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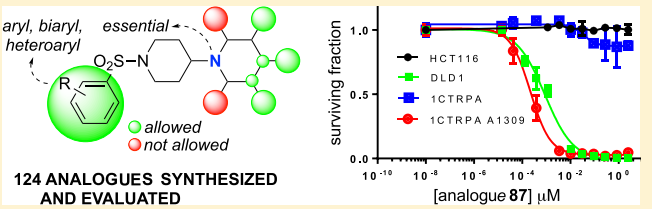
Design and Synthesis of TASIN Analogues Specifically Targeting Colorectal Cancer Cell Lines with Mutant Adenomatous Polyposis Coli (APC)

Wentian Wang,[†] Lu Zhang,[‡] Lorraine Morlock,[†] Noelle S. Williams,[†] Jerry W. Shay,[‡] and Jef K. De Brabander*[,†]

[†]Departments of Biochemistry and [‡]Cell Biology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75390-9038, United States

Supporting Information

ABSTRACT: Despite advances in targeted anticancer therapies, there are still no small-molecule-based therapies available that specifically target colorectal cancer (CRC) development and progression, the second leading cause of cancer deaths. We previously disclosed the discovery of truncating adenomatous polyposis coli (APC)-selective inhibitor 1 (TASIN-1), a small molecule that specifically targets colorectal cancer cells lines with truncating mutations in the adenomatous polyposis coli (APC) tumor suppressor gene through inhibition of cholesterol biosynthesis. Here, we report a medicinal chemistry evaluation of a collection of TASIN analogues and activity against colon cancer cell lines and an isogenic cell line pair reporting on the status of APC-dependent selectivity. A number of potent and selective analogues were identified, including compounds with good metabolic stability and pharmacokinetic properties. The compounds reported herein represent a first-in-class genotype-selective series that specifically target *apc* mutations present in the majority of CRC patients and serve as a translational platform toward a targeted therapy for colon cancer.



INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer deaths resulting in ∼600 000 deaths worldwide every year (49 700 in the United States and 152 000 in the European Union).[1] Despite the fact that the disease etiology for the majority of CRCs is fairly well understood, there are still no therapies available that specifically target oncogenotypes that drive CRC development and progression.[2−4] In addition to early detection (colonoscopy and genetic testing) and surgical removal of precancerous adenomatous polyps (adenomas), current treatment options for advanced CRC include surgery, radiation therapy, and chemotherapy.[2−4] A large body of studies have shown that the primary initiating event in both familial adenomatous polyposis (FAP) and sporadic CRC is a loss of function of the adenomatous polyposis coli (APC) tumor suppressor gene leading to aberrant crypts and early adenomas.[5−7] According to the model of Fearon and Vogelstein, these early events in the adenoma to adenocarcinoma sequence cause genomic instability leading to the acquisition of additional mutations in various oncogenes such as KRAS or BRAF, SMAD4, TGF-β, and frequently in the tumor suppressor TP53.[8,9] Although the full spectrum of biological pathways regulated by the large multifunctional *apc* protein remains a topic of debate,[10] it is now commonly accepted that wild-type APC (APC^{wt}) is essential for intestinal cell differentiation and crypt homeostasis at least in part via regulation of the Wnt signaling pathway.[11,12] It is estimated that mutations in the APC gene occur in >80% of patients diagnosed with CRC with >90% of those mutations targeting the mutation cluster region leading to defined truncated APC (APC^{TR}) gene products.[13−15,5,6] While loss of tumor-suppressive function of APC mutations is believed to be important for CRC tumorigenesis,[8,9] increasing evidence suggests that the truncated form of the mutant APC^{TR} protein also endows these tumors with gain-of-function properties.[10,16−19] For instance, a recent paper co-authored by some of us documented that *apc*-truncations relieve the autoinhibition of C-terminal activation of Asef (APC-selective guanine exchange factor) leading to downstream Golgi fragmentation via activation of an Asef-ROCK-MLC2 signaling pathway.[20]

In light of the above, we reasoned that small-molecule cytotoxins that specifically target colon cancer cell lines with APC^{TR} while sparing normal cells with APC^{WT} would provide for a potential highly selective therapy for the vast majority of CRC patients. This approach is further supported by a recent study demonstrating that introduction of APC^{WT} in colon cancer models reestablishes normal intestinal crypt homeostasis and function, even in the presence of potent oncogenic drivers such as Kras and p53.[21] We have recently described a potent small molecule that selectively kills CRC cells with

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truncated *apc* protein termed truncated APC-selective inhibitor 1 (TASIN-1) using a 200 000 compound high-throughput screen (HTS) to identify small molecules with selective cytotoxic activity against an experimentally developed human colonic epithelial cell (HCEC) line with introduced oncogenes (KRAS, CDK4, TERT), coupled with loss of tumor suppressor function (p53) and expressing a mutant *apc* protein truncated at amino acid residue AA1309 (1CTRPA A1309).[22] TASIN-1 was not toxic against the isogenic HCEC cell line that expressed the wild-type *apc* protein (1CTRPA), and selectivity for *apc*-truncating mutations was retained in every human cell line (normal and cancer) that we tested. Based on serum and sterol rescue experiments, we postulated that TASIN-1 exerts its cytotoxic effects through inhibition of cholesterol biosynthesis at the level of emopamil-binding protein (EBP), the enzyme that isomerizes a Δ8,9 to a Δ7,8 double bond.[22] Furthermore, TASIN-1 inhibited the growth of human tumor xenografts in mice implanted with tumors derived from DLD-1 or HT29 (APC^{TR}), but not HCT116 (APC^{WT}) CRC cell lines.[22] Also, TASIN-1 treatment significantly reduced the number of polyps and tumor size in the colons of a genetically engineered mouse *apc* inactivation model of colonic adenoma-carcinoma progression (*CPC;APC* mice).[23] In addition, TASIN-treated mice (90 day treatment) gained weight and did not show any signs of overt toxicity (histopathology, liver function, kidney function, and blood cell counts all looked normal).[22] Given these promising initial results with TASIN-1, we further characterized the TASIN chemotype and present herein our results related to an extensive medicinal chemistry program that delineates the structure−activity relationships (SAR) within this scaffold. A number of very potent and selective analogues were identified, including compounds with good metabolic stability against murine microsomal fractions (S9) and pharmacokinetic (PK) properties. The small molecules reported herein thus represent a first-in-class genotype-selective series that specifically target *apc* mutations present in the vast majority of CRC patients and therefore serve as a translational platform toward a potential targeted therapy for colon cancer. Finally, although we speculate that TASINs target the cholesterol biosynthesis enzyme EBP, we have no direct evidence for this interaction. Therefore, the current SAR studies are also essential for the development of photoactivatable probe reagents for pull-down studies in an unbiased search for the molecular target of TASINs, efforts that are currently being pursued in our laboratory.

RESULTS AND DISCUSSION

SAR Design and Primary Assays. The starting point for the described SAR studies is the HTS hit-compound TASIN-1.[22] TASIN-1 (**6**) is typified by an arylsulfonamide attached to a 1,4′-bipiperidine (Figure 1). The objectives for the enclosed SAR studies encompassed optimization for potency, selectivity, and the absorption, distribution, metabolism, and excretion properties via exploration of the following structural characteristics: (i) functionalization and substitution patterns in the sulfonylated aromatic ring, or replacement with biaryl or heteroaryl groups; (ii) substitution patterns in the terminal piperidine ring; (iii) replacement of the terminal piperidine ring with other heterocycles, aromatic rings, or acyclic substituents; (iv) replacement of the central sulfonylated piperidine ring with other ring systems or an acyclic tether; and (v) replacement of the sulfonamide with an amide, a carbamate, an urea, a sulfone, or a sulfamamide. All new

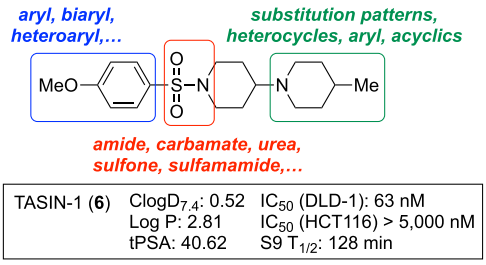

Figure 1. Structure, properties, and analogue design of TASIN-1 (**6**).

compounds were initially evaluated in a cell proliferation assay (CellTiter-Glo, Promega) using two human colorectal cancer cell lines, one with a truncating mutation in the APC gene (DLD-1) and one with wild-type APC status (HCT116). The assay was performed under low-serum conditions (HCEC medium supplemented with 0.2% fetal bovine serum) as described before.[22] A select set of compounds were additionally evaluated against another human CRC cell line with truncating mutations in the APC gene (HT29) and a pair of diploid isogenic HCEC-derived cell lines (CTRPA, APC^{WT}; CTRPA A1309, APC^{TR}).[22] Finally, the select compounds were evaluated for in vitro metabolic stability using mouse liver S9 fractions and in vivo PK properties.

Synthesis. The synthesis of analogues **5**−**91**, **101**, **103**, **104**, **113**, **115**, **116**, **124**, and **126**−**129** is shown in Scheme 1. Standard sulfonylation of substituted 1,4′-bipiperidines **1a**−**c**, 4-(pyrrolidin-1-yl)piperidine (**1d**), or 1-(piperidin-4-yl)-azepane (**1e**) with a variety of commercially available aryl- or heteroaryl-sulfonyl chlorides at room temperature (rt) provided analogues **5**−**9**, **11**−**24**, **26**−**51**, **57**−**60**, **71**−**91**, **101**, **103**, and **104**.[24] A subsequent hydrogenolysis of nitro-substituted analogues **7** and **24** over Pd/C at room temperature yielded aniline analogues **10** and **25**. The 2-, 3-, and 4-bromophenylsulfonamide analogues **17**, **29**, and **30**, respectively, offered viable starting materials for further diversification toward biaryl-substituted congeners **52**−**56** and **61**−**70** via Suzuki cross-coupling with commercially available arylboronic acids.[25] Variants in the bipiperidinyl moiety were prepared via reaction of the corresponding heterocyclic amines **1f**−**l** with 2,4,6-trimethylphenylsulfonyl chloride under the same standard sulfonylation conditions.[24]

Additional sulfonamide analogues not directly available from direct sulfonylation of commercially available amines were synthesized via procedures outlined in Scheme 2. First, reaction of piperidine-4-one (**2a**) or 4-aminocyclohexan-1-one (**2b**) with phenyl-, 4-bromophenyl-, or 2,4,6-trimethylphenylsulfonyl chloride provided intermediate sulfonamides **3a**−**c** and 2,4,6-trimethyl-*N*-(4-oxocyclohexyl)-benzenesulfonamide (not shown, derived from **2b**).[24] Subsequent reductive amination ($NaBH(OAc)_3$ or $NaCNBH_3$) of these materials with a variety of amines yielded analogues **97**−**100**, **102**, **106**−**111**, **114**, and **123**.[26] Analogue **105** was obtained after an additional condensation of the intermediate 4-((1-(mesitylsulfonyl)piperidin-4-yl)amino)butan-2-ol with paraformaldehyde. Analogue **117** was derived from acylation of intermediate *N*-benzyl-1-(mesitylsulfonyl)piperidin-4-amine, which upon subsequent hydrogenolysis yielded analogue **118**. Analogue **96** was made from hydroxyethyl-substituted analogue **100** (R = −4-$(CH_2)_2OH$) via a sequence of reactions including Swern oxidation, addition of (4-(trimethylsilyl)but-3-yn-1-yl)magnesium bromide, silyl-depro-

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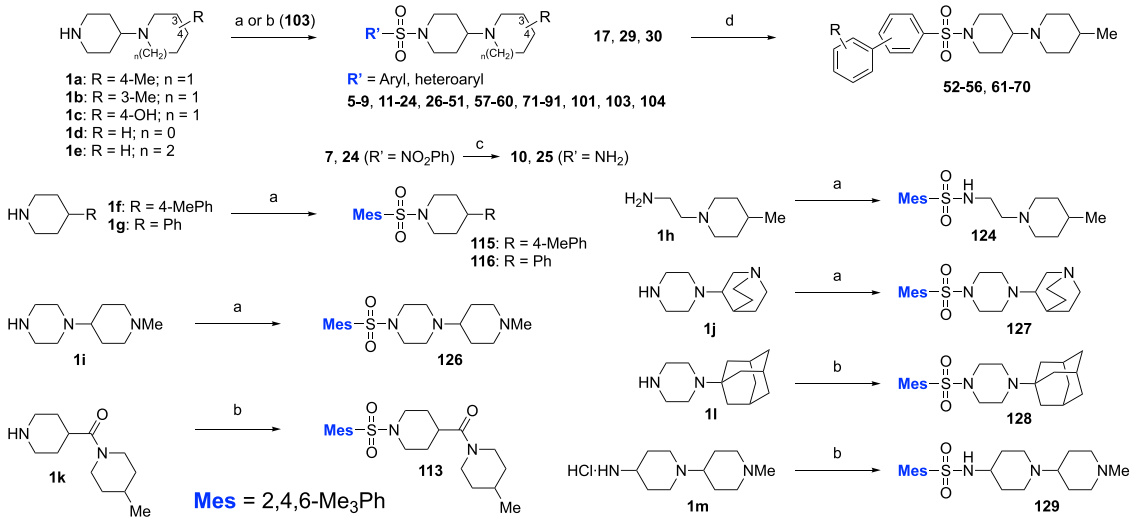
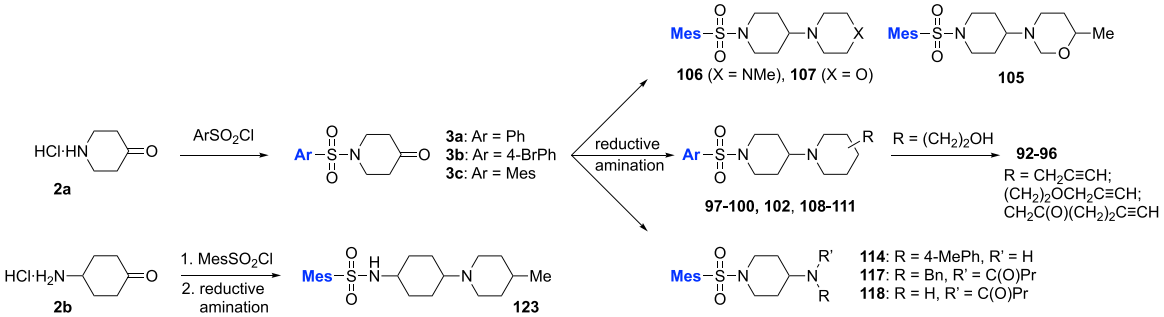
Scheme 1. Synthesis of Aromatic and Heteroaromatic Sulfonamide Analogues via Sulfonylation/Cross-Coupling[a]



[a]Reagents and conditions: (a) amine **1a–d**, **1f–j**, RSO_2Cl, $^iPr_2NEt$, CH_2Cl_2, rt; (b) amine **1e**, **1k–m**, RSO_2Cl, K_2CO_3, $CHCl_3/H_2O$ (1/1), rt; (c) Pd/C, H_2, MeOH, rt; and (d) $ArB(OH)_2$, $Pd(PPh_3)_4$ (10 mol %), aqueous (aq) Na_2CO_3 (2 M)/tetrahydrofuran (THF) (1/10), reflux. Mes, mesitylene, 2,4,6-Me_3Ph.

Scheme 2. Synthesis of Sulfonamide Analogues via Sulfonylation/Reductive Amination



tection, and oxidation to the ketone with Dess–Martin periodinane. Analogues **92–94** are derived after reductive amination of arylsulfonylpiperidinone **3a** or **3b** with 2- or 4-(hydroxyethyl)piperidine, followed by alkylation with propargyl bromide (→**94**, **95**). Alternatively, the same reductive amination products were oxidized to the aldehyde, followed by the Gilbert–Seyferth (→**92**) or the Corey–Fuchs alkynylation (→**93**).

The 1,3-dioxanyl-containg analogue **112** (1.56:1 mixture of cis/trans isomers) was synthesized from 4-hydroxymethylpiperidine **2c** via sulfonylation (→**4**), followed by the Swern oxidation and condensation with 2-methyl-1,3-propanediol (Scheme 3). The synthesis of analogue **125** relied on a copper-catalyzed Buchwald amination of 1-iodo-4-(2,4,6-trimethylphenylsulfonyl)benzene with 4-methylpiperidine.[27] We also explored analogues wherein the sulfonamide linker is replaced with various other functionality. As shown in Scheme 3, condensation of 4-methyl-1,4′-bipiperidine with 4-trifluoromethoxybenzoic acid provided amide analogue **119**, whereas reaction with 4-methoxyphenyl carbonochloridate or 4-methoxyphenylisocyanate yielded carbamate analogue **120** and urea analogue **121**, respectively. Finally, reaction of piperidinone **2b** with (4-methoxyphenyl)sulfamoyl chloride, followed by reductive amination with 4-methylpiperidine furnished analogue **122**.

SAR of Monocyclic Functionalized Arylsulfonamides. Our SAR studies initiated with an evaluation of the arylsulfonamide moiety. As shown in Table 1, compared to the parent 4-methoxyphenyl-substituted comparator TASIN-1 (**6**), replacement with an unsubstituted phenyl ring (→**5**) led to about a 5-fold reduction in antiproliferative activity. A survey of various para-substituents indicated that strongly electron-withdrawing (−NO_2, **7**; −CO_2Me, **8**; or −CN, **9**) or polar hydrophilic substituents (−NH_2, **10**) were not tolerated. Increasing the size of the 4-alkoxy substituent from methoxy (**6**) to a propoxy (**18**), butoxy (**19**), or benzyloxy (**20**) also led to a significant drop in activity. That steric hindrance in the para-position might be the culprit was in agreement with the observation that the 4-methyl-substituted analogue **11** yielded single-digit nanomolar activity (IC_{50} = 9.1 nM), whereas increasing the size of the 4-alkyl substituent (ethyl, **12**; isopropyl, **13**; or *t*-butyl, **14**) abrogated activity in the DLD-1 cell line. Replacement of the 4-methoxy group with fluorinated congeners (−OCF_3, **21**; −$OCHF_2$, **22**) or halides (−Cl, **16**; −Br, **17**) improved potency 4- to 28-fold, in agreement with smaller hydrophobic van der Waals-interacting substituents being preferred at this position. An exception was noted for the 4-trifluoromethylphenyl analogue **15**, which was 20-fold less active than the corresponding 4-methylphenyl analogue **11**. Although less extensively explored, single meta-substituents that improved activity versus the unsubstituted parent **5** were

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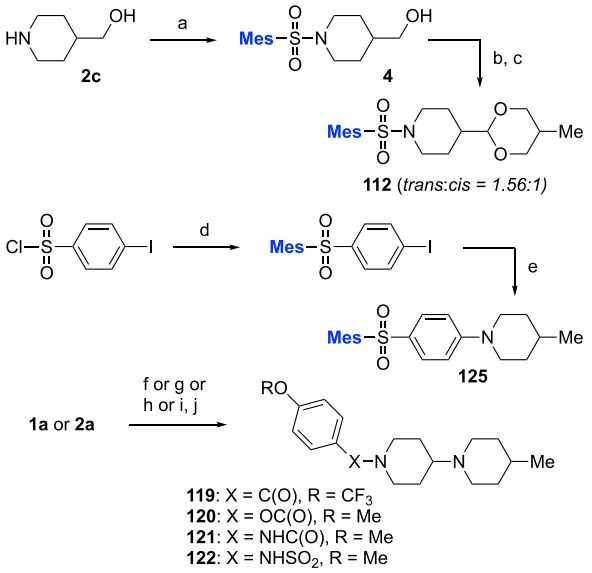
Scheme 3. Synthesis of Analogues 112, 125, and 119−122[a]



[a]Reagents and conditions: (a) amine **2c**, RSO_2Cl, $^iPr_2NEt$, CH_2Cl_2, rt; (b) $(COCl)_2$, dimethyl sulfoxide (DMSO), CH_2Cl_2; then −78 °C, Et_3N, −78 °C → rt; (c) $MeC(CH_2OH)_3$, cat. PPTS, $MgSO_4$, PhMe, reflux; (d) $AlCl_3$, CH_2Cl_2, rt; (e) 4-Me-piperidine, CuI, proline, K_2CO_3, DMSO, 90 °C; (f) **1a**, 4-CF_3OPhCO_2H, EDC·HCl, DMAP, CH_2Cl_2, rt; (g) **1a**, 4-MeOPhOC(O)Cl, K_2CO_3, Et_2O, 0 °C → rt; (h) **1a**, 4-MeOPhNCO, CH_2Cl_2, 0 °C → rt; (i) **2a**, 4-$MeOPhNHSO_2Cl$, Et_3N, Na_2SO_4, CH_2Cl_2, rt; (j) 4-Me-piperidine, $NaBH(OAc)_3$, AcOH, DCE, rt. DCE, 1,2-dichloroethane; DMAP, *N*,*N*-dimetylaminopyridine; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; Mes, 2,4,6-Me_3Ph; PPTS, pyridinium *para*-toluenesulfonic acid.

restricted to methyl (**26**, IC_{50} = 25 nM) and bromine (**29**, IC_{50} = 3.2 nM), whereas 3-methoxy, 3-nitro, 3-amino, 3-trifluoromethyl, and 3-chloro substitution (**23**−**25**, **27**, **28**) led to a virtual complete loss of antiproliferative activity. *Ortho*-bromo substitution (**30**) also provided high potency (IC_{50} = 3 nM). Trends for a series of disubstituted arylsulfonamides were less clear. Addition of a 2-methoxy substituent to the 4-methylphenyl analogue **11** (IC_{50} = 9.1 nM) yielded an inactive compound **34**, whereas 2-methoxy substitution did not diminish activity in combination with 3-bromo (**33** vs **29**) and dramatically increased potency of an otherwise inactive monosubstituted *meta*-methoxyphenyl analogue (**32**, IC_{50} = 4.5 nM vs **23**). The 2,4-dimethoxyphenyl analogue (**31**) lost about 2-fold in potency versus the 4-methoxyphenyl comparator (**6**). Interestingly, a 3-trifluoromethyl group enhanced significantly the activity of the otherwise inactive *para*-nitrophenyl analogue (**35**, IC_{50} = 56 nM vs **7**, IC_{50} = 981 nM), but diminished the activity of the *para*-chlorophenyl parent (**39**, IC_{50} = 17 nM vs **16**, IC_{50} = 2.2 nM). Additional introduction of an *ortho*-ethyl or -chloride substituent slightly enhanced activity (**38**, IC_{50} = 0.6 nM and **41**, IC_{50} = 1 nM vs **17**, IC_{50} = 3.1 nM and **16**, IC_{50} = 2.2 nM respectively), whereas a 2-trifluoromethoxy group had minimal effect (**45**, IC_{50} = 5 nM vs **17**, IC_{50} = 3.1 nM). When attaching an additional methyl, trifluoromethyl, or chlorine to the meta-position, the potency of the corresponding monosubstituted *para*-methyl, -trifluoromethyl, -chloro, or -bromo analogues was diminished 1.3- to 7.7-fold (**37**, IC_{50} = 24 nM; **39**, IC_{50} = 17 nM; **40**, IC_{50} = 2.9 nM; **43**, IC_{50} = 12 nM vs **11**, IC_{50} = 9.1 nM; **16**, IC_{50} = 2.2 nM; **17**, IC_{50} = 3.1 nM). The 2-cyano-5-methylphenyl analogue **36** was 11-fold less active than *ortho*-methylphenyl comparator **26**. The 3,5-dichlorophenyl analogue **42** displayed very weak activity, unlike other dihalo substitution patterns (**40**, **41**, **43**). Based on the moderate activity of compounds **44** and **50**, fluorine substitution did not appear beneficial.

Although not perfect and with some exceptions (e.g., **16**, **17**, **37**, **42**), the SAR patterns of substituted arylphenylsulfonamide analogues correlated best with a Hansch-type $\pi-\sigma$ parameter dependency,[28,29] in addition to steric restrictions at the 4-position. Specifically, potent analogues in this series are characterized by substitution with relatively apolar substituents with low electron-withdrawing ability (Br, Cl, alkyl, MeO, CF_3O, CHF_2O), particularly beneficial at the ortho- and para-positions, but restricted in size at the 4-position. Combining these features in a set of trisubstituted arylsulfonamides resulted in a series of very potent compounds (**46**−**49**, IC_{50} = 0.03−3.0 nM). Overall, 15 analogues displayed IC_{50} values below 5 nM against the DLD-1 colon cancer cell line, with two breaking the picomolar barrier (**47**, IC_{50} = 30 pM and **49**, IC_{50} = 600 pM). None of the compounds tested registered any activity in the corresponding colon cancer cell line with wild-type APC status (HCT116), attesting to their highly specific genotype-selective mode of action. Unfortunately, 11 were rapidly metabolized with half-lives between 5 and 30 min when subjected to murine S9 microsomal fractions, and another 3 with half-lives between 32 and 41 min. Only the 4-difluoromethoxyphenyl analogue **22** retained very potent cellular activity (IC_{50} = 4.8 nM) while exhibiting excellent microsomal stability ($T_{1/2}$ >240 min). The 3-chloro-4-bromophenyl analogue **43** was slightly less potent (IC_{50} = 12 nM) but also exhibited acceptable microsomal stability ($T_{1/2}$ = 43 min). Not surprisingly, given the bipiperidinyl moiety, the Clog $D_{7.4}$ value for all potent analogues was below 2.93 (range, 0.41−2.93; Clog *P* range, 3.21−4.91). Other parameters such as rotatable bonds, hydrogen bond donors and acceptors, total polar surface area (range, 40.62−59.08), and molecular weight (MW) (range, 336−485) are also within the range of druglike properties for orally available small molecules.

SAR of Biarylsulfonamides. Next, we decided to briefly explore *ortho*-, *meta*-, and *para*-aryl-substituted phenylsulfonamides (biaryl analogues, Table 2). In the ortho-series, only the unsubstituted biphenyl analogue **51** displayed potent selective cytotoxicity against the DLD-1 cell line with truncating APC mutations. *Ortho*-biphenyl analogues with additional substituents at the 4′-position (**52**−**55**) were >120-fold less active, indicating a potential size restriction along the 4′-vector. For *para*-biphenyls, the unsubstituted biphenyl analogue **56** and those with additional 4′-substitution (**57**, **58**) were significantly less potent than those with additional 2′-substituents (**59**, **60**). We had previously observed that bulkier substituents in the para-position of the arylsulfonamide were dendrimental to activity (Table 1, **12**−**14** and **18**−**20**). However, given the potent activity of **59** and **60**, both containing a large aryl group in the para-position, one might speculate that this size restriction is limited to three-dimensional substituents, and space is allowed for a flat properly oriented aryl ring. For the biaryl series of analogues, the meta-position appears to be the sweet spot for connecting the additional aromatic ring, and all *meta*-biaryl analogues **61**−**70** displayed potent activity with IC_{50}'s between 2 and 41 nM. The biaryl series of analogues also appeared to provide opportunities to improve metabolism. Indeed, with the exception of analogues **51**, **66**, and **67**, all

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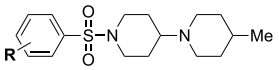
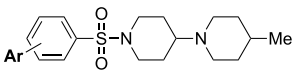
Table 1. SAR of Arylsulfonamide Analogues 5−50



cpd	R	DLD-1 IC_{50} (nM)[a]	S9 $T_{1/2}$ (min)[b]	Clog $D_{7.4}$[c]	cpd	R	DLD-1 IC_{50} (nM)[a]	S9 $T_{1/2}$ (min)[b]	Clog $D_{7.4}$[c]
5	H	294 ± 7.6	NA	0.69	**28**	3-Cl	>5000	NA	1.31
6	4-MeO	63 ± 5.6	182	0.52	**29**	3-Br	3.2 ± 0.06	13	1.47
7	4-NO_2	981 ± 22.6	NA	0.66	**30**	2-Br	3 ± 0.25	6	1.48
8	4-MeO_2C	>5000	NA	0.72	**31**	3,4-$(OMe)_2$	138 ± 12	NA	0.37
9	4-CN	2800	NA	2.28	**32**	2,5-$(OMe)_2$	4.5 ± 0.2	9.4	0.41
10	4-NH_2	>5000	NA	−0.17	**33**	2-MeO, 5-Br	2 ± 0.006	9	1.33
11	4-Me	9.1 ± 0.6	19	1.2	**34**	2-MeO, 4-Me	>5000	NA	1.06
12	4-Et	>5000	NA	1.64	**35**	3-CF_3, 4-NO_2	56 ± 1.6	NA	1.55
13	4-^{i}Pr	685 ± 24	NA	1.93	**36**	2-CN, 5-Me	285 ± 3.9	NA	1.09
14	4-^{t}Bu	>5000	NA	2.23	**37**	3,4-Me_2	24 ± 1.2	NA	1.71
15	4-CF_3	185 ± 8.7	NA	1.57	**38**	2-Et, 4-Br	0.6 ± 0.02	9.1	2.47
16	4-Cl	2.2 ± 0.04	41	1.3	**39**	3-CF_3, 4-Cl	17 ± 1.2	32	2.18
17	4-Br	3.1 ± 0.08	32	1.46	**40**	3,4-Cl_2	2.9 ± 0.34	33	1.91
18	4-PrO	452 ± 2.6	NA	1.4	**41**	2,4-Cl_2	1 ± 0.002	15	1.93
19	4-BuO	2300	NA	1.85	**42**	3,5-Cl_2	3400	NA	1.92
20	4-BnO	385 ± 9.4	NA	2.25	**43**	3-Cl, 4-Br	12 ± 0.5	43	2.08
21	4-CF_3O	16 ± 0.7	NA	2.12	**44**	2,4-F_2	102 ± 3.5	NA	1.02
22	4-CHF_2O	4.8 ± 0.5	>240	1.46	**45**	2-CF_3O, 4-Br	5 ± 0.07	5	2.93
23	3-MeO	>5000	NA	0.54	**46**	2-Me, 4-MeO, 5-^{i}Pr	3 ± 0.23	8	2.27
24	3-NO_2	>5000	NA	0.67	**47**	2,4,6-Me_3	0.03 ± 0.0001	5	2.2
25	3-NH_2	3400	NA	−0.14	**48**	2,4-Cl_2, 5-Me	2 ± 0.05	6.5	2.44
26	3-Me	25 ± 2.1	NA	1.2	**49**	2,4-Cl_2, 6-Me	0.6 ± 0.01	7.2	2.43
27	3-CF_3	>5000	NA	1.58	**50**	3,5-F_2, 4-Br	107 ± 5.3	NA	1.78

[a]IC_{50} values represent the half-maximal (50%) inhibitory concentration as determined in the CellTiter-Glo (Promega) assay. Error represents standard deviation (SD) (n = 3). All compounds were inactive when counterscreened against the HCT116 cell line (IC_{50} > 5 μM). [b]$T_{1/2}$ values represent the half life for compound phase I metabolic stability using female ICR/CD-1 mouse liver S9 fractions. NA = not assayed. [c]Calculated using MarvinSketch (version 6.3.0).

Table 2. SAR of Biaryl Sulfonamide Analogues 51−70



cpd	Ar	DLD-1 IC_{50} (nM)[a]	S9 $T_{1/2}$ (min)[b]	Clog $D_{7.4}$[c]
51	2-Ph	0.96 ± 0.002	<6	2.35
52	2-(4′-ClPh)	202 ± 7.6	NA	2.95
53	2-(4′-MeOPh)	1000	NA	2.19
54	2-(4′-MePh)	366 ± 9.6	NA	2.86
55	2-(4′-CF_3Ph)	122 ± 8.6	NA	3.22
56	4-Ph	258 ± 14	NA	2.34
57	4-(4′-ClPh)	105 ± 7.6	NA	2.94
58	4-(4′-MeOPh)	263 ± 25	NA	2.18
59	4-(2′-MeOPh)	26 ± 0.5	289	2.19
60	4-(2′-FPh)	5 ± 0.06	210	2.49
61	3-Ph	2 ± 0.3	31	2.34
62	3-(4′-ClPh)	15 ± 2.1	147	2.95
63	3-(4′MeOPh)	23 ± 0.9	144	2.19
64	3-(4′-MePh)	11 ± 1.0	115	2.86
65	3-(4′-FPh)	12 ± 0.6	77	2.49
66	3-(2′-MeOPh)	21 ± 0.2	15	2.19
67	3-(2′-FPh)	10 ± 0.9	17	2.49
68	3-(2′-CF_3Ph)	10 ± 0.03	37	3.22
69	3-(3′,5′-Me_2Ph)	41 ± 1.1	>240	3.37
70	3-(2′-naphthyl)	2 ± 0.0001	204	3.33

[a]IC_{50} values represent the half-maximal (50%) inhibitory concentration as determined in the CellTiter-Glo (Promega) assay. Error represents SD (n = 3). All compounds were inactive when counterscreened against the HCT116 cell line (IC_{50} > 5 μM). [b]$T_{1/2}$ values represent the half-life for compound phase I metabolic stability using female ICR/CD-1 mouse liver S9 fractions. NA = not assayed. [c]Calculated using MarvinSketch (version 6.3.0).

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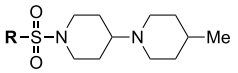
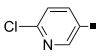
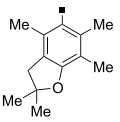
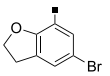
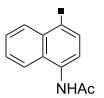
Table 3. SAR of Heterocyclic and Fused Bicyclic Sulfonamide Analogues 71−90



Cpd	R	DLD-1 IC_{50} (nM)[a]	S9 $T_{1/2}$ (min)[b]	$ClogD_{7.4}$[c]	Cpd	R	DLD-1 IC_{50} (nM)[a]	S9 $T_{1/2}$ (min)[b]	$ClogD_{7.4}$[c]
71		2,400	NA	−0.49	**81**		1.6 ± 0.03	10	0.63
72		>5,000	NA	0.35	**82**		>5,000	NA	1.42
73		>5,000	NA	0.08	**83**		853 ± 43	NA	0.35
74		3,700	NA	0.33	**84**		62 ± 4.3	NA	0.32
75		>5,000	NA	0.28	**85**		1.2 ± 0.03	67	2.78
76		>5,000	NA	−1.71	**86**		96 ± 7.3	5	1.37
77		>5,000	NA	−0.5	**87**		0.65 ± 0.002	<5	1.69
78		>5,000	NA	−0.55	**88**		0.1 ± 0.02	14	2.3
79		>5,000	NA	−0.53	**89**		1,100	NA	0.93
80		1,800	NA	0.53	**90**		225 ± 13	NA	0.47

[a]IC_{50} values represent the half-maximal (50%) inhibitory concentration as determined in the CellTiter-Glo (Promega) assay. Error represents SD (n = 3). All compounds were inactive when counterscreened against the HCT116 cell line (IC_{50} > 10 μM). [b]$T_{1/2}$ values represent the half-life for compound phase I metabolic stability using female ICR/CD-1 mouse liver S9 fractions. NA = not assayed (compounds **71−80** were also not assayed for microsomal stability). [c]Calculated using MarvinSketch (version 6.3.0).

other potent biaryl analogues had acceptable half-lives between 31 and 289 min in the in vitro murine S9 microsomal stability assay. Despite these initial promising results within the biaryl series, we decided not to further pursue them in light of the significant price to be paid in terms of increased molecular weight and lipophilicity (Clog $D_{7.4}$ range, 2.19−3.37; Clog P range, 4.8−5.7; ClipE range, 3.58−6.67).

SAR of Heterocyclic and Fused Bicyclic Sulfonamides. In our search for heterocyclic and fused bicyclic replacements for the arylsulfonamide ring, it became quickly apparent that the more desirable (druglike properties) heterocyclic ring systems such as pyridines, imidazoles, thiazoles, and isoxazoles were not a fruitful avenue of pursuit (see Table 3). With the exception of thiazole **81**, all such heterocyclic replacements led to inactive compounds (**71−80**, **82**). Interestingly, although the methyl-substituted chlorothiazole **81** was very potent (IC_{50} = 1.6 nM), removing the methyl substituent (**80**), or replacement with an isopropyl substituent (**82**) largely abolished activity of these chlorothiazoles. Despite the potency and excellent Clog $D_{7.4}$ of 0.63 (ClipE 8.17), the chlorothiazole analogue **81** was rapidly metabolized in murine S9 microsomal fractions ($T_{1/2}$ = 10 min). On the other hand, activity results for the relatively apolar fused benzodioxoles and dihydrobenzofurans were more in alignment with the results displayed in Table 1. Although benzodioxole **83** displayed mediocre activity (IC_{50} = 853 nM), the corresponding isomeric benzodioxole **84** exhibited a 14-fold improvement (IC_{50} = 62 nM). Bromodihydrobenzopyran **86** was of intermediate potency (IC_{50} = 96 nM), while introduction of additional methyl groups led to the very potent and metabolically stable analogue **85** (IC_{50} = 1.2 nM; $T_{1/2}$ (S9) = 67 min) but increased lipophilicity (Clog $D_{7.4}$ = 2.78; Clog P = 5.4; ClipE = 6.14). Finally, lipophilic naphtyl analogues **87** and **88** were very potent (0.1−0.65 nM; ClipE 7.50−7.70) but metabolically labile ($T_{1/2}$ < 5−14 min), while the more polar acetamidonaphtyl and isoquinoline analogues **89** and **90** largely lost activity.

SAR of the Terminal Piperidine Ring. With a rather extensive survey of the arylsulfonamide moiety completed, the

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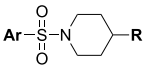
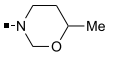
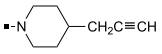
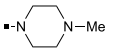
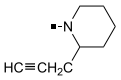
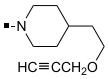
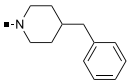
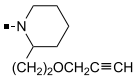
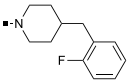
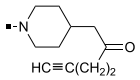
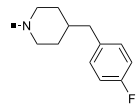
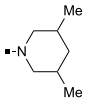
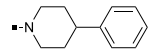
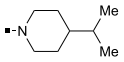
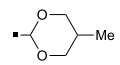
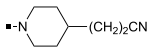
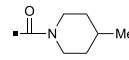
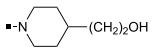
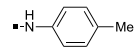
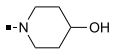
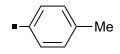
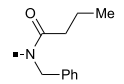
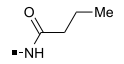
Table 4. SAR of Terminal Piperidine Ring Analogues 91−118



Cpd	R	Ar	DLD-1 IC_{50} (nM)[a]	$ClogD_{7.4}$[c]	Cpd	R	Ar	DLD-1 IC_{50} (nM)[a]	$ClogD_{7.4}$[c]
91		4-CFH_2OPh	105 ± 21	1.41	**105**		Mes	92 ± 1.23	2.94
92		4-BrPh	0.2 ±0.03	1.55	**106**		Mes	1,100	1.57
93		Ph	>5,000	1.05	**107**		Mes	3,100	2.32
94		Ph	85 ± 6.8	0.67	**108**		Mes	3.5 ± 0.03	3.76
95		Ph	>5,000	0.44	**109**		Mes	74 ± 4.5	4.04
96		Mes	3 ± 0.04	3.21	**110**		Mes	18 ± 0.7	3.93
97		Mes	17 ± 0.9	2.22	**111**		Mes	865 ± 89	3.44
98		Mes	0.3 ± 0.002	2.83	**112**		Mes	>5,000	3.52
99		Mes	>5,000	1.97	**113**		Mes	>5,000	3.42
100		Mes	19 ± 0.8	1.31	**114**		Mes	2,900	4.36
101		Mes	106 ± 7.9	1.01	**115**		Mes	2,200	5.35
102		Mes	2,200	2.1	**116**		Mes	>5,000	4.85
103		Mes	5.3±2.0[b]	2.09	**117**		Mes	>5,000	4.69
104		4-MeOPh	3,203	-0.15	**118**		Mes	>5,000	2.74

[a]IC_{50} values represent the half-maximal (50%) inhibitory concentration as determined in the CellTiter-Glo (Promega) assay. Error represents SD (n = 3). [b]Error represents SD (n = 2). All compounds were inactive when counterscreened against the HCT116 cell line (IC_{50} > 5 μM). [c]Calculated using MarvinSketch (version 6.3.0).

next phase entailed evaluation of the terminal piperidine ring. As shown in Table 4, moving the terminal methyl group from the 4- to the 3-position as in analogue **91** reduced activity ∼20-fold versus the comparator **22** (105 vs 4.8 nM). Replacement of the 4-methyl with a propargyl (**92**) or propargyloxyethyl (**94**) increased activity significantly versus comparators **17** and **5** (0.2 and 85 nM vs 3.1 and 294 nM). Moving those two substituents to the 2-position as in analogues **93** and **95** on the other hand was not tolerated. Other groups that were tolerated in the 4-position in decreasing order of potency are isopropyl (**98**, 0.3 nM), benzyl (**108**, 3.5 nM), 2-oxohex-5-yn-1-yl (**96**, 3 nM), (4-fluorophenyl)methyl (**110**, 18 nM), 2-hydroxyethyl (**100**, 19 nM), (2-fluorophenyl)methyl (**109**, 74 nM), and hydroxy (**101**, 106 nM). A phenyl (**111**) or 2-cyanoethyl (**99**) in that position greatly diminished activity (865−7400 nM). The unsubstituted piperidine **102** lost almost all activity, whereas the 3,5-Me_2-substituted analogue **97** was active at 17 nM. When other nitrogen-containing ring systems were evaluated, it was revealed that pyrrolidine **104**, morpholine **107**, and piperazine **106** all lost activity, whereas 1,3-oxazinane **105** was of intermediate potency (IC_{50} = 92 nM). Only azepane **103** retained single-digit nanomolar potency. Removing the ring-nitrogen altogether, such as in 1,3-dioxane analogue **112** and phenyl or tolyl analogues **115** and **116**, led to a complete loss of activity. Introducing a carbonyl between the two piperidine ring systems (**113**) or replacing the terminal piperidine ring with acyclic substituents such as aniline **114**, or amides **117** and **118** were also unproductive. To conclude this section, the above results indicate that a basic nitrogen within a six- to seven-membered ring (piperidine or azepine) is crucial for retaining cellular activity. A number of substituents, mostly hydrophobic in nature that can include

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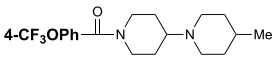
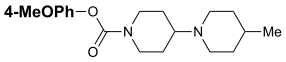
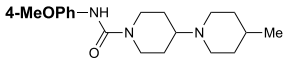
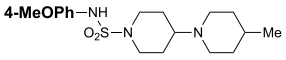
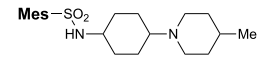
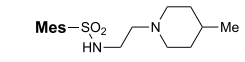
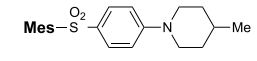
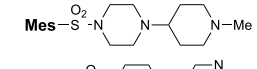
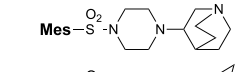
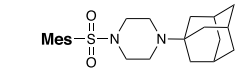
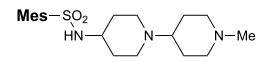
aliphatic, hydroxylated alkyl, propargylic, ether, ketone, or benzylic substitution are well tolerated. Introduction of an additional polar nitrogen or oxygen in the terminal azacycle is contraindicated for bioactivity. Of the single-digit nanomolar compounds, azepane **103** had the lowest Clog $D_{7.4}$ (2.09) and an acceptable ClipE of 6.19. Other analogues within this series with similar ClipE values are **94**, **98**, and **100** (ClipE 6.40–6.69). The alkyne-containing analogue **92** displayed the best lipophilic efficiency (ClipE 8.15) within this series and is only matched by analogues **47** and **81** (see Table 6).

Miscellaneous SAR. The final structural attributes to be explored are the role of the sulfonamide functionality and the central piperidine ring. As shown in Table 5, replacement of the sulfonamide linker with an amide (**119**, IC_{50} = 426 nM), urea (**121**, IC_{50} = 1360 nM), or sulfamamide linker (**122**, IC_{50} = 814 nM) led to a significant 13- to 90-fold reduction in activity compared to their sulfonamide congeners **22** and **6** (IC_{50} = 4.8 and 63 nM). The carbamate replacement **120** fared better with a more marginal 4-fold drop versus sulfonamide **6**—a modification that further lowered the Clog $D_{7.4}$ to 0.5. Substitution of the central piperidine ring with an amino-cyclohexyl (**123**), aminoethyl (**124**), or phenyl linker (**125**) led to a substantial or complete loss of activity. Finally, replacement of the bipiperidine with an amino-bipiperidine (**129**), *N*-(*N*-methylpiperidin-4-yl)piperazine (**126**), or adamantanylpiperazine (**128**) led to compounds with mediocre potency. Of interest for future analogue design, a quinuclidine analogue **127** with altered position of the tertiary nitrogen retained significant activity (IC_{50} = 83 nM), was metabolically stable (S9 $T_{1/2}$ = 193 min), and decreased Clog $D_{7.4}$ significantly to 0.87.

Table 5. Miscellaneous SAR

	Compound	DLD-1 IC_{50} (nM)[a]	Clog$D_{7.4}$[b]
119		426 ± 24.5	1.54
120		256 ± 10	0.5
121		1,360	0.03
122		814 ± 21	−0.27
123		380 ± 3.5	2.45
124		1,900	3.06
125		>5,000	5.71
126		426 ± 42	0.75
127		84 ± 7.6	0.87
128		231 ± 4.4	3.8
129		958	0.43

[a]IC_{50} values represent the half-maximal (50%) inhibitory concentration as determined in the CellTiter-Glo (Promega) assay. Error represents SD (n = 3). All compounds were inactive when counterscreened against the HCT116 cell line (IC_{50} > 5 μM). [b]Calculated using MarvinSketch (version 6.3.0).

Activity in Other Cell Lines. As disclosed previously, TASIN-1 (**6**) was identified as a selective cytotoxin that specifically kills colon cancer cell lines with truncating mutations in the APC tumor suppressor gene. Above we described an extensive medicinal chemistry effort to identify analogues of TASIN-1 with improved potency and physicochemical properties. To ensure that these analogues remained on target, we have additionally counterscreened them for activity against the HCT-116 cell line with wild-type APC. In Table 6, we represent additional cytotoxicity data for a selection of 23 analogues that displayed single-digit nanomolar activity against the DLD-1 cell line. All 23 analogues were found to be equally effective against another human colon cancer cell line with truncating APC mutations (HT29). Given the heterogeneous genetic background between all of these cultured human colon cancer cell lines (DLD-1, HT29, HCT116), we further evaluated these analogues against an isogenic cell line pair derived from primary human colonic epithelial (HCEC) cells. As disclosed previously,[30] introduction of cyclin-dependent kinase 4 (CDK4), telomerase (T), into primary HCEC cells was sufficient to produce an immortalized, nontransformed diploid cell line (CT) with multipotent stemlike characteristics that can differentiate in three-dimensional culture conditions. Additional introduction

Table 6. Antiproliferative Activity of Selected Analogues in Cell Lines with Truncated APC

	IC_{50} ± (nM)[a]			
cpd	DLD-1	HT-29	CTRPA A1309[b]	CLipE
6	63 ± 5.6	53 ± 2.3	122 ± 6.5	6.68
22	4.8 ± 0.5	2 ± 0.1	3.8 ± 0.7	6.86
29	3.2 ± 0.06	1.2 ± 0.07	6.9 ± 0.8	7.02
30	3 ± 0.25	3 ± 0.05	2.8 ± 0.03	7.04
32	4.5 ± 0.2	4 ± 0.1	10.5 ± 0.3	7.94
33	2 ± 0.006	2 ± 0.004	0.7 ± 0.02	7.37
38	0.6 ± 0.02	0.5 ± 0.1	0.8 ± 0.03	6.75
40	2.9 ± 0.34	2.2 ± 0.06	8.2 ± 0.63	6.63
45	5 ± 0.07	4 ± 0.02	9.6 ± 0.3	5.37
46	3 ± 0.23	2.2 ± 0.3	3.4 ± 0.7	6.25
47	0.03 ± 0.0001	0.9 ± 0.08	0.04 ± 0.002	8.32
48	2 ± 0.05	1.1 ± 0.04	3.2 ± 0.4	6.26
49	0.6 ± 0.01	0.45 ± 0.01	0.7 ± 0.05	6.79
51	0.96 ± 0.002	0.74 ± 0.03	1.2 ± 0.06	6.67
60	5 ± 0.06	6 ± 0.07	10.2 ± 0.8	5.81
61	2 ± 0.3	2 ± 0.07	1.6 ± 0.3	6.36
81	1.6 ± 0.03	1.5 ± 0.03	3.4 ± 0.3	8.17
85	1.2 ± 0.03	0.8 ± 0.03	1.5 ± 0.08	6.14
87	0.65 ± 0.002	0.34 ± 0.02	0.94 ± 0.01	7.50
92	0.2 ± 0.03	0.12 ± 0.05	0.9 ± 0.07	8.15
96	3 ± 0.04	2.1 ± 0.07	3.4 ± 0.8	5.31
98	0.3 ± 0.002	0.2 ± 0.001	0.6 ± 0.003	6.69
108	3.5 ± 0.03	3 ± 0.2	4.3 ± 0.1	4.70

[a]IC_{50} values represent the half-maximal (50%) inhibitory concentration as determined in the CellTiter-Glo (Promega) assay. Error represents SD (n = 3). All compounds were inactive when counterscreened against the HCT116 cell line with wild-type APC status (IC_{50} > 5 μM). [b]All compounds were inactive when counterscreened against the isogenic CTRPA cell line with wild-type APC status (IC_{50} > 5 μM).

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Table 7. Pharmacokinetics of Compounds 6, 16, 22, and 92 in Mouse[a]

			plasma PK						large intestinal PK			
cpd	route	dose (mg/kg)	$T_{1/2}$ (min)	C_{max} (ng/mL)	T_{max} (min)	AUC_{last} (ng min/mL)	Vz (mL)	CL (mL/min)	$T_{1/2}$ (min)	C_{max} (ng/g)	T_{max} (min)	AUC_{last} (ng min/g)
6	i.p.	10	48	2390	10	104 103	162	2.32	570	10 678	10	737 709
22	i.v.	5	162	742	10	197 571	135	0.58	912	1816	10	511 878
22	i.p.	10	168	1117	10	205 914	156	0.64	903	10 146	10	790 425
22	p.o.	20	182	691	10	328 296	153	0.58	506	3252	10	890 969
16	i.v.	10	81	191	30	21 581	1243	10.6	13 861	1414	10	262 874
92	i.v.	10	135	303	10	39 146	1152	5.92	504	2974	10	559 037
92	i.p.	10	171	145	10	27 904	1390	5.64	678	5754	10	633 289

[a]Elimination half-life ($T_{1/2}$), maximum observed concentration (C_{max}), time to C_{max} (T_{max}), apparent volume of distribution during terminal phase (Vz), area under the concentration−time curve from time zero to the last measured concentration (AUC_{last}), clearance (CL), intravenous (i.v.), intraperitoneal (i.p.), per os (p.o.).

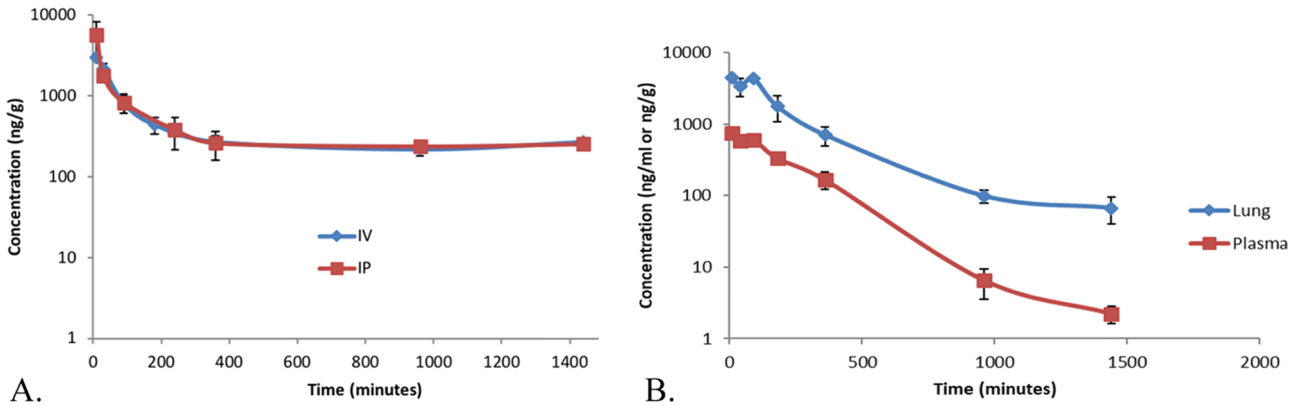

Figure 2. (A) Concentration−time curve in the large intestine for analogue **92** when dosed 10 mg/kg i.v. or i.p. (B) Concentration−time curve in the plasma and lung for analogue **22** when dosed 5 mg/kg i.v.

of oncogenic $KRAS^{V12}$, mutant TP53 (key-alterations in CRC), and knockdown of APC established the **CTRPA** cell line.[22] Additional ectopic expression of mutant APC truncated at amino acid 1309 led to the isogenic APC^{mut} cell line (CTRPA A1309).[22] As can be seen from data in Table 6, all compounds retained exquisite selectivity for cells with truncating APC mutations with low nanomolar IC_{50}'s in CTRPA A1309 and no apparent effect on the isogenic cell line CTRPA (IC_{50} > 5 μM).

PK Properties of Select Compounds. As a prelude for future in vivo efficacy studies in xenografts and genetic models of CRC,[22] we selected compounds **16**, **22**, and **92** for in vivo pharmacokinetic (PK) analysis because of their cellular potency (IC_{50} < 5 nM) and low microsomal clearance (murine S9 $T_{1/2}$, 41−240 min; CL_{int}, 2.9−16.9 μL/(min mg protein)). As can be seen from the data compiled in Table 7, the PK characteristics of analogues **16**, **22**, and **92** mirrored those of the previously characterized TASIN-1 (**6**).[22] When dosed intravenously (i.v.), analogues **16** (5 mg/kg), **22** (10 mg/kg), and **92** (10 mg/kg) had low to moderate plasma clearance between 0.58 and 10.6 mL/min, a half-life between 1.35 and 2.8 h, and a C_{max} between 191 and 742 ng/mL 10−30 min after dosing. Plasma exposure for analogues **16** and **92**, while good, was significantly lower than for analogue **22** and TASIN-1 (**6**). Intraperitoneal (i.p.) dosing led to similar plasma clearance, C_{max}, terminal half-life, and exposure as for the i.v. route. The % plasma protein binding was determined using ultrafiltration (**22**, 69% bound) or rapid equilibrium dialysis (RED) (**92**, 83% bound; **6**, 8% bound). We selected compound **22** for oral bioavailablity, which was determined to be excellent (52%, 20 mg/kg) and leading to higher plasma and intestinal exposures than when dosed i.v. at 5 mg/kg. Future efficacy studies will include evaluation of select compounds in a genetically engineered mouse *apc* inactivation model of colonic adenoma-carcinoma progression (*CPC;APC* mice).[22] Therefore, we assessed the PK of these compounds in the large intestine, the intended target organ. Gratifyingly, large intestinal exposure was excellent, irrespective of the delivery method and between 2.6- and 23-fold higher than the plasma exposure. The T_{max} was achieved 10 min after dosing with a terminal half-life between 8 and 15 h except analogue **16** with an extraordinarily long half-life of 231 h. Examination of the concentration−time curves indicated that elimination reached a plateau phase after an initial seemingly normally decaying half-life (e.g. Figure 2A). This behavior results in the apparent high AUC numbers for this class of compounds. The observed accumulation in the large intestine is likely not limited to this organ. For example, a PK analysis of analogue **22** indicated similar levels of accumulation in the lung (5.7-fold higher than plasma) and probably other highly perfused organs (Figure 2B). As a result, the volume of distribution for analogues **22**, **16**, and **92** was large, ranging from 5.87 to 63 L/kg. This phenomenon is not unexpected as many lipohilic amine drugs are known to be deposited in highly perfused, lysosome-rich organs via lysosomal trapping.[31,32] Together with their ability to bind phospholipids, this lysosomal trapping contributes to presystemic extraction and the large volume of distribution of many cationic amphiphilic drugs, including imipramine, tamoxifen, propranolol, and others.[32,33] Although we have not yet experimentally assessed lysosomal trapping for

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the analogues described herein, a future evaluation is warranted as lysosomal accumulation has, in some instances, been implicated as a cause for phospholipidosis.[34] These studies will include a comprehensive histological evaluation of tissues after repeat dosing experiments as part of a full toxicological evaluation of potential lead compounds.

CONCLUSIONS

There are currently no small molecule therapeutics that target specifically oncogenotypes that drive the development and progression of colorectal cancers. Germline truncating mutations in the APC tumor suppressor gene lead to familial adenomatous polyposis (FAP) and early development of CRC, whereas somatic truncating APC mutations are observed in the vast majority of sporadic CRC patients. We previously disclosed the discovery of TASIN-1, a small molecule that selectively targets human colorectal cancer cell lines expressing mutant-APC with high specificity through inhibition of endogenous cholesterol biosynthesis.[22] Here, we reported an extensive structure−activity relationship study through the design of analogues of TASIN-1 exploring the structural determinants responsible for cellular activity and selectivity. This study identified several very potent analogues with good druglike properties that inhibit CRC cells with mutant APC in the single-digit nanomolar to picomolar range, while being innocuous for cells with wild-type APC. Several of these potent analogues exhibited acceptable metabolically stability in murine microsomal fractions, and excellent in vivo exposure whether dosed i.v., i.p., or orally. The high intestinal exposure and half-life of this class bodes well for future efficacy studies in genetic or orthotopic animal models of CRC. However, we note that this significant intestinal accumulation and long half-life could indicate a potential lysosomal trapping of these lipophilic amines, an issue that will be explored in future studies. Lipophilic basic amine drugs are also potentially liable for off-target activity against potassium and sodium channels. Given that our SAR studies indicate that a protonatable amine is absolutely essential for activity, we will have to evaluate our compound collection against these and other potential off-target interactions. In this context, future studies will focus on analogues that perturb the pK_a to the 7.5−8.5 range, which is known to limit potassium and sodium channel activity and also may limit the effect of lysosomal accumulation. The SAR studies described herein have not attempted to address these specific issues yet, but indicate that the TASINs represent an excellent scaffold for such SAR-driven optimization, and we are therefore confident that ongoing studies will enable the identification of novel translatable leads for a potential targeted therapy for colorectal cancer.

EXPERIMENTAL SECTION

Cytotoxicity Assay. Activity of each analogue was evaluated as described before.[22] Briefly, DLD-1, HT29, HCT116, CTRPA, or CTRPA A1309 cells were seeded in a 96-well plate in triplicate at a density of 3000 cells/well in HCEC medium supplemented with 0.2% fetal bovine serum and treated with compound at nine-point 3-fold dilution series for 72 h. Cell viability was determined using the CellTiter-Glo (Promega) assay according to manufacturer's instruction. Each value was normalized to cells treated with DMSO, and the IC_{50} values were calculated using GraphPad Prism software.

In Vitro Liver S9 Stability. Female ICR/CD-1 mouse S9 fractions were purchased from Bioreclamation/IVT (Chestertown, MD). S9 protein (0.025 mL, 0.5 mg) was added on ice to a 15 mL glass screw cap tube followed by 0.350 mL of a 50 mM Tris, pH 7.5 solution, containing the compound of interest. The tube was then placed in a 37 °C shaking water bath for 5 min and 0.125 mL of an reduced nicotinamide adenine dinucleotide phosphate (NADPH)-regenerating system (1.7 mg/mL NADP, 7.8 mg/mL glucose 6-phosphate, 6 U/mL glucose 6-phosphate dehydrogenase in 2% w/v $NaHCO_3$/10 mm $MgCl_2$) was added for analysis of phase I metabolism. After addition of all reagents, the final concentration of compound was 2 μM, and S9 protein 1 mg/mL. At varying time points after addition of phase I cofactors, the reaction was stopped by the addition of 0.5 mL of methanol containing 0.2% formic acid and either tolbutamide or *n*-benzylbenzamide as internal standard. Time 0 samples were stopped prior to placing the samples at 37 °C, and the NADPH-regenerating system was added immediately thereafter. The samples were incubated for 10 min at rt and then spun at 16 100*g* for 5 min in a microcentrifuge. The supernatant was analyzed by liquid chromatography (LC)−tandem mass spectrometry (MS/MS) using a Sciex 3200 or 4000 Qtrap mass spectrometer coupled to a Shimadzu Prominence LC with the mass spectrometer in multiple reaction monitoring (MRM) mode. The method described by McNaney et al.[35] was used with modification for the determination of metabolic stability half-life by substrate depletion. A "% remaining" value was used to assess metabolic stability of a compound over time. The LC−MS/MS peak area of the incubated sample at each time point was divided by the LC−MS/MS peak area of the time 0 (T_0) sample and multiplied by 100. The natural logarithm (ln) of the % remaining of compound was then plotted versus time (in min), and a linear regression curve plotted going through *y*-intercept at ln(100). The metabolism of some compounds failed to show linear kinetics at a later time point, so those time points were excluded. The half-life ($T_{1/2}$) was calculated as $T_{1/2}$ = 0.693/slope. Compound stability was also evaluated at 0 and 240 min in reaction buffer only minus S9 protein to determine chemical stability.

Protein Binding. Protein binding was determined using either ultrafiltration (**22**) or rapid equilibrium dialysis (RED; **92**), as described in Wang et al.[36] Binding in plasma was evaluated using undiluted plasma and plasma diluted with one part plasma and three parts phosphate-buffered saline (PBS), while binding in large intestine was evaluated using large intestinal tissue homogenates prepared using a 3-fold volume of PBS. Values were corrected for dilution as described[37] by the following equation

$$\text{undiluted fu} = \frac{1/D}{((1/\text{fu}_2) - 1) + 1/D}$$

where D = dilution factor of 4 and fu_2 = free fraction using diluted matrix

Mouse PK Analysis. Animal work for the pharmacokinetic studies described in this manuscript has been approved and conducted under the oversight of the UT Southwestern Institutional Animal Care and Use Committee. UT Southwestern uses the "Guide for the Care and Use of Laboratory Animals" when establishing animal research standards. Seven PK experiments are reported in the manuscript. Each PK experiment utilized 24 female CD1 mice at 5−6 weeks of age (obtained from Charles River), which were euthanized in groups of three at eight time points for collection of blood and tissues. Thus, a total of 168 mice were used. The animals were housed in standard microisolator cages and were administered inhibitor compounds in 0.2 mL by i.p. (10 mg/kg) or i.v. (5 or 10 mg/kg) injection or oral gavage (20 mg/kg) formulated as follows: **16** and **92**: 10% DMSO/10% poly(ethylene glycol) (PEG)-400/80% 50 mM citrate buffer, pH 5.4; **22**: 10% ethanol/10% PEG-400/80% 50 mM citrate buffer, pH 4.4. The animals were euthanized by inhalation overdose of CO_2 in groups of three at 10, 30, 90, 180, 360, 960, and 1440 min post dose, and blood was collected by cardiac puncture, using acidified citrate dextrose as the anticoagulant. In some cases, large intestine was also isolated, intestinal contents flushed, and the tissue snap-frozen. Plasma was isolated from blood by centrifugation at 9600*g* for 10 min and stored at −80 °C until analysis. Tissues were homogenized in a 3-fold volume of PBS (final homogenate volume in mL = weight of tissue in g × 4). Plasma or tissue homogenate (0.1 mL) was

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precipitated with 0.2 mL of an organic crash solution containing either methanol or acetonitrile, 0.15% formic acid, and an internal standard (*n*-benzylbenzamide). Extraction conditions were optimized prior to PK analysis for efficient and reproducible recovery over a 3 log range of concentrations. The solution was centrifuged twice at 16 100*g* for 5 min. The final supernatant was analyzed by LC−MS/MS as described above, and compound concentrations were determined in reference to a standard curve prepared by addition of the appropriate compound to blank plasma or tissue homogenate. A value of 3× above the signal obtained in the blank plasma was designated the limit of detection (LOD). The limit of quantitation (LOQ) was defined as the lowest concentration at which back calculation yielded a concentration within 20% of the theoretical value and above the LOD signal. The LOQ values were as follows: 0.5 ng/mL for **16** and **92**, and 5 ng/mL for **22**. Compound concentrations in large intestine were calculated by subtracting the amount of compound in the residual blood in that tissue based on reference values for large intestinal vasculature.[38] Pharmacokinetic parameters were determined using the noncompartmental analysis tool in Phoenix WinNonlin (Certara, Corp., Princeton, NJ).

Chemistry. *General Information.* Unless otherwise specified, all commercially available reagents were used as received. All reactions using dried solvents were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Dry solvent was dispensed from a solvent purification system that passes solvent through two columns of dry neutral alumina. Silica gel chromatographic purifications were performed by flash chromatography with silica gel (Sigma, grade 60, 230−400 mesh) packed in glass columns (the eluting solvent was determined by thin-layer chromatography, TLC), or with an Isco CombiFlash system using Redisep Rf Flash columns with size ranging from 4 to 80 g. Analytical TLC was performed on glass plates coated with 0.25 mm silica gel using UV or by iodide or $KMnO_4$ staining for visualization. Melting points are uncorrected. Routine ^1H and proton-decoupled ^{13}C NMR spectra were obtained on a Bruker 400 MHz NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) from low to high field relative to residual solvent. Multiplicities are given as: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), and multiplet (m). All synthetic compounds exhibited >95% purity, as determined by LC−MS analysis performed on an Agilent 1100 high-performance liquid chromatography system using an Eclipse XDB-C18 column (4.6 × 150 mm^2, 5 μm; Agilent) that was coupled to an Agilent G1956A (or 6120) electrospray ionization (ESI) mass spectrometer run in the positive mode with a scan range of 100−1100 m/z. Liquid chromatography was carried out at a flow rate of 0.5 mL/min at 20 °C with a 5 μL injection volume, using the gradient elution with aqueous acetonitrile containing 0.1% formic acid. The gradient was adjusted based on the different polarities of different compounds. High-resolution mass spectrometry (HRMS) data were obtained from the Shimadzu Center for Advanced Analytical Chemistry (SCAAC) at UT Arlington.

General Procedure A for the Preparation of Sulfonamides 4−9, 11−24, 26−51, 57, 58, 71−91, 104, 115, 116, 124, and 126−128 from Sulfonyl Chlorides and Amines. A mixture of amine (1.0 equiv), sulfonyl chloride (1.1 equiv), and *N*,*N*-diisopropyl ethylamine (1.5 equiv) in CH_2Cl_2 (5 mL/mmol amine) was stirred at room temperature overnight. The reaction solution was then poured into a saturated aqueous $NaHCO_3$ solution (20 mL/mmol amine) and extracted with CH_2Cl_2 (3 × 20 mL/mmol amine). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified through flash chromatography or Isco CombiFlash ($MeOH/CH_2Cl_2$, or MeOH/EtOAc eluent mixture; gradient adjusted based on the different polarity of different compounds), or by recrystallization to provide the corresponding sulfonamides with >95% purity.

General Procedure B for the Preparation of Sulfonamides 3a−c, 103, and 113 from Sulfonyl Chlorides and Amine Hydrochloride Salts. A biphasic mixture of sulfonyl chloride (1.2 equiv), amine hydrochloride salt (1.0 equiv), and K_2CO_3 (2.5 equiv) in $CHCl_3$ (2 mL/mmol amine hydrochloride salt) and water (2 mL/mmol amine hydrochloride salt) was stirred vigorously at room temperature for 20 h followed by the addition of saturated aqueous $NaHCO_3$ (25 mL/mmol of amine hydrochloride salt). The resulting solution was extracted with CH_2Cl_2 (3 × 20 mL/mmol of amine hydrochloride salt) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified through flash chromatography or Isco CombiFlash ($MeOH/CH_2Cl_2$, or hexanes/EtOAc eluent mixture; gradient adjusted based on the different polarities of different compounds) to provide the corresponding sulfonamides with >95% purity.

General Procedure C for the Preparation of Biarylsulfonamides 52−56 and 59−70 via Suzuki Cross-Coupling. To a flame-dried flask equipped with a reflux condenser were added (bromophenylsulfonyl)-4-methyl-1,4′-bipiperidine (1.0 equiv), phenylboronic acid (1.58 equiv), $Pd(PPh_3)_4$ (0.1 equiv), THF (14.5 mL/mmol sulfonamide), and aqueous Na_2CO_3 (2 M; 1.45 mL/mmol sulfonamide). The mixture was degassed through freeze−pump−thaw cycling and was refluxed for 3−12 h. After being cooled down to room temperature, the reaction suspension was diluted with water (45.5 mL/mmol sulfonamide), stirred for 10 min, and extracted with CH_2Cl_2 (3 × 54.5 mL/mmol sulfonamide). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified through flash chromatography or Isco CombiFlash ($MeOH/CH_2Cl_2$, or MeOH/EtOAc eluent mixture; gradient adjusted based on the different polarity of different compounds) to provide the corresponding biarylsulfonamides with >95% purity.

General Procedure D for the Reductive Amination of *N*-Arylsulfonyl-piperidin-4-ones 3a−c, or *N*-Mesitylsulphonyl-4-aminocyclohexanone. A mixture of ketone (1.0 equiv), amine (1.0 equiv), AcOH (1.0 equiv), and CH_2Cl_2 (or DCE) (5 mL/mmol amine) was stirred at room temperature for 15 min before $NaBH(OAc)_3$ (1.5 equiv) was added. The resulting suspension was stirred at room temperature with a reaction time ranging from 20 to 89 h. The reaction was then quenched by dropwise addition of saturated aqueous $NaHCO_3$ (30 mL/mmol of amine) at 0 °C, and the resulting biphasic solution was extracted with CH_2Cl_2 (3 × 30 mL/mmol amine). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified through flash chromatography or Isco CombiFlash ($MeOH/CH_2Cl_2$, or hexanes/EtOAc eluent mixture; gradient adjusted based on the different polarity of different compounds) to provide the corresponding reductive amination product with >95% purity.

1-(Phenylsulfonyl)piperidin-4-one (3a). Reaction of amine hydrochloride salt **2a** with benzenesulfonyl chloride (Procedure B) yielded **3a** as a white solid (93%); mp 105−108 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85−7.73 (m, 2H), 7.66−7.58 (m, 1H), 7.58−7.48 (m, 2H), 3.39 (t, J = 6.2 Hz, 4H), 2.52 (t, J = 6.2 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.6, 136.3, 133.2, 129.3, 127.5, 45.9, 40.7. The analytical data were consistent with the literature report.[39]

1-(4-Bromophenylsulfonyl)piperidin-4-one (3b). Reaction of amine hydrochloride salt **2a** with 4-bromobenzene-1-sulfonyl chloride (Procedure B) yielded **3b** as a white solid (82%); mp 155−158 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.79−7.57 (m, 4H), 3.39 (t, J = 6.3 Hz, 4H), 2.54 (t, J = 6.3 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.1, 135.5, 132.6, 128.9, 128.4, 45.8, 40.6.

1-(Mesitylsulfonyl)piperidin-4-one (3c). Reaction of amine hydrochloride salt **2a** with 2,4,6-trimethylbenzene-1-sulfonyl chloride (Procedure B) yielded **3c** as a white solid (95%); mp 102−105 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 2H), 3.50 (t, J = 6.2 Hz, 4H), 2.61 (s, 6H), 2.52 (t, J = 6.2 Hz, 4H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 138.3, 135.6, 127.4, 126.8, 39.6, 36.3, 18.1, 16.2. LC−MS (ESI) calcd for $C_{14}H_{20}NO_3S$ $[M + H]^+$ 282.1, found 282.1.

(1-(Mesitylsulfonyl)piperidin-4-yl)methanol (4). Reaction of amine **2c** with 2,4,6-trimethylbenzene-1-sulfonyl chloride (Procedure A) yielded **4** as a white solid (78%); mp 85−88 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 2H), 3.56 (d, J = 12.3 Hz, 2H), 3.43 (d, J = 6.3 Hz, 2H), 2.71 (td, J = 12.3, 2.6 Hz, 2H), 2.57 (s, 6H), 2.26 (s,

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3H), 2.00−1.80 (m, 1H), 1.73 (dd, J = 13.6, 2.9 Hz, 2H), 1.63−1.48 (m, 1H), 1.18 (qd, J = 11.9, 4.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 140.3, 131.9, 131.7, 67.0, 44.1, 38.3, 28.1, 22.8, 20.9. HRMS (ESI-time-of-flight (TOF)) calcd for $C_{15}H_{23}NO_3SNa$ $[M + Na]^+$ 320.1291, found 320.1280.

4-Methyl-1′-(phenylsulfonyl)-1,4′-bipiperidine (5). Reaction of amine **1a** with $PhSO_2Cl$ (Procedure A) yielded **5** as a pale yellow solid (92%); mp 154−156 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 7.3 Hz, 2H), 7.65−7.58 (m, 1H), 7.54 (t, J = 7.7 Hz, 2H), 3.87 (d, J = 11.9 Hz, 2H), 2.80 (d, J = 11.8 Hz, 2H), 2.32−2.20 (m, 3H), 2.14 (t, J = 11.4 Hz, 2H), 1.86 (d, J = 11.7 Hz, 2H), 1.72−1.59 (m, 4H), 1.40 − 1.28 (m, 1H), 1.27−1.12 (m, 2H), 0.91 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 132.7, 129.0, 127.6, 61.3, 49.1, 46.1, 33.9, 30.8, 26.9, 21.7. HRMS (ESI-TOF) calcd for $C_{17}H_{27}N_2O_2S$ $[M + H]^+$ 323.1788, found 323.1774.

1′-((4-Methoxyphenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (6). Reaction of amine **1a** with 4-methoxybenzene-1-sulfonyl chloride (Procedure A) yielded **6** as a white solid (94%); mp 109−112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 3.83−3.74 (d, J = 12.0 Hz, 2H), 2.76 (d, J = 11.7 Hz, 2H), 2.28−2.04 (m, 5H), 1.88−1.75 (d, J = 12.9 Hz, 2H), 1.72−1.54 (m, 4H), 1.36−1.23 (m, 1H), 1.23−1.08 (m, 2H), 0.87 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 129.8, 127.6, 114.1, 61.5, 55.6, 49.5, 46.2, 34.6, 31.0, 27.3, 21.9. HRMS (ESI-TOF) calcd for $C_{18}H_{29}N_2O_3S$ $[M + H]^+$ 353.1893, found 353.1883.

4-Methyl-1′-((4-nitrophenyl)sulfonyl)-1,4′-bipiperidine (7). Reaction of amine **1a** with 4-nitrobenzene-1-sulfonyl chloride (Procedure A) yielded **7** as a yellow solid (76%); mp 165−168 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 8.8 Hz, 2H), 7.91 (d, J = 8.8 Hz, 2H), 3.85 (d, J = 12.3 Hz, 2H), 2.76 (d, J = 11.6 Hz, 2H), 2.31 (td, J = 12.0, 2.5 Hz, 2H), 2.21 (tt, J = 11.5, 3.7 Hz, 1H), 2.10 (td, J = 11.5, 2.5 Hz, 2H), 1.84 (d, J = 12.0 Hz, 2H), 1.62 (qd, J = 12.0, 4.0 Hz, 4H), 1.38−1.21 (m, 1H), 1.14 (qd, J = 12.0, 3.7 Hz, 2H), 0.86 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 142.4, 128.7, 124.3, 61.2, 49.5, 46.1, 34.5, 30.9, 27.4, 21.8. HRMS (ESI-TOF) calcd for $C_{17}H_{26}N_3O_4S$ $[M + H]^+$ 368.1639, found 368.1633.

Methyl 4-((4-Methyl-[1,4′-bipiperidin]-1′-yl)sulfonyl)-benzoate (8). Reaction of amine **1a** with methyl 4-(chlorosulfonyl)-benzoate (Procedure A) yielded **8** as a white solid (54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.1 Hz, 2H), 7.80 (d, J = 8.7 Hz, 2H), 3.93 (s, 3H), 3.84 (d, J = 12.1 Hz, 2H), 2.76 (d, J = 11.0 Hz, 2H), 2.38−2.02 (m, 5H), 1.83 (d, J = 11.9 Hz, 2H), 1.71−1.51 (m, 4H), 1.37−1.23 (m, 1H), 1.16 (qd, J = 12.0, 3.8 Hz, 2H), 0.87 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 140.2, 133.8, 130.2, 127.6, 61.4, 52.6, 49.4, 46.1, 34.4, 30.9, 27.3, 21.8. HRMS (ESI-TOF) calcd for $C_{19}H_{29}N_2O_4S$ $[M + H]^+$ 381.1843, found 381.1843.

4-((4-Methyl-[1,4′-bipiperidin]-1′-yl)sulfonyl)benzonitrile (9). Reaction of amine **1a** with 4-cyanobenzene-1-sulfonyl chloride (Procedure A) yielded **9** as a white solid (92%); mp 184−186 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (q, J = 8.5 Hz, 4H), 3.85 (d, J = 12.1 Hz, 2H), 2.77 (d, J = 11.6 Hz, 2H), 2.31 (t, J = 12.0 Hz, 2H), 2.22 (tt, J = 11.6, 3.6 Hz, 1H), 2.11 (t, J = 12.2 Hz, 2H), 1.85 (d, J = 11.6 Hz, 2H), 1.71−1.55 (m, 4H), 1.37−1.24 (m, 1H), 1.25−1.10 (m, 2H), 0.89 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 132.8, 128.1, 117.3, 116.4, 61.2, 49.5, 46.1, 34.6, 31.0, 27.4, 21.8. HRMS (ESI-TOF) calcd for $C_{18}H_{26}N_3O_2S$ $[M + H]^+$ 348.1740, found 348.1737.

4-((4-Methyl-[1,4′-bipiperidin]-1′-yl)sulfonyl)aniline (10). To a 50 mL flask were added 4-methyl-1′-((4-nitrophenyl)-sulfonyl)-1,4′-bipiperidine **7** (0.1004 g, 0.33 mmol), methanol (3 mL), and Pd/C (one spatula, 10% on active carbon). The reaction flask was sealed by a septum, and after the removal of air using vacuum, a hydrogen balloon was fitted on the top of the septum. The reaction suspension was then stirred at room temperature for 22 h and filtered through a pad of celite. The filtrate was concentrated under reduced pressure to provide the desired product (0.09 g, >95%) as a colorless gel. ^{1}H NMR (400 MHz, CD_3OD) δ 7.41 (d, J = 8.7 Hz, 2H), 6.69 (d, J = 8.7 Hz, 2H), 3.84−3.63 (m, 2H), 2.83 (d, J = 11.7 Hz, 2H), 2.31−2.06 (m, 5H), 1.87 (d, J = 14.5 Hz, 2H), 1.62 (d, J = 14.1 Hz, 2H), 1.51 (qd, J = 12.2, 4.1 Hz, 2H), 1.41−1.23 (m, 1H), 1.16 (qd, J = 12.4, 3.7 Hz, 2H), 0.89 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 153.1, 129.4, 121.2, 112.9, 61.3, 49.1, 45.9, 33.7, 30.7, 26.9, 20.8. HRMS (ESI-TOF) calcd for $C_{17}H_{27}N_3O_2SNa$ $[M + Na]^+$ 360.1716, found 360.1719.

4-Methyl-1′-tosyl-1,4′-bipiperidine (11). Reaction of amine **1a** with 4-methylbenzene-1-sulfonyl chloride (Procedure A) yielded **11** as a white solid (67%); mp 139−142 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 3.80 (d, J = 11.9 Hz, 2H), 2.79 (d, J = 11.1 Hz, 2H), 2.39 (s, 3H), 2.30−2.07 (m, 5H), 1.84 (d, J = 10.9 Hz, 2H), 1.69−1.53 (m, 4H), 1.40−1.09 (m, 3H), 0.86 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 132.9, 129.6, 127.7, 61.6, 49.4, 46.0, 34.1, 30.8, 27.1, 21.7, 21.5. HRMS (ESI-TOF) calcd for $C_{18}H_{29}N_2O_2S$ $[M + H]^+$ 337.1944, found 337.1937.

1′-((4-Ethylphenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (12). Reaction of amine **1a** with 4-ethylbenzene-1-sulfonyl chloride (Procedure A) yielded **12** as a brown solid (>95%); mp 108−110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.9 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 3.82 (d, J = 11.6 Hz, 2H), 2.78 (d, J = 11.2 Hz, 2H), 2.70 (q, J = 7.6 Hz, 2H), 2.22 (t, J = 12.1 Hz, 3H), 2.12 (t, J = 10.8 Hz, 2H), 1.82 (d, J = 12.2 Hz, 2H), 1.62 (td, J = 12.3, 8.2 Hz, 4H), 1.39−1.08 (m, 6H), 0.87 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 133.3, 128.4, 127.8, 61.5, 49.4, 46.1, 34.4, 30.9, 28.8, 27.2, 21.8, 15.1. HRMS (ESI-TOF) calcd for $C_{19}H_{31}N_2O_2S$ $[M + H]^+$ 351.2101, found 351.2093.

1′-((4-Isopropylphenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (13). Reaction of amine **1a** with 4-isopropylbenzene-1-sulfonyl chloride (Procedure A) yielded **13** as a yellow solid (79%); mp 144−147 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 3.81 (d, J = 12.3 Hz, 2H), 2.94 (p, J = 6.9 Hz, 1H), 2.75 (d, J = 11.7 Hz, 2H), 2.31−2.15 (m, 3H), 2.09 (td, J = 11.7, 2.7 Hz, 2H), 1.80 (d, J = 11.7 Hz, 2H), 1.68−1.52 (m, 4H), 1.36−1.03 (m, 3H), 1.24 (d, J = 6.9 Hz, 6H), 0.86 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 133.4, 127.8, 127.0, 61.4, 49.4, 46.1, 34.5, 34.1, 30.9, 27.2, 23.6, 21.8. HRMS (ESI-TOF) calcd for $C_{20}H_{33}N_2O_2S$ $[M + H]^+$ 365.2257, found 365.2247.

1′-((4-(*tert*-Butyl)phenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (14). Reaction of amine **1a** with 4-(*tert*-butyl)benzene-1-sulfonyl chloride (Procedure A) yielded **14** as a yellow solid (85%); mp 173−176 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64, 7.49 (ABq, J_{AB} = 8.6 Hz, 4H), 3.83 (d, J = 12.0 Hz, 2H), 2.77 (d, J = 11.2 Hz, 2H), 2.31−2.18 (m, 3H), 2.13 (t, J = 11.3 Hz, 2H), 1.82 (d, J = 12.2 Hz, 2H), 1.70−1.51 (m, 4H), 1.31 (s, 9H), 1.30−1.25 (m, 1H), 1.24−1.11 (m, 2H), 0.86 (d, J = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 133.1, 127.5, 125.9, 61.5, 49.4, 46.1, 35.1, 34.3, 31.1, 30.9, 27.1, 21.8. HRMS (ESI-TOF) calcd for $C_{21}H_{35}N_2O_2S$ $[M + H]^+$ 379.2414, found 379.2418.

4-Methyl-1′-((4-(trifluoromethyl)phenyl)sulfonyl)-1,4′-bipiperidine (15). Reaction of amine **1a** with 4-(trifluoromethyl)-benzene-1-sulfonyl chloride (Procedure A) yielded **15** as a yellow solid (87%); mp 175−178 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86, 7.77 (ABq, J_{AB} = 8.2 Hz, 4H), 3.85 (d, J = 12.1 Hz, 2H), 2.75 (d, J = 11.7 Hz, 2H), 2.28 (t, J = 11.4 Hz, 3H), 2.19 (tt, J = 11.5, 3.6 Hz, 1H), 2.09 (td, J = 11.3, 2.4 Hz, 2H), 1.83 (d, J = 11.5 Hz, 2H), 1.62 (qd, J = 12.4, 4.0 Hz, 4H), 1.38−1.21 (m, 1H), 1.14 (qd, J = 11.9, 3.8 Hz, 2H), 0.87 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 134.4 (q, J = 33.1 Hz), 128.1, 126.2 (q, J = 3.7 Hz), 123.2 (q, J = 272.9 Hz), 61.3, 49.4, 46.1, 34.4, 30.9, 27.3, 21.8. HRMS (ESI-TOF) calcd for $C_{18}H_{26}F_3N_2O_2S$ $[M + H]^+$ 391.1662, found 391.1654.

1′-((4-Chlorophenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (16). Reaction of amine **1a** with 4-chlorobenzene-1-sulfonyl chloride (Procedure A) yielded **16** as a white solid (67%); mp 152−155 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 3.93−3.69 (m, 2H), 2.80 (dt, J = 11.6, 3.4 Hz, 2H), 2.23 (td, J = 12.0, 2.5 Hz, 3H), 2.15 (t, J = 11.3 Hz, 2H), 1.84 (d, J = 12.6 Hz, 2H), 1.71−1.54 (m, 4H), 1.42−1.26 (m, 1H), 1.25−1.12 (m, 2H), 0.87 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 134.6, 129.3, 129.0, 61.4, 49.4, 46.0, 34.2, 30.8, 27.2, 21.7. HRMS

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(ESI-TOF) calcd for $C_{17}H_{26}ClN_2O_2S$ $[M + H]^+$ 357.1398, found 357.1393.

1′-((4-Bromophenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (17). Reaction of amine **1a** with 4-bromobenzene-1-sulfonyl chloride (Procedure A) yielded **17** as a white solid (83%); mp 165−168 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75−7.45 (m, 4H), 3.81 (d, J = 11.9 Hz, 2H), 2.75 (d, J = 11.5 Hz, 2H), 2.38−1.96 (m, 5H), 1.81 (d, J = 11.8 Hz, 2H), 1.73−1.52 (m, 4H), 1.37−1.22 (m, 1H), 1.22−1.06 (m, 2H), 0.87 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2, 132.3, 129.1, 127.7, 61.3, 49.5, 46.1, 34.6, 31.0, 27.3, 21.9. HRMS (ESI-TOF) calcd for $C_{17}H_{26}BrN_2O_2S$ $[M + H]^+$ 401.0893, found 401.0886.

4-Methyl-1′-((4-propoxyphenyl)sulfonyl)-1,4′-bipiperidine (18). Reaction of amine **1a** with 4-propoxybenzene-1-sulfonyl chloride (Procedure A) yielded **18** as a white solid (>95%); mp 118−121 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.9 Hz, 2H), 6.95 (d, J = 8.9 Hz, 2H), 3.95 (t, J = 6.6 Hz, 2H), 3.80 (d, J = 11.4 Hz, 2H), 2.76 (d, J = 10.9 Hz, 2H), 2.15 (dt, J = 37.1, 11.5 Hz, 5H), 1.88−1.72 (m, 4H), 1.71−1.52 (m, 4H), 1.37−1.24 (m, 1H), 1.15 (q, J = 11.8 Hz, 2H), 1.03 (t, J = 7.4 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 129.7, 127.3, 114.5, 69.9, 61.5, 49.5, 46.2, 34.6, 31.0, 27.3, 22.4, 21.9, 10.5. HRMS (ESI-TOF) calcd for $C_{20}H_{33}N_2O_3S$ $[M + H]^+$ 381.2206, found 381.2210.

1′-((4-Butoxyphenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (19). Reaction of amine **1a** with 4-butoxybenzene-1-sulfonyl chloride (Procedure A) yielded **19** as a pink solid (82%); mp 137−139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.7 Hz, 2H), 6.94 (d, J = 8.7 Hz, 2H), 3.99 (t, J = 6.5 Hz, 2H), 3.80 (d, J = 12.3 Hz, 2H), 2.78 (d, J = 11.3 Hz, 2H), 2.27−2.06 (m, 5H), 1.88−1.72 (m, 4H), 1.70−1.55 (m, 4H), 1.47 (h, J = 7.4 Hz, 2H), 1.39−1.24 (m, 1H), 1.24−1.10 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 129.7, 127.2, 114.5, 68.1, 61.6, 49.4, 46.1, 34.4, 31.0, 30.9, 27.2, 21.8, 19.1, 13.8. HRMS (ESI-TOF) calcd for $C_{21}H_{35}N_2O_3S$ $[M + H]^+$ 395.2363, found 395.2361.

1′-((4-(Benzyloxy)phenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (20). Reaction of amine **1a** with 4-(benzyloxy)benzene-1-sulfonyl chloride (Procedure A) yielded **20** as a white solid (84%); mp 157−159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.8 Hz, 2H), 7.48−7.27 (m, 4H), 7.04 (d, J = 8.8 Hz, 2H), 5.10 (s, 2H), 3.81 (d, J = 11.5 Hz, 2H), 2.77 (d, J = 10.9 Hz, 2H), 2.31−2.04 (m, 5H), 1.89−1.76 (m, 2H), 1.68−1.53 (m, 4H), 1.37−1.08 (m, 3H), 0.88 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 135.8, 129.8, 128.7, 128.4, 127.9, 127.5, 115.0, 70.4, 61.5, 49.5, 46.2, 34.5, 31.0, 27.3, 21.9. HRMS (ESI-TOF) calcd for $C_{24}H_{33}N_2O_3S$ $[M + H]^+$ 429.2206, found 429.2195.

4-Methyl-1′-((4-(trifluoromethoxy)phenyl)sulfonyl)-1,4′-bipiperidine (21). Reaction of amine **1a** with 4-(trifluoromethoxy)-benzene-1-sulfonyl chloride (Procedure A) yielded **21** as a yellow solid (>95%); mp 168−170 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 3.84 (d, J = 12.0 Hz, 2H), 2.79 (d, J = 11.7 Hz, 2H), 2.35−2.19 (m, 3H), 2.13 (t, J = 11.4 Hz, 2H), 1.86 (d, J = 10.8 Hz, 2H), 1.71−1.55 (m, 4H), 1.39−1.11 (m, 3H), 0.88 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1 (q, J = 1.8 Hz), 134.7, 129.7, 120.8 (q, J = 1.1 Hz), 120.2 (q, J = 259.5 Hz), 61.3, 49.5, 46.1, 34.6, 31.0, 27.3, 21.8. HRMS (ESI-TOF) calcd for $C_{18}H_{26}F_3N_2O_3S$ $[M + H]^+$ 407.1611, found 407.1615.

1′-((4-(Difluoromethoxy)phenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (22). Reaction of amine **1a** with 4-(difluoromethoxy)-benzene-1-sulfonyl chloride (Procedure A) yielded **22** as a light orange solid (69%); mp 132−135 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2 H), 6.61 (t, J = 72.6 Hz, 1H), 3.83 (d, J = 12.1 Hz, 2H), 2.77 (d, J = 11.7 Hz, 2H), 2.33−2.16 (m, 3 H), 2.11 (td, J = 11.6, 2.5 Hz, 2H), 1.84 (d, J = 13.2 Hz, 2H), 1.69−1.52 (m, 4 H), 1.30 (dddt, J = 13.3, 9.7, 6.5, 3.5 Hz, 1H), 1.16 (qd, J = 12.0, 3.8 Hz, 2H), 0.89 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1 (t, J = 2.9 Hz), 132.9, 129.8, 119.3, 115.2 (t, J = 262.5 Hz), 61.4, 49.5, 46.1, 34.6, 31.0, 27.3, 21.8. HRMS (ESI-TOF) calcd for $C_{18}H_{26}F_2N_2O_3SNa$ $[M + Na]^+$ 411.1524, found 411.1529.

1′-((3-Methoxyphenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (23). Reaction of amine **1a** with 3-methoxybenzene-1-sulfonyl chloride (Procedure A) yielded **23** as a yellow solid (85%); mp 81−83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (t, J = 8.0 Hz, 1H), 7.29 (ddd, J = 7.7, 1.6, 0.9 Hz, 1H), 7.22 (dd, J = 2.6, 1.6 Hz, 1H), 7.08 (ddt, J = 8.3, 2.6, 0.8 Hz, 1H), 3.83 (s, 3H), 3.82 (d, J = 12.0 Hz, 2H), 2.79 (d, J = 11.7 Hz, 2H), 2.25 (td, J = 12.0, 2.6 Hz, 3H), 2.18−2.07 (m, 2H), 1.84 (d, J = 12.3 Hz, 2H), 1.72−1.53 (m, 4H), 1.37−1.13 (m, 3H), 0.87 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 137.2, 130.0, 119.7, 118.8, 112.5, 61.5, 55.6, 49.4, 46.1, 34.3, 30.9, 27.2, 21.8. HRMS (ESI-TOF) calcd for $C_{18}H_{29}N_2O_3S$ $[M + H]^+$ 353.1893, found 353.1898.

4-Methyl-1′-((3-nitrophenyl)sulfonyl)-1,4′-bipiperidine (24). Reaction of amine **1a** with 3-nitrobenzene-1-sulfonyl chloride (Procedure A) yielded **24** as a yellow solid (77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.42 (d, J = 8.2 Hz, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 3.86 (d, J = 12.1 Hz, 2H), 2.75 (d, J = 11.6 Hz, 2H), 2.32 (td, J = 12.0, 2.5 Hz, 2H), 2.19 (tt, J = 11.5, 3.6 Hz, 1H), 2.09 (td, J = 11.6, 2.5 Hz, 2H), 1.84 (d, J = 12.5 Hz, 2H), 1.71−1.52 (m, 4H), 1.37−1.20 (m, 1H), 1.13 (qd, J = 12.1, 4.0 Hz, 2H), 0.86 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 138.8, 133.0, 130.4, 127.1, 122.6, 61.2, 49.5, 46.1, 34.5, 31.0, 27.4, 21.8. HRMS (ESI-TOF) calcd for $C_{17}H_{26}N_3O_4S$ $[M + H]^+$ 368.1639, found 368.1630.

3-((4-Methyl-[1,4′-bipiperidin]-1′-yl)sulfonyl)aniline (25). This compound was prepared as a yellow gel (55%) by hydrogenation of **24** in the same manner as for the preparation of **10**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.24 (t, J = 7.9 Hz, 1H), 7.01 (t, J = 2.0 Hz, 1H), 6.91 (dddd, J = 23.6, 8.1, 2.0, 1.0 Hz, 2H), 3.76 (d, J = 12.3 Hz, 2H), 3.29 (p, J = 1.7 Hz, 1H), 2.83 (d, J = 10.7 Hz, 2H), 2.28 (td, J = 12.4, 2.4 Hz, 2H), 2.23−2.07 (m, 3H), 1.87 (d, J = 12.9 Hz, 2H), 1.62 (dd, J = 13.3, 3.5 Hz, 2H), 1.52 (qd, J = 12.3, 4.1 Hz, 2H), 1.40−1.23 (m, 2H), 1.16 (qd, J = 12.1, 3.8 Hz, 2H), 0.89 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 149.1, 136.3, 129.3, 118.5, 115.4, 112.5, 61.2, 49.1, 45.9, 33.7, 30.7, 26.9, 20.7. HRMS (ESI-TOF) calcd for $C_{17}H_{27}N_3O_2SNa$ $[M + Na]^+$ 360.1716, found 360.1703.

4-Methyl-1′-(*m*-tolylsulfonyl)-1,4′-bipiperidine (26). Reaction of amine **1a** with 3-methylbenzene-1-sulfonyl chloride (Procedure A) yielded **26** as a yellow solid (86%); mp 90−93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.43 (m, 2H), 7.41−7.31 (m, 2H), 3.81 (d, J = 12.0 Hz, 2H), 2.80 (d, J = 11.8 Hz, 2H), 2.39 (s, 3H), 2.34−2.06 (m, 5H), 1.85 (d, J = 12.3 Hz, 2H), 1.68−1.55 (m, 4H), 1.37−1.13 (m, 3H), 0.86 (d, J = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 135.8, 133.5, 128.8, 127.9, 124.8, 61.6, 49.4, 46.0, 34.1, 30.8, 27.1, 21.7, 21.4. HRMS (ESI-TOF) calcd for $C_{18}H_{29}N_2O_2S$ $[M + H]^+$ 337.1944, found 337.1937.

4-Methyl-1′-((3-(trifluoromethyl)phenyl)sulfonyl)-1,4′-bipiperidine (27). Reaction of amine **1a** with 3-(trifluoromethyl)-benzene-1-sulfonyl chloride (Procedure A) yielded **27** as a pink solid (90%); mp 123−125 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.67 (t, J = 7.9 Hz, 1H), 3.85 (d, J = 12.0 Hz, 2H), 2.79 (d, J = 11.6 Hz, 2H), 2.27 (tt, J = 11.8, 3.7 Hz, 3H), 2.19−2.06 (m, 2H), 1.86 (d, J = 11.5 Hz, 2H), 1.70−1.48 (m, 4H), 1.35−1.25 (m, 1H), 1.18 (qd, J = 11.9, 3.7 Hz, 2H), 0.87 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 131.8 (q, J = 33.4 Hz), 130.8, 129.9, 129.4 (q, J = 3.5 Hz), 124.5 (q, J = 3.7 Hz), 121.8, 61.3, 49.4, 46.0, 34.2, 30.8, 27.2, 21.7. HRMS (ESI-TOF) calcd for $C_{18}H_{26}F_3N_2O_2S$ $[M + H]^+$ 391.1661, found 391.1666.

1′-((3-Chlorophenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (28). Reaction of amine **1a** with 3-chlorobenzene-1-sulfonyl chloride (Procedure A) yielded **28** as a yellow solid (74%); mp 122−124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 3.83 (d, J = 11.7 Hz, 2H), 2.80 (d, J = 10.9 Hz, 2H), 2.28 (td, J = 11.8, 2.5 Hz, 3H), 2.15 (t, J = 11.3 Hz, 2H), 1.87 (d, J = 12.7 Hz, 2H), 1.72−1.56 (m, 4H), 1.40−1.14 (m, 3H), 0.88 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 135.3, 132.8, 130.3, 127.5, 125.7, 61.4, 49.4, 46.1, 34.2, 30.8, 27.2, 21.7. HRMS (ESI-TOF) calcd for $C_{17}H_{26}ClN_2O_2S$ $[M + H]^+$ 357.1398, found 357.1386.

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1′-((3-Bromophenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (29). Reaction of amine **1a** with 3-bromobenzene-1-sulfonyl chloride (Procedure A) yielded **29** as a white solid (65%); mp 125−126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.66 (dd, J = 13.3, 7.9 Hz, 2H), 7.37 (t, J = 7.9 Hz, 1H), 3.80 (d, J = 11.7 Hz, 2H), 2.74 (d, J = 11.0 Hz, 2H), 2.16 (dt, J = 73.4, 11.4 Hz, 5H), 1.81 (d, J = 12.7 Hz, 2H), 1.60 (td, J = 12.4, 8.1 Hz, 4H), 1.34−1.22 (m, 1H), 1.20−1.02 (m, 2H), 0.85 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 135.7, 130.5, 130.3, 126.1, 123.1, 61.3, 49.5, 46.1, 34.6, 31.0, 27.4, 21.9. HRMS (ESI-TOF) calcd for $C_{17}H_{26}BrN_2O_2S$ $[M + H]^+$ 401.0893, found 401.0886.

1′-((2-Bromophenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (30). Reaction of amine **1a** with 2-bromobenzene-1-sulfonyl chloride (Procedure A) yielded **30** as a white solid (>95%); mp 82−84 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, J = 7.8, 1.8 Hz, 1H), 7.70 (dd, J = 7.8, 1.4 Hz, 1H), 7.37 (dtd, J = 24.2, 7.5, 1.6 Hz, 2H), 3.85 (d, J = 12.8 Hz, 2H), 2.91−2.62 (m, 4H), 2.33 (tt, J = 11.5, 3.5 Hz, 1H), 2.11 (td, J = 11.5, 2.4 Hz, 2H), 1.80 (d, J = 12.2 Hz, 2H), 1.65−1.50 (m, 4H), 1.35−1.22 (m, 1H), 1.15 (qd, J = 12.2, 3.8 Hz, 2H), 0.86 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 135.7, 133.5, 132.2, 127.4, 120.4, 61.7, 49.5, 45.6, 34.6, 31.0, 27.8, 21.9. HRMS (ESI-TOF) calcd for $C_{17}H_{26}BrN_2O_2S$ $[M + H]^+$ 401.0893, found 401.0891.

1′-((3,4-Dimethoxyphenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (31). Reaction of amine **1a** with 3,4-dimethoxybenzene-1-sulfonyl chloride (Procedure A) yielded **31** as a white solid (78%); mp 132−134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 8.4, 2.1 Hz, 1H), 7.18 (d, J = 2.1 Hz, 1H), 6.92 (d, J = 8.5 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.80 (d, J = 11.9 Hz, 2H), 2.77 (d, J = 11.7 Hz, 2H), 2.30−2.04 (m, 5H), 1.82 (d, J = 11.2 Hz, 2H), 1.69−1.54 (m, 4H), 1.37−1.25 (m, 1H), 1.16 (qd, J = 12.1, 3.8 Hz, 2H), 0.87 (d, J = 6.3 Hz, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 148.9, 127.8, 121.5, 110.5, 110.1, 61.5, 56.2, 56.1, 49.5, 46.2, 34.5, 31.0, 27.3, 21.8. HRMS (ESI-TOF) calcd for $C_{19}H_{31}N_2O_4S$ $[M + H]^+$ 383.1999, found 383.1991.

1′-((2,5-Dimethoxyphenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (32). Reaction of amine **1a** with 2,5-dimethoxybenzenesulfonyl chloride (Procedure A) yielded **32** as a white solid (95%); mp 75−78 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 3.1 Hz, 1H), 7.00 (dd, J = 9.0, 3.1 Hz, 1H), 6.90 (d, J = 9.0 Hz, 1H), 3.87 (d, J = 12.8 Hz, 2H), 3.83 (s, 3H), 3.75 (s, 3H), 2.77 (d, J = 11.6 Hz, 2H), 2.57 (t, J = 12.4 Hz, 2H), 2.27 (t, J = 11.5 Hz, 1H), 2.10 (t, J = 11.5 Hz, 2H), 1.77 (d, J = 13.8 Hz, 2H), 1.64−1.47 (m, 4H), 1.36−1.22 (m, 1H), 1.21−1.08 (m, 2H), 0.86 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 151.0, 127.3, 120.0, 115.9, 113.9, 61.9, 56.6, 56.0, 49.5, 45.9, 34.6, 31.0, 27.9, 21.9. HRMS (ESI-TOF) calcd for $C_{19}H_{31}N_2O_4S$ $[M + H]^+$ 383.1999, found 383.1991.

1′-((5-Bromo-2-methoxyphenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (33). Reaction of amine **1a** with 5-bromo-2-methoxybenzene-1-sulfonyl chloride (Procedure A) yielded **33** as a yellow solid (92%); mp 98−102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 2.6, Hz, 1H), 7.59 (dd, J = 8.8, 2.6 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 3.96−3.88 (d, J = 13.6 Hz, 2H), 3.90 (s, 3H), 2.84 (d, J = 10.9 Hz, 2H), 2.64 (td, J = 12.5, 2.5 Hz, 2H), 2.38 (d, J = 12.2 Hz, 1H), 2.17 (t, J = 11.7 Hz, 2H), 1.85 (d, J = 12.7 Hz, 2H), 1.68−1.52 (m, 4H), 1.40−1.14 (m, 3H), 0.91 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 136.8, 133.8, 128.7, 114.1, 112.3, 61.8, 56.3, 49.5, 45.9, 34.6, 31.0, 28.0, 21.9. HRMS (ESI-TOF) calcd for $C_{18}H_{27}BrN_2O_3SNa$ $[M + Na]^+$ 453.0818, found 453.0805.

1′-((2-Methoxy-4-methylphenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (34). Reaction of amine **1a** with 2-methoxy-4-methylphenylsulfonyl chloride (Procedure A) yielded **34** as a yellow solid (88%); mp 95−98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 7.9 Hz, 1H), 6.85−6.69 (m, 2H), 3.87 (d, J = 12.4 Hz, 2H), 3.85 (s, 3H), 2.78 (d, J = 11.1 Hz, 2H), 2.54 (d, J = 12.4 Hz, 2H), 2.35 (s, 3H), 2.27 (tt, J = 11.8, 3.6 Hz, 1H), 2.12 (td, J = 11.5, 2.7 Hz, 2H), 1.78 (d, J = 12.5 Hz, 2H), 1.64−1.47 (m, 4H), 1.37−1.23 (m, 1H), 1.22−1.08 (m, 2H), 0.86 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 145.5, 131.6, 123.5, 121.0, 112.9, 61.9, 55.8, 49.5, 45.9, 34.5, 31.0, 27.9, 21.9, 21.8. HRMS (ESI-TOF) calcd for $C_{19}H_{31}N_2O_3S$ $[M + H]^+$ 367.2050, found 367.2061.

4-Methyl-1′-((4-nitro-3-(trifluoromethyl)phenyl)sulfonyl)-1,4′-bipiperidine (35). Reaction of amine **1a** with 4-nitro-3-(trifluoromethyl)benzene-1-sulfonyl chloride (Procedure A) yielded **35** as a yellow solid (86%); mp 175−178 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.08 (dd, J = 8.4, 1.8 Hz, 1H), 7.98 (d, J = 8.3 Hz, 1H), 3.87 (d, J = 11.7 Hz, 2H), 2.77 (d, J = 11.7 Hz, 2H), 2.38 (td, J = 12.0, 2.5 Hz, 2H), 2.25 (tt, J = 11.4, 3.6 Hz, 1H), 2.11 (td, J = 11.4, 2.6 Hz, 2H), 1.87 (d, J = 12.1 Hz, 2H), 1.73−1.56 (m, 4H), 1.38−1.24 (m, 1H), 1.16 (qd, J = 11.7, 3.5 Hz, 2H), 0.88 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 141.4, 132.2, 127.1 (q, J = 5.2 Hz), 125.9, 124.7 (d, J = 35.3 Hz). 121.1 (d, J = 274.2 Hz), 61.0, 49.5, 46.0, 34.5, 30.9, 27.4, 21.8. HRMS (ESI-TOF) calcd for $C_{18}H_{25}F_3N_3O_4S$ $[M + H]^+$ 436.1512, found 436.1515.

4-Methyl-2-((4-methyl-[1,4′-bipiperidin]-1′-yl)sulfonyl)-benzonitrile (36). Reaction of amine **1a** with 2-cyano-5-methylbenzene-1-sulfonyl chloride (Procedure A) yielded **36** as a light pink solid (94%); mp 118−121 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 3.92 (d, J = 12.2 Hz, 2H), 2.78 (d, J = 12.3 Hz, 2H), 2.59 (t, J = 12.2 Hz, 2H), 2.47 (s, 3H), 2.31 (t, J = 11.7 Hz, 1H), 2.12 (t, J = 11.3 Hz, 2H), 1.84 (d, J = 14.5 Hz, 2H), 1.71−1.51 (m, 4H), 1.37−1.24 (m, 1H), 1.17 (q, J = 12.5 Hz, 2H), 0.87 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 140.3, 135.4, 133.2, 130.8, 116.5, 107.8, 61.5, 49.5, 45.8, 34.5, 31.0, 27.5, 21.8. HRMS (ESI-TOF) calcd for $C_{19}H_{28}N_3O_2S$ $[M + H]^+$ 362.1897, found 362.1885.

1′-((3,4-Dimethylphenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (37). Reaction of amine **1a** with 3,4-dimethylbenzene-1-sulfonyl chloride (Procedure A) yielded **37** as a yellow solid (89%); mp 87−89 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 3.81 (d, J = 12.0 Hz, 2H), 2.78 (d, J = 11.5 Hz, 2H), 2.30 (s, 6H), 2.16 (m, 5H), 1.82 (d, J = 11.5 Hz, 2H), 1.69−1.54 (m, 4H), 1.38−1.24 (m, 1H), 1.17 (qd, J = 12.0, 3.6 Hz, 2H), 0.87 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 137.7, 133.1, 130.1, 128.4, 125.3, 61.5, 49.4, 46.2, 34.4, 30.9, 27.2, 21.8, 19.9, 19.9. HRMS (ESI-TOF) calcd for $C_{19}H_{31}N_2O_2S$ $[M + H]^+$ 351.2101, found 351.2091.

1′-((4-Bromo-2-ethylphenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (38). Reaction of amine **1a** with 4-bromo-2-ethylbenzene-1-sulfonyl chloride (Procedure A) yielded **38** as a white solid (92%); mp 87−91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.42 (dd, J = 8.4, 2.0 Hz, 1H), 3.75 (d, J = 12.4 Hz, 2H), 2.96 (q, J = 7.6 Hz, 2H), 2.83 (d, J = 7.6 Hz, 2H), 2.60 (td, J = 12.4, 2.4 Hz, 2H), 2.40−2.27 (m, 1H), 2.20−2.05 (m, 2H), 1.84 (d, J = 7.6 Hz, 2H), 1.68−1.48 (m, 4H), 1.38−1.13 (m, 6H), 0.89 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 134.8, 133.9, 131.7, 129.0, 127.8, 61.6, 49.5, 45.1, 34.4, 30.9,27.7, 25.9, 21.8, 15.4. HRMS (ESI-TOF) calcd for $C_{19}H_{30}Br\ N_2O_2S$ $[M + H]^+$ 429.1206, found 429.1202.

1′-((4-Chloro-3-(trifluoromethyl)phenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (39). Reaction of amine **1a** with 4-chloro-3-(trifluoromethyl)benzene-1-sulfonyl chloride (Procedure A) yielded **39** as a light brown solid (>95%); mp 118−120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.84 (dd, J = 8.5, 2.1 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 3.84 (d, J = 12.1 Hz, 2H), 2.78 (d, J = 11.1 Hz, 2H), 2.37−2.18 (m, 3H), 2.12 (td, J = 11.5, 2.7 Hz, 2H), 1.86 (d, J = 11.8 Hz, 2H), 1.71−1.52 (m, 4H), 1.36−1.24 (m, 1H), 1.17 (qd, J = 11.9, 3.8 Hz, 2H), 0.88 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 135.7, 132.4, 131.7, 129.5 (q, J = 32.6 Hz), 126.7 (q, J = 5.3 Hz), 122.0 (q, J = 274.1 Hz), 61.3, 49.4, 45.9, 34.1, 30.8, 27.1, 21.7. HRMS (ESI-TOF) calcd for $C_{18}H_{25}ClF_3N_2O_2S$ $[M + H]^+$ 425.1261, found 425.1272.

1′-((3,4-Dichlorophenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (40). Reaction of amine **1a** with 3,4-dichlorobenzene-1-sulfonyl chloride (Procedure A) yielded **40** as a light brown solid (86%); mp 160−162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 1.9 Hz, 1H), 7.66−7.44 (m, 2H), 3.81 (d, J = 12.1 Hz, 2H), 2.76 (d, J = 11.2 Hz, 2H), 2.29 (td, J = 11.9, 2.5 Hz, 2H), 2.20 (tt, J = 11.5, 3.5 Hz, 1H), 2.10 (td, J = 11.5, 2.4 Hz, 2H), 1.84 (d, J = 11.5 Hz, 2H), 1.62

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(ddt, J = 16.3, 12.5, 5.6 Hz, 4H), 1.36−1.23 (m, 1H), 1.15 (qd, J = 11.8, 11.2, 3.7 Hz, 2H), 0.87 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 136.2, 133.8, 131.1, 129.4, 126.6, 61.3, 49.5, 46.1, 34.6, 31.0, 27.4, 21.8. HRMS (ESI-TOF) calcd for $C_{17}H_{25}Cl_2N_2O_2S$ $[M + H]^+$ 391.1008, found 391.1018.

1′-((2,4-Dichlorophenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (41). Reaction of amine **1a** with 2,4-dichlorobenzene-1-sulfonyl chloride (Procedure A) yielded **41** as a light orange solid (88%); mp 75−78 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.6 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.33 (dd, J = 8.5, 2.0 Hz, 1H), 3.85 (d, J = 12.9 Hz, 2H), 2.81 (d, J = 11.7 Hz, 2H), 2.71 (td, J = 12.5, 2.4 Hz, 2H), 2.37 (tt, J = 11.7, 3.5 Hz, 1H), 2.14 (td, J = 11.0, 2.2 Hz, 2H), 1.83 (d, J = 12.1 Hz, 2H), 1.67−1.47 (m, 4H), 1.38−1.25 (m, 1H), 1.25−1.11 (m, 2H), 0.87 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 135.2, 133.2, 132.9, 131.8, 127.2, 61.6, 49.5, 45.6, 34.4, 30.9, 27.8, 21.8. HRMS (ESI-TOF) calcd for $C_{17}H_{25}Cl_2N_2O_2S$ $[M + H]^+$ 391.1008, found 391.1013.

1′-((3,5-Dichlorophenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (42). Reaction of amine **1a** with 3,5-dichlorobenzene-1-sulfonyl chloride (Procedure A) yielded **42** as a pink solid (92%); mp 128−131 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 2.0 Hz, 2H), 7.57 (t, J = 1.9 Hz, 1H), 3.92−3.76 (m, 2H), 2.83 (d, J = 6.2 Hz, 2H), 2.47−2.25 (m, 3H), 2.17 (t, J = 11.3 Hz, 2H), 1.90 (d, J = 14.2 Hz, 2H), 1.65 (td, J = 12.6, 4.1 Hz, 4H), 1.37−1.27 (m, 1H), 1.27−1.13 (m, 2H), 0.90 (d, J = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 136.1, 132.7, 125.8, 61.3, 49.5, 46.0, 34.2, 30.8, 27.2, 21.7. HRMS (ESI-TOF) calcd for $C_{17}H_{25}Cl_2N_2O_2S$ $[M + H]^+$ 391.1008, found 391.1001.

1′-((4-Bromo-3-chlorophenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (43). Reaction of amine **1a** with 4-bromo-3-chlorobenzene-1-sulfonyl chloride (Procedure A) yielded **43** as a white solid (95%); mp 169−171 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87−7.70 (m, 2H), 7.46 (d, J = 8.4 Hz, 1H), 3.81 (d, J = 11.8 Hz, 2H), 2.76 (d, J = 10.7 Hz, 2H), 2.29 (t, J = 12.3 Hz, 2H), 2.20 (tt, J = 11.5, 4.1 Hz, 1H), 2.15−2.05 (m, 2H), 1.84 (d, J = 12.3 Hz, 2H), 1.74−1.52 (m, 4H), 1.38−1.23 (m, 1H), 1.22−1.07 (m, 2H), 0.87 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 135.8, 134.4, 129.1, 127.9, 126.6, 61.3, 49.5, 46.1, 34.6, 31.0, 27.4, 21.8. HRMS (ESI-TOF) calcd for $C_{17}H_{25}ClBrN_2O_2S$ $[M + H]^+$ 435.0503, found 435.0515.

1′-((2,4-Difluorophenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (44). Reaction of amine **1a** with 2,4-difluorobenzene-1-sulfonyl chloride (Procedure A) yielded **44** as a white solid (88%); mp 165−168 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−7.73 (m, 2H), 7.63 (dd, J = 8.5, 1.6 Hz, 2H), 7.41 (td, J = 8.7, 6.3 Hz, 1H), 7.05−6.83 (m, 2H), 3.87 (d, J = 12.0 Hz, 2H), 2.77 (d, J = 11.6 Hz, 2H), 2.31 (td, J = 12.0, 2.5 Hz, 2H), 2.27−2.17 (m, 1H), 2.12 (td, J = 11.6, 2.4 Hz, 2H), 1.84 (d, J = 12.9 Hz, 2H), 1.71−1.53 (m, 4H), 1.37−1.24 (m, 1H), 1.24−1.09 (m, 2H), 0.88 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (dd, J = 251.0, 11.9 Hz), 159.8 (dd, J = 251.8, 11.9 Hz), 139.4 (d, J = 1.6 Hz), 135.4, 131.5 (dd, J = 9.6, 4.6 Hz), 129.4 (d, J = 3.1 Hz), 127.9, 123.5 (dd, J = 13.3, 3.9 Hz), 112.0 (dd, J = 21.3, 3.8 Hz), 104.7 (t, J = 10.0 Hz), 61.4, 49.5, 46.2, 34.5, 31.0, 27.3, 21.8. MS (ESI) calcd for $C_{17}H_{25}F_2N_2O_2S$ $[M + H]^+$ 359.2, found 359.2.

1′-((4-Bromo-2-(trifluoromethoxy)phenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (45). Reaction of amine **1a** with 4-bromo-2-(trifluoromethoxy)benzene-1-sulfonyl chloride (Procedure A) yielded **45** as a yellow solid (67%); mp 108−110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.9 Hz, 1H), 7.58−7.45 (m, 2H), 3.85 (d, J = 12.7 Hz, 2H), 2.78 (dt, J = 11.9, 3.3 Hz, 2H), 2.59 (td, J = 12.5, 2.5 Hz, 2H), 2.29 (tt, J = 11.5, 3.6 Hz, 1H), 2.11 (td, J = 11.5, 2.4 Hz, 2H), 1.82 (dt, J = 12.7, 2.7 Hz, 2H), 1.69−1.45 (m, 4H), 1.40−1.24 (m, 1H), 1.23−1.05 (m, 2H), 0.88 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 132.7, 130.1, 129.8, 127.9, 123.90, 121.3, 61.5, 49.5, 45.7, 34.59, 31.0, 27.8, 21.8. HRMS (ESI-TOF) calcd for $C_{18}H_{25}BrF_3N_2O_3S$ $[M + H]^+$ 485.0716, found 485.0724.

1′-((5-Isopropyl-4-methoxy-2-methylphenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (46). Reaction of amine **1a** with 5-isopropyl-4-methoxy-2-methylbenzene-1-sulfonyl chloride (Procedure A) yielded **46** as a brown solid (94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 6.71 (s, 1H), 3.88−3.84 (d, J = 12.8 Hz, 2H), 3.83 (s, 3H), 3.02 (p, J = 6.9 Hz, 1H), 2.80 (d, J = 11.0 Hz, 2H), 2.51 (td, J = 12.5, 2.5 Hz, 2H), 2.34−2.26 (m, 1H), 2.32 (s, 3H), 2.15 (td, J = 11.4, 2.5 Hz, 2H), 1.80 (d, J = 11.8 Hz, 2H), 1.67−1.51 (m, 4H), 1.37−1.11 (m, 3H), 1.16 (d, J = 6.8 Hz, 6H), 0.86 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 142.3, 139.1, 128.0, 123.8, 114.1, 62.0, 56.0, 49.4, 45.8, 34.3, 30.9, 28.7, 27.7, 23.2, 21.8, 19.7. HRMS (ESI-TOF) calcd for $C_{22}H_{37}N_2O_3S$ $[M + H]^+$ 409.2519, found 409.2511.

1′-(Mesitylsulfonyl)-4-methyl-1,4′-bipiperidine (47). Reaction of amine **1a** with 2,4,6-trimethylbenzene-1-sulfonyl chloride (Procedure A) yielded **47** as a yellow solid (>95%); mp 62−65 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (s, 2H), 3.62 (d, J = 12.5 Hz, 2H), 2.85 (d, J = 12.4 Hz, 2H), 2.75 (t, J = 12.4 Hz, 2H), 2.61 (s, 6H), 2.34 (t, J = 11.5 Hz, 1H), 2.29 (s, 3H), 2.12 (t, J = 11.4 Hz, 2H), 1.86 (d, J = 11.1 Hz, 2H), 1.63 (d, J = 13.4 Hz, 2H), 1.50 (qd, J = 12.3, 4.0 Hz, 2H), 1.39−1.27 (br, 1H), 1.27−1.13 (m, 2H), 0.90 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 140.4, 131.8, 131.7, 61.8, 49.6, 44.0, 34.6, 31.0, 27.7, 22.8, 21.9, 20.9. HRMS (ESI-TOF) calcd for $C_{20}H_{33}N_2O_2S$ $[M + H]^+$ 365.2257, found 365.2252.

1′-((2,4-Dichloro-5-methylphenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (48). Reaction of amine **1a** with 2,4-dichloro-5-methylbenzene-1-sulfonyl chloride (Procedure A) yielded **48** as a white solid (83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.49 (s, 1H), 3.87 (d, J = 12.9 Hz, 2H), 2.82 (d, J = 11.2 Hz, 2H), 2.71 (td, J = 12.4, 2.4 Hz, 2H), 2.38 (s, 3H), 2.36−2.26 (m, 1H), 2.15 (t, J = 11.2 Hz, 2H), 1.83 (d, J = 11.6 Hz, 2H), 1.65−1.51 (m, 4H), 1.39−1.25 (m, 1H), 1.06 (t, J = 12.0 Hz, 2H), 0.89 (d, J = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 135.5, 134.6, 133.6, 132.0, 129.9, 61.7, 49.5, 45.6, 34.5, 31.0, 27.7, 21.8, 19.6. HRMS (ESI-TOF) calcd for $C_{18}H_{27}Cl_2N_2O_2S$ $[M + H]^+$ 405.1165, found 405.1165.

1′-((2,4-Dichloro-6-methylphenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (49). Reaction of amine **1a** with 2,4-dichloro-6-methylbenzene-1-sulfonyl chloride (Procedure A) yielded **49** as a white solid (93%); mp 89−91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 2.3 Hz, 1H), 7.19 (dd, J = 2.3, 0.9 Hz, 1H), 3.79 (d, J = 12.7 Hz, 2H), 2.93−2.73 (m, 4H), 2.67 (s, 3H), 2.45−2.27 (m, 1H), 2.14 (td, J = 11.3, 2.5 Hz, 2H), 1.83 (dd, J = 12.3, 3.4 Hz, 2H), 1.57 (dtd, J = 24.4, 11.6, 4.0 Hz, 4H), 1.30 (ddt, J = 12.8, 6.4, 3.7 Hz, 1H), 1.18 (qd, J = 12.0, 3.9 Hz, 2H), 0.89 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 137.7, 135.3, 134.2, 131.6, 130.2, 61.7, 49.5, 45.0, 34.6, 31.0, 27.9, 24.0, 21.8. HRMS (ESI-TOF) calcd for $C_{18}H_{27}Cl_2N_2O_2S$ $[M + H]^+$ 405.1165, found 405.1161.

1′-((4-Bromo-3,5-difluorophenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (50). Reaction of amine **1a** with 4-bromo-3,5-difluorobenzene-1-sulfonyl chloride (Procedure A) yielded **50** as a white solid (73%); mp 161−163 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.27 (m, 2H), 3.81 (d, J = 12.0 Hz, 2H), 2.77 (d, J = 11.7 Hz, 2H), 2.34 (td, J = 12.0, 2.5 Hz, 2H), 2.22 (tt, J = 11.4, 3.6 Hz, 1H), 2.10 (td, J = 11.5, 2.5 Hz, 2H), 1.85 (d, J = 11.4 Hz, 2H), 1.71−1.55 (m, 4H), 1.37−1.24 (m, 1H), 1.16 (qd, J = 11.8, 3.8 Hz, 2H), 0.88 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9 (dd, J = 255.0, 3.8 Hz), 137.9 (t, J = 7.6 Hz), 111.0 (m), 103.9, 103.7 (t, J = 96.4 Hz), 61.2, 49.5, 46.1, 34.5, 31.0, 27.4, 21.8. HRMS (ESI-TOF) calcd for $C_{17}H_{24}BrF_2N_2O_2S$ $[M + H]^+$ 437.0704, found 437.0695.

1′-([1,1′-Biphenyl]-2-ylsulfonyl)-4-methyl-1,4′-bipiperidine (51). Reaction of amine **1a** with [1,1′-biphenyl]-2-sulfonyl chloride (Procedure A) yielded **51** as a yellow solid (>95%); mp 106−109 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, J = 8.0, 1.6 Hz, 1H), 7.56 (td, J = 7.6, 1.6 Hz, 1H), 7.46 (td, J = 7.6, 1.6 Hz, 1H), 7.43−7.36 (m, 5H), 7.30 (dd, J = 7.6, 1.6 Hz, 1H), 3.29 (d, J = 12.8, 2H), 2.71 (d, J = 10.8 Hz, 2H), 2.22 (td, J = 12.6, 2.5 Hz, 3H), 2.09 (t, J = 10.4 Hz, 2H), 1.90−1 49 (m, 4H), 1.36−1.13 (m, 5H), 0.88 (d, J = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 139.7, 137.1, 133.0, 132.2, 130.3, 129.6, 127.7, 127.5, 61.7, 49.3, 44.4, 34.4, 31.0, 27.2, 21.8. HRMS (ESI-TOF) calcd for $C_{23}H_{31}N_2O_2S$ $[M + H]^+$ 399.2101, found 399.2101.

1′-((4′-Chloro-[1,1′-biphenyl]-2-yl)sulfonyl)-4-methyl-1,4′-bipiperidine (52). Reaction of **30** with 4-(chlorophenyl)boronic acid (Procedure C) yielded **52** as a black gel (66%). ^{1}H NMR (400

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MHz, $CDCl_3$) δ 8.08 (dd, J = 8.0, 1.2 Hz, 1H), 7.55 (td, J = 7.5, 1.4 Hz, 1H), 7.47 (td, J = 7.8, 1.5 Hz, 1H), 7.34 (s, 4H), 7.26 (dd, J = 7.6, 1.4 Hz, 1H), 3.32 (d, J = 12.4 Hz, 2H), 2.70 (d, J = 11.6 Hz, 2H), 2.36−2.15 (m, 3H), 2.08 (td, J = 11.7, 2.5 Hz, 2H), 1.60 (s, 4H), 1.38−1.02 (m, 5H), 0.87 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 140.3, 138.1, 137.0, 133.8, 132.8, 132.4, 131.0, 130.3, 127.8, 127.6, 61.5, 49.3, 44.6, 34.5, 31.0, 27.3, 21.8. LC−MS (ESI) calcd for $C_{23}H_{30}ClN_2O_2S$ $[M + H]^+$ 433.2, found 433.2.

1′-((4′-Methoxy-[1,1′-biphenyl]-2-yl)sulfonyl)-4-methyl-1,4′-bipiperidine (53). Reaction of **30** with (4-methoxyphenyl)-boronic acid (Procedure C) yielded **53** as a black gel (59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, J = 7.9, 1.4 Hz, 1H), 7.52 (td, J = 7.5, 1.4 Hz, 1H), 7.44−7.40 (m, 1H), 7.35−7.31 (m, 2H), 7.30−7.23 (m, 1H), 6.93−6.87 (m, 2H), 3.81 (s, 3H), 3.31 (d, J = 12.9 Hz, 2H), 2.68 (d, J = 11.6 Hz, 2H), 2.34−2.12 (m, 3H), 2.06 (td, J = 11.6, 2.5 Hz, 2H), 1.57 (d, J = 12.5 Hz, 4H), 1.39−1.01 (m, 5H), 0.86 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 141.4, 137.1, 133.2, 132.2, 132.0, 130.9, 130.3, 128.5, 128.4, 127.2, 112.9, 61.6, 55.3, 49.3, 44.6, 34.6, 31.0, 27.3, 21.9. HRMS (ESI-TOF) calcd for $C_{24}H_{33}N_2O_3S$ $[M + H]^+$ 429.2206, found 429.2199.

4-Methyl-1′-((4′-methyl-[1,1′-biphenyl]-2-yl)sulfonyl)-1,4′-bipiperidine (54). Reaction of **30** with *p*-tolylboronic acid (Procedure C) yielded **54** as a brown gel (23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, J = 8.0, 1.4 Hz, 1H), 7.54 (td, J = 7.5, 1.4 Hz, 1H), 7.44 (td, J = 7.7, 1.5 Hz, 1H), 7.28 (d, J = 7.9 Hz, 3H), 7.18 (d, J = 7.8 Hz, 2H), 3.33 (d, J = 13.1 Hz, 2H), 2.84 (d, J = 10.7 Hz, 2H), 2.43 (t, J = 12.6 Hz, 1H), 2.37 (s, 3H), 2.22 (td, J = 12.6, 2.4 Hz, 4H), 1.76−1.58 (m, 4H), 1.47−1.19 (m, 5H), 0.90 (d, J = 4.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 137.5, 136.9, 136.7, 133.1, 132.3, 130.2, 129.4, 128.2, 127.3, 62.0, 49.1, 44.2, 33.4, 30.6, 26.7, 21.5, 21.2. HRMS (ESI-TOF) calcd for $C_{24}H_{33}N_2O_2S$ $[M + H]^+$ 413.2257, found 413.2264.

4-Methyl-1′-((4′-(trifluoromethyl)-[1,1′-biphenyl]-2-yl)-sulfonyl)-1,4′-bipiperidine (55). Reaction of **30** with (4-(trifluoromethyl)phenyl)boronic acid (Procedure C) yielded **55** as a black solid (12%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, J = 8.0, 1.4 Hz, 1H), 7.65 (d, J = 8.1 Hz, 2H), 7.59 (tt, J = 7.5, 1.1 Hz, 1H), 7.56−7.49 (m, 3H), 7.29 (dd, J = 7.7, 1.4 Hz, 1H), 3.30 (d, J = 12.8 Hz, 2H), 2.73 (d, J = 11.0 Hz, 2H), 2.31 (td, J = 12.6, 2.4 Hz, 3H), 2.10 (t, J = 12.3 Hz, 2H), 1.64 (t, J = 12.4 Hz, 4H), 1.35−1.12 (m, 5H), 0.88 (d, J = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 140.1, 136.9, 132.7, 132.5, 130.3, 130.1, 130.0, 129.8, 128.2, 124. 4 (q, J = 3.7 Hz), 61.6, 49.3, 44.5, 34.3, 30.9, 27.1, 21.7. HRMS (ESI-TOF) calcd for $C_{24}H_{30}F_3N_2O_2S$ $[M + H]^+$ 467.1975, found 467.1967.

1′-([1,1′-Biphenyl]-4-ylsulfonyl)-4-methyl-1,4′-bipiperidine (56). Reaction of **17** with phenylboronic acid (Procedure C) yielded **56** as a white solid (21%); mp 178−181 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.64−7.56 (m, 2H), 7.52−7.45 (m, 2H), 7.45−7.37 (m, 1H), 3.90 (d, J = 12.1 Hz, 2H), 2.84 (d, J = 10.8 Hz, 2H), 2.32 (td, J = 12.1, 2.5 Hz, 3H), 2.20 (t, J = 11.9 Hz, 2H), 1.91 (d, J = 12.6 Hz, 2H), 1.77−1.57 (m, 4H), 1.42−1.12 (m, 3H), 0.90 (d, J = 5.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 139.2, 134.6, 129.1, 129.1, 128.5, 128.2, 127.6, 127.3, 61.6, 49.4, 46.1, 34.1, 30.8, 27.1, 21.7. HRMS (ESI-TOF) calcd for $C_{23}H_{31}N_2O_2S$ $[M + H]^+$ 399.2101, found 399.2097.

1′-((4′-Chloro-[1,1′-biphenyl]-4-yl)sulfonyl)-4-methyl-1,4′-bipiperidine (57). Reaction of amine **1a** with 4′-chloro-[1,1′-biphenyl]-4-sulfonyl chloride (Procedure A) yielded **57** as a white solid (87%); mp 205−207 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88−7.75 (m, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 3.87 (d, J = 12.0 Hz, 2H), 2.76 (d, J = 10.9 Hz, 2H), 2.41−2.02 (m, 5H), 1.83 (dd, J = 12.3, 3.6 Hz, 2H), 1.70−1.46 (m, 4H), 1.37−1.05 (m, 3H), 0.87 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 137.7, 135.1, 134.7, 129.2, 128.5, 128.3, 127.4, 61.4, 49.5, 46.2, 34.6, 31.0, 27.3, 21.8. HRMS (ESI-TOF) calcd for $C_{23}H_{30}ClN_2O_2S$ $[M + H]^+$ 433.1711, found 433.1706.

1′-((4′-Methoxy-[1,1′-biphenyl]-4-yl)sulfonyl)-4-methyl-1,4′-bipiperidine (58). Reaction of amine **1a** with 4′-methoxy-[1,1′-biphenyl]-4-sulfonyl chloride (Procedure A) yielded **58** as a white solid (92%); mp 195−198 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.72 (m, 2H), 7.66 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 8.7 Hz, 2H), 7.04−6.88 (m, 2H), 3.88 (d, J = 12.0 Hz, 2H), 3.84 (s, 3H), 2.76 (d, J = 11.6 Hz, 2H), 2.40−1.95 (m, 5H), 1.83 (d, J = 10.7 Hz, 2H), 1.71−1.48 (m, 4H), 1.36−1.23 (m, 1H), 1.23−1.04 (m, 2H), 0.87 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 145.1, 133.9, 131.6, 128.4, 128.2, 126.9, 114.5, 61.5, 55.4, 49.5, 46.2, 34.6, 31.0, 27.4, 21.9. HRMS (ESI-TOF) calcd for $C_{24}H_{33}N_2O_3S$ $[M + H]^+$ 429.2206, found 429.2203.

1′-((2′-Methoxy-[1,1′-biphenyl]-4-yl)sulfonyl)-4-methyl-1,4′-bipiperidine (59). Reaction of amine **1a** with 2′-methoxy-[1,1′-biphenyl]-4-sulfonyl chloride (Procedure A) yielded **59** as a colorless gel (88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.3 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.35 (t, J = 7.9 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 7.07−6.91 (m, 2H), 3.86 (d, J = 11.6 Hz, 2H), 3.80 (s, 3H), 2.77 (d, J = 11.4 Hz, 2H), 2.32 (t, J = 11.3 Hz, 2H), 2.22 (tt, J = 11.6, 3.7 Hz, 1H), 2.11 (t, J = 10.8 Hz, 2H), 1.83 (d, J = 11.2 Hz, 2H), 1.73−1.52 (m, 4H), 1.37−1.23 (m, 1H), 1.16 (qd, J = 11.9, 3.7 Hz, 2H), 0.87 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 143.2, 134.2, 130.7, 130.0, 129.8, 128.6, 127.3, 121.0, 111.3, 61.4, 55.5, 49.4, 46.1, 34.5, 31.0, 27.3, 21.8. HRMS (ESI-TOF) calcd for $C_{24}H_{33}N_2O_3S$ $[M + H]^+$ 429.2206, found 429.2205.

1′-((2′-Fluoro-[1,1′-biphenyl]-4-yl)sulfonyl)-4-methyl-1,4′-bipiperidine (60). Reaction of amine **1a** with 2′-fluoro-[1,1′-biphenyl]-4-sulfonyl chloride (Procedure A) yielded **60** as a colorless gel (73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.76 (m, 2H), 7.72−7.64 (m, 2H), 7.42 (td, J = 7.7, 1.8 Hz, 1H), 7.39−7.33 (m, 1H), 7.24 (dd, J = 6.3, 1.3 Hz, 1H), 7.22−7.12 (m, 1H), 3.87 (d, J = 12.0 Hz, 2H), 2.77 (d, J = 11.5 Hz, 2H), 2.42−2.17 (m, 3H), 2.11 (td, J = 11.7, 2.4 Hz, 2H), 1.84 (d, J = 13.6 Hz, 2H), 1.72−1.54 (m, 4H), 1.36−1.23 (m, 1H), 1.24−1.09 (m, 2H), 0.87 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6 (d, J = 249.1 Hz), 140.3 (d, J = 1.3 Hz), 135.2, 130.6 (d, J = 3.1 Hz), 130.2 (d, J = 8.3 Hz), 129.5 (d, J = 3.2 Hz), 127.8, 127.2 (d, J = 13.0 Hz), 124.7 (d, J = 3.7 Hz), 116.3 (d, J = 22.6 Hz), 61.4, 49.4, 46.2, 34.5, 31.0, 27.3, 21.8. HRMS (ESI-TOF) calcd for $C_{23}H_{30}FN_2O_2S$ $[M + H]^+$ 417.2007, found 417.1995.

1′-([1,1′-Biphenyl]-3-ylsulfonyl)-4-methyl-1,4′-bipiperidine (61). Reaction of **29** with phenylboronic acid (Procedure C) yielded **61** as a black gel (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (t, J = 1.8 Hz, 1H), 7.79 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H), 7.71 (ddd, J = 7.8, 1.8, 1.1 Hz, 1H), 7.62−7.55 (m, 3H), 7.50−7.43 (m, 1H), 7.43−7.36 (m, 1H), 3.87 (d, J = 12.0 Hz, 2H), 2.77 (d, J = 11.7 Hz, 2H), 2.28 (td, J = 12.0, 2.5 Hz, 2H), 2.20 (td, J = 8.1, 4.1 Hz, 1H), 2.11 (td, J = 11.5, 2.4 Hz, 2H), 1.83 (d, J = 11.6 Hz, 2H), 1.72−1.54 (m, 4H), 1.37−1.23 (m, 1H), 1.17 (qd, J = 12.1, 3.8 Hz, 2H), 0.87 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 142.3, 139.2, 136.7, 131.3, 129.4, 129.1, 128.3, 127.2, 126.2, 126.1, 61.4, 49.4, 46.2, 34.4, 31.0, 27.3, 21.8. HRMS (ESI-TOF) calcd for $C_{23}H_{31}N_2O_2S$ $[M + H]^+$ 399.2101, found 399.2096.

1′-((4′-Chloro-[1,1′-biphenyl]-3-yl)sulfonyl)-4-methyl-1,4′-bipiperidine (62). Reaction of **29** with 4-(chlorophenyl)boronic acid (Procedure C) yielded **62** as a pink solid (58%); mp 124−126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (t, J = 1.8 Hz, 1H), 7.72 (ddt, J = 15.7, 7.9, 1.4 Hz, 2H), 7.58 (t, J = 7.8 Hz, 1H), 7.54−7.48 (m, 2H), 7.45−7.39 (m, 2H), 3.86 (d, J = 12.1 Hz, 2H), 2.80 (dt, J = 11.5, 3.1 Hz, 2H), 2.27 (td, J = 12.1, 2.4 Hz, 3H), 2.13 (t, J = 10.6 Hz, 2H), 1.86 (d, J = 13.3 Hz, 2H), 1.72−1.52 (m, 4H), 1.38−1.14 (m, 3H), 0.87 (d, J = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 137.6, 136.9, 134.5, 131.1, 129.6, 129.2, 128.5, 126.5, 125.8, 61.5, 49.4, 46.1, 34.2, 30.8, 27.1, 21.7. HRMS (ESI-TOF) calcd for $C_{23}H_{30}ClN_2O_2S$ $[M + H]^+$ 433.1711, found 433.1705.

1′-((4′-Methoxy-[1,1′-biphenyl]-3-yl)sulfonyl)-4-methyl-1,4′-bipiperidine (63). Reaction of **29** with (4-methoxyphenyl)-boronic acid (Procedure C) yielded **63** as a yellow solid (44%); mp 107−109 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.58−7.47 (m, 3H), 6.98 (d, J = 8.5 Hz, 2H), 3.87 (d, J = 12.2 Hz, 2H), 3.84 (s, 3H), 2.80 (d, J = 10.0 Hz, 2H), 2.27 (td, J = 12.0, 2.4 Hz, 3H), 2.15 (t, J = 11.9 Hz, 2H), 1.87 (d, J = 11.7 Hz, 2H), 1.75−1.53 (m, 4H), 1.38−1.19 (m, 3H), 0.88 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 141.9, 136.6, 131.6, 130.8, 129.4, 128.3, 125.6, 125.5, 114.5, 61.5,

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55.4, 49.4, 46.1, 34.2, 30.8, 27.1, 21.7. HRMS (ESI-TOF) calcd for $C_{24}H_{33}N_2O_3S$ $[M + H]^+$ 429.2206, found 429.2206.

4-Methyl-1′-((4′-methyl-[1,1′-biphenyl]-3-yl)sulfonyl)-1,4′-bipiperidine (64). Reaction of **29** with *p*-tolylboronic acid (Procedure C) yielded **64** as a yellow solid (95%); mp 103−105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.49 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 7.9 Hz, 2H), 3.87 (d, J = 11.9 Hz, 2H), 2.81 (d, J = 11.2 Hz, 2H), 2.40 (s, 3H), 2.31−2.20 (m, 3H), 2.17 (t, J = 11.8 Hz, 2H), 1.86 (d, J = 12.4 Hz, 2H), 1.74−1.55 (m, 4H), 1.40−1.12 (m, 3H), 0.88 (d, J = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 138.3, 136.6, 136.3, 131.1, 129.8, 129.4, 127.0, 125.9, 125.8, 61.5, 49.4, 46.1, 34.1, 30.8, 27.1, 21.7, 21.1. HRMS (ESI-TOF) calcd for $C_{24}H_{33}N_2O_2S$ $[M + H]^+$ 413.2257, found 413.2258.

1′-((4′-Fluoro-[1,1′-biphenyl]-3-yl)sulfonyl)-4-methyl-1,4′-bipiperidine (65). Reaction of **29** with (4-fluorophenyl)boronic acid (Procedure C) yielded **65** as a white solid (63%); mp 131−134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.76−7.66 (m, 2H), 7.60−7.50 (m, 3H), 7.14 (t, J = 8.6 Hz, 2H), 3.86 (d, J = 11.9 Hz, 2H), 2.75 (d, J = 11.5 Hz, 2H), 2.28 (td, J = 12.1, 2.5 Hz, 2H), 2.18 (tt, J = 11.5, 3.6 Hz, 1H), 2.09 (td, J = 11.5, 2.4 Hz, 2H), 1.82 (d, J = 11.8 Hz, 2H), 1.70−1.51 (m, 4H), 1.38−1.20 (m, 1H), 1.21−1.06 (m, 2H), 0.86 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.94 (d, J = 248.1 Hz), 141.27, 136.89, 135.39 (d, J = 3.3 Hz), 131.11, 129.53, 128.89 (d, J = 8.3 Hz), 126.26, 125.88, 116.02 (d, J = 21.6 Hz), 61.40, 49.47, 46.20, 34.58, 31.01, 27.36, 21.86. HRMS (ESI-TOF) calcd for $C_{23}H_{30}FN_2O_2S$ $[M + H]^+$ 417.2007, found 417.2018.

1′-((2′-Methoxy-[1,1′-biphenyl]-3-yl)sulfonyl)-4-methyl-1,4′-bipiperidine (66). Reaction of **29** with (2-methoxyphenyl)-boronic acid (Procedure C) yielded **66** as an orange gel (53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.73 (dt, J = 7.8, 1.4 Hz, 1H), 7.67 (dt, J = 8.0, 1.4 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 7.39−7.27 (m, 2H), 7.08−6.94 (m, 2H), 3.86 (d, J = 12.0 Hz, 2H), 3.78 (s, 3H), 2.77 (d, J = 11.6 Hz, 2H), 2.43−2.17 (m, 3H), 2.13 (t, J = 11.0 Hz, 2H), 1.82 (d, J = 12.1 Hz, 2H), 1.71−1.52 (m, 4H), 1.38−1.24 (m, 1H), 1.24−1.10 (m, 2H), 0.87 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 139.5, 135.5, 133.7, 130.7, 129.6, 128.7, 128.6, 128.5, 125.8, 121.0, 111.3, 61.5, 55.5, 49.4, 46.2, 34.5, 31.0, 27.3, 21.8. HRMS (ESI-TOF) calcd for $C_{24}H_{33}N_2O_3S$ $[M + H]^+$ 429.2206, found 429.2192.

1′-((2′-Fluoro-[1,1′-biphenyl]-3-yl)sulfonyl)-4-methyl-1,4′-bipiperidine (67). Reaction of **29** with (2-fluorophenyl)boronic acid (Procedure C) yielded **67** as a yellow gel (74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 1.6 Hz, 1H), 7.79−7.68 (m, 2H), 7.57 (t, J = 7.8 Hz, 1H), 7.41 (td, J = 7.7, 1.9 Hz, 1H), 7.38−7.31 (m, 1H), 7.25−7.18 (m, 1H), 7.14 (ddd, J = 10.8, 8.2, 1.2 Hz, 1H), 3.86 (d, J = 12.1 Hz, 2H), 2.80 (d, J = 11.8 Hz, 2H), 2.29 (td, J = 12.1, 2.5 Hz, 3H), 2.21−2.08 (m, 2H), 1.87 (d, J = 12.6 Hz, 2H), 1.70−1.46 (m, 4H), 1.39−1.05 (m, 3H), 0.86 (d, J = 5.9 Hz, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 159.58 (d, J = 248.6 Hz), 136.83, 136.38, 133.19 (d, J = 3.0 Hz), 132.03 (d, J = 9.9 Hz), 130.55 (d, J = 3.0 Hz), 130.06 (d, J = 8.3 Hz), 129.15, 127.94 (d, J = 3.1 Hz), 126.64, 124.69 (d, J = 3.7 Hz), 116.27 (d, J = 22.5 Hz), 61.50, 49.38, 46.06, 34.11, 30.78, 27.10, 21.71. HRMS (ESI-TOF) calcd for $C_{23}H_{30}FN_2O_2S$ $[M + H]^+$ 417.2007, found 417.1999.

4-Methyl-1′-((2′-(trifluoromethyl)-[1,1′-biphenyl]-3-yl)-sulfonyl)-1,4′-bipiperidine (68). Reaction of **29** with (2-(trifluoromethyl)phenyl)boronic acid (Procedure C) yielded **68** as a yellow solid (37%); mp 110−112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80−7.68 (m, 3H), 7.61−7.47 (m, 4H), 7.30 (d, J = 8.0 Hz, 1H), 3.82 (d, J = 12.1 Hz, 1H), 2.79 (d, J = 11.7 Hz, 2H), 2.35−2.18(m, 3H), 2.13 (td, J = 11.5, 2.4 Hz, 2H), 1.84 (d, J = 10.8 Hz, 2H), 1.70−1.53 (m, 4H), 1.38−1.25 (m, 1H), 1.25−1.12 (qd, J = 12.0, 3.8 Hz, 2H), 0.87 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 139.3 (q, J = 2.1 Hz), 135.8, 133.2, 131.8, 131.7, 128.6, 128.2, 128.1 (q, J = 1.6 Hz), 126.9, 126.2 (q, J = 5.3 Hz), 124.0 (q, J = 274.0 Hz), 61.5, 49.4, 46.1, 34.3, 30.9, 27.2, 21.8. HRMS (ESI-TOF) calcd for $C_{24}H_{30}F_3N_2O_2S$ $[M + H]^+$ 467.1975, found 467.1981.

1′-((3′,5′-Dimethyl-[1,1′-biphenyl]-3-yl)sulfonyl)-4-methyl-1,4′-bipiperidine (69). Reaction of **29** with (3,5-dimethylphenyl)-boronic acid (Procedure C) yielded **69** as a yellow solid (45%); mp 120−123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.77 (dt, J = 7.7, 1.4 Hz, 1H), 7.68 (dd, J = 7.8, 3.0 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.19 (s, 2H), 7.03 (s, 1H), 3.86 (d, J = 12.0 Hz, 2H), 2.77 (d, J = 11.3 Hz, 2H), 2.37 (s, 6H), 2.33−2.16 (m, 3H), 2.11 (t, J = 11.1 Hz, 2H), 1.83 (dt, J = 12.2, 3.1 Hz, 2H), 1.72−1.54 (m, 4H), 1.39−1.08 (m, 3H), 0.87 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 139.2, 138.7, 136.5, 131.3, 129.9, 129.3, 126.1, 125.1, 61.4, 49.4, 46.2, 34.4, 30.9, 27.2, 21.8, 21.4. HRMS (ESI-TOF) calcd for $C_{25}H_{35}N_2O_2S$ $[M + H]^+$ 427.2414, found 427.2407.

4-Methyl-1′-((3-(naphthalen-2-yl)phenyl)sulfonyl)-1,4′-bipiperidine (70). Reaction of **29** with naphthalen-2-ylboronic acid (Procedure C) yielded **70** as a yellow gel (29%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 9.7 Hz, 2H), 7.96−7.82 (m, 4H), 7.72 (ddd, J = 10.5, 8.2, 1.6 Hz, 2H), 7.62 (t, J = 7.8 Hz, 1H), 7.56−7.47 (m, 2H), 3.90 (d, J = 11.9 Hz, 2H), 2.79 (d, J = 11.2 Hz, 2H), 2.38−2.20 (m, 3H), 2.13 (t, J = 10.8 Hz, 2H), 1.87 (d, J = 12.5 Hz, 2H), 1.74−1.51 (m, 4H), 1.39−1.13 (m, 3H), 0.88 (d, J = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 136.8, 136.5, 133.5, 132.9, 131.5, 129.6, 128.9, 128.3, 127.7, 126.7, 126.6, 126.3, 126.3, 125.0, 61.5, 49.4, 46.2, 34.3, 30.9, 27.2, 21.8. HRMS (ESI-TOF) calcd for $C_{27}H_{33}N_2O_2S$ $[M + H]^+$ 449.2257, found 449.2254.

4-Methyl-1′-(pyridin-3-ylsulfonyl)-1,4′-bipiperidine (71). Reaction of amine **1a** with pyridine-3-sulfonyl chloride (Procedure A) yielded **71** as a yellow solid (86%); mp 144−147 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.82 (d, J = 4.9 Hz, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.49 (dd, J = 8.0, 4.9 Hz, 1H), 3.88 (d, J = 12.3 Hz, 2H), 2.78 (d, J = 11.9 Hz, 2H), 2.32 (td, J = 12.0, 2.4 Hz, 2H), 2.22 (tt, J = 11.6, 3.6 Hz, 1H), 2.12 (t, J = 11.6 Hz, 2H), 1.86 (d, J = 11.9 Hz, 2H), 1.75−1.55 (m, 4H), 1.38−1.23 (m, 1H), 1.17 (qd, J = 12.0, 3.7 Hz, 2H), 0.89 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 148.4, 135.2, 133.1, 123.7, 61.3, 49.5, 46.0, 34.5, 31.0, 27.3, 21.8. HRMS (ESI-TOF) calcd for $C_{16}H_{25}ClN_3O_2SNa$ $[M + Na]^+$ 346.1560, found 346.1566.

1′-((2-Chloropyridin-3-yl)sulfonyl)-4-methyl-1,4′-bipiperidine (72). Reaction of amine **1a** with 2-chloropyridine-3-sulfonyl chloride (Procedure A) yielded **72** as a white solid (71%); mp 122−124 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, J = 4.9 Hz, 1H), 8.38 (d, J = 7.8 Hz, 1H), 7.40 (dd, J = 7.8, 4.8 Hz, 1H), 3.92 (d, J = 13.0 Hz, 2H), 2.83 (t, J = 12.5 Hz, 4H), 2.38 (t, J = 11.5 Hz, 1H), 2.15 (t, J = 11.0 Hz, 2H), 1.86 (d, J = 12.5 Hz, 2H)., 1.72−1.53 (m, 4H), 1.38−1.26 (m, 1H), 1.25−1.13 (m, 2H), 0.90 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 144.5, 136.9, 130.5, 118.5, 57.6, 45.6, 41.9, 30.7, 27.1, 24.0, 17.9. HRMS (ESI-TOF) calcd for $C_{16}H_{24}ClN_3O_2SNa$ $[M + Na]^+$ 380.1170, found 380.1160.

1′-((2-Fluoropyridin-3-yl)sulfonyl)-4-methyl-1,4′-bipiperidine (73). Reaction of amine **1a** with 2-fluoropyridine-3-sulfonyl chloride (Procedure A) yielded **73** as a white solid (>95%); mp 120−123 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, J = 4.9 Hz, 1H), 8.29 (dd, J = 9.2, 7.6 Hz, 1H), 7.37 (dd, J = 7.6, 4.9 Hz, 1H), 3.96 (d, J = 12.6 Hz, 2H), 2.81 (d, J = 11.5 Hz, 2H),, 2.67 (t, J = 12.4 Hz, 2H), 2.34 (ddd, J = 11.5, 8.0, 3.5 Hz, 1H), 2.15 (t, J = 10.4 Hz, 2H), 1.87 (d, J = 12.1 Hz, 2H), 1.74−1.55 (m, 4H), 1.32 (ddt, J = 10.3, 6.9, 4.1 Hz, 1H), 1.27−1.11 (m, 2H), 0.91 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.75 (d, J = 244.0 Hz), 147.68 (d, J = 14.3 Hz), 138.2, 118.2, 117.9, 57.5, 45.6, 41.9, 30.7, 27.1, 23.8, 17.9. HRMS (ESI-TOF) calcd for $C_{16}H_{24}FN_3O_2SNa$ $[M + Na]^+$ 364.1465, found 364.1462.

1′-((6-Chloropyridin-3-yl)sulfonyl)-4-methyl-1,4′-bipiperidine (74). Reaction of amine **1a** with 6-chloropyridine-3-sulfonyl chloride (Procedure A) yielded **74** as a white solid (80%); mp 178−182 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.99 (dd, J = 8.4, 2.3 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 3.87 (d, J = 12.0 Hz, 2H), 2.81 (d, J = 8.5 Hz, 2H), 2.35 (t, J = 12.0 Hz, 2H), 2.25 (t, J = 11.4 Hz, 1H), 2.14 (t, J = 11.3 Hz, 2H), 1.89 (d, J = 11.3 Hz, 2H), 1.75−1.58 (m, 4H), 1.33 (br, 1H), 1.28−1.10 (m, 2H), 0.91 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 148.6, 137.7, 132.1, 124.7, 61.3, 49.5, 46.0, 34.4, 30.9, 27.3, 21.8. HRMS (ESI-TOF) calcd for $C_{16}H_{24}ClN_3O_2SNa$ $[M + Na]^+$ 380.1170, found 380.1171.

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1′-((5-Bromopyridin-3-yl)sulfonyl)-4-methyl-1,4′-bipiperidine (75). Reaction of amine **1a** with 5-bromopyridine-3-sulfonyl chloride (Procedure A) yielded **75** as a white solid (79%); mp 171−173 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (s, 2H), 8.18 (t, J = 2.0 Hz, 1H), 3.89 (d, J = 11.6 Hz, 2H), 2.81 (d, J = 11.0 Hz, 2H), 2.39 (td, J = 12.0, 2.5 Hz, 2H), 2.25 (d, J = 11.9 Hz, 1H), 2.14 (t, J = 11.6 Hz, 2H), 1.90 (d, J = 12.8 Hz, 2H), 1.78−1.57 (m, 4H), 1.43−1.29 (m, 1H), 1.28−1.11 (m, 2H), 0.91 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 146.2, 137.4, 134.5, 121.0, 61.2, 49.5, 46.0, 34.5, 31.0, 27.3, 21.8. HRMS (ESI-TOF) calcd for $C_{16}H_{24}BrN_3O_2SNa$ $[M + Na]^+$ 424.0665, found 424.0668.

1,3-Dimethyl-5-((4-methyl-[1,4′-bipiperidin]-1′-yl)sulfonyl)-pyrimidine-2,4(1*H*,3*H*)-dione (76). Reaction of amine **1a** with 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-sulfonyl chloride (Procedure A) yielded **76** as a white solid (78%); mp 212−215 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 3.94 (d, J = 12.8 Hz, 2H), 3.50 (s, 3H), 3.35 (s, 3H), 2.93 (d, J = 11.6 Hz, 2H), 2.85 (t, J = 12.7 Hz, 2H), 2.56 (t, J = 11.7 Hz, 1H), 2.26 (t, J = 11.9 Hz, 2H), 1.92 (d, J = 11.9 Hz, 2H), 1.75−1.58 (m, 4H), 1.48−1.20 (m, 3H), 0.93 (d, J = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 150.8, 148.1, 112.6, 61.6, 49.2, 46.0, 37.9, 33.8, 30.7, 28.3, 27.5, 21.7. HRMS (ESI-TOF) calcd for $C_{17}H_{28}N_4O_4SNa$ $[M + Na]^+$ 407.1723, found 407.1725.

4-Methyl-1′-((1-methyl-1*H*-imidazol-2-yl)sulfonyl)-1,4′-bipiperidine (77). Reaction of amine **1a** with 1-methyl-1*H*-imidazole-2-sulfonyl chloride (Procedure A) yielded **77** as a white solid (51%); mp 153−156 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 1.1 Hz, 1H), 6.92 (d, J = 1.1 Hz, 1H), 3.96 (d, J = 12.2 Hz, 2H), 3.89 (s, 3H), 3.05 (t, J = 12.5 Hz, 2H), 2.89 (d, J = 10.8 Hz, 2H), 2.54 (s, 1H), 2.24 (s, 2H), 1.94 (d, J = 12.5 Hz, 2H), 1.81−1.58 (m, 4H), 1.31 (s, 3H), 1.06−0.79 (d, J = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 128.2, 124.4, 61.8, 49.4, 46.6, 34.8, 34.1, 30.9, 27.3, 21.7. HRMS (ESI-TOF) calcd for $C_{15}H_{26}N_4O_2SNa$ $[M + Na]^+$ 349.1669, found 349.1673.

4-Methyl-1′-((1-methyl-1*H*-imidazol-4-yl)sulfonyl)-1,4′-bipiperidine (78). Reaction of amine **1a** with 1-methyl-1*H*-imidazole-4-sulfonyl chloride (Procedure A) yielded **78** as a yellow solid (61%); mp 139−142 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.42 (s, 1H), 3.90 (d, J = 13.0 Hz, 2H), 3.75 (s, 3H), 2.80 (d, J = 9.9 Hz, 2H), 2.57 (t, J = 12.1 Hz, 2H), 2.26 (t, J = 11.5 Hz, 1H), 2.13 (t, J = 10.5 Hz, 2H), 1.83 (d, J = 12.1 Hz, 2H), 1.69−1.57 (m, 4H), 1.31 (br, 1H), 1.26−1.12 (m, 2H), 0.90 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 138.3, 124.4, 61.7, 49.5, 46.3, 34.6, 34.0, 31.1, 27.4, 21.9. HRMS (ESI-TOF) calcd for $C_{15}H_{26}N_{24}O_2SNa$ $[M + Na]^+$ 349.1669, found 349.1660.

3,5-Dimethyl-4-((4-methyl-[1,4′-bipiperidin]-1′-yl)sulfonyl)-isoxazole (79). Reaction of amine **1a** with 3,5-dimethylisoxazole-4-sulfonyl chloride (Procedure A) yielded **79** as a white solid (28%); mp 158−161 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (d, J = 11.9 Hz, 2H), 2.80 (d, J = 11.5 Hz, 2H), 2.61 (s, 3H), 2.50 (t, J = 12.0 Hz, 2H), 2.38 (s, 3H), 2.27 (tt, J = 11.4, 3.5 Hz, 1H), 2.14−2.06 (m, 2H), 1.87 (d, J = 11.6 Hz, 2H), 1.72−1.50 (m, 4H), 1.38−1.24 (m, 1H), 1.25−1.09 (m, 2H), 0.89 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 158.0, 113.7, 61.3, 49.6, 45.4, 34.6, 31.0, 27.5, 21.9, 13.0, 11.4. HRMS (ESI-TOF) calcd for $C_{16}H_{28}N_3O_3S$ $[M + H]^+$ 342.1846, found 342.1854.

2-Chloro-5-((4-methyl-[1,4′-bipiperidin]-1′-yl)sulfonyl)-thiazole (80). Reaction of amine **1a** with 2-chlorothiazole-5-sulfonyl chloride (Procedure A) yielded **80** as a pale yellow solid (51%); mp 141−143 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 3.82 (d, J = 10.4 Hz, 2H), 2.83 (d, J = 8.6 Hz, 2H), 2.45 (td, J = 12.3, 2.7 Hz, 2H), 2.32 (t, J = 11.4 Hz, 1H), 2.16 (t, J = 11.5 Hz, 2H), 1.92 (d, J = 12.3 Hz, 2H), 1.74−1.56 (m, 4H), 1.39−1.13 (m, 3H), 0.89 (d, J = 6.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 144.9, 134.4, 61.2, 49.5, 46.0, 34.2, 30.8, 27.1, 21.7. HRMS (ESI-TOF) calcd for $C_{14}H_{22}ClN_3O_2S_2Na$ $[M + Na]^+$ 386.0734, found 386.0745.

2-Chloro-4-methyl-5-((4-methyl-[1,4′-bipiperidin]-1′-yl)-sulfonyl)thiazole (81). Reaction of amine **1a** with 2-chloro-4-methylthiazole-5-sulfonyl chloride (Procedure A) yielded **81** as a white solid (64%); mp 117−119 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (d, J = 13.5 Hz, 2H), 2.82 (d, J = 11.0 Hz, 2H), 2.60 (s, 3H), 2.53 (t, J = 12.0 Hz, 2H), 2.34 (t, J = 11.9 Hz, 1H), 2.15 (t, J = 11.4 Hz, 2H), 1.91 (d, J = 12.7 Hz, 2H), 1.65 (m, 4H), 1.45−1.29 (m, 1H), 1.28−1.12 (m, 2H), 0.89 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 154.4, 128.9, 61.3, 49.5, 46.0, 34.3, 30.9, 27.3, 21.8, 16.8. HRMS (ESI-TOF) calcd for $C_{15}H_{25}ClN_3O_2S_2$ $[M + H]^+$ 378.1071, found 378.1060.

2-Chloro-4-cyclopropyl-5-((4-methyl-[1,4′-bipiperidin]-1′-yl)sulfonyl)thiazole (82). 2-Chloro-4-cyclopropylthiazole (0.3531 g, 2.21 mmol; see the SI for synthesis) was dissolved in anhydrous THF (7 mL) at −78 °C, followed by dropwise addition of *n*-BuLi (2.5 M in hexane, 1.0 mL, 2.50 mmol) under argon in 10 min. The solution mixture was stirred for 20 min at −78 °C and anhydrous SO_2 gas (generated from dropwise addition of sodium sulfite to concentrated aq HCl; the generated SO_2 gas was passed through concentrated H_2SO_4) was bubbled through the reaction solution at −78 °C for 10 min and then at room temperature for 1 h. Upon the evaporation of solvents, the residue was dissolved in anhydrous CH_2Cl_2 (6 mL) and NCS (0.4726 g, 3.54 mmol) was added. The resulting suspension was stirred at room temperature for 16 h. The suspension was then filtered and the filtrate was concentrated to about 10 mL, followed by addition of DIPEA (1.0 mL, 5.75 mmol) and 4-methyl-1,4′-bipiperidine **1a** (0.4998 g, 2.75 mmol). The reaction mixture was stirred at room temperature for 5.5 h and then poured into saturated $NaHCO_3$ solution (60 mL). The biphasic solution was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified through flash chromatography on silica gel (1:19 CH_3OH/CH_2Cl_2), followed by recrystallization from a mixture of CH_2Cl_2 and hexane to afford the desired product as a yellow solid (0.5398 g, 60% over two steps); mp 139−141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (d, J = 12.2 Hz, 2H), 2.80 (d, J = 11.6 Hz, 2H), 2.62−2.44 (m, 3H), 2.31 (tt, J = 11.6, 3.5 Hz, 1H), 2.12 (td, J = 11.6, 2.6 Hz, 2H), 1.88 (d, J = 12.6 Hz, 2H), 1.70−1.53 (m, 4H), 1.38−1.24 (m, 1H), 1.18 (qd, J = 11.8, 3.7 Hz, 2H), 1.11−0.99 (m, 4H), 0.87 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 154.6, 126.3, 61.2, 49.4, 46.1, 34.4, 30.9, 27.3, 21.8, 11.4, 10.9. HRMS (ESI-TOF) calcd for $C_{17}H_{27}ClN_3O_2S_2$ $[M + H]^+$ 404.1228, found 404.1226.

1′-(Benzo[*d*][1,3]dioxol-4-ylsulfonyl)-4-methyl-1,4′-bipiperidine (83). Reaction of amine **1a** with benzo[*d*][1,3]dioxole-4-sulfonyl chloride (Procedure A) yielded **83** as a yellow solid (86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (dd, J = 8.1, 1.2 Hz, 1H), 6.96 (dd, J = 7.8, 1.3 Hz, 1H), 6.89 (t, J = 8.0 Hz, 1H), 6.06 (s, 2H), 3.88 (d, J = 12.4 Hz, 2H), 2.79 (d, J = 11.7 Hz, 2H), 2.43 (td, J = 12.3, 2.4 Hz, 2H), 2.28 (tt, J = 11.6, 3.6 Hz, 1H), 2.13 (td, J = 11.6, 2.4 Hz, 2H), 1.84 (d, J = 14.8 Hz, 2H), 1.71−1.50 (m, 4H), 1.36−1.25 (m, 1H), 1.19 (qd, J = 11.9, 3.7 Hz, 2H), 0.87 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 145.2, 121.7, 121.5, 118.8, 112.5, 102.2, 61.6, 49.4, 45.9, 34.3, 30.9, 27.3, 21.8. HRMS (ESI-TOF) calcd for $C_{18}H_{27}N_2O_4S$ $[M + H]^+$ 367.1686, found 367.1686.

1′-((3,4-Dimethoxyphenyl)sulfonyl)-4-methyl-1,4′-bipiperidine (84). Reaction of amine **1a** with benzo[*d*][1,3]dioxole-5-sulfonyl chloride (Procedure A) yielded **84** as a light orange solid (82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dt, J = 8.2, 1.6 Hz, 1H), 7.13 (t, J = 1.6 Hz, 1H), 6.87 (dd, J = 8.1, 1.2 Hz, 1H), 6.05 (s, 2H), 3.78 (d, J = 10.9 Hz, 2H), 2.77 (d, J = 11.0 Hz, 2H), 2.30−2.04 (m, 5H), 1.82 (d, J = 10.7 Hz, 2H), 1.70−1.53 (m, 4H), 1.38−1.23 (m, 1H), 1.22−1.08 (m, 2H), 0.87 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 148.1, 129.3, 123.2, 108.2, 107.9, 102.3, 61.5, 49.5, 46.2, 34.5, 31.0, 27.3, 21.8. HRMS (ESI-TOF) calcd for $C_{18}H_{27}N_2O_4S$ $[M + H]^+$ 367.1681, found 367.1686.

4-Methyl-1′-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)-1,4′-bipiperidine (85). Reaction of amine **1a** with 2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-sulfonyl chloride (Procedure A) yielded **85** as a pale yellow oil (95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (d, J = 12.0 Hz, 2H), 2.97 (s, 2H), 2.89 (br, 2H), 2.75 (dt, J = 12.0, 4.0 Hz, 2H), 2.50 (s, 3H), 2.46 (s, 3H), 2.41 (br, 1H), 2.14 (br, 2H), 2.10 (s, 3H), 1.90 (d, J = 12.0 Hz, 2H), 1.64 (d, J = 12.0 Hz, 2H), 1.58−1.43 (m, 2H), 1.48 (s, 6H), 1.40−1.08 (m, 3H), 0.87 (d, J = 4.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ

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159.9, 140.8, 135.3, 125.8, 125.0, 117.9, 86.8, 61.9, 49.6, 43.9, 43.1, 34.5, 31.0, 28.6, 27.7, 21.8, 19.2, 17.6, 12.5. HRMS (ESI-TOF) calcd for $C_{24}H_{39}N_2O_3S$ $[M + H]^+$ 435.2676, found 435.2664.

1′-((5-Bromo-2,3-dihydrobenzofuran-7-yl)sulfonyl)-4-methyl-1,4′-bipiperidine (86). Reaction of amine **1a** with 5-bromo-2,3-dihydrobenzofuran-7-sulfonyl chloride (Procedure A) yielded **86** as a white solid (86%); mp 128−132 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.43 (s, 1H), 4.70 (t, J = 8.9 H z, 2H), 3.89 (d, J = 12.3Hz, 2H), 3.24 (t, J = 9.0 Hz, 2H), 2.79 (d, J = 11.9 Hz, 2H), 2.50 (t, J = 12.4 Hz, 2H), 2.27 (tt, J = 11.7, 3.7 Hz, 1H), 2.12 (t, J = 11.5 Hz, 2H), 1.82 (d, J = 11.2 Hz, 2H), 1.67−1.51 (m, 4H), 1.38−1.25 (m, 1H), 1.17 (qd, J = 11.9, 3.7 Hz, 2H), 0.88 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 132.3, 132.2, 130.7, 121.0, 111.8, 73.0, 61.7, 49.5, 46.0, 34.6, 31.0, 29.0, 27.6, 21.9. HRMS (ESI-TOF) calcd for $C_{19}H_{28}Br$ N_2O_3S $[M + H]^+$ 443.0999, found 443.0989.

4-Methyl-1′-(naphthalen-1-ylsulfonyl)-1,4′-bipiperidine (87). Reaction of amine **1a** with naphthalene-1-sulfonyl chloride (Procedure A) yielded **87** as a yellow gel (79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 8.6 Hz, 1H), 8.20 (d, J = 7.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.3 Hz, 1H), 7.69−7.44 (m, 3H), 3.91 (d, J = 12.5 Hz, 2H), 2.74 (d, J = 11.4 Hz, 2H), 2.53 (td, J = 12.3, 2.1 Hz, 2H), 2.20 (tt, J = 11.3, 3.5 Hz, 1H), 2.06 (t, J = 11.5 Hz, 2H), 1.80 (d, J = 12.3 Hz, 2H), 1.65−1.43 (m, 4H), 1.38−1.21 (m, 1H), 1.22−1.06 (m, 2H), 0.87 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3, 133.0, 130.4, 128.9, 128.8, 128.0, 126.8, 125.2, 124.1, 61.5, 49.5, 45.5, 34.6, 31.0, 27.7, 21.9. HRMS (ESI-TOF) (ESI) calcd for $C_{21}H_{28}N_2O_2S$ $[M + H]^+$ 373.1950, found 373.1944.

1′-((4-Chloronaphthalen-1-yl)sulfonyl)-4-methyl-1,4′-bipiperidine (88). Reaction of amine **1a** with 4-chloronaphthalene-1-sulfonyl chloride (Procedure A) yielded **88** as a white solid (71%); mp 129−132 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80−8.72 (m, 1H), 8.43−8.36 (m, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.69 (dd, J = 6.6, 3.3 Hz, 2H), 7.64 (d, J = 8.0 Hz, 1H), 3.87 (d, J = 12.4 Hz, 2H), 2.75 (d, J = 11.0 Hz, 2H), 2.55 (td, J = 12.2, 2.4 Hz, 2H), 2.23 (t, J = 12.0 Hz, 1H), 2.06 (t, J = 11.3 Hz, 2H), 1.81 (d, J = 13.1 Hz, 2H), 1.66−1.45 (m, 4H), 1.35−1.21 (m, 1H), 1.15 (dd, J = 13.4, 9.6 Hz, 2H), 0.87 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 132.3, 131.5, 130.1, 130.0, 128.7, 127.9, 125.7, 125.4, 124.6, 61.5, 49.5, 45.5, 34.5, 31.0, 27.7, 21.8. HRMS (ESI-TOF) calcd for $C_{21}H_{28}ClN_2O_2S$ $[M + H]^+$ 407.1555, found 407.1551.

***N*-(4-((4-Methyl-[1,4′-bipiperidin]-1′-yl)sulfonyl)-naphthalen-1-yl)acetamide (89).** Reaction of amine **1a** with 4-acetamidonaphthalene-1-sulfonyl chloride (Procedure A) yielded **89** as a yellow solid (64%); mp 113−117 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 8.8 Hz, 1H), 8.17−8.05 (m, 2H), 7.87 (s, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.57−7.37 (m, 2H), 3.86 (d, J = 9.6 Hz, 2H), 2.80 (d, J = 11.6 Hz, 2H), 2.52 (t, J = 12.4 Hz, 2H), 2.36 (t, J = 12.8 Hz, 1H), 2.31 (s, 3H), 2.15 (t, J = 11.6 Hz, 3H), 1.83 (d, J =13.6 Hz, 2H), 1.66−1.45 (m, 4H), 1.35−1.20 (m, 3H), 0.88 (d, J = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 133.3, 133.2, 130.6, 129.5, 129.4, 128.1, 127.7, 124.3, 123.9,123.4, 61.6, 49.3, 45.3, 33.7, 30.7, 27.2, 24.0, 21.6. HRMS (ESI-TOF) calcd for $C_{23}H_{32}N_3O_3S$ $[M + H]^+$ 430.2159, found 430.2165.

5-((4-Methyl-[1,4′-bipiperidin]-1′-yl)sulfonyl)isoquinoline (90). Reaction of amine **1a** with isoquinoline-5-sulfonyl chloride (Procedure A) yielded **90** as a white solid (51%); mp 123−126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.66 (d, J = 6.0 Hz, 1H), 8.48 (d, J = 6.0 Hz, 1H), 8.36 (dd, J = 7.6, 1.6 Hz, 1H), 8.19 (d, J = 6.0 Hz, 1H), 7.69 (dd, J = 8.2, 7.4 Hz, 1H), 3.90 (d, J = 12.4 Hz, 2H), 2.74 (d, J = 10.8 Hz, 2H), 2.51 (td, J = 12.0, 2.4 Hz, 2H), 2.26−2.15 (m, 1H), 2.12−2.03 (m, 2H), 1.81 (d, J = 11.6 Hz, 2H), 1.64−1.45 (m, 4H), 1.36−1.20 (m, 1H), 1.19−1.06 (m, 2H), 0.86 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 145.1, 134.0, 133.7, 132.6, 131.9, 129.1, 125.8, 117.7, 61.4, 49.9, 45.6, 34.5, 31.0, 27.7, 21.6. HRMS (ESI-TOF) calcd for $C_{20}H_{28}N_3O_2S$ $[M + H]^+$ 396.1716, found 396.1710.

1′-((4-(Difluoromethoxy)phenyl)sulfonyl)-3-methyl-1,4′-bipiperidine (91). Reaction of amine **1b** with 4-(difluoromethoxy)-benzenesulfonyl chloride (Procedure A) yielded **91** as a pale yellow solid (76%); mp 88−91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H), 6.60 (t, J = 72.6 Hz, 1H), 3.84 (d, J = 11.9 Hz, 2H), 2.85−2.56 (m, 2H), 2.37−2.15 (m, 3H), 2.04 (t, J = 11.4 Hz, 1H), 1.83 (d, J = 11.3 Hz, 2H), 1.78−1.42 (m, 7H), 0.90−0.73 (m, 1H), 0.82 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 133.0, 129.8, 119.3, 115.2 (t, J = 262.7 Hz), 61.5, 57.6, 49.5, 46.2, 33.3, 31.5, 27.2, 27.1, 25.9, 19.8. HRMS (ESI-TOF) calcd for $C_{18}H_{26}N_2O_3F_2S$ $[M + H]^+$ 389.1699, found 389.1705.

1′-((4-Bromophenyl)sulfonyl)-4-(prop-2-yn-1-yl)-1,4′-bipiperidine (92). The synthesis of **92** is described in the Supporting Information (SI). mp 161−164 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78−7.54 (m, 4H), 3.83 (d, J = 12.0, 2H), 2.83 (dt, J = 11.8 Hz, 2H), 2.33−2.17 (m, 3H), 2.19−2.04 (m, 4H), 1.96 (t, J = 2.7 Hz, 1H), 1.88−1.73 (m, 4H), 1.64 (qd, J = 12.2, 4.1 Hz, 2H), 1.53−1.37 (m, 1H), 1.37−1.17 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2, 132.3, 129.1, 127.8, 82.7, 69.4, 61.3, 49.2, 46.1, 35.5, 31.9, 27.3, 25.4. HRMS (ESI-TOF) calcd for $C_{19}H_{26}BrN_2O_2S$ $[M + H]^+$ 425.0893, found 425.0894.

1′-(Phenylsulfonyl)-2-(prop-2-yn-1-yl)-1,4′-bipiperidine (93). The synthesis of **93** is described in the Supporting Information. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−7.70 (m, 2H), 7.63−7.57 (m, 1H), 7.57−7.50 (m, 2H), 3.85 (d, J = 12.1 Hz, 2H), 2.78−2.57 (m, 3H), 2.36−2.19 (m, 4H), 1.94 (t, J = 2.7 Hz, 1H), 1.89−1.39 (m, 9H), 1.35−1.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 232.7, 129.0, 127.6, 82.1, 70.0, 56.4, 55.5, 46.5, 46.0, 45.2, 31.8, 30.1, 26.0, 24.2, 23.2, 21.7. HRMS (ESI-TOF) calcd for $C_{19}H_{27}N_2O_2S$ $[M + H]^+$ 347.1788, found 347.1799.

1′-(Phenylsulfonyl)-4-(2-(prop-2-yn-1-yloxy)ethyl)-1,4′-bipiperidine (94). To a solution of 2-(1′-(phenylsulfonyl)-[1,4′-bipiperidin]-4-yl)ethanol (0.0585 g, 0.17 mmol; prepared from **3a** with 4-piperidineethanol; see the SI) in anhydrous THF (1 mL) was added a suspension of KH (30% in mineral oil, 0.0275 g, 0.21 mmol) in anhydrous THF (0.5 mL) via a syringe at room temperature. After stirring for 45 min, propargyl bromide (80% in toluene, 0.038 mL, 0.43 mmol) was added dropwise via a syringe and the solution was stirred at room temperature for 7.5 h. After the evaporation of solvents, the residue was purified by flash chromatography (1/19 CH_3OH/CH_2Cl_2) to afford the desired product **94** as a yellow gel (0.0072 g, 11%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.69 (m, 2H), 7.63−7.57 (m, 1H), 7.57−7.49 (m, 2H), 4.11 (d, J = 2.3 Hz, 2H), 3.95−3.80 (m, 2H), 3.53 (t, J = 6.4 Hz, 2H), 2.85 (d, J = 10.7 Hz, 2H), 2.41 (t, J = 2.4 Hz, 1H), 2.30−2.13 (m, 5H), 1.87 (d, J = 12.6 Hz, 2H), 1.79−1.59 (m, 4H), 1.52 (q, J = 6.5 Hz, 2H), 1.45−1.36 (m, 1H), 1.32−1.22 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 132.7, 129.0, 127.6, 79.9, 74.2, 67.6, 61.6, 58.1, 49.3, 46.1, 35.9, 32.6, 32.2, 27.1. HRMS (ESI-TOF) calcd for $C_{21}H_{30}N_2O_3SNa$ $[M + Na]^+$ 413.1869, found 413.1863.

1′-(Phenylsulfonyl)-2-(2-(prop-2-yn-1-yloxy)ethyl)-1,4′-bipiperidine (95). To a solution of 2-(1′-(phenylsulfonyl)-[1,4′-bipiperidin]-2-yl)ethan-1-ol (0.0830 g, 0.24 mmol; prepared from **3a** with 2-piperidineethanol; see the SI) in anhydrous THF (2 mL) was added NaH (60%, 0.0192 g, 0.48 mmol) at 0 °C. The reaction solution was stirred at 0 °C for 15 min and propargyl bromide (80% in toluene, 0.075 mL, 0.67 mmol) was added via a syringe. The reaction solution was stirred at 0 °C for another 30 min and was allowed to warm up to room temperature and stirred for 3 h before a second portion of NaH (60%, 0.0175 g, 0.44 mmol) in anhydrous THF (1 mL) was introduced. The reaction solution was then stirred for 18 h at room temperature, and water (10 mL) was added to quench the reaction, followed by the extraction with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. After the purification by flash chromatography (1/19 CH_3OH/CH_2Cl_2), the product **95** was obtained as a yellow gel (0.0132 g, 18%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−7.69 (m, 2H), 7.64−7.56 (m, 1H), 7.56−7.48 (m, 2H), 4.06 (d, J = 2.4 Hz, 2H), 3.83 (d, J = 11.9 Hz, 2H), 3.58−3.37 (m, 2H), 2.73 (dd, J = 39.3, 10.5 Hz, 3H), 2.35 (t, J = 2.4 Hz, 1H), 2.33−2.16 (m, 3H), 1.88−1.70 (m, 4H), 1.69−1.19 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 132.8, 129.1, 127.6, 79.6, 74.4, 67.1, 58.2, 55.5, 55.0, 46.4, 45.9, 45.4, 30.3, 29.8, 29.7, 25.6, 24.2,

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23.0. HRMS (ESI-TOF) calcd for $C_{21}H_{31}N_2O_3S$ $[M + H]^+$ 391.2050, found 391.2048.

1-(1′-(Mesitylsulfonyl)-[1,4′-bipiperidin]-4-yl)hex-5-yn-2-one (96). The synthesis of **96** is described in the Supporting Information. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 2H), 3.61 (d, J = 12.8 Hz, 2H), 2.88 (d, J = 11.2 Hz, 2H), 2.71 (td, J = 12.2, 2.4 Hz, 2H), 2.63−2.58 (m, 2H), 2.57 (s, 6H), 2.41 (qd, J = 8.4, 7.0, 3.5 Hz, 3H), 2.32 (d, J = 6.8 Hz, 2H), 2.26 (s, 3H), 2.19 (t, J = 12.3 Hz, 2H), 1.90 (t, J = 2.7 Hz, 1H), 1.84 (d, J = 16.0 Hz, 3H), 1.67 (d, J = 10.9 Hz, 2H), 1.49 (qd, J = 12.2, 4.2 Hz, 2H), 1.34−1.22 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7, 142.5, 140.4, 131.9, 131.6, 83.0, 68.7, 61.8, 49.2, 43.9, 41.9, 32.0, 31.7, 27.4, 22.8, 20.9, 12.9. HRMS (ESI-TOF) calcd for $C_{25}H_{37}N_2O_3S$ $[M + H]^+$ 445.2519, found 445.2524.

1′-(Mesitylsulfonyl)-3,5-dimethyl-1,4′-bipiperidine (97). Reaction of **3c** with 3,5-dimethylpiperidine (Procedure D) yielded **97** as a colorless oil (37%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 2H), 3.61 (d, J = 12.4 Hz, 2H), 2.87−2.66 (m, 4H), 2.59 (s, 6H), 2.47−2.29 (m, 1H), 2.27 (s, 3H), 1.82 (d, J = 13.6 Hz, 2H), 1.74−1.39 (m, 7H), 0.81 (d, J = 5.8 Hz, 6H), 0.47 (q, J = 11.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 140.4, 131.8, 131.8, 61.8, 57.2, 44.1, 42.3, 31.4, 27.5, 22.8, 20.9, 19.7. HRMS (ESI-TOF) calcd for $C_{21}H_{35}N_2O_2S$ $[M + H]^+$ 379.2414, found 379.2406.

4-Isopropyl-1′-(mesitylsulfonyl)-1,4′-bipiperidine (98). Reaction of **3c** with 4-isopropylpiperidine (Procedure D) yielded **98** as a yellow oil (46%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 2H), 3.60 (d, J = 12.7 Hz, 2H), 2.90 (dd, J = 11.5 Hz, 2H), 2.72 (t, J = 12.4 Hz, 2H), 2.59 (d, J = 2.3 Hz, 6H), 2.38−2.29 (m, 1H), 2.28 (s, 3H), 2.06 (t, J = 10.6 Hz, 2H), 1.85 (d, J = 11.2 Hz, 2H), 1.63 (d, J = 11.3 Hz, 2H), 1.49 (td, J = 12.1, 4.1 Hz, 2H), 1.44−1.32 (m, 1H), 1.30−1.14 (m, 2H), 1.01−0.87 (m, 1H), 0.83 (d, J = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 140.4, 131.8, 131.7, 61.8, 50.0, 44.0, 42.6, 32.4, 29.6, 27.7, 22.8, 20.9, 19.8. HRMS (ESI-TOF) calcd for $C_{22}H_{37}N_2O_2S$ $[M + H]^+$ 393.2570, found 393.2567.

3-(1′-(Mesitylsulfonyl)-[1,4′-bipiperidin]-4-yl)propanenitrile (99). *tert*-Butyl 4-(2-cyanoethyl)piperidine-1-carboxylate (**S10**, 0.328 g, 1.38 mmol; see the SI for synthesis) was stirred with HCl (1 mL) in 1,4-dioxane (4 mL) at room temperature for 2 h. After the evaporation of the solvents, the 4-(2-cyanoethyl)piperidine hydrochloride acid salt was neutralized by shaking with saturated $NaHCO_3$ solution at 0 °C, followed by extraction with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide 3-(piperidin-4-yl)propanenitrile, which was used for the next step without further purification. Reaction of the above-prepared 3-(piperidin-4-yl)-propanenitrile and 1-(mesitylsulfonyl)piperidin-4-one (**3c**) (Procedure D) yielded **99** as a white gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 2H), 3.63 (d, J = 12.3 Hz, 2H), 2.90 (d, J = 10.7 Hz, 2H), 2.74 (td, J = 12.4, 2.4 Hz, 2H), 2.60 (s, 6H), 2.35 (t, J = 7.2 Hz, 3H), 2.29 (s, 3H), 2.14 (t, J = 9.6 Hz, 2H), 1.84 (d, J = 12.7 Hz, 2H), 1.71 (d, J = 12.3 Hz, 2H), 1.63−1.34 (m, 5H), 1.27−1.16 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 140.4, 131.9, 131.7, 119.7, 61.8, 49.2, 44.0, 34.8, 31.8, 31.7, 27.6, 22.8, 21.0, 14.6. HRMS (ESI-TOF) calcd for $C_{22}H_{34}N_3O_2S$ $[M + H]^+$ 404.2366, found 404.2361.

2-(1′-(Mesitylsulfonyl)-[1,4′-bipiperidin]-4-yl)ethanol (100). Reaction of **3c** with 4-piperidineethanol (Procedure D) yielded **100** as a white solid (66%); mp 82−85 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 2H), 3.66 (t, J = 6.6 Hz, 2H), 3.62 (d, J = 12.6 Hz, 2H), 2.86 (d, J = 11.6 Hz, 2H), 2.73 (td, J = 12.5, 2.4 Hz, 2H), 2.60 (s, 6H), 2.40−2.28 (m, 1H), 2.28 (s, 3H), 2.11 (td, J = 11.6, 2.4 Hz, 2H), 1.84 (d, J = 12.7 Hz, 2H), 1.69 (d, J = 13.2 Hz, 2H), 1.63 (s, 1H), 1.55−1.33 (m, 5H), 1.21 (qd, J = 11.7, 11.0, 3.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 140.4, 131.9, 131.7, 61.8, 60.4, 49.5, 44.0, 39.4, 32.6, 32.5, 27.7, 22.8, 21.0. HRMS (ESI-TOF) calcd for $C_{21}H_{35}N_2O_3S$ $[M + H]^+$ 395.2363, found 395.2365.

1′-(Mesitylsulfonyl)-[1,4′-bipiperidin]-4-ol (101). To a mixture of [1,4′-bipiperidin]-4-ol (**1c**, 0.2075 g, 1.13 mmol) and ^{i}Pr$_2$NEt (0.27 mL, 1.55 mmol) in CH_2Cl_2 (3 mL) was dropwise added 2,4,6-trimethylbenzene-1-sulfonyl chloride (0.2154 g, 0.98 mmol, in 2 mL CH_2Cl_2) over 10 min. The reaction mixture was stirred at room temperature overnight and then poured into saturated aqueous $NaHCO_3$ (20 mL). The biphasic solution was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried by Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via flash chromatography (1/19 MeOH/CH_2Cl_2) to afford the desired product (0.214 g, 65%) as a white solid; mp 120−123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 2H), 3.74−3.59 (br, 1H), 3.60 (d, J = 12.9 Hz, 2H), 2.85−2.65 (m, 4H), 2.59 (s, 6H), 2.46−2.22 (m, 3H), 2.28 (s, 3H), 1.96−1.78 (m, 4H), 1.64−1.30 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 140.3, 131.9, 131.6, 67.6, 61.4, 46.7, 43.9, 34.5, 27.6, 22.8, 20.9. HRMS (ESI-TOF) calcd for $C_{19}H_{31}N_2O_3S$ $[M + H]^+$ 367.2050, found 367.2058.

1′-(Mesitylsulfonyl)-1,4′-bipiperidine (102). Reaction of **3c** with piperidine (Procedure D) yielded **102** as a colorless gel (67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (s, 2H), 3.62 (d, J = 11.7 Hz, 2H), 2.74 (t, J = 12.1 Hz, 2H), 2.60 (s, 6H), 2.47 (s, 4H), 2.38−2.30 (m, 1H), 2.28 (s, 3H), 1.85 (d, J = 11.5 Hz, 2H), 1.52−1.60 (m, 4H), 1.52−1.44 (m, 2H), 1.44−1.37 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 140.4, 131.8, 131.8, 62.2, 50.2, 44.1, 27.5, 26.3, 24.6, 22.8, 20.9. HRMS (ESI-TOF) calcd for $C_{19}H_{30}N_2O_2SNa$ $[M + Na]^+$ 373.1920, found 373.1910.

1-(1-(Mesitylsulfonyl)piperidin-4-yl)azepane (103). Reaction of amine hydrochloride salt **1e** with 2,4,6-trimethylbenzene-1-sulfonyl chloride (Procedure B) yielded **103** as an orange gel (90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 2H), 3.71 (d, J = 11.8 Hz, 2H), 3.62 (br, 1H), 3.18−2.89 (br, 4H), 2.77 (t, J = 12.7 Hz, 2H), 2.58 (s, 6H), 2.29 (s, 3H), 2.10 (d, J = 12.5 Hz, 2H), 1.82 (s, 4H), 1.76−1.54 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 140.3, 132.0, 132.0, 132.0, 131.5, 63.3, 51.2, 43.8, 26.9, 26.6, 26.4, 22.8, 21.0. HRMS (ESI-TOF) calcd for $C_{20}H_{33}N_2O_2S$ $[M + H]^+$ 365.2257, found 365.2253.

1-((4-Methoxyphenyl)sulfonyl)-4-(pyrrolidin-1-yl)piperidine (104). Reaction of amine **1d** with 4-methoxybenzene-1-sulfonyl chloride (Procedure A) yielded **104** as a pale yellow oil (70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.0 Hz, 2H), 6.97 (d, J = 8.0 Hz, 2H), 3.86 (s, 3H), 3.68 (d, J = 12.0 Hz, 2H), 2.51 (s, 4H), 2.36 (dt, J = 12.0, 4.0 Hz, 2H), 2.04−1.86 (m, 3H), 1.75 (s, 4H), 1.61 (q, J = 12.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 129.8, 127.8, 114.1, 60.8, 55.6, 51.3, 45.0, 30.4, 23.2. HRMS (ESI-TOF) calcd for $C_{16}H_{25}N_2O_3S$ $[M + H]^+$ 325.1580, found 325.1571.

3-(1-(Mesitylsulfonyl)piperidin-4-yl)-6-methyl-1,3-oxazinane (105). Reaction of **3c** with 4-aminobutan-2-ol (Procedure D) yielded 4-((1-(mesitylsulfonyl)piperidin-4-yl)amino)butan-2-ol as a white solid (82%); mp 105−108 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (s, 2H), 3.96 (ddd, J = 8.9, 5.8, 2.4 Hz, 1H), 3.55 (d, J = 12.5 Hz, 2H), 3.05 (dt, J = 11.9, 4.2 Hz, 1H), 2.83 (tt, J = 12.5, 3.3 Hz, 2H), 2.76 (td, J = 11.1, 2.9 Hz, 1H), 2.61 (s, 7H), 2.30 (s, 3H), 1.96 (t, J = 12.8 Hz, 2H), 1.63 (d, J = 14.9 Hz, 1H), 1.53−1.42 (m, 1H), 1.39−1.27 (m, 2H), 1.16 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 140.4, 131.9, 131.6, 69.5, 54.4, 45.5, 43.1, 43.0, 37.0, 31.8, 31.5, 23.6, 22.8, 21.0. HRMS (ESI-TOF) calcd for $C_{18}H_{30}N_2O_3SNa$ $[M + Na]^+$ 377.1869, found 377.1856.

A solution of the above-prepared 4-((1-(mesitylsulfonyl)piperidin-4-yl)amino)butan-2-ol (0.119 g, 0.34 mmol), paraformaldehyde (0.0143 g, 0.48 mmol), Mg_2SO_4 (0.2091 g, 1.74 mmol), and pyridinium *p*-toluenesulfonate (PPTS) (0.0025 g, 0.01 mmol) in anhydrous toluene (4 mL) was refluxed for 3 h and then cooled to room temperature. The suspension was poured into saturated aqueous $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via flash chromatography (1/19 MeOH/CH_2Cl_2) to provide the desired product **105** as a colorless gel (0.0555 g, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 2H), 4.61 (dd, J = 10.0, 2.3 Hz, 1H), 4.16 (d, J = 10.1 Hz, 1H), 3.63−3.50 (m, 3H), 3.11 (ddt, J = 13.4, 4.4, 2.2 Hz, 1H), 2.89−2.68 (m, 4H), 2.58 (s, 6H), 2.27 (s, 3H), 1.92 (dp, J = 12.2, 2.8 Hz, 2H), 1.65−1.29 (m, 4H), 1.15 (d, J = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 140.4, 131.9, 131.6, 81.6, 73.6, 55.0, 46.5, 43.4, 30.3, 29.8, 29.2, 22.8, 21.8, 20.9. HRMS (ESI-TOF) calcd for $C_{19}H_{30}N_2O_3SNa$ $[M + Na]^+$ 389.1869, found 389.1874.

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1-(1-(Mesitylsulfonyl)piperidin-4-yl)-4-methylpiperazine (106). Reaction of **3c** with 1-methylpiperazine (Procedure D) yielded **106** as a colorless gel (74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 2H), 3.59 (d, J = 12.6 Hz, 2H), 2.73 (t, J = 12.3 Hz, 2H), 2.58 (s, 6H), 2.55 (s, 4H), 2.49−2.35 (br, 4H), 2.36−2.29 (s, 1H), 2.26 (s, 3H), 2.25 (s, 3H), 1.84 (d, J = 11.6 Hz, 2H), 1.59−1.34 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 140.4, 131.8, 131.7, 61.2, 55.3, 48.9, 45.9, 43.7, 27.8, 22.8, 20.9. HRMS (ESI-TOF) calcd for $C_{19}H_{32}N_3O_2S$ $[M + H]^+$ 366.2210, found 366.2199.

4-(1-(Mesitylsulfonyl)piperidin-4-yl)morpholine (107). Reaction of **3c** with morpholine (Procedure D) yielded **107** as a colorless gel (74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (s, 2H), 3.68 (s, 4H), 3.60 (d, J = 12.9 Hz, 2H), 2.75 (t, J = 12.3 Hz, 2H), 2.59 (s, 6H), 2.50 (s, 4H), 2.27 (s, 4H), 1.87 (d, J = 14.5 Hz, 2H), 1.46 (qd, J = 11.6, 3.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 140.4, 140.4, 131.9, 131.6, 67.1, 61.5, 49.7, 43.6, 27.7, 22.8, 20.9. HRMS (ESI-TOF) calcd for $C_{18}H_{29}N_2O_3S$ $[M + H]^+$ 353.1893, found 353.1889.

4-Benzyl-1′-(mesitylsulfonyl)-1,4′-bipiperidine (108). Reaction of **3c** with 4-benzylpiperidine (Procedure D) yielded **108** as a light brown oil (68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.22 (m, 2H), 7.21−7.06 (m, 3H), 6.92 (s, 2H), 3.61 (d, J = 12.4 Hz, 2H), 2.92 (s, 2H), 2.72 (td, J = 12.5, 2.4 Hz, 2H), 2.58 (s, 6H), 2.50 (d, J = 7.0 Hz, 2H), 2.40−2.26 (br, 1H), 2.28 (s, 3H), 2.08 (t, J = 17.9 Hz, 1H), 1.85 (d, J = 12.8 Hz, 2H), 1.64 (d, J = 12.8 Hz, 2H), 1.49 (d, J = 11.5 Hz, 3H), 1.41−1.12 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 140.5, 140.4, 131.9, 131.7, 129.1, 128.2, 125.8, 61.9, 49.6, 44.0, 43.1, 38.1, 32.3, 27.6, 22.8, 21.0. HRMS (ESI-TOF) calcd for $C_{26}H_{37}N_2O_2S$ $[M + H]^+$ 441.2570, found 441.2567.

4-(2-Fluorobenzyl)-1′-(mesitylsulfonyl)-1,4′-bipiperidine (109). To a solution of 1-(mesitylsulfonyl)piperidin-4-one (**3c**, 0.2855 g, 1.02 mmol) and 4-(2-fluorobenzyl)piperidine (0.1936 g, 1.00 mmol) in anhydrous DCE (6 mL) was added $Ti(O\textit{i}\text{-}Pr)_4$ (0.60 mL, 2.05 mmol) and the solution was stirred at 80 °C for 6.5 h. After cooling to 0 °C, $NaBH_4$ (0.1271 g, 3.34 mmol) in EtOH (6 mL) was added dropwise and the solution was stirred at room temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (30 mL), extracted with CH_2Cl_2 (3 × 30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified via flash chromatography (1/19 MeOH/CH_2Cl_2 then 100% EtOAc) to afford the product **109** as a light brown gel (0.1444 g, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17−7.05 (m, 2H), 7.03−6.92 (m, 2H), 6.90 (s, 2H), 3.59 (d, J = 12.5 Hz, 2H), 2.86 (d, J = 11.7 Hz, 2H), 2.70 (td, J = 12.4, 2.4 Hz, 2H), 2.57 (s, 6H), 2.55−2.48 (m, 2H), 2.44−2.30 (m, 1H), 2.25 (s, 3H), 2.09 (td, J = 11.7, 2.4 Hz, 2H), 1.83 (d, J = 14.5 Hz, 2H), 1.61 (d, J = 13.1 Hz, 2H), 1.58−1.41 (m, 3H), 1.39−1.22 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2 (d, J = 244.6 Hz), 142.5, 140.4, 131.9, 131.7, 131.5 (d, J = 5.1 Hz), 127.6 (d, J = 8.1 Hz), 127.2 (d, J = 16.2 Hz), 123.7 (d, J = 3.5 Hz), 115.1 (d, J = 22.5 Hz), 61.8, 49.4, 43.9, 36.8, 35.9, 32.0, 27.5, 22.8, 20.9. HRMS (ESI-TOF) calcd for $C_{26}H_{36}FN_2O_2S$ $[M + H]^+$ 459.2476, found 459.2470.

4-(4-Fluorobenzyl)-1′-(mesitylsulfonyl)-1,4′-bipiperidine (110). Reaction of **3c** and 4-(4-fluorobenzyl)piperidine in the same manner as for the preparation of **109** yielded **110** as a colorless gel (31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09−7.00 (m, 2H), 6.97−6.87 (m, 4H), 3.60 (d, J = 12.6 Hz, 2H), 2.86 (d, J = 11.5 Hz, 2H), 2.72 (td, J = 12.5, 2.4 Hz, 2H), 2.58 (s, 6H), 2.46 (d, J = 7.0 Hz, 2H), 2.35 (t, J = 11.8 Hz, 1H), 2.27 (s, 3H), 2.08 (dd, J = 12.8, 10.2 Hz, 2H), 1.83 (d, J = 12.1 Hz, 2H), 1.61 (d, J = 12.8 Hz, 2H), 1.55−1.36 (m, 3H), 1.34−1.15 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2 (d, J = 243.4 Hz), 142.5, 140.4, 136.1 (d, J = 3.3 Hz), 131.9, 131.7, 130.3 (d, J = 7.7 Hz), 114.9 (d, J = 21.0 Hz), 61.8, 49.5, 44.0, 42.2, 38.1, 32.2, 27.6, 22.8, 20.9. HRMS (ESI-TOF) calcd for $C_{26}H_{36}FN_2O_2S$ $[M + H]$+ 459.2476, found 459.2477.

1′-(Mesitylsulfonyl)-4-phenyl-1,4′-bipiperidine (111). Reaction of **3c** with 4-phenylpiperidine (Procedure D) yielded **111** as a white solid (90%); mp 141−144 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.26 (m, 2H), 7.25−7.16 (m, 3H), 6.95 (s, 2H), 3.66 (d, J = 12.5 Hz, 2H), 3.03 (d, J = 11.0 Hz, 2H), 2.78 (t, J = 12.5 Hz, 2H), 2.62 (s, 6H), 2.54−2.37 (m, 2H), 2.30 (s, 3H), 2.30−2.20 (m, 2H), 1.99−1.66 (m, 6H), 1.56 (qd, J = 12.2, 4.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 140.5, 131.9, 131.7, 128.4, 126.8, 126.2, 61.9, 50.0, 44.0, 42.9, 33.7, 27.7, 22.8, 21.0. HRMS (ESI-TOF) calcd for $C_{25}H_{35}N_2O_2S$ $[M + H]^+$ 427.2414, found 427.2405.

1-(Mesitylsulfonyl)-4-(5-methyl-1,3-dioxan-2-yl)piperidine (112). The synthesis of compound **112**, obtained as a mixture of cis/trans isomers (1:1.56), is described in the Supporting Information. Trans: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 2H), 4.16 (d, J = 5.4 Hz, 1H), 3.97 (dd, J = 11.8, 4.7 Hz, 2H), 3.55 (d, J = 10.2 Hz, 2H), 3.20 (t, J = 11.5 Hz, 2H), 2.70 (t, J = 12.4 Hz, 2H), 2.58 (s, 6H), 2.26 (s, 3H), 2.07−1.90 (m, 1H), 1.77 (d, J = 14.4 Hz, 2H), 1.64−1.54 (m, 1H), 1.42−1.24 (m, 2H), 0.66 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 140.5, 140.4, 131.8, 103.4, 71.8, 44.0, 40.3, 29.5, 26.1, 22.8, 20.9, 12.3. Cis: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 2H), 4.26 (d, J = 5.1 Hz, 1H), 3.84 (d, J = 11.5 Hz, 2H), 3.74 (d, J = 10.1 Hz, 2H), 3.55 (d, J = 10.2 Hz, 2H), 2.70 (t, J = 12.4 Hz, 2H), 2.58 (s, 6H), 2.26 (s, 3H), 1.77 (d, J = 14.4 Hz, 2H), 1.64−1.54 (m, 1H), 1.54−1.47 (m, 1H), 1.42−1.24 (m, 2H), 1.20 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 140.5, 140.4, 103.9, 73.2, 44.0, 40.3, 29.1, 25.9, 22.8, 20.9, 15.8. HRMS (ESI-TOF) (ESI) calcd for $C_{19}H_{29}NO_4SNa$ $[M + Na]^+$ 390.1710, found 390.1706.

(1-(Mesitylsulfonyl)piperidin-4-yl)(4-methylpiperidin-1-yl)-methanone (113). Reaction of amine **1k** (see the SI for synthesis) with 2,4,6-trimethylbenzene-1-sulfonyl chloride (Procedure B) yielded **113** as a light brown solid (86%); mp 122−124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 2H), 4.49 (d, J = 13.2 Hz, 1H), 3.77 (d, J = 15.5 Hz, 1H), 3.53 (dt, J = 12.1, 3.6 Hz, 2H), 2.94 (td, J = 12.5, 11.6, 2.3 Hz, 1H), 2.85−2.70 (m, 2H), 2.56 (s, 6H), 2.54−2.38 (m, 2H), 2.24 (s, 3H), 1.82−1.45 (m, 7H), 1.08−0.92 (m, 2H), 0.88 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 142.6, 140.5, 131.8, 131.3, 45.7, 43.6, 42.2, 38.0, 34.9, 33.8, 31.1, 28.1, 27.8, 22.7, 21.6, 20.9; HRMS (ESI-TOF) calcd for $C_{21}H_{32}N_2O_3SNa$ $[M + Na]^+$ 415.2026, found 415.2017.

1-(Mesitylsulfonyl)-*N*-(*p*-tolyl)piperidin-4-amine (114). Reaction of **3c** with *p*-toluidine (Procedure D) yielded **114** as a white solid (61%); mp 148−151 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03−6.89 (m, 4H), 6.51 (d, J = 8.3 Hz, 2H), 3.56 (dt, J = 13.2, 3.5 Hz, 2H), 3.36 (tt, J = 10.1, 3.9 Hz, 1H), 2.91 (ddd, J = 12.8, 11.2, 2.7 Hz, 2H), 2.61 (s, 6H), 2.29 (s, 3H), 2.21 (s, 3H), 2.06 (dd, J = 13.2, 3.8 Hz, 2H), 1.54−1.32 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 142.6, 140.5, 131.9, 131.6, 129.9, 127.2, 113.8, 50.0, 43.2, 31.8, 22.8, 21.0, 20.4. HRMS (ESI-TOF) calcd for $C_{21}H_{28}N_2O_2SNa$ $[M + Na]^+$ 395.1764, found 395.1771.

1-(Mesitylsulfonyl)-4-(*p*-tolyl)piperidine (115). Reaction of amine **1f** with 2,4,6-trimethylbenzene-1-sulfonyl chloride (Procedure A) yielded **115** as a pale yellow solid (73%); mp 87−90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (q, J = 8.1 Hz, 4H), 6.95 (s, 2H), 3.69 (d, J = 12.1 Hz, 2H), 2.86 (t, J = 12.5 Hz, 2H), 2.64 (s, 6H), 2.62−2.51 (m, 1H), 2.30 (d, J = 1.9 Hz, 6H), 1.86 (d, J = 13.0 Hz, 2H), 1.67 (dtd, J = 13.4, 12.2, 4.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 142.1, 140.5, 136.0, 131.9, 131.8, 129.2, 126.6, 44.9, 41.8, 32.7, 22.9, 21.0. HRMS (ESI-TOF) calcd for $C_{21}H_{27}NO_2SNa$ $[M + Na]^+$ 380.1655, found 380.1652.

1-(Mesitylsulfonyl)-4-phenylpiperidine (116). Reaction of amine **1g** with 2,4,6-trimethylbenzene-1-sulfonyl chloride (Procedure A) yielded **116** as a yellow solid (93%); mp 88−90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (m, 2H), 7.23−7.14 (m, 3H), 6.96 (s, 2H), 3.71 (d, J = 12.3 Hz, 2H), 2.87 (t, J = 12.4 Hz, 2H), 2.65 (s, 6H), 2.64−2.54 (m, 1H), 2.30 (s, 3H), 1.88 (d, J = 13.2 Hz, 2H), 1.70 (dtd, J = 13.7, 12.1, 4.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 142.5, 140.5, 131.9, 131.8, 128.5, 126.7, 126.5, 44.9, 42.2, 32.6, 22.9, 21.0. HRMS (ESI-TOF) calcd for $C_{20}H_{25}NO_2SNa$ $[M + Na]^+$ 366.1498, found 366.1489.

***N*-Benzyl-*N*-(1-(mesitylsulfonyl)piperidin-4-yl)butyramide (117).** Reaction of **3c** with benzylamine (Procedure D) yielded *N*-benzyl-1-(mesitylsulfonyl)piperidin-4-amine as a yellow oil (>95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.19 (m, 5H), 6.92 (s, 2H), 3.77 (s, 2H), 3.52 (d, J = 13.3 Hz, 2H), 3.52 (d, J = 13.3 Hz, 2H), 2.68−2.58 (m, 1H), 2.59 (s, 6H), 2.27 (s, 3H), 1.90 (d, J = 12.1 Hz, 2H), 1.45−1.22 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5,

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140.4, 131.9, 131.7, 128.6, 128.5, 128.0, 127.8, 127.1, 53.7, 50.8, 42.9, 31.7, 22.8, 21.0. HRMS (ESI-TOF) calcd for $C_{21}H_{29}N_2O_2S$ $[M + H]^+$ 373.1944, found 373.1942.

A mixture of the above-prepared *N*-benzyl-1-(mesitylsulfonyl)-piperidin-4-amine (0.4135 g, 1.11 mmol), butyryl chloride (0.13 mL, 1.24 mmol), and $^iPr_2NEt$ (0.28 mL, 1.70 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 23 h. CH_2Cl_2 (25 mL) was added and the solution was washed with saturated aqueous $NaHCO_3$ (25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified via flash chromatography (1/9 MeOH/CH_2Cl_2) to afford the desired product **117** as a yellow gel (4:1 ratio of two rotamers; 0.2351 g, 48%). ^1H NMR (400 MHz, $CDCl_3$ at 50 °C) δ 7.62−7.18 (m, 3H), 7.15 (d, J = 7.4 Hz, 2H), 6.90 (s, 2H), 4.70−4.35 (m, 1H), 4.48 (s, 2H), 3.63 (d, J = 11.6 Hz, 2H), 2.96−2.68 (m, 2H), 2.56 (s, 6H), 2.35−2.10 (br, 2H), 2.26 (s, 3H), 1.65 (s, 6H), 0.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer δ 174.0, 142.5, 140.2, 138.1, 131.9, 131.8, 128.8, 127.3, 125.7, 51.7, 46.9, 44.2, 35.7, 29.1, 22.8, 20.9, 18.7, 13.8. HRMS (ESI-TOF) calcd for $C_{25}H_{34}N_2O_3SNa$ $[M + Na]^+$ 465.2182, found 465.2190.

***N*-(1-(Mesitylsulfonyl)piperidin-4-yl)butyramide (118).** To a solution of *N*-benzyl-*N*-(1-(mesitylsulfonyl)piperidin-4-yl)butyramide **117** (0.1338 g, 0.30 mmol) in methanol (4 mL) was added palladium on carbon (10 wt %). The flask was evacuated by vacuum and refilled by a hydrogen balloon. This evacuation/refill was repeated three times and the reaction suspension was stirred under hydrogen at room temperature for 18 h. The reaction suspension was then filtered through a pad of celite and washed with methanol. Upon evaporation of the solvent, compound **118** was obtained as a yellow solid (0.0662 g, 62%); mp 144−147 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 2H), 5.82−5.25 (br, 1H), 3.95 (s, 1H), 3.58 (d, J = 11.4 Hz, 2H), 2.90 (s, 2H), 2.60 (s, 6H), 2.29 (s, 3H), 2.25−2.06 (br, 2H), 1.95 (s, 2H), 1.73−1.59 (br, 2H), 1.58−1.40 (br, 2H), 1.04−0.83 (br, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 142.6, 140.3, 132.0, 131.7, 46.1, 43.4, 39.0, 31.7, 22.9, 21.0, 19.3, 13.8. HRMS (ESI-TOF) calcd for $C_{18}H_{28}N_2O_3SNa$ $[M + Na]^+$ 375.1713, found 375.1715.

(4-Methyl-[1,4′-bipiperidin]-1′-yl)(4-(trifluoromethoxy)-phenyl)methanone (119). A mixture of 4-(trifluoromethoxy)-benzoic acid (0.2024 g, 0.98 mmol), DMAP (0.0200 g, 0.16 mmol), and EDC hydrochloride (0.2166 g, 1.13 mmol) in CH_2Cl_2 (6 mL) was stirred at room temperature for 0.5 h. 4-Methyl-1,4′-bipiperidine (0.1847 g, 1.01 mmol) was added and the resulting solution was stirred at room temperature for 26.5 h. The reaction solution was diluted with CH_2Cl_2 (60 mL) and washed with brine (60 mL) and saturated aqueous $NaHCO_3$ (60 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (1:19 MeOH/CH_2Cl_2) to afford compound **119** (0.2434 g, 67%) as a white solid; mp 72−75 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.3 Hz, 2H), 4.73 (d, J = 12.8 Hz, 1H), 3.75 (d, J = 13.6 Hz, 1H), 3.00 (s, 1H), 2.87 (d, J = 11.4 Hz, 2H), 2.75 (s, 1H), 2.50 (t, J = 11.4 Hz, 1H), 2.14 (t, J = 11.5 Hz, 2H), 1.87 (d, J = 49.0 Hz, 2H), 1.70−1.28 (m, 5H), 1.20 (qd, J = 11.8, 3.8 Hz, 2H), 0.90 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 149.9 (q, J = 1.8 Hz), 134.7, 128.7, 120.9, 120.3 (q, J = 258.0 Hz), 62.1, 49.8 and 49.5 (rotamers), 47.4 and 42.0 (rotamers), 34.6, 31.0, 29.2 and 27.8 (rotamers), 21.9. HRMS (ESI-TOF) (ESI) calcd for $C_{19}H_{25}N_2O_2F3$ $[M + Na]^+$ 393.1754, found 393.1760.

4-Methoxyphenyl 4-Methyl-[1,4′-bipiperidine]-1′-carboxylate (120). To a solution of 4-methyl-1,4′-bipiperidine (0.1831g, 1.01 mmol) and K_2CO_3 (0.1522 g, 1.10 mmol) in Et_2O (15 mL) was added 4-methoxyphenyl carbonochloridate (0.15 mL, 1.00 mmol) at 0 °C. The resulting suspension was allowed to warm up to room temperature gradually and stirred for 5 h. The suspension was then poured into H_2O (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (9/1 CH_2Cl_2/CH_3OH) to afford compound **120** as a white solid (0.2647 g, 79%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, J = 9.1 Hz, 2H), 6.83 (d, J = 9.1 Hz, 2H), 4.33 (s, 2H), 3.75 (s, 3H), 3.09 (d, J = 11.0 Hz, 2H), 2.93 (s, 1H), 2.79 (t, J = 11.8 Hz, 2H), 2.41 (s, 2H), 2.05 (s, 2H), 1.84−1.37 (m, 7H), 0.94 (d, J = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 153.8, 144.8, 122.5, 114.3, 62.7, 55.6, 49.6, 49.2, 43.7, 32.8, 30.3, 27.5, 26.8, 21.4. HRMS (ESI-TOF) (ESI) calcd for $C_{19}H_{29}N_2O_3$ $[M + H]^+$ 333.2173, found 333.2189.

***N*-(4-Methoxyphenyl)-4-methyl-[1,4′-bipiperidine]-1′-carboxamide (121).** To a 15 mL flame-dried flask were added 4-methyl-1,4′-bipiperidine (0.1889 g, 1.04 mmol), DCM (6 mL), and 1-isocyanato-4-methoxybenzene (0.1674 g, 1.12 mmol) at 0 °C sequentially. The resulting solution was then allowed to warm to room temperature and stirred for 22 h. After the evaporation of solvents, the residue was purified through flash chromatography on silica gel (1:19 MeOH/CH_2Cl_2) to afford the entitled product as a white solid (0.2032 g, 59%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.9 Hz, 2H), 6.80 (d, J = 8.9 Hz, 2H), 6.38 (s, 1H), 4.08 (d, J = 13.2 Hz, 2H), 3.75 (s, 3H), 2.93−2.72 (m, 4H), 2.53−2.33 (m, 1H), 2.14 (t, J = 11.6 Hz, 2H), 1.83 (d, J = 11.9 Hz, 2H), 1.64 (d, J = 13.8 Hz, 1H), 1.49 (qd, J = 12.4, 4.2 Hz, 2H), 1.42−1.26 (m, 1H), 1.20 (qd, J = 11.9, 3.5 Hz, 2H), 0.90 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 155.4, 132.2, 122.3, 114.0, 62.2, 55.5, 49.6, 44.0, 34.7, 31.1, 28.0, 21.9. HRMS (ESI-TOF) (ESI) calcd for $C_{19}H_{30}N_3O_2$ $[M + H]^+$ 332.2333, found 332.2326.

***N*-(4-Methoxyphenyl)-4-oxopiperidine-1-sulfonamide (122).** A solution of 4-methoxyaniline (1.8932 g, 15.39 mmol) in CH_2Cl_2 (18 mL) was cooled to −10 °C and chlorosulfonic acid (0.34 mL, 5.13 mmol) was added dropwise in 10 min. The resulting suspension was allowed to warm to room temperature and stirred for 3 h. After filtration, the solid was dried under reduced pressure and suspended in toluene (15 mL), followed by addition of PCl_5 (1.0239 g, 4.92 mmol). The reaction mixture was stirred at 75 °C for 3.5 h and filtered. The filtrate was concentrated under reduced pressure to afford 4-MeOPhNHSO$_2$Cl, which was used without further purification.

A suspension of piperidin-4-one hydrochloride hydrate (**2a**, 0.7689 g, 5.03 mmol), Na_2SO_4 (1.2132 g, 7.19 mmol), and Et_3N (2.9 mL, 2.1054 g, 20.85 mmol) in CH_2Cl_2 (15 mL) was stirred vigorously, followed by addition of 4-MeOPhNHSO$_2$Cl as prepared above. The reaction mixture was stirred at room temperature for 20 h and poured into 0.5 N aqueous HCl (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (1/1 EtOAc/hexane) to afford *N*-(4-methoxyphenyl)-4-oxopiperidine-1-sulfonamide as a brown gel (0.1552 g, 11% over two steps). ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 8.9 Hz, 2H), 7.02 (s, 1H), 6.84 (d, J = 8.9 Hz, 2H), 3.77 (s, 3H), 3.53 (t, J = 6.2 Hz, 4H), 2.42 (t, J = 6.2 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 157.7, 129.2, 124.2, 114.6, 55.5, 46.0, 40.8. MS (ESI) calcd for $C_{12}H_{17}N_2O_4S$ $[M + H]^+$ 285.1, found 285.1.

Reaction of the above-prepared *N*-(4-methoxyphenyl)-4-oxopiperidine-1-sulfonamide (0.1102 g, 0.39 mmol) with 4-methylpiperidine (Procedure D) yielded **122** as a pale yellow gel (0.0217 g, 15%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.8 Hz, 2H), 6.84 (dd, J = 8.9, 2.3 Hz, 2H), 3.88 (d, J = 12.7 Hz, 2H), 3.79 (d, J = 1.8 Hz, 3H), 3.16 (d, J = 11.7 Hz, 2H), 2.92 (s, 1H), 2.74 (t, J = 12.2 Hz, 2H), 2.50 (t, J = 11.5 Hz, 2H), 2.13−1.93 (m, 3H), 1.88−1.56 (m, 6H), 1.55−1.39 (m, 1H), 0.97 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 130.1, 123.9, 114.4, 62.3, 55.5, 49.0, 45.5, 31.4, 29.6, 25.9, 21.0. HRMS (ESI-TOF) calcd for $C_{18}H_{30}N_3O_3S$ $[M + H]^+$ 368.2002, found 368.1991.

2,4,6-Trimethyl-*N*-(4-(4-methylpiperidin-1-yl)cyclohexyl)-benzenesulfonamide (123). A mixture of *tert*-butyl (4-oxocyclohexyl)carbamate (0.4296 g, 2.02 mmol), HCl (37%, 2 mL), and 1,4-dioxane (6 mL) was stirred at room temperature for 3.5 h. Upon evaporation of solvents, the residue (**2b**) was reacted with 2-mesitylenesulfonyl chloride according to Procedure B to yield 2,4,6-trimethyl-*N*-(4-oxocyclohexyl)benzenesulfonamide as a light yellow gel (83%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 2H), 5.36−5.26 (br, 1H), 3.64−3.40 (m, 1H), 2.63 (s, 6H), 2.40−2.31 (m, 2H), 2.30−2.20 (m, 5H), 2.04−1.93 (m, 2H), 1.79−1.67 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 138.9, 134.3, 132.1, 49.6, 38.4, 32.2, 22.9, 20.9.

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Reaction of the above-prepared 2,4,6-trimethyl-*N*-(4-oxocyclohexyl)benzenesulfonamide with 4-methylpiperidine (Procedure D) yielded **123** as a light yellow gel (13%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 2H), 6.36 (s, 1H), 3.45−3.20 (m, 3H), 3.02 (t, J = 11.7, 1H), 2.74 (dt, J = 13.9, 7.9 Hz, 2H), 2.59 (s, 6H), 2.26 (s, 3H), 2.10−1.65 (m, 10H), 1.62−1.35 (m, 3H), 0.94 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 139.0, 133.7, 132.1, 64.0, 49.1, 47.1, 30.9, 29.9, 23.0, 20.9, 20.8. HRMS (ESI-TOF) calcd for $C_{21}H_{35}N_2O_2S$ $[M + H]^+$ 379.2414, found 379.2427.

2,4,6-Trimethyl-*N*-(2-(4-methylpiperidin-1-yl)ethyl)-benzenesulfonamide (124). Reaction of amine **1h** with 2,4,6-trimethylbenzene-1-sulfonyl chloride (Procedure A) yielded **124** as a yellow gel (>95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 2H), 2.86 (d, J = 5.2 Hz, 2H), 2.61 (s, 6H), 2.52 (d, J = 11.6 Hz, 2H), 2.28 (d, J = 5.9 Hz, 2H), 2.26 (s, 3H), 1.82 (td, J = 11.9, 2.6 Hz, 2H), 1.52 (d, J = 13.1 Hz, 2H), 1.36−1.20 (m, 1H), 1.07 (qd, J = 12.5, 3.7 Hz, 2H), 0.86 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 139.0, 133.3, 131.8, 55.8, 53.3, 39.0, 34.2, 30.6, 22.9, 21.8, 20.9. HRMS (ESI-TOF) calcd for $C_{17}H_{29}N_2O_2S$ $[M + H]^+$ 325.1944, found 325.1947.

1-(4-(Mesitylsulfonyl)phenyl)-4-methylpiperidine (125). On the basis of a literature report,[40] a mixture of 4-iodobenzenesulfonyl chloride (0.9232 g, 3.02 mmol), mesitylene (120 mg, 3.09 mmol), and $AlCl_3$ (0.4956 g, 3.73 mmol) in CH_2Cl_2 (15 mL) was stirred for 3 h at room temperature. The mixture was then poured into 45 mL of 5% aqueous HCl and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were concentrated under reduced pressure to about 50 mL and then washed with saturated aqueous $NaHCO_3$ (45 mL) and brine (45 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (10/1 hexane/EtOAc) to give the desired product 2-((4-iodophenyl)sulfonyl)-1,3,5-trimethylbenzene (0.5707 mg, 48%) as pale yellow solid. mp 118−121 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91−7.72 (d, J = 8.0 Hz, 2H), 7.57−7.35 (d, J = 7.8 Hz, 2H), 6.93 (s, 2H), 2.56 (s, 6H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 143.2, 140.0, 138.1, 133.3, 132.3, 127.6, 99.9, 22.8, 21.0.

To a solution of the above-prepared 2-((4-iodophenyl)sulfonyl)-1,3,5-trimethylbenzene (0.2879 g, 0.75 mmol), CuI (0.0145 g, 0.076 mmol), L-proline (0.0176 g, 0.15 mmol), and K_2CO_3 (0.2160 g, 1.57 mmol) in DMSO (6 mL) was added 4-methylpiperidine (0.18 mL, 1.52 mmol), and the reaction suspension was stirred vigorously at 90 °C for 67 h. After cooling to room temperature, water (30 mL) was added followed by extraction with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated, and the residue was purified by flash chromatography (10/1 hexane/EtOAc) to afford the title compound **125** as a white solid (0.0636 g, 24%); mp 103−105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.9 Hz, 2H), 6.90 (s, 2H), 6.84 (d, J = 8.6 Hz, 2H), 3.79 (d, J = 12.9 Hz, 2H), 2.84 (t, J = 13.4 Hz, 2H), 2.61 (s, 6H), 2.27 (s, 3H), 1.71 (d, J = 13.0 Hz, 2H), 1.64−1.47 (m, 1H), 1.25 (q, J = 12.3 Hz, 2H), 0.96 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 139.6, 135.3, 132.0, 128.2, 113.7, 48.1, 33.5, 30.7, 22.9, 21.8, 21.0. HRMS (ESI-TOF) calcd for $C_{21}H_{27}NO_2SNa$ $[M + Na]^+$ 380.1655, found 380.1660.

1-(Mesitylsulfonyl)-4-(1-methylpiperidin-4-yl)piperazine (126). Reaction of amine **1i** with 2,4,6-trimethylbenzenesulfonyl chloride (Procedure A) yielded **126** as a colorless gel (>95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 2H), 3.23−3.04 (m, 4H), 2.85 (d, J = 12.2 Hz, 2H), 2.59 (s, 6H), 2.57−2.48 (m, 4H), 2.26 (s, 3H), 2.22 (s, 3H), 2.22−2.15 (m, 1H), 1.89 (t, J = 12.0 Hz, 2H), 1.69 (d, J = 11.0 Hz, 2H), 1.51 (qd, J = 12.3, 3.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 140.4, 131.9, 131.3, 61.4, 55.3, 48.4, 46.1, 44.7, 28.0, 23.0, 21.0. LC−MS (ESI) calcd for $C_{19}H_{32}N_3O_2S$ $[M + H]^+$ 366.2, found 366.2.

3-(4-(Mesitylsulfonyl)piperazin-1-yl)quinuclidine (127). Reaction of amine **1j** with 2,4,6-trimethylbenzenesulfonyl chloride (Procedure A) yielded **127** as a white solid (42%); mp > 300 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 2H), 3.34−3.12 (m, 9H), 3.04 (dd, J = 12.0, 4.0 Hz, 1H), 2.60 (s, 6H), 2.45 (s, 5H), 2.30 (s, 4H), 2.16−1.95 (m, 2H), 1.85−1.75 (m, 1H), 1.74−1.62 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 140.5, 132.0, 131.0, 59.1, 52.8, 50.3, 46.6, 45.6, 44.1, 23.0, 22.9, 22.1, 20.9, 17.7. HRMS (ESI-TOF) calcd for $C_{20}H_{32}N_3O_2S$ $[M + H]^+$ 378.2210, found 378.2200.

1-(Adamantan-1-yl)-4-(mesitylsulfonyl)piperazine (128). Reaction of amine **1l** with 2,4,6-trimethylbenzene-1-sulfonyl chloride (Procedure B) yielded **128** as a yellow solid (70%); mp 182−184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 2H), 3.20−3.02 (m, 4H), 2.68−2.61 (m, 4H), 2.60 (s, 6H), 2.27 (s, 3H), 2.05 (s, 3H), 1.70−1.49 (m, 14H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 140.4, 131.9, 131.4, 54.0, 45.2, 43.7, 38.5, 36.8, 29.5, 23.1, 20.9. HRMS calcd for $C_{23}H_{35}N_2O_2S$ $[M + H]^+$ 403.2414, found 403.2407.

2,4,6-Trimethyl-*N*-(1′-methyl-[1,4′-bipiperidin]-4-yl)-benzenesulfonamide (129). Reaction of amine hydrochloride salt **1m** with 2,4,6-trimethylbenzene-1-sulfonyl chloride (Procedure B) yielded **128** as a yellow gel (81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 2H), 4.73 (s, 1H), 3.04 (s, 1H), 2.84 (d, J = 12.1 Hz, 2H), 2.69 (d, J = 12.0 Hz, 2H), 2.59 (s, 6H), 2.25 (s, 3H), 2.20 (s, 3H), 2.19−2.05 (m, 3H), 1.87 (t, J = 10.6 Hz, 2H), 1.76−1.59 (m, 4H), 1.50 (qd, J = 12.2, 3.8 Hz, 2H), 1.44−1.31 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 138.7, 135.0, 131.9, 61.4, 55.4, 50.7, 47.6, 46.0, 33.2, 27.7, 22.9, 20.9. HRMS (ESI-TOF) calcd for $C_{20}H_{34}N_3O_2S$ $[M + H]^+$ 380.2366, found 380.2359.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.9b00532.

Biological assay data and SMILES structures for all tested compounds (Table S1); procedures and characterization of synthetic intermediates; and copies of ^{1}H and ^{13}C spectra (PDF)

Molecular formula strings (CSV)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Jef.DeBrabander@UTSouthwestern.edu. Tel: (214) 648-7808. Fax: (214) 648-0320.

ORCID

Jef K. De Brabander: 0000-0001-8816-5798

Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare the following competing financial interest(s): Jef K. De Brabander and Jerry W. Shay are scientific cofounders and hold equity in Barricade Therapeutics, Inc. whom holds the license to the TASIN compounds disclosed in this manuscript.

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ABBREVIATIONS

APC, adenomatous polyposis coli; CRC, colorectal cancer; FAP, familial adenomatous polyposis; HCEC, human colonic epithelial cell; HTS, high-throughput screen; PK, pharmacokinetics; SAR, structure−activity relationship; TASIN, truncated APC-selective inhibitor

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