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Structure property relationships of *N*-acylsulfonamides and related bioisosteres

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The *N*-acylsulfonamide functional group is a feature of the pharmacophore of several biologically active molecules, including marketed drugs. Although this acidic moiety presents multiple points of attachments that could be exploited to introduce structural diversification, depending on the circumstances, the replacement of the functional group itself with a suitable surrogate, or bioisostere, may be desirable. A number of *N*-acylsulfonamide bioisosteres have been developed over the years that provide opportunities to modulate both structure and physicochemical properties of this important structural motif. To enable an assessment of the relative impact on physicochemical properties that these replacements may have compared to the *N*-acylsulfonamide group, we conducted a structure-property relationship study based on matched molecular pairs, in which the *N*-acylsulfonamide moiety of common template reference structures is replaced with a series of bioisosteres. The data presented, which include an assessment of relative changes in acidity, permeability, lipophilicity and intrinsic solubility, provides a basis for informed decisions when deploying *N*-acylsulfonamides, or surrogates thereof, in analog design.

1. Introduction

Acidic moieties are of great importance in drug design as they can significantly impact, through ionic and electrostatic interactions, both physicochemical properties (*e.g.*, lipophilicity), ADME-PK parameters, as well as on target/off target interactions (*e.g.*, with proteins) of biologically active compounds [1]. As a result, the modulation of one or more properties of the acidic moiety of candidate compounds can have important ramifications, especially during the hit/lead optimization process.

The *N*-acylsulfonamide group is an acidic moiety that is frequently employed in medicinal chemistry as a carboxylic acid bioisostere [2–6], with several reported examples in which such a replacement led to improved derivatives [7–10]. This structural motif, however, can also be in itself a constituent of the pharmacophore as exemplified in many different classes of biologically active compounds [11], including antivirals [12], antibacterial [13,14], and antiproliferative agents [15–17]. The importance of *N*-acylsulfonamides in the field of drug design and medicinal chemistry is evident by the fact that as many as nine novel *N*-acylsulfonamide drugs (Fig. 1) have been marketed in the USA between 2015 and 2020 [18]. Moreover, a review of the literature revealed that between 2019 and 2020, >50 research articles have been published in medicinal chemistry journals in which *N*-acylsulfonamides were studied for a variety of indications.

Although the *N*-acylsulfonamide structural motif presents alternative points of attachment that provide opportunities for structural diversification and modulation of physicochemical properties, on occasions, the replacement of this functional group itself with a suitable bioisostere may be desirable. The success of this strategy, however, like any isosteric replacement strategy, is highly context dependent and ultimately relies upon the availability of alternative structures that could be considered as potential surrogates. The concept of isosteric replacement has evolved significantly since it was first introduced. The current conception, which presents bioisosteres more as molecular metaphors rather than close structural equivalents of what they are replacing, is

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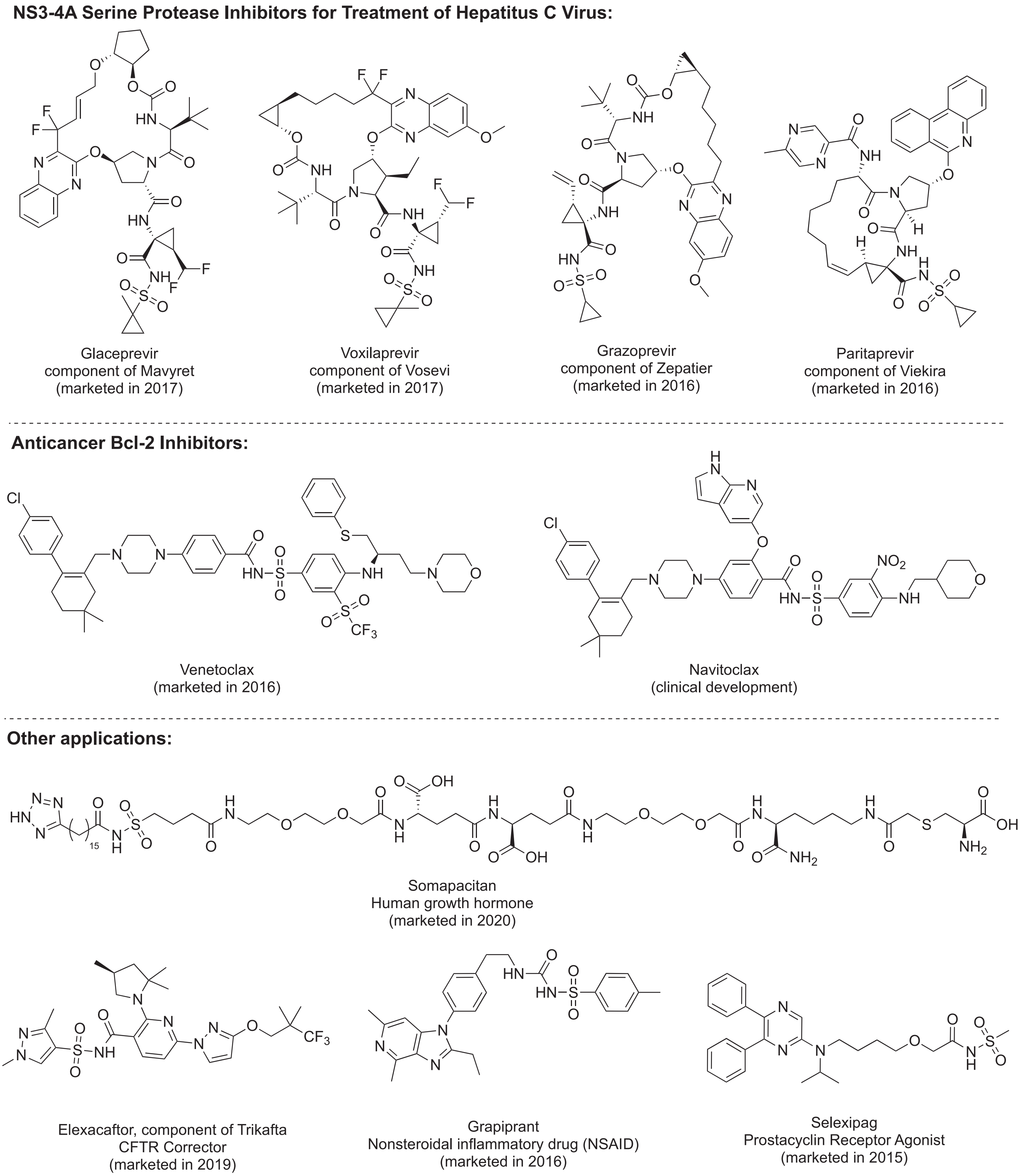


Fig. 1. Examples of *N*-acylsulfonamides that are either marketed or are in advanced stages of clinical development.

considerably broader than originally conceived and leads to the evaluation of a relatively wide range of alternative structures that could potentially emulate the desired biological activity [19–21]. In the case of the *N*-acylsulfonamide, over the years, a select number of surrogates have been introduced in which the carbonyl moiety is replaced with an oxetane or a 5-membered ring heterocycle (Fig. 2A). These structures likely originate from earlier observations that 5-membered ring heterocycles, such as triazoles, isoxazoles and others, have found broad applications as possible mimetics of different carboxylic acid derived functional groups [22–25].

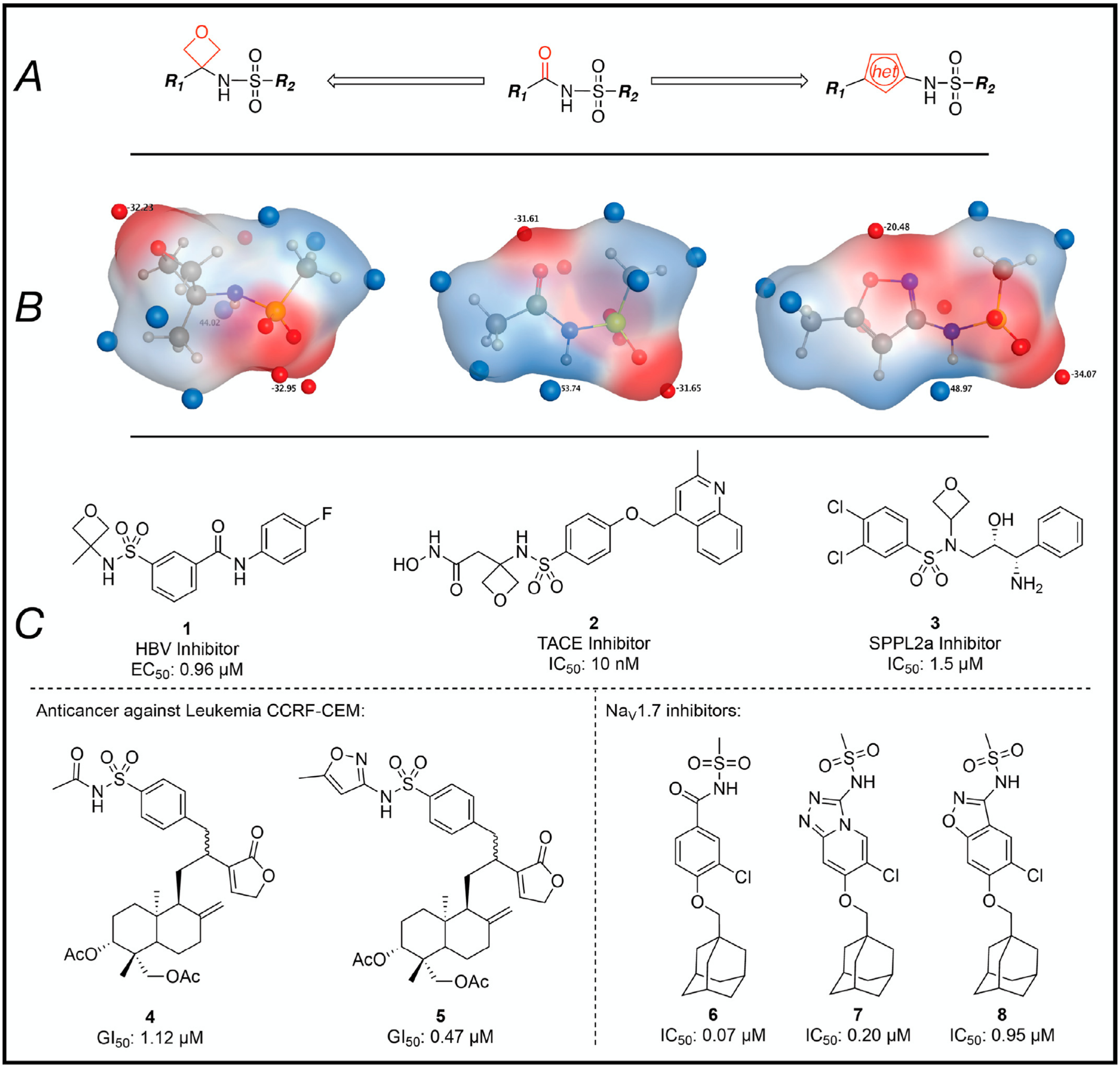


Fig. 2. (*A*) General outline of *N*-acylsulfonamide bioisosteres that are based on replacement of the carbonyl moiety with either an oxetane or a 5-membered heteroaromatic. (*B*) comparison of Gaussian-optimized geometry and electrostatic potential maps of the *N*-acylsulfonamide moiety (center) and the corresponding oxetane (left) and isoxazole (right) derivatives. The areas colored in red and blue represent respectively negative and positive regions of the electrostatic potential; the corresponding surface minima and maxima are indicated as red and blue spheres. (*C*) Representative literature examples [37–39], including match paired comparisons, **4** and **5**, as well as **6**–**8** [35,36].

Likewise, the oxetane ring is known to be a potentially effective replacement of the carbonyl moiety of ketones, aldehydes, carboxylic acids, esters and amides [26–31], and this presumably led to its incorporation in *N*-acylsulfonamides [32,33]. Compared to the parent *N*-acylsulfonamide structure, these replacements can be expected to introduce some changes in terms of properties (*e.g.*, acidity), geometry and/or electrostatic potential (Fig. 2B). However, interestingly, different examples have been reported in which incorporation of such structural motifs resulted in biologically active analogs in a variety of contexts (*e.g.*, see **1**–**3**, **5**, **7** and **8**, Fig. 2C) [33–40]. Among these examples, the match paired molecules, **4** and **5**, as well as **6**–**8**, are especially notable as they reveal a comparable biological activity between the *N*-acylsulfonamide and the corresponding surrogate [35,36].

Given the importance of *N*-acylsulfonamides in medicinal chemistry and the potential utility of *N*-acylsulfonamide bioisosteres in analog design, an assessment of the relative impact on physicochemical properties that these replacements can have, compared to the parent *N*-acylsulfonamide group, may ultimately facilitate informed decisions in the hit/lead optimization stage. As a result, to enable an informative and meaningful comparison of the properties of these structures, we constructed a focused set of matched molecular pairs (MMP) comprised of different *N*-acylsulfonamides and related derivatives, as well as a series of corresponding surrogates, and evaluated how these replacements can affect key physicochemical properties, such as: (*a*) acidity (pK_a); (*b*) lipophilicity ($logD_{7.4}$); (*c*) intrinsic solubility; and (*d*) passive diffusion in a parallel artificial membrane permeability assay (PAMPA). Finally, an assessment of the hydrogen bonding ability of selected examples was also conducted.

2. Results

Library Design and Synthesis. The compound library was designed following a general strategy utilized previously in structure property relationship (SPR) studies of carboxylic acid bioisosteres [41], in which the phenylpropionic acid fragment was used as structural template for analog design. The *N*-acylsulfonamide derivative **9** and related sulfuric diamide derivative **10** (Table 1), the physicochemical properties of which had been determined in these earlier studies [41], were chosen here as reference *N*-acylsulfonamide molecules. In addition, to better capture the differences in physicochemical properties that may arise from different substitutions and alternative orientations of the *N*-acylsulfonamide group, two additional control compounds, **11** and **12** (Table 1), were also included. For each of the four reference compounds, a series of related derivatives bearing different surrogates of the *N*-acylsulfonamide group were synthesized leading to a total of 24 entries (**9**–**32**, Table 1). Among the different classes of bioisosteres evaluated in the study are structures that have already been exemplified in analog design that are based on *N*-acyl moiety replacement with either a 5-membered ring heteroaromatic, such as isoxazole and 1,2,3-triazole, or an oxetane ring. In addition, since previous studies from our laboratories suggested that appropriately substituted thietanes may also serve as effective surrogates of the acyl group [26], a series of examples of *N*-acylsulfonamide derivatives bearing these 4-membered ring heterocycles were also chosen so as to expand the scope of the study beyond the examples of *N*-acylsulfonamide bioisosteres described in the literature. A comparison of the geometry and electrostatic potential of these structures relative to the corresponding *N*-acylsulfonamides is presented in Supporting Information.

Reference *N*-acylsulfonamide-derived compounds, **9**–**11**, were either already available (**9** and **10**) or prepared (**11**) from phenylpropionic acid as described previously [41], while reference compound **12** was obtained via aminolysis of phenethylsulfonyl chloride, followed by *N*-acylation with acetic anhydride. The synthesis of all other test compounds is highlighted in Schemes 1 and 2. Sulfonamide **13** was prepared by sulfonylating commercially available 3-methyloxetan-3-amine (**33**) under basic conditions (Scheme 1).

Oxetane and thietane derivatives, **15**–**20**, were prepared in five steps starting from commercially available oxetan-3-one (**34**) and thietan-3-one (**35**). Condensation of the appropriate ketone and (*S*)-(−)-2-methyl-2-propanesulfinamide to the corresponding imines (**36** and **37**) followed by treatment with trimethylsulfoxonium iodide (TMSOI), led to aziridines **38** and **39**, which were then subjected to ring opening using benzylmagnesium chloride to provide *N*-protected amines **40** and **41** [42–44]. Finally, deprotection under acidic conditions to the amine **42** and **43**, followed by sulfonylation, furnished the desired sulfonamides **15**–**20** (Scheme 1).

Thietane-1-oxide (**21**–**23**) and −1,1-dioxide compounds (**24**–**26**) were obtained from thietane **43**. Thus, oxidation of **43** with *m*-CPBA furnished a separable mixture of *trans*- and *cis*- 1-oxido-3-phenethylthietan-3-amines, **44** and **45**. The major *cis*-isomer, **45**, was then used for the synthesis of sulfonamides **21**–**23**. Alternatively, oxone mediated conversion of **43** to the corresponding 1,1-dioxide, **46**, followed by *N*-sulfonylation, yielded sulfonamides **24**–**26** (Scheme 1), while acylation of **46** with acetic anhydride provided acetamide **14** [45].

Isoxazole derivatives **27**–**29** were obtained via cyclocondensation of α-ketonitrile **47** in the presence of hydroxylamine, followed by sulfonylation of the resulting amino-isoxazole **48** with the appropriate sulfonyl chloride or sulfamoyl chloride [46] (Scheme 2). Likewise, triazole compounds **30**–**32** were prepared via sulfonylation of commercially available 1-phenyl-1*H*-1,2,3-triazol-4-amine **49** (Scheme 2).

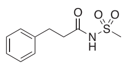
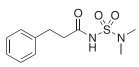
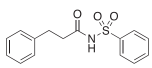
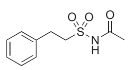
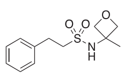
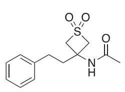
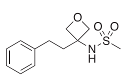
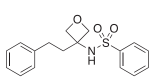
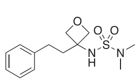
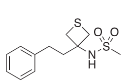
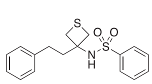
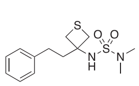
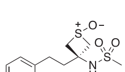
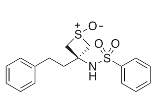
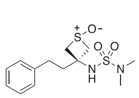
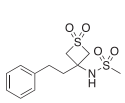
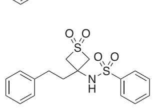
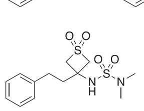
In addition to the structures of final product being established by ^{1}H and ^{13}C NMR, as well as IR, and HRMS, X-ray structures of selected compounds (**15**, **16**, **18**, **19**, **21**) were also obtained (see Supporting Information).

Determination of Physicochemical Properties. All test compounds were initially evaluated for chemical stability in aqueous buffer (pH 7.4) by determining the percentage of remaining compound after 5 h of incubation. The results of this initial screening confirmed that the test compounds were generally stable (*i.e.*, >90% unchanged) suggesting that spontaneous hydrolysis under typical assay buffer conditions would not be a limiting factor. Next, evaluation of physicochemical properties of test compounds included the determination of: (*a*) acidity (pK_a); (*b*) lipophilicity ($logD_{7.4}$); (*c*) intrinsic solubility; and (*d*) passive diffusion in a PAMPA assay. Determination of pK_a values was conducted via potentiometric titrations using a Sirius T3 (Pion, Inc.). Likewise, the logP and $logD_{7.4}$ values of compounds **9**–**13**, **15**, **21**, **24**, **26**–**32** were obtained via potentiometric titrations, while for selected compounds (**14**, **16**–**20**, **22**, **23**, **25**) the $logD_{7.4}$ determinations were conducted via shake-flask method. Calculated logP, $logD_{7.4}$, and pK_a values were also obtained for comparison employing ChemAxon [47]. For all solid compounds, the melting point (mp) of crystalline material was obtained and from the knowledge of mp and logP values, the intrinsic solubility was estimated via the general solubility equation [48,49]. Finally, an estimation of hydrogen bonding ability of selected compounds (*i.e.*, **9**, **12**, **13**, and **15**) was conducted using experimental ΔlogP values in various solvents via potentiometric titrations [50–54]. The results from these studies are summarized in Tables 1 and 2.

From the data accumulated in this study, different elements of SPRs can be identified. First, within each series of compounds (denoted with different symbols in Fig. 3), the reference *N*-acylsulfonamides, **9**–**12**, were found to be generally the most acidic, as well as the least permeable and lipophilic molecules, with **10** and **11** being comparatively more lipophilic and permeable than the two other controls, **9** and **12**. Although a good overall correlation linking the $logD_{7.4}$ values and the apparent permeability coefficients (*Papp*) was observed across the entire data set ($r^2 = 0.890$, Fig. 3), some interesting discrepancies were noted. For example, the results from the PAMPA assay indicate a possible difference in permeability between **9** and **12**, with the latter being more permeable than the former. This result may be somewhat unexpected considering that these two compounds are structural isomers characterized by very similar pK_a and $logD_{7.4}$ values.

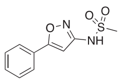
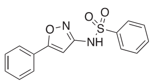
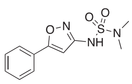
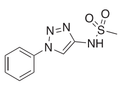
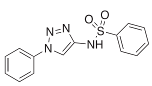
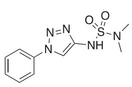
We have previously observed that differences in PAMPA permeability values of compounds having similar acidity and lipophilicity may be ascribed to the differential degree of hydrogen bonding and solvation [41]. However, in the particular case of **9** and **12**, these two compounds are structural isomers that share identical polar surface area (tPSA = 63.24 Å^2) suggesting that the ability to hydrogen bond of these two isomers may be closely comparable. Thus, to assess experimentally possible differences in hydrogen bonding between **9** and **12**, we evaluated the difference in the partition coefficients (ΔlogP) of each of the two test compounds when the partition solvent is changed from the protic solvent, *n*-octanol, to a non-polar aprotic hydrocarbon, such as cyclohexane, heptane or toluene (Table 2). The ΔlogP values have been used

Table 1
Calculated and experimental properties of test compounds.

Cmpd	Structure	mp (°C)[a]	% Stability aq. buffer pH 7.4–7.6[b]	Intrinsic solubility (mol/L)[c]	logP[d]	$logD_{7.4}$[e]	logP calc[f]	$logD_{7.4}$ calc[f]	PAMPA			pK_a[j]	pK_a calc[f]
									Pe (cm/s)[g]	% retention[h]	log_{Papp}[i]		
9		105.5 −106.5	99.6	3.89E−2	1.10 ± 0.01	−0.64 (−1.02)	0.86	−0.27	3.45E −7	1.35E−2	−6.46	4.75 ± 0.01 (4.94)	4.08
10		103.0 −104.0	94.3	1.14E−2	1.66 ± 0.02	0.12 (0.17)	0.99	−0.15	1.53E −6	2.15E−2	−5.81	5.79 ± 0.01 (5.86)	4.12
11		107.8 −108.5	100.0	9.97E−4	2.67 ± 0.01	−0.09	2.92	1.78	1.64E −6	−3.05E-2	−5.79	4.49 ±0.04	4.24
12		76.2 −78.4	91.4	8.65E−2	1.04 ± 0.01	−0.87	0.78	−0.36	1.00E −06	−5.00E−2	−6.00	4.91 ±0.01	4.09
13		43.1 −44.0	100.0	5.43E−2	1.58 ±0.06	1.58	0.83	0.83	6.79E −6	−3.20E−2	−5.17	10.45 ± 0.01	9.59
14		135.3 −136.8	94.5	1.62E−3	[l]	1.18[k]	0.10	0.10	2.11E −6	−1.20E-2	−5.68	>12	13.53
15		71.4 −71.9	100.0	2.65E−2	1.61 ± 0.03	1.61	0.76	0.76	8.44E −6	0.157	−5.1	10.05 ±0.01	9.59
16		105.8 −107.2	94.1	6.38E−4	[l]	2.76[k]	2.81	2.81	7.06E −6	0.260	−5.2	10.29 ±0.12	10.15
17		ND	93.7	3.47E−2	[l]	1.96[k]	0.89	0.89	1.02E −5	5.89E−2	−4.99	11.02 ±0.01	9.78
18		115.2 −116.0	91.5	1.43E−3	[l]	2.44[k]	1.34	1.34	1.46E −05	0.439	−4.8	10.45 ± 0.02	10.70
19		74.2 −75.8	92.8	1.10E−3	[l]	2.96[k]	3.40	3.40	ND	ND	ND	>12	10.16
20		56.6 −58.9	93.5	2.20E−3	[l]	2.83[k]	1.47	1.47	1.14E −5	0.373	−4.9	11.93 ± 0.05	10.89
21		151.2 −154.2	100.0	2.20E−2	0.88 ± 0.02	0.87	−0.43	−0.43	ND	ND	ND	9.87 ± 0.01	10.16
22		135.3 −136.8	90.3	4.268E−2	[l]	0.76[k]	1.62	1.62	2.91E −6	5.07E−2	−5.54	9.80 ± 0.06	10.16
23		127.1 −127.8	93.4	1.06E−2	[l]	1.45[k]	−0.30	−0.31	3.41E −6	7.13E−2	−5.47	10.33 ± 0.02	10.42
24		108.3 −108.7	100.0	4.32E−2	1.03 ±0.01	1.03	−0.24	−0.25	3.66E −06	−3.00E-3	−5.4	9.44 ± 0.02	9.07
25		182.5 −184.2	98.3	1.06E-3	[l]	1.89[k]	1.81	1.81	ND	ND	ND	10.22 ± 0.15	10.16
26		100.2 −101.5	100.0	8.16E−3	1.83 ± 0.05	1.82	−0.11	−0.12	4.43E −6	0.105	−5.35	9.58 ± 0.01	9.35

(continued on next page)

Table 1 (*continued*)

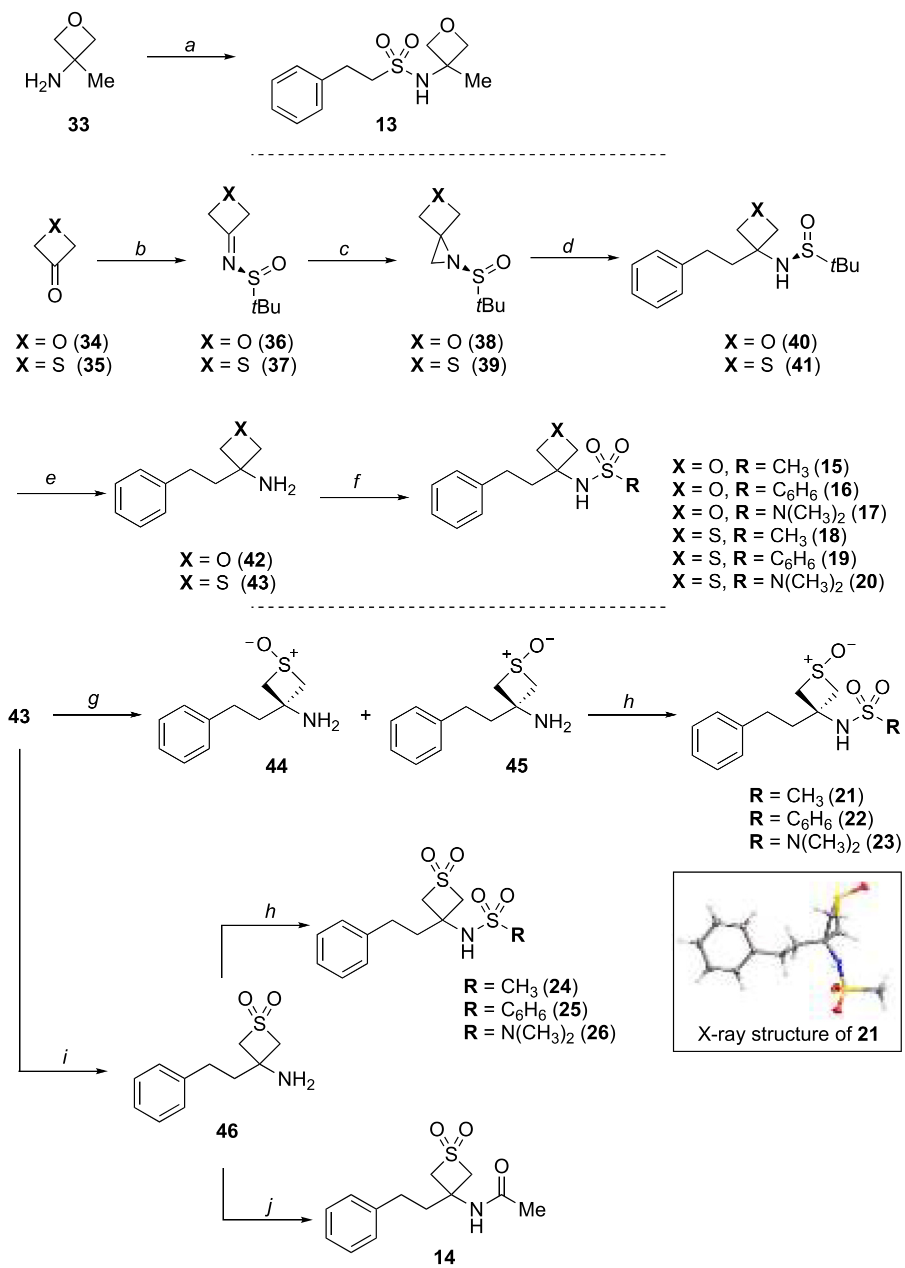
Cmpd	Structure	mp (°C)[a]	% Stability aq. buffer pH 7.4–7.6[b]	Intrinsic solubility (mol/L)[c]	logP[d]	$logD_{7.4}$[e]	logP calc[f]	$logD_{7.4}$ calc[f]	PAMPA Pe (cm/s)[g]	PAMPA % retention[h]	PAMPA log_{Papp}[i]	pK_a[j]	pK_a calc[f]
27		158.0–158.8	97.7	3.85E−2	0.58 ± 0.02	−0.42	1.21	0.42	1.16E−6	3.42E−2	−5.94	5.22 ± 0.01	6.44
28		164.8–166.0	95.5	2.17E−3	1.76 ± 0.03	0.99	3.26	2.24	5.79E−6	−4.81E−2	−5.24	6.62 ± 0.02	5.82
29		152.5–152.9	97.3	2.36E−2	0.85 ± 0.01	0.42	1.33	0.95	2.87E−6	0.131	−5.54	5.62 ± 0.02	7.17
30		156.0–157.5	93.5	1.05E−2	1.16 ± 0.03	0.06	0.57	−0.19	2.42E−6	−4.07E−2	−5.62	6.34 ± 0.01	6.48
31		163.7–164.5	93.3	3.62E−4	2.55 ± 0.04	1.06	2.63	1.59	4.09E−6	2.76E−4	−5.39	5.93 ± 0.05	5.72
32		158.5–159.7	93.9	2.75E−3	1.72 ± 0.01	0.69	0.70	0.34	3.77E−6	−4.43E−2	−5.42	6.42 ± 0.01	7.20

§ Test compound was an oil.
a Melting point of crystalline material.
b Test compound (%) remaining after 5 h of incubation at rt in aqueous buffer (BICCA® Simulated intestinal fluid, without pancreatin; pH 7.40–7.60) as determined by relative changes in peak area of LC/MS chromatograms over time.
c Intrinsic solubility determined from the general solubility equation (GSE) by using experimentally determined logP and mp values.
d Log of the partition coefficient between *n*-octanol and water (unless otherwise noted, logP determinations were conducted via potentiometric titrations using a Sirius T3, Pion, Inc).
e Log of the distribution coefficient between *n*-octanol and aqueous buffer at pH 7.4 (unless otherwise noted, $logD_{7.4}$ determinations were conducted via potentiometric titrations using a Sirius T3, Pion, Inc).
f Calculated values using ChemAxon [47].
g Effective permeability (PAMPA assay run by Analiza, Inc).
h Membrane retention.
i Log of the apparent permeability coefficient (P_{app}).
j pK_a values determined by potentiometric titrations using a Sirius T3, Pion, Inc (values in brackets are from [41]).
k $logD_{7.4}$ value determined via shake-flask assay (experiment run by Analiza, Inc).
l logP value is considered equal to the $logD_{7.4}$ as these compounds exhibit pK_a values > 9.4; ND = not determined.

before to estimate the propensity of compounds to hydrogen bond [50,55], and this parameter has been found to correlate well with passive diffusion [51,53,56,57]. Interestingly, although **9** and **12** have identical tPSA, which would suggest a near identical hydrogen bonding ability, the ΔlogP values of isomer **9** were found to be consistently higher (0.15–0.50) than the corresponding values of **12** regardless of the aprotic solvent used in the experiment. By comparison, the relative difference in ΔlogP values in the case for the oxetane derivatives, **13** and **15**, which are also structural isomers but with more closely comparable PAMPA permeability values, appeared to be generally narrower (0.09–0.14, Table 2). These results suggest that the *N*-acylsulfonamide, **9**, has greater propensity to hydrogen bond than the structural isomer, **12**, and this likely results in comparatively tighter solvation and lower permeability in the PAMPA assay.

Among the different series of model compounds, the derivatives of acylsulfonamide **9** (shown as circles in Fig. 3) exhibit a wider and more evenly distributed change in properties compared to other series, with relative increases in lipophilicity, permeability and acidity that ranged respectively: 0.2–3.1 ($logD_{7.4}$); 0.5–1.7 (log_{Papp}); 0.5–5.7 (pK_a). Notably, the oxetane/thietane derivatives of **9** (*e.g.*, **15**, **18**, **21** and **24**) are significantly less acidic with pK_a values that are >5 units higher than the pK_a value of **9**. The reduced acidic character of these compounds, however, may not be always associated with a reduction in hydrogen bonding ability as suggested again by ΔlogP values (Table 2) that in the case of oxetane derivative, **15**, appear to be within the range of values registered for *N*-acylsulfonamide **9** and **12**. This is in agreement with other reports of the oxetane ring being an excellent HB acceptor, often better than carbonyls [58,59].

Further comparison of the properties of different series of model compounds suggests that in the case of **9** and **10** (circles and squares in Fig. 3) the impact that each of the 4- and 5-membered ring carbonyl replacements have on compound lipophilicity and permeability follows a similar trend. Within each series of analogs and for both parameters (*i.e.*, $logD_{7.4}$ and log_{Papp}) the isoxazole derivatives (**27**, **29**) registered the smallest increase relative to the corresponding *N*-acylsulfonamides, while the oxetane and thietane derivatives (**15**, **17**, **18**, **20**) produced the largest differential in lipophilicity and permeability. This trend is less evident in the case of compounds derived from **11** (triangles in Fig. 3). Although the oxetane (**16**) and thietane (**19**) derivatives are still the most lipophilic members within this series, the corresponding thietane-1-oxide (**22**), isoxazole (**28**) and triazole (**31**) compounds appear to fall within a relatively narrow range of $logD_{7.4}$ values. Some series-specific differences can also be seen when plotting the relative changes in intrinsic solubility values (Fig. 4). However, in the majority of cases, carbonyl replacement with a 1,2,3-triazole (*i.e.*, **30**,



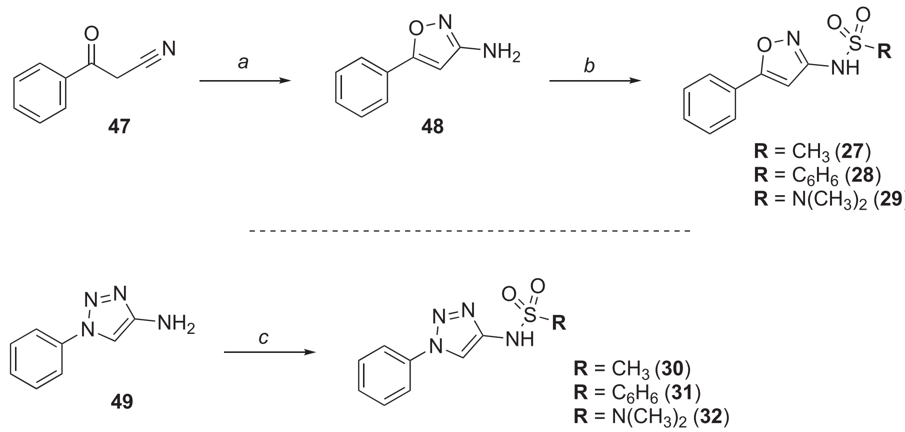
Scheme 1. Reagents and conditions: (a) Et_3N, 2-phenylethane-1-sulfonyl chloride, CH_2Cl_2, 0 °C to rt, 16 h, (34%); (b) (*S*)-(−)-2-methyl-2-propanesulfinamide, Ti(*i*PrO)$_4$, CH_2Cl_2, reflux, 16 h, (77%); (c) TMSOI, NaH, DMSO, rt, 2 h, (39–49%); (d) benzylmagnesium chloride, CuI, THF, −30 to 0 °C, 1 h, (48–90%); (e) HCl, CH_3OH, 0 °C to rt, 16 h, (62%); (f) Et_3N, appropriate sulfonyl chloride or sulfamoyl chloride, CH_2Cl_2, 0 °C to rt, 16 h, (24–68%); (g) *m*-CPBA, CH_2Cl_2, −78 °C, 2 h, (70%); (h) Et_3N, appropriate sulfonyl or sulfamoyl chloride, CH_2Cl_2, 0 °C to rt, 16 h, (15–78%); (i) oxone, acetone/H_2O (1:1), 0 °C to rt, 16 h, (47%); (g) acetic anhydride, AgOTf, CH_2Cl_2, 0 °C to rt, 2 h, (67%).

31, and **32**) or a thietane (*e.g.*, **18** and **20**) appears to result in a relative decrease in intrinsic solubility, whereas replacement with an isoxazole (*i.e.*, **27**, **28**, and **29**) or a thietane-1-oxide (*e.g.*, **22**) produces solubility values that are either similar or above the intrinsic solubility of the corresponding control compound.

Finally, comparison of calculated and experimental values, showed that the pK_a predictions (ChemAxon [47]) are generally accurate across the entire data set ($r^2 = 0.95$, Fig. 5A). However, the r^2 values are significantly lower if the linear regression analysis is performed separately within the more and less acidic compound clusters (Fig. 5A). A relatively modest correlation was also noted between calculated and experimental log$D_{7.4}$ values ($r^2 = 0.57$, Fig. 5B). These observations suggest that although the rapid, inexpensive availability of predicted pK_a and lipophilicity values remains undeniably a great resource to medicinal chemistry, especially in programs requiring the rapid assessment of large number of compounds, experimental determinations are clearly necessary in SPR studies.

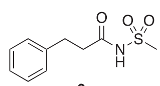
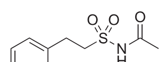
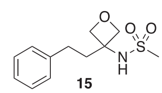
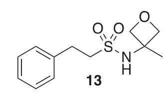
3. Discussion

The isosteric replacement of specific atoms, functional groups, or fragments with appropriate surrogate structures is a validated strategy in medicinal chemistry that can be utilized to modulate the intrinsic physicochemical properties of compounds of interest, resulting in derivatives with potentially improved



Scheme 2. Reagents and conditions: (a) $NH_2OH\cdot HCl$, NaOH, H_2O/EtOH (1:1), 80 °C, 2 h, (36%); (b) appropriate sulfonyl chloride or sulfamoyl chloride, pyridine, 0 °C to rt, 16 h, (18–75%); (c) appropriate sulfonyl chloride or sulfamoyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt, 16 h, (21–27%).

Table 2
The ΔlogP values of selected compounds.[a]

	 9	 12	 15	 13
$\Delta logP_{cyclohexane}$	2.13 ± 0.04	1.63 ± 0.05	1.87 ± 0.04	2.01 ± 0.09
$\Delta logP_{heptane}$	1.63 ± 0.05	1.48 ± 0.04	1.60 ± 0.05	1.72 ± 0.13
$\Delta logP_{toluene}$	0.89 ± 0.03	0.40 ± 0.06	0.43 ± 0.04	0.52 ± 0.07

[a] $\Delta logP = logP_{octanol\text{-}water} - logP_{hydrocarbon\text{-}water}$; the partition coefficients in different solvents were experimentally determined via potentiometric titrations (see Supporting Information).

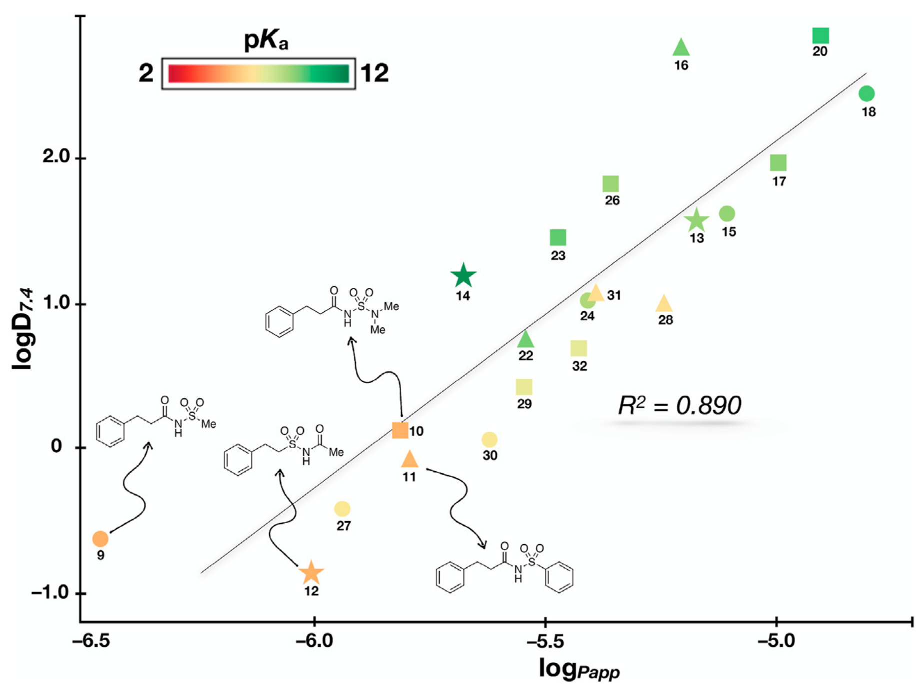


Fig. 3. Plot showing lipophilicity (*i.e.*, $logD_{7.4}$), acidity (*i.e.*, pK_a), and permeability (*i.e.*, log_{Papp}) of test compounds. Each of the four reference compounds (structures shown) and their corresponding analogs are identified with different symbols.

pharmacokinetics and/or pharmacodynamics [20]. Considering that the outcome of any isosteric replacement can vary considerably depending on the particular context in which it is applied, a screening and evaluation of alternative isosteres is almost invariably needed. Under these circumstances, knowledge of the relative ranking of different isosteres based on experimentally determined physicochemical properties can be helpful to enable informed decisions in the analog design process. Structure property

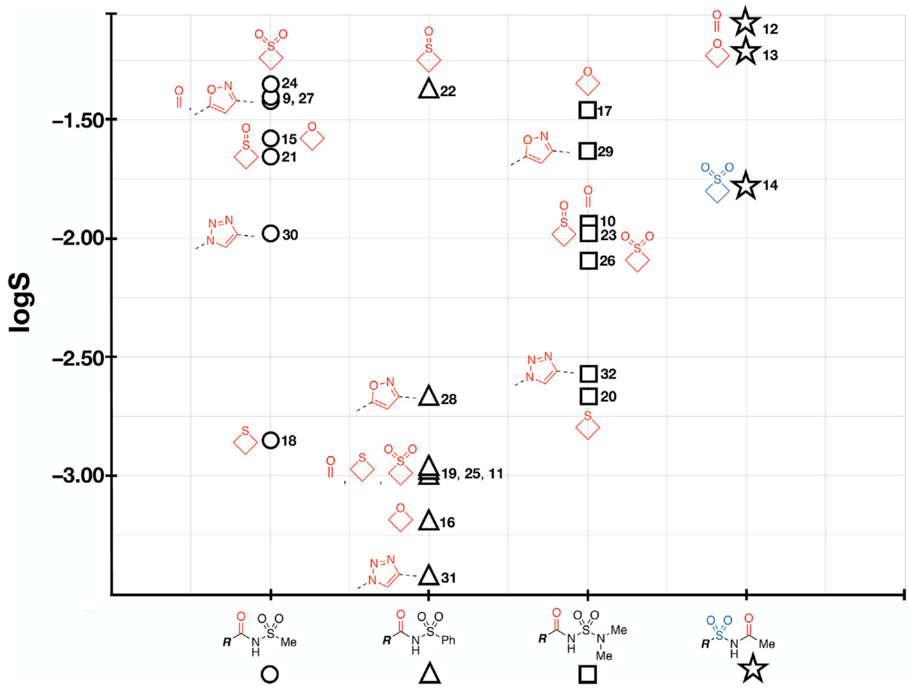


Fig. 4. Plot of the log of the intrinsic solubility (*S*) of the different series of test compounds; logS values are obtained from the general solubility equation [logS = −logP − 0.01 × (mp − 25) + 0.5] by using experimentally determined mp and logP values.

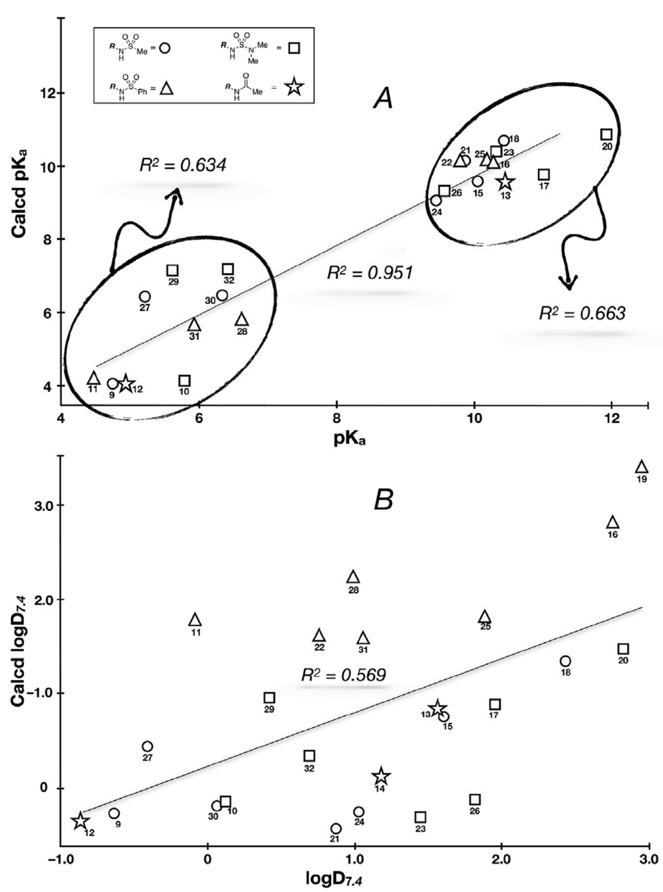


Fig. 5. Comparison between experimental and calculated pK_a (A) and $logD_{7.4}$ values (B).

relationship studies that are based on comparisons between MMPs comprise an effective strategy to reveal relative differences and trends associated with specific chemical transformations. As such, this strategy is especially suited to investigate the property space of isosteric replacements [41]. The present study aimed at assessing the properties of different representative *N*-acylsulfonamides, as well as different classes of related surrogates. With respect to the four *N*-acylsulfonamides examined in these studies, the data collected illustrate that, as expected, relatively simple manipulations of the substituent at the sulfur center (*e.g.*, **9** − **12**) can be exploited to modulate the physicochemical properties of these compounds. Perhaps of particular interest is the observation that the alternative arrangement of the *N*-acylsulfonamide group, as in **9** and **12**, produces structural isomers that exhibit different hydrogen bonding ability, as determined by ΔlogP values, that in turn correlates with different apparent permeability coefficients in the PAMPA assay.

With respect to the *N*-acylsulfonamide surrogates examined, examples were included where the carbonyl moiety is replaced with either a 5-membered ring heteroaromatic or an oxetane ring, as these structural motifs already found applications in drug design as *N*-acylsulfonamide bioisosteres. Moreover, a series of thietane derivatives were also included and depending on the particular oxidation state of the thietane sulfur atom, these compounds could significantly expand the range of properties of their respective series. Although the *N*-(thietan-3-yl)sulfonamide substructure is still relatively rare and unexplored and the possible *bioisosteric* relationships of these derivatives have not yet been investigated, a comparison of geometry and electrostatic potential of the *N*-acylsulfonamide **9**, and the corresponding oxetane/thietane derivatives (Fig. 6 and Supporting Information) would suggest that these types of structures may potentially serve as candidate replacements. In addition, considering that the model compounds studied here were derived from the same phenylpropionyl structural template used in earlier SPR studies of carboxylic acid bioisosteres [26,41], the physicochemical properties of these novel structures could be

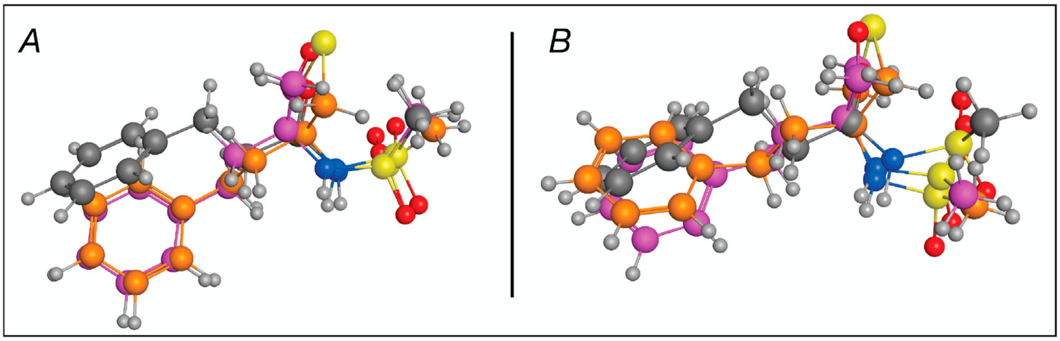


Fig. 6. Overlay of the X-ray structures (A) and structures obtained via Gaussian geometry optimization (B) of compound **9** (grey), **15** (purple), and **18** (orange).

directly compared against different classes of acidic moieties, gaining additional insight.

Indeed, comparison of the p*K*a, $\log D_{7.4}$ and PAMPA permeability data of the different sets of compounds (Fig. 7 and Supporting Information) shows that many of the thietane derivatives fall within the property space of acidic moieties, with selected structures being near *isometric* with other acidic groups. For example, the acidity, lipophilicity and permeability of **24** and **26** appear to be closely comparable respectively to the hydroxamic ester **50** and acid **51** derivatives. Likewise, interestingly, the physicochemical properties of amide **14** are similar to the properties of the corresponding phenethylsulfonamide **52**. Although these similarities in physicochemical properties cannot be used to infer bioisosteric relationships, these results may help to further contextualize the properties of the novel structures and to provide a rationale for their possible use in medicinal chemistry programs.

Thus, taken together, these similarities as well as the general trends of SPRs identified in this study may facilitate informed decisions when deploying *N*-acylsulfonamides, or surrogates thereof, in analog design.

4. Conclusions

The results from this study provide an assessment of the physicochemical properties of different *N*-acylsulfonamides, as well as a series of corresponding surrogate structures. This data set may be helpful in drug design efforts that involve the incorporation or replacement of *N*-acylsulfonamides. In addition, by complementing and expanding previous SPR studies of carboxylic acid bioisosteres, the data presented may contribute in further defining the property space of acidic moieties and their surrogates.

5. Materials and methods

All solvents and reagents were reagent grade. The hexane solvent was a mixture of isomers. All reagents were purchased from reputable vendors and used as received. Thin layer chromatography (TLC) was performed with 200 μM MilliporeSigma precoated silica gel aluminum sheets. TLC spots were visualized under UV light or using $KMnO_4$ stain. Flash chromatography was performed with SiliaFlash P60 (particle size 40–63 μM) supplied by Silicycle. Melting points were taken from Mel-Temp II by Barnstead Thermolyne, using an Omega digital thermometer. Infrared (IR) spectra were recorded on a PerkinElmer FT-IR spectrometer. Proton and carbon NMR spectra were recorded on a 600 MHz NMR spectrometer. Chemical shifts were reported relative to residual solvent's peak. High-resolution mass spectra were measured at the University of California San Diego Molecular Mass Spectrometry

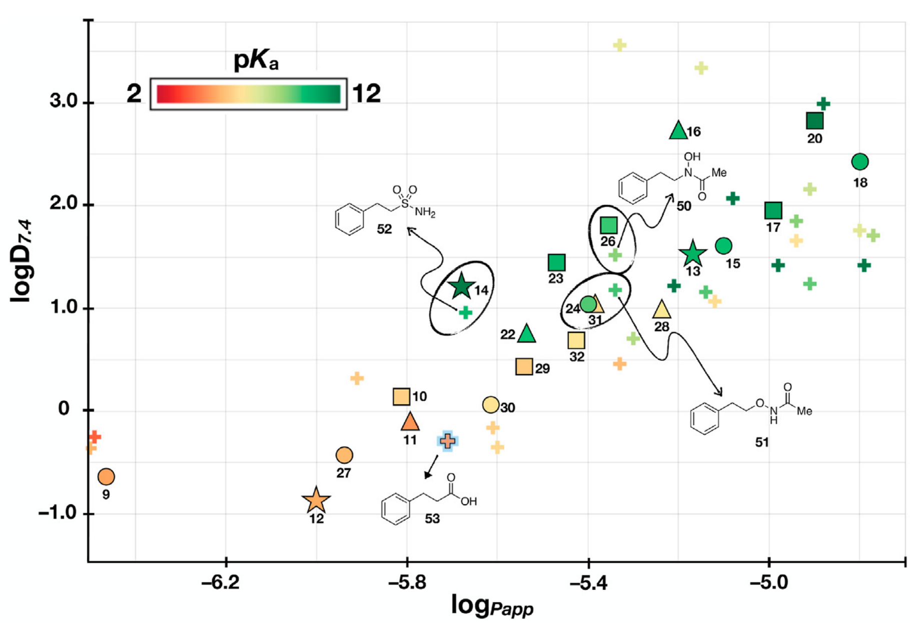


Fig. 7. Comparison of lipophilicity (*i.e.*, $\log D_{7.4}$), acidity (*i.e.*, pK_a), and permeability (*i.e.*, $\log P_{app}$) of test compounds *vs* other classes of carboxylic acid bioisosteres from [41] (crosses). Structures and data for all compounds are in the Supporting Information.

Facility. Single crystal X-ray structure determinations were performed at the University of California San Diego Crystallography Facility. Analytical reverse phase high-performance liquid chromatography (HPLC) was performed using a SunFire C18 (4.6 × 50 mm, 5 mL) analytical column, while preparative reverse phase HPLC purifications were performed using a SunFire preparative C18 OBD column (5 μm 19 × 50 mm) on a Gilson instrument. Samples were analyzed with analytical HPLC and employed 10%–90% of CH_3CN in H_2O over 6–12 min and flow rate of 2 mL/min. Samples purified by preparative HPLC employed 10%–90% of CH_3CN in H_2O over 6–20 min and flow rate of 20 mL/min. All final compounds were found to be >95% pure by HPLC/UV.

3-Phenyl-*N*-(phenylsulfonyl)propanamide (11). To a solution of phenylpropionic acid (0.500 g, 3.33 mmol, 1.00 eq), EDC·HCl (0.766 g, 4.00 mmol, 1.20 eq) and DMAP (0.488 g, 4.00 mmol, 1.20 eq) in anh. CH_2Cl_2 (20.0 mL), benzenesulfonamide (0.523 g, 3.33 mmol, 1.00 eq) was added at rt under N_2. The resulting mixture was stirred at reflux for 8 h and then at rt for an additional 48 h. The reaction was quenched with H_2O, then extracted with CH_2Cl_2 (× 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (up to 15% of EtOAc in hexane) provided the title compound as a white solid (0.641 g, 2.22 mmol, 67%). ^1H NMR (600 MHz, $CDCl_3$) δ 8.03–7.96 (m, 2H), 7.66 (t, J = 7.5 Hz, 1H), 7.54 (t, J = 7.9 Hz, 2H), 7.24–7.13 (m, 3H), 7.09–6.97 (m, 2H), 2.87 (t, J = 7.7 Hz, 2H), 2.56 (t, J = 7.7 Hz, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.33, 139.48, 138.31, 133.91, 128.93, 128.52, 128.13, 126.32, 37.84, 30.18 ppm. HRMS (ES^+) calculated for $C_{15}H_{15}NO_3S$ $[M + H]^+$ 290.0845, found 290.0846. IR (neat) ν 3107.25, 2886.93, 1682.94, 1460.06, 1452.37, 1344.62, 1170.12, 1089.75, 1072.22 cm^{-1}.

***N*-(Phenethylsulfonyl)acetamide (12).** Synthesis of **12** followed previously described procedures with some modifications [60]. To a solution of 2-phenylethane-1-sulfonyl chloride (0.500 g, 2.44 mmol, 1.00 eq) in anh. CH_2Cl_2 (6.0 mL), NH_3 (7.0 M in methanol, 1.74 mL, 5.00 eq) was added dropwise at −78 °C under N_2. The reaction mixture was slowly warmed to rt and stirred at this temperature for 3 h. The resulting mixture was neutralized with 1.0 M HCl and extracted with EtOAc (× 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting material was used in the subsequent step without further purification (0.452 g, 2.44 mmol, quantitative yield). ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 (t, J = 7.7 Hz, 2H), 7.27 (d, J = 7.2 Hz, 1H), 7.22 (d, J = 7.2 Hz, 2H), 3.88 (s, 2H), 3.40–3.34 (m, 2H), 3.19–3.13 (m, 2H) ppm. To a solution of 2-phenylethane-1-sulfonamide (0.100 g, 0.540 mmol, 1.00 eq), DMAP (0.007 g, 0.055 mmol, 0.10 eq), and Et_3N (0.164 g, 1.62 mmol, 3.00 eq) in anh. CH_2Cl_2 (5.0 mL), acetic anhydride (0.138 g, 1.35 mmol, 2.50 eq) was added at −78 °C under N_2. The mixture was slowly warmed to rt and stirred for 24 h. The resulting mixture was diluted with H_2O and extracted with EtOAc (× 3). The combined organic extracts were dried over Mg_2SO_4, filtered, and concentrated in vacuo. Purification by reverse phase HPLC (10%–90% CH_3CN in H_2O) provided the title compound as an off-white solid (0.018 g, 0.079 mmol, 15%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 (t, J = 7.6 Hz, 2H), 7.27 (d, J = 7.9 Hz, 1H), 7.23 (d, J = 7.5 Hz, 2H), 3.75 (t, J = 7.7 Hz, 2H), 3.15 (t, J = 7.7 Hz, 2H), 1.94 (s, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.05, 136.93, 129.12, 128.67, 127.34, 53.95, 29.65, 23.60 ppm. HRMS (ES^+) calculated for $C_{10}H_{14}NO_3S$ $[M + Na]^+$ 250.0508, found 250.0509. IR (neat) ν 3238.70, 2925.23, 1722.07, 1404.68, 1326.17, 1146.20, 1135.20 cm^{-1}.

***N*-(3-Methyloxetan-3-yl)-2-phenylethane-1-sulfonamide (13).** To a solution of 3-methyloxetan-3-amine (0.050 g, 0.570 mmol, 1.00 eq) in anh. CH_2Cl_2 (5.0 mL), Et_3N (0.170 g, 1.70 mmol, 3.00 eq) was added at 0 °C under N_2, followed by 2-phenylethane-1-sulfonyl chloride (0.350 g, 1.70 mmol, 3.00 eq). The resulting mixture was warmed to rt and stirred overnight. After 16 h, H_2O was added, and the crude was extracted with EtOAc (× 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (up to 30% of EtOAc in hexane) provided the title compound (0.050 g, 0.200 mmol, 34%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 (t, J = 7.6 Hz, 2H), 7.27 (s, 1H), 7.22 (d, J = 7.5 Hz, 2H), 4.70 (d, J = 6.8 Hz, 2H), 4.53 (s, 1H), 4.41 (d, J = 6.8 Hz, 2H), 3.38–3.30 (m, 2H), 3.19–3.13 (m, 2H), 1.72 (s, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.80, 129.11, 128.57, 127.23, 83.13, 57.76, 56.19, 30.23, 24.71 ppm. HRMS (ES^+) calculated for $C_{12}H_{18}NO_3S$ $[M + Na]^+$ 278.0821, found 278.0822. IR (neat) ν 3265.69, 2965.91, 2880.01, 1455.03, 1312.55, 1128.64, 1007.16 cm^{-1}.

***N*-(1,1-Dioxido-3-phenethylthietan-3-yl)acetamide (14).** To a solution of 3-amino-3-phenethylthietane 1,1-dioxide **46** (0.060 g, 0.270 mmol, 1.00 eq) in anh. CH_2Cl_2, acetic anhydride (0.054 g, 0.530 mmol, 2.00 eq) was added at 0 °C under N_2, followed by addition of silver triflate (0.001 g, 0.004 mmol, 0.01 eq). The mixture was stirred at this temperature for 30 min, then stirred at rt for 2 h. The solvent was evaporated in vacuo. Purification via silica gel column chromatograph (up to 50% EtOAc in hexane) provided the title compound (0.048 g, 0.180 mmol, 67%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.30 (t, J = 7.5 Hz, 2H), 7.24–7.20 (m, 1H), 7.18–7.14 (m, 2H), 5.81 (s, 1H), 4.24–4.18 (m, 2H), 4.11–4.06 (m, 2H), 2.64 (dd, J = 8.8, 6.4 Hz, 2H), 2.49 (dd, J = 8.7, 6.5 Hz, 2H), 1.91 (s, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.36, 139.86, 129.01, 128.45, 126.79, 74.30, 45.26, 38.77, 31.26, 23.54 ppm. HRMS (ES^+) calculated for $C_{13}H_{17}NO_3S$ $[M + Na]^+$ 290.0821, found 290.0821. IR (neat) ν 3298.61, 1647.68, 1540.27, 1455.85, 1358.84, 1315.32, 1301.07, 1286.78, 1194.79, 1137.89, 1072.13, 1033.51 cm^{-1}.

3-Phenethyloxetan-3-amine (42) and ***N*-(3-phenethyloxetan-3-yl)methanesulfonamide (15).** To (S)-2-methyl-N-(3-phenethyloxetan-3-yl)propane-2-sulfinamide **40** (0.150 g, 0.533 mmol, 1.00 eq) in anh. CH_3OH (4.0 mL), a solution of HCl (2.13 mL, 1.25 M solution in CH_3OH, 2.67 mmol, 5.00 eq) was added dropwise at 0 °C under N_2. The mixture was stirred at rt overnight. The mixture was concentrated in vacuo, and the resulting material was used in the next step without purification. To 3-phenethyloxetan-3-amine hydrochloride salt in anh. CH_2Cl_2 (4.0 mL), Et_3N (0.150 mL, 1.07 mmol, 2.00 eq) was added at 0 °C under N_2, followed by the addition of methanesulfonyl chloride (0.083 mL, 1.07 mmol, 2.00 eq) dropwise at 0 °C. The reaction mixture was stirred at rt overnight. The reaction was then quenched with H_2O, and the resulting mixture was extracted with EtOAc (× 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (up to 30% of EtOAc in hexane) provided the title compound as a white solid (0.051 g, 0.197 mmol, 37% over two steps). ^1H NMR (600 MHz, $CDCl_3$) δ 7.31 (t, J = 7.6 Hz, 2H), 7.22 (d, J = 7.9 Hz, 3H), 4.73 (d, J = 7.0 Hz, 3H), 4.48 (d, J = 7.0 Hz, 2H), 3.09 (s, 3H), 2.81–2.72 (m, 2H), 2.44–2.38 (m, 2H) ppm. ^{13}C NMR (150 MHz, CDCl3) δ 140.53, 128.90, 128.44, 126.61, 81.29, 59.60, 44.58, 38.54, 30.16, 24.91 ppm. HRMS (ES^+) calculated for $C_{12}H_{17}NO_3S$ $[M + Na]^+$ 278.0821, found 278.0821. IR (neat) ν 3142.48, 3029.94, 2954.18, 2931.24, 2886.46, 1682.06, 1601.77, 1469.16, 1453.11, 1348.08, 1308.44, 1154.59 cm^{-1}.

***N*-(3-Phenethyloxetan-3-yl)benzenesulfonamide (16).** Following the same procedure described for the synthesis of **15**, using (S)-2-methyl-N-(3-phenethyloxetan-3-yl)propane-2-sulfinamide **40** (0.173 g, 1.95 mmol, 1.00 eq), benzenesulfonyl chloride (0.345 g, 1.95 mmol, 2.00 eq), and Et_3N (0.198 g, 1.95 mmol, 2.00 eq). Purification by silica gel column chromatography (up to 20% EtOAc in hexane) provided the title compound (0.210 g, 0.662 mmol, 68%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.93 (d, J = 8.1 Hz, 2H), 7.67–7.60 (m, 1H), 7.55 (t, J = 7.8 Hz, 2H), 7.24 (t, J = 7.3 Hz, 2H), 7.21–7.15 (m, 1H), 7.00–6.91 (m, 2H), 5.01 (s, 1H), 4.61 (d, $J = 7.0$ Hz, 2H), 4.35 (d, $J = 7.0$ Hz, 2H), 2.47–2.40 (m, 2H), 2.36–2.29 (m, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.02, 140.70, 133.13, 129.51, 129.48, 128.38, 127.01, 126.28, 81.28, 59.25, 38.37, 29.85 ppm. HRMS (ES^+) calculated for $C_{17}H_{19}NO_3S$ $[M + Na]^+$ 340.0978, found 340.0975. IR (neat) ν 3115.92, 2981.87, 1444.04, 1320.06, 1147.53, 1092.66 cm^{-1}.

***N,N*-Dimethyl-[3-(2-phenylethyl)oxetane-3-yl]sulfamoylamine (17)**. Following the same procedure described for the synthesis of **15,** using (*S*)-2-methyl-*N*-(3-phenethyloxetan-3-yl)propane-2-sulfinamide **40** (0.173 g, 0.976 mmol, 1.00 eq), dimethylsulfamoyl chloride (0.280 g, 1.95 mmol, 2.00 eq), and Et_3N (0.198 g, 1.95 mmol, 2.00 eq). Purification by silica gel column chromatography (up to 20% EtOAc in hexane) provided the title compound (0.098 g, 0.340 mmol, 35%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (t, $J = 7.7$ Hz, 2H), 7.22 (d, $J = 6.8$ Hz, 3H), 4.74 (d, $J = 7.0$ Hz, 2H), 4.45 (d, $J = 6.8$ Hz, 2H), 4.38 (s, 1H), 2.86 (s, 6H), 2.75–2.70 (m, 2H), 2.43–2.35 (m, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.98, 128.78, 128.46, 126.41, 81.08, 59.23, 38.43, 38.01, 30.01 ppm. HRMS (ES^+) calculated for $C_{13}H_{20}N_2O_3S$ $[M + H]^+$ 285.1267, found 285.1268. IR (neat) ν 2923.70, 1455.67, 1326.43, 1144.23, 1050.98, 1033.09 cm^{-1}.

***N*-(3-Phenethylthietan-3-yl)methanesulfonamide (18)**. To a solution of 3-phenethylthietan-3-amine **43** (0.245 g, 1.27 mmol, 1.00 eq) in anh. CH_2Cl_2 (5.0 mL), Et_3N (0.256 g, 2.53 mmol, 2.00 eq) was added, followed by methanesulfonyl chloride (0.290 g, 2.53 mmol, 2.00 eq) at 0 °C under N_2. The reaction mixture was stirred at rt overnight. H_2O was added, and the crude was extracted with EtOAc (× 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (up to 30% of EtOAc in hexane) provided the title compound (0.118 g, 0.435 mmol, 34%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (t, $J = 7.6$ Hz, 2H), 7.24 (d, $J = 7.2$ Hz, 3H), 4.66 (s, 1H), 3.66 (d, $J = 9.9$ Hz, 2H), 3.14 (d, $J = 10.1$ Hz, 2H), 3.08 (s, 3H), 2.76 (dd, $J = 10.4$, 6.5 Hz, 2H), 2.49 (dd, $J = 10.3$, 6.6 Hz, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.75, 128.86, 128.48, 126.49, 63.28, 44.79, 39.95, 38.16, 29.85 ppm. HRMS (ES^+) calculated for $C_{12}H_{17}NO_2S_2$ $[M + Na]^+$ 294.0593, found 294.0592. IR (neat) ν 3234.79, 2967.55, 1732.48, 1442.63, 1307.46, 1153.47, 1130.11 cm^{-1}.

***N*-(3-Phenethylthietan-3-yl)benzenesulfonamide (19).** Following the same procedure described for the synthesis of **18**, using of 3-phenethylthietan-3-amine **43** (0.200 g, 1.03 mmol, 1.00 eq), Et_3N (0.209 g, 2.07 mmol, 2.00 eq) and benzenesulfonyl chloride (0.365 g, 2.07 mmol, 2.00 eq). Purification by silica gel column chromatography (up to 20% EtOAc in hexane) provided the title compound (0.270 g, 0.810 mmol, 78%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96–7.90 (m, 2H), 7.64–7.58 (m, 1H), 7.57–7.49 (m, 2H), 7.27 (d, $J = 2.0$ Hz, 1H), 7.24 (d, $J = 2.0$ Hz, 1H), 7.22–7.15 (m, 1H), 7.06–6.99 (m, 2H), 4.89 (s, 1H), 3.54–3.48 (m, 2H), 3.02–2.95 (m, 2H), 2.54–2.48 (m, 2H), 2.45–2.40 (m, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.48, 140.93, 133.02, 129.43, 128.56, 126.98, 126.16, 63.00, 39.63, 38.08, 29.60 ppm. HRMS (ES^+) calculated for $C_{17}H_{19}NO_2S_2$ $[M + Na]^+$ 356.0749, found 356.0749. IR (neat) ν 3276.99, 2948.31, 1448.03, 1320.15, 1154.08, 1090.87, 1063.51 cm^{-1}.

***N,N*-Dimethyl-[3-(2-phenylethyl)thietan-3-yl]sulfamoylamine (20)**. Following the same procedure described for the synthesis of **18**, using of 3-phenethylthietan-3-amine **43** (0.050 g, 0.260 mmol, 1.00 eq), Et_3N (0.052 g, 0.520 mmol, 2.00 eq) and dimethylsulfamoyl chloride (0.074 g, 0.520 mmol, 2.00 eq). Purification by silica gel column chromatography (up to 20% EtOAc in hexane) provided the title compound (0.024 g, 0.080 mmol, 24%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (t, $J = 7.6$ Hz, 2H), 7.25–7.20 (m, 3H), 4.38 (s, 1H), 3.69 (d, $J = 9.9$ Hz, 2H), 3.09 (d, $J = 10.3$ Hz, 2H), 2.84 (s, 6H), 2.74–2.72 (m, 2H), 2.47–2.45 (m, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.15, 128.73, 128.51, 126.31, 62.92, 39.76, 38.00, 37.68, 29.70 ppm. HRMS (ES^+) calculated for $C_{13}H_{20}N_2O_2S_2$ $[M + Na]^+$ 323.0858, found 323.0861. IR (neat) ν 2923.28, 2853.49, 1453.49, 1323.19, 1143.97, 1033.10, 1054.35 cm^{-1}.

***cis-N*-(1-Oxido-3-phenethylthietan-3-yl)methanesulfonamide (21).** Following the same procedure described for the synthesis of **18**, using of *cis*-3-amino-3-phenethylthietane 1-oxide **38** (0.030 g, 0.140 mmol, 1.00 eq), Et_3N (0.04 g, 0.430 mmol, 3.00 eq) and methanesulfonyl chloride (0.049 g, 0.043 mmol, 3.00 eq). Purification by reverse phase HPLC (10%–90% CH_3CN in H_2O) provided the title compound (0.028 g, 0.097 mmol, 68%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (t, $J = 7.5$ Hz, 2H), 7.23 (t, $J = 7.3$ Hz, 1H), 7.19 (d, $J = 7.5$ Hz, 2H), 5.44 (s, 1H), 3.97–3.88 (m, 2H), 3.70–3.59 (m, 2H), 3.08 (s, 3H), 2.77–2.68 (m, 2H), 2.07 (dd, $J = 10.1$, 6.4 Hz, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.77, 128.97, 128.39, 126.78, 62.78, 51.54, 44.75, 42.53, 29.97 ppm. HRMS (ES^+) calculated for $C_{12}H_{17}NO_3S_2$ $[M + Na]^+$ 310.0542, found 310.0542. IR (neat) ν 3125.00, 2862.28, 1465.89, 1310.97, 1033.39, 1022.67 cm^{-1}.

***cis-N*-(1-Oxido-3-phenethylthietan-3-yl)benzenesulfonamide (22).** Following the same procedure described for the synthesis of **18**, using of *cis*-3-amino-3-phenethylthietane 1-oxide **38** (0.030 g, 0.133 mmol, 1.00 eq), Et_3N (0.040 g, 0.400 mmol, 3.00 eq) and benzenesulfonyl chloride (0.071 g, 0.400 mmol, 3.00 eq). Purification by reverse phase HPLC (10%–90% CH_3CN in H_2O) provided the title compound (0.034 g, 0.093 mmol, 70%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (d, $J = 7.9$ Hz, 2H), 7.64 (t, $J = 7.5$, 1H), 7.56 (t, $J = 7.7$ Hz, 2H), 7.28 (s, 1H), 7.20 (t, $J = 7.4$ Hz, 2H), 7.02 (d, $J = 7.7$ Hz, 2H), 5.02 (s, 1H), 3.78–3.70 (m, 2H), 3.39–3.33 (m, 2H), 2.60–2.54 (m, 2H), 2.00–1.94 (m, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.73, 139.79, 133.53, 129.71, 128.85, 128.39, 127.22, 126.67, 62.90, 51.09, 42.57, 29.78 ppm. HRMS (ES^-) calculated for $C_{17}H_{19}NO_3S_2$ $[M + Na]^+$ 372.0699, found 372.0700.

***cis*-3-[(Dimethylsulfamoyl)amino]-3-(2-phenylethyl)-1lambda4-thietan-1-one (23).** Following the same procedure described for the synthesis of **18**, using of *cis*-3-amino-3-phenethylthietane 1-oxide **38** (0.060 g, 0.290 mmol, 1.00 eq), Et_3N (0.087 g, 0.860 mmol, 3.00 eq) and dimethylsulfamoyl chloride (0.120 g, 0.860 mmol, 3.00 eq). Purification by reverse phase HPLC (10%–90% CH_3CN in H_2O) provided the title compound (0.014 g, 0.44 mmol, 15%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (t, $J = 7.5$ Hz, 2H), 7.22 (td, $J = 7.2$, 1.5 Hz, 1H), 7.21–7.17 (m, 2H), 4.65 (s, 1H), 3.90–3.82 (m, 2H), 3.64–3.57 (m, 2H), 2.86 (s, 6H), 2.75–2.67 (m, 2H), 2.06–1.99 (m, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) 140.13, 128.89, 128.44, 126.63, 62.43, 50.98, 42.53, 38.02, 29.83 ppm. HRMS (ES^+) calculated for $C_{13}H_{20}N_2O_3S_2$ $[M + Na]^+$ 339.0808, found 339.0801.

***N*-(1,1-Dioxido-3-phenethylthietan-3-yl)methanesulfonamide (24).** Following the same procedure described for the synthesis of **18**, using of 3-amino-3-phenethylthietane 1,1-dioxide **46** (0.050 g, 0.220 mmol, 1.00 eq), Et_3N (0.067 g, 0.670 mmol, 3.00 eq) and methanesulfonyl chloride (0.076 g, 0.670 mmol, 3.00 eq). Purification by reverse phase HPLC (10%–90% CH_3CN in H_2O) provided the title compound (0.043 g, 0.014 mmol, 64%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (t, $J = 7.6$ Hz, 2H), 7.22 (dd, $J = 27.3$, 7.3 Hz, 3H), 5.50 (s, 1H), 4.36–4.28 (m, 2H), 4.13–4.07 (m, 2H), 3.13 (s, 3H), 2.84–2.73 (m, 2H), 2.49–2.37 (m, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.29, 129.06, 128.45, 126.94, 74.73, 48.35, 44.75, 41.64, 30.86 ppm. HRMS (ES^-) calculated for $C_{12}H_{17}NO_4S_2$ $[M - H]^-$ 302.0526, found 302.0526. IR (neat) ν 3275.93, 3028.34, 2924.35, 1455.59, 1315.13, 1232.45, 1143.38, 1090.29 cm^{-1}.

***N*-(1,1-Dioxido-3-phenethylthietan-3-yl)benzenesulfonamide (25).** Following the same procedure described for the synthesis of **18**, using of 3-amino-3-phenethylthietane 1,1-dioxide **46** (0.030 g, 0.133 mmol, 1.00 eq), Et_3N (0.040 g, 0.399 mmol, 3.00 eq) and benzenesulfonyl chloride (0.071 g, 0.399 mmol, 3.00 eq). Purification by reverse phase HPLC (10%–90% CH_3CN in H_2O) provided the title compound (0.034 g, 0.093 mmol, 70%). ^{1}H NMR (600 MHz, $CDCl_3$ δ 8.71 (s, 1H), 7.85–7.80 (m, 2H), 7.65–7.61 (m, 1H), 7.57 (td, *J* = 8.0, 7.5, 2.1 Hz, 2H), 7.13–7.09 (m, 2H), 7.05 (dd, *J* = 8.5, 6.3 Hz, 1H), 6.74–6.70 (m, 2H), 4.34–4.29 (m, 2H), 4.23 (d, *J* = 14.8 Hz, 2H), 2.21–2.15 (m, 2H), 1.98–1.92 (m, 2H) ppm. ^{13}C NMR (150 MHz, DMSO-d_6) δ 142.50, 140.49, 132.99, 129.63, 128.29, 128.19, 126.50, 126.00, 74.13, 46.86, 40.97, 29.75 ppm. HRMS (ES$^-$) calculated for $C_{17}H_{19}NO_4S_2$ [M − H]$^-$ 364.0683, found 364.0685. IR (neat) ν 3235.00, 2919.23, 1449.08, 1342.17, 1302.06, 1243.77, 1161.36 cm^{-1}.

3-[(Dimethylsulfamoyl)amino]-3-(2-phenylethyl)-1lambda6-thietane-1,1-dione (26). Following the same procedure described for the synthesis of **18**, using of 3-amino-3-phenethylthietane 1,1-dioxide **46** (0.080 g, 0.355 mmol, 1.00 eq), Et_3N (0.108 g, 1.07 mmol, 3.00 eq) and dimethylsulfamoyl chloride (0.153 g, 1.07 mmol, 3.00 eq). Purification by reverse phase HPLC (10%–90% CH_3CN in H_2O) provided the title compound (0.018 g, 0.054 mmol, 15%). ^{1}H NMR (600 MHz, CDCl3) δ 7.31 (t, *J* = 7.6 Hz, 2H), 7.25–7.18 (m, 3H), 4.68 (s, 1H), 4.36–4.29 (m, 2H), 4.07–4.02 (m, 2H), 2.88 (s, 6H), 2.78 (dd, *J* = 6.8, 4.0 Hz, 2H), 2.46–2.40 (m, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.54, 129.02, 128.53, 126.87, 74.27, 48.00, 41.35, 38.06, 30.86 ppm. HRMS (ES$^+$) calculated for $C_{12}H_{17}NO_4S_2$ [M + Na]$^+$ 355.0747, found 355.0760. IR (neat) ν 3258.71, 1453.15, 1341.72, 1310.12, 1249.77, 1153.23 cm^{-1}.

***N*-(5-Phenylisoxazol-3-yl)methanesulfonamide (27).** To a solution of 5-phenylisoxazol-3-amine **48** (0.030 g, 0.190 mmol, 1.00 eq) in anh. CH_2Cl_2 (1.8 mL), Et_3N (0.038 g, 0.370 mmol, 2.00 eq) and methanesulfonyl chloride (0.026 g, 0.220 mmol, 1.20 eq) were added at 0 °C under N_2. The reaction mixture was slowly warmed to rt and stirred at this temperature overnight. After 16 h, solvent was removed in vacuo. Purification by silica gel column chromatography (up to 30% EtOAc in hexane) provided the desired product (0.025 g, 0.10 mmol, 56%). ^{1}H NMR (600 MHz, CD_3OD) δ 7.84 (dd, *J* = 7.7, 2.0 Hz, 2H), 7.55–7.49 (m, 3H), 6.74 (s, 1H), 3.21 (s, 3H) ppm. ^{13}C NMR (150 MHz, CD_3OD) δ 171.63, 159.90, 131.62, 130.08, 126.60, 93.83, 49.00, 40.70 ppm. HRMS (ES$^+$) calculated for $C_{10}H_{10}N_2O_3S$ [M + Na]$^+$ 261.0310, found 261.0305. IR (neat) ν 2919.22, 2850.47, 1623.00, 1578.33, 1470.58, 1332.46, 1152.41, 1042.94 cm^{-1}.

***N*-(5-Phenylisoxazol-3-yl)benzenesulfonamide (28).** Synthesis of **28** was previously described [61]. To a solution of 5-phenylisoxazol-3-amine **48** (0.030 g, 0.190 mmol, 1.00 eq) in anh. pyridine (1.8 mL), benzenesulfonyl chloride (0.043 g, 0.240 mmol, 1.30 eq) was added at 0 °C under N_2. The reaction mixture was slowly warmed to rt and stirred at this temperature overnight. The solvent was then removed in vacuo. Purification by silica gel column chromatography (up to 30% EtOAc in hexane) provided the desired product (0.042 g, 0.140 mmol, 75%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.5, 2.3 Hz, 2H), 7.76 (dd, *J* = 6.7, 3.2 Hz, 2H), 7.62–7.56 (m, 1H), 7.52–7.45 (m, 5H), 6.80 (s, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.25, 157.96, 139.01, 133.83, 130.96, 129.55, 129.20, 127.19, 126.98, 125.99, 93.27 ppm. HRMS (ES$^+$) calculated for $C_{15}H_{12}N_2O_3S$ [M + H]$^+$ 301.0639, found 301.0639. IR (neat) ν 2963.47, 1616.6, 1578.49, 1470.68, 1398.46, 1317.67, 1165.18, 1082.67 cm^{-1}.

***N*-(5-Phenylisoxazol-3-yl)-*N,N*-dimethylaminesulfonamide (29).** Following the same procedure described for the synthesis of **28**, using 5-phenylisoxazol-3-amine **48** (0.030 g, 0.190 mmol, 1.00 eq) and dimethylsulfamoyl chloride (0.035 g, 0.240 mmol, 1.30 eq). Purification by reverse phase HPLC (10%–90% CH_3CN in H_2O) provided the desired product (0.009 g, 0.034 mmol, 18%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.77 (dd, *J* = 6.6, 3.3 Hz, 2H), 7.52–7.45 (m, 3H), 6.73 (d, *J* = 3.3 Hz, 1H), 2.93 (s, 6H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.88, 159.01, 130.89, 129.18, 127.05, 125.97, 93.24, 38.48 ppm. HRMS (ES$^+$) calculated for $C_{11}H_{13}N_3O_3S$ [M + H]$^+$ 268.0750, found 268.0753. IR (neat) ν 2918.50, 1621.68, 1596.55, 1577.84, 1470.33, 1417.05, 1399.21, 1355.58, 1166.61, 1035.13 cm^{-1}.

***N*-(1-Phenyl-1H-1,2,3-triazol-4-yl)methanesulfonamide (30).** Following the same procedure described for the synthesis of **18**, 1-phenyl-1*H*-1,2,3-triazol-4-amine (0.030 g, 0.190 mmol, 1.00 eq), methanesulfonyl chloride (0.024 g, 0.210 mmol, 1.10 eq), and Et_3N (0.021 g, 0.210 mmol, 1.10 eq). Purification by silica gel column chromatography (up to 30% EtOAc in hexane) provided the desired product (0.012 g, 0.050 mmol, 27%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, *J* = 2.4 Hz, 1H), 7.77–7.73 (m, 2H), 7.56 (td, *J* = 7.8, 2.2 Hz, 2H), 7.48 (dd, *J* = 8.6, 6.4 Hz, 1H), 6.74 (s, 1H), 3.12 (s, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.83, 136.91, 130.04, 129.46, 120.54, 114.88, 40.30 ppm. HRMS (ES$^+$) calculated for $C_9H_{11}N_4O_2S$ [M + H]$^+$ 239.0597, found 239.0599. IR (neat) ν 2919.65, 1597.66, 1573.98, 1498.02, 1411.81, 1345.55, 1330.76, 1215.67, 1153.87, 1053.08 cm^{-1}.

***N*-(1-Phenyl-1H-1,2,3-triazol-4-yl)benzenesulfonamide (31).** Following the same procedure described for the synthesis of **18**, using 1-phenyl-1H-1,2,3-triazol-4-amine (0.030 g, 0.190 mmol, 1.00 eq), benzenesulfonyl chloride (0.033 g, 0.19 mmol, 1.00 eq), and Et_3N (0.019 g, 0.190 mmol, 1.00 eq). Purification by reverse phase HPLC (10%–90% CH_3CN in H_2O) provided the desired compound (0.012 g, 0.040 mmol, 21%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (d, *J* = 2.4 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 2H), 7.73 (dd, *J* = 6.3, 4.3 Hz, 2H), 7.57–7.51 (m, 3H), 7.49–7.44 (m, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.19, 139.07, 136.95, 133.57, 130.00, 129.40, 129.32, 127.21, 120.43, 113.40 ppm. HRMS (ES$^+$) calculated for $C_{12}H_{13}N_4O_2S$ [M + H]$^+$ 301.0754, found 301.0755. IR (neat) ν 2922.24, 1567.23, 1492.90, 1449.21, 1414.92, 1353.95, 1333.27, 1164.36, 1093.35, 1053.00 cm^{-1}.

***N*-(1-Phenyl-1H-1,2,3-triazol-4-yl)-*N,N*-dimethylaminesulfonamide (32).** Following the same procedure described for the synthesis of **15**, using 1-phenyl-1*H*-1,2,3-triazol-4-amine (0.030 g, 0.190 mmol, 1.00 eq), dimethylsulfamoyl chloride (0.027 g, 0.19 mmol, 1.00 eq), and Et_3N (0.019 g, 0.190 mmol, 1.00 eq). Purification by reverse phase HPLC (10%–90% CH_3CN in H_2O) provided the desired compound (0.013 g, 0.049 mmol, 26%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.77–7.72 (m, 2H), 7.54 (dd, *J* = 8.8, 7.3 Hz, 2H), 7.48–7.45 (m, 1H), 2.89 (s, 6H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.99, 137.02, 129.99, 129.28, 120.46, 113.65, 38.60 ppm. HRMS (ES$^+$) calculated for $C_{10}H_{14}N_5O_2S$ [M + H]$^+$ 268.0863, found 268.0864. IR (neat) ν 2917.46, 1597.33, 1576.48, 1494.69, 1426.58, 1364.30, 1232.86, 1164.11, 1148.06 cm^{-1}.

(*S*)-2-Methyl-*N*-(oxetan-3-ylidene)propane-2-sulfinamide (36). Synthesis of **36** closely followed previously described procedures.[42, 43] ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 5.80 (ddd, *J* = 15.4, 4.5, 2.1 Hz, 1H), 5.67 (ddd, *J* = 15.4, 4.4, 2.0 Hz, 1H), 5.53–5.41 (m, 2H), 1.27 (s, 9H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.98, 85.45, 85.34, 57.40, 21.77 ppm. HRMS (ES$^+$) calculated for $C_7H_{14}NO_2S$ [M + H]$^+$ 176.0740, found 176.0741. IR (neat) ν 2961.88, 2926.46, 1696.95, 1626.13, 1456.15, 1362.66, 1264.92, 1131.77, 1079.36 cm^{-1}.

(*S*)-2-Methyl-*N*-(thietan-3-ylidene)propane-2-sulfinamide (37). Synthesis of **37** closely followed previously described procedures [42,43], using 3-thietanone (5.00 g, 56.7 mmol, 1.00 eq), (*S*)-(−)-2-methylpropane-2-sulfinamide (8.25 g, 68.1 mmol, 1.20 eq), and titanium (IV) *iso*propoxide (32.3 g, 113 mmol, 2.00 eq). Purification by silica gel column chromatography (up to 10% of EtOAc in hexane) provided the title compound as a light brown liquid (8.40 g, 44.0 mmol, 77%). ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 4.74 (dd, *J* = 17.2, 4.5 Hz, 1H), 4.50 (dd, *J* = 17.1, 4.2 Hz, 1H), 4.24 (dd, *J* = 16.1, 4.5 Hz, 1H), 4.14 (dd, *J* = 15.9, 4.3 Hz, 1H), 1.20 (s, 9H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.05, 57.87, 46.48, 45.10, 22.39 ppm. HRMS (ES$^+$) calculated for $C_7H_{14}NOS_2$ [M + H]$^+$ 192.0511, found 192.0513. IR (neat) ν 2959.04, 2944.88, 2869.80, 1784.77, 1657.29, 1456.15, 1395.24, 1362.66, 1264.92, 1164.35, 1077.95 cm^{-1}.

***(S)*-1-(*tert*-Butylsulfinyl)-5-oxa-1-azaspiro[2.3]hexane (38).** Synthesis of **38** closely followed previously described procedure.[43] ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.04 (d, *J* = 7.9 Hz, 1H), 5.00−4.88 (m, 1H), 4.82 (d, *J* = 7.9 Hz, 1H), 4.78 (d, *J* = 7.2 Hz, 1H), 2.67 (s, 1H), 1.98 (s, 1H), 1.22 (s, 9H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 78.35, 75.66, 56.94, 40.92, 22.51 ppm. HRMS (ES^+) calculated for $C_8H_{16}NO_2S$ $[M + H]^+$ 190.0896, found 190.0897. IR (neat) ν 2954.79, 2872.64, 1456.15, 1393.82, 1362.66, 1301.72, 1150.19, 1066.62 cm^{-1}.

***(S)*-1-(*tert*-Butylsulfinyl)-5-thia-1-azaspiro[2.3]hexane (39).** Synthesis of **39** closely followed previously described procedure [43], using of NaH (1.84 g, 46.0 mmol, 1.10 eq), trimethylsulfoxonium iodide (10.1 g, 46.0 mmol, 1.10 eq), and (*S*)-2-methyl-*N*-(thietan-3-ylidene)propane-2-sulfinamide **37** (8.00 g, 41.8 mmol, 1.00 eq). Purification by silica gel column chromatography (up to 10% of EtOAc in hexane) provided the title compound (3.35 g, 16.3 mmol, 39%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.98 (d, *J* = 10.1 Hz, 1H), 3.80 (d, *J* = 9.7 Hz, 1H), 3.23 (d, *J* = 10.1 Hz, 1H), 3.17 (d, *J* = 9.7 Hz, 1H), 2.71 (s, 1H), 2.03 (s, 1H), 1.21 (s, 9H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 57.17, 42.89, 36.33, 33.72, 22.65 ppm. HRMS (ES^+) calculated for $C_8H_{16}NOS_2$ $[M + H]^+$ 206.0668, found 206.0668. IR (neat) ν 2853.38, 2927.88, 1514.22, 1454.73, 1357.00, 1263.51, 1170.03, 1124.69, 1055.28 cm^{-1}.

***(S)*-2-Methyl-*N*-(3-phenethyloxetan-3-yl)propane-2-sulfinamide (40).** To a solution of copper (I) iodide (0.101 g, 0.528 mmol, 0.10 eq) in anh. THF (35 mL), benzylmagnesium chloride (11.0 mL, 1.40 M solution in THF-Me, 15.9 mmol, 3.00 eq) was added at rt under N_2. The mixture was cooled to −30 °C using an CH_3CN/dry ice bath. 1-(*tert*-Butylsulfinyl)-5-oxa-1-azaspiro[2.3] hexane **38** (1.00 g, 5.28 mmol, 1.00 eq) in anh. THF (5.0 mL) was added dropwise at −30 °C. The reaction was stirred at this temperature for 10 min, after which it was warmed to 0 °C and stirred for 1 h. Satd. aq. NaCl was added and the reaction was warmed to rt. The resulting crude was extracted with EtOAc (× 3), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (up to 50% EtOAc in hexane) provided the title compound (1.34 g, 4.75 mmol, 90%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.6 Hz, 2H), 7.20 (dd, *J* = 8.1, 5.9 Hz, 3H), 4.74 (d, *J* = 6.8 Hz, 1H), 4.69 (d, *J* = 7.0 Hz, 1H), 4.51 (d, *J* = 6.8 Hz, 1H), 4.47 (d, *J* = 6.6 Hz, 1H), 3.72 (s, 1H), 2.68 (t, *J* = 8.1 Hz, 2H), 2.45−2.30 (m, 2H), 1.25 (d, *J* = 2.2 Hz, 9H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.04, 128.76, 128.49, 126.38, 82.52, 82.33, 59.99, 56.11, 38.96, 29.91, 22.63 ppm. HRMS (ES^+) calculated for $C_{15}H_{24}NO_2S$ $[M + H]^+$ 282.1522, found 282.1520. IR (neat) ν 3413.74, 3138.94, 2959.96, 2875.47, 1492.98, 1356.15, 1368.33, 1338.58, 1263.51, 1164.35, 1114.14, 1083.61, 1004.29 cm^{-1}.

***(S)*-2-Methyl-*N*-(3-phenethylthietan-3-yl)propane-2-sulfinamide (41).** Following the same procedure described for the synthesis of **40** using 1-(*tert*-butylsulfinyl)-5-thia-1-azaspiro[2.3] hexane **39** (1.00 g, 4.87 mmol, 1.00 eq), benzylmagnesium chloride (14.6 mL, 1.0 M solution in THF-Me, 15.9 mmol, 3.00 eq), and copper (I) iodide (0.093 g, 0.487 mmol, 0.10 eq). Purification by silica gel column chromatography (up to 25% EtOAc in hexane) provided the title compound (0.696 g, 2.34 mmol, 48%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33−7.29 (m, 2H), 7.24−7.19 (m, 3H), 3.67 (s, 1H), 3.60 (d, *J* = 9.7 Hz, 1H), 3.54 (d, *J* = 10.1 Hz, 1H), 3.19 (dd, *J* = 9.9, 1.5 Hz, 1H), 3.13 (dd, *J* = 9.8, 1.4 Hz, 1H), 2.68 (ddd, *J* = 9.0, 6.5, 1.9 Hz, 2H), 2.49−2.43 (m, 1H), 2.42−2.35 (m, 1H), 1.24 (s, 9H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.26, 128.75, 128.52, 126.31, 63.68, 56.19, 40.82, 39.25, 29.50, 22.66 ppm. HRMS (ES^+) calculated for $C_{15}H_{24}NOS_2$ $[M + H]^+$ 298.1294, found 298.1296. IR (neat) ν 3199.85, 2943.46, 1495.81, 1453.32, 1362.66, 1263.51, 1218.18, 1162.94, 1051.03 cm^{-1}.

3-Phenethylthietan-3-amine (43). To a solution of (*S*)-2-methyl-*N*-(3-phenethylthietan-3-yl)propane-2-sulfinamide **41** (0.670 g, 2.25 mmol, 1.00 eq) in anh. CH_3OH (11.0 mL), a solution of HCl (9.01 mL, 1.25 M solution in CH_3OH, 2.67 mmol, 5.00 eq) was added dropwise at 0 °C under N_2. The mixture was stirred at rt overnight. The mixture was concentrated in vacuo, and the resulting salt was dissolved in minimal H_2O and the pH of the solution was brought to 9. The mixture was then extracted with EtOAc (× 3), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (up to 20% EtOAc in hexane) provided the title compound (0.270 g, 1.40 mmol, 62%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.7 Hz, 2H), 7.25−7.17 (m, 3H), 3.23−3.10 (m, 4H), 2.74−2.66 (m, 2H), 2.15−2.08 (m, 2H), 1.98 (d, *J* = 14.3 Hz, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.85, 128.64, 128.49, 60.55, 42.45, 41.50, 29.89 ppm. HRMS (ES^+) calculated for $C_{11}H_{15}NS$ $[M + H]^+$ 194.0998, found 194.1002. IR (neat) ν 3349.61, 2972.83, 2924.02, 2843.43, 1602.51, 1490.12, 1448.10 cm^{-1}.

***trans*-3-Amino-3-phenethylthietane 1-oxide (44) and *cis*-3-amino-3-phenethylthietane 1-oxide (45).** To a solution of 3-phenethylthietan-3-amine **43** (0.100 g, 0.517 mmol, 1.00 eq) in anh. CH_2Cl_2 (2.5 mL), a solution of *m*-CPBA (0.136 g, 0.569 mmol, 1.10 eq) in anh. CH_2Cl_2 (1.5 mL) was added dropwise at −78 °C under N_2. The reaction was stirred at this temperature for 2 h, and then the reaction was quenched with H_2O and satd. $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (× 3) and washed with brine. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (up to 30% of EtOAc in hexane) led to the separation of product **44** (0.011 g, 0.053 mmol, 10%) and product **45** (0.076 g, 0.360 mmol, 70%). *trans*-3-Amino-3-phenethylthietane 1-oxide (**44**): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.7 Hz, 2H), 7.20 (dd, *J* = 26.5, 7.5 Hz, 3H), 3.47 (dd, *J* = 8.8, 3.1 Hz, 2H), 3.03 (dd, *J* = 8.8, 3.1 Hz, 2H), 2.71−2.61 (m, 2H), 2.03−1.93 (m, 2H), 1.25 (s, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.52, 128.83, 128.40, 63.91, 51.44, 47.21, 29.86 ppm. HRMS (ES^+) calculated for $C_{11}H_{15}NOS$ $[M + Na]^+$ 232.0767, found 232.0768. IR (neat) ν 3362.74, 2923.99, 1602.64, 1373.96, 1224.97, 1051.38, 1033.11 cm-1 *cis*-3-Amino-3-phenethylthietane 1-oxide (**45**). ^{1}H NMR (600 MHz, $CDCl_3$) δ 77.30 (t, *J* = 7.6 Hz, 2H), 7.24−7.12 (m, 3H), 3.92−3.79 (m, 2H), 3.21−3.02 (m, 2H), 2.75−2.58 (m, 2H), 1.87 (s, 2H), 1.83−1.72 (m, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.74, 128.78, 128.34, 65.78, 48.82, 43.89, 30.03 ppm. HRMS (ES^+) calculated for $C_{11}H_{15}NOS$ $[M + Na]^+$ 232.0767, found 232.0767. IR (neat) ν 3372.63, 2913.66, 1602.52, 1492.51, 1453.07, 1044.94, 1028.83, 1018.41 cm^{-1}.

3-Amino-3-phenethylthietane 1,1-dioxide (46). To a solution of 3-phenethylthietan-3-amine **43** (0.100 g, 0.517 mmol, 1.00 eq) in acetone (2.5 mL), a solution of Oxone® (0.477 g, 1.55 mmol, 3.00 eq) in H_2O (2.5 mL) was added dropwise at 0 °C. The mixture was stirred at this temperature for 10 min, then warmed to rt and stirred overnight. The reaction mixture was then cooled to 0 °C and a solution of Na_2SO_3 (1.0 M, 5.0 mL) was added. The resulting mixture was extracted with EtOAc (× 3) and washed with brine. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (up to 25% of EtOAc in hexane) provided the title compound (0.055 g, 0.240 mmol, 47%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.6 Hz, 2H), 7.25−7.17 (m, 3H), 4.09−4.03 (m, 2H), 3.85−3.80 (m, 2H), 2.75 (dd, *J* = 9.6, 6.6 Hz, 2H), 2.19−2.11 (m, 2H), 1.80 (s, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.17, 128.90, 128.46, 76.55, 44.58, 43.71, 31.18, 24.25, 24.05 ppm. HRMS (ES^+) calculated for $C_{11}H_{16}NO_2S$ $[M + H]^+$ 226.0896, found 226.0897. IR (neat) ν 3385.41, 3313.17, 3017.12, 2920.80, 2852.81, 1494.39, 1389.57, 1303.17, 1229.51, 1179.94, 1041.69, 1077.95 cm^{-1}.

5-Phenylisoxazol-3-amine (48). Synthesis of **48** closely followed previously described procedures [46,62]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.7 Hz, 2H), 7.43 (dt, *J* = 8.8, 6.4 Hz, 3H), 6.09 (s, 1H), 3.99 (s, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.64, 163.84, 130.17, 128.96, 127.77, 125.76, 92.04 ppm. HRMS (ES^+) calculated for $C_6H_9N_2O$ $[M + H]^+$ 161.0709, found 161.0710. IR (neat) ν 3444.90, 3324.50, 1621.88, 1517.06, 1488.73, 1342.83, 1264.92, 1051.03 cm^{-1}.

Stability Studies. Stock solutions (5 mM) were prepared in DMSO. From the stock solution, test compounds solutions (100 μM final concentration) were prepared and stirred in BICCA® Simulated intestinal fluid (without pancreatin, pH 7.40−7.60) at rt. Percentages of compound left after 5 h of incubation were determined by assessing relative change in peak area of the analytical LC/MS chromatograms. LC/MS conditions employed gradients of CH_3CN in H_2O (from 10% to 90% CH_3CN) over 4 min and flow rate of 2 mL/min.

Determination of Physicochemical Properties. Determinations of pK_a values were obtained via automated potentiometric titrations using a Sirius T3 instrument (Pion, Inc) according to manufacturer instructions. Three or more titrations were performed from pH 1.8 to pH 12.2 using ionic strength adjusted water (0.15 M KCl), acid (0.5 M HCl) and base (0.5 M KOH). For compounds with relatively low aqueous solubility (**16** and **25**), the pK_a determinations were conducted using a cosolvent (methanol) protocol; Yasuda-Shedlovsky extrapolation method was used to extrapolate the pK_a at 0% cosolvent. LogP measurements of compounds with known experimental pK_a were obtained via potentiometric titrations using a Sirius T3 instrument (Pion, Inc). $LogD_{7.4}$ values were extrapolated from the measured logP. $LogD_{7.4}$ of selected compounds with pK_a values > 10 (*i.e.*, **14**, **16** − **20**, **22**, **23**, **25**) were measured via shake-flask method (experiments carried out by Analiza, Inc). Effective permeability values ($logP_{app}$) were measured by Parallel Artificial Membrane Permeability Assay (PAMPA) using the Corning Gentest™ pre-coated PAMPA plate system with quantitation by HPLC-UV (experiments carried out by Analiza, Inc).

Computational Studies. All molecular modelling experiments were performed on Asus WS X299 PRO Intel® i9-10980XE CPU @ 3.00 GHz × 36 running Ubuntu 18.04. Molecular Operating Environment (MOE) [63], Gaussian 09 [64] and Multiwfn [65] were used as molecular modelling software. The molecular structures were initially prepared by MOE QuikPrep tool generating possible ionization states at pH 7 ± 2, followed by a molecular superposition using the Refined flexible alignment. Successively, all the geometries were optimized in the vacuum-phase using B3LYP/6−311++G(d,p) Pople basis set of density functional theory (DFT) by Gaussian 09 software. Quantitative calculation of the electrostatic potential (ESP) distribution of the molecule was performed using a constant electronic density of 0.002 au. The ESP surface minima and maxima values were generated by Multiwfn using the same optimized structures at which the final electron densities and electrostatic potentials were calculated.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmech.2021.113399.

List of Nonstandard Abbreviations

m-CPBA	*meta*-chloroperbenzoic acid
TMSOI	trimethylsulfoxonium iodide;
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.

References

[1] G. Iain, R.S. Obach, A.S. Dennis, M. Zhuang, A.A. Alexander, B. Kevin, K. Amit, W. Don, D. Deepak, P. Chandra, V. Alf, Metabolism, Pharmacokinetics and Toxicity of Functional Groups: Impact of Chemical Building Blocks on ADMET, RSC, 2010, pp. P001−P530.

[2] S.R. Borhade, R. Svensson, P. Brandt, P. Artursson, P.I. Arvidsson, A. Sandström, Preclinical characterization of acyl sulfonimidamides: potential carboxylic acid bioisosteres with tunable properties, ChemMedChem 10 (2015) 455−460.

[3] T. Pinter, S. Jana, R.J.M. Courtemanche, F. Hof, Recognition properties of carboxylic acid bioisosteres: anion binding by tetrazoles, aryl sulfonamides, and acyl sulfonamides on a calix[4]arene scaffold, J. Org. Chem. 76 (2011) 3733−3741.

[4] D.E. Uehling, K.H. Donaldson, D.N. Deaton, C.E. Hyman, E.E. Sugg, D.G. Barrett, R.G. Hughes, B. Reitter, K.K. Adkison, M.E. Lancaster, F. Lee, R. Hart, M.A. Paulik, B.W. Sherman, T. True, C. Cowan, Synthesis and evaluation of potent and selective β3 adrenergic receptor agonists containing acylsulfonamide, sulfonylsulfonamide, and sulfonylurea carboxylic acid isosteres, J. Med. Chem. 45 (2002) 567−583.

[5] M.P. Winters, C. Crysler, N. Subasinghe, D. Ryan, L. Leong, S. Zhao, R. Donatelli, E. Yurkow, M. Mazzulla, L. Boczon, C.L. Manthey, C. Molloy, H. Raymond, L. Murray, L. McAlonan, B. Tomczuk, Carboxylic acid bioisosteres acylsulfonamides, acylsulfamides, and sulfonylureas as novel antagonists of the CXCR2 receptor, Bioorg. Med. Chem. 18 (2008) 1926−1930.

[6] N.F. Pelz, Z. Bian, B. Zhao, S. Shaw, J.C. Tarr, J. Belmar, C. Gregg, D.V. Camper, C.M. Goodwin, A.L. Arnold, J.L. Sensintaffar, A. Friberg, O.W. Rossanese, T. Lee, E.T. Olejniczak, S.W. Fesik, Discovery of 2-Indole-acylsulfonamide myeloid cell leukemia 1 (Mcl-1) inhibitors using fragment-based methods, J. Med. Chem. 59 (2016) 2054−2066.

[7] Y.K. Yee, P.R. Bernstein, E.J. Adams, F.J. Brown, L.A. Cronk, K.C. Hebbel, E.P. Vacek, R.D. Krell, D.W. Snyder, A novel series of selective leukotriene antagonists: exploration and optimization of the acidic region in 1,6-disubstituted indoles and indazoles, J. Med. Chem. 33 (1990) 2437−2451.

[8] V.J. Winton, C. Aldrich, L.L. Kiessling, Carboxylate surrogates enhance the antimycobacterial activity of UDP-galactopyranose mutase probes, ACS Infect. Dis. 2 (2016) 538−543.

[9] P.M. Scola, A.X. Wang, A.C. Good, L.-Q. Sun, K.D. Combrink, J.A. Campbell, J. Chen, Y. Tu, N. Sin, B.L. Venables, S.-Y. Sit, Y. Chen, A. Cocuzza, D.M. Bilder, S. D'Andrea, B. Zheng, P. Hewawasam, M. Ding, J. Thuring, J. Li, D. Hernandez, F. Yu, P. Falk, G. Zhai, A.K. Sheaffer, C. Chen, M.S. Lee, D. Barry, J.O. Knipe, W. Li, Y.-H. Han, S. Jenkins, C. Gesenberg, Q. Gao, M.W. Sinz, K.S. Santone, T. Zvyaga, R. Rajamani, H.E. Klei, R.J. Colonno, D.M. Grasela, E. Hughes, C. Chien, S. Adams, P.C. Levesque, D. Li, J. Zhu, N.A. Meanwell, F. McPhee, Discovery and early clinical evaluation of BMS-605339, a potent and orally efficacious tripeptidic acylsulfonamide NS3 protease inhibitor for the treatment of hepatitis C virus infection, J. Med. Chem. 57 (2014) 1708−1729.

[10] K. Rikimaru, T. Wakabayashi, H. Abe, H. Imoto, T. Maekawa, O. Ujikawa, K. Murase, T. Matsuo, M. Matsumoto, C. Nomura, H. Tsuge, C.D. Mol, G.P. Snell, K.A. Bragstad, B.-C. Sang, D.R. Dougan, T. Tanaka, N. Katayama, Y. Horiguchi, Y. Momose, A new class of non-thiazolidinedione, non-carboxylic-acid-based highly selective peroxisome proliferator-activated receptor (PPAR) γ agonists: design and synthesis of benzylpyrazole acylsulfonamides, Bioorg. Med. Chem. 20 (2012) 714−733.

[11] A. Ammazzalorso, B. De Filippis, L. Giampietro, R. Amoroso, N-acylsulfonamides: Synthetic routes and biological potential in medicinal chemistry, Chem. Biol. Drug Des. 90 (2017) 1094−1105.

[12] T. Pilot-Matias, R. Tripathi, D. Cohen, I. Gaultier, T. Dekhtyar, L. Lu, T. Reisch, M. Irvin, T. Hopkins, R. Pithawalla, T. Middleton, T. Ng, K. McDaniel, Y.S. Or, R. Menon, D. Kempf, A. Molla, C. Collins, In vitro and in vivo antiviral activity and resistance profile of the hepatitis C virus NS3/4A protease inhibitor ABT-450, Antimicrob. Agents Chemother. 59 (2015) 988−997.

[13] D.E. Ehmann, J.E. Demeritt, K.G. Hull, S.L. Fisher, Biochemical characterization of an inhibitor of Escherichia coli UDP-N-acetylmuramyl-l-alanine ligase, Biochim. Biophys. Acta 1698 (2004) 167−173.

[14] V. Patil, M. Kale, A. Raichurkar, B. Bhaskar, D. Prahlad, M. Balganesh, S. Nandan, P. Shahul Hameed, Design and synthesis of triazolopyrimidine acylsulfonamides as novel anti-mycobacterial leads acting through inhibition of acetohydroxyacid synthase, Bioorg. Med. Chem. Lett 24 (2014) 2222−2225.

[15] T. Meier, M. Uhlik, S. Chintharlapalli, M. Dowless, R. Van Horn, J. Stewart, W. Blosser, J. Cook, D. Young, X. Ye, G. Evans, K. Credille, D. Ballard, L. Huber, A. Capen, M. Chedid, R. Ilaria, M.C. Smith, L. Stancato, Tasisulam sodium, an antitumor agent that inhibits mitotic progression and induces vascular normalization, Mol. Canc. Therapeut. 10 (2011) 2168−2178.

[16] T. Oltersdorf, S.W. Elmore, A.R. Shoemaker, R.C. Armstrong, D.J. Augeri, B.A. Belli, M. Bruncko, T.L. Deckwerth, J. Dinges, P.J. Hajduk, M.K. Joseph,

S. Kitada, S.J. Korsmeyer, A.R. Kunzer, A. Letai, C. Li, M.J. Mitten, D.G. Nettesheim, S. Ng, P.M. Nimmer, J.M. O'Connor, A. Oleksijew, A.M. Petros, J.C. Reed, W. Shen, S.K. Tahir, C.B. Thompson, K.J. Tomaselli, B. Wang, M.D. Wendt, H. Zhang, S.W. Fesik, S.H. Rosenberg, An inhibitor of Bcl-2 family proteins induces regression of solid tumours, Nature 435 (2005) 677−681.

[17] A.J. Souers, J.D. Leverson, E.R. Boghaert, S.L. Ackler, N.D. Catron, J. Chen, B.D. Dayton, H. Ding, S.H. Enschede, W.J. Fairbrother, D.C.S. Huang, S.G. Hymowitz, S. Jin, S.L. Khaw, P.J. Kovar, L.T. Au - Lam, J. Au - Lee, H.L. Au - Maecker, K.C. Au - Marsh, K.D. Au - Mason, M.J. Au - Mitten, P.M. Au - Nimmer, A. Au - Oleksijew, C.H. Au - Park, C.-M. Au - Park, D.C. Au - Phillips, A.W. Au - Roberts, D. Au - Sampath, J.F. Au - Seymour, M.L. Au - Smith, G.M. Au - Sullivan, S.K. Au - Tahir, C. Au - Tse, M.D. Au - Wendt, Y. Au - Xiao, J.C. Au - Xue, H. Au - Zhang, R.A. Au - Humerickhouse, S.H. Au - Rosenberg, S.W. Au - Elmore, ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets, Nat. Med. 19 (2013) 202−213.

[18] United States Food and Drug Administration. http://www.fda.gov accessed on 12/22/2020.

[19] N.A. Meanwell, Fluorine and fluorinated motifs in the design and application of bioisosteres for drug design, J. Med. Chem. 61 (2018) 5822−5880.

[20] N. Meanwell, Synopsis of some recent tactical application of bioisosteres in drug design, J. Med. Chem. 54 (2011) 2529−2591.

[21] N. Brown, Bioisosteres in Medicinal Chemistry, vol. 54, Wiley, 2012. Wiley-VCH.

[22] E. Bonandi, M.S. Christodoulou, G. Fumagalli, D. Perdicchia, G. Rastelli, D. Passarella, The 1,2,3-triazole ring as a bioisostere in medicinal chemistry, Drug Discov. Today 22 (2017) 1572−1581.

[23] A. Giraudo, J. Krall, B. Nielsen, T.E. Sørensen, K.T. Kongstad, B. Rolando, D. Boschi, B. Frølund, M.L. Lolli, 4-Hydroxy-1,2,3-triazole moiety as bioisostere of the carboxylic acid function: a novel scaffold to probe the orthosteric γ-aminobutyric acid receptor binding site, Eur. J. Med. Chem. 158 (2018) 311−321.

[24] S. Sainas, P. Temperini, J.C. Farnsworth, F. Yi, S. Møllerud, A.A. Jensen, B. Nielsen, A. Passoni, J.S. Kastrup, K.B. Hansen, D. Boschi, D.S. Pickering, R.P. Clausen, M.L. Lolli, Use of the 4-hydroxytriazole moiety as a bioisosteric tool in the development of ionotropic glutamate receptor ligands, J. Med. Chem. 62 (2019) 4467−4482.

[25] I. Mohammed, I.R. Kummetha, G. Singh, N. Sharova, G. Lichinchi, J. Dang, M. Stevenson, T.M. Rana, 1,2,3-Triazoles as amide bioisosteres: discovery of a new class of potent HIV-1 vif antagonists, J. Med. Chem. 59 (2016) 7677−7682.

[26] P. Lassalas, K. Oukoloff, V. Makani, M. James, V. Tran, Y. Yao, L. Huang, K. Vijayendran, L. Monti, J.Q. Trojanowski, V.M.Y. Lee, M.C. Kozlowski, A.B. Smith, K.R. Brunden, C. Ballatore, Evaluation of oxetan-3-ol, thietan-3-ol, and derivatives thereof as bioisosteres of the carboxylic acid functional group, ACS Med. Chem. Lett. 8 (2017) 864−868.

[27] N.H. Powell, G.J. Clarkson, R. Notman, P. Raubo, N.G. Martin, M. Shipman, Synthesis and structure of oxetane containing tripeptide motifs, Chem. Commun. 50 (2014) 8797−8800.

[28] J.D. Beadle, A. Knuhtsen, A. Hoose, P. Raubo, A.G. Jamieson, M. Shipman, Solid-phase synthesis of oxetane modified peptides, Org. Lett. 19 (2017) 3303−3306.

[29] G.P. Möller, S. Müller, B.T. Wolfstädter, S. Wolfrum, D. Schepmann, B. Wünsch, E.M. Carreira, Oxetanyl amino acids for peptidomimetics, Org. Lett. 19 (2017) 2510−2513.

[30] M. McLaughlin, R. Yazaki, T.C. Fessard, E.M. Carreira, Oxetanyl peptides: novel peptidomimetic modules for medicinal chemistry, Org. Lett. 16 (2014) 4070−4073.

[31] S. Kumari, A.V. Carmona, A.K. Tiwari, P.C. Trippier, Amide bond bioisosteres: strategies, synthesis, and successes, J. Med. Chem. 63 (2020) 12290−12358.

[32] J.G. Varnes, T. Gero, S. Huang, R.B. Diebold, C. Ogoe, P.T. Grover, M. Su, P. Mukherjee, J.C. Saeh, T. Macintyre, G. Repik, K. Dillman, K. Byth, D.J. Russell, S. Ioannidis, Towards the next generation of dual Bcl-2/Bcl-xL inhibitors, Bioorg. Med. Chem. Lett 24 (2014) 3026−3033.

[33] C.-C. Yang, S.-C. Wi, N. Zhong, M.-Y. Lin, C.-C. Tu, Benzenesulfonamide Derivatives and Method for Treating Cancer, 2018. U. S. Patent US20180311190A1.

[34] B.B. Touré, K. Miller-Moslin, N. Yusuff, L. Perez, M. Doré, C. Joud, W. Michael, L. DiPietro, S. van der Plas, M. McEwan, F. Lenoir, M. Hoe, R. Karki, C. Springer, J. Sullivan, K. Levine, C. Fiorilla, X. Xie, R. Kulathila, K. Herlihy, D. Porter, M. Visser, The role of the acidity of N-heteroaryl sulfonamides as inhibitors of Bcl-2 family protein−protein interactions, ACS Med. Chem. Lett. 4 (2013) 186−190.

[35] S.G.S. Kandanur, S. Nanduri, N.R. Golakoti, Synthesis and biological evaluation of new C-12(α/β)-(N-) sulfamoyl-phenylamino-14-deoxy-andrographolide derivatives as potent anti-cancer agents, Bioorg. Med. Chem. Lett 27 (2017) 2854−2862.

[36] T. Focken, S. Chowdhury, A. Zenova, M.E. Grimwood, C. Chabot, T. Sheng, I. Hemeon, S.M. Decker, M. Wilson, P. Bichler, Q. Jia, S. Sun, C. Young, S. Lin, S.J. Goodchild, N.G. Shuart, E. Chang, Z. Xie, B. Li, K. Khakh, G. Bankar, M. Waldbrook, R. Kwan, K. Nelkenbrecher, P. Karimi Tari, N. Chahal, L. Sojo, C.L. Robinette, A.D. White, C.-A. Chen, Y. Zhang, J. Pang, J.H. Chang, D.H. Hackos, J.P. Johnson, C.J. Cohen, D.F. Ortwine, D.P. Sutherlin, C.M. Dehnhardt, B.S. Safina, Design of conformationally constrained acyl sulfonamide isosteres: identification of N-([1,2,4]Triazolo[4,3-a]pyridin-3-yl) methane-sulfonamides as potent and selective hNaV1.7 inhibitors for the treatment of pain, J. Med. Chem. 61 (2018) 4810−4831.

[37] J.-G. Boiteau, G. Ouvry, J.-M. Arlabosse, S. Astri, A. Beillard, Y. Bhurruth-Alcor, L. Bonnary, C. Bouix-Peter, K. Bouquet, M. Bourotte, I. Cardinaud, C. Comino, B. Deprez, D. Duvert, A. Féret, F. Hacini-Rachinel, C.S. Harris, A.-P. Luzy, A. Mathieu, C. Millois, N. Orsini, J. Pascau, A. Pinto, D. Piwnica, G. Polge, A. Reitz, K. Reversé, N. Rodeville, P. Rossio, D. Spiesse, S. Tabet, N. Taquet, L. Tomas, E. Vial, L.F. Hennequin, Discovery and process development of a novel TACE inhibitor for the topical treatment of psoriasis, Bioorg. Med. Chem. 26 (2018) 945−956.

[38] K. Vandyck, G. Rombouts, B. Stoops, A. Tahri, A. Vos, W. Verschueren, Y. Wu, J. Yang, F. Hou, B. Huang, K. Vergauwen, P. Dehertogh, J.M. Berke, P. Raboisson, Synthesis and evaluation of N-Phenyl-3-sulfamoyl-benzamide derivatives as capsid assembly modulators inhibiting hepatitis B virus (HBV), J. Med. Chem. 61 (2018) 6247−6260.

[39] J. Velcicky, C.J.N. Mathison, V. Nikulin, D. Pflieger, R. Epple, M. Azimioara, C. Cow, P.-Y. Michellys, P. Rigollier, D.R. Beisner, U. Bodendorf, D. Guerini, B. Liu, B. Wen, S. Zaharevitz, T. Brandl, Discovery of orally active hydroxyethylamine based SPPL2a inhibitors, ACS Med. Chem. Lett. 10 (2019) 887−892.

[40] P.S. Humphries, R. Bersot, J. Kincaid, E. Mabery, K. McCluskie, T. Park, T. Renner, E. Riegler, T. Steinfeld, E.D. Turtle, Z.-L. Wei, E. Willis, Carbazole-containing sulfonamides and sulfamides: discovery of cryptochrome modulators as antidiabetic agents, Bioorg. Med. Chem. Lett 26 (2016) 757−760.

[41] P. Lassalas, B. Gay, C. Lasfargeas, M.J. James, T. Van, K.G. Vijayendran, K.R. Brunden, M.C. Kozlowski, C.J. Thomas, A.B. Smith III, D.M. Huryn, C. Ballatore, Structure property relationships of carboxylic acid isosteres, J. Med. Chem. 59 (2016) 3183−3203.

[42] G. Liu, D.A. Cogan, T.D. Owens, T.P. Tang, J.A. Ellman, Synthesis of enantiomerically pure N-tert-Butanesulfinyl imines (tert-Butanesulfinimines) by the direct condensation of tert-butanesulfinamide with aldehydes and ketones, J. Org. Chem. 64 (1999) 1278−1284.

[43] P.J. Hamzik, J.D. Brubaker, Reactions of oxetan-3-tert-butylsulfinimine for the preparation of substituted 3-aminooxetanes, Org. Lett. 12 (2010) 1116−1119.

[44] D.M. Hodgson, S.P. Hughes, A.L. Thompson, T.D. Heightman, Terminal aziridines by α-deprotonation/electrophile trapping of N-protected aziridine, Org. Lett. 10 (2008) 3453−3456.

[45] R. Das, D. Chakraborty, Silver Triflate Catalyzed Acetylation of Alcohols, Thiols, Phenols, and Amines, 2011, pp. 1621−1625. Synthesis-Stuttgart.

[46] L. Johnson, J. Powers, F. Ma, K. Jendza, B. Wang, E. Meredith, N. Mainolfi, A reliable synthesis of 3-amino-5-alkyl and 5-amino-3-alkyl isoxazoles, Synthesis-Stuttgart 45 (2013) 171−173.

[47] https://chemaxon.com/products/calculators-and-predictors (accessed on 12/22/2020).

[48] A.P. Hill, R.J. Young, Getting physical in drug discovery: a contemporary perspective on solubility and hydrophobicity, Drug Discov. Today 15 (2010) 648−655.

[49] N. Jain, S.H. Yalkowsky, Estimation of the aqueous solubility I: application to organic nonelectrolytes, J. Pharm. Sci. 90 (2001) 234−252.

[50] M.H. Abraham, H.S. Chadha, G.S. Whiting, R.C. Mitchell, Hydrogen bonding. 32. An analysis of water-octanol and water-alkane partitioning and the delta log P parameter of seiler, J. Pharm. Sci. 83 (1994) 1085−1100.

[51] R.A. Conradi, A.R. Hilgers, N.F. Ho, P.S. Burton, The influence of peptide structure on transport across Caco-2 cells, Pharm. Res. (N. Y.) 8 (1991) 1453−1460.

[52] N. el Tayar, B. Testa, P. Carrupt, Polar intermolecular interactions encoded in partition-coefficients - an indirect estimation of hydrogen-bond parameters of polyfunctional solutes, J. Phys. Chem. 96 (1992) 1455−1459.

[53] A. Toulmin, J.M. Wood, P.W. Kenny, Toward prediction of alkane/water partition coefficients, J. Med. Chem. 51 (2008) 3720−3730.

[54] M. Shalaeva, G. Caron, Y. Abramov, T. O'Connell, M. Plummer, G. Yalamanchi, K. Farley, G. Goetz, L. Philippe, M. Shapiro, Integrating intramolecular hydrogen bonding (IMHB) considerations in drug discovery using delta logP as a tool, J. Med. Chem. 56 (2013) 4870−4879.

[55] N. el Tayar, R.S. Tsai, B. Testa, P.A. Carrupt, A. Leo, Partitioning of solutes in different solvent systems: the contribution of hydrogen-bonding capacity and polarity, J .Pharm. Sci. 80 (1991) 590−598.

[56] J.T. Goodwin, R.A. Conradi, N.F. Ho, P.S. Burton, Physicochemical determinants of passive membrane permeability: role of solute hydrogen-bonding potential and volume, J. Med. Chem. 44 (2001) 3721−3729.

[57] F.T. Huque, K. Box, J.A. Platts, J. Comer, Permeability through DOPC/dodecane membranes: measurement and LFER modelling, Eur. J. Pharmaceut. Sci. 23 (2004) 223−232.

[58] M. Berthelot, F. Besseau, C. Laurence, The hydrogen-bond basicity pKHB scale of peroxides and ethers, Eur. J. Org Chem. 1998 (1998) 925−931.

[59] F. Besseau, M. Lucon, C. Laurence, M. Berthelot, Hydrogen-bond basicity pK(HB) scale of aldehydes and ketones, J. Chem. Soc., Perkin Trans. (1998) 101−107.

[60] J. Zinczuk, I.H. Sorokin, O.O. Orazi, R.A. Corral, Intramolecular sulphonamidomethylation. Part II [1,2] fused heterocycles from 2-phenylethanesulphonamides, J. Heterocycl. Chem. 29 (1991) 859−866.

[61] P. Stupple, H. Lagiakos, R. Foitzik, M. Camerino, G. Nikolakopoulos, T. Bozikis, W. Kersen, S. Walker, J. Bert, A Compound of Formula (I), or a Pharmaceutically Acceptable Salt Thereof, 2020. W. I. P. O. Patent WO 2020/002587 A1.

[62] M. Rowbottom, R. Faraoni, Q. Chao, B. Campbell, A. Lai, E. Setti, M. Ezawa, K. Sprankle, S. Abraham, L. Tran, B. Struss, M. Gibney, R. Armstrong,

R. Gunawardane, R. Nepomuceno, I. Valenta, H. Hua, M. Gardner, M. Cramer, D. Gitnick, D. Insko, J. Apuy, S. Jones-Bolin, A. Ghose, T. Herbertz, M. Ator, B. Dorsey, B. Ruggeri, M. Williams, S. Bhagwat, J. James, M. Holladay, Identification of 1-(3-(6,7-Dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea hydrochloride (CEP-32496), a highly potent and orally efficacious inhibitor of V-RAF murine sarcoma viral oncogene homologue B1 (BRAF) V600E, J. Med. Chem. 55 (2012) 1082−1105.

[63] Molecular operating environment (MOE), montreal, QC, Canada, H3A 2R7. http://www.Chemcomp.com, 2019 (accessed on 12/22/2020).

[64] Gaussian 98, Gaussian, Inc., Pittsburgh, PA, 1998. http://www.gaussian.com/ (accessed on 12/22/2020).

[65] T. Lu, F. Multiwfn Chen, A multifunctional wavefunction analyzer, J. Comput. Chem. 33 (2012) 580−592.