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Evaluation of *tert*-Butyl Isosteres: Case Studies of Physicochemical and Pharmacokinetic Properties, Efficacies, and Activities

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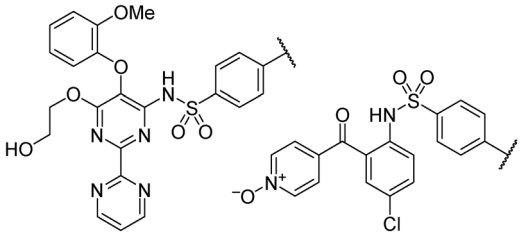
The *tert*-butyl group is a common motif in medicinal chemistry. Its incorporation into bioactive compounds is often accompanied by unwanted property modulation, such as increased lipophilicity and decreased metabolic stability. Several alternative substituents are available for the drug discovery process. Herein, physicochemical data of two series of drug analogues of bosentan and vercirnon are documented as part of a comparative study of *tert*-butyl, pentafluorosulfanyl, trifluoromethyl, bicyclo[1.1.1]pentanyl, and cyclopropyl-trifluoromethyl substituents.

Introduction

The *tert*-butyl group is a substituent often encountered in drugs. Examples of pharmaceutically active ingredients bearing this entity include salbutamol,[1] GlaxoSmithKline's β2-adrenergic receptor agonist, remikiren,[2] Roche's renin inhibitor, and terfenadin,[3] Sanofi-Aventis' antihistamine. The incorporation of a *tert*-butyl group onto a scaffold of interest, however, is often accompanied by a decrease in metabolic stability, a phenomenon known to correlate with lipophilicity (log *P*, log *D*).[4] Such issues are addressed early on in the modeDunning Jr.rn drug discovery process through the identification of replacements or scaffold hopping to ensure the viability of a drug candidate throughout the discovery process and to minimize dropout rates at later stages. There are a number of surrogate groups that could be considered as *tert*-butyl isosteres, namely pentafluorosulfanyl (SF_5),[5,6] bicyclo[1.1.1]pentanyl (BCP),[7,8] and cyclopropyl-trifluoromethyl (cyclopropyl-CF_3).[9] Surprisingly, these have not yet found widespread use in this context, which may result from the lack of comparative physicochemical data available to those active in the discipline. Herein, we present two case studies (Figure 1) focused on *tert*-butyl surro-



log*D* (**1a**–**e**):	**e** < **b** < **c** < **a** < **d**
log*D* (**2a**–**e**):	**e** < **b** < **a** < **d**
pK_a (**1a**–**e**):	**b** < **e** < **c** ≈ **a** < **d**
pK_a (**2a**–**e**):	**b** < **e** < **c** < **a** < **d**
Cl (**1a**–**e**):	**b** ≈ **e** < **c** < **d** < **a**
Cl (**2a**–**e**):	**e** < **b** < **c** < **a** < **d**
aq. solubility (**1a**–**e**):	**c** < **e** < **d** < **a** < **b**
aq. solubility (**2a**–**e**):	**a** ≈ **c** ≈ **d** ≈ **e** < **b**
PAMPA (**1a**–**e**):	**b** < **e** < **c** ≈ **a** < **d**
PAMPA (**2a**–**e**):	**d** < **b** < **e**

Figure 1. Summary of selected parameters investigated in this work for bosentan and vercirnon analogues: log*D* = intrinsic distribution coefficient between octanol and aqueous buffer (pH 7.4); pK_a = acidity constant determined spectrophotometrically at 23 ± 1 °C; Cl = intrinsic clearance (μM min^{-1} mg^{-1}); aqueous solubility was determined by using the lyophilization solubility assay (LYSA) at pH 6.5; PAMPA = membrane permeability as derived from the parallel artificial membrane permeability assay.

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gates that provide fundamental information for use in the drug discovery process. The work includes assessment of bioactivities of drug analogues of bosentan (**1a**) and vercirnon (**2a**) as well as important in vitro data on chemical and biological stability (pH and metabolic liabilities), cytochrome P450 enzyme inhibition, membrane permeability, distribution coefficients, ionization constants, and aqueous solubility (at pH 6.5). To the best of our knowledge, this is the only comprehensive study that allows a direct comparison of *tert*-butyl isosteres in terms of these important parameters.

In the context of our ongoing efforts to access novel structures in uncharted chemical space, we recently introduced small saturated heterocycles[10,11] and spirocycles[12,13] for use as novel building blocks in discovery medicinal chemistry programs. In line with these interests, we and others have focused increased attention on the pentafluorosulfanyl group (SF_5).[14–17] It was originally described by Sheppard in 1960[18] and has found selected applications recently in materials science, crop protection, and pharmaceuticals.[19] The few reports on SF_5 drug analogues describe its use for the replacement of CF_3 and *tert*-butyl substituents. However, these examples are, with two exceptions described below, strictly limited to the comparison of bioactivity. For example, Wipf et al. synthesized two SF_5 analogues of the CF_3-containing antimalarial mefloquine and demonstrated the analogues to display equivalent antimalarial activity.[5] Additionally, Diederich and co-workers published a study on typanothione reductase inhibitors in which the SF_5- and CF_3-substituted analogues proved superior to the *tert*-butyl counterpart.[20] The finding of improved activity was attributed to the smaller size of these two relative to *tert*-butyl. Pentafluorosulfanyl analogues of 5-hydroxytryptamine receptor inhibitors fluoxetine, fenfluramine, and norfenfluramine were synthesized by Welch and Lim. These investigators noted that SF_5 exhibits conventional substituent influences in radioligand binding assays and that the selectivity for certain 5-HT receptor subtypes was enhanced by the switch from CF_3 to SF_5.[21] The O'Hagan research group published a work in which the CF_3 group of the allosteric calcium receptor agonist cinacalcet was replaced by SF_5 and documented similar biological profiles for both compounds.[22] In 2011, Phillips and Rathod disclosed lead optimization efforts of triazolopyrimidine-based analogues with antimalarial activity, in which CF_3 and SF_5 analogues were among the most potent compounds and exhibited favorable physicochemical properties.[23,24] Recently, Zanda and colleagues disclosed work on cannabinoid receptor ligands in which the SF_5 group was compared with CF_3 and *tert*-butyl. Evaluating experimentally derived log*P* values and radioligand binding assays, they concluded that SF_5 is a bioisostere of CF_3 and possibly of *tert*-butyl.[6] Herein, we substantiate this finding by providing additional, directly comparable physicochemical data. The results we describe also complement recent work from GlaxoSmithKline that was limited to the specific comparison of CF_3 and SF_5 analogues of a dopamine antagonist with respect to clearance rates, CYP inhibition constants, and a collection of in vivo pharmacokinetic (PK) properties.[25]

A recent publication from Novartis describes the cyclopropyl-CF_3 group as a useful substituent, particularly as a replacement for *tert*-butyl. According to the investigators, this group possesses significantly improved metabolic stability over its *tert*-butyl counterpart in simple model compounds.[9] In separate work, researchers at Gilead confirmed this trend in the context of NS5B inhibitors as promising anti-HIV drugs.[26]

The bicyclo[1.1.1]pentane motif has been incorporated by Novo Nordisk researchers as a phenyl ring isostere in compounds that interact with metabotropic glutamate receptors[27] and later by Pfizer scientists focusing on γ-secretase inhibitors.[8] In addition, it was used in a study on quinolone antibacterials and shown to be more active than structurally closely related ciprofloxacin.[28] Compounds incorporating bicyclo[1.1.1]pentane were also compared with counterparts including fluorinated cyclic and open-chain alkyl groups, and this group was found to be a reasonable surrogate with respect to calculated log*P*, clearance rates, and Caco-2 permeability.[29] Despite the wide ranging studies, there has been no direct comprehensive comparison of the various groups.

We became interested in a comparative examination of all five groups in a wide range of assays and chose two prominent biologically active components for this work. Bosentan (**1a**) is a dual endothelin receptor antagonist used for the treatment of pulmonary arterial hypertension.[30] Vercirnon (**2a**) is a CCR-9 receptor antagonist originally developed for the treatment of inflammatory bowel disease.[31] Both compounds share a *para*-substituted *tert*-butylphenyl sulfonamide unit (Figure 1). Their straightforward synthesis and the availability of robust bioassays to determine functional activity of the derived analogues made them ideal starting points for an investigation of *tert*-butyl isosteres.

We examined the following parameters to derive a full physicochemical profile of all compounds:

1. pH: stability of compounds in aqueous media was determined at pH 1, pH 4, pH 6.5, pH 8, and pH 10.
2. CYP inhibition: compounds were tested for inhibition of three P450 enzyme isoforms (2D6, 3A4, and 2C9).
3. log*D*: partition coefficients between an aqueous buffer (pH 7.4) and octanol were determined.
4. Membrane permeability was determined by using the parallel artificial membrane permeability assay (PAMPA).
5. pK_a: ionization constants were determined by spectrophotometric analysis at different pH values.
6. Solubility was determined according to the lyophilization solubility assay (LYSA)[32] at pH 6.5.
7. Metabolic stability: intrinsic clearance rates were determined in human, mouse, and rat liver microsome preparations.

A simple web-based calculation using the freely available *molinspiration* software revealed the volumes of the substituents used in this study relative to *tert*-butyl, namely $\Delta V = V_{analogue} - V_{t\text{-butyl}}$.[33] Their size increases in the order CF_3 ($\Delta V = -34.9$ Å^3) < SF_5 ($\Delta V = -11.1$ Å^3) < BCP ($\Delta V = -4.1$ Å^3) < *t*-butyl < cyclopropyl-CF_3 ($\Delta V = +4.4$ Å^3) (Figure 2). With CF_3 being significantly smaller, the similar volumes of the other substituents paired with their different shapes and electronic

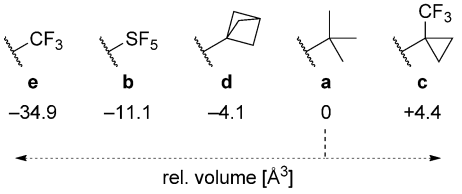


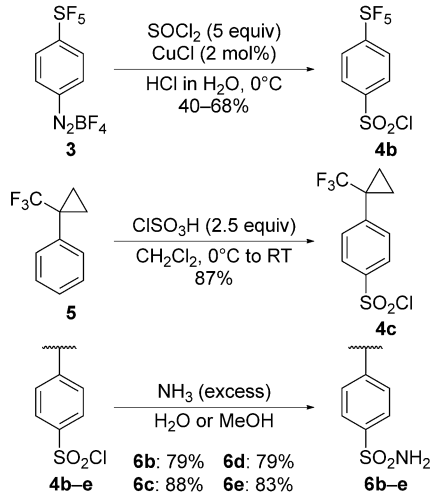
Figure 2. Relative volumes of substituents in this study.[33]

properties offer valuable opportunities for structure–activity studies in the context of any discovery program.

Results and Discussion

Synthesis

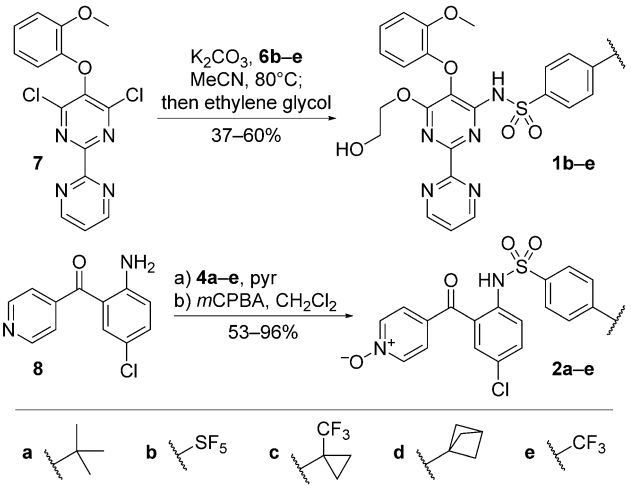
We commenced the synthetic efforts with the preparation of sulfonyl chlorides **4b**–**c** and sulfonyl amides **6b**–**e** (Scheme 1).



Scheme 1. Synthesis of sulfonyl chlorides and sulfonamides.

Previously unknown SF_5-substituted sulfonyl chloride **4b** was prepared from diazonium tetrafluoroborate **3**.[34,35] When a solution of **3** in acetonitrile was added to a mixture of thionyl chloride, 2 mol% copper(I) chloride and concentrated hydrochloric acid in water at 0 °C, **4b** was isolated in 68% yield after simple filtration. This material was sufficiently pure to be used in the next step. Further purification by column chromatography on silica led to decomposition (40% yield). It is important to note that **3**→**4** represents the first instance describing the synthesis of this SF_5-arene sulfonyl chloride. We anticipate it will find wide use for the preparation of novel arene sulfonamide derivatives. Cyclopropyl-CF_3-substituted sulfonyl chloride **4c** was prepared by chlorosulfonation of **5** in dichloromethane in 87% yield as a single regioisomer. Subsequent aminolysis of arene sulfonyl chlorides **4b**–**e** using excess ammonia in water or methanol furnished the corresponding sulfonamides **6b**–**e** in 79–88% yield (Scheme 1).

Analogues of bosentan and vercirnon were synthesized according to known routes (Scheme 2).[36,37] A mixture of potassium carbonate, bispyrimidine **7**, and the respective sulfonamide **6b**–**e** in acetonitrile was heated at 80 °C until the starting material was consumed. Subsequent addition of ethylene glycol and prolonged heating at 80 °C afforded bosentan analogues **1b**–**e** in 37–60% yield. The reaction of **8** with sulfonyl chlorides **4a**–**e** in pyridine at room temperature afforded the corresponding sulfonamides, which were transformed into the respective vercirnon analogues **2a**–**e** by *m*CPBA oxidation in dichloromethane in 53–96% yield over the two steps. Interestingly, reactions with CF_3- and SF_5-substituted sulfonylchlorides showed considerable amounts of the sulfonimide byproducts during the first step of the sequence. We attribute this to the strong electron-withdrawing properties of the two groups, rendering sulfonyl chlorides **4b** and **4e** highly reactive.



Scheme 2. Synthesis of bosentan and vercirnon analogues.

Biological activity

Both drug analogue series are antagonists of ET_A, ET_B, and CCR9 G-protein-coupled receptors. In both cases bioactivity could be measured by a fluorescence imaging plate reader (FLIPR) calcium assay using cells expressing the respective receptor, a fluorescent calcium indicator, the naturally occurring agonist, and drug analogues **1a**–**e**/**2a**–**e**.

For bosentan derivatives **1a**–**e**, Chinese hamster ovary (CHO) cells expressing the human endothelin receptor subtype A (ET_A receptor) or the ET_B receptor, respectively, the cytosol of which had been loaded with the fluorescent calcium indicator fluo-4, were incubated with a dilution series of antagonists **1a**–**e**. Addition of the natural agonist endothelin 1 (ET-1) induces Ca^{2+} efflux from the endoplasmic reticulum into the cytosol, where it can be quantified by measuring the resulting fluorescence upon binding to fluo-4.

Experiments at various antagonist concentrations allow the determination of IC_{50} values (Table 1). At ET_A, SF_5- and CF_3-bosentan (**1b**, **1e**) exhibit IC_{50} values ~10-fold higher than bosentan **1a** (112 and 130 nM versus 11 nM for **1a**). The cyclopropyl-CF_3 and BCP analogues show about the same IC_{50} values as *tert*-butyl-bosentan (9 and 4 nM). A similar trend could be ob-

Table 1. Bioassay of bosentan analogues.

Compound		IC_{50} [nM] ET_A[a]	ET_B[b]
1a		11 ± 1.7[c]	179[d]
1b		112 ± 12.1[c]	994[d]
1c		9[d]	66[d]
1d		4[d]	64[d]
1e		130[d]	2720[d]

[a] IC_{50} value at human endothelin receptor subtype A. [b] IC_{50} value at human endothelin receptor subtype B. [c] $n=3$, measured in duplicates per experiment. [d] $n=1$, measured in duplicates.

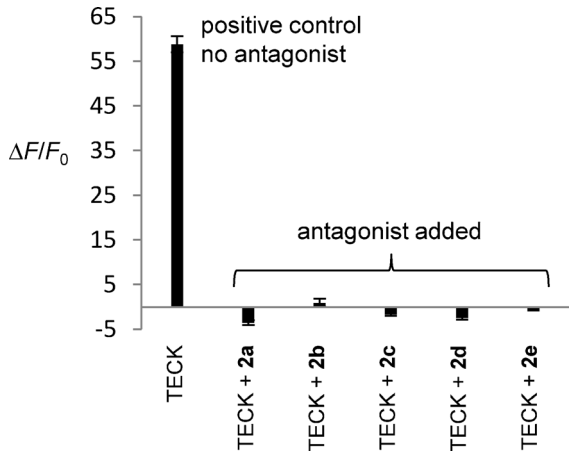


Figure 3. CCR9 Ca^{2+} response to TECK and TECK + antagonists: all measurements were conducted at a concentration of 50 nM for each component. $\Delta F = F_{max} - F_0$; $n=1$, measured in triplicates. Bar graphs shown are mean ± SD.

served at ET_B. Accordingly, SF_5- and CF_3-bosentan exhibit 5- and 15-fold higher IC_{50} values than the parent drug (994 and 2720 nM versus 179 nM). However, at this receptor cyclopropyl-CF_3- and BCP-bosentan are significantly more active (66 and 64 nM). These results are in agreement with findings reported by Neidhart and colleagues, who found that analogues bearing lipophilic electron-donating *para* substituents in the sulfonamide group are most potent.[38]

For the vercirnon series, Ready-to-Assay CCR9 chemokine receptor expressing cells (Merck-Millipore) were incubated with fluo-4. Addition of the thymus-expressed chemokine (TECK), which acts as a CCR9 agonist, induces Ca^{2+} efflux from the endoplasmic reticulum into the cytosol, leading to a peak in fluorescence. For the readout, baseline fluorescence was recorded for 30 s (F_0), then an aqueous solution of TECK or TECK + antagonist was added to the cells, resulting in a final concentration of 50 nM for both TECK agonist and antagonist. Biologically active ligands would be expected to abolish the calcium release. The resulting fluorescence was recorded, and the maximum value (F_{max}) was normalized to baseline fluorescence before the addition of ligands to the cells ($F_{max} - F_0/F_0$; see Supporting Information for details).

Figure 3 shows the results obtained. Sole addition of TECK induces a significant fluorescence response (+58%). As shown, this response is inhibited by every antagonist tested when applied in equimolar concentration of 50 nM. Thus, we can conclude that functional activity is retained throughout the series upon replacement of the original *tert*-butyl group in **2a** by the substituents **b**–**e**.[39]

MDO parameters

Table 2 summarizes experimentally derived multidimensional optimization (MDO) parameters of the drug analogues that formed the basis of the study. In aqueous media, all compounds are stable in the range pH 1–10. The bosentan series behaves well in the CYP inhibition assay, with only SF_5- and CF_3-substituted analogues showing slight CYP inhibition of the 2C9 subtype in the double-digit micromolar range (IC_{50}: 17 and 13 μM). In contrast, inhibition of this subtype seems to be a general issue in the vercirnon series, with IC_{50} values between 3.9 and 11 μM. Compounds **1a**–**d** show similar permeability values from 41 to 47 nm s^{-1}, whereas the corresponding value for **1e** (CF_3) is lower (28 nm s^{-1}). Interestingly, this order is reversed in compounds **2a**–**e**, in which the CF_3 analogue exhibits the highest permeability (96 nm s^{-1}) exceeding SF_5 (65 nm s^{-1}) and BCP (19 nm s^{-1}). In accordance with recent work comparing *tert*-butyl with CF_3 and SF_5[6] the lipophilicity increases in the order $CF_3 < SF_5 <$ cyclopropyl-$CF_3 <$ *t*-butyl < BCP in both series. The electronic properties of the various substituents are reflected in the pK_a values. It comes as no surprise that SF_5-substituted analogues bear the most acidic sulfonamide proton in both series. The pK_a values increase in the order $SF_5 < CF_3 <$ cyclopropyl-$CF_3 \approx$ *tert*-butyl < BCP.

For bosentan and its analogues, the introduction of SF_5 proves favorable for solubility (604 versus 520 mg L^{-1} for *tert*-butyl analogue **1a**). This is especially interesting when compared with the CF_3 analogue **1e** (128 mg L^{-1}). Surprisingly, introduction of the cyclopropyl-CF_3 group appears to be detrimental to solubility (31 mg L^{-1}), whereas the BCP analogue **1d** is similar to the parent compound **1a** in this regard, with a solubility of 484 mg L^{-1}. Ionization constants influence both log *D* and LYSA values. However, with pK_a values being at least 1.7 units below the buffer pH value, all analogues should be present mainly as anions, so that differences in solubility could be attributed mainly to the polarities of the substituents. Nevertheless, these findings should be considered with care due to the limited precision of the LYSA. In contrast, the vercirnon analogues generally showed low solubilities; however, it is interesting to note that the SF_5 vercirnon analogue **2b** is the most soluble in the series.

All replacements tend to be metabolically more stable than the *tert*-butyl group itself with few exceptions. SF_5- and CF_3-substituted analogues are metabolically the most stable in

Table 2. Physicochemical data of bosentan, vercirnon, and their analogues.

Compd		Aq. Stab.[a]	CYP IC_{50} [μM] 2C9; 2D6; 3A4[b]	log *D*[c]	PAMPA[d]	PAMPA Details[e]	pK_a[f]	LYSA[g]	hCl[h]	mCl[h]	rCl[h]
Bosentan											
1a		stable	>50; >50; >50	0.99±0.04	46±8	82; 0; 18	4.6±0.4	520±50	<10	13±9	37±9
1b		stable	17±13; >50; >50	0.37±0.06	41±5	81; 4; 15	3.9±0.4	604±30	<10	<10	<10
1c		stable	>50; >50; >50	0.81±0.03	47±5	77; 7; 16	4.6±0.02	31±2	<10	15±5	<10
1d		stable	>50; >50; >50	1.27±0.03	43±3	71; 15; 14	4.8±4	484±29	<10	16±5	16±5
1e		stable	13±6; >50; >50	0.14±0.04	28±4	87; 1; 11	4.1±0.4	218±50	<10	<10	<10
Vercirnon											
2a		stable	11±6; >50; >50	2.84±0.08	–[j]	–[j]	6.8±0.4	<0.6	14±3	68±4	34±3
2b		stable	3.9±0.5; >50; >50	1.73±0.02	65±8	40; 49; 11	5.8±0.4	3.6±0.3	<10	18±4	<10
2c		stable	5.1±1.4; >50; >50	–[i]	–[j]	–[j]	6.5±0.03	<0.6	<10	50±11	20±10
2d		stable	8.6±2.8; >50; >50	3.01±0.02	19±7	19; 80; 1	6.9±0.02	<0.6	<10	230±13	52±11
2e		stable	5.4±2.3; >50; >50	1.39±0.04	96	40; 44; 16	6.1±0.02	<0.6	<10	<10	<10

[a] Compound stability measured in aqueous buffer at pH 1.0; 4.0; 6.5; 8.0; 10.0. [b] Cytochrome P450 inhibition constants of the isoforms indicated. [c] log *D* = intrinsic distribution coefficient between octanol and aqueous buffer (pH 7.4). [d] Membrane permeability ($nm\,s^{-1}$) as derived from the parallel artificial membrane permeability assay (PAMPA). [e] PAMPA retention values (%): in donor compartment; in membrane; in acceptor compartment. [f] Acidities determined spectrophotometrically at 23±1 °C. [g] Solubility ($mg\,L^{-1}$) determined by lyophilization solubility assay (LYSA) at pH 6.5. [h] Metabolic stability; values describe intrinsic clearance (Cl, [$\mu m\,min^{-1}\,mg^{-1}$]) in human (h), mouse (m), and rat (r) microsomes. [i] Poor data quality. [j] Precipitation during assay.

both series, with clearance rates $<10\ \mu m\,min^{-1}\,mg^{-1}$ in human, mouse, and rat microsomes (except for **2b** in mouse microsomes: $18\ \mu m\,min^{-1}\,mg^{-1}$). The study confirms slightly higher stability for the cyclopropyl-CF_3 group in comparison with *tert*-butyl, as recently claimed for simple test compounds,[9] although attenuated from what would have been expected on the basis of the model compounds. The largest difference was found between **1a** and **1c** in rat microsomes (change from 37 to $<10\ \mu m\,min^{-1}\,mg^{-1}$). Interestingly, BCP vercirnon **2d** is significantly more susceptible to metabolism in mouse and rat microsomes than other analogues.

Conclusions

In summary, we have synthesized a collection of several analogues of bosentan and vercirnon, replacing the *tert*-butyl group by CF_3, SF_5, cyclopropyl-CF_3, and bicyclo[1.1.1]pentane. It is important to note that the last three of these substituents are relatively new in drug discovery. The study provides full physicochemical characterization as well as data on bioactivity across the series, complementing previous studies that largely include pairwise comparisons or that are limited to reporting biological activity. The compounds that form the basis of the study remained biologically active. In the bosentan series, for which appropriate IC_{50} values could be derived, two exhibited even higher potency than the parent drug. Most importantly, the derived data on metabolic stability, solubility, log *P*, pK_a, and permeability render these heretofore atypical substituents as candidates for the future standard arsenal available to medicinal chemists. Thus, we expect these structures to be considered with increased frequency in drug discovery programs.

Experimental Section

Commercial chemicals were purchased from ABCR, Acros, Alfa-Aesar, Apollo Scientific, Combi-Blocks, Fluka, Fluorochem, Merck, Sigma–Aldrich, or TCI and were used without further purification. Reactions were magnetically stirred and monitored by thin-layer chromatography on Merck silica gel 60 F_{254} TLC glass plates (visualized with UV fluorescence quenching at 254 nm and by $KMnO_4$ or ceric ammonium nitrate (CAN) stain). Flash column chromatography was performed with Fluka silica gel (230–400 mesh, 60 Å) eluting with distilled technical-grade solvents. The yields refer to purified compounds. NMR data were recorded on Bruker Ascend (400 MHz), Bruker AV (400, 500, 600 MHz), or Bruker DRX (400, 500,

600 MHz) spectrometers at 25 °C. Chemical shifts (δ) are reported in ppm with the residual solvent signal as internal standard. The data are reported as s = singlet, d = doublet, t = triplet, m = multiplet, br = broad signal, coupling constant(s) J in Hz. ^{13}C and ^{19}F NMR spectra were recorded with broad-band ^{1}H decoupling. Service measurements were performed by the NMR service team of the Laboratorium für Organische Chemie at ETH Zürich by Philipp Zumbrunnen, Rainer Frankenstein, and René Arnold under the direction of Dr. Marc-Olivier Ebert. IR spectra were recorded on a PerkinElmer Spectrum Two FT-IR (UATR) instrument as thin films. Absorptions are given in wavenumbers (cm^{-1}). Mass spectrometric analyses were performed as high-resolution ESI measurements on a Bruker Daltonics maXis ESI-QTOF instrument or as high-resolution EI measurements on a Waters Micromass AutoSpec Ultima instrument by the mass spectrometry service of the Laboratorium für Organische Chemie at ETH Zürich by Louis Bertschi, Rolf Häfliger, and Oswald Greter under the direction of Dr. Xiangyang Zhang.

***N*-(6-(2-Hydroxyethoxy)-5-(2-methoxyphenoxy)-[2,2′-bipyrimidin]-4-yl)-4-(pentafluorosulfanyl)benzenesulfonamide (1 b)**. *Procedure A*. 4,6-Dichloro-5-(2-methoxyphenoxy)-2,2′-bipyrimidine **7** (170 mg, 0.49 mmol, 1 equiv), 4-pentafluorosulfanylbenzenesulfonamide **6 b** (145 mg, 0.51 mmol, 1.05 equiv) and potassium carbonate (572 mg, 4.14 mmol) were mixed in MeCN (1.7 mL) and heated at 80 °C. After 2 h, LC–MS analysis showed clean formation of sulfonamide intermediate. Ethylene glycol (1.7 mL, 30.7 mmol) was added via syringe and it was stirred at 80 °C for 19 h. Water was added, and the pH was adjusted to pH 2 with aq. HCl. Extraction with EtOAc, washing with brine, drying (Na_2SO_4), filtration and concentration afforded a white solid. NMR showed residual ethylene glycol. The material was suspended in Et_2O. It was sonicated and filtered (washing with Et_2O) to yield the product as colorless solid (113 mg, 0.18 mmol, 37%). ^{1}H NMR (400 MHz, CD_3OD): δ = 8.95 (dd, J = 5.0, 1.5 Hz, 2H), 8.03 (d, J = 8.4 Hz, 2H), 7.83–7.66 (m, 2H), 7.56 (t, J = 4.9 Hz, 1H), 7.12–6.84 (m, 2H), 6.80–6.64 (m, 1H), 6.52 (dd, J = 7.9, 1.3 Hz, 1H), 4.56–4.39 (m, 2H), 3.85 (s, 3H), 3.78–3.64 ppm (m, 2H); ^{13}C NMR (101 MHz, CD_3OD): δ = 163.0, 159.1, 155.8, 150.6, 149.4, 148.5, 129.0, 127.0, 123.6, 122.8, 121.9, 116.1, 114.3, 70.1, 62.2, 56.8 ppm; ^{19}F NMR (282 MHz, CD_3OD): δ = 85.99–79.48 (m), 61.23 ppm (d, J = 148.1 Hz); IR ($\tilde{\nu}$): 3402, 2965, 1561, 1522, 1500, 1470, 1440, 1402, 1381, 1351, 1293, 1252, 1208, 1178, 1135, 1075, 1028, 830, 745, 666, 644, 599, 585, 566 cm^{-1}; HRMS m/z (ESI) [M^+]: calcd ($C_{23}H_{20}F_5N_5O_6S_2 + H^+$) 622.0848, found 622.0835.

***N*-(6-(2-Hydroxyethoxy)-5-(2-methoxyphenoxy)-[2,2′-bipyrimidin]-4-yl)-4-(1-(trifluoromethyl)cyclopropyl)benzenesulfonamide (1 c)**. Synthesized according to procedure A from **7** (63 mg, 0.18 mmol) and **6 c** (49 mg, 0.185 mmol). Colorless solid (66 mg, 0.11 mmol, 60%). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 11.52 (br, 1H), 9.09 (m, J = 4.7 Hz, 2H), 8.48–8.35 (m, 2H), 7.73–7.56 (m, 3H), 7.14–6.94 (m, 2H), 6.80 (m, J = 7.2 Hz, 1H), 6.71 (m, J = 7.8 Hz, 1H), 4.68 (br, 1H), 4.38–4.30 (m, 2H), 3.79 (br, 3H), 3.47 (br, 2H), 1.42–1.32 (m, 2H), 1.19–1.12 ppm (m, 2H); ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 161.3, 157.9, 155.3, 151.0, 149.0, 145.7, 140.2, 131.0, 129.2, 126.2 (q, J = 272 Hz), 123.5, 121.7, 120.5, 115.9, 113.1, 68.4, 59.0, 55.8, 28.9, 27.5 (q, J = 32 Hz), 9.8 ppm; ^{19}F NMR (377 MHz, [D_6]DMSO) δ = −68.15 ppm; IR ($\tilde{\nu}$): 3404, 3328, 2928, 1585, 1557, 1500, 1482, 1443, 1433, 1408, 1386, 1377, 1359, 1359, 1332, 1311, 1297, 1278, 1258, 1246, 1230, 1202, 1183, 1165, 1149, 1123, 1114, 1094, 1079, 1059, 1040, 1030, 1020, 996, 960, 939, 885, 853, 831, 806, 786, 755, 743, 724, 705, 695, 668, 635, 608, 691, 581, 554, 536, 511, 465, 445, 416 cm^{-1}; HRMS m/z (ESI) [M^+]: calcd ($C_{27}H_{24}F_3N_5O_6S + H^+$) 604.1472, found 604.1472.

4-(Bicyclo[1.1.1]pentan-1-yl)-*N*-(6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-[2,2′-bipyrimidin]-4-yl)benzenesulfonamide (1 d). Synthesized according to procedure A from **7** (77 mg, 0.222 mmol) and **6 d** (51 mg, 0.228 mmol). After completion of the reaction, water was added and it was extracted with CH_2Cl_2. The organic phase was concentrated, taken up in MeOH and precipitated with Et_2O. Filtration and washing with Et_2O afforded the product as colorless solid (72 mg, 0.128 mmol, 58%). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 9.00 (d, J = 4.9 Hz, 2H), 7.94–7.70 (br, 2H), 7.63 (t, J = 4.9 Hz, 1H), 7.19–7.05 (br, 2H), 7.03 (m, 1H), 6.91 m, 1H), 6.75–6.63 (m, 1H), 6.34 (br, J = 9.3 Hz, 1H), 4.86 (br, 1H), 4.32–4.29 (m, 2H), 3.83 (s, 3H), 3.62–3.50 (m, 2H), 2.52 (s, 1H), 2.01 ppm (s, 6H); ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 162.3, 162.3, 160.7, 157.9, 148.4, 146.8, 143.7, 142.8, 127.2, 124.9, 122.6, 121.3, 120.4, 113.3, 113.0, 67.8, 62.8, 59.7, 55.8, 51.6, 46.4, 26.3 ppm; IR ($\tilde{\nu}$): 3376, 2967, 2871, 1560, 1524, 1500, 1469, 1440, 1400, 1382, 1348, 1294, 1251, 1208, 1177, 1131, 1081, 1026, 887, 837, 804, 740, 697, 641, 610, 571, 424 cm^{-1}; HRMS m/z (ESI) [M^+]: calcd ($C_{28}H_{27}N_5O_6S + H^+$) 562.1755, found 562.1752.

***N*-(6-(2-Hydroxyethoxy)-5-(2-methoxyphenoxy)-[2,2′-bipyrimidin]-4-yl)-4-(trifluoromethyl)benzenesulfonamide (1 e)**. Synthesized according to procedure A from **7** (90 mg, 0.258 mmol) and **6 e** (59 mg, 0.262 mmol). After completion of the reaction, water was added and it was extracted with CH_2Cl_2. The solids in the organic phase were filtered off, taken up in MeOH and precipitated with Et_2O. Filtration and washing with Et_2O afforded the product as colorless solid (78 mg, 0.138 mmol, 54%). ^{1}H NMR (600 MHz, CD_3OD): δ = 9.09 (d, J = 5.0 Hz, 2H), 7.89 (d, J = 8.1 Hz, 2H), 7.62 (t, J = 5.0 Hz, 1H), 7.56 (d, J = 8.2 Hz, 2H), 7.02–6.88 (m, 2H), 6.70 (m, 1H), 6.39–6.30 (m, 1H), 4.41 (m, 2H), 3.79 (s, 3H), 3.67–3.59 ppm (m, 2H); ^{13}C NMR (151 MHz, CD_3OD): δ = 163.2, 162.29, 160.5, 160.1, 155.3, 150.5, 148.9, 148.4, 133.7 (q, J = 32 Hz), 128.3, 127.8, 126.3, 125.1 (q, J = 272 Hz), 123.7, 123.1, 121.9, 116.3, 114.3, 70.3, 61.9, 56.9 ppm; ^{19}F NMR (471 MHz, CD_3OD): δ = −64.41 ppm; IR ($\tilde{\nu}$): 3497, 3072, 2923, 2853, 1618, 1558, 1501, 1455, 1403, 1349, 1322, 1255, 1191, 1142, 1120, 1107, 1080, 1061, 1027, 1017, 656, 875, 832, 806, 788, 739, 716, 688, 650, 636, 610, 596, 550, 479, 428, 403 cm^{-1}; HRMS m/z (ESI) [M^+]: calcd ($C_{24}H_{20}F_3N_5O_6S + H^+$) 564.1159, found 564.1161.

4-(2-(4-(*tert*-Butyl)phenylsulfonamido)-5-chlorobenzoyl)pyridine 1-oxide (2 a). This compound was prepared as described.[33]

***N*-(4-Chloro-2-isonicotinoylphenyl)-4-(pentafluorosulfanyl)benzenesulfonamide (2 b-SI)**. *Procedure B*. **4 b** (90 mg, 0.30 mmol, 1 equiv) and **8**[40] (69 mg, 0.85 mmol, 1 equiv) were mixed in pyridine (1.0 mL) and it was stirred at room temperature overnight. The reaction mixture was concentrated. Toluene (2 mL) was added, and it was concentrated again (3×). Column chromatography (silica, CH_2Cl_2 + 0.6% MeOH) yielded the product as a light-yellow wax. Trituration with Et_2O or recrystallization from EtOH afforded the product as colorless solid (66 mg, 45%); mp (EtOH): 185 °C. *Note: side product is the doubly sulfonylated product.* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.16 (s, 1H), 8.87–8.74 (m, 2H), 7.90–7.72 (m, 5H), 7.58 (dd, J = 8.9, 2.5 Hz, 1H), 7.33 (d, J = 2.5 Hz, 1H), 7.23–7.13 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.7, 157.1 (m), 150.8, 143.6, 142.1, 137.5, 135.4, 133.0, 130.2, 128.0 (m), 127.3, 125.4, 124.4, 122.2 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = 82.46–80.42 (m), 62.45 ppm (d, J = 150.8 Hz); IR ($\tilde{\nu}$): 1650, 1497, 1396, 1347, 1328, 1293, 1249, 1173, 1102, 912, 840, 770, 736, 669, 655, 601, 480 cm^{-1}; HRMS m/z (ESI) [M^+]: calcd ($C_{18}H_{12}ClF_5N_2O_3S_2 + H^+$) 498.9971, found 498.9970.

4-(5-Chloro-2-(4-(pentafluorosulfanyl)phenylsulfonamido)benzoyl)pyridine 1-oxide (**2b**). *Procedure C*. **2b-SI** (88 mg, 0.176 mmol, 1.0 equiv) and *m*CPBA (52.2 mg, 0.212 mmol, 1.2 equiv) were mixed in CH_2Cl_2 (1 mL) and it was stirred at room temperature until TLC showed complete conversion. The mixture was concentrated and subjected to column chromatography (silica, CH_2Cl_2 + 2% MeOH) to yield **2b** (83 mg, 0.182 mmol, 91%) as a light-yellow solid; mp (EtOH): 225 °C; R_f (CH_2Cl_2 + 3% MeOH): 0.17. It can be recrystallized from EtOH as colorless solid. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.43 (s, 1H), 8.30 (d, J = 6.6 Hz, 2H), 8.08 (d, J = 8.5 Hz, 2H), 7.79 (d, J = 8.5 Hz, 2H), 7.71–7.40 (m, 4H), 7.03 ppm (d, J = 8.4 Hz, 1H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 189.6, 155.2 (m), 142.7, 139.1, 135.5, 132.9, 132.2, 131.4, 131.3, 129.8, 128.3, 128.0, 127.2, 126.8 ppm; ^{19}F NMR (282 MHz, [D$_6$]DMSO): δ = 84.89 (m, 1F), 63.49 ppm (d, J = 151.4 Hz, 4F); IR ($\tilde{\nu}$): 2658, 1683, 1610, 1446, 1395, 1351, 1286, 1234, 1178, 1169, 1154, 1101, 1033, 967, 879, 836, 785, 735, 665, 626, 610, 600, 585, 567, 535, 520, 496, 483, 467 cm^{-1}; HRMS *m/z* (ESI) [M^+]: calcd ($C_{18}H_{12}ClF_5N_2O_4S_2 + H^+$) 514.9920, found 514.9920.

***N*-(4-Chloro-2-isonicotinoylphenyl)-4-(1-(trifluoromethyl)cyclopropyl)benzenesulfonamide** (**2c-SI**). Prepared according to procedure B from **8** (70 mg, 0.30 mmol, 1 equiv) **4c** (110 mg, 0.39 mmol, 1.3 equiv) in pyridine (1 mL). Purified twice on silica (CH_2Cl_2 + 1.8% MeOH + 1.2% HCOOH; then hexane/EtOAc 6:4). Isolated as a yellow foam (145 mg, 99%). It could be precipitated from cold toluene/heptane as a pale solid; mp (toluene/heptane): 139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.17 (s, 1H), 8.79–8.71 (m, 2H), 7.77 (d, J = 8.9 Hz, 1H), 7.75–7.68 (m, 2H), 7.52 (dd, J = 8.9, 2.5 Hz, 1H), 7.49–7.43 (m, 2H), 7.30 (d, J = 2.5 Hz, 1H), 7.22–7.18 (m, 2H), 1.39–1.33 (m, 2H), 0.96–0.90 ppm (m, J = 1.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.7, 150.6, 143.9, 141.9, 138.9, 138.2, 135.2, 132.9, 132.0, 129.3, 127.3, 125.8 (q, J = 273.9 Hz), 124.9, 123.8, 122.2, 28.1 (q, J = 33.8 Hz), 10.2 ppm; ^{19}F NMR (377 MHz, $CDCl_3$): δ = −69.63 ppm; IR ($\tilde{\nu}$): 1648, 1598, 1567, 1478, 1408, 1388, 1359, 1328, 1296, 1247, 1169, 1154, 1133, 1095, 1078, 1040, 1019, 958, 906, 828, 770, 753, 730, 695, 673, 654, 590, 579, 528, 477, 439 cm^{-1}; HRMS *m/z* (ESI) [M^+]: calcd ($C_{22}H_{16}ClF_3N_2O_3S + H^+$) 481.0595, found 481.0596.

4-(5-Chloro-2-(4-(1-(trifluoromethyl)cyclopropyl)phenylsulfonamido)benzoyl)pyridine 1-oxide (**2c**). Prepared according to procedure C from *m*CPBA (30 mg, 0.122 mmol) and **2c-SI** (47 mg, 0.098 mmol) in CH_2Cl_2 (1 mL). Column chromatography (silica, CH_2Cl_2 + 2% MeOH) yielded **2c** (47 mg, 0.095 mmol, 97%) as a pale-yellow solid. It can be recrystallized from EtOH as colorless solid; mp (EtOH): 211 °C; R_f (CH_2Cl_2 + 3%MeOH): 0.15. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.77 (s, 1H), 8.24–8.16 (m, 2H), 7.76 (d, J = 8.8 Hz, 1H), 7.73–7.67 (m, 2H), 7.55 (dd, J = 8.9, 2.5 Hz, 1H), 7.51–7.41 (m, 2H), 7.41–7.34 (m, 3H), 1.44–1.35 (m, 2H), 1.00–0.92 ppm (m, J = 1.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.7, 142.0, 139.6, 139.0, 137.5, 134.8, 132.1, 132.0, 131.7, 129.9, 127.4, 126.6, 126.0, 125.9 (q, J = 273.9 Hz) 124.7, 28.2 (q, J = 33.8 Hz), 10.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −69.65 ppm; IR ($\tilde{\nu}$): 2682, 1682, 1610, 1446, 1342, 1287, 1235, 1153, 1131, 1080, 967, 878, 841, 826, 783, 711, 673, 625, 607, 593, 577, 519, 495, 484, 461.6 cm^{-1}; HRMS *m/z* (ESI) [M^+]: calcd ($C_{22}H_{16}ClF_3N_2O_4S + H^+$) 497.0544, found 497.0544.

4-(Bicyclo[1.1.1]pentan-1-yl)-*N*-(4-chloro-2-isonicotinoylphenyl)benzenesulfonamide (**2d-SI**). Prepared according to procedure B from **8** (70 mg, 0.30 mmol, 1.0 equiv) and **6d** (102 mg, 0.42 mmol, 1.4 equiv) in pyridine (1 mL). Purified twice on silica (CH_2Cl_2 + 1.8% MeOH + 1.2% HCOOH; then hexane/EtOAc 6:4). Isolated as a yellow foam (127 mg, 96%); R_f (CH_2Cl_2 + 3% MeOH): 0.17. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.00 (s, 1H), 8.81–8.75 (m, 2H), 7.78 (d, J = 8.9 Hz, 1H), 7.67–7.60 (m, 2H), 7.53 (dd, J = 8.9, 2.5 Hz, 1H), 7.29 (d, J = 2.4 Hz, 1H), 7.23–7.13 (m, 4H), 2.56 (s, 1H), 2.03 ppm (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.3, 150.5, 147.4, 143.8, 138.2, 136.4, 134.9, 132.5, 129.3, 127.2, 126.9, 125.5, 124.4, 122.4, 52.2, 46.5, 27.0 ppm; IR ($\tilde{\nu}$): 2968, 2910, 2872, 1648, 1596, 1566, 1477, 1407, 1386, 1340, 1327, 1292, 1247, 1209, 1182, 1165, 1116, 1092, 1063, 1017, 958, 597, 836, 769, 743, 721, 682, 653, 594, 567, 525, 476 cm^{-1}; HRMS *m/z* (ESI) [M^+]: calcd ($C_{23}H_{19}ClN_2O_3S + H^+$) 439.0878, found 439.0879.

4-(2-(4-(Bicyclo[1.1.1]pentan-1-yl)phenylsulfonamido)-5-chlorobenzoyl)pyridine 1-oxide (**2d**). Prepared according to procedure C from **2d-SI** (40 mg, 0.091 mmol, 1.0 equiv) and *m*CPBA (29.2 mg, 0.118 mmol, 1.3 equiv) in CH_2Cl_2 (1 mL) to yield **2d** (41 mg, 0.090 mmol, 99%) as pale-yellow solid; mp (EtOH): 209 °C; R_f (CH_2Cl_2 + 3% MeOH): 0.16. It can be recrystallized from EtOH as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.39 (s, 1H), 8.16 (d, J = 6.6 Hz, 2H), 7.74 (d, J = 8.9 Hz, 1H), 7.59–7.51 (m, 3H), 7.37–7.29 (m, 3H), 7.14–7.09 (m, 2H), 2.56 (s, 1H), 2.01 ppm (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.1, 147.5, 139.5, 137.2, 136.4, 134.5, 131.8, 131.0, 130.0, 127.3, 127.0, 126.9, 126.7, 125.9, 77.48, 52.3, 46.5, 27.1 ppm; IR ($\tilde{\nu}$): 2972, 2872, 1648, 1607, 1477, 1443, 1388, 1338, 1282, 1247, 1210, 1166, 1092, 906, 838, 736, 683, 626, 610, 568, 519 cm^{-1}; HRMS *m/z* (ESI) [M^+]: calcd ($C_{23}H_{19}ClN_2O_4S + H^+$) 455.0827, found 455.0827.

***N*-(4-Chloro-2-isonicotinoylphenyl)-4-(trifluoromethyl)benzenesulfonamide** (**2e-SI**). Prepared according to procedure B from **8** (70 mg, 0.30 mmol, 1 equiv) and 4-(trifluoromethyl)benzene-1-sulfonyl chloride (88 mg, 0.36 mmol, 1.2 equiv) in pyridine (1 mL). Purified twice on silica (CH_2Cl_2 + 1.8% MeOH + 1.2% HCOOH; then hexane/EtOAc 6:4) to yield a colorless solid (73 mg, 55%); mp (EtOH): 196 °C. It can be recrystallized from EtOH. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.15 (s, 1H), 8.84–8.73 (m, 2H), 7.92–7.85 (m, 2H), 7.80 (d, J = 8.9 Hz, 1H), 7.64 (dt, J = 7.3, 1.0 Hz, 2H), 7.57 (dd, J = 8.9, 2.4 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 7.21–7.16 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.7, 150.8, 143.6, 142.4, 137.7, 135.3, 135.2 (q, J = 33.5 Hz), 133.0, 130.0, 128.0, 126.5, 125.3, 124.2, 123.0 (q, J = 273.4 Hz), 122.2 ppm; ^{19}F NMR (377 MHz, $CDCl_3$): δ = −63.26 ppm; IR ($\tilde{\nu}$): 2643, 1688, 1601, 1559, 1476, 1414, 1404, 1344, 1324, 1277, 1252, 1226, 1191, 1158, 1110, 1093, 1061, 1017, 1007, 965, 922, 893, 860, 836, 812, 783, 729, 710, 698, 669, 648, 597, 557, 514, 493, 466 cm^{-1}; HRMS *m/z* (ESI) [M^+]: calcd ($C_{19}H_{12}ClF_3N_2O_3S + H^+$) 441.0282, found 441.0282.

4-(5-Chloro-2-(4-(trifluoromethyl)phenylsulfonamido)benzoyl)pyridine 1-oxide (**2e**). Synthesized according to procedure C from **2e-SI** (39 mg, 0.088 mmol, 1.0 equiv) and *m*CPBA (26 mg, 0.106 mmol, 1.2 equiv) in CH_2Cl_2 (0.3 mL) to give **2e** (39 mg, 0.085 mmol, 96%) as pale-yellow solid; mp (EtOH): 215 °C; R_f (CH_2Cl_2 + 3% MeOH): 0.13. It can be recrystallized from EtOH as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.69 (s, 1H), 8.24–8.16 (m, 2H), 7.90–7.82 (m, 2H), 7.74 (d, J = 8.8 Hz, 1H), 7.66–7.59 (m, 2H), 7.57 (dd, J = 8.8, 2.4 Hz, 1H), 7.41–7.33 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.3, 142.4, 139.6, 136.9, 135.0, 134.8, 131.7, 131.6, 130.5, 128.0, 126.6, 126.5, 126.5, 125.2 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −63.25 ppm; IR ($\tilde{\nu}$): 2660, 1679, 1607, 1481, 1442, 1404, 1340, 1323, 1304, 1286, 1243, 1166, 1154, 1108, 1091, 1061, 1016, 966, 876, 847, 830, 785, 745, 716, 708, 678, 668, 612, 604, 556, 512, 490, 481, 463 cm^{-1}; HRMS *m/z* (ESI) [M^+]: calcd ($C_{19}H_{12}ClF_3N_2O_4S + H^+$) 457.0231, found 457.0233.

4-(Trifluoromethyl)benzenediazonium tetrafluoroborate (**3**). 4-Pentafluorosulfanylaniline hydrochloride (2 g, 7.8 mmol, 1.0 equiv)

was dissolved in a mixture of EtOH (78 mL) and HBF_4 (48% in water, 3.11 mL, 23.5 mmol) and cooled to 0 °C (ice bath). Then isoamyl nitrite (1.8 mL, 13.3 mmol) was added slowly and it was stirred for 1 h. Et_2O (5× volume, ~400 mL) was added to precipitate the product (stirring for ~25 min at 0 °C). The product was isolated by filtration (leaving the mother liquor at 4 °C gives a second crop of product). The filter cake was dissolved in a minimum amount of acetone, and the diazonium salt was precipitated by the addition of Et_2O. Filtration afforded the product as colorless solid (1501 mg + 380 mg (second crop), 5.9 mmol, 76%). ^{1}H NMR (400 MHz, CD_3CN): $\delta = 8.73$ (app d, $J = 9.2$ Hz, 2H), 8.47–8.27 ppm (m, 2H); ^{13}C NMR (101 MHz, CD_3CN): $\delta = 161.7$ (m), 134.9, 130.7 (m), 120.3 ppm; ^{19}F NMR (377 MHz, CD_3CN): $\delta = 78.59$–77.00 (m, 1F), 60.92 (d, $J = 149.6$ Hz, 4F), −150.85 ppm (s, 4F); IR ($\tilde{\nu}$): 3119, 2307, 1575, 1420, 1303, 1042, 838, 755, 675, 606, 579, 546, 520 cm^{-1}; HRMS *m/z* (ESI) [M^+]: calcd ($F_5SPhN_2^+$) 231.0010, found 231.0021.

4-(Pentafluorosulfanyl)benzene-1-sulfonyl chloride (**4b**). Thionyl chloride (310 μL, 4.25 mmol) was added dropwise to water (1.7 mL) at 0 °C (ice bath). After 10 min it was allowed to stir at room temperature for 40 min. After cooling to 0 °C, conc. HCl (430 μL) was added followed by CuCl (2 mg, 0.02 mmol) and it was stirred for 5 min. Then a solution of **3** (270 mg, 0.85 mmol) in MeCN (300 μL) was added dropwise (rinsing the syringe with additional 100 μL) and it was stirred at 0 °C for 1 h. The solution turned yellow and a precipitate formed. Filtration afforded a yellow solid (175 mg, 68%) which can be used as such or further purified by flash chromatography (silica, hexanes) to give a colorless solid (101 mg, 40%); R_f (hexane): 0.18. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.21$–8.14 (m, 2H), 8.08–8.01 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta =$ 158.90–157.73 (m), 146.67, 128.41–127.57 ppm (m); ^{19}F NMR (377 MHz, $CDCl_3$): $\delta = 81.49$–79.57 (m), 62.37 ppm (d, $J = 150.1$ Hz); IR ($\tilde{\nu}$): 1403, 1382, 1299, 1201, 1181, 1097, 831, 821, 731, 665, 598, 584, 573, 560, 524, 456, 421 cm^{-1}; HRMS *m/z* (EI) [M^+]: calcd ($C_6H_4ClF_5O_2S_2$) 301.9261, found 301.9256.

4-(1-(Trifluoromethyl)cyclopropyl)benzene-1-sulfonyl chloride (**4c**). 1-(Trifluoromethyl)cyclopropyl)benzene (purchased from Apollo Scientific; 431 mg, 2.3 mmol, 1 equiv) was dissolved in CH_2Cl_2 (3.3 mL) and cooled to −5–0 °C using a salt/ice bath. Chlorosulfonic acid (388 μL, 5.8 mmol, 2.5 equiv) was then added dropwise. It was stirred overnight at room temperature. The mixture was poured onto ice, followed by extraction with CH_2Cl_2. The combined organics were washed with satd $NaHCO_3$ and brine. Drying ($MgSO_4$), filtration and concentration followed by flash chromatography (silica, hexane/EtOAc 9:1) yielded **3** as colorless solid (572 mg, 2.0 mmol, 87%); R_f (hexane): 0.13. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.11$–7.95 (m, 2H), 7.79–7.65 (m, 2H), 1.53–1.44 (m, 2H), 1.15–1.07 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 144.1$, 143.9, 132.5, 127.1, 126.7 (q, $J = 274$ Hz), 28.3 (q, $J = 34$ Hz), 10.2 ppm (q, $J = 2$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -69.62$ ppm; IR ($\tilde{\nu}$): 1596, 1402, 1378, 1360, 1333, 1290, 1192, 1168, 1144, 1128, 1087, 1073, 1045, 1016, 949, 827, 779, 751, 667, 575, 551, 509, 437 cm^{-1}; HRMS *m/z* (EI) [M^+]: calcd ($C_{10}H_8ClF_3O_2S^+$) 283.9886, found 283.9881.

4-(Bicyclo[1.1.1]pentan-1-yl)benzene-1-sulfonyl chloride (**4d**). Provided by SpiroChem. Colorless solid; R_f (hexane): 0.20. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.95$ (app d, $J = 8.5$ Hz, 2H), 7.42 (app d, $J =$ 8.5 Hz, 2H), 2.62 (s, 1H), 2.15 ppm (s, 8H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 149.7$, 142.4, 127.4, 127.1, 46.7, 27.2 ppm; IR ($\tilde{\nu}$): 2984, 2916, 2879, 1589, 1400, 1377, 1363, 1325, 1293, 1210, 1186, 1164, 1143, 1101, 1081, 1059, 1011, 966, 944, 863, 842, 832, 775, 738, 718, 577, 557, 543, 504, 421 cm^{-1}; HRMS *m/z* (EI) [M^+]: calcd ([$M-$H]$^+$) 241.0085, found 241.0088, calcd ([$M-$Cl]$^+$) 207.0475, found 207.0478.

4-(Pentafluorosulfanyl)benzenesulfonamide (**6b**). Compound **4b** (68 mg, 0.23 mmol) was dissolved in 7 M NH_3 in MeOH (1 mL) and stirred for 30 min at 0 °C. The solvent was evaporated and the residue purified on silica (hexane/EtOAc 7:3–6:4) to yield the product as colorless solid (50 mg, 0.17 mmol, 79%); R_f (hexane/EtOAc 6:4): 0.45. ^{1}H NMR (400 MHz, CD_3CN): $\delta = 8.11$–7.91 (m, 4H), 5.86 ppm (s, 2H); ^{13}C NMR (101 MHz, CD_3CN): $\delta = 156.5$ (m), 147.6, 128.1, 128.0 ppm (m); ^{19}F NMR (377 MHz, CD_3CN): $\delta = 83.48$–80.95 (m), 61.86 ppm (d, $J = 148.2$ Hz); IR ($\tilde{\nu}$): 3378, 6260, 3108, 1562, 1399, 1332, 1312, 1291, 1161, 1104, 935, 881, 820, 732, 668, 598, 582, 551, 504, 428 cm^{-1}; HRMS *m/z* (ESI) [M^+]: calcd [$M + Na^+$] 288.0277, found 288.0283.

4-(1-(Trifluoromethyl)cyclopropyl)benzenesulfonamide (**6c**). Compound **4c** (183 mg, 0.64 mmol) was suspended in a 25% solution of NH_3 in water (3 mL) and stirred for 2 h at room temperature. Extraction with EtOAc, drying ($MgSO_4$), filtration and concentration followed by flash chromatography (silica, hexane/EtOAc 8:2–7:3) yielded the product as colorless solid (150 mg, 0.57 mmol, 88%); R_f (hexane/EtOAc 6:4): 0.40. ^{1}H NMR (400 MHz, CD_3CN): $\delta =$ 7.96–7.77 (m, 2H), 7.74–7.60 (m, 2H), 5.69 (s, 2H), 1.50–1.35 (m, 2H), 1.22–1.11 ppm (m, $J = 1.7$ Hz, 2H); ^{13}C NMR (101 MHz, CD_3CN): $\delta = 144.4$, 141.3, 133.0, 127.4 (q, $J = 272$ Hz), 127.1, 28.7 (q, $J =$ 33 Hz), 10.6 ppm (q, $J = 2$ Hz); ^{19}F NMR (376 MHz, CD_3CN): $\delta =$ −70.24 ppm; IR ($\tilde{\nu}$): 3358, 3286, 3255, 1599, 1531, 1496, 1423, 1399, 1361, 1332, 1317, 1285, 1163, 1150, 1135, 1124, 1097, 1076, 1037, 1019, 948, 914, 849, 828, 823, 781, 752, 732, 671, 600, 578, 548, 496, 459, 436, 426, 404 cm^{-1}; HRMS *m/z* (ESI) [M^+]: calcd ($C_{10}H_{10}F_3NO_2S + H^+$) 288.0277, found 288.0283.

4-(Bicyclo[1.1.1]pentan-1-yl)benzenesulfonamide (**6d**). Compound **4d** (276 mg, 1.14 mmol) was suspended in 25% aq. NH_3 (3 mL) and stirred for 5 h at room temperature. Extraction with EtOAc, drying ($MgSO_4$), filtration and concentration followed by flash chromatography (silica, hexane/EtOAc 8:2–5:5) yielded the product as colorless solid (200 mg, 0.90 mmol, 79%); R_f (hexane/EtOAc 7:3): 0.27. ^{1}H NMR (400 MHz, CD_3CN): $\delta = 7.93$–7.66 (m, 2H), 7.48–7.26 (m, 2H), 5.61 (s, 3H), 2.56 (s, 1H), 2.12 ppm (s, 6H); ^{13}C NMR (101 MHz, CD_3CN): $\delta = 147.0$, 142.3, 127.5, 127.0, 52.8, 47.3, 27.6 ppm; IR ($\tilde{\nu}$): 3346, 3268, 2961, 2910, 2875, 1598, 1538, 1450, 1403, 1326, 1286, 1213, 1190, 1172, 1096, 1065, 1018, 958, 915, 885, 834, 776, 741, 666, 631, 606, 560, 541, 458, 426, 407 cm^{-1}; HRMS *m/z* (ESI) [$M + Na^+$]: calcd ($C_{11}H_{13}NO_2S + Na^+$) 246.0559, found 246.0565.

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Evaluation of *tert*-Butyl Isosteres: Case Studies of Physicochemical and Pharmacokinetic Properties, Efficacies, and Activities

The alternative scene: Given how common the *tert*-butyl group is in medicinal chemistry, we set out to explore some isosteric alternatives in hopes of identifying motifs that circumvent the common drawbacks imparted by *tert*-butyl groups, such as increased lipophilicity and lower metabolic stability.