Design, Synthesis, and Evaluation of Naphthalene-Sulfonamide Antagonists of Human CCR8

Tracy J. Jenkins,*,† Bing Guan,† Mingshi Dai,† Gang Li,† Thomas E. Lightburn,† Shan Huang,† B. Scott Freeze,† Douglas F. Burdi,† Swanee Jacutin-Porte,† Robert Bennett,† Weirong Chen,† Charles Minor,† Shomir Ghosh,† Christopher Blackburn,† Kenneth M. Gigstad,† Matthew Jones,† Roland Kolbeck,‡ Wei Yin,§ Sean Smith,‡ Daniel Cardillo,‡ Timothy D. Ocain,‡ and Geraldine C. Harriman†

Department of Medicinal Chemistry, Department of Pharmacology, and Drug Safety and Disposition, Millennium Pharmaceuticals, 40 Landsdowne Street, Cambridge, Massachusetts 02139

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The design, synthesis, and structure−activity relationship development of naphthalene-derived human CCR8 antagonists is described. *In vitro* binding assay results of these investigations are reported, critical interactions of the antagonists with CCR8 are defined, and preliminary physicochemical and pharmacokinetic data for the naphthalene scaffold are presented.

Introduction

Chemokines are chemotactic cytokines that regulate development, activation, and recruitment of leukocytes through binding and activation of seven transmembrane G-protein coupled receptors. Four chemokine subgroups, CXC, CC, C, and CX3C, have been defined based on the spacing of conserved cysteine residues at the *N*-terminus.[1] Unlike most chemokine receptors, which are activated by multiple chemokines, CCR8, which is the subject of this report, has only one known human endogenous ligand, CCL1 (also known as I-309). Additionally, the pox-viral chemokine MC148 and the human herpes virus 8 (HHV-8) derived chemokine vMIP I have been identified as being a specific human CCR8 antagonist and agonist, respectively.[2]

A number of cell types express CCR8, including monocytes and endothelial cells as well as phagocytic macrophages and activated microglial cells in the human central nervous system. CCR8 is also expressed in active demyelinating multiple sclerosis (MS) lesions, in progressive multifocal leukoencephalopathy (PML), and in cerebral ischemia.[3] Furthermore, expression of CCR8 has been noted in endothelial-derived spindle cells of human Kaposi sarcoma biopsies.[4] The expression of CCR8 is selectively up-regulated upon activation of T-helper-2 (Th2) cells,[5] which are the primary source of the cytokines IL-4, IL-5, and IL-13. These cytokines, in turn, are major mediators of inflammation, airway hyper-reactivity, and mucus hyper-secretion in bronchial asthma.[6] Additionally, the CCR8 ligand, CCL1, has anti-apoptotic activity in adult T-cell leukemia (ATL), caused by human T-cell leukemia virus type 1 (HTLV-1).[7]

Based on the expression pattern of CCR8, activation of the receptor by CCL1 is suspected to play an important role in various diseases including allergic asthma, multiple sclerosis, and cancer. Following up on our previously reported work,[8,9] our research efforts aimed to identify small molecule antagonists to probe the role of CCR8−CCL1 interactions in these diseases and provide novel therapeutics for their treatment. In this paper, we describe the design, synthesis, and structure−activity relationship (SAR) development of a series of naphthalene-sulfonamide CCR8 antagonists.

* To whom correspondence should be addressed. Phone: (617)-679-7425. Fax: (617)-444-1483. E-mail: tracy.jenkins@biogenidec.com.
† Department of Medicinal Chemistry.
‡ Department of Pharmacology.
§ Drug Safety and Disposition.

To begin, the screening of our compound collection in a human CCR8 binding assay led to the discovery of several potential leads possessing high affinity for this receptor. Naphthalene-sulfonamide **1** (Figure 1, FMAT K_i = 57 nM, FLIPR IC_{50} = 150 nM)[10] was one such antagonist and will be the focus of the following discussion.

To investigate the SAR, we prepared analogs of **1**, incorporating changes that would aid the elucidation of the structural features required for binding to human CCR8. Through an iterative process of synthesis and biological evaluation, we have gained insight into the pharmacophore for this class of compounds. In addition, we have prepared several derivatives with extremely high (i.e., picomolar) affinity for CCR8. Selected *in vitro* results of these investigations are reported, and key binding interactions are described. A follow-up report focusing on *in vivo* profiling and optimization of drug-like properties will be released in due course.

Chemistry

Our investigation began with an evaluation of the importance of each of the two hydrogen-bond donors found in naphthalene-sulfonamide **1**. Thus, 4-amino-1-naphthalenesulfonic acid was first protected as the phthalimide derivative (Scheme 1), which was followed by conversion to the corresponding sulfonyl chloride and treatment with the 4-methoxyaniline to afford sulfonamide **2**. Deprotection, amine methylation, and acylation then provided tertiary amide **3**, in which the amide proton has been replaced by a methyl substituent.

To probe the role of the sulfonamide proton, tertiary sulfonamides were next prepared (Scheme 2). Here, 4-amino-1-naphthalenesulfonic acid was first acylated with benzoyl chloride, followed by chlorination using thionyl chloride to afford sulfonyl chloride **4**. Treatment with a series of secondary amines then provided tertiary sulfonamides **5a**−**e**. This procedure was also employed using primary amines to generate several secondary sulfonamides **6a**−**g** (see Tables 1 and 3, respectively, for a list of selected "R" groups).

Having found the two hydrogen bond donors to be essential for activity, we proceeded with the design and synthesis of analogs of **1** bearing replacements for the sulfonamide linker, as in **9** (Scheme 3), which contains a carboxamide, or as in compound **11**, which incorporates an aminomethyl linker. To this end, treatment of commercially available 4-bromonaphthalen-1-amine with the desired acid chloride afforded bromide **7**.

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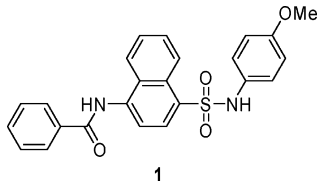

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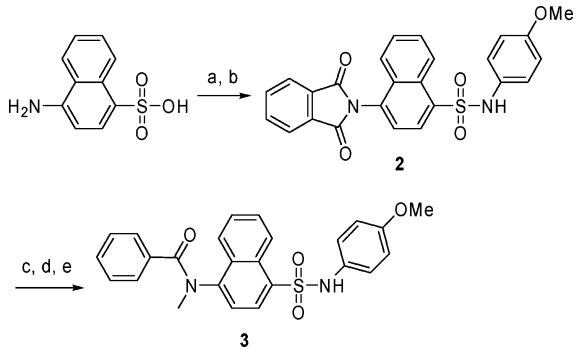
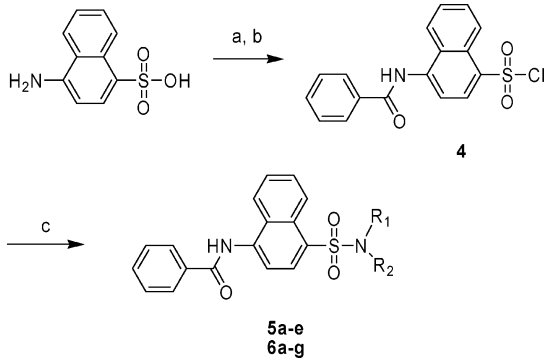
Figure 1. Naphthalene-sulfonamide **1**.

Scheme 1. Preparation of Naphthalene-Sulfonamide **3**, Bearing Only One H-Bond Donor[a]



[a] Reagents and conditions: (a) phthaloyl chloride, pyridine, reflux; (b) (i) $SOCl_2$, DMF, rt; (ii) *p*-methoxyaniline, Et_3N, CH_2Cl_2; (c) H_2NNH_2, MeOH, rt; (d) MeI, K_2CO_3, DMF; (e) benzoyl chloride, Et_3N, CH_2Cl_2, rt.

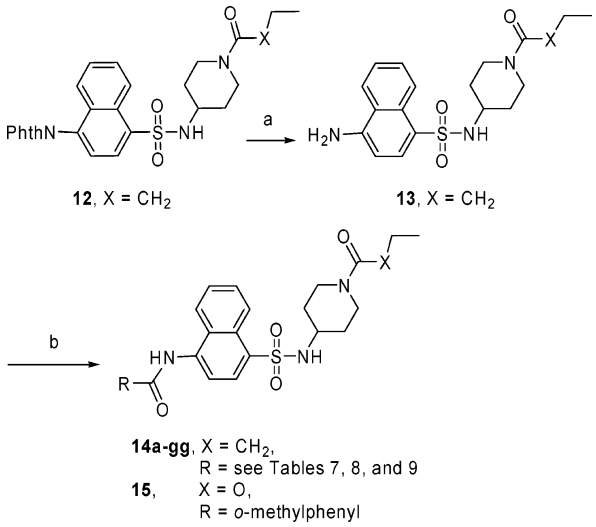
Scheme 2. Preparation of Tertiary Sulfonamides **5a**−**e** and Secondary Sulfonamides **6a**−**g**[a]



[a] Reagents and conditions: (a) RCOCl, pyridine, reflux; (b) $SOCl_2$, DMF, rt; (c) HNR_1R_2, Et_3N, CH_2Cl_2.

A one-pot sequence entailing halogen metal exchange of bromide **7** with *s*-BuLi/NaH, followed by treatment with either carbon dioxide or dimethylformamide (DMF), provided the key intermediates, carboxylic acid **8** and aldehyde **10**, respectively. Subsequent EDC-mediated coupling of carboxylic acid **8** with

Scheme 4. General Procedure for Preparation of Left-Hand Side Amide Variants[a]



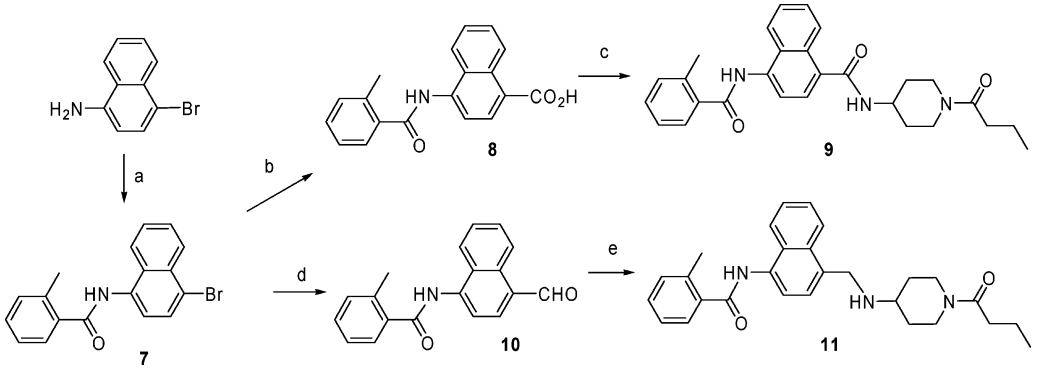
[a] Reagents and conditions: (a) H_2NNH_2, MeOH, rt.; (b) RCOCl, DMAP, pyridine, 60 °C.

commercially available 4-amino-1-*tert*-butyloxycarbonyl-piperidine (4-amino-1-Boc-piperidine), followed by deprotection and acylation, then provided the desired amide **9**. Alternatively, treatment of aldehyde **10** with the 4-amino-1-Boc-piperidine under reductive amination conditions, again followed by deprotection and acylation, provided the desired secondary amine **11**.

The above SAR studies led to the identification of piperidyl-substituted sulfonamides possessing general structure **14** or **15** (Scheme 4) as promising leads for further development. Thus, based upon this scaffold, a systematic investigation for optimal left-hand amide substituents was initiated. To this end, piperidyl sulfonamide **12** (Scheme 4) was prepared following the general route depicted in Scheme 1. This entailed protection of 4-amino-1-naphthalenesulfonic as the phthalimide (Phth) derivative, followed by conversion to the sulfonyl chloride and treatment with the requisite amine coupling partner. With sulfonamide **12** in hand, hydrazine was employed to effect removal of the phthalimide protecting group, furnishing amine **13**. Introduction of a series of acid chloride coupling partners then afforded amides **14a**−**gg**, bearing a diverse range of left-hand amide substituents. Carbamate **15** was generated independently, according to the synthetic route described in Scheme 2.

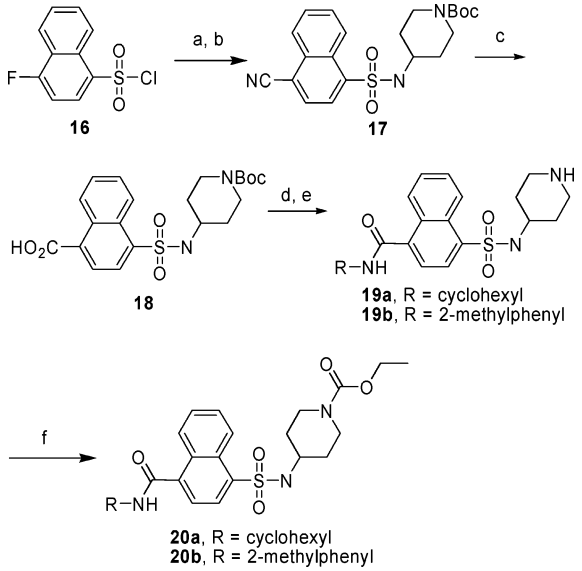
Ultimately, this method proved successful for the preparation of many analogs (see Tables 7−9), however, its utility was limited to amino connectivity on the left-hand side of the

Scheme 3. Preparation of Sulfonamide Replacement Analogs[a]



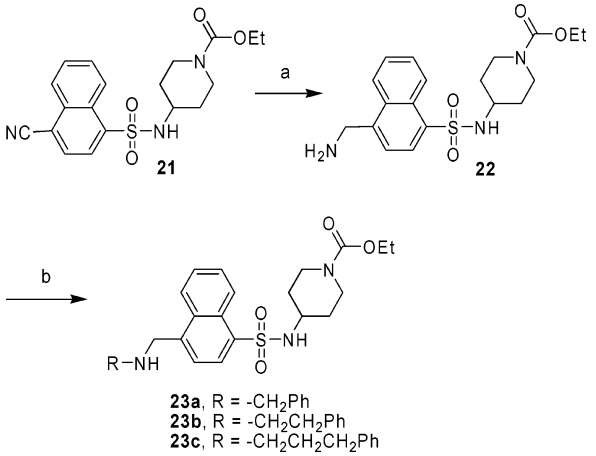
[a] Reagents and conditions: (a) 2-methylbenzoyl chloride, ET_3N, CH_2Cl_2, rt; (b) NaH, *s*-BuLi, THF, CO_2, −78 °C−rt; (c) (i) EDCI, pyridine, 4-amino-1-Boc-piperidine, rt; (ii) 4 N HCL, dioxane; (iii) butyryl chloride, Et_3N, CH_2Cl_2, rt; (d) NaH, *s*-BuLi, THF, DMF, −78 °C−rt; (e) (i) $Na(AcO)_3BH$, Boc-piperidine amine, CH_3OH, rt; (ii) 4 N HCl, dioxane; (iii) butyryl chloride, Et_3N, CH_2Cl_2, rt.

Scheme 5. Scheme for the Synthesis of "Reversed" Left-Hand Amides **20a** and **20b**[a]



[a] Reagents and conditions: (a) 4-amino-1-Boc-piperidine, NEt_3, CH_2Cl_2; (b) NaCN, DMF, 60 °C; (c) KOH, MeOH/H_2O, 100 °C; (d) R-NH_2, EDC, Et_3N, CH_2Cl_2, rt; (e) 4 N HCl, dioxane; (f) EtOCOCl, NEt_3.

Scheme 6. General Scheme for the Synthesis of Aminomethyl Analogs[a]



[a] Reagents and conditions: (a) $NaBH_4/CoCl_3$, EtOH, rt; (b) RCHO, $NaBH_3CN$, MeOH/AcOH.

naphthyl ring system. To investigate the incorporation of alternate left-hand substituents, routes specific for the functionality of interest were required. For example, compounds having the left-hand amide functionality "reversed" were synthesized as depicted in Scheme 5. This effort began with commercially available 4-fluoro-1-naphthalenesulfonyl chloride **16**, which upon treatment with 4-amino-1-Boc-piperidine and then sodium cyanide afforded cyanonaphthalene **17**. Next, cyanonaphthalene **17** was hydrolyzed under basic conditions to afford the requisite carboxylic acid **18**, at which point coupling with either 2-methylaniline or cyclohexylamine and subsequent removal of the Boc carbamate furnished the reversed amides **19a** and **19b**, respectively, in good overall yields. Installation of the ethyl carbamate moiety then provided the desired reversed amide congeners **20a** and **20b**.

Alternatively, benzyl amine derivatives of the left-hand side (**23a**−**c**, Scheme 6) were readily obtained by borohydride-mediated reduction of the cyanonaphthalene **21** under cobalt catalysis and subsequent reductive amination of the resultant amine **22** with a series of aldehydes.

Continuing our investigation of the left-hand functionality, ether and ester derivatives were both accessed from commercially available alcohol **24**, as illustrated in Scheme 7. First, benzyl protection of the naphthol followed by chlorination and sulfonamide formation furnished benzyl ether **26**. For the production of the ester derivative, the benzyl group of **26** was removed under hydrogenolytic conditions to afford naphthol **27**. Treatment of the naphthol with benzoyl chloride then provided the desired ester **28**.

After determination of an optimal left-hand amide substituent, we returned our attention to the right-hand side, focusing on the incorporation of diverse substituents at the piperidine nitrogen (Scheme 8). Beginning with sulfonyl chloride **29** (which was prepared as described in Scheme 2), amination with 4-amino-1-Boc-piperidine and deprotection provided key intermediate **30**, at which point introduction of a series of coupling partners then afforded the title sulfonamides. This tactic allowed the ready incorporation of amide (**31a**−**o**), carbamate (**32a**−**e**), or urea (**33a**−**n**) functionality as piperidine appendages and would ultimately lead to the generation of several compounds exhibiting binding affinities for CCR8 in the low nanomolar to picomolar range, as discussed in the sections to follow.

Results and Discussion

The naphthalene-sulfonamide derivatives prepared in this study[11] were evaluated in an *in vitro* binding assay (FLIPR and/or FMAT)[10] to determine their affinity for human CCR8. Although this manuscript deals primarily with SAR with respect to *in vitro* potency, our screening paradigm allowed for parallel evaluation of various properties in addition to potency, including ortholog cross reactivity, *in vitro* selectivity, eADME properties, including P450 CYP inhibition, metabolic stability, and permeability.

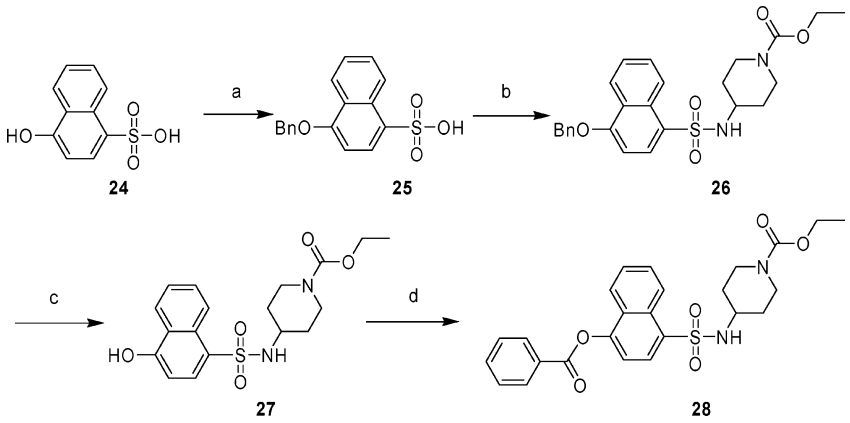
To establish the SAR of this series of compounds, each variable of naphthalene-sulfonamide **1** was systematically modified, including the key H-bond donor/acceptors, right-hand sulfonamide substituents, the left-hand naphthyl appendages, and finally the naphthyl substitution patterns. The following structure−activity tables examine each of these variables in turn and report the *in vitro* activity of the derived compounds against human CCR8.

We begin our discussion by examining the effects of substitution of the key H-bond donor/acceptor amide and sulfonamide moieties, using the high-throughput screening hit **1** (Figure 1) as a starting point. The importance of the left-hand side amide proton became immediately apparent, as each of the tertiary derivatives that were prepared (**2** and **3**, Table 1) were completely devoid of binding activity. Likewise, all compounds bearing a tertiary sulfonamide (i.e., not possessing a H-bond donor) displayed drastically lowered affinity for CCR8 (**5a**−**5e**, Table 1).

Furthermore, as illustrated in Table 2, replacement of the sulfonamide with a carboxamide (**9**) or a secondary amine (**11**) led to diminished activity against CCR8, indicating that the acidic sulfonamide was preferred for potent activity.

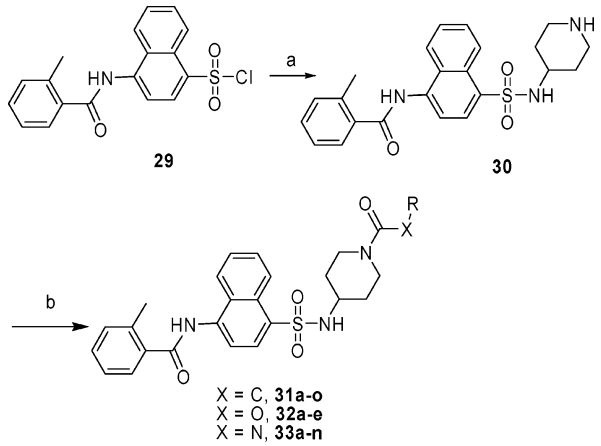
Having identified that both the amide proton and the sulfonamide proton are necessary for potent antagonism of CCR8, we next focused our attention on understanding the effect of modifying the sulfonamide substituent (right-hand side) of the molecule. Here, removal of the methoxy substituent from **1**, as in **6a** (Table 3), reduced potency by over an order of

Scheme 7. Synthesis of Ether **26** and Ester **28**[a]



[a] Reagents and conditions: (a) BnBr, Na_2CO_3, DMF, rt; (b) (i) $SOCl_2$, DMF, rt; (ii) ethyl-4-aminopiperidine-1-carboxylate, Et_3N, CH_2Cl_2; (c) H_2 (1atm), 5% Pd/C, MeOH; (d) PhCOCl, pyridine, CH_2Cl_2, rt.

Scheme 8. General Procedure for the Incorporation of Piperidine Substituents[a]



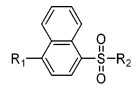
[a] Reagents and conditions: (a) (i) 4-amino-1-Boc-piperidine, NEt_3, CH_2Cl_2; (ii) 4 N HCl in dioxane, THF, rt; (b) for amides, RCOCl, Et_3N, CH_2Cl_2, rt or RCO_2H, EDCI, Et_3N, CH_2Cl_2; for ureas, RNCO, CH_2Cl_2, rt, ClCONHR, CH_2Cl_2, NEt_3 or carbonyl-1,1-diimidazole, HNR_1R_2; for carbamates, ROCOCl, NEt_3.

magnitude, while insertion of a methylene spacer between the naphthalene-sulfonamide core and the phenyl moiety, as in **6b**, resulted in a slight decrease in the binding affinity. The pyridyl congener **6c** and several noncyclic alkyl derivatives (data not shown) demonstrated very poor binding affinity (>3.3 uM) and, thus, were not further pursued. On the other hand, the effect of replacing the right-hand phenyl ring of **6a** with a cyclohexyl group, as in **6d**, was particularly striking, resulting in a 400-fold improvement in activity.

In an effort to increase the solubility of this compound, a piperidyl moiety was introduced as a surrogate for the cyclohexyl group. Interestingly, while the unsubstituted piperidine congener **6e** showed a significant loss in binding affinity, the protected *tert*-butyl carbamate **6f** retained potency on par with cyclohexyl analog **6d**, suggesting that the basic amine was detrimental. Furthermore, not only was modulation of amine basicity important, but the steric size of the carbamate also had a dramatic impact on binding, as the ethyl carbamate derivative **6g** bound to CCR8 with a K_i of 170 picomolar, a 22-fold improvement over the branched *t*-butyl analog **6f**.

Having identified piperidyl carbamates such as **6g** to be extremely potent CCR8 antagonists, we set out to identify the appropriate functionality for the left-hand side of the naphthalene. In the event, the left-hand side proved to be far less

Table 1. Impact of Amide Hydrogen Bonds on Activity

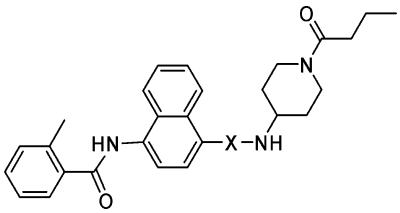


	R_1	R_2	K_i, hFMAT (nM)
1			42.6 +/- 2.8
2			>44000
3			>15000
5a			>44000
5b			>30000
5c			>30000
5d			7745 +/- 271
5e			>30000

sensitive to modification than was the right-hand sulfonamide, with a number of substituent types affording compounds that retained low nanomolar potency, as summarized in Table 4. For example, addition of an *ortho*-methyl subtituent to the phenyl ring in **6g**, as in **15**, furnished a compound with a binding potency of 1.6 nM, while the "reversed-amide" counterpart **20b** proved to be quite potent as well (5.2 nM). Similarly, "reversed" cyclohexyl amide **20a** retained low nanomolar binding to CCR8. Decreases in the binding affinity were observed when an ether (**26**) or ester (**28**) linkage were substituted for the amide (223-fold and 96-fold, respectively).

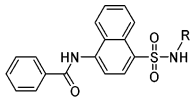
As illustrated with compounds **23a**−**c**, where the terminal phenyl ring is separated from the napthalene sulfonamide core by an aminomethyl group bearing various methylene tether lengths, binding affinity is not drastically altered as the tether length is increased from one to three methylene units. On the other hand, replacement of the left-hand amide with a urea moiety (**34**) resulted in a 93-fold loss of binding potency. Most

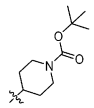
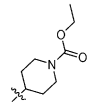
Table 2. Sulfonamide Replacement Derivatives



	X	hFLIPR IC_{50} (nM)
14b	$-SO_2-$	0.3 ± 0.01
9	$-CO-$	>3300
11	$-CH_2-$	>3300

Table 3. Modification of the Sulfonamide Substituent



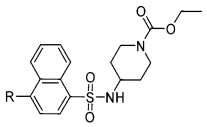
	R	K_i, hFMAT (nM)
1		126.0 +/- 1.5
6a		1760 +/- 506
6b		233.1 +/- 49.0
6c		3277.0 +/- 955.0
6d		4.4 +/- 1.2
6e		578.0 +/- 180.0
6f		15.2 +/- 8.6
6g		0.17 +/- 0.05

dramatically, truncation to an unsubstituted heteroatom moiety, as in naphthol **27** or naphthylamine **35**, led to compounds that were devoid of activity (>5 μM), suggesting that a hydrophobic group is required for potent binding.

Our initial examination of left-hand side functional groups also provided another important insight. Despite demonstrating the most potent binding affinities to human CCR8 that we had yet observed, we found that compound **6g** suffered from a metabolic liability, specifically amidase cleavage in rodent plasma [$T_{1/2}$ (mouse plasma) = 0.5 h]. Pleasingly, we discovered that introduction of an *ortho*-methyl substitutent on the phenyl ring (as in **15**) remediated the rodent plasma stability issue [$T_{1/2}$ (mouse plasma) = 8.2 h] while retaining single digit nanomolar binding affinity. As a consequence, many of the future derivatives utilized this *o*-methylphenyl amide moiety.

With the metabolic liability of the left-hand amide resolved, we next sought to probe further the role of the right-hand side piperidine moiety and its pendent functionality. To this end, we synthesized and evaluated urea **33c** and amide **14b** (Table 5), which both exhibited *in vitro* binding potency on par with ethyl carbamate **15**. The effects of varying the cycloamine ring size were also investigated, wherein the five-membered (**36**) and four-membered (**37**) ring sizes led to similarly potent compounds, though both were some 100-fold less potent at CCR8 than was piperidyl amide **14b**.

Table 4. Derivatives Incorporating Variations of the Left-Hand Amide Substituent



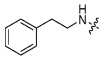
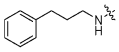
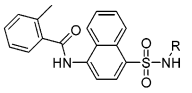
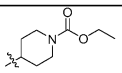
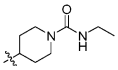
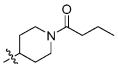
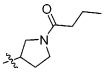
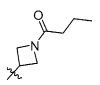
	R	K_i, hFMAT (nM)
6g		0.17 +/- 0.05
15		1.60 +/- 0.07
20a		9.5 +/- 0.5
20b		5.21 +/- 2.90
26		37.9 +/- 16.8
28		16.4 +/- 2.9
23a		45.6 +/- 12.8
23b		35.7 +/- 0.6
23c		32.1 +/- 4.7
34		125.6 +/- 4.7
27	-OH	>5000
35	$-NH_2$	>5000

Table 5. Modification of the Piperidine Substituent and Heterocycle Ring Size



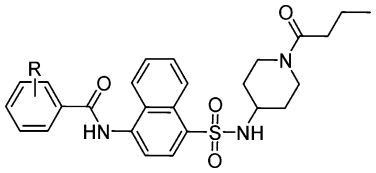
	R	K_i, hFMAT (nM)
15		1.6+/- 0.07
33c		2.2 +/- 3.2
14b		0.30 +/- 0.01
36		34.3 +/- 5.5
37		50.9 +/- 27.8

Before moving forward, we also sought to examine the piperidine substituent with respect to eADME properties, including metabolic stability and permeability. We found that while carbamates, as represented by compound **15** (Table 5), ureas (e.g., **33c**, Table 5), and amides (e.g., **14b**, Table 5), were all nearly equipotent with respect to binding affinity, they could be prioritized using Caco-2 and *in vitro* clearance data. Specifically, Caco-2 transport measurements (Table 6) showed that carbamate **15** and amide **14b** displayed acceptable efflux ratio values of around 1.3, while urea **33c** exhibited an efflux

Table 6. Permeability and Intrinsic Clearance Data for Selected Compounds

	Caco2 ($P_{app} \times 10^6$ cm/s)			
	A to B	B to A	ratio	CL_{int} (L/hr/kg)
15	17	24	1.4	5.7
33c	1.9	22	11	2.8
14b	25	34	1.3	3.1

Table 7. Substituted Phenyl Amides



	R	IC_{50} FLIPR (nM)
14a	H	12.5 ± 3.7
14b	2-Me	5.20 ± 0.6
14c	3-Me	5.10 ± 1.2
14d	4-Me	9.50 ± 2.5
14e	2-F	19.2 ± 5.4
14f	3-F	20.0 ± 5.2
14g	4-F	59.5 ± 15.0
14h	4-ethyl	10.8 ± 3.2
14i	4-*n*-butyl	15.3 ± 5.1
14j	4-*t*-butyl	6.90 ± 0.7
14k	4-*n*-pentyl	36.1 ± 10.6
14l	4-benzyloxy	24.6 ± 3.8

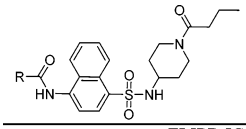
ratio of 11, indicating that it may be a P-gp substrate. The human *in vitro* hepatic clearance was also assessed *via* microsomal incubation studies. In this case, both amide **14b** and urea **33c** demonstrated hepatic stability superior to carbamate **15**. Based upon these data, we chose the propyl amide as a preferred piperidine substituent to include during our next investigation, which entailed a more thorough screening of left-hand amide substituents.

Recalling that the *o*-methylphenyl amide substituent had imparted both excellent potency and high metabolic stability, we nonetheless undertook a more systematic search for an even more potent left-hand amide substituent that retained plasma stability. In this study, we examined first substituents and substitution pattern about the phenyl ring moiety, the results of which are summarized in Table 7. Heteroaryl replacements for the phenyl ring are then shown in Table 8, while alkyl, cycloalkyl, and saturated heterocyclic amide derivatives are reported in Table 9.

Beginning with the substituted phenyl amides (Table 7), no clear preference was observed for *ortho*, *meta*, or *para* substitution (e.g., **14b**−**d** and **14e**−**g**). Likewise, neither alkyl groups of various sizes (e.g., **14a**−**d** and **14h**−**l**) nor fluorine substitution (**14e**−**g**) had a dramatic impact on binding. A number of other substituents exhibited the same general trends but failed to improve the potency (data not shown).

Heterocyclic replacements for the phenyl ring were likewise well-tolerated (Table 8), though none proved superior to the substituted phenyl analogs. In this series, substituted five-membered heterocycles (**14n**−**q**) were preferred over the lone unsubstituted congener (**14m**), while the activity of the six-membered heterocycles evaluated ranged from moderate (**14s**, **14t**, **14v**, and **14w**) to reasonably good (**14r** and **14u**). The influence of heteroatom placement within the heteroaryl ring was also noteworthy, as the *ortho* (**14u**) and *para* (**14w**) pyridyl substituents were preferred over the *meta* regioisomer **14v**.

Table 8. Heteroaryl Replacements for the Phenyl Ring



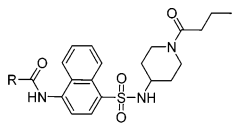
	R	FLIPR IC_{50} (nM)
14m		1519 +/- 202.0
14n		23.6 +/- 5.1
14o		37.0 +/- 7.1
14p		46.9 +/- 13.1
14q		20.4 +/- 4.4
14r		43.9 +/- 10.1
14s		280.0 +/- 10.1
14t		1004.0 +/- 587.0
14u		41.7 +/- 6.7
14v		885.1 +/- 15.0
14w		100.0 +/- 32.9

Consistent binding affinity was also noted when cycloalkyl groups replaced the phenyl ring, as summarized in Table 9. Here, in contrast to the heterocyclic replacements, the six-membered ring size was preferred (cf. **14bb** vs **14x**, **y**, **z**, and **aa**). Heteroatom insertion into the cycloalkyl ring resulted in a decrease in potency, as substituted piperidyl congener **14cc** exhibited greatly diminished activity toward human CCR8, while the pyran derivative **14dd** exhibited 34-fold lower binding than the cyclohexyl analog **14bb**. Finally, compounds bearing acyclic moieties (as in **14ee** and **14ff**) were, in general, less potent than the cycloalkyl derivatives, with the exception of those bearing a pendent phenyl substituent, as in example **14gg**.

By now we had developed a fairly robust picture of the naphthalene scaffold requirements for potent binding to CCR8. Most critical was the secondary sulfonamide, as no other promising surrogates were found. With respect to the left-hand substituent, while a number of functional groups were well-tolerated (see Tables 4, 7, 8, and 9), the *ortho*-methylphenyl amide ultimately provided the best mix of *in vitro* potency and pharmacokinetic properties. Likewise, the piperidyl sulfonamide substituent had proven to be optimal, though there was flexibility in the pendent functionality of the piperidine ring, as carbamates, ureas, and amides were all exceedingly potent antagonists. As such, our next investigations were directed toward uncovering the most favorable substituent to append to the piperidine ring.

As noted previously (Table 6 and accompanying text), amide-functionalized piperidines exhibited a favorable mix of clearance and permeability properties, so we began this study by exploring amide substituents with varying steric and electronic properties (Table 10). For example, a slight decrease in potency was noted

Table 9. Alkyl, Cycloalkyl, and Saturated Heterocyclic Replacements for the Phenyl Ring

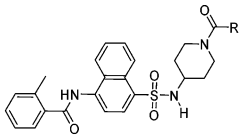


	R	FLIPR IC_{50} (nM)
14x		367.7 +/- 34.3
14y		57.9 +/- 0.6
14z		365.0 +/- 44.2
14aa		144.5 +/- 37.1
14bb		6.1 +/- 0.2
14cc		>1900
14dd		205.9 +/- 0.6
14ee		638.5 +/- 227.0
14ff		612.5 +/- 228.5
14gg		7.65 +/- 2.4

as the propyl moiety in **14b** was truncated to an ethyl group and then a methyl group (**31a** and **31b**, respectively). Replacement of the alkyl chains with three- (**31c**) or five-membered (**31d**) cycloalkyl rings also had minimal impact on activity. Likewise, appending **31b** with a terminal hydroxyl, as in **31e**, with a methyl ether, as in **31f**, or with a primary amine, as in **31g**, resulted in a series of compounds that were roughly equipotent. To investigate the effect of chain length, a series of compounds were prepared in which the terminal amine was separated from the amide functionality via methylene spacers of varying lengths. Binding data showed a slight preference for shorter chain lengths (cf. **31g**−**i** vs **31j**), with the optimal tether length being three methylene units (**31i**, K_i = 1.5 nM). With respect to heterocyclic ring attachments, introduction of a nitrogen into the ring, as in azetidine **31k** and pyrrolidine **31l**, led to a 5-fold improvement in activity when compared to the carbocyclic counterparts. Similar potency was realized with an alanine-derived appendage, as in **31m**. Finally, the larger phenyl and substituted-phenyl amides (**31n** and **31o**, respectively) were by and large 1 to 2 orders of magnitude less potent than the other analogs prepared in this section.

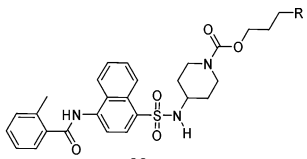
For completeness, the carbamate and urea functionalized piperidine subclasses were also explored further, albeit to a lesser extent (Tables 11 and 12, respectively). Beginning with the carbamates, our investigation demonstrated that the SAR drawn from the amide subclass was largely transferable to the carbamates (data not shown). As such, many of the analogues prepared featured an alkyl chain spacer appended with an amine moiety, as in **32a**−**e** (Table 11). Interestingly, while a four-atom spacer was disfavored in the case of the amides (i.e., **31j**), the four-atom spacer was quite well-tolerated in the context of the carbamates. Attempts to modulate potency by adding steric bulk to the terminal amine moiety had minimal impact. While the data indicate a slight preference for small alkyl groups (**32a**,**b**) and small heterocycles (**32c**), larger amine groups such as dimethylmorpholine (**32d**) and tetrahydroquinoline (**32e**) were also tolerated with reasonable potency (<30 nM).

Table 10. Amide Modification of the Piperidine Nitrogen



	R	K_i, hFMAT (nM)
14b		0.3 +/- 0.01
31a		2.5 +/- 0.7
31b		6.7+/- 0.4
31c		7.2 +/- 1.7
31d		9.1 +/- 1.5
31e		5.4 +/- 0.5
31f		15.8 +/- 1.9
31g		4.1 +/- 0.6
31h		11.3 +/- 0.3
31i		1.6 +/- 0.3
31j		199.0 +/- 57.0
31k		1.5 +/- 0.4
31l		1.0 +/- 0.2
31m		0.7 +/- 0.05
31n		81.1 +/- 24.4
31o		114.0 +/- 14.5

Table 11. Selected Carbamate Piperidine Derivatives



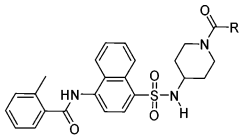
32a-e

	R	FLIPR IC_{50} (nM)
32a	-NMe_2	9.8 +/- 3.1
32b	-NEt_2	14.5 +/- 5.1
32c		4.2 +/- 1.3
32d		19.6 +/- 1.7
32e		28.6 +/- 6.3

Next, a variety of secondary and tertiary urea-functionalized piperidine derivatives were prepared; their binding affinities are summarized in Table 12. For example, while primary urea **33a** showed only moderate potency, the binding affinity of alkyl-substituted ureas was notable but tended to decrease as steric bulk was added (**33b**−**f**). However, tertiary ureas were well tolerated and exhibited similar potency to the corresponding secondary urea (cf. **33b** vs **33g**). Significant potency was realized with small cyclic tertiary ureas. However, there was little difference noted between four-, five-, and six-membered rings (**33h**, **33i**, and **33j**, respectively). Introduction of an additional heteroatom into the six-membered ring had little effect on potency (e.g., piperazine **33k** and morpholine **33l**). Interestingly, in contrast with the previously discussed amide and carbamate subclasses, analogs with an *n*-propyl linker capped by an amine, as in **33m** and **33n**, were somewhat less potent.

The final SARs examined in this investigation entailed modification of the naphthalene core by varying the regiochem-

Table 12. Selected Urea Piperidine Derivatives



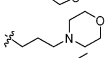
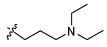
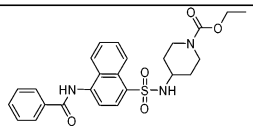
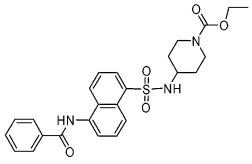
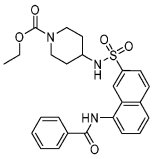
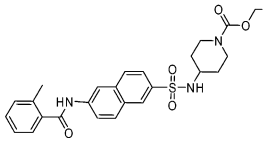
	R	K_i, hFMAT (nM)
33a	-NH_2	243.0 +/- 68.0
33b	-NHMe	0.7 +/- 0.04
33c	-NHEt	2.2 +/- 0.3
33d	-NH*n*-Pr	77.4 +/- 0.6
33e	-NH*i*-Pr	77.7 +/- 4.7
33f	-NHPh	108.0 +/- 70.0
33g	-NMe_2	1.6 +/- 0.05
33h		3.5 +/- 1.3
33i		1.1 +/- 0.01
33j		4.2 +/- 0.3
33k		4.2 +/- 1.3
33l		6.3 +/- 3.3
33m		71.0 +/- 43.0
33n		566.5 +/- 236.0

Table 13. Naphthalene Regioisomers

	Structure	K_i, hFMAT (nM)
6g		0.17 +/- 0.02
38a		2.3 +/- 0.6
38b		2033 +/- 240
38c		>44000

istry of the functional group connectivity (Table 13). In this series, the 1,5-regioisomer **38a** showed 14-fold lower binding affinity than the 1,4-regioisomer **6g**, while the 1,7-regioisomer (**38b**) was several orders of magnitude less potent. Finally, the 2,6-regioisomer (**38c**) was devoid of any binding affinity. Although not discussed in this manuscript, several derivatives based on the 1,5-substituted naphthalene scaffold were prepared, and the previously discussed SAR for the 1,4-regioisomer transferred quite well to the 1,5-scaffold with little loss in overall binding potency.

From the SARs discussed, we have developed a thorough understanding of the critical interactions between the naphthalene-sulfonamide scaffold and human CCR8. Hydrogen bonds involving both the right-hand side sulfonamide and left-hand amide functionality are clearly critical, as alkylation of either the amide or sulfonamide functionality is quite detrimental to potency. Furthermore, while our most potent compounds incorporated an amide moiety on the left-hand side of the naphthalene core, we noted that a wide variety of substitutents were tolerated at this position, suggesting the presence of a large hydrophobic pocket. Likewise, a wide array of secondary sulfonamide substituents were tolerated, though substituted piperidyl derivatives were preferred. Further derivatization of the piperidine nitrogen as an amide, carbamate, amine, or urea all afforded potent analogs, including a number of compounds that exhibited subnanomolar binding affinity to human CCR8. Finally, our studies demonstrated that the substitution pattern of the naphthalene core was important for binding and that the 1,4- and 1,5-regioisomers were preferred and were roughly equipotent. A report concerning the impact of naphthalene core replacements will follow in due course.

Applying our screening paradigm, we also evaluated PK and selectivity properties for selected compounds. In general, the compounds tested showed at least 300-fold selectivity versus GPCRs, including chemokine receptors (e.g., **15**, <20% inhibition at 10 uM against the standard Novascreen panel).[12] They did not significantly inhibit P450 isozymes, including CYP 3A4 (IC_{50} > 10 uM). Furthermore, these compounds did not display significant hERG binding in HEK293 cells (e.g., **15**, K_i > 10 uM).[13] Unfortunately, however, the oral bioavailability of these compounds is low to moderate with low clearance rates and *V*ss, for example, **15** [rat (10 mpk po, 1 mpk iv, F = 2%, $t_{1/2}$ = 2.6 h, *V*ss = 1.6 L/kg, and CL = 1.4 L/h/kg) and dog (10 mpk po, 1 mpk iv, F = 10%, $t_{1/2}$ = 3.7 h, *V*ss = 1.5 L/kg, and CL = 0.42 L/h/kg)]. We have since explored solubility and formulation-based approaches to remediate the poor bioavailability. Accordingly, a second follow up report will detail our efforts to improve the PK profile (i.e., increase oral bioavailability and volume of distribution) of our CCR8 antagonists and will also address issues such as plasma protein binding and whole blood potency.

Experimental Section

Materials and Methods—Pharmacology. FLIPR—Calcium Mobilization Assay. CHO/Gα16 cells stably expressing human CCR8 were plated on 384-well plates (Falcon) at a density of 4×10^3 cells/well and cultured for 2 days at 37 °C and 5% CO_2. On the third day, the cells were incubated with Fluo-3TM (5 uM) for 1 h (37 °C, 5% CO_2), and excess dye was removed by extensively washing the cells. To measure the potency of CCR8 antagonists to inhibit CCL1-induced increases of intracellular Ca^{2+}, plates were loaded onto a Fluorometric Imaging Plate Reader (FLIPR2TM, Molecular Devices, Inc., Sunnyvale, CA) and either incubated with different concentrations of antagonists (100% DMSO) or DMSO alone (negative control), resulting in a final DMSO concentration of 1%. After 3 min of preincubation with antagonists, Ca^{2+}-flux was induced by adding the CCR8 ligand CCL1 (R&D Systems) at a final concentration of 2 nM. Antagonist IC_{50} values were calculated using XLFit 4.0TM (IDBS, Guildford, U.K.).

FMAT Binding Assay. A suspension was prepared of L1.2/hCCR8 cells at 4.0×10^5 cells/mL in a binding buffer (Buffer consisting of Hanks balanced salt solution (without phenol red), 10 mM HEPES, 0.1% fatty acid free BSA, 0.02% sodium azide). A solution of 0.375 nM of human CCL1 (biotinylated at the C-terminus of the ligand after an additional lysine residue using the Applied Biosystems 433 peptide synthesizer) and 0.375 nM of mouse Cy-5 Mab-α-Biotin (Jackson ImmunoResearch Laboratories, Inc., code number 200-172-096) was prepared in binding buffer immediately prior to the assay.

A dilution series of 10 mM stock concentrations of the test compounds were prepared in DMSO and further diluted into binding buffer defined above to three times the final assay concentration. A ten-point concentration−response curve is constructed for each compound, starting at 10 μM (final assay concentration in binding buffer). An amount equal to 25 μL of each concentration of test was transferred into the appropriate wells of a 384-well plate. Cold 100 nM CCL1 (25 μL; R and D Systems: catalog number 272-I/CF) was then transferred into empty wells to serve as a control for nonspecific binding. Biotinylated human CCL1 (25 μL of the 0.375 nM)/0.375 nM Cy5-α-biotin solution were then transferred into each well of the same 384-well plate, followed by addition of 25 μL of the resuspended cell solution into each well. The components were mixed in wells by covering the plate with aluminum foil and rotating for 0.5 h. The plates were allowed to incubate at room temperature for approximately 1−2 h and then read on a FMAT 8100 HTS system (purchased from Applied Biosystems, PMT= 490/518 or 537/568, set threshold = 1SD MAT). Average fluorescence reported for each concentration was normalized to percent inhibition based on negative (no inhibitor) and positive (100 nM excess unlabeled CCL1 (R and D Systems)) controls.

Materials and Methods−Chemistry. All reactions involving air-sensitive reagents were performed under a nitrogen atmosphere. Reagents were used as received from commercial suppliers unless otherwise noted. Anhydrous solvents such as dimethylformamide (DMF), tetrahydrofuran (THF), and dichloromethane (CH_2Cl_2) were obtained either from Aldrich Chemical Co. in Sure/Seal bottles or from Mallinckrodt Baker, Inc., as ultra low water solvent. ^{1}H NMR data were recorded using either a Bruker UltraShield 300 MHz/54 mm instrument equipped with Bruker B-ACS60 auto sampler or a Varian 300 MHz instrument. Chemical shifts are expressed in ppm from tetramethylsilane resonance in the indicated solvent (TMS: 0.0 ppm), and coupling constants (*J*-values) are given in hertz (Hz). ^{1}H NMR data are reported in the following order: ppm, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet; br, broad), and number of protons. Intermediates and final compounds were purified by chromatography using one of the following instruments, unless otherwise noted: (1*)* Biotage 4-channel Quad UV Flash Collector equipped with a Quad 1 Pump Module and the Quad 12/25 cartridge module; (2) Isco combi-flash chromatography instrument; or (3) HPLC/MS system equipped with Waters 2700 sample manager auto-injector, Waters 600 controller and pumps, Waters 996 diode array detector, Micro Mass Platform LCZ mass spectrometer, and Gilson FC-204 fraction collector. Solvents A (99% water/1% CH_3CN/0.1% formic acid) and B (95% CH_3CN/5% water/0.1% formic acid) were used for gradient elution of the compounds using Phenomenex Luna 15 micron, C18(2) 100A, 250 × 21.2 mm column at 20 mL/min flow rate. The reported yields represent the yields obtained for the final step of the sequence before optimization. LC/MS spectra were obtained using a Micro-Mass Platform LC (Phenomenex C18 column, 5 micron, 50 × 4.6 mm) equipped with a Gilson 215 liquid handler. High-resolution mass spectra (HRMS) were obtained using a QSTAR XL quadruple-time-of-flight mass spectrometer (Applied Biosystems/MDS Sciex) coupled with an Agilent 1100 series HPLC system (binary pump, autosampler, and degasser).

Experimental Procedures. General Procedure A. *N*-[4-(4-Methoxy-phenylsulfamoyl)-naphthalen-1-yl]-benzamide (1). This compound was prepared in three steps starting from commercially available 4-amino-1-naphthalenesulfonic acid, as shown below.

Step 1. To a solution of 4-amino-naphthalene-1-sulfonic acid (2.3 g, 10.0 mmol) in pyridine (15 mL) was added benzoyl chloride (1.4 mL, 12.0 mmol), and the resultant solution was stirred at 100 °C for 17 h. The solvent was then removed under vacuum, and the crude material was recrystallized from MeOH (2×) to afford 4-benzoylamino-naphthalene-1-sulfonic acid pyridinium salt (2.0 g) as a gray solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.92 (m, 3H), 8.60 (m, 1H), 8.00 (m, 6H), 7.55 (m, 6H); LC/MS *m*/*z* 327 $[M - H]^-$.

Step 2. 4-Benzoylamino-naphthalene-1-sulfonyl chloride (4). To a solution of the above pyridinium salt (2.4 g, 5.9 mmol) in DMF (10 mL) was added thionyl chloride (0.6 mL, 8.8 mmol). The reaction mixture was stirred at 25 °C for 3 h, at which point the reaction was quenched by pouring into ice water and then filtered to afford **4** (1.8 g) as a pale white solid. This material was used without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.88 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 6.7 Hz, 2H), 7.97 (d, J = 7.7 Hz, 2H), 7.55 (m, 6H).

Step 3. To a solution of **4** (0.32 g, 0.93 mmol) in CH_2Cl_2 (20 mL) were added Et_3N (0.26 mL, 1.85 mmol) and *p*-anisidine (0.14 g, 1.11 mmol). The reaction mixture was stirred at 25 °C for 17 h, at which point the reaction was quenched with water and extracted several times with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated to provide the crude product as a viscous yellow oil. The oil was purified via HPLC, affording **1** as a white solid (0.19 g, 47%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.78 (d, J = 6.8 Hz, 1H), 8.11 (m, 2H), 8.04 (d, J = 7.9 Hz, 2H), 7.70 (m, 7H), 6.85 (d, J = 8.9 Hz, 2H), 6.60 (d, J = 8.9 Hz, 2H), 3.62 (s, 3H); LC/MS *m*/*z* 433 $[M + H]^+$; HRMS calcd for $C_{24}H_{20}N_2O_4S$ $[M + H]^+$, 433.1222; found, 433.1235.

4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-naphthalene-1-sulfonic Acid (4-Methoxy phenyl)-amide (2). The title compound was prepared following general procedure A using phthaloyl dichloride instead of benzoyl chloride. Yield: 0.8 g (42%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (d, J = 8.5 Hz, 1H), 8.20 (d, J = 7.7 Hz, 1H), 8.02 (m, 2H), 7.87 (m, 2H), 7.66 (m, 3H), 7.42 (d, J = 7.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 6.69 (d, J = 8.7 Hz, 2H), 3.72 (s, 3H); LC/MS *m*/*z* 459 $[M + H]^+$; HRMS calcd for $C_{25}H_{18}N_2O_5S$ $[M + H]^+$, 459.1014; found, 459.1023.

***N*-(4-{[(4-Methoxyphenyl)amino]sulfonyl}-1-naphthyl)-*N*-methylbenzamide (3). Step 1.** To a solution of **2** (2.8 g, 6.3 mmol) in MeOH (50 mL) was added hydrazine (5 mL, 158 mmol). The resultant solution was stirred at 55 °C for 2 h, at which point the precipitate was removed via filtration and washed with a small amount of MeOH. The filtrate was collected and the solvent was removed *in vacuo* to provide a pale yellow solid (1.2 g, 58%). **Step 2.** To a DMF (5 mL) solution of the above solid (0.20 g, 0.62 mmol) were added MeI (43 μL, 0.68 mmol) and K_2CO_3 (0.17 g, 1.24 mmol). The reaction mixture was stirred at 25 °C for 17 h. The reaction mixture was quenched with water and extracted several times with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Column chromatography of the crude product provided the desired methylated intermediate (0.18 g, 85%). **Step 3.** To a CH_2Cl_2 (5 mL) solution of the intermediate generated in Step 2 (80 mg, 0.24 mmol) were added Et_3N (67 μL, 0.48 mmol) and benzoyl chloride (40 μL, 0.35 mmol). The reaction mixture was stirred at 25 °C for 17 h. Concentration and purification by column chromatography provided **3** (45 mg, 42%) as a light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.23 (m, 2H), 8.10 (m, 3H), 7.90 (d, J = 8.2 Hz, 1H), 7.60 (m, 5H), 7.03 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 3.72 [s, 3H], 3.18 (s, 3H); LC/MS *m*/*z* 445 $(M- H)^+$; HRMS calcd for $C_{25}H_{20}N_2O_4S$ $[M + H]^+$, 447.1378; found, 447.1386.

Sulfonamides 5a−5c and 5e. These compounds were prepared according to general procedure A from the appropriate starting materials. Sulfonamide **5d** was purchased from a commercial source.

***N*-[4-(Methyl-phenyl-sulfamoyl)-naphthalen-1-yl]-benzamide (5a).** ^{1}H NMR (300 MHz, CD_3OD) δ 8.29 (d, J = 6.9 Hz, 1H), 8.12 (m, 2H), 8.05 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.1 Hz, 1H), 8.55 (m, 4H), 7.37 (m, 1H), 7.26 (m, 3H), 7.12 (m, 2H), 3.25 (s, 3H); LC/MS *m*/*z* 417 $[M + H]^+$; HRMS calcd for $C_{24}H_{20}N_2O_3S$ $[M + H]^+$, 417.1273; found, 417.1288.

***N*-(4-Diethylsulfamoyl-naphthalen-1-yl)-benzamide (5b).** ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.60 (d, J = 8.8 Hz, 1H), 8.05 (m, 5H), 7.60 (m, 5H), 3.35 (q, J = 7.0 Hz, 4H), 1.07 (t, J = 7.0 Hz, 6H); LC/MS *m*/*z* 383 $[M + H]^+$; HRMS calcd for $C_{21}H_{22}N_2O_3S$ $[M + H]^+$, 383.1429; found, 383.1445.

***N*-(4-(Piperidin-1-ylsulfonyl)naphthalen-1-yl)benzamide (5c).** ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.68 (s, 1H), 8.70 (d, J = 8.5

Hz, 1H) 8.22 (m, 2H), 8.09 (d, $J = 7.4$ Hz, 2H), 7.88 (d, $J = 8.0$ Hz, 1H), 7.66 (m, 4H), 3.32 (s, 1H), 3.10 (m, 4H), 1.40 (m, 6H); LC/MS *m*/*z* 395 $[M + H]^+$; HRMS calcd for $C_{22}H_{22}N_2O_3S$ $[M + H]^+$, 395.1429; found, 395.1448.

***N*-[4-(4-Methyl-piperazine-1-sulfonyl)-naphthalen-1-yl]benzamide (5e).** ^{1}H NMR (300 MHz, CD_3OD) δ 8.74 (d, $J = 6.8$ Hz, 1H), 8.37 (d, $J = 8.0$ Hz, 1H), 8.15 (m, 2H), 8.08 (d, $J = 8.1$ Hz, 2H), 7.86 (d, $J = 8.1$ Hz, 1H), 7.55 (m, 4H), 3.36 (m, 4H), 2.86 (m, 4H), 2.50 (s, 3H); LC/MS *m*/*z* 410 $[M + H]^+$; HRMS calcd for $C_{26}H_{23}N_3O_3S$ $[M + H]^+$, 410.1538; found, 410.1534.

Sulfonamides 6a−6d. These compounds were prepared according to general procedure A from the appropriate starting materials.

***N*-(4-Phenylsulfamoyl-naphthalen-1-yl)-benzamide (6a).** ^{1}H NMR (300 MHz, CD_3OD) δ 8.76 (d, $J = 6.8$ Hz, 1H), 8.16 (d, $J = 7.9$ Hz, 1H), 8.05 (d, $J = 7.8$ Hz, 1H), 7.96 (d, $J = 8.0$ Hz, 2H), 7.60 (m, 6H), 7.00 (m, 5H); LC/MS *m*/*z* 403 $[M + H]^+$; HRMS calcd for $C_{23}H_{18}N_2O_3S$ $[M + H]^+$, 403.1116; found, 403.1118.

***N*-{4-[(Benzylamino)sulfonyl]-1-naphthyl}benzamide (6b).** ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.71 (d, $J = 6.9$ Hz, 1H), 8.18 (m, 2H), 8.11 (d, $J = 8.0$ Hz, 2H), 7.90 (d, $J = 8.2$ Hz, 1H), 7.60 (m, 5H), 7.40 (m, 5H), 4.05 (s, 2H); LC/MS *m*/*z* 417 $[M + H]^+$; HRMS calcd for $C_{22}H_{20}N_2O_3S$ $[M + H]^+$, 417.1273; found, 417.1289.

***N*-{4-[(Pyridin-4-ylmethyl)-sulfamoyl]-naphthalen-1-yl}-benzamide (6c).** ^{1}H NMR (300 MHz, CD_3OD) δ 8.76 (d, $J = 6.8$ Hz, 1H), 8.22 (d, $J = 8.0$ Hz, 2H), 8.14 (d, $J = 8.5$ Hz, 1H), 8.09 (d, $J = 8.1$ Hz, 2H), 7.74 (d, $J = 8.1$ Hz, 1H), 7.60 (m, 6H), 7.08 (d, $J = 6.5$ Hz, 2H), 4.10 (s, 2H); LC/MS *m*/*z* 418 $[M + H]^+$; HRMS calcd for $C_{23}H_{19}N_3O_3S$ $[M + H]^+$, 418.1225; found, 418.1245.

***N*-(4-Cyclohexylsulfamoyl-naphthalen-1-yl)-benzamide (6d).** ^{1}H NMR (300 MHz, CD_3OD) δ 8.80 (d, $J = 6.8$ Hz, 1H), 8.33 (d, $J = 8.1$ Hz, 1H), 8.20 (d, $J = 8.1$ Hz, 1H), 8.08 (d, $J = 8.0$ Hz, 2H), 7.85 (d, $J = 8.0$ Hz, 1H), 7.66 (m, 5H), 3.05 (br, 1H), 1.60 (m, 3H), 1.48 (m, 1H), 1.35 (m, 1H), 1.25 (m, 5H); LC/MS *m*/*z* 409 $[M + H]^+$; HRMS calcd for $C_{23}H_{24}N_2O_3S$ $[M + H]^+$, 409.1586; found, 409.1596.

***N*-[4-(Piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide Formic Acid Salt (6e).** The title compound was prepared according to general procedure A, substituting *tert*-butyl 4-aminopiperidine-1-carboxylate for *p*-anisidine, followed by Boc deprotection. ^{1}H NMR (300 MHz, CD_3OD) δ 8.75 (d, $J = 7.5$ Hz, 1H), 8.46 (s, 1H), 8.30 (d, $J = 7.5$ Hz, 1H), 8.18 (d, $J = 7.0$ Hz, 1H), 8.05 (m, 2H), 7.82 (d, $J = 7.5$ Hz, 1H), 7.62 (m, 5H), 3.21 (m, 3H), 2.90 (m, 2H), 1.80 (m, 2H), 1.60 (m, 2H); LC/MS *m*/*z* 410 $[M + H]^+$; HRMS calcd for $C_{22}H_{23}N_3O_3S$ $[M + H]^+$, 410.1538; found, 410.1543.

Sulfonamides 6f and 6g. These compounds were prepared according to general procedure A from the appropriate starting materials.

4-(4-Benzoylamino-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic Acid *tert*-Butyl Ester (6f). ^{1}H NMR (300 MHz, CD_3OD) δ 8.75 (d, $J = 7.5$ Hz, 1H), 8.30 (d, $J = 7.5$ Hz, 1H), 8.18 (d, $J = 7.0$ Hz, 1H), 8.05 (m, 2H), 7.82 (d, $J = 7.5$ Hz, 1H), 7.62 (m, 5H), 3.82 (d, $J = 15.0$ Hz, 2H), 3.25 (m, 1H), 2.75 (m, 2H), 1.55 (m, 2H), 1.35 (s, 9H), 1.25 (m, 2H); LC/MS *m*/*z* 510 $[M + H]^+$; HRMS calcd for $C_{27}H_{31}N_3O_5S$ $[M + H]^+$, 510.2062; found, 510.2048.

4-(4-Benzoylamino-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic Acid Ethyl Ester (6g). ^{1}H NMR (300 MHz, CD_3OD) δ 8.75 (d, $J = 7.5$ Hz, 1H), 8.30 (d, $J = 7.5$ Hz, 1H), 8.18 (d, $J = 7.0$ Hz, 1H), 8.05 (m, 2H), 7.82 (d, $J = 7.5$ Hz, 1H), 7.62 (m, 5H), 4.02 (q, $J = 7.1$ Hz, 2H), 3.82 (d, $J = 15.0$ Hz, 2H), 3.25 (m, 1H), 2.75 (m, 2H), 1.55 (m, 2H), 1.25 (m, 2H), 1.18 (t, $J = 7.1$ Hz, 3H); LC/MS *m*/*z* 482 $[M + H]^+$; HRMS calcd for $C_{25}H_{27}N_3O_5S$ $[M + H]^+$, 482.1749; found, 482.1766.

***N*-(4-Bromo-1-naphthyl)-2-methylbenzamide (7).** To solution of 4-bromonaphthalen-1-amine (1.01 g, 45.0 mmol) in THF (100 mL) were added pyridine (9.1 mL, 113 mmol) and 2-methylbenzoyl chloride (7.0 mL, 54.0 mmol). The reaction mixture was stirred at 25 °C for 17 h, at which point the solvent was removed *in vacuo*. The crude mixture was then triturated by addition of toluene and filtration of the resulting solid, which was washed with hexane and water to provide **7**. The material thus obtained was used without further purification. LCMS *m*/*z* 342 $[M + H]^+$.

4-[(2-Methylbenzoyl)amino]-1-naphthoic Acid (8). To a solution of **7** (1.70 g, 5.00 mmol) in THF (30 mL) was added NaH (568 mg, 24.0 mmol). The reaction mixture was stirred at 25 °C for 1 h and then cooled to −78 °C, at which point *sec*-butyl lithium was added dropwise as a solution in cyclohexane (1.4 M solution, 7.1 mL, 10.0 mmol). The resulting mixture was stirred at −78 °C for 1 h and then quenched by addition of dry ice, at which point the mixture was acidified to pH 3 by addition of 6 N HCl. The mixture was then extracted with EtOAc (3×), and the combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated. Precipitation of the product from a water/MeOH mixture then afforded the desired acid **8**. LCMS *m*/*z* 306 $[M + H]^+$.

***N*-(1-Butyrylpiperidin-4-yl)-4-[(2-methylbenzoyl)amino]-1-naphthamide (9). Step 1.** To a solution of **8** (305 mg, 1.00 mmol) in pyridine (5 mL) were added *tert*-butyl 4-aminopiperidine-1-carboxylate (214 mg, 1.07 mmol) and EDCI (383 mg, 2.00 mmol). The reaction mixture was stirred at 25 °C for 17 h, and the solution was concentrated *in vacuo*, affording the requisite *N*-Boc protected intermediate (LCMS *m*/*z* 488 $[M + H]^+$), which was subsequently stirred in 4 M HCl/dioxane (5.0 mL) at 25 °C for 5 h, to afford 4-[(2-methylbenzoyl)amino]-*N*-piperidin-4-yl-1-naphthamide as the corresponding HCl salt. LCMS *m*/*z* 388 $[M + H]^+$. **Step 2.** To a solution of the product from Step 1 in CH_2Cl_2 (10.0 mL) was added Et_3N (0.417 mL, 3.00 mmol) and butanoyl chloride (0.157 mL, 1.50 mmol). The reaction mixture was stirred at 25 °C for 17 h, followed by aqueous workup and HPLC purification, to afford **9** (142 mg, yield 48%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.44 (s, 1H), 8.52 (d, $J = 6.6$ Hz, 1H), 8.21 (m, 2H), 7.65 (m, 5H), 7.40 (m, 3H), 4.33 (m, 1H), 4.13 (m, 1H), 3.88 (m, 1H), 3.17 (m, 1H), 2.77 (m, 1H), 2.48 (s, 3H), 2.29 (t, $J = 6.9$ Hz, 2H), 1.94 (m, 2H), 1.47 (m, 4H), 0.90 (t, $J = 7.1$ Hz, 3H); LC/MS *m*/*z* 458 $[M + H]^+$; HRMS calcd for $C_{28}H_{31}N_3O_3$ $[M + H]^+$, 458.2443; found, 458.2458.

***N*-(4-Formyl-1-naphthyl)-2-methylbenzamide (10).** To a solution of **7** (1.40 g, 4.10 mmol) in THF at −78 °C was added dropwise *s*-butyl lithium as a solution in cyclohexane (1.4 M solution, 11.8 mL, 16.5 mmol). The reaction mixture was stirred at −78 °C for 1 h, at which time the reaction was quenched with DMF (2.0 mL) followed by the addition of water (2.0 mL). The mixture was then diluted with EtOAc, the layers were separated, and the aqueous layer was extracted with EtOAc (2×). The combined organic layers were washed successively with saturated $NaHCO_3$ solution, 1 N HCl solution, and brine and then dried over $MgSO_4$. Filtration and concentration then provided **10**, which was used without further purification. LCMS *m*/*z* 290 $[M + H]^+$.

***N*-(4-{[(1-Butyrylpiperidin-4-yl)amino]methyl}-1-naphthyl)-2-methylbenzamide (11). Step 1.** To a solution of **10** (289 mg, 1.00 mmol) in MeOH (10 mL) were added *tert*-butyl 4-aminopiperidine-1-carboxylate (268 mg, 1.34 mmol) and sodium triacetoxyborohydride (318 mg, 1.50 mmol). The reaction mixture was stirred at 25 °C for 17 h, at which time the solution was concentrated *in vacuo*, and the resulting residue was diluted with EtOAc and washed with water (1×). The organic layer was dried over $MgSO_4$, filtered, and concentrated to provide the desired *N*-Boc-protected intermediate, which was used without further purification; LCMS *m*/*z* 474 $[M + H]^+$. The above intermediate was next stirred in 4 M HCl/dioxane (5.0 mL) at 25 °C for 5 h, at which point removal of the solvent *in vacuo* provided 2-methyl-*N*-{4-[(piperidin-4-ylamino)methyl]-1-naphthyl}benzamide as the corresponding HCl salt; LCMS *m*/*z* 374 $[M + H]^+$. **Step 2.** To a mixture of the above intermediate in CH_2Cl_2 (10 mL) were added Et_3N (0.417 mL, 3.00 mmol) and butanoyl chloride (0.157 mL, 1.50 mmol). The reaction mixture was stirred at 25 °C for 17 h. Subsequent aqueous workup, concentration of the resulting organic layer, and purification via reverse phase HPLC then afforded **11** as a white solid (113 mg, yield 28%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.21 (d, $J = 8.1$ Hz, 1H), 8.12 (d, $J = 7.5$ Hz, 1H), 7.62 (m, 5H), 7.40 (m, 3H), 4.49 (d, $J = 12.9$ Hz, 1H), 4.31 (s, 2H), 3.98 (d, $J = 13.5$ Hz, 1H), 3.14

(m, 1H), 2.93 (m, 1H), 2.74 (t, J = 12.0 Hz, 1H), 2.57 (s, 3H), 2.38 (m, 2H), 2.07 (m, 2H), 1.63 (m, 2H), 1.36 (m, 2H), 0.98 (m, 3H); LC/MS m/z 444 $[M + H]^+$; HRMS calcd for $C_{28}H_{33}N_3O_2$ $[M + H]^+$, 444.2651; found, 444.2662.

***N*-(1-Butyrylpiperidin-4-yl)-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)naphthalene-1-sulfonamide (12).** This compound was prepared according to the five-step sequence outlined below.

Step 1. 4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)naphthalene-1-sulfonic Acid Pyridinium Salt. To a solution of 4-aminonaphthalene-1-sulfonic acid (4.9 g 10.0 mmol) in pyridine (15 mL) was added phthaloyl dichloride (3.2 mL, 22 mmol), and the resultant solution was stirred at 80 °C for 17 h. The solvent was removed *in vacuo*, and the crude material was recrystallized from MeOH (2×) to provide the title compound (2.0 g) as a gray solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.90 (m, 2H), 8.57 (m, 1H), 8.00 (m, 7H), 7.77 (d, J = 8.4 Hz, 1H), 7.58 (m, 2H), 7.49 (m, 2H).

Step 2. 4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)naphthalene-1-sulfonyl Chloride. To a solution of the sulfonic acid generated in Step 1 (2.0 g 4.6 mmol) in DMF (10 mL) was added thionyl chloride (0.5 mL, 6.95 mmol). The resultant solution was stirred at 25 °C for 3 h. The reaction was then quenched by pouring into ice water, and this mixture was directly filtered to provide the title compound (1.4 g) as a pale white solid, which was used without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.95 (d, J = 8.4 Hz, 1H), 8.00 (m, 5H), 7.73 (d, J = 8.3 Hz, 1H), 7.58 (m, 2H), 7.49 (m, 1H).

Step 3. *tert*-Butyl 4-(1-(1,3-Dioxoisoindolin-2-yl)naphthalene-4-sulfonamido)piperidine-1-carboxylate. To a solution of the sulfonyl chloride generated in Step 2 (1.11 g, 3.0 mmol) in CH_2Cl_2 (30 mL) were added *tert*-butyl 4-aminopiperidine-1-carboxylate (600 mg, 3.00 mmol) and Et_3N (1.25 mL, 9.00 mmol). The resultant solution was stirred at 25 °C for 3 h, at which point the reaction mixture was quenched with water and extracted with CH_2Cl_2 (3×). The solvent was removed *in vacuo* to provide the title compound as a pale white solid, which was used without further purification. LC/MS m/z 536 $[M + H]^+$.

Step 4. 4-(1,3-Dioxoisoindolin-2-yl)-*N*-(piperidin-4-yl)naphthalene-1-sulfonamide. To a solution of the product from Step 3 (1.60 g, 3.0 mmol) in MeOH (20 mL) was added HCl as a 1 N solution in diethyl ether (35 mL, 35.0 mmol). The resultant solution was stirred at 25 °C for 3 h, at which point the solvent was removed *in vacuo* to provide the title compound (665 mg) as a white solid, which was used without further purification. LC/MS m/z 436 $[M + H]^+$.

Step 5. *N*-(1-Butyrylpiperidin-4-yl)-4-(1,3-dioxoisoindolin-2-yl)naphthalene-1-sulfonamide (12). To a solution of the sulfonamide from Step 4 (665 mg, 1.53 mmol) in CH_2Cl_2 (20 mL) were added butyl chloride (159 μL, 1.53 mmol) and Et_3N (639 μL, 4.59 mmol). The resultant solution was stirred at 25 °C for 3 h, at which point the reaction was quenched with water and extracted with CH_2Cl_2 (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (hexane/ethyl acetate, 60/40 as eluent) afforded the desired compound **12** (410 mg, 53%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (d, J = 9.0 Hz, 1H), 8.38 (d, J = 7.8 Hz, 1H), 8.03 (m, 2H), 7.87 (m, 2H), 7.67 (m, 3H), 7.53 (d, J = 7.5 Hz, 1H), 5.43 (d, J = 7.8 Hz, 1H), 4.30 (m, 1H), 3.67 (m, 1H), 3.41 (m, 1H), 2.99 (m, 1H), 2.70 (m, 1H), 2.22 (m, 2H), 1.79 (m, 1H), 1.58 (m, 2H), 1.34 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H); LC/MS m/z 506 $[M + H]^+$.

4-Amino-*N*-(1-butyrylpiperidin-4-yl)naphthalene-1-sulfonamide (13). To a solution of **12** (380 mg, 0.752 mmol) in MeOH (5.00 mL) was added hydrazine (119 μL, 3.76 mmol), at which point precipitation was observed, signaling completion of the reaction. The solvent was removed *in vacuo*, and the crude product was dissolved in CH_2Cl_2 and washed with water (3×). The organic layer was dried over $MgSO_4$, filtered, and concentrated to provide the title compound (275 mg, 97%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, J = 8.7 Hz, 1H), 8.09 (d, J = 8.1 Hz, 1H), 7.85 (d, J = 7.5 Hz, 1H), 7.62 (m, 1H), 7.52 (m, 1H), 6.69 (d, J = 8.1 Hz, 1H), 4.88 (d, J = 7.2 Hz, 1H), 4.16 (m, 1H), 3.61 (m, 1H), 3.25 (m, 1H), 2.94 (m, 1H), 2.62 (m, 1H), 2.18 (m, 2H), 1.73 (m, 1H), 1.54 (m, 3H), 1.20 (m, 3H), 0.88 (t, J = 7.5 Hz, 3H); LC/MS m/z 376 $[M + H]^+$.

General Procedure B. *N*-(4-{[(1-Butyrylpiperidin-4-yl)amino]-sulfonyl}-1-naphthyl)benzamide (14a). To a vial containing benzoyl chloride (0.046 mL, 0.40 mmol) were added a solution of **13** (45 mg, 0.12 mmol) in 1,2-dichloroethane (0.6 mL), pyridine (0.6 mL), and 4-(dimethylamino)pyridine (2.81 mg, 0.023 mmol). After being shaken at 100 °C for 3 h, the solution was concentrated *in vacuo* to provide a crude residue, which was partitioned between saturated aqueous sodium bicarbonate (2.0 mL) and CH_2Cl_2 (3 mL). The aqueous layer was further extracted with CH_2Cl_2 (1×), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification by HPLC provided **14a** (0.020 g, 35%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.62 (d, J = 7.6 Hz, 1H), 8.22 (d, J = 8.2 Hz, 1H), 8.12 (d, J = 8.3 Hz, 1H), 8.02 (m, 3H), 7.59 (m, 5H), 5.21 (d, J = 7.6 Hz, 1H), 4.17 (d, J = 14.7 Hz, 1H), 3.61 (d, J = 13.9 Hz, 1H), 3.28 (m, 1H), 2.92 (t, J = 11.5 Hz, 1H), 2.54 (t, J = 11.1 Hz, 1H), 2.18 (t, J = 7.9 Hz, 2H), 1.76 (d, J = 12.1 Hz, 1H), 1.55 (m, 3H), 1.21 (q, J = 11.0 Hz, 1H), 1.05 (q, J = 11.1 Hz, 1H), 0.89 (t, J = 7.3 Hz, 3H); LC/MS m/z 480 $[M + H]^+$; HRMS calcd for $C_{26}H_{29}N_3O_4S$ $[M + H]^+$, 480.1957; found, 480.1935.

Amides 14b−14v. These compounds were prepared according to general procedure B from the appropriate starting materials.

***N*-(4-{[(1-Butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)-2-methylbenzamide (14b).** ^{1}H NMR (300 MHz, CD_3OD) δ 8.78 (m, 1H), 8.33 (m, 1H), 8.23 (m, 1H), 7.94 (m, 1H), 7.71 (m, 3H), 7.39 (m, 3H), 4.19 (m, 1H), 3.74 (m, 1H), 3.33 (m, 1H), 3.01 (m, 1H), 2.64 (m, 1H), 2.54 (s, 3H), 2.27 (t, J = 7.5 Hz, 2H), 1.62 (m, 2H), 1.55 (m, 2H), 1.29 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H); LC/MS $[M + 1]^+$ m/z 494; HRMS calcd for $C_{27}H_{31}N_3O_4S$ $[M + H]^+$, 494.2113; found, 494.2121.

***N*-(4-{[(1-Butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)-3-methylbenzamide (14c).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, J = 7.8 Hz, 1H), 8.53 (s, 1H), 8.32 (s, 2H), 8.02 (d, J = 7.6 Hz, 1H), 7.81 (m, 2H), 7.70 (m, 2H), 7.46 (d, J = 4.1 Hz, 2H), 4.77 (d, J = 7.62 Hz, 1H), 4.25 (d, J = 13.5 Hz, 1H), 3.65 (d, J = 13.9 Hz, 1H), 3.33 (m, 1H), 2.96 (t, J = 13.3 Hz, 1H), 2.57 (t, J = 12.6 Hz, 1H), 2.49 (s, 3H), 2.20 (t, J = 7.1 Hz, 2H), 1.80 (d, J = 12.7 Hz, 1H), 1.57 (m, 3H), 1.20 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H); LC/MS m/z 494 $[M + H]^+$; HRMS calcd for $C_{27}H_{31}N_3O_4S$ $[M + H]^+$, 494.2113; found, 494.2137.

***N*-(4-{[(1-Butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)-4-methylbenzamide (14d).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.59 (d, J = 7.7 Hz, 1H), 8.14 (d, J = 8.3 Hz, 1H), 7.96 (t, J = 8.8 Hz, 4H), 7.56 (quin, J = 6.6 Hz, 2H), 7.32 (d, J = 8.4 Hz, 1H), 5.58 (d, J = 7.6 Hz, 1H), 4.11 (d, J = 13.5 Hz, 1H), 3.56 (d, J = 14 Hz, 1H), 3.24 (m, 1H), 2.87 (t, J = 11.6 Hz, 1H), 2.50 (t, J = 11.8 Hz, 1H), 2.45 (s, 3H), 2.14 (t, J = 7.7 Hz, 2H), 1.69 (d, J = 10.5 Hz, 1H), 1.52 (m, 2H), 1.17 (q, J = 10.6 Hz, 1H), 0.99 (q, J = 10.5 Hz, 1H), 0.87 (t, J = 7.4 Hz, 3H); LC/MS m/z 494 $[M + H]^+$; HRMS calcd for $C_{27}H_{31}N_3O_4S$ $[M + H]^+$, 494.2113; found, 494.2105.

***N*-[4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-fluoro-benzamide (14e).** ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.73 (s, 1H), 8.69 (dd, J = 8.4, 1.8 Hz, 1H), 8.28 (dd, J = 7.2, 2.7 Hz, 1H), 8.21 (d, J = 7.1 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.1 Hz, 1H), 7.83 (m, 1H), 7.76 (m, 2H), 7.64 (m, 1H), 7.40 (m, 2H), 4.00 (m, 1H), 3.59 (m, 1H), 3.26 (m, 1H), 2.93 (m, 1H), 2.59 (m, 2H), 2.17 (t, J = 7.5 Hz, 2H), 1.46 (m, 2H), 1.43 (m, 2H), 1.17 (m, 1H), 0.82 (t, J = 7.5 Hz, 3H), LC/MS m/z 496 $[M - H]^-$, 498 $[M + H]^+$; HRMS calcd for $C_{26}H_{28}FN_3O_4S$ $[M + H]^+$, 498.1862; found, 498.1874.

***N*-(4-{[(1-Butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)-3-fluorobenzamide (14f).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, J = 7.6 Hz, 1H), 8.50 (s, 1H), 8.31 (q, J = 8.2 Hz, 2H), 8.01 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 8.9 Hz, 1H), 7.71 (m, 3H), 7.57 (q, J = 8.2 Hz, 1H), 7.35 (t, J = 8.2 Hz, 1H), 4.67 (d, J = 7.6 Hz, 1H), 4.26 (d, J = 13.4 Hz, 1H), 3.74 (t, J = 6.9 Hz, 1H), 3.66 (d, J = 15.4 Hz, 1H), 3.33 (m, 1H), 2.97 (t, J = 12.9 Hz, 1H), 2.59 (t,

J = 12.8 Hz, 1H), 2.20 (t, J = 7.7 Hz, 2H), 1.85 (t, J = 6.7 Hz, 1H), 1.79 (s, 1H), 1.90 (m, 1H), 1.27 (m, 1H), 1.13 (m, J = Hz, 1H), 0.91 (t, J = 7.3 Hz, 3H); LC/MS m/z 498 $[M + H]^+$; HRMS calcd for $C_{26}H_{28}FN_3O_4S$ $[M + H]^+$, 498.1862; found, 498.1886.

***N*-(4-{[(1-Butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)-4-fluorobenzamide (14g).** ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$ (1:1)) δ 8.65 (d, J = 7.6 Hz, 1H), 8.56 (s, 1H), 8.29 (d, J = 8.2 Hz, 1H), 8.19 (d, J = 8.2 Hz, 1H), 8.03 (m, 3H), 7.68 (m, 2H), 7.25 (t, J = 8.5 Hz, 1H), 4.82 (d, J = 7.6 Hz, 1H), 4.23 (d, J = 13.5 Hz, 1H), 3.64 (d, J = 15.3 Hz, 1H), 3.32 (m, 1H), 2.95 (t, J = 11.6 Hz, 1H), 2.57 (t, J = 11.7 Hz, 1H), 2.20 (t, J = 7.6 Hz, 2H), 1.85 (m, 5H), 1.24 (m, 1H), 1.11 (m, 1H), 0.90 (t, J = 7.3 Hz, 3H); LC/MS m/z 498 $[M + H]^+$; HRMS calcd for $C_{26}H_{28}FN_3O_4S$ $[M + H]^+$, 498.1862; found, 498.1853.

***N*-(4-{[(1-Butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)-4-ethylbenzamide (14h).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, J = 7.6 Hz, 1H), 8.54 (s, 1H), 8.32 (s, 2H), 8.01 (d, J = 7.7 Hz, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.69 (m, 2H), 7.40 (d, J = 8.2 Hz, 2H), 4.75 (d, J = 7.7 Hz, 1H), 4.25 (d, J = 13.5 Hz, 1H), 3.65 (d, J = 15.2 Hz, 1H), 3.34 (m, 1H), 2.96 (t, J = 12.9 Hz, 1H), 2.77 (q, J = 7.6 Hz, 2H), 2.59 (t, J = 12.7 Hz, 1H), 2.20 (t, J = 7.6 Hz, 2H), 1.83 (m, 2H), 1.58 (m, 2H), 1.31 (t, J = 7.6 Hz, 3H), 1.17 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H); LC/MS m/z 508 $[M + H]^+$; HRMS calcd for $C_{28}H_{33}N_3O_4S$ $[M + H]^+$, 508.2270; found, 508.2283.

4-Butyl-*N*-(4-{[(1-Butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)benzamide (14i). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.60 (d, J = 8.3 Hz, 1H), 8.15 (d, J = 8.3 Hz, 1H), 7.98 (m, 4H), 7.56 (m, 2H), 7.34 (d, J = 8.3 Hz, 2H), 5.54 (d, J = 8.2 Hz, 1H), 4.12 (d, J = 13.6 Hz, 1H), 3.57 (d, J = 13.5 Hz, 1H), 3.25 (m, 1H), 2.88 (t, J = 11.4 Hz, 1H), 2.71 (t, J = 7.6 Hz, 2H), 2.50 (t, J = 10.9 Hz, 1H), 2.14 (t, J = 8.4 Hz, 2H), 1.64 (m, 3H), 1.53 (m, 3H), 1.88 (m, 2H), 1.17 (m, 1H), 1.01 (m, 1H), 0.95 (t, J = 7.4 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H); LC/MS m/z 536 $[M + H]^+$; HRMS calcd for $C_{30}H_{37}N_3O_4S$ $[M + H]^+$, 536.2583; found, 536.2588.

4-*tert*-Butyl-*N*-(4-{[(1-butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)benzamide (14j). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (d, J = 2.7 Hz, 1H), 8.61 (d, J = 9.3 Hz, 1H), 8.17 (d, J = 8.2 Hz, 1H), 8.02 (m, 4H), 7.59 (m, 4H), 5.44 (t, J = 7.3 Hz, 1H), 4.14 (d, J = 13.5 Hz, 1H), 3.58 (d, J = 13.9 Hz, 1H), 3.26 (m, 1H), 2.89 (t, J = 11.3 Hz, 1H), 2.52 (t, J = 11.3 Hz, 1H), 2.15 (t, J = 7.6 Hz, 2H), 1.73 (m, 2H), 1.53 (m, 2H), 1.38 (s, 9H), 1.22 (m, 1H), 1.03 (m, 1H), 0.88 (t, J = 7.3 Hz, 3H); LC/MS m/z 536 $[M + H]^+$; HRMS calcd for $C_{30}H_{37}N_3O_4S$ $[M + H]^+$, 536.2583; found, 536.2557.

***N*-(4-{[(1-Butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)-4-pentylbenzamide (14k).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.59 (d, J = 8.2 Hz, 1H), 8.15 (d, J = 8.2 Hz, 1H), 7.99 (t, J = 8 Hz, 3H), 7.56 (m, 2H), 7.33 (d, J = 7.7 Hz, 2H), 5.54 (d, J = 7.6 Hz, 1H), 4.11 (d, J = 13.4 Hz, 1H), 3.56 (d, J = 13.4 Hz, 1H), 3.24 (m, 1H), 2.87 (t, J = 11.8 Hz, 1H), 2.69 (t, J = 7.6 Hz, 2H), 2.50 (t, J = 11.4 Hz, 1H), 2.14 (t, J = 7.6 Hz, 2H), 1.66 (m, 3H), 1.52 (m, 3H), 1.34 (m, 4H), 1.17 (q, J = 10.6, 1H), 1.01 (q, J = 10.4, Hz, 1H), 0.88 (m, 7H); LC/MS m/z 550 $[M + H]^+$; HRMS calcd for $C_{27}H_{31}N_3O_4S$ $[M + H]^+$, 550.2739; found, 550.2758.

4-(Benzyloxy)-*N*-(4-{[(1-butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)benzamide (14l). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.57 (d, J = 8 Hz, 1H), 8.10 (d, J = 8.3 Hz, 1H), 8.02 (d, J = 9.4 Hz, 2H), 7.96 (d, J = 8.7 Hz, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.53 (m, 2H), 7.40 (m, 5H), 7.07 (d, J = 8.9 Hz, 2H), 5.65 (d, J = 7.6 Hz, 1H), 5.14 (s, 2H), 4.09 (d, J = 13.5 Hz, 1H), 3.54 (d, J = 13.7 Hz, 1H), 3.25 (m, 1H), 2.85 (t, J = 11.5 Hz, 1H), 2.47 (t, J = 11.2 Hz, 1H), 2.13 (t, J = 7.4 Hz, 2H), 1.67 (d, J = 10.5 Hz, 1H), 1.53 (m, 2H), 1.44 (d, J = 13.5 Hz, 1H), 1.14 (m, 1H), 0.93 (m, 1H), 0.87 (t, J = 7.3 Hz, 3H); LC/MS m/z 586 $[M + H]^+$; HRMS calcd for $C_{33}H_{35}N_3O_5S$ $[M + H]^+$, 586.2375; found, 586.2363.

***N*-(4-{[(1-Butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)-3-furamide (14m).** ^{1}H NMR (300 MHz, CD_3OD) δ 8.75 (d, J = 7.9 Hz, 1H), 8.31 (m, 2H), 8.17 (d, J = 7.7 Hz, 1H), 7.75 (m, 4H), 7.03 (s, 1H), 4.18 (d, J = 13.2 Hz, 1H), 3.74 (d, J = 13.2 Hz, 1H), 3.35 (m, 1H), 3.03 (m, 1H), 2.67 (m, 1H), 2.27 (m, 2H), 1.55 (m, 4H), 1.32 (m, 2H), 0.90 (m, 3H); LC/MS m/z 470 $[M + H]^+$; calcd for $C_{24}H_{27}N_3O_5S$ $[M + H]^+$, 470.1749; found, 470.1765.

***N*-(4-{[(1-Butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)-1-benzothiophene-2-carboxamide (14n).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.62 (m, 1H), 8.23 (d, J = 8.1 Hz, 1H), 8.15 (d, J = 9.9 Hz, 2H), 8.04 (m, 1H), 7.92 (m, 2H), 7.66 (m, 2H), 7.49 (m, 2H), 4.98 (d, J = 7.7 Hz, 1H), 4.20 (d, J = 13.6 Hz, 1H), 3.63 (d, J = 14.3 Hz, 1H), 3.29 (m, 1H), 2.92 (m, 1H), 2.54 (m, 1H), 2.19 (t, J = 7.6 Hz, 2H), 1.76 (m, 1H), 1.59 (m, 3H), 1.22 (m, 1H), 1.05 (m, 1H), 0.90 (t, J = 7.4 Hz, 3H); LC/MS m/z 536 $[M + H]^+$; HRMS calcd for $C_{28}H_{29}N_3O_4S_2$ $[M + H]^+$, 536.1677; found, 536.1666.

3-*tert*-Butyl-*N*-(4-{[(1-butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)-1-methyl-1*H*-pyrazole-5-carboxamide (14o). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (m, 1H), 8.40 (s, 1H), 8.29 (d, J = 8.3 Hz, 1H), 8.15 (d, J = 8.2 Hz, 1H), 7.99 (m, 1H), 7.70 (m, 2H), 6.72 (s, 1H), 4.79 (d, J = 7.6 Hz, 1H), 4.20 (s, 3H), 3.64 (d, J = 13.4 Hz, 1H), 3.31 (m, 1H), 2.95 (m, 1H), 2.54 (m, 1H), 2.20 (t, J = 7.6 Hz, 2H), 1.80 (m, 1H), 1.59 (m, 3H), 1.38 (s, 9H), 1.29 (s, 1H), 1.25 (s, 1H), 1.08 (m, 1H), 0.91 (t, J = 7.4 Hz, 3H); LC/MS m/z 540 $[M + H]^+$; HRMS calcd for $C_{28}H_{37}N_5O_4S$ $[M + H]^+$, 540.2644; found, 540.2647.

***N*-(4-{[(1-Butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)-5-methyl-2-(trifluoromethyl)-3-furamide (14p).** ^{1}H NMR (300 MHz, CD_3OD) δ 8.75 (d, J = 8.4 Hz, 1H), 8.32 (m, J = 6.9 Hz, 1H), 8.17 (d, J = 7.3 Hz, 1H), 7.86 (d, J = 7.3 Hz, 1H), 7.73 (m, 2H), 6.74 (s, 1H), 4.16 (m, 1H), 3.71 (m, 1H), 3.35 (m, 1H), 3.03 (m, 1H), 2.66 (m, 1H), 2.45 (s, 3H), 2.27 (m, 2H), 1.54 (m, 4H), 1.30 (m, 2H), 0.91 (m, 3H); LC/MS m/z 552 $[M + H]^+$; calcd for $C_{26}H_{28}F_3N_3O_5S$ $[M + H]^+$, 552.1780; found, 552.1758.

***N*-(4-{[(1-Butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)-1-methyl-1*H*-imidazole-2-carboxamide (14q).** ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.66 (s, 1H), 8.69 (m, 1H), 8.11 (m, 4H), 7.74 (m, 2H), 7.51 (m, 1H), 7.17 (m, 1H), 4.02 (m, 4H), 3.62 (m, 1H), 3.23 (m, 1H), 2.92 (m, 1H), 2.59 (m, 1H), 2.16 (m, 2H), 1.55 (m, 4H), 1.22 (m, 2H), 0.80 (m, 3H); LC/MS m/z 484 $[M + H]^+$; calcd for $C_{24}H_{29}N_5O_4S$ $[M + H]^+$, 484.2018; found, 484.2023.

***N*-(4-{[(1-Butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)-2-chloro-6-methylisonicotinamide (14r).** LC/MS m/z 530.059 $[M + H]^+$; $C_{26}H_{29}ClN_4O_4S$, found 529.13; HRMS calcd for $C_{26}H_{29}ClN_4O_4S$ $[M + H]^+$, 529.1676; found, 529.1701.

***N*-[4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-nicotinamide (14s).** ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.76 (s, 1H), 8.68 (d, J = 8.7 Hz, 1H), 8.59 (d, J = 4.2 Hz, 1H), 8.31 (d, J = 7.8 Hz, 1H), 8.24 (d, J = 7.8 Hz, 1H), 8.10 (d, J = 7.5 Hz, 1H), 8.04 (d, J = 7.2 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.73 (m, 2H), 7.41 (m, 1H), 4.00 (d, J = 13.5 Hz, 1H), 3.61 (d, J = 13.5 Hz, 1H), 3.23 (m, 1H), 2.93 (t, J = 11.7 Hz, 1H), 2.66 (s, 3H), 2.59 (m, 1H), 2.17 (t, J = 10.2 Hz, 2H), 1.48 (m, 2H), 1.43 (m, 2H), 1.19 (m, 2H), 0.82 (t, J = 7.2 Hz, 3H); LC/MS m/z 493 $[M - H]^-$, 495 $[M + H]^+$; HRMS calcd for $C_{26}H_{30}N_4O_4S$ $[M + H]^+$, 495.2066; found, 495.2075.

***N*-(4-{[(1-Butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)-pyrazine-2-carboxamide (14t).** LC/MS m/z 482 $[M + H]^+$; HRMS calcd for $C_{24}H_{27}N_5O_4S$ $[M + H]^+$, 482.1862; found, 482.1857.

***N*-(4-{[(1-Butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)-pyridine-2-carboxamide (14u).** LC/MS m/z 481 $[M + H]^+$; $C_{25}H_{28}N_4O_4S$, found 481.18; HRMS calcd for $C_{25}H_{28}N_4O_4S$ $[M + H]^+$, 481.1909; found, 481.1933.

***N*-(4-{[(1-Butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)-nicotinamide (14v).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.44 (d, J = 11.8 Hz, 2H), 8.81 (d, J = 4.6 Hz, 1H), 8.58 (d, J = 8.5 Hz, 1H), 8.42 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.50 (t, J = 6.8 Hz, 2H), 6.27 (d, J = 7.7 Hz, 1H), 4.12 (d, J = 13.4 Hz, 1H), 3.56 (d, J = 13.5 Hz, 1H), 3.14 (m, 1H), 2.84 (t, J = 11.4 Hz, 1H), 2.42 (t, J = 11.4 Hz, 1H), 2.16 (m, 2H), 1.69 (m, 1H), 1.55 (m, 2H), 1.39 (m, 1H), 1.24 (s, 1H), 1.09 (m, 1H), 0.88

(m, 3H); LC/MS *m/z* 481 $[M + H]^+$; HRMS calcd for $C_{25}H_{28}N_4O_4S$ $[M + H]^+$, 481.1909; found, 481.1907.

Ethyl 4-({[4-(Isonicotinoylamino)-1-naphthyl]sulfonyl}amino)-piperidine-1-carboxylate (14w). Pyridine (0.5 mL) was added to a sealed vial containing **13** (37.7 mg, 0.1 mmol) and isonicotinic acid (12.3 mg, 0.1 mmol), and the resulting solution was cooled to −78 °C. A solution of $POCl_3$ (10.3 μL, 0.11 mmol) in CH_2Cl_2 (90 μL) was then added to the sealed tube, and the resulting solution was allowed to warm to 25 °C over 2 h. The resultant solution was concentrated *in vacuo*, at which point purification by HPLC afforded the desired product (0.002 g, 4%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90 (d, *J* = 6.1 Hz, 2H), 8.66 (d, *J* = 9.9 Hz, 1H), 8.55 (s, 1H), 8.32 (d, *J* = 8.2 Hz, 1H), 8.24 (d, *J* = 8.2 Hz, 1H), 8.00 (m, 1H), 7.87 (d, *J* = 6.5 Hz, 2H), 7.71 (m, 2H), 4.60 (d, *J* = 7.5 Hz, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.88 (m, 2H), 3.30 (m, 1H), 2.76 (m, 2H), 1.64 (m, 1H), 1.25 (m, 1H), 1.20 (m, 4H); LC/MS *m/z* 483 $[M + H]^+$; HRMS calcd for $C_{24}H_{26}N_4O_5S$ $[M + H]^+$, 483.1702; found, 483.1678.

Amides 14x−14gg. These compounds were prepared according to general procedure B from the appropriate starting materials.

Cyclopropanecarboxylic Acid [4-(1-Butyryl-piperidin-4-yl-sulfamoyl)-naphthalen-1-yl]-amide (14x). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.64 (m, 1H), 8.33 (m, 1H), 8.13 (d, *J* = 8.1 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.98 (d, *J* = 8.1 Hz, 1H), 7.73 (m, 2H), 3.98 (m, 1H), 3.59 (m, 1H), 3.19 (m, 1H), 2.90 (m, 1H), 2.61 (m, 1H), 2.13 (m, 3H), 1.40 (m, 4H), 1.16 (m, 2H), 0.88 (d, *J* = 6.0 Hz, 4H), 0.80 (t, *J* = 7.2 Hz, 3H); LC/MS *m/z* 442 $[M - H]^-$, 444 $[M + H]^+$; HRMS calcd for $C_{23}H_{29}N_3O_4S$ $[M + H]^+$, 444.1957; found, 444.1977.

Cyclobutanecarboxylic Acid [4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-amide (14y). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.98 (s, 1H), 8.62 (d, *J* = 8.4 Hz, 1H), 8.21 (d, *J* = 8.2 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.70 (m, 2H), 3.59 (m, 2H), 3.51 (m, 1H), 3.13 (m, 1H), 2.67 (m, 2H), 2.24 (m, 4H), 2.16 (m, 2H), 1.99 (m, 1H), 1.84 (m, 1H), 1.42 (m, 2H), 1.37 (m, 2H), 1.10 (m, 2H), 0.81 (t, *J* = 7.2 Hz, 3H); LC/MS *m/z* 457 $[M- H]^-$, 459 $[M + H]^+$; HRMS calcd for $C_{24}H_{31}N_3O_4S$ $[M + H]^+$, 458.2113; found, 458.2103.

Cyclopentanecarboxylic Acid [4-(1-Butyryl-piperidin-4-yl-sulfamoyl)-naphthalen-1-yl]-amide (14z). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.66 (m, 1H), 8.34 (m, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.71 (m, 2H), 3.98 (m, 1H), 3.59 (m, 1H), 3.19 (m, 1H), 3.09 (m, 1H), 2.90 (m, 1H), 2.57 (m, 1H), 2.16 (m, 2H), 1.94 (m, 2H), 1.81 (m, 2H), 1.71 (m, 2H), 1.62 (m, 2H), 1.40 (m, 4H), 1.16 (m, 2H), 0.81 (t, *J* = 7.2 Hz, 3H); LC/MS *m/z* 471 $[M - H]^-$, 473 $[M + H]^+$; HRMS calcd for $C_{25}H_{33}N_3O_4S$ $[M + H]^+$, 472.2270; found, 472.2269.

***N*-(4-{[(1-Butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)-2-cyclopentylacetamide (14aa).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, *J* = 8.9 Hz, 1H), 8.23 (d, *J* = 8.2 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.63 (m, 2H), 4.87 (d, *J* = 7.7 Hz, 1H), 4.21 (d, *J* = 13.4 Hz, 1H), 3.63 (d, *J* = 13.9 Hz, 1H), 3.28 (m, 1H), 2.94 (m, 1H), 2.57 (m, 3H), 2.41 (m, 1H), 2.19 (t, *J* = 7.6 Hz, 2H), 1.96 (m, 2H), 1.69 (m, 4H), 1.57 (m, 4H), 1.29 (m, 3H), 1.09 (m, 1H), 0.89 (t, *J* = 7.3 Hz, 3H); LC/MS *m/z* 486 $[M + H]^+$; HRMS calcd for $C_{26}H_{35}N_3O_4S$ $[M + H]^+$, 486.2426; found, 486.2424.

Cyclohexanecarboxylic Acid [4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-amide (14bb). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.64 (dd, *J* = 7.2, 2.1 Hz, 1H), 8.25 (dd, *J* = 7.2, 2.1 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 8.03 (d, *J* = 8.1 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.71 (m, 2H), 3.98 (m, 1H), 3.59 (m, 1H), 3.18 (m, 1H), 2.91 (m, 1H), 2.61 (m, 2H), 2.16 (m, 2H), 1.90 (m, 2H), 1.77 (m, 2H), 1.67 (m, 2H), 1.35 (m, 10H), 0.81 (t, *J* = 7.2 Hz, 3H); LC/MS *m/z* 484 $[M - H]^-$, 486 $[M + H]^+$; HRMS calcd for $C_{26}H_{35}N_3O_4S$ $[M + H]^+$, 486.2426; found, 486.2437.

1-Methyl-piperidine-4-carboxylic Acid [4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-amide (14cc). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.64 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.29 (dd, *J* = 8.1, 2.1 Hz, 1H), 8.14 (d, *J* = 8.1 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.72 (m, 2H), 3.62 (m, 2H), 3.40 (m, 2H), 3.15 (m, 1H), 2.95 (m, 2H), 2.78−2.67 (m, 6H), 2.17 (m, 2H), 2.09 (m, 2H), 2.0 (m, 2H), 1.84 (m, 1H), 1.43 (m, 2H), 1.39 (m, 1H), 1.18 (m, 2H), 0.82 (t, *J* = 7.2 Hz, 3H); LC/MS *m/z* 501 $[M + H]^+$; HRMS calcd for $C_{26}H_{36}N_4O_4S$ $[M + H]^+$, 501.2535; found, 501.2533.

Tetrahydro-pyran-4-carboxylic Acid [4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-amide (14dd). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.65 (d, *J* = 7.5 Hz, 1H), 8.27 (d, *J* = 7.5 Hz, 1H), 8.15 (d, *J* = 8.1 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 7.71 (m, 2H), 3.97 (m, 3H), 3.61 (m, 1H), 3.40 (m, 2H), 3.19 (m, 1H), 2.90 (m, 2H), 2.56 (m, 1H), 2.15 (t, *J* = 7.5 Hz, 2H), 1.82 (m, 2H), 1.74 (m, 2H), 1.42 (m, 4H), 1.13 (m, 2H), 0.81 (t, *J* = 7.5 Hz, 3H); LC/MS *m/z* 488 $[M + H]^+$; HRMS calcd for $C_{25}H_{33}N_3O_5S$ $[M + H]^+$, 488.2219; found, 488.2209.

***N*-(4-{[(1-Butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)-2-ethylbutanamide (14ee).** LC/MS *m/z* 474 $[M + H]^+$; $C_{25}H_{35}N_3O_4S$ found, 474.18; HRMS calcd for $C_{25}H_{35}N_3O_4S$ $[M + H]^+$, 474.2426; found, 474.2422.

***N*-(4-{[(1-Butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)-3,3-dimethylbutanamide (14ff).** ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.64 (m, 1H), 8.26 (m, 1H), 8.14 (d, *J* = 7.6 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.94 (m, 1H), 7.70 (m, 2H), 3.98 (m, 1H), 3.60 (m, 1H), 3.20 (m, 1H), 2.90 (m, 1H), 2.56 (m, 1H), 2.41 (s, 2H), 2.15 (t, *J* = 7.3 Hz, 2H), 1.41 (m, 4H), 1.20 (m, 2H), 1.08 (s, 9H), 0.80 (t, *J* = 7.3 Hz, 3H); LC/MS *m/z* 474 $[M + H]^+$; HRMS calcd for $C_{25}H_{35}N_3O_4S$ $[M + H]^+$, 474.2426; found, 474.2420.

***N*-(4-{[(1-Butyrylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)-2-phenylbutanamide (14gg).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, *J* = 8.0 Hz, 1H), 8.21 (m, 2H), 7.80 (s, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.46 (m, 5H), 7.41 (m, 1H), 7.31 (m, 1H), 4.68 (d, *J* = 7.7 Hz, 1H), 4.21 (m, 1H), 3.64 (m, 2H), 3.25 (m, 1H), 2.93 (m, 1H), 2.55 (m, 1H), 2.40 (m, 1H), 2.18 (t, *J* = 7.6 Hz, 2H), 1.98 (m, 1H), 1.74 (m, 1H), 1.56 (m, 3H), 1.37 (s, 1H), 1.21 (m, 1H), 0.99 (t, *J* = 7.6 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 3H); LC/MS *m/z* 522 $[M + H]^+$; HRMS calcd for $C_{29}H_{35}N_3O_4S$ $[M + H]^+$, 522.2426; found, 522.2427.

4-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic Acid Ethyl Ester (15). The title compound was prepared following general procedure A, using 2-methyl benzoyl chloride instead of benzoyl chloride in Step 1 and using 4-amino-piperidine-1-carboxylic acid ethyl ester instead of *p*-anisidine in Step 3. Yield: 2.32 g (84%) of a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 8.74 (d, *J* = 8.54, 1H), 8.31 (d, *J* = 8.1 Hz, 1H), 8.23 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.72 (m, 3H), 7.39 (m, 3H), 4.04 (q, *J* = 7.3 Hz, 2H), 3.83 (m, 2H), 3.25 (m, 1H), 2.78 (m, 2H), 2.55 (s, 3H), 1.56 (m, 2H), 1.28 (m, 2H), 1.18 (t, *J* = 7.3 Hz, 3H); LC/MS $[M + H]^+$ *m/z* 496; HRMS calcd for $C_{26}H_{29}N_3O_5S$ $[M+H]^+$, 496.1906; found, 496.1914.

4-(4-Cyano-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic Acid *tert*-Butyl Ester (17). This compound was prepared in the following three steps. **Step 1.** 1-Fluoronaphthalene (20.0 g, 0.14 mol) was added in small portions to a stirred solution of chlorosulfonic acid (79 g, 45 mL, 0.68 mol) at 25 °C. The reaction mixture was stirred for 30 min until gas evolution ceased, at which point it was poured carefully over a mixture of ice (300 g) and CH_2Cl_2 (300 mL). The organic layer was separated, washed with water (2×) and brine (2×), and then dried over $MgSO_4$. Filtration and concentration *in vacuo* afforded 4-fluoro-naphthalene-1-sulfonyl chloride **16** (27.6 g, 82%) as a tan solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (m, 1H), 8.38 (m, 1H), 8.28 (m, 1H), 7.88 (m, 1H), 7.77 (m, 1H), 7.26 (m, 1H).

Step 2. To a solution of **16** (10.0 g, 40.9 mmol) in THF (100 mL) were added 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester (8.19 g, 40.9 mmol) and Et_3N (4.14 g, 5.75 mL, 40.9 mmol). The reaction mixture was stirred at 25 °C for 17 h, at which point the solvent was removed *in vacuo*. CH_2Cl_2 (250 mL) was added, and the organic layer was washed with water (2×) and brine (2×)

and then dried over $MgSO_4$. Filtration and concentration *in vacuo* afforded 4-(4-fluoro-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester as a yellow foam (15.1 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, J = 8.4 Hz, 1H), 8.26 (m, 2H), 7.69 (m, 2H), 7.20 (m, 1H), 4.92 (d, J = 7.8 Hz, 1H), 3.82 (m, 2H), 3.26 (m, 1H), 2.70 (m, 2H), 1.61 (m, 2H), 1.40 (s, 9H), 1.24 (m, 2H); LC/MS m/z 409 $[M + H]^+$.

Step 3. To a solution of the product from Step 2 (2.00 g, 4.9 mmol) in DMF (20 mL) were added sodium cyanide (1.2 g, 24.5 mmol) and tetra-*n*-butylammonium bromide (7.9 g, 24.5 mmol). The reaction mixture was stirred at 100 °C for 17 h and then diluted with CH_2Cl_2 (100 mL). The organic layer was washed with water (2×) and brine (2×) and then dried over $MgSO_4$, followed by filtration and concentration *in vacuo*, affording a dark oil. Flash column chromatography (98:2 CH_2Cl_2/MeOH) afforded a dark oil that was rechromatographed (99:1 CH_2Cl_2/MeOH) to afford **17** as an orange solid (640 mg, 31%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (m, 1H), 8.40 (m, 1H), 8.34 (m, 1H), 8.00 (d, J = 7.5 Hz, 1H), 7.83 (m, 2H), 4.80 (d, J = 7.8 Hz, 1H), 3.87 (m, 2H), 3.32 (m, 1H), 2.61 (m, 2H), 1.63 (m, 2H), 1.38 (s, 9H), 1.27 (m, 2H); LC/MS m/z 414 $[M - H]^-$.

4-(4-Carboxy-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic Acid *tert*-Butyl Ester (18). A mixture of **17** (0.48 g, 1.15 mmol) in aqueous potassium hydroxide (20 mL, 1.8 N, 36 mmol) and isopropanol (25 mL) was stirred at 75 °C for 48 h. After removing isopropanol *in vacuo*, the aqueous layer was washed with EtOAc. The aqueous layer was then acidified to pH 3 and extracted with EtOAc (3×). The combined organic layers were washed with water and brine and then dried over $MgSO_4$. Filtration and concentration *in vacuo* afforded **18** as a tan foam (360 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.03 (m, 1H), 8.70 (m, 1H), 8.33 (dd, J = 15.9, 7.5 Hz, 2H), 7.74 (m, 2H), 4.78 (d, J = 7.8 Hz, 1H), 3.85 (m, 2H), 3.31 (m, 1H), 2.71 (m, 2H), 1.62 (m, 2H), 1.40 (s, 9H), 1.27 (m, 2H); LC/MS m/z 433 $[M - H]^-$; HRMS calcd for $C_{21}H_{26}N_2O_6S$ $[M + Na]^+$, 457.1409; found, 457.1392.

4-(Piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic Acid Cyclohexylamide HCl Salt (19a). Step 1. To a solution of **18** (400 mg, 0.92 mmol) in CH_2Cl_2 (5 mL) were added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (350 mg, 1.84 mmol), 1-hydroxybenzotriazole (186 mg, 1.38 mmol), Et_3N (0.38 mL, 2.76 mmol), and cyclohexylamine (0.16 mL, 1.38 mmol). The reaction mixture was stirred at 25 °C for 17 h and then diluted with CH_2Cl_2 (30 mL). The organic layer was washed with water (2×) and brine (2×) and then dried over Na_2SO_4. Filtration and concentration *in vacuo* afforded a foam that was purified via flash column chromatography (98:2 CH_2Cl_2/MeOH) to afford 4-(4-cyclohexylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (320 mg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (dd, J = 7.2, 1.8 Hz, 1H), 8.31 (dd, J = 7.2, 1.8 Hz, 1H), 8.26 (d, J = 7.5 Hz, 1H), 7.68 (m, 2H), 7.59 (d, J = 7.5 Hz, 1H), 5.91 (m, 1H), 4.64 (d, J = 7.8 Hz, 1H), 4.12 (m, 1H), 3.82 (m, 2H), 3.22 (m, 1H), 2.68 (m, 2H), 2.13 (m, 2H), 1.79 (m, 2H), 1.57 (m, 6H), 1.38 (s, 9H), 1.27 (m, 4H); LC/MS m/z 516 $[M + H]^+$; HRMS calcd for $C_{27}H_{37}N_3O_5S$ $[M + H]^+$, 516.2532; found, 516.2534. **Step 2.** A solution of the product from Step 1 (320 mg, 0.62 mmol) in 4 N HCl/dioxane (10 mL) was stirred at 25 °C for 2 h and then concentrated *in vacuo* to afford **19a** (271 mg, 97%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.68 (d, J = 8.4 Hz, 1H), 8.59 (d, J = 7.8 Hz, 1H), 8.40 (d, J = 7.2 Hz, 1H), 8.15 (m, 2H), 7.72 (m, 2H), 7.60 (d, J = 7.5 Hz, 1H), 3.75 (m, 1H), 3.67 (m, 1H), 3.08 (m, 2H), 2.80 (m, 2H), 2.54 (m, 1H), 1.92 (m, 2H), 1.74 (m, 2H), 1.62 (m, 4H), 1.48 (m, 1H), 1.32 (m, 4H), 1.25 (m, 1H); LC/MS m/z 416 $[M + H]^+$; HRMS calcd for $C_{22}H_{29}N_3O_3S$ $[M + H]^+$, 416.2008; found, 416.2012.

4-(4-Cyclohexylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic Acid Ethyl Ester (20a). To a solution of **19a** (87 mg, 0.19 mmol) in CH_2Cl_2 (2 mL) were added Et_3N (58 mg, 0.08 mL, 0.57 mmol) and ethyl chloroformate (41 mg, 0.037 mL, 0.39 mmol). The reaction mixture was stirred at 25 °C for 17 h, at which point the solvent was removed *in vacuo*. The crude residue was directly purified *via* column chromatography (eluent: 99:1 CH_2Cl_2/MeOH) to afford **20a** as a white solid (60 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (dd, J = 7.5, 2.1 Hz, 1H), 8.30 (dd, J = 7.5, 2.1 Hz, 1H), 8.25 (d, J = 7.5 Hz, 1H), 7.64 (m, 2H), 7.54 (d, J = 7.5 Hz, 1H), 5.96 (m, 1H), 4.74 (m, 1H), 4.10 (m, 1H), 4.03 (q, J = 14.1 Hz, 2H), 3.86 (m, 2H), 3.22 (m, 1H), 2.68 (m, 2H), 2.12 (m, 2H), 1.79 (m, 2H), 1.68 (m, 1H), 1.58 (m, 2H), 1.47 (m, 2H), 1.24 (m, 6H), 1.18 (t, J = 7.5 Hz, 3H); LC/MS m/z 488 $[M + H]^+$; HRMS calcd for $C_{25}H_{33}N_3O_5S$ $[M + H]^+$, 488.2219; found, 488.2213.

***N*-(2-Methylphenyl)-4-[(piperidin-4-ylamino)sulfonyl]-1-naphthamide HCl Salt (19b) and 4-(4-*o*-Tolylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic Acid Ethyl Ester (20b).** The title compounds were prepared from **18** according to the procedure described for **19a** and **20a**. Yield: 60 mg (64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, J = 8.1 Hz, 1H), 8.46 (d, J = 8.4 Hz, 1H), 8.33 (d, J = 7.5 Hz, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.79 (d, J = 7.2 Hz, 1H), 7.71 (m, 2H), 7.55 (s, 1H), 7.30 (m, 1H), 7.21 (m, 1H), 4.71 (d, J = 7.5 Hz, 1H), 4.05 (q, J = 14.1 Hz, 2H), 3.89 (m, 2H), 3.27 (m, 1H), 2.72 (m, 2H), 2.31 (s, 3H), 1.65 (m, 2H), 1.26 (m, 2H), 1.20 (t, J = 7.5 Hz, 3H); LC/MS m/z 494 $[M - H]^-$; HRMS calcd for $C_{26}H_{29}N_3O_5S$ $[M + H]^+$, 496.1906; found, 496.1918.

4-(4-Cyano-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic Acid Ethyl Ester (21). Step 1. To a THF (15 mL) solution of **16** (730 mg, 2.99 mmol) were added 4-amino-piperidine-1-carboxylic acid ethyl ester (1.03 g, 3.58 mmol) and Et_3N (3.5 mL, 15.0 mmol). The reaction mixture was stirred at 25 °C for 17 h, at which point the solvent was removed *in vacuo*. CH_2Cl_2 (50 mL) was added, and the organic layer was washed with water (2×) and brine (2×) and then dried over $MgSO_4$. Filtration and concentration *in vacuo* afforded the crude product that was chromatographed (50:50 hexanes/EtOAc) to afford 4-(4-fluoro-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester 924 mg (81% yield). LC/MS m/z 381 $[M + H]^+$. **Step 2.** To a DMF (5.0 mL) solution of the product from Step 1 (924 mg, 2.43 mmol) were added NaCN (429 mg, 8.76 mmol) and tetra-*n*-butylammonium bromide (2.82 g, 8.76 mmol). The reaction mixture was stirred at 100 °C for 17 h and then diluted with CH_2Cl_2 (50 mL). The organic layer was washed water (3×) and brine (3×) and then dried over $MgSO_4$. Filtration and concentration *in vacuo* afforded a dark oil, which was purified by column chromatography (98:2 CH_2Cl_2/MeOH) to afford a dark oil that was rechromatographed (99:1 CH_2Cl_2/MeOH) to furnish **21** (770 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (m, 1H), 8.40 (m, 1H), 8.34 (m, 1H), 7.97 (m, 1H), 7.83 (m, 2H), 5.70 (d, J = 7.6 Hz, 1H), 4.03 (q, J = 7.1 Hz, 2H), 3.88 (m, 2H), 3.32 (m, 1H), 2.75 (m, 2H), 1.64 (m, 2H), 1.28 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H); LC/MS m/z 386 $[M - H]^-$.

4-(4-Aminomethyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic Acid Ethyl Ester (22). To an EtOH (10 mL) solution of **21** (615 mg, 1.59 mmol) at 0 °C was added cobalt chloride (207 mg, 1.59 mmol). The reaction mixture was stirred at 0 °C for 5 min under argon, at which point $NaBH_4$ (181 mg, 4.77 mmol) was added. The resultant solution was stirred at 0 °C for 30 min further and then allowed to warm to 25 °C. After stirring for another 30 min, the resultant mixture was quenched with water and the aqueous layer was extracted with CH_2Cl_2 (3×). The organic extracts were combined, washed with brine (1×), and dried over $MgSO_4$. The solution was filtered and concentrated *in vacuo* to give the crude product, which was purified by column chromatography (CH_2Cl_2/MeOH) to afford **22** (268 mg, 43.0%). LC/MS m/z 392 $[M + H]^+$.

4-[4-(Benzylamino-methyl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic Acid Ethyl Ester Formic Acid Salt (23a). The title compound was made following the procedure described for **23b**. Yield: 0.015 g (14%) of a yellow solid. ^{1}H NMR (300 MHz, CD_3OD) δ 8.73 (d, J = 8.0 Hz, 1H), 8.29 (s, 1H), 8.22 (d, J = 7.5 Hz, 1H), 8.04 (m, 1H), 7.68 (m, 3H), 7.40 (m, 3H), 7.20 (m, 2H), 4.59 (s, 2H), 4.23 (s, 2H), 3.97 (q, J = 7.0 Hz, 2H), 3.67 (m, 2H), 3.16 (m, 1H), 2.70 (m, 2H), 1.44 (m, 2H), 1.22 (m, 2H), 1.13 (t, J = 7.0 Hz, 3H); LC/MS m/z 482 $[M + H]^+$; HRMS calcd for $C_{26}H_{31}N_3O_4S$ $[M + H]^+$, 482.2113; found, 482.2120.

4-[4-(Phenethylamino-methyl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic Acid Ethyl Ester (23b). To a solution of **22** (277 mg, 0.708 mmol) in MeOH (10 mL) were added phenylacetaldehyde (0.147 mL, 1.42 mmol) and $NaBH_3CN$ (223 mg, 3.55 mmol). The reaction mixture was stirred at 25 °C for 2 h, at which point the solution was concentrated *in vacuo to* give a solid, which was purified by reverse phase HPLC, affording **23b** (5 mg, 6.4%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 8.74 (m, 1H), 8.19 (m, 2H), 7.67 (m, 2H), 7.59 (m, 1H), 7.22 (m, 5H), 4.35 (s, 2H), 4.05 (q, J = 7.1 Hz, 2H), 3.78 (m, 2H), 3.18 (m, 1H), 2.92 (m, 4H), 2.62 (m, 2H), 1.48 (m, 2H), 1.25 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H); LC/MS m/z 496 $[M + H]^+$; HRMS calcd for $C_{27}H_{33}N_3O_4S$ $[M + H]^+$, 496.2270; found, 496.2275.

4-{4-[(3-Phenyl-propylamino)-methyl]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic Acid Ethyl Ester (23c). The title compound was made following the procedure described for **23b**. Yield: 0.003 g (3.5%) of a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 8.74 (m, 1H), 8.25 (m, 1H), 8.20 (d, J = 7.5 Hz, 1H), 7.70 (m, 2H), 7.59 (m, 1H), 7.19 (m, 5H), 4.33 (s, 2H), 4.05 (q, J = 7.1 Hz, 2H), 3.78 (d, J = 13.6 Hz, 2H), 3.18 (m, 1H), 2.73 (m, 6H), 1.90 (m, 2H), 1.48 (m, 2H), 1.23 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H); LC/MS m/z 510 $[M + H]^+$; HRMS calcd for $C_{28}H_{35}N_3O_4S$ $[M + H]^+$, 510.2426; found, 510.2425.

4-(Benzyloxy)naphthalene-1-sulfonic Acid Potassium Salt (25). To a solution of **24** (3.5 g, 10 mmol) in MeOH (50 mL) were added benzylbromide (2.8 mL, 20 mmol) and KOH (2.24 g, 40 mmol) as a solution in water (4 mL). The reaction mixture was stirred at 25 °C for 20 h. The mixture was then filtered, and the solid was washed with a small amount of MeOH (5 mL) to afford **25** (3.1 g), which was used without further purification.

Ethyl 4-(1-(Benzyloxy)naphthalene-4-sulfonamido)piperidine-1-carboxylate (26). To a solution of **25** (0.3 g, 0.89 mmol) in DMF (5 mL) was added thionyl chloride (0.074 mL, 1.07 mmol). The reaction mixture was stirred at 25 °C for 18 h, at which time Et_3N (0.75 mL, 5.4 mmol) and 4-amino-piperidine-1-carboxylic acid ethyl ester (0.31 mL, 1.79 mmol) were added. The reaction mixture was stirred for 19 h further, and the solvent was then removed *in vacuo*. The crude residue was directly purified by HPLC to afford **26** (0.29 g, 63%, 2 steps). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.58 (d, J = 8.4 Hz, 1H), 8.32 (d, J = 8.1 Hz, 1H), 8.12 (d, J = 8.3 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.70 (m, 4H), 7.38 (m, 2H), 7.20 (d, J = 8.4 Hz, 1H), 5.39 (s, 2H), 3.92 (q, J = 7.1 Hz, 2H), 3.65 (m, 2H), 3.11 (m, 1H), 2.73 (m, 2H), 1.40 (m, 2H), 1.15 (m, 2H), 1.10 (t, J = 7.1 Hz, 3H); LC/MS m/z 469 $[M + H]^+$; HRMS calcd for $C_{25}H_{28}N_2O_5S$ $[M + H]^+$, 469.1797; found, 469.1820.

Ethyl 4-(1-Hydroxynaphthalene-4-sulfonamido)piperidine-1-carboxylate (27). To a solution of **26** (0.10 g, 0.21 mmol) in MeOH (10 mL) was added Pd/C (10%, 30 mg, 0.028 mmol). The reaction vessel was charged with H_2 (50 psi) and shaken for 17 h. After removing the solid via filtration, the MeOH solution was concentrated under vacuum to afford **27** (0.03 g, 38%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.2 (s, 1H), 8.53 (d, J = 8.5 Hz, 1H), 8.25 (d, J = 8.1 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.66 (m, 1H), 6.91 (d, J = 8.2 Hz, 1H), 3.94 (q, J = 7.0 Hz, 2H), 3.65 (m, 2H), 3.31 (s, 1H), 3.06 (m, 1H), 2.72 (m, 2H), 1.49 (m, 2H), 1.16 (m, 2H), 1.10 (t, J = 7.2 Hz, 3H); LC/MS m/z 379 $[M + H]^+$; HRMS calcd for $C_{18}H_{22}N_2O_5S$ $[M + H]^+$, 379.1327; found, 379.1343.

Ethyl 4-({[4-(Benzoyloxy)-1-naphthyl]sulfonyl}amino)-piperidine-1-carboxylate (28). To a solution of **24** (3.5 g, 10 mmol) in pyridine (20 mL) was added benzoyl chloride (1.4 mL, 12 mmol) at 25 °C. The reaction mixture was stirred at reflux for 20 h, at which point the solvent was removed *in vacuo* to provide crude 4-(benzoyloxy)naphthalene-1-sulfonic acid pyridinium salt (4.2 g, orange solid), which was used without further purification. To a DMF (10 mL) solution of the above pyridinium salt (1.2 g, 3.0 mmol) was added thionyl chloride (0.25 mL, 3.6 mmol) at 0 °C. The reaction mixture was stirred for 17 h while allowing to warm slowly to 25 °C, followed by the addition of Et_3N (1.25 mL, 9.0 mmol) and 4-amino-piperidine-1-carboxylic acid ethyl ester (0.51 mL, 3.0 mmol). The reaction mixture was stirred at 25 °C for 4 h further, and the solvent was removed *in vacuo*. The crude residue was directly purified via HPLC to afford **28** (0.03 g, 5%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.72 (d, J = 8.6 Hz, 1H), 8.24 (m, 3H), 8.05 (d, J = 8.3 Hz, 1H), 7.70 (m, 6H), 3.95 (q, J = 7.0 Hz, 2H), 3.69 (m, 2H), 3.31 (s, 1H), 3.26 (m, 2H), 2.78 (m, 2H), 1.51 (m, 2H), 1.20 (m, 2H), 1.11 (t, J = 7.1 Hz, 3H); LC/MS m/z 483 $[M + H]^+$; HRMS calcd for $C_{25}H_{26}N_2O_6S$ $[M + H]^+$, 483.1589; found, 483.1610.

General Procedure C: Preparation of Right-Hand Side Amides. The title compounds were prepared following the three-step sequence outlined below.

Step 1. 4-(2-Methylbenzamido)naphthalene-1-sulfonyl Chloride (29). The title compound was prepared according to the procedure described for the production of **4**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, J = 8.1 Hz, 1H), 8.46 (m, 1H), 8.39 (m, 1H), 8.01 (d, J = 8.1 Hz, 1H), 7.81 (m, 1H), 7.69 (m, 1H), 7.59 (m, 1H), 7.42 (m, 1H), 7.31 (m, 2H), 2.53 (s, 3H).

Step 2. 2-Methyl-*N*-{4-[(piperidin-4-ylamino)sulfonyl]-1-naphthyl}benzamide HCl Salt (30). To a solution of **29** (4.0 g, 11 mmol) in THF (150 mL) were added *tert*-butyl 4-aminopiperidine-1-carboxylate (2.2 g, 0.011 mmol) and Et_3N (2.2 mL, 17 mmol). The reaction mixture was stirred at 25 °C for 3 h and then filtered. The filtrate was collected, and the solvent was removed *in vacuo* to provide a yellow solid (5.5 g). This solid was dissolved in 4 N HCl/dioxane solution (20 mL) and stirred at 25 °C for 2 h. Removal of the solvent *in vacuo* then afforded **30** (5.0 g, 98%) as a white solid. ^{1}H NMR (300 MHz, MeOH) δ 8.75 (d, J = 7.7 Hz, 1H), 8.33 (d, J = 7.9 Hz, 1H), 8.23 (m, 1H), 7.94 (d, J = 8.7 Hz, 1H), 7.71 (m, 3H), 7.39 (m, 3H), 3.49 (m, 1H), 3.15 (m, 2H), 2.90 (m, 2H), 2.50 (s, 3H), 2.21 (m, 1H), 1.82 (m, 2H), 1.59 (m, 1H); LC/MS $[M + 1]^+$ m/z 424.

Step 3. Method 1: Preparation of Amides Using Acid Chloride Reagents. 2-Methyl-*N*-[4-(1-propionyl-piperidin-4-yl-sulfamoyl)-naphthalen-1-yl]-benzamide (31a). To a mixture of **30** (391 mg, 0.85 mmol) in THF (15 mL) were added propionyl chloride (0.103 mL, 1.19 mmol) and Et_3N (0.726 mL, 8.33 mmol). The reaction was stirred at 25 °C for 20 h and then filtered. The filtrate was concentrated *in vacuo*, followed by purification via column chromatography, to provide **31a** (210 mg, 52%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 8.78 (m, 1H), 8.33 (d, J = 7.9 Hz, 1H), 8.23 (m, 1H), 7.94 (m, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 4.19 (m, 1H), 3.72 (m, 1H), 3.25 (m, 1H), 3.01 (m, 1H), 2.69 (m, 1H), 2.55 (s, 3H), 2.41 (q, J = 7.5 Hz, 2H), 1.61 (m, 2H), 1.31 (m, 2H), 1.02 (t, J = 7.5 Hz, 3H); LC/MS $[M + 1]^+$ m/z 480; HRMS calcd for $C_{26}H_{29}N_3O_4S$ $[M + H]^+$, 480.1957; found, 480.1968.

Method 2: Preparation of Amides from Carboxylic Acid Reagents. *N*-{4-[({1-[(2*S*)-2-Aminopropanoyl]piperidin-4-yl}-amino)sulfonyl]-1-naphthyl}-2-methylbenzamide HCl Salt (31m). To a mixture of **30** (690 mg, 1.50 mmol) in CH_2Cl_2 (12 mL) were added HOBT (223 mg, 1.65 mmol), EDCI (345 mg, 1.80 mmol), *N*-methylmorpholine (455 mg, 4.50 mmol), and (*s*)-2-*tert*-butoxycarbonylamino-propionic acid (181 mg, 0.80 mmol). The reaction mixture was stirred at 25 °C for 20 h and then filtered, and the filtrate was concentrated *in vacuo*. The crude mixture was suspended in 4 N HCl/dioxane (20 mL) and stirred for 2 h. The reaction mixture was filtered, and the collected solid was washed with dioxane to afford **31m** (560 mg, 70%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 8.75 (m, 1H), 8.33 (d, J = 8.1 Hz, 1H), 8.23 (m, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 4.30 (m, 1H), 4.14 (m, 1H), 3.65 (m, 1H), 3.34 (m, 1H), 3.08 (m, 1H), 2.80 (m, 1H), 2.55 (s, 3H), 1.66 (m, 2H), 1.33 (m, 5H); LC/MS $[M + 1]^+$ m/z 495; HRMS calcd for $C_{26}H_{30}N_4O_4S$ $[M + H]^+$, 495.2066; found, 495.2080.

Amides 31b−31d. The title compounds were prepared according to general procedure C from the appropriate starting materials, employing Method 1 for Step 3.

***N*-(4-{[(1-Acetylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)-2-methylbenzamide (31b).** ^{1}H NMR (300 MHz, CD_3OD) δ 8.77 (m, 1H), 8.33 (d, J = 7.9 Hz, 1H), 8.25 (m, 1H), 7.94 (m, 1H), 7.72 (m, 3H), 7.40 (m, 3H), 4.16 (m, 1H), 3.67 (m, 1H), 3.25 (m,

1H), 3.03 (m, 1H), 2.65 (m, 1H), 2.56 (s, 3H), 1.20 (s, 3H), 1.60 (m, 2H), 1.30 (m, 2H); LC/MS $[M + 1]^+$ *m/z* 466.

***N*-[4-(1-Cyclopropanecarbonyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (31c).** ^{1}H NMR (300 MHz, CD_3-OD) δ 8.78 (m, 1H), 8.33 (m, 1H), 8.25 (m, 1H), 7.94 (m, 1H), 7.71 (m, 3H), 7.41 (m, 3H), 4.17 (m, 2H), 3.13 (m, 1H), 2.71 (m, 2H), 2.54 (s, 3H), 1.84 (m, 1H), 1.71 (m, 1H), 1.59 (m, 1H), 1.29 (m, 2H), 0.79 (m, 4H); LC/MS $[M + 1]^+$ *m/z* 492; HRMS calcd for $C_{27}H_{29}N_3O_4S$ $[M + H]^+$, 492.1957; found, 492.1963.

***N*-[4-(1-Cyclopentanecarbonyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (31d).** The title compound was made following general procedure C. ^{1}H NMR (300 MHz, CD_3-OD) δ 8.78 (m, 1H), 8.33 (m, 1H), 8.25 (m, 1H), 7.94 (m, 1H), 7.71 (m, 3H), 7.41 (m, 3H), 4.19 (m, 1H), 3.88 (m, 1H), 3.00 (m, 2H), 2.68 (m, 2H), 2.54 (s, 3H), 1.65 (m, 9H), 1.29 (m, 3H); LC/MS $[M + 1]^+$ *m/z* 520; HRMS calcd for $C_{29}H_{33}N_3O_4S$ $[M + H]^+$, 520.2270; found, 520.2279.

Amides 31e−31l. The title compounds were prepared according to general procedure C from the appropriate starting materials, employing Method 2 for Step 3.

***N*-{4-[1-(2-Hydroxy-acetyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (31e).** ^{1}H NMR (300 MHz, CD_3-OD) δ 8.78 (m, 1H), 8.33 (d, $J = 8.1$ Hz, 1H), 8.23 (m, 1H), 7.94 (m, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 4.16 (m, 1H), 4.13 (s, 2H), 3.55 (m, 1H), 3.34 (m, 1H), 2.95 (m, 1H), 2.74 (m, 1H), 2.55 (s, 3H), 1.63 (m, 2H), 1.41 (m, 2H); LC/MS $[M + 1]^+$ *m/z* 482; HRMS calcd for $C_{25}H_{27}N_3O_5S$ $[M + H]^+$, 482.1749; found, 482.1756.

***N*-{4-[1-(2-Methoxy-acetyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (31f).** ^{1}H NMR (300 MHz, CD_3-OD) δ 8.76 (m, 1H), 8.33 (d, $J = 8.3$ Hz, 1H), 8.23 (m, 1H), 7.94 (m, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 4.08 (m, 4H), 3.63 (m, 1H), 3.34 (s, 3H), 2.98 (m, 1H), 2.71 (m, 1H), 2.55 (s, 3H), 1.61 (m, 2H), 1.30 (m, 2H); LC/MS $[M + 1]^+$ *m/z* 496; HRMS calcd for $C_{26}H_{29}N_3O_5S$ $[M + H]^+$, 496.1906; found, 496.1912.

***N*-{4-[1-(2-Amino-acetyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide Formic Acid Salt (31g).** ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.66 (br, 1H), 8.70 (m, 1H), 8.30 (s, 1H), 8.20 (m, 2H), 7.94 (d, $J = 8.7$ Hz, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 4.05 (m, 1H), 3.60 (m, 4H), 2.95 (m, 1H), 2.74 (m, 1H), 2.49 (s, 3H), 1.55 (m, 2H), 1.31 (m, 2H); LC/MS $[M + 1]^+$ *m/z* 481; HRMS calcd for $C_{25}H_{28}N_4O_4S$ $[M + H]^+$, 481.1909; found, 481.1917.

***N*-{4-[1-(3-Amino-propionyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide Formic Acid Salt (31h).** ^{1}H NMR (300 MHz, CD_3OD) δ 8.75 (m, 1H), 8.53 (s, 1H), 8.31 (d, $J = 8.1$ Hz, 1H), 8.24 (m, 1H), 7.92 (d, $J = 8.1$ Hz, 1H), 7.70 (m, 3H), 7.38 (m, 3H), 4.19 (m, 1H), 3.65 (m. 1H), 3.05 (m, 3H), 2.71 (m, 1H), 2.62 (m, 3H), 2.55 (s, 3H), 1.62 (m, 2H), 1.29 (m, 2H); LC/MS $[M + 1]^+$ *m/z* 495; HRMS calcd for $C_{26}H_{30}N_4O_4S$ $[M + H]^+$, 495.2066; found, 495.2085.

***N*-{4-[1-(4-Amino-butyryl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide Formic Acid Salt (31i).** ^{1}H NMR (300 MHz, CD_3OD) δ 8.75 (m, 1H), 8.51 (s, 1H), 8.31 (m, 1H), 8.24 (m, 1H), 7.89 (m, 1H), 7.68 (m, 3H), 7.38 (m, 3H), 4.16 (m, 1H), 3.69 (m. 1H), 3.00 (m, 1H), 2.85 (m, 2H), 2.69 (m, 1H), 2.55 (s, 3H), 2.42 (m, 2H), 1.82 (m, 2H), 1.60 (m, 3H), 1.28 (m, 2H); LC/MS $[M + 1]^+$ *m/z* 509; HRMS calcd for $C_{27}H_{32}N_4O_4S$ $[M + H]^+$, 509.2222; found, 509.2229.

***N*-[4-({[1-(5-Aminopentanoyl)piperidin-4-yl]amino}sulfonyl)-1-naphthyl]-2-methyl-benzamide Formic Acid Salt (31j).** ^{1}H NMR (300 MHz, CD_3OD) δ 8.76 (m, 1H), 8.53 (s, 1H), 8.32 (d, $J = 8.1$ Hz, 1H), 8.24 (m,1H), 7.93 (d, $J = 8.1$ Hz, ,1H), 7.70 (m, 3H), 7.39 (m, 3H), 4.18 (m, 1H), 3.72 (m. 1H), 3.01 (m, 1H), 2.86 (m, 2H), 2.70 (m, 1H), 2.55 (s, 3H), 2.36 (m, 2H), 1.60 (m, 6H), 1.30 (m, 3H); LC/MS $[M + 1]^+$ *m/z* 523; HRMS calcd for $C_{28}H_{34}N_4O_4S$ $[M + H]^+$, 523.2379; found, 523.2383.

***N*-[4-({[1-(Azetidin-3-ylcarbonyl)piperidin-4-yl]amino}sulfonyl)-1-naphthyl]-2-methyl-benzamide Formic Acid Salt (31k).** ^{1}H NMR (300 MHz, CD_3OD) δ 8.75 (m, 1H), 8.52 (s, 1H), 8.31 (d, $J = 8.1$ Hz, 1H), 8.23 (m, 1H), 7.93 (d, $J = 8.1$ Hz, 1H), 7.71 (m, 3H), 7.39 (m, 3H), 4.13 (m, 5H), 3.90 (m. 1H), 3.37 (m, 2H), 2.96 (m, 1H), 2.76 (m, 1H), 2.55 (s, 3H), 1.62 (m, 2H), 1.30 (m, 2H); LC/MS $[M + 1]^+$ *m/z* 507; HRMS calcd for $C_{27}H_{30}N_4O_4S$ $[M + H]^+$, 507.2066; found, 507.2059.

2-Methyl-*N*-{4-[({1-[(2*S*)-pyrrolidin-2-ylcarbonyl]piperidin-4-yl}amino)sulfonyl]-1-naphthyl}benzamide) Formic Acid Salt (31l). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.66 (br, 1H), 8.70 (m, 1H), 8.26 (s, 1H), 8.23 (m, 2H), 7.96 (d, $J = 8.3$ Hz, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 4.03 (m, 2H), 3.40 (m, 2H), 3.02 (m, 2H), 2.78 (m, 2H), 2.49 (s, 3H), 2.06 (m, 1H), 1.62 (m, 5H), 1.25 (m, 2H); LC/MS $[M + 1]^+$ *m/z* 521; HRMS calcd for $C_{28}H_{32}N_4O_4S$ $[M + H]^+$, 521.2222; found, 521.2244.

Amides 31n and 31o. The title compounds were prepared according to general procedure C from the appropriate starting materials, employing Method 1 for Step 3.

***N*-(4-{[(1-Benzoylpiperidin-4-yl)amino]sulfonyl}-1-naphthyl)-2-methylbenzamide (31n).** ^{1}H NMR (300 MHz, CD_3OD) δ 8.75-(m, 1H), 8.31 (d, $J = 7.7$ Hz, 1H), 8.22 (m, 1H), 7.92 (d, $J = 8.1$ Hz, 1H), 7.71 (m, 3H), 7.36 (m, 8H), 4.29 (m, 1H), 3.51 (m. 1H), 3.35 (m, 1H), 2.96 (m, 2H), 2.54 (s, 3H), 1.62 (m, 2H), 1.35 (m, 2H); LC/MS $[M + 1]^+$ *m/z* 528; HRMS calcd for $C_{30}H_{29}N_3O_4S$ $[M + H]^+$, 528.1957; found, 528.1974

***N*-{4-[({1-[4-(Dimethylamino)benzoyl]piperidin-4-yl}amino)-sulfonyl]-1-naphthyl}-2-methylbenzamide (31o).** ^{1}H NMR (300 MHz, CD_3OD) δ 8.76(m, 1H), 8.32 (d, $J = 8.1$ Hz, 1H), 8.23 (m, 1H), 7.93 (m,1H), 7.71 (m, 3H), 7.36 (m, 3H), 7.22 (d, $J = 8.6$ Hz, 2H), 6.69 (d, $J = 8.6$ Hz, 2H), 4.00 (br, 2H), 3.38 (m, 1H), 3.00 (m, 2H), 2.96 (s, 6H), 2.54 (s, 3H), 1.60 (m, 2H), 1.32 (m, 2H); LC/MS $[M + 1]^+$ *m/z* 571; HRMS calcd for $C_{32}H_{34}N_4O_4S$ $[M + H]^+$, 571.2379; found, 571.2378.

3-(Dimethylamino)propyl 4-[({4-[(2-Methylbenzoyl)amino]-1-naphthyl}sulfonyl)amino]piperidine-1-carboxylate Formic Acid Salt (32a). The title compound was made following the procedure described for **32d**. ^{1}H NMR (300 MHz, CD_3OD) δ 8.75 (d, $J = 7.5$ Hz, 1H), 8.38 (s, 1H), 8.31 (d, $J = 7.8$ Hz, 1H), 8.23 (d, $J = 8.8$ Hz, 1H), 7.92 (m, 1H), 7.70 (m, 3H), 7.37 (m, 3H), 4.08 (m, 2H), 3.82 (d, $J = 13.5$ Hz, 2H), 3.22 (m, 2H), 3.09 (m, 2H), 2.85 (m, 1H), 2.84 (s, 6H), 2.55 (s, 3H), 2.00 (m, 2H), 1.57 (m, 2H), 1.30 (m, 2H); LC/MS *m/z* 553 $[M + H]^+$; HRMS calcd for $C_{29}H_{36}N_4O_5S$ $[M + H]^+$, 553.2484; found, 553.2469.

3-(Diethylamino)propyl 4-[({4-[(2-Methylbenzoyl)amino]-1-naphthyl}sulfonyl)amino]piperidine-1-carboxylate Formic Acid Salt (32b). The title compound was made following the procedure described for **32d**. ^{1}H NMR (300 MHz, CD_3OD) δ 8.75 (d, $J = 7.5$ Hz, 1H), 8.38 (s, 1H), 8.31 (d, $J = 8.1$ Hz, 1H), 8.24 (d, $J = 7.8$ Hz, 1H), 7.94 (m, 1H), 7.71 (m, 3H), 7.37 (m, 3H), 4.09 (m, 2H), 3.83 (d, $J = 13.5$ Hz, 2H), 3.16 (m, 7H), 2.55 (s, 3H), 1.99 (m, 3H), 1.57 (m, 2H), 1.26 (m, 9H); LC/MS *m/z* 581 $[M + H]^+$; HRMS calcd for $C_{31}H_{40}N_4O_5S$ $[M + H]^+$, 581.2797; found, 581.2822.

3-Pyrrolidin-1-ylpropyl 4-[({4-[(2-Methylbenzoyl)amino]-1-naphthyl}sulfonyl)amino]piperidine-1-carboxylate Formic Acid Salt (32c). The title compound was made following the procedure described for 32d. ^{1}H NMR (300 MHz, CD_3OD) δ 8.75 (d, $J = 8.4$ Hz, 1H), 8.38 (s, 1H), 8.30 (d, $J = 8.1$ Hz, 1H), 8.23 (d, $J = 8.1$ Hz, 1H), 7.93 (m, 1H), 7.71 (m, 3H), 7.38 (m, 3H), 4.08 (s, 3H), 3.82 (d, $J = 13.8$ Hz, 3H), 3.17 (m, 2H), 2.85 (m, 3H), 2.55 (s, 3H), 2.02 (m, 7H), 1.58 (m, 2H), 1.29 (m, 3H); LC/MS *m/z* 579 $[M + H]^+$; HRMS calcd for $C_{31}H_{38}N_4O_5S$ $[M + H]^+$, 579.2461; found, 579.2610.

3-(2,6-Dimethylmorpholin-4-yl)propyl-4-[({4-[(2-methylbenzoyl)amino]-1-naphthyl}sulfonyl)amino]piperidine-1-carboxylate Formic Acid Salt (32d). Step 1. To a solution of **30** (468 mg, 1.0 mmol) in DMF (10 mL) at 0 °C were added Et_3N (0.663 mL, 5.0 mmol) and 3-bromopropyl chloroformate (0.13 mL, 1.2 mmol). The reaction mixture was stirred at 0 °C for 4 h. Aqueous workup then afforded 3-bromopropyl 4-(1-(2-methylbenzamido)naphthalene-4-sulfonamido)piperidine-1-carboxylate as an off-white solid (411 mg), which was used without further purification**. Step 2.** To a DMF (10 mL) solution of the product from Step 1 (411 mg, 0.70 mmol) were added Cs_2CO_3 (1.10 g, 3.5 mmol) and 2,6-dimethyl-

morpholine (0.172 mL, 1.4 mmol). The resultant solution was stirred at 100 °C for 12 h, then quenched with water and filtered. The solid was purified via HPLC to provide **32d** (113 mg, 26%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 8.72 (d, J = 8.1 Hz, 1H), 8.38 (s, 1H), 8.23 (m, 2H), 7.89 (d, J = 7.8 Hz, 1H), 7.67 (m, 3H), 7.37 (m, 3H), 4.03 (m, 2H), 3.76 (m, 3H), 3.24 (m, 5H), 2.83 (m, 4H), 2.51 (s, 3H), 2.30 (t, J = 11.4 Hz, 2H), 1.93 (m, 2H), 1.53 (d, J = 11.1 Hz, 2H), 1.18 (m, 7H); LC/MS m/z 623 $[M + H]^+$; HRMS calcd for $C_{33}H_{42}N_4O_4S$ $[M + H]^+$, 623.2903; found, 623.2905.

3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)propyl 4-[({4-[(2-Methylbenzoyl)amino]-1-naphthyl}sulfonyl)amino]piperidine-1-carboxylate Formic Acid Salt (32e). The title compound was made following the procedure described for **32d**. ^{1}H NMR (300 MHz, CD_3OD) δ 8.76 (d, J = 8.4 Hz, 1H), 8.38 (s, 1H), 8.28 (m, 2H), 7.93 (d, J = 7.8 Hz, 1H), 7.75 (m, 3H), 7.39 (m, 3H), 7.22 (m, 4H), 4.30 (s, 2H), 4.14 (t, J = 4.5 Hz, 2H), 3.83 (d, J = 13.2 Hz, 2H), 3.44 (t, J = 5.7 Hz, 2H), 3.17 (m, 5H), 2.83 (m, 2H), 2.56 (s, 3H), 2.11 (m, 2H), 1.57 (d, J = 10.8 Hz, 2H), 1.30 (m, 2H); LC/MS m/z 641 $[M + H]^+$; HRMS calcd for $C_{36}H_{40}N_4O_5S$ $[M + H]^+$, 641.2797; found, 641.2796.

4-(1-(2-Methylbenzamido)naphthalene-4-sulfonamido)piperidine-1-carboxamide (33a). To a suspension of **30** (500 mg, 1.08 mmol) in 10 mL THF were added Et_3N (150 μL, 1.49 mmol) and isocyanato(trimethyl)silane (578 μL, 4.3 mmol), and the reaction mixture was stirred at 25 °C for 17 h. The mixture was then cooled in an ice bath and aqueous ammonium chloride (10 mL) was added. The reaction mixture was directly extracted with EtOAc (3×), and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford a white solid. Purification via HPLC then provided **33a** (0.13 g, 26%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 8.78 (m, 1H), 8.30 (m, 2H), 7.96 (m, 1H), 7.73 (m, 3H), 7.43 (m, 3H), 3.77 (m, 2H), 2.77 (m, 2H), 2.59 (m, 1H), 2.56 (s, 3H), 1.57 (m, 2H), 1.33 (m, 2H); LC/MS m/z 467 $[M + H]^+$; HRMS calcd for $C_{24}H_{26}N_4O_4S$ $[M + H]^+$, 467.1753; found, 467.1753.

Ureas 33b−33g. These compounds were prepared following the procedure described for **33a** from the appropriate starting materials. The reported yields represent the yields obtained for the final step of the sequence.

4-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic Acid Methylamide (33b). ^{1}H NMR (300 MHz, CD_3OD) δ 8.76 (m, 1H), 8.33 (d, J = 8.3 Hz, 1H), 8.23 (m, 1H), 7.94 (d, J = 8.3 Hz, 1H), 7.71 (m, 3H), 7.39 (m, 3H), 3.73 (m, 2H), 3.25 (m, 1H), 2.72 (m, 2H), 2.65 (s, 3H), 2.56 (s, 3H), 1.53 (m, 2H), 1.28 (m, 2H); LC/MS $[M + 1]^+$ m/z 481; HRMS calcd for $C_{25}H_{28}N_4O_4S$ $[M + H]^+$, 481.1909; found, 481.1909.

4-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic Acid Ethylamide (33c). Yield: 0.477 g (69%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 8.78 (d, J = 7.9 Hz, 1H), 8.33 (d, J = 8.5 Hz, 1H), 8.23 (d, J = 7.3 Hz, 1H), 7.94 (d, J = 7.3 Hz, 1H), 7.71 (m, 3H), 7.39 (m, 3H), 3.73 (m, 2H), 3.23 (m, 1H), 3.11 (q, J = 6.1 Hz, 2H), 2.69 (m, 2H), 2.54 (s, 3H), 1.53 (m, 2H), 1.29 (m, 2H), 1.04 (t, J = 6.1 Hz, 3H); LC/MS $[M + H]^+$ m/z 495; HRMS calcd for $C_{26}H_{30}N_4O_4S$ $[M + H]^+$, 495.2066; found, 495.2083.

4-[({4-[(2-Methylbenzoyl)amino]-1-naphthyl}sulfonyl)amino]-*N*-propylpiperidine-1-carboxamide (33d). ^{1}H NMR (300 MHz, CD_3OD) δ 8.75 (m, 1H), 8.33 (d, J = 7.9 Hz, 1H), 8.23 (m, 1H), 7.94 (m, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 3.75 (m, 2H), 3.25 (m, 1H), 3.06 (t, J = 7.2 Hz, 2H), 2.74 (m, 2H), 2.59 (s, 3H), 1.59 (m, 2H), 1.49 (m, 2H), 1.30 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H); LC/MS $[M + 1]^+$ m/z 509; HRMS calcd for $C_{27}H_{32}N_4O_4S$ $[M + H]^+$, 509.2222; found, 509.2239.

***N*-Isopropyl-4-[({4-[(2-methylbenzoyl)amino]-1-naphthyl}-sulfonyl)amino]piperidine-1-carboxamide (33e).** ^{1}H NMR (300 MHz, CD_3OD) δ 8.78 (d, 1H), 8.33 (d, J = 8.3 Hz, 1H), 8.23 (m, 1H), 7.94 (m, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 3.76 (m, 2H), 3.25 (m, 2H), 2.71 (m, 2H), 2.57 (s, 3H), 1.59 (m, 2H), 1.30 (m, 2H), 1.05 (d, J = 8.3 Hz, 6H); LC/MS $[M + 1]^+$ m/z 509; HRMS calcd for $C_{27}H_{32}N_4O_4S$ $[M + H]^+$, 509.2222; found, 509.2240.

4-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic Acid Phenylamide (33f). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.64 (s, 1H), 8.69 (d, J = 8.2 Hz, 1H), 8.38 (s, 1H), 8.25 (m, 2H), 8.11 (d, J = 7.3 Hz, 1H), 7.95 (d, J = 7.9 Hz, 1H), 7.74 (m, 3H), 7.39 (m, 5H), 7.17 (t, J = 7.6 Hz, 2H), 6.88 (t, J = 7.3 Hz, 1H), 3.83 (d, J = 13.4 Hz, 2H), 3.32 (s, 3H), 3.25 (m, 1H), 2.77 (t, J = 11.3 Hz, 2H), 1.48 (m, 2H), 1.25 (m, 2H); LC/MS m/z 543 $[M + H]^+$; HRMS calcd for $C_{30}H_{30}N_4O_4S$ $[M + H]^+$, 543.2066; found, 543.2078.

4-({[4-(Benzoylamino)-1-naphthyl]sulfonyl}amino)-*N*,*N*-dimethylpiperidine-1-carboxamide (33g). To a suspension of **30** (322 mg, 0.70 mmol) in THF (10 mL) were added dimethylcarbamoyl chloride (90 μL, 0.98 mmol) and Et_3N (682 μL, 4.9 mmol). The reaction mixture was stirred at 25 °C for 2 h and then filtered. The filtrate was concentrated *in vacuo*, and the crude residue was purified via HPLC to afford **33g** (0.137 g, yield 40%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.6 (s, 1H), 8.68 (d, J = 7.3, 1H), 8.24 (m, 2H), 8.08 (m, 1H), 7.94 (m, 1H), 7.71 (m, 3H), 7.36 (m, 3H), 3.58 (m, 1H), 2.63 (s, 6H), 2.59 (m, 4H), 1.74 (s, 1H), 1.45 (m, 2H), 1.26 (m, 2H); LC/MS m/z 495 $[M + H]^+$; HRMS calcd for $C_{26}H_{30}N_4O_4S$ $[M + H]^+$, 495.2066; found, 495.2049.

***N*-{4-[1-(Azetidine-1-carbonyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (33h).** The title compound was prepared according to the procedure described for **33n**, using azetidine instead of *N*,*N*-diethyl-1,3-propanediamine. ^{1}H NMR (300 MHz, CD_3OD) δ 8.76 (d, J = 8.1 Hz, 1H), 8.32 (m, 1H), 8.23 (d, J = 7.7 Hz, 1H), 7.93 (d, J = 7.3 Hz, 1H), 7.73 (m, 3H), 7.39 (m, 3H), 3.93 (m, 4H), 3.60 (d, J = 13.6 Hz, 2H), 3.25 (m, 1H), 2.72 (t, J = 11.6 Hz, 2H), 2.56 (s, 3H), 2.18 (m, 2H), 1.54 (m, 2H), 1.30 (m, 2H); LC/MS m/z 507 $[M + H]^+$; HRMS calcd for $C_{27}H_{30}N_4O_4S$ $[M + H]^+$, 507.2066; found, 507.2084.

2-Methyl-*N*-[4-({[1-(pyrrolidin-1-ylcarbonyl)piperidin-4-yl]-amino}sulfonyl)-1-naphthyl]benzamide (33i). The title compound was prepared according to the procedure described for **33g**, using pyrrolidine-1-carbonyl chloride instead of dimethylcarbamoyl chloride. ^{1}H NMR (300 MHz, CD_3OD) δ 8.76 (d, J = 8.3 Hz, 1H), 8.32 (d, J = 8.1 Hz, 1H), 8.24 (m, 1H), 7.92 (d, J = 7.7 Hz, 1H), 7.71 (m, 3H), 7.39 (m, 3H), 3.50 (d, J = 11.4 Hz, 2H), 3.20 (m, 5H), 2.77 (t, J = 11.4 Hz, 2H), 2.56 (s, 3H), 1.81 (m, 2H), 1.58 (m, 2H), 1.33 (m, 2H), 0.92 (m, 2H); LC/MS m/z 521 $[M + H]^+$; HRMS calcd for $C_{28}H_{32}N_4O_4S$ $[M + H]^+$, 521.2222; found, 521.2238.

2-Methyl-*N*-{4-[1-(piperidine-1-carbonyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-benzamide (33j). The title compound was prepared according to the procedure described for **33g**, using piperidine-1-carbonyl chloride instead of dimethylcarbamoyl chloride. ^{1}H NMR (300 MHz, CD_3OD) δ 8.78 (d, 1H), 8.32 (d, J = 8.3 Hz, 1H), 8.25 (m, 1H), 7.94 (d, J = 8.3 Hz, 1H), 7.71 (m, 3H), 7.39 (m, 3H), 3.41 (m, 4H), 3.15 (m, 5H), 2.72 (m, 2H), 2.56 (s, 3H), 1.58 (m, 8H); LC/MS $[M + 1]^+$ m/z 535; HRMS calcd for $C_{29}H_{34}N_4O_4S$ $[M + H]^+$, 535.2379; found, 535.2393.

2-Methyl-*N*-{4-[1-(4-methyl-piperazine-1-carbonyl)-piperidin-4-ylsulfamoyl]-aphthalen-1-yl}-benzamide Formic Acid Salt (33k). The title compound was prepared according to the procedure described for **33n**, using 1-methylpiperazine instead of *N*,*N*-diethyl-1,3-propanediamine. ^{1}H NMR (300 MHz, CD_3OD) δ 8.76 (d, J = 8.3 Hz, 1H), 8.40 (s, 1H), 8.32 (d, J = 8.1 Hz, 1H), 8.24 (m, 1H), 7.92 (d, J = 7.7 Hz, 1H), 7.71 (m, 3H), 7.39 (m, 3H), 3.50 (d, J = 11.4 Hz, 2H), 3.20 (m, 5H), 2.77 (t, J = 11.4 Hz, 2H), 2.66 (m, 4H), 2.56 (s, 3H), 2.46 (s, 3H), 1.57 (m, 2H), 1.33 (m, 2H); LC/MS m/z 550 $[M + H]^+$; HRMS calcd. for $C_{29}H_{35}N_5O_4S$ $[M + H]^+$ 550.2488, found 550.2469.

2-Methyl-*N*-[4-({[1-(morpholin-4-ylcarbonyl)piperidin-4-yl]-amino}sulfonyl)-1-naphthyl]benzamide (33l). The title compound was prepared according to the procedure described for **33g**, using morpholine-4-carbonyl chloride instead of dimethylcarbamoyl chloride. ^{1}H NMR (300 MHz, CD_3OD) δ 8.76 (m, 1H), 8.31 (d, J = 7.7 Hz, 1H), 8.24 (m, 1H), 7.94 (m, 1H), 7.70 (m, 3H), 7.37 (m,

3H), 3.58 (m, 4H), 3.51 (m, 2H), 3.15 (m, 4H), 2.74 (m, 2H), 2.55 (s, 3H), 1.54 (m, 2H), 1.31 (m, 3H); LC/MS *m*/*z* 537 $[M + H]^+$; HRMS calcd for $C_{28}H_{32}N_4O_5S$ $[M + H]^+$, 537.2171; found, 537.2183.

4-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic Acid (3-Morpholin-4-yl-propyl)-amide Formic Acid Salt (33m). The title compound was prepared according to the procedure described for **33n** (below), using 3-morpholin-4-yl-propylamine instead of *N*,*N*-diethyl-1,3-propanediamine. ^{1}H NMR (300 MHz, CD_3OD) δ 8.76 (d, $J = 8.5$ Hz, 1H), 8.39 (s, 1H), 8.32 (d, $J = 7.9$ Hz, 1H), 8.24 (d, $J = 8.3$ Hz, 1H), 7.92 (d, $J = 7.9$ Hz, 1H), 7.74 (m, 3H), 7.38 (m, 3H), 3.79 (m, 6H), 3.18 (m, 2H), 2.92 (m, 4H), 2.76 (m, 4H), 2.56 (s, 3H), 2.04 (s, 1H), 1.79 (m, 2H), 1.57 (m, 2H), 1.28 (m, 2H); LC/MS *m*/*z* 594 $[M + H]^+$; HRMS calcd for $C_{31}H_{39}N_5O_5S$ $[M + H]^+$, 594.2750; found, 594.2740.

4-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic Acid (3-Diethylamino-propyl)-amide Formic Acid Salt (33n). This compound was prepared according to the three-step sequence that follows. **Step 1.** To a solution of **30** (6.90 g, 15.0 mmol) in THF (100 mL) at 25 °C were added carbonyl diimidazole (3.97 g, 1.59 mmol) and Et_3N (4.2 mL, 30.0 mmol). The reaction mixture was stirred at 25 °C for 24 h, at which point the reaction was quenched with water and the aqueous layer was extracted with CH_2Cl_2 (3×). The organic extracts were combined, washed with brine, and dried over $MgSO_4$. The solution was filtered, concentrated *in vacuo*, and purified by column chromatography (98:2 CH_2Cl_2/MeOH) to afford *N*-{4-[1-(imidazole-1-carbonyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (6.8 g, 87.7%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.6 (s, 1H), 8.70 (d, $J = 8.2$ Hz, 1H), 8.20 (m, 3H), 7.95 (m, 2H), 7.65 (m, 3H), 7.38 (m, 4H), 6.98 (s, 1H), 3.70 (d, $J = 13.4$ Hz, 2H), 3.33 (m, 1H), 3.07 (m, 2H), 2.47 (s, 3H), 1.62 (m, 2H), 1.40 (m, 2H); LC/MS *m*/*z* 518 $[M + H]^+$.

Step 2. To a solution of the product from Step 1 (2.8 g, 5.41 mmol) in acetonitrile (25 mL) was added methyl iodide (3.07 g, 21.6 mmol). The reaction mixture was stirred at 50 °C for 17 h and then concentrated *in vacuo* to afford 1-methyl-3-{4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carbonyl}-3*H*-imidazol-1-ium iodide, which was used without further purification. LC/MS *m*/*z* 532 $[M + H]^+$.

Step 3. To a solution of the product from Step 2 (150 mg, 0.228 mmol) in CH_2Cl_2 (5 mL) and DMF (5 mL) were added *N*,*N*-diethyl-1,3-propanediamine (0.033 mL, 0.228 mmol) and Et_3N (0.053 μL, 0.228 mmol). The reaction mixture was stirred at 25 °C for 2 h, at which point the solution was concentrated *in vacuo* and directly purified by reverse phase HPLC to afford **33n** (0.141 g, 74%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 8.76 (d, $J = 8.0$ Hz, 1H), 8.52 (s, 1H), 8.32 (d, $J = 8.1$ Hz, 1H), 8.24 (m, 1H), 7.93 (d, $J = 7.9$ Hz, 1H), 7.72 (m, 3H), 7.39 (m, 3H), 3.75 (d, $J = 13.6$ Hz, 2H), 3.30 (m, 3H), 3.18 (m, 4H), 3.05 (t, $J = 7.5$ Hz, 2H), 2.77 (t, $J = 11.4$ Hz, 2H), 2.56 (s, 3H), 1.83 (m, 2H), 1.57 (m, 2H), 1.33 (m, 8H); LC/MS *m*/*z* 580 $[M + H]^+$; HRMS calcd for $C_{31}H_{41}N_5O_4S$ $[M + H]^+$, 580.2957; found, 580.2978.

Ethyl 4-[({4-[(Piperidin-1-ylcarbonyl)amino]-1-naphthyl}-sulfonyl)amino]piperidine-1-carboxylate (34). The title compound was prepared according to general procedure A, using piperidine-1-carbonyl chloride instead of benzoyl chloride in Step 1, and using 4-amino-piperidine-1-carboxylic acid ethyl ester instead of *p*-anisidine in Step 3. Yield: 0.007 g (4.5%) of a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 8.80 (m, 1H), 8.25 (m, 1H), 8.10 (m, 1H), 7.65 (m, 2H), 7.50 (m, 1H), 4.05 (m, 2H), 3.80 (m, 2H), 3.55 (m, 4H), 3.20 (m, 1H), 2.75 (m, 2H), 1.65 (m, 5H), 1.25 (m, 5H), 1.18 (m, 3H); LC/MS *m*/*z* 489 $[M + H]^+$.

Ethyl 4-(1-Aminonaphthalene-4-sulfonamido)piperidine-1-carboxylate (35). Step 1. 4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)naphthalene-1-sulfonic Acid Pyridinium Salt. To a solution of 4-amino-naphthalene-1-sulfonic acid (4.9 g 10.0 mmol) in pyridine (15 mL) was added phthaloyl dichloride (3.2 mL, 22 mmol), and the resultant solution was stirred at 80 °C for 17 h. The solvent was removed *in vacuo*, and the crude material was recrystallized from MeOH (2×) to provide the title compound (2.0 g) as a gray solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.90 (m, 2H), 8.57 (m, 1H), 8.00 (m, 7H), 7.77 (d, $J = 8.4$ Hz, 1H), 7.58 (m, 2H), 7.49 (m, 2H).

Step 2. 4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)naphthalene-1-sulfonyl Chloride. To a solution of the sulfonic acid generated in Step 1 (2.0 g 4.6 mmol) in DMF (10 mL) was added thionyl chloride (0.5 mL, 6.95 mmol). The resultant solution was stirred at 25 °C for 3 h. The reaction was then quenched by pouring into ice water, and this mixture was directly filtered to provide the title compound (1.4 g) as a pale white solid, which was used without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.95 (d, $J = 8.4$ Hz, 1H), 8.00 (m, 5H), 7.73 (d, $J = 8.3$ Hz, 1H), 7.58 (m, 2H), 7.49 (m, 1H).

Step 3. To a solution of the above sulfonyl chloride (3.3 g 10.1 mmol) in CH_2Cl_2 (80 mL) were added Et_3N (2.8 mL, 20.2 mmol) and 4-amino-piperidine-1-carboxylic acid ethyl ester (2.1 mg, 12.1 mmol). The resultant solution was stirred at 25 °C for 17 h, at which point it was quenched with water and extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated to provide a yellow oil, which was purified via chromatography to afford ethyl 4-({[4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-naphthyl]sulfonyl}amino)piperidine-1-carboxylate as a pale white solid (3.0 g, yield 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, $J = 8.5$ Hz, 1H), 8.40 (d, $J = 8.0$ Hz, 1H), 8.03 (m, 2H), 7.88 (m, 2H), 7.63 (m, 2H), 7.58 (m, 2H), 4.90 (m, 1H), 4.25 (q, $J = 6.9$ Hz, 2H), 3.95 (m, 2H), 3.40 (m, 1H), 2.80 (m, 2H), 1.75 (m, 2H), 1.20 (m, 5H); LC/MS *m*/*z* 508 $[M + H]^+$.

Step 4. To a solution of the product from Step 1 (2.3 g, 4.5 mmol) in MeOH (50 mL) was added hydrazine (1.4 mL, 45.4 mmol) at 25 °C. The clear colorless solution became cloudy and precipitation was observed. The solid was filtered and the filtrate was concentrated *in vacuo* to afford the desired product (1.7 g, 100%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.46 (d, $J = 8.6$ Hz, 1H), 8.20 (d, $J = 8.3$ Hz, 1H) 7.86 (d, $J = 8.3$ Hz, 1H), 7.55 (m, 2H), 6.63 (m, 2H), 3.93 (q, $J = 7.2$ Hz, 2H), 3.63 (m, 3H), 3.00 (m, 1H), 2.72 (m, 2H), 1.40 (m, 2H), 1.08 (m, 2H), 1.07 (t, $J = 7.2$ Hz, 3H); LC/MS *m*/*z* 378 $[M + H]^+$; HRMS calcd for $C_{18}H_{23}N_3O_4S$ $[M + H]^+$, 378.1487; found, 378.1506.

(±)-*N*-(4-{[(1-Butyrylpyrrolidin-3-yl)amino]sulfonyl}-1-naphthyl)-2-methylbenzamide (36). The title compound was prepared according to general procedure C (Method 1), using *tert*-butyl 3-aminopyrrolidine-1-carboxylate instead of *tert*-butyl 4-aminopiperidine-1-carboxylate for Step 2. ^{1}H NMR (300 MHz, CD_3OD) δ 8.74 (m, 1H), 8.31 (dd, $J = 7.9$, 4.5 Hz, 1H), 8.24 (m, 1H), 7.95 (m, 1H), 7.70 (m, 3H), 7.42 (m, 1H), 7.34 (m, 2H), 3.95 (m, 1H), 3.50 (m, 3H), 3.25 (m, 1H), 2.54(s, 3H), 2.16 (m, 1H), 2.00 (1.85, 3H), 1.60 (m, 2H), 0.98 (m, 3H); LC/MS *m*/*z* 480 $[M + H]^+$; HRMS calcd for $C_{26}H_{29}N_3O_4S$ $[M + H]^+$, 480.1957; found, 480.1980.

***N*-(4-{[(1-Butyrylazetidin-3-yl)amino]sulfonyl}-1-naphthyl)-2-methylbenzamide (37).** The title compound was prepared according to general procedure C (Method 1), using *tert*-butyl 3-aminoazetidine-1-carboxylate instead of *tert*-butyl 4-aminopiperidine-1-carboxylate in Step 2. ^{1}H NMR (300 MHz, CD_3OD) δ 8.78 (m, 1H), 8.28 (m, 2H), 7.99 (m, 1H), 7.74 (m, 3H), 7.38 (m, 3H), 4.18 (m, 2H), 3.92 (m, 1H), 3.77 (m, 1H), 3.52 (m, 1H), 2.56 (s, 3H), 1.96 (t, $J = 7.5$ Hz, 2H), 1.51 (m, 2H), 0.86 (t, $J = 7.3$ Hz, 3H). LC/MS *m*/*z* 466 $[M + H]^+$; HRMS calcd for $C_{25}H_{27}N_3O_4S$ $[M + H]^+$, 466.1800; found, 466.1793.

Ethyl 4-({[5-(Benzoylamino)-1-naphthyl]sulfonyl}amino)-piperidine-1-carboxylate (38a). The title compound was prepared according to general procedure A, using 5-amino-naphthalene-1-sulfonic acid instead of 4-amino-naphthalene-1-sulfonic acid in Step 1 and using 4-amino-piperidine-1-carboxylic acid ethyl ester instead of *p*-anisidine in Step 3. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.56 (d, $J = 8.7$ Hz, 1H), 8.22 (m, 2H), 8.02 (m, 2H), 7.78 (d, $J = 7.2$ Hz, 1H), 7.61 (m, 1H), 7.47 (m, 4H), 6.72 (br, 1H), 3.97 (q, $J = 7.2$ Hz, 2H), 3.80 (m, 2H), 3.15 (m, 1H), 2.67 (m, 2H), 1.55 (m, 2H), 1.34 (m, 2H), 1.12 (t, $J = 7.2$ Hz, 3H). LC/MS

$[M + 1]^+$ *m*/*z* 482; HRMS calcd for $C_{25}H_{27}N_3O_5S$ $[M + H]^+$, 482.1749; found, 482.1758.

4-(8-Benzoylamino-naphthalene-2-sulfonylamino)-piperidine-1-carboxylic Acid Ethyl Ester (38b). The title compound was prepared according to general procedure A, using 8-aminonaphthalene-2-sulfonic acid instead of 4-amino-naphthalene-1-sulfonic acid in Step 1 and using 4-amino-piperidine-1-carboxylic acid ethyl ester instead of *p*-anisidine in Step 3. ^{1}H NMR (300 MHz, CD_3-OD) δ 8.62 (s, 1H), 8.05 (m, 3H), 7.90 (m, 2H), 7.60 (m, 5H), 4.00 (q, $J = 7.1$ Hz, 2H), 3.80 (d, $J = 15.0$ Hz, 2H), 3.20 (m, 1H), 2.80 (m, 2H), 1.65 (m, 2H), 1.20 (m, 2H), 1.15 (t, $J = 7.1$ Hz, 3H); LC/MS *m*/*z* 482 $[M + H]^+$; HRMS calcd for $C_{25}H_{27}N_3O_5S$ $[M + H]^+$, 482.1749; found, 482.1759.

4-[6-(2-Methyl-benzoylamino)-naphthalene-2-sulfonylamino]-piperidine-1-carboxylic Acid Ethyl Ester (38c). The title compound was prepared according to general procedure A, using 6-amino-naphthalene-2-sulfonic acid for 4-amino-naphthalene-1-sulfonic acid 2-methyl-benzoyl chloride for benzoyl chloride in Step 1 and using 4-amino-piperidine-1-carboxylic acid ethyl ester instead of *p*-anisidine in Step 3. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.65 (s, 1H), 8.55 (s, 1H), 8.33 (s, 1H), 8.05 (m, 2H), 7.75 (m, 3H), 7.45 (m, 1H), 7.35(m, 1H), 7.30 (m, 2H), 3.90 (q, $J = 7.1$ Hz, 2H), 3.65 (d, $J = 15.0$ Hz, 2H), 3.15 (m, 1H), 2.72 (m, 2H), 2.35 (s, 3H), 1.50 (m, 2H), 1.20 (m, 2H), 1.05 (t, $J = 7.1$ Hz, 3H); LC/MS *m*/*z* 496 $[M + H]^+$; HRMS calcd for $C_{26}H_{29}N_3O_5S$ $[M + H]^+$, 480.1957; found, 480.1980.

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Supporting Information Available: Tabulated data from the Novascreen panel for compound **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) In the early stages of the program, compound potency was determined using FLIPR, which was also useful in identifying any undesired agonist activity. Later, a higher throughput FMAT binding assay was developed and implemented as the primary screening paradigm. While not shown, there was excellent correlation between FMAT (K_i) and FLIPR (IC_{50}) values. For clarity, SAR tables are organized using data from one or the other of these assays but not both.

(11) Naphthalene core replacement results will be disclosed in a subsequent manuscript.

(12) A table containing selected data from the Novascreen panel is presented in the Supporting Information section. Note that, although only select entries are reproduced here, compound **15** displayed <20% inhibition at 10 μM across all 40 receptors evaluated.

(13) HEK-293 cells that were stably transfected with hERG cDNA were obtained according to Zhou, Z.; Gong, Q.; Ye, B.; Fan, Z.; Makielski, J. C.; Robertson, G. A. *Biophys. J.* **1998**, *74*, 230. Membrane homogenates were prepared from cell pellets, suspended in 50 mM Tris-HCl buffer (pH 7.4), containing 10 mM KCl and 1 mM $MgCl_2$, and centrifuged at 4 °C. The hERG binding assay was conducted as described in the following references: (a) Finlayson, K.; Sharkey, J. In *Optimization in Drug Discovery*; Yan, Z., Caldwell, G. W., Eds.; Humana Press: Totowa, NJ, 2004; pp 353−368. (b) Diaz, G. J.; Daniell, K.; Leitza, S. T.; Martin, R. L.; Su, Z.; McDermott, J. S.; Cox, B. F.; Gintant, G. A. *J. Pharmacol. Toxicol. Methods* **2004**, *50*, 187.

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