hz, 3 H). Anal. ($C_{25}H_{32}N_2O_4S$·TFA·H_2O) C, H, N.

2-[({2-[(1*Z*)-3-(Diethylamino)-1-butenyl]-4-fluorophenyl}-sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (24h). The title compound was prepared from **17b** and (*Z*)-3-(diethylamino)-1-butenyl-tributylstannane using method I. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.90 (dd, J = 8.92, 5.49 Hz, 1 H); 7.22 (td, J = 8.47, 2.54 Hz, 1 H); 7.00−7.17 (m, 4 H); 5.86 (t, J = 11.20 Hz, 1 H); 4.15−4.31 (m, 1 H); 3.35−3.45 (m, 1 H); 3.10−3.27 (m, 3 H); 2.98−3.09 (m, 1 H); 2.66−2.80 (m, 4 H); 1.66−1.81 (m, 4 H); 1.11−1.23 (m, 3 H); 0.99−1.12 (m, 3 H). Anal. ($C_{25}H_{31}FN_2O_4S$·1.2 TFA) C, H, N.

2-[({2-[(1*E*)-3-(Diethylamino)-1-propenyl]phenyl}sulfonyl)-amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (25a). The title compound was prepared from **17a** and *N*,*N*-diethyl-*N*-[(2*E*)-3-(tributylstannyl)-2-propenyl]amine using method I. MS (ESI(+)) *m*/*e* 443 (M + H)$^+$; MS (ESI(−)) *m*/*e* 441 (M − H)$^-$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.80 (s, 1H), 9.53 (s, 1H), 7.78 (m, 2H), 7.64 (m, 1H), 7.55 (d, J = 15.51 Hz, 1H), 7.47 (m, 1H), 6.94 (d, J = 8.23 Hz, 1H), 6.60 (d, J = 8.10 Hz, 1H), 6.27 (ddd, J = 15.23, 7.48, 7.20 Hz, 1H), 3.87 (d, J = 7.00 Hz, 2H), 3.16 (q, J = 6.82 Hz, 4H), 2.64 (d, J = 4.53 Hz, 4H), 1.65 (m, 4H), 1.22 (t, J = 7.27 Hz, 6H). Anal. ($C_{24}H_{30}N_2O_4S$·1.1 TFA) C, H, N.

2-[({2-[(1*E*)-4-(Diethylamino)-1-butenyl]phenyl}sulfonyl)-amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (25b). The title compound was prepared from **17a** and *N*,*N*-diethyl-*N*-[(3*E*)-4-(tributylstannyl)-3-butenyl]amine using method I. MS (ESI-(+)) *m*/*e* 457 (M + H)$^+$; MS (ESI(−)) *m*/*e* 455 (M − H)$^-$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (dd, J = 7.96, 1.37 Hz, 1H), 7.67 (m, 1H), 7.58 (t, J = 7.96 Hz, 1H), 7.37 (t, J = 8.23 Hz, 1H), 7.25 (d, J = 15.64 Hz, 1H), 6.92 (d, J = 8.23 Hz, 1H), 6.65 (m, 1H), 6.21 (ddd, J = 15.40, 6.90, 6.79 Hz, 1H), 3.18 (m, 6H), 2.61 (m, 6H), 1.64 (m, 4H), 1.20 (t, J = 7.27 Hz, 6H). Anal. ($C_{25}H_{32}N_2O_4S$·TFA) C, H, N.

2-[({2-[(1*E*)-5-(Diethylamino)-1-pentenyl]phenyl}sulfonyl)-amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (25c). The title compound was prepared from **17a** and *N*,*N*-diethyl-*N*-[(4*E*)-5-(tributylstannyl)-4-pentenyl]amine according to method I. MS (ESI(+)) *m*/*e* 471 (M + H)$^+$; MS (ESI(−)) *m*/*e* 469 (M − H)$^-$; 1H NMR (400 MHz, DMSO-d_6) δ 7.93 (m, 1H), 7.57 (m, 1H), 7.51 (t, J = 6.97 Hz, 1H), 7.35 (m, 1H), 7.17 (d, J = 15.89 Hz, 1H), 7.11 (d, J = 8.31 Hz, 1H), 6.81 (m, 1H), 6.30 (m, 1H), 3.05 (m, 6H), 2.86 (s, 2H), 2.55 (s, 2H), 2.28 (q, J = 6.11 Hz, 2H), 2.01 (s, 2H), 1.55 (m, 4H), 1.21 (t, J = 6.72 Hz, 6H). Anal. ($C_{26}H_{34}N_2O_4S$·HCl·H_2O) C, H, N.

Methyl 2-(*N*-(2-Trimethylsilylethoxymethyl)-{[2-bromophenyl]-sulfonyl}amino)-5,6,7,8-tetrahydro-1-naphthalene-carboxylate (26a). To a suspension of NaH (60% in mineral oil, 1.5 g, 37.5 mmol) in 120 mL of THF was added **17a** (12.7 g, 30 mmol) in portions. After gas evolution was complete, SEM-Cl (6.6 mL, 37.5 mmol) was added over 5 min. After 105 min, the reaction was quenched by the addition of 5 mL of 5% aqueous $NaHCO_3$. The reaction was then diluted with 300 mL of 5% aqueous $NaHCO_3$, and extracted twice with 300 mL EtOAc. The combined organic layers were washed with 250 mL of 10% aqueous NaCl (back-washed with 200 mL EtOAc), and the combined EtOAc layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chased twice with heptane, and then to the resulting slurry was added 80 mL of heptane. The solids were isolated by filtration and washed with an additional 25 mL of heptane. Following drying in vacuo at 35 °C, 16 g (96%) of the product was isolated. MS (ESI(+)) *m*/*e* 571 (M + NH_4)$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 7.82, 1.92 Hz, 1 H), 7.71 (dd, J = 7.75, 1.30 Hz, 1 H), 7.36 (td, J = 7.55, 1.92 Hz, 1 H), 7.31 (td, J = 7.55, 1.51 Hz, 1 H), 7.17 (d, J = 8.24 Hz, 1 H), 7.09 (d, J = 8.23 Hz, 1 H), 5.27 (s, 1 H), 3.71 (m, 2 H), 3.66 (s, 3 H), 2.75 (t, J = 5.83 Hz, 2 H), 2.51 (s, 2 H), 1.72 (m, 4 H), 0.94 (m, 2 H), 0.02 (s, 9 H).

Methyl 2-(*N*-(2-Trimethylsilylethoxymethyl)-{[2-bromo-4-fluorophenyl]sulfonyl}amino)-5,6,7,8-tetrahydro-1-naphthalene-carboxylate (26b). To a suspension of NaH (60% in mineral oil, 4.90 g, 122.5 mmol) in 325 mL of THF was added **17b** (43.33 g, 98.97 mmol) in portions. After 30 min, SEM-Cl (21.6 mL, 122.5 mmol) was added over 5 min. After 45 min, the reaction was quenched by the slow addition of 350 mL of 5% aqueous $NaHCO_3$. The reaction was then extracted with 350 mL of EtOAc. The organic layers were washed with 250 mL of 10% aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated. The residue was triturated with 600 mL of hexanes and the solids isolated by filtration. The filtrate was concentrated and the residues dissolved in a minimum amount of EtOAc, and then diluted with 150 mL of hexanes. The precipitate was collected and the solids combined to provide 46.14 g (82%) of the title compound. MS (ESI(+)) *m*/*e* 574, 572 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.91 (dd, 1 H), 7.75 (dd, 1 H), 7.36 (td, 1 H), 7.22 (d, 1 H), 7.14 (d, 1 H), 3.62 (bd s, 5 H), 3.31 (s, 2 H), 2.74 (m, 4 H), 2.35 (m, 2 H), 1.67 (m, 4 H), 0.86 (m, 2 H), 0.01 (s, 9 H).

Methyl 2-(*N*-(2-Trimethylsilylethoxymethyl)-{[2-((*Z*)-3-hydroxy-prop-1-enyl)phenyl]sulfonyl}amino)-5,6,7,8-tetrahydro-1-naph-thalene-carboxylate (27a). A flask containing **26a** (10 g, 18 mmol) and $Pd(Pt\text{-}Bu_3)_2$ (0.92 g, 1.8 mmol) was purged with N_2, then 72 mL of degassed (N_2) toluene was added, followed by (*Z*)-tributyl-(3-hydroxy-prop-1-enyl)stannane[28] (7.5 g, 21.6 mmol). The reaction was heated to 50 °C for 2 h and allowed to cool to ambient temperature. The product solution was loaded directly onto a silica gel column and eluted with 30%:60% EtOAc/hexanes to provide 5.7 g (60%) of the product. MS (ESI(+)) *m*/*e* 549 (M + NH_4)$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, J = 7.96, 1.24 Hz, 1 H), 7.49 (td, J = 7.55, 1.37 Hz, 1 H), 7.32 (td, J = 7.72, 1.30 Hz, 1 H), 7.20 (d, J = 7.00 Hz, 1 H), 7.03 (d, J = 8.23 Hz, 1 H), 6.98 (d, J = 11.53 Hz, 1 H), 6.87 (d, J = 8.23 Hz, 1 H), 5.96 (dt, J = 11.56, 6.98 Hz, 1 H), 5.12 (s, 1 H), 4.14 (d, J = 7.00 Hz, 2 H), 3.64 (s, 3 H), 3.40−3.56 (m, 2 H), 2.71−2.82 (m, 2 H), 2.63 (s, 2 H), 2.05 (s, 1 H), 1.68−1.81 (m, 4 H), 0.78−0.90 (m, 3 H), −0.05 (s, 9 H).

Methyl 2-(*N*-(2-Trimethylsilylethoxymethyl)-{[2-((*Z*)-3-hydroxyprop-1-enyl)-4-fluorophenyl]sulfonyl}amino)-5,6,7,8-tetrahydro-1-naphthalene-carboxylate (27b). A 50 mL microwave reaction vessel containing **26b** (5.73 g, 10 mmol), $Pd(Pt\text{-}Bu_3)_2$ (0.558 g, 0.7 mmol), and (*Z*)-tributyl-(3-hydroxy-prop-1-enyl)stannane[28] (4.11 g, 11 mmol) in DMF (30 mL) was heated to 150 °C for 10 min and allowed to cool to ambient temperature. The solution was diluted with EtOAc, shaken with brine, filtered through Celite, washed again with brine, and then dried over $MgSO_4$. Chromatography on silica gel, eluting with 10%:20% EtOAc/hexanes provided 5.44 g (99%) of the product. MS (ESI(+)) *m*/*e* 567 $(M + NH_4)^+$, 572 $(M + Na)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, $J = 7.96$, 1.24 Hz, 1 H), 7.49 (td, $J = 7.55$, 1.37 Hz, 1 H), 7.32 (td, $J = 7.72$, 1.30 Hz, 1 H), 7.20 (d, $J = 7.00$ Hz, 1 H), 7.03 (d, $J = 8.23$ Hz, 1 H), 6.98 (d, $J = 11.53$ Hz, 1 H), 6.87 (d, $J = 8.23$ Hz, 1 H), 5.96 (dt, $J = 11.56$, 6.98 Hz, 1 H), 5.12 (s, 1 H), 4.14 (d, $J = 7.00$ Hz, 2 H), 3.64 (s, 3 H), 3.40−3.56 (m, 2 H), 2.71−2.82 (m, 2 H), 2.63 (s, 2 H), 2.05 (s, 1 H), 1.68−1.81 (m, 4 H), 0.78−0.90 (m, 3 H), −0.05 (s, 9 H).

Allylic Amine Synthesis. Method J. 2-[({2-[(1*Z*)-3-(Dimethylamino)-1-propenyl]phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (24m). To a solution of 1 mmol of **27a** in 5 mL of CH_2Cl_2 in an ice/water bath was added *i*-Pr_2NEt (0.40 mL, 2.3 mmol) and then MsCl (0.09 mL, 1.15 mmol). After 75 min, 2.5 mL of a 2 M solution of dimethylamine in toluene (5 mmol) was added and the reaction warmed to ambient temperature, diluted with CH_2Cl_2, and washed with 10% aqueous NaCl. The CH_2Cl_2 layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by silica gel chromatography to yield 457 mg (82%) of the SEM-protected methyl ester. MS (ESI(+)) *m*/*e* 559 $(M + H)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (m, 1 H), 7.48 (m, 1 H), 7.27 (m, 2 H), 7.02 (d, $J = 8.23$ Hz, 1 H), 6.94 (d, $J = 8.23$ Hz, 1 H), 6.84 (d, $J = 11.66$ Hz, 1 H), 5.84 (dt, $J = 11.73$, 6.83 Hz, 1 H), 5.09 (s, 2 H), 3.64 (s, 3 H), 3.57 (m, 2 H), 3.00 (dd, $J = 6.79$, 1.30 Hz, 2 H), 2.74 (t, $J = 5.28$ Hz, 2 H), 2.61 (s, 2 H), 2.23 (s, 6 H), 1.72 (m, 4 H), 0.88 (dd, $J = 9.06$, 7.68 Hz, 2 H), −0.02 (s, 9 H).

The intermediate (0.41 g, 0.7 mmol) and lithium iodide (0.28 g, 2.1 mmol) in pyridine (7 mL) were heated in a microwave reactor at 150 °C for 40 min and then concentrated in vacuo. The crude product was purified by C_{18} reverse-phase HPLC using acetonitrile/water/0.1% TFA to provide **24m** (0.182 g, 49%). MS (ESI(+)) *m*/*e* 415 $(M + H)^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 9.84 (s, 1 H), 9.71 (s, 1 H), 7.79 (d, $J = 7.96$ Hz, 1 H), 7.66 (t, $J = 7.34$ Hz, 1 H), 7.50 (t, $J = 7.68$ Hz, 1 H), 7.30 (d, $J = 8.64$ Hz, 2 H), 6.96 (d, $J = 8.51$ Hz, 1 H), 6.62 (d, $J = 8.23$ Hz, 1 H), 5.86 (dt, $J = 11.80$, 6.86 Hz, 1 H), 3.82 (d, $J = 6.45$ Hz, 2 H), 2.68 (s, 6 H), 2.61 (m, 4 H), 1.65 (m, 4 H). Anal. ($C_{22}H_{26}N_2O_4S$·1.5 TFA) C, H, N.

2-[({2-[(1*Z*)-3-(1-Pyrrolidinyl)-1-propenyl]phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (24i). The title compound was prepared from **27a** and pyrrolidine using method J. MS (ESI(+)) *m*/*e* 441 $(M + H)^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1 H), 9.72 (s, 1 H), 7.79 (dd, $J = 7.82$, 0.96 Hz, 1 H), 7.65 (td, $J = 7.55$, 1.10 Hz, 1 H), 7.49 (t, $J = 7.68$ Hz, 1 H), 7.32 (d, $J = 7.41$ Hz, 1 H), 7.26 (d, $J = 11.66$ Hz, 1 H), 6.97 (d, $J = 8.23$ Hz, 1 H), 6.68 (d, $J = 8.23$ Hz, 1 H), 5.89 (dt, $J = 11.70$, 6.84 Hz, 1 H), 3.88 (d, $J = 6.45$ Hz, 2 H), 3.42 (s, 2 H), 2.92 (s, 2 H), 2.64 (s, 4 H), 1.83 (s, 4 H), 1.65 (m, 4 H). Anal. ($C_{25}H_{30}N_2O_4S$·1.4 TFA) C, H, N.

2-[({2-[(1*Z*)-3-(1-Pyrrolidinyl)-1-propenyl]-4-fluorophenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (24j). The title compound was prepared from **27b** and pyrrolidine using method J. MS (APCI(+)) *m*/*e* 449 $(M + H)^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 7.88 (dd, 1 H), 7.25 (d, 1 H), 7.18 (td, 1 H), 7.13 (d, 1 H), 7.06 (m, 2 H), 5.97 (m, 1 H), 3.91 (dd, 2 H), 3.60 (m, 2 H), 2.98 (m, 2 H), 2.73 (s, 4 H), 2.00 (m, 4 H), 1.72 (m, 4 H). Anal. ($C_{24}H_{27}FN_2O_4S$·TFA) C, H, N.

2-[({2-[(1*Z*)-3-Ethyl-3-(2-hydroxyethyl)-1-propenyl]phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (24k). The title compound was prepared from **27a** and *N*-ethyl-*N*-(2-hydroxyethyl)amine using method J. MS (ESI(+)) *m*/*e* 459 $(M + H)^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 9.69 (m, 2 H), 7.80 (dd, $J = 7.82$, 1.10 Hz, 1 H), 7.65 (td, $J = 7.51$, 1.03 Hz, 1 H), 7.50 (t, $J = 7.27$ Hz, 1 H); 7.35 (d, $J = 7.55$ Hz, 1 H); 7.31 (d, $J = 11.94$ Hz, 1 H), 6.97 (d, $J = 8.37$ Hz, 1 H), 6.67 (d, $J = 8.23$ Hz, 1 H), 5.95 (dt, $J = 11.87$, 6.90 Hz, 1 H), 3.86 (d, $J = 6.31$ Hz, 2 H), 3.61 (m, 2 H), 3.10 (m, 4 H), 2.64 (d, $J = 3.02$ Hz, 4 H), 1.66 (m, 4 H), 1.01 (t, $J = 7.20$ Hz, 3 H). Anal. ($C_{24}H_{30}N_2O_5S$·TFA·0.5 H_2O) C, H, N.

2-[({2-[(1*Z*)-3-(1-4-methylpiperazinyl)-1-propenyl]phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (24l). The title compound was prepared from **27a** and *N*-methylpiperazine using method J. MS (ESI(+)) *m*/*e* 470 $(M + H)^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, 1 H), 7.65 (m, 1 H), 7.49 (t, 1 H), 7.36 (d, 1 H), 7.21 (d, 1 H), 6.99 (d, 1 H), 6.67 (d, 1 H), 5.88 (m, 1 H), 3.48 (m, 2H), 3.30−2.85 (m, 8H), 2.79 (s, 3H), 2.67 (m, 4 H), 1.68 (m, 4 H). Anal. ($C_{25}H_{31}N_3O_4S$·2 TFA) C, H, N.

2-[({2-[(1*Z*)-3-(Dimethylamino)-1-propenyl]-4-fluorophenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (24n). The title compound was prepared from **27b** and dimethylamine using method J. MS (ESI(+)) *m*/*e* 433 $(M + H)^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 7.81 (dd, 1 H), 7.35 (dt,1 H), 7.28−7.21 (m, 2 H), 7.01 (d, 1 H), 6.69 (d, 1 H), 5.90 (m, 1 H), 3.87 (d, 2 H), 2.70 (s, 6 H), 2.65 (m, 4 H), 1.67 (m, 4 H). Anal. ($C_{22}H_{25}FN_2O_4S$· TFA) C, H, N.

2-[({2-[(1*Z*)-3-(*N*-Ethyl-*N*-methylamino)-1-propenyl]-phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (24o). The title compound was prepared from **27b** and *N*-methylethylamine using method J. MS (ESI(+)) *m*/*e* 427 $(M + H)^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 7.81 (d, 1 H), 7.68 (t, 1 H), 7.52 (t, 1 H), 7.33 (d, 2 H), 6.98 (d, 1 H), 6.68 (d, 1 H), 5.89 (dt, 1 H), 3.82 (d, 2 H), 3.05 (m, 2H), 2.68 (s, 3 H), 2.65 (m, 4 H), 1.65 (m, 4 H), 1.09 (t, 3H). Anal. ($C_{23}H_{28}N_2O_4S$·TFA) C, H, N.

2-[({2-[(1*Z*)-3-(*N*-2-Hydroxyethyl-*N*-methylamino)-1-propenyl]-phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (24p). The title compound was prepared from **27b** and *N*-methylethanolamine using method J. MS (ESI(+)) *m*/*e* 445 $(M + H)^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 7.82 (d, 1 H), 7.68 (t, 1 H), 7.52 (t, 1 H), 7.35 (d, 2 H), 6.99 (d, 1 H), 6.66 (d, 1 H), 5.94 (dt, 1 H), 3.87 (d, 2 H), 3.63 (m, 2H), 3.10 (m, 2H), 2.69 (s, 3 H), 2.66 (m, 4 H), 1.67 (m, 4 H). Anal. ($C_{23}H_{28}N_2O_5S$·TFA) C, H, N.

2-[({2-[(1*Z*)-3-(*N*-(1-Methylethyl)-*N*-methylamino)-1-propenyl]-phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (24q). The title compound was prepared from **27b** and *N*-methylisopropyllamine using method J. MS (ESI(+)) *m*/*e* 443 $(M + H)^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, 1 H), 7.67 (t, 1 H), 7.51 (t, 1 H), 7.35 (d, 2 H), 6.98 (d, 1 H), 6.73 (m, 1 H), 5.94 (dt, 1 H), 3.79 (d, 2 H), 3.54 (m, 1 H), 2.66 (s, 3 H), 2.58 (m, 4 H), 1.66 (m, 4 H), 1.09 (d, 6H). Anal. ($C_{24}H_{30}N_2O_4S$· TFA) C, H, N.

Method K. 2-[({2-[4-(Diethylamino)butyl]phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (28c). A solution of **17a** (848 mg, 2.0 mmol), *N*,*N*-diethyl-*N*-[(3*Z*)-4-(tributylstannyl)-3-butenyl]amine (1.10 g, 2.6 mmol), and bis(tri-*tert*-butylphosphine)palladium (212 mg, 0.4 mmol) in 4 mL of degassed toluene was stirred at ambient temperature for 20 h. The mixture was concentrated and chromatographed on silica (0:15% triethylamine/EtOAc) to give 0.95 g of (100%) methyl 2-[({2-[(1*E*)-4-(diethylamino)-1-butenyl]phenyl}sulfonyl)-amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylate. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, $J = 7.96$ Hz, 1H), 7.46 (m, 2H), 7.25 (m, 1H), 7.16 (d, $J = 15.78$ Hz, 1H), 6.93 (d, $J = 8.20$ Hz, 1H), 6.84 (d, $J = 8.23$ Hz, 1H), 6.06 (m, 1H), 5.29 (s, 1H), 3.74 (s, 3H), 2.69 (m, 4H), 2.59 (m, 6H), 2.38 (m, 2H), 1.70 (m, 4H), 1.00 (t, $J = 7.14$ Hz, 6H).

A portion of the product (350 mg, 0.75 mmol) in methanol (12 mL) was hydrogenated with H_2 over 90 mg (30 wt %) of 10% Pd/C. After 4.5 h, the reaction was filtered through diatomaceous earth (Celite). The pad was washed with methanol, and the filtrates were concentrated to provide 332 mg (94%) of methyl 2-[({2-[4-

(diethylamino)butyl]phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylate; MS (ESI(+)) *m/e* 473 $(M + H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, $J = 7.82$ Hz, 1H), 7.42 (t, $J = 7.14$ Hz, 1H), 7.30 (d, $J = 7.55$ Hz, 1H), 7.21 (t, $J = 7.68$ Hz, 1H), 7.05 (d, $J = 8.37$ Hz, 1H), 6.99 (d, $J = 8.51$ Hz, 1H), 3.72 (s, 3H), 2.95 (m, 2H), 2.69 (m, 4H), 2.53 (m, 6H), 1.68 (m, 6H), 1.58 (m, 2H), 1.00 (t, $J = 7.14$ Hz, 6H).

The methyl ester (306 mg, 0.65 mmol) and LiI (348 mg, 2.6 mmol) in 6 mL of pyridine were heated in a microwave reactor at 150 °C for 35 min and then concentrated in vacuo. The crude product was purified by C_{18} reverse-phase HPLC using acetonitrile/water/0.1% TFA to provide **28c** (210 mg, 71% yield). MS (ESI-(+)) *m/e* 459 $(M + H)^+$; MS (ESI(−)) *m/e* 457 $(M - H)^-$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 9.26 (s, 1H), 7.75 (dd, $J = 8.03$, 1.30 Hz, 1H), 7.55 (td, $J = 7.55$, 1.37 Hz, 1H), 7.42 (dd, $J = 7.75$, 1.17 Hz, 1H), 7.32 (td, $J = 7.65$, 1.30 Hz, 1H), 6.96 (d, $J = 8.37$ Hz, 1H), 6.69 (d, $J = 8.37$ Hz, 1H), 3.09 (q, $J = 7.23$ Hz, 4H), 3.03 (m, 2H), 2.96 (m, 2H), 2.64 (m, 4H), 1.64 (m, 8H), 1.17 (t, $J = 7.27$ Hz, 6H). Anal. ($C_{25}H_{34}N_2O_4S$·TFA) C, H, N.

2-[({2-[3-(Diethylamino)propyl]phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (28a). The title compound was prepared from **17a** and *N*,*N*-diethyl-*N*-[(2*E*)-3-(tributylstannyl)-2-propenyl]amine according to method K. MS (APCI(+)) *m/e* 445 $(M + H)^+$; MS (APCI(−)) *m/e* 443 $(M - H)^-$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (dd, $J = 7.83$, 1.22 Hz, 1H), 7.50 (m, 1H), 7.40 (d, $J = 7.58$ Hz, 1H), 7.29 (m, 2H), 6.85 (d, $J = 8.31$ Hz, 1H), 3.01 (m, 8H), 2.84 (m, 2H), 2.57 (m, 2H), 1.75 (m, 2H), 1.57 (m, 4H), 1.18 (t, $J = 7.21$ Hz, 6H). Anal. ($C_{24}H_{32}N_2O_4S$· TFA) C, H, N.

2-[({2-[3-(Diethylamino)propyl]-4-fluorophenyl}sulfonyl)-amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (28b). The title compound was prepared from **17b** and *N*,*N*-diethyl-*N*-[(2*E*)-3-(tributylstannyl)-2-propenyl]amine according to method K. MS (ESI(+)) *m/e* 463 $(M + H)^+$; ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.85 (m, 1H), 7.22 (m, 1H), 7.08−7.05 (m, 3H), 3.22 (m, 4H), 3.18 (m, 1H), 3.06 (m, 1H), 2.93 (m, 2H), 2.74 (m, 4H), 2.02 (m, 2H), 1.74 (m, 4H), 1.31 (t, 6H). Anal. ($C_{24}H_{31}FN_2O_4S$·TFA) C, H, N.

2-[({2-[5-(Diethylamino)pentyl]phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (28d). The compound was prepared from **17a** and *N*,*N*-diethyl-*N*-[(4*E*)-5-(tributylstannyl)-4-pentenyl]amine according to method K. MS (ESI(+)) *m/e* 473 $(M + H)^+$; MS (ESI(−)) *m/e* 471 $(M - H)^-$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (s, 1H), 7.79 (d, $J = 7.83$ Hz, 1H), 7.53 (t, $J = 7.58$ Hz, 1H), 7.42 (d, $J = 7.58$ Hz, 1H), 7.32 (t, $J = 7.58$ Hz, 1H), 6.94 (d, $J = 8.31$ Hz, 1H), 6.81 (d, $J = 8.07$ Hz, 1H), 4.09 (s, 1H), 3.08 (q, $J = 7.25$ Hz, 4H), 2.96 (m, 4H), 2.70 (s, 2H), 2.62 (s, 2H), 1.66 (m, 8H), 1.41 (m, 2H), 1.19 (t, $J = 7.21$ Hz, 6H). Anal. ($C_{26}H_{36}N_2O_5S$·HCl) C, H, N.

2-[({2-[3-(Dimethylamino)propyl]phenyl}sulfonyl)amino]-5,6,7,8-tetrahydro-1-naphthalenecarboxylic Acid (28e). The title compound was prepared from **17a** and *N*,*N*-dimethyl-*N*-[(2*E*)-3-(tributylstannyl)-2-propenyl]amine according to method K. MS (ESI(+)) *m/e* 417 $(M + H)^+$; ^{1}H NMR (400 MHz, MeOH-d_4) ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (d, 1H), 7.60 (t, 1H), 7.47 (d, 1H), 7.36 (t, 1H), 6.98 (d, 1H), 6.72 (d, 1H), 3.13 (m, 2H), 2.98 (m, 2H), 2.78 (s, 6H), 2.66 (m, 4H), 1.93 (m, 2H), 1.65 (m, 4H). Anal. ($C_{22}H_{28}N_2O_4S$·TFA) C, H, N.

Methyl 2-[(2-Bromo-4-fluoro-benzenesulfonyl)-(2-methoxy-ethoxymethyl)-amino]-5,6,7,8-tetrahydronaphthalene-1-carboxylate (29). To a 25 mL three-neck flask equipped with a mechanical stirrer, a J-Kem temperature probe, and a dry nitrogen line was charged **17b** (3.34 g, 7.55 mmol) in 32 mL of dry THF. To this mixture was slowly added 60% sodium hydride dispersion (0.44 g, 11.0 mmol). Once the foaming subsided, a solution of MEM-Cl (1.24 g, 9.95 mmol) in 8 mL of THF was added, and the mixture was stirred at room temperature overnight. The following morning the crude reaction mixture was adsorbed onto 16 g of flash grade silica and purified on a short flash column with 20% ethyl acetate in hexanes. Pooling fractions yielded 3.50 g of pure product as an off white solid (87.5% yield). MS (ESI$(M + NH_4)^+$) *m/e* 548; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, $J = 8.85$, 5.83 Hz, 1H), 7.44 (dd, $J = 8.03$, 2.54 Hz, 1H), 7.21 (d, $J = 8.23$ Hz, 1H), 7.10 (d, $J = 8.37$ Hz, 1H), 6.99 (ddd, $J = 8.92$ 7.55, 2.47 Hz, 1H), 3.85 (s, 2H), 3.67 (s, 3H), 3.56 (t, $J = 4.60$ Hz, 2H), 3.36 (s, 3H), 2.74 (t, $J = 5.56$ Hz, 2H), 2.49 (s, 2H), 165−176 (m, 4H).

Methyl 2-[[4-Fluoro-2-(2-hydroxymethyl-cyclopropyl)-benzenesulfonyl]-(2-methoxy-ethoxymethyl)-amino]-5,6,7,8-tetrahydronaphthalene-1-carboxylate (30). To a 50 mL three-neck round-bottomed flask equipped with a heating mantle, a J-Kem temperature controller, and a dry nitrogen line was charged **29** (1.02 g, 1.923 mmol), bis-tri-*tert*-butylphosphine palladium (0.099 g, 0.194 mmol), $Pd_2(dba)_3$ (0.057 g, 0.62 mmol), and 9 mL of degassed toluene. To this mixture was added, via syringe, a solution of (2-tributylstannanyl-cyclopropyl)-methanol[28] in 0.5 mL of degassed toluene. The reaction was warmed to 90 °C and stirred at this temperature overnight. The following day, the reaction mixture was purified by flash chromatography (10% ethyl acetate in hexane) to yield 514 mg (52.7%) of product as an oil. MS (ESI$(M + H)^+$) *m/e* 522; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, $J = 8.85$, 5.83 Hz, 1H), 7.03 (q, $J = 8.14$ Hz, 2H), 6.96 (dd, $J = 9.88$, 2.61 Hz, 1H), 6.86 (ddd, $J = 8.82$, 7.72, 2.68 Hz, 1H), 3.73 (s, 2H), 3.64 (s,3H), 3.51 (t, $J = 4.67$ Hz, 2H), 3.34 (s, 3H), 2.67−2.77 (m, 4H), 2.59 (s, 1H), 1.73 (s, 4H), 1.49−1.61 (m, 3H), 1.30−1.39 (m, 3H), 0.90 (t, $J = 7.34$ Hz, 4H).

Method L. 2-[2-(2-Diethylaminomethyl-cyclopropyl)-4-fluorobenzenesulfonylamino]-5,6,7,8-tetrahydronaphthalene-1-carboxylic Acid (32a). To a 25 mL three-neck round-bottomed flask equipped with a magnetic stirrer, a heating mantle, a J-Kem temperature controller, a reflux condenser, and a dry nitrogen line was added **30** (0.248 g, 0.48 mmol) and 1 mL of pyridine. After mixing to dissolve, mesyl chloride (0.131 g, 1.14 mmol) was added, and the reaction was monitored by HPLC. After 4.6 h, the starting material was consumed, and the reaction was concentrated under a stream of dry nitrogen. The residue was dissolved in 3 mL of diethylamine and heated under reflux for 5 h. After concentrating the crude product, it was purified by flash chromatography (silica, 5% methanol in methylene chloride) to provide **31a** (0.244 g, 89%). MS (ESI$(M + H)^+$) *m/e* 577; ^{1}H NMR (400 MHz, methanol-d_4) δ 7.18 (dd, $J = 10.02$, 2.61 Hz, 1H), 7.09 (dd, $J = 8.30$, 2.40 Hz, 2H), 4.84 (s, 6H), 3.70 (s, 3H), 3.46−3.53 (m, 8H), 3.13 (q, $J = 7.41$ Hz, 4H), 2.74−2.81 (m, 2H), 2.22 (d, $J = 13.58$ Hz, 1H), 1.75 (s, 3H), 1.33−1.42 (m, 2H), 1.17 (t, $J = 7.27$ Hz, 6H).

A mixture of **31a** (0.220 g, 0.419 mmol) and LiI (0.165 g, 1.2 mmol) in dry pyridine (4.2 mL) was heated in a microwave reactor at 160 °C for 25 min. The crude product was concentrated to a thick oil by drying under a stream of dry nitrogen and then purified by flash chromatography (silica, 5% methanol in methylene chloride). The purified product (114 mg, 57%) was then treated with excess trifluoroacetic acid in methylene chloride to provide **32a** as the TFA salt. MS (ESI$(M + H)^+$) *m/e* 475; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.97 (dd, $J = 8.85$, 5.69 Hz, 1H), 7.14 (d, $J = 8.51$ Hz, 1H), 6.97−7.02 (m, 2H), 6.92 (dd, $J = 9.61$, 2.33 Hz, 1H), 3.11 (d, $J = 5.08$ Hz, 4H), 3.00 (d, $J = 7.00$ Hz, 1H), 2.83 (s, 2H), 2.68 (s, 2H), 2.17−2.25 (m, 1H), 1.82 (s, 1H), 1.64−1.73 (m, 4H), 1.45 (s, 1H), 1.25−1.28 (m, 1H), 1.19 (dt, $J = 18.49$, 7.22, 6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.78, 163.24, 138.63, 135.41 134.24, 132.39, 117.35, 117.23, 114.21, 52.84, 46.99, 46.29, 29.68, 28.66, 23.04, 22.50, 15.46, 8.72, 8.56, 0.40. Anal. ($C_{25}H_{31}FN_2O_4S$·TFA) C, H, N.

2-[2-(2-Dimethylaminomethyl-cyclopropyl)-4-fluorobenzenesulfonylamino]-5,6,7,8-tetrahydronaphthalene-1-carboxylic Acid (32b). The title compound was prepared from **30** and dimethylamine according to method L. MS (ESI$(M + H)^+$) *m/e* 447; ^{1}H NMR (400 MHz, CD_3OD) δ 7.92 (dd, $J = 8.78$, 5.76 Hz, 1H), 7.04−7.15 (m, 4H), 3.30 (dt, $J = 3.09$, 1.61 Hz, 1H), 3.16 (dd, $J = 13.04$, 4.25 Hz, 1H), 2.79−2.83(m, 7H), 2.70−2.77(m, 4H), 2.23 (dd, $J = 13.04$, 10.57 Hz, 1H), 1.68−1.77 (m, 5H), 1.34−1.45 (m, 2H); Anal. ($C_{23}H_{27}FN_2O_4S$·1.5 TFA·H_2O) C, H, N.

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Supporting Information Available: Details of the synthesis and characterization of the organostannane intermediates used in the synthesis of compounds **24**−**25**, elemental analysis results for the test compounds, and biological assay conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

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