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Discovery of Tertiary Sulfonamides as Potent Liver X Receptor Antagonists

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Tertiary sulfonamides were identified in a HTS as dual liver X receptor (LXR, NR1H2, and NR1H3) ligands, and the binding affinity of the series was increased through iterative analogue synthesis. A ligand-bound cocrystal structure was determined which elucidated key interactions for high binding affinity. Further characterization of the tertiary sulfonamide series led to the identification of high affinity LXR antagonists. GSK2033 (**17**) is the first potent cell-active LXR antagonist described to date. **17** may be a useful chemical probe to explore the cell biology of this orphan nuclear receptor.

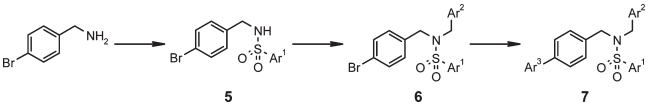
Introduction

The nuclear receptor (NR[a]) superfamily of ligand-activated transcription factors comprises 48 members in the human genome; as NRs bind to their cognate ligands, conformational changes are induced which modulate cofactor recruitment and, consequently, the expression of target genes.[1] LXRα (NR1H2) and LXRβ (NR1H2) are NRs which play important roles in lipid homeostasis and serve as intracellular sensors of cholesterol load.[2] Endogenous ligands include oxysterols such as 24(*S*),25-epoxycholesterol (**1**, Chart 1).[3,4] The potent dual LXRα/β agonists T1317 (**2**) and GW3965 (**3**) have been used as chemical probes to uncover biology of the LXRs and their roles in mammalian physiology.[5,6] These chemical probes have been used to identify LXR target genes, such as sterol regulatory element binding protein 1c (SREBP-1c) and carbohydrate response element binding protein (ChREBP) through which the receptor regulates hepatic lipogenesis.[7,8] This liability has limited the utility of LXR agonists as drugs for the treatment or prevention of cardiovascular disease.[9]

In an effort to identify a new class of LXR ligands devoid of the hepatic liability, we conducted a high-throughput screen (HTS) of the GlaxoSmithKline compound collection using a fluorescence resonance energy transfer (FRET) assay to measure the interaction between the LXRβ ligand-binding domain (LBD) and a peptide containing the second NR box of steroid receptor coactivator-1 (SRC-1). Hit compounds were further characterized in a radioligand binding assay. The screen delivered the biaryl tertiary sulfonamide **4**, representing a new LXR chemotype. Optimization of this series led to the identification of potent LXR ligands with an unprecedented range of functional activity, from full agonists to full antagonists.

Results and Discussion

To optimize activity of the initial hit **4**, analogues were prepared via the three-step synthetic route shown. 4-Bromobenzylamine was reacted with a variety of sulfonyl chlorides, and the resulting sulfonamides **5** were alkylated with benzylic and heterobenzylic halides to produce tertiary sulfonamides **6**. Suzuki coupling formed the desired biaryl species **7**. Utilizing this three-step sequence, arrays of several hundred compounds were prepared.



Screening of the tertiary sulfonamides in an LXRβ competition binding assay revealed several SAR trends. Systematic truncation of **4** showed that the piperazine was not required but defined the importance of the biaryl moiety in maintaining binding affinity (data not shown). Modification of the tertiary sulfonamide revealed several important findings as highlighted by the data in Table 1. The sulfonamide group was required for high LXR affinity; replacement of the sulfonyl with a carbonyl or a methylene spacer (as in **9** and **10**) reduced LXR affinity. Certain biaryl substituents at R^1 led to a boost in affinity with **11** and **12**, which incorporated a 3-$MeSO_2$ group showing the best activity. All subsequent arrays maintained the 3-$MeSO_2$ group, and results from the binding assay demonstrated that receptor affinity could be maintained near 10 nM with a range of sulfonamide substituents R^2, as in **12**−**15** and **18**.

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[a] Abbreviations: ABCA1, ATP-binding cassette transporter A1; AF-2, activation function 2; ChREBP, carbohydrate response element binding protein; FRET, fluorescence resonance energy transfer; HTS, high throughput screen; LBD, ligand-binding domain; LXR, liver X receptor; NR, nuclear receptor; SRC-1, steroid receptor coactivator 1; SREBP-1c, sterol regulatory element binding protein 1c; TIF2, transcriptional intermediary factor 2.

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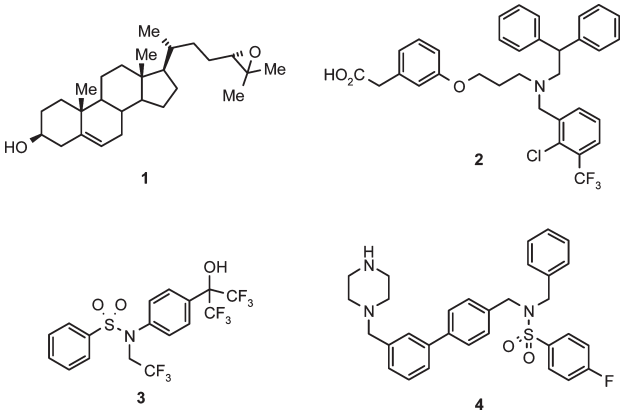
To date, ligand-bound LXR cocrystal structures have been published for **1**−**3**.[10−12] These crystal structures exhibit plasticity with ligand-binding pockets that vary in size and shape depending on the nature of the ligand. Whereas **1**−**3** show different interactions with residues in the pocket that are distal to AF-2, they activate the receptor by promoting similar electrostatic interactions between a conserved histidine on helix 10/11 and tryptophan on the C-terminal activation function-2 (AF-2) helix.[13]

To elucidate the intermolecular interactions for a high affinity tertiary sulfonamide presented here, we obtained the cocrystal structure of **18** with the human LXRβ ligand LBD and a 12 residue peptide containing the third NR box of transcriptional intermediary factor 2 (TIF2). As illustrated in Figure 1, we observed the canonical three-layered α-helical fold where the C-terminal AF-2 helix is packed against the ligand-binding pocket in a conformation that enables coactivator binding. Intermolecular contacts between **18** and the receptor are dominated by hydrophobic side chains that line the binding pocket. The sulfonamide oxygen O1 lies poised to interact with NE2 of His 435 in helix 10/11, but the 3.9 Å distance is too long to invoke a hydrogen bond. Sulfonamide oxygen O2 is directed toward a region formed by hydrophobic side chain atoms from Thr 272, Ala 275, Leu 453, and Trp 457.

Chart 1. Known LXR Ligands **1**−**3** and LXR HTS Hit **4**

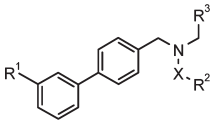


Chlorine from the 2-chloro-6-fluorobenzyl moiety resides 3.4 Å from His 435 NE2 and the entire functional group occupies much of the same hydrophobic pocket as one of the benzhydryl phenyl rings in **2** or the trifluoroethyl substituent in **3**. The *N*-methylimidazole extends far deeper into a hydrophobic pocket than the *gem*-dimethyl group of **1**, the 2-chloro-3-trifluoromethylbenzyl group of **2**, or the trifluoromethyl groups of **3** so that its methyl is positioned 3.2 Å from Phe 268 CE1 and 3.5 Å from Leu 442 CD2. Only on the distal end of the biaryl moiety is a hydrogen bond noted. Methyl sulfone oxygen atom O3 accepts a 3.0 Å hydrogen bond from the backbone NH of Leu330 in the β-hairpin loop between helix 5 and 6; the guanidinium NH1 side chain atom of Arg 319 at the end of helix 5 is also 3.0 Å from methyl sulfone oxygen atom O3.

The tertiary sulfonamide arrays were further characterized in a heterologous reporter assay utilizing CV-1 cells transiently expressing an LXR-Gal4 chimera along with a reporter harboring the Gal4 enhancer region linked to a luciferase reporter gene. Consistent with the binding data, many tertiary sulfonamides were potent agonists in the transactivation assay (Table 2). No subtype selectivity greater than 10-fold was observed. Nearly all of the compounds (**11**−**14**) profiled as full agonists, with efficacy in the transactivation assay comparable to the first generation LXR agonists **2** and **3**. However, **15** with its bulky 2,4,6-trimethylphenyl group profiled as a partial agonist relative to **2**. Subsequent variation of the R^3 substituent demonstrated that efficacy could be further reduced to such an extent that no agonist response was observed with **17** in the transactivation assay.

Given that **17** showed high binding affinity for LXR and that the chemical modifications relative to other compounds in the series were not predicted to affect cell permeability, it was profiled as a potential LXR antagonist. Remarkably, **17** demonstrated potent antagonism of **2** (LXRα pIC_{50} = 7.0 and LXRβ pIC_{50} = 7.4) with no evidence of cell toxicity. To further characterize the functional activity of **17**, we tested its ability to block the induction of known LXR target genes. In intact cells stimulated with LXR agonist **3** (50 nM), **17** showed a dose-dependent reduction in the expression of the ATP-binding cassette transporter A1 (ABCA1) in THP-1 cells and

Table 1. Evaluation of LXRβ Binding Affinity of Tertiary Sulfonamides



8-18

compd	R^1	X	R^2	R^3	LXRβ binding pIC_{50}
2					8.1
3					7.7
4					6.4
8	H	SO_2	Ph	2-Cl-4-F-Ph	5.5
9	H	CH_2	Ph	2-Cl-4-F-Ph	< 5.0
10	H	CO	Ph	2-Cl-4-F-Ph	< 5.0
11	$MeSO_2$	SO_2	Ph	2-Cl-4-F-Ph	8.4
12	$MeSO_2$	SO_2	Ph	2-Cl-6-F-Ph	8.3
13	$MeSO_2$	SO_2	cyclopropyl	2-Cl-6-F-Ph	8.2
14	$MeSO_2$	SO_2	2-Me-Ph	2-Cl-6-F-Ph	7.9
15	$MeSO_2$	SO_2	2,4,6-Me_3-Ph	2-Cl-6-F-Ph	7.8
16	$MeSO_2$	SO_2	2,4,6-Me_3-Ph	2-Cl-4-F-Ph	7.1
17	$MeSO_2$	SO_2	2,4,6-Me_3-Ph	5-CF_3-2-furanyl	7.5
18	$MeSO_2$	SO_2	1-Me-4-imidazolyl	2-Cl-6-F-Ph	8.0

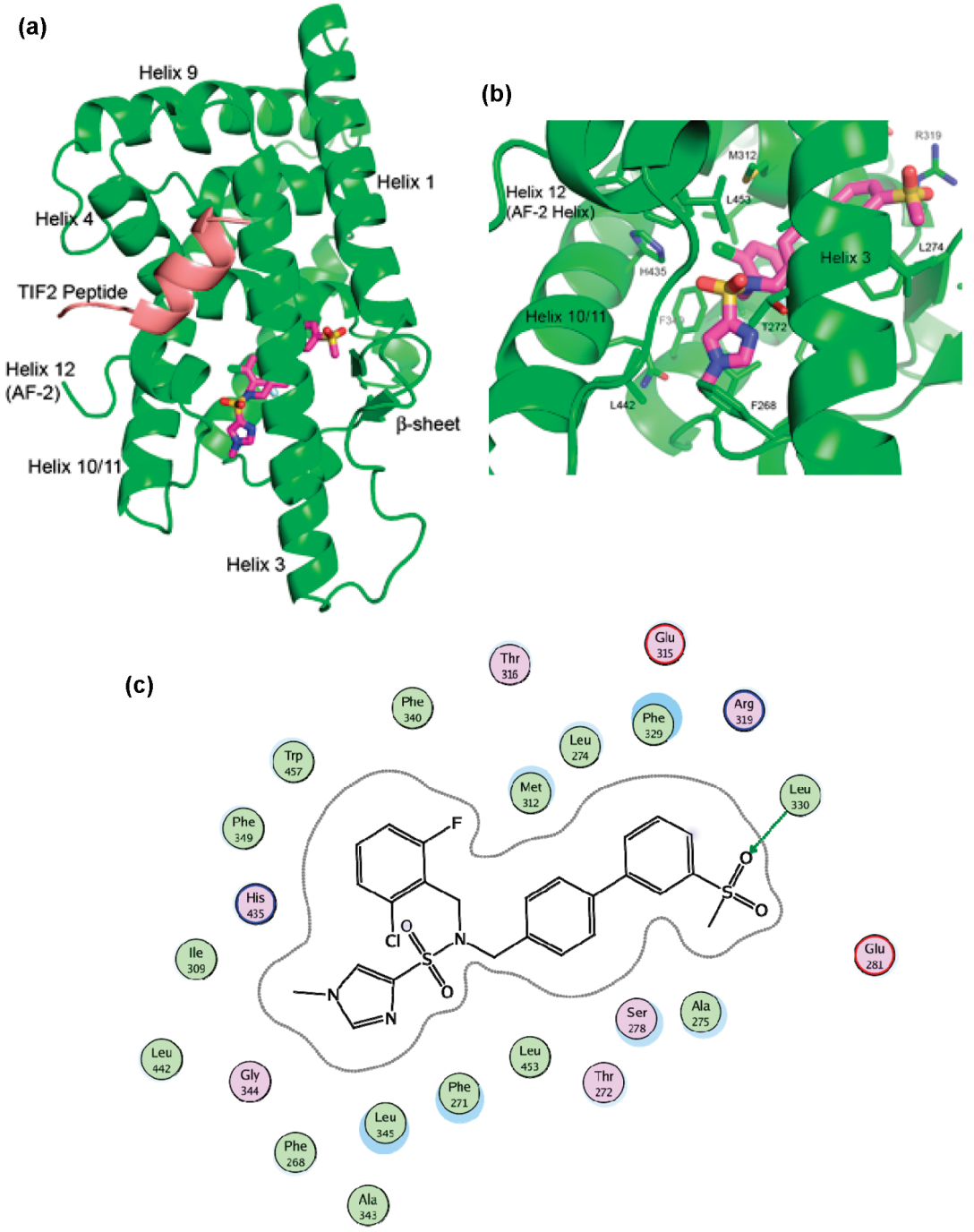


Figure 1. Crystal structure of agonist **18** bound to LXRβ and TIF2 peptide. (A) Global view of the human LXRβ ligand binding domain (green ribbon), TIF2 L*XX*LL peptide (salmon ribbon) and GSK1305158 (magenta sticks). The agonist occupies the ligand binding pocket behind helix 3, allowing helix 12 to adopt the active conformation and pack against the LBD facilitating TIF2 binding. (B) Zoomed view looking toward the required sulfonamide group. Sulfonamide oxygen O1 lies too distant to hydrogen bond with His 435 in helix 12. On the opposite end of the ligand, a hydrogen bond is observed between methyl sulfone oxygen O3 and the Leu 330 backbone amide in the β-hairpin. The remaining intermolecular contacts are hydrophobic core interactions. (C) Two dimensional compound interaction diagram depicting adjacent residues and the hydrogen bonding interaction with Leu 330 backbone amide. The crystal structure is available from the RCSB with access code 3L0E and is further described in the Supporting Information.

SREBP-1c in HepG2 cells (Figure 2a). Levels of ABCA1 expression were driven below that observed in the absence of stimulation with **3**, suggesting that even *basal* gene expression could be antagonized. Indeed, in untreated HepG2 and THP-1 cells, **17** antagonized the expression of these genes with apparent IC_{50} values less than 100 nM (Figure 2b). Consistent with the latter observation, **17** reduced the basal level of triglycerides in HepG2 cells (Figure 2c).

The partial agonism and antagonism of **15**−**17** might be explained by the much greater size of the compounds that could lead to perturbation of the receptor ligand binding domain. Smaller compounds, such as **18**, bind to the ligand binding pocket of LXRβ and provide a stabilization of the protein through hydrophobic interactions with the protein involving residues along Helix 3, Helix 4, Helix 10/11, and the Helix 12 loop. However, as the compounds increased in size

Table 2. Evaluation of LXR Transactivation by Tertiary Sulfonamides[a]

	LXR GAL4 pEC_{50} (RE)	
compd	LXRα	LXRβ
2	6.1 (1.0)	6.3 (1.0)
3	7.2 (1.1)	7.0 (1.1)
11	8.0 (1.0)	8.5 (0.9)
12	8.2 (1.2)	9.0 (1.2)
13	7.0 (0.9)	7.7 (1.0)
14	7.9 (1.2)	8.5 (1.0)
15	7.1 (0.5)	7.8 (0.6)
16	6.9 (0.2)	7.0 (0.3)
17	ia	ia
18	7.1 (1.0)	7.1 (0.9)

[a] Abbreviations: RE, relative efficacy compared to first generation LXR agonist **2**; ia, inactive.

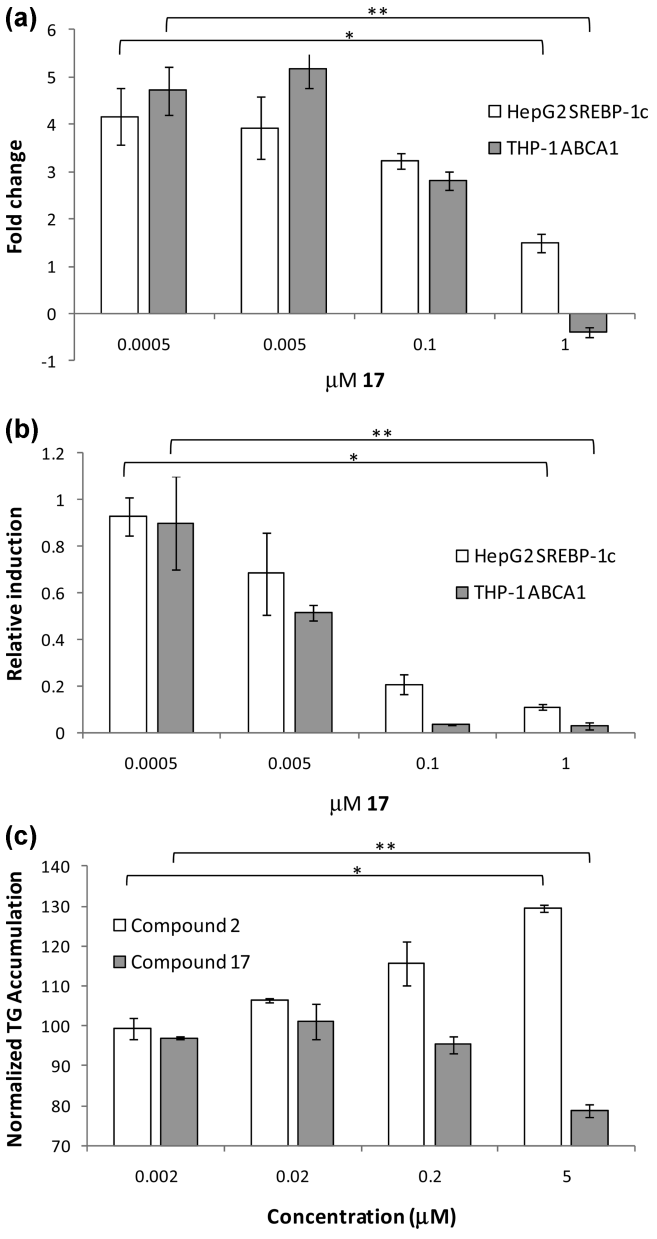


Figure 2. (a) Fold induction of LXR target gene expression cells treated with 50 nM **3** (*,* $p < 0.0005$); (b) relative induction of LXR target genes in nonstimulated cells (*,** $p < 0.0005$); (c) dose-dependent stimulation (**2**) and repression (**17**) of triglyceride accumulation in HepG2 cells (*, ** $p < 0.005$).

and hydrophobic character, the bulky substituents (such as those found in **17**) were more likely to perturb the conformation of the protein, particularly the region of the binding pocket constituting Helix 3, Helix 10/11, and the loop before Helix 12. Because these helices and the Helix 12 loop reside near the coactivator binding pocket, the bulky ligands may disrupt the binding of coactivator proteins, leading to partial agonism and, eventually, full antagonism.

The interesting functional profile of **17** prompted further efforts to define its utility as a chemical probe for the LXRs. The tertiary sulfonamide series in general showed good selectivity against a broad panel of NR assays, and in particular, **17** was inactive ($XC_{50} > 10$ μM) in cellular and biochemical NR assays, including PXR, LRH-1, and FXR. However, **17** showed rapid clearance ($Cl_{int} > 1.0$ mL/min/mg prot) in rat and human liver microsome assays. The rapid hepatic metabolism of **17** precludes its use in vivo. As such, **17** is a useful chemical probe for LXR in cellular studies only.

Conclusion

In summary, tertiary sulfonamides were identified in a high throughput screen as dual LXR ligands, and the binding affinity of the series was increased through iterative analogue synthesis. A ligand-bound cocrystal structure was determined which elucidated key interactions for high binding affinity. Further characterization of the tertiary sulfonamide series led to the identification of high affinity LXR antagonists. GSK2033 (**17**) is the first potent cell-active LXR antagonist described to date.[14−18] **17** may be a useful chemical probe to further define the cell biology of this orphan nuclear receptor.

Experimental Section

Compound solvents and reagents were reagent grade and used without purification unless otherwise noted. All ^{1}H NMR spectra were recorded on a Varian 400 MHz spectrometer. Chemical shifts (δ) are reported downfield from tetramethylsilane (Me_4Si) in parts per million (ppm) of the applied field. Peak multiplicities are abbreviated: singlet, s; broad singlet, bs; doublet, d; triplet, t; quartet, q; multiplet, m. Coupling constants (J) are reported in hertz. LCMS analyses were conducted using a Waters Acquity UPLC system with UV detection performed from 210 to 350 nm with the MS detection performed on a Waters Acquity SQD spectrometer. Purities of compounds **8**−**18** were >98% as determined by LCMS.

General Procedure for the Preparation of Tertiary Sulfonamides. 4-Iodobenzylamine (3.20 g, 13.7 mmol), triethylamine (7.65 mL, 104 mmol), and an arylsulfonyl chloride (16.5 mmol, 1.2 equiv) were added to CH_2Cl_2 (40 mL). After allowing this reaction mixture to stir overnight, water was added to precipitate the product and the solution was acidified with 10 M H_2SO_4. The solids were collected by filtration and triturated with diethyl ether to yield a secondary sulfonamide. In a subsequent step, the secondary sulfonamide (4.1 mmol), a substituted arylboronic acid (4.9 mmol, 1.2 equiv), palladium acetate (0.4 mmol), tri(*o*-tolyl)phosphine (0.8 mmol), and sodium carbonate (8.2 mmol) were added to a mixture of ethylene glycol dimethyl ether (8 mL) and water (2 mL). After heating under a nitrogen atmosphere at 65 °C for 4 h, the reaction mixture was then diluted with EtOAc and washed with saturated aqueous $NaHCO_3$. The organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Trituration with diethyl ether afforded the biaryl secondary sulfonamide. In a subsequent step, the biaryl sulfonamide (0.09 mmol), a benzylic or heterobenzylic bromide (0.011 mmol), MP-carbonate (0.045 mmol), and DMF (0.4 mL) were combined and heated at 95 °C overnight with stirring. After cooling to room

temperature, the reaction mixture was diluted with CH_2Cl_2, filtered, and concentrated under an N_2 stream. The residue was then dissolved in DMF/MeOH and purified on an Agilent 1100 Series HPLC (70 mm × 30 mm Phenomenex column packed with Luna 5 μm C18 stationary phase) using 50−100% MeCN/water + 0.05% CF_3CO_2H elution to yield the desired biaryl tertiary sulfonamide product.

2,4,6-Trimethyl-*N*-{[3′-(methylsulfonyl)-4-biphenylyl]methyl}-*N*-{[5-(trifluoromethyl)-2-furanyl]methyl}benzenesulfonamide (17). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.55 (s, 6 H) 3.29 (s, 3 H) 4.34 (s, 2 H) 4.41 (s, 2 H) 6.39 (d, J = 3.48 Hz, 1 H) 7.03 (d, J = 2.09 Hz, 1 H) 7.07 (s, 2 H) 7.29 (d, J = 8.00 Hz, 2 H) 7.61−7.82 (m, 3 H) 7.91 (d, J = 8.00 Hz, 1 H) 8.01 (d, J = 8.00 Hz, 1 H) 8.13 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ 20.1, 22.8, 41.2, 44.6, 50.0, 110.2, 112.4 (J_{CF} = 2.8 Hz), 117.5, 120.2, 125.8, 126.1, 127.5, 129.5, 129.9, 132.1, 132.2, 132.6, 135.6, 138.7, 140.4, 141.3, 142.1, 143.1, 152.8. ^{19}F NMR ($CDCl_3$) δ −64.7. MS (ESI): m/z 592 $(M + H)^+$. HRMS for $C_{29}H_{29}F_3NO_5S_2$ calcd 592.1426; obsd 592.1439.

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Supporting Information Available: Spectroscopic data for compounds **8**−**18**, assay protocols, and X-ray crystallography details.This material is available free of charge via the Internet at http://pubs.acs.org.

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