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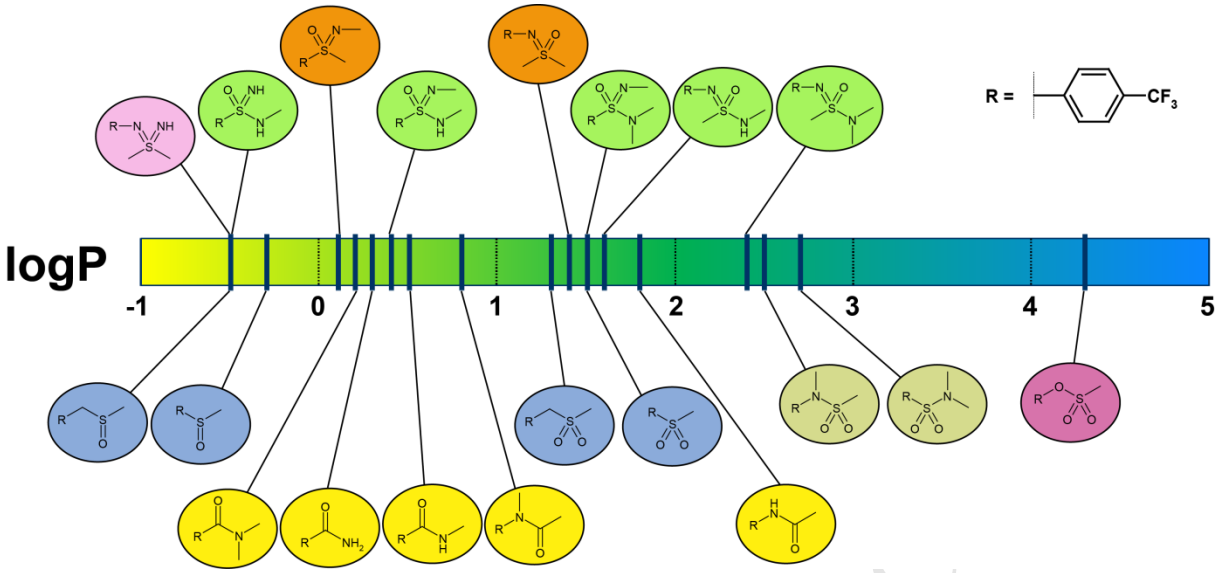

Sulfoximines from a Medicinal Chemist's Perspective: Physicochemical and in vitro Parameters Relevant for Drug Discovery

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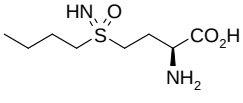
KEYWORDS

Synthesis, Sulfoximines, Sulfondiimides, Sulfonimidamides, Metabolic stability, Permeability, Solubility.

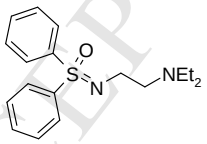
1. Introduction

Until recently, sulfoximines remained a rather unrecognized class of compounds despite the fact that their discovery dates back to the early 1950s. [1] We realized that even experienced chemists are surprised to learn of the high chemical stability of the sulfonimidoyl moiety, [2,3] and many have never considered applying such compounds in their own research programs.

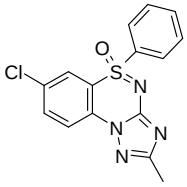
Although one particular compound, namely buthionine sulfoximine [4,5] (BSO, **1**) has over 6,200 SciFinder entries, [6] its recognition in the chemical community remained rather low. A small number of other sulfoximines such as compounds **2**, [7] **3, [**8**] 4, [**9**] 5, [**10**] 6, [**11**]** and **7 [**12**]** were published as bioactive agents by various companies and researchers (Figure 1), but to date no sulfoximine has been approved for a therapeutic application. [13]



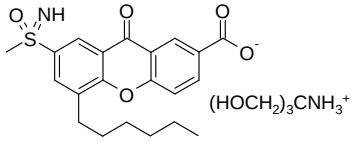
BSO (**1**)



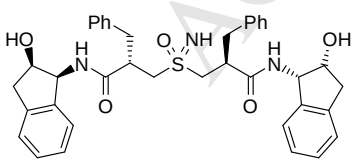
Suloxifen (**2**)
(Gödecke)



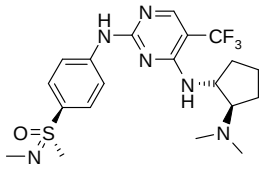
Gö 4962 (**3**)
(Gödecke)



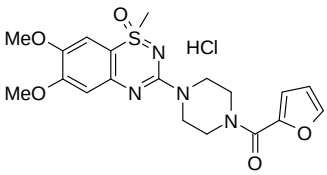
RU 31156 (Sudexanox, **4**)
(Roussel Uclaf)



HIV-1 protease inhibitor **5**



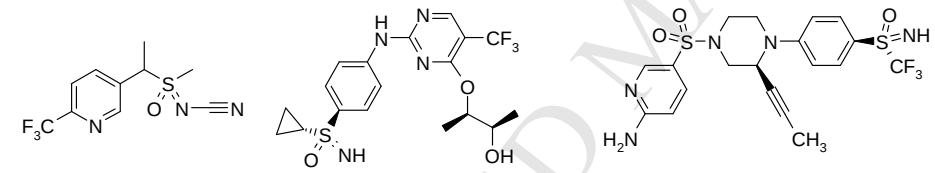
PYK2 inhibitor **6**
(Pfizer)



α-Adrenergic receptor blocker **7**
(Eli Lilly)

Figure 1. Bioactive sulfoximines – early discoveries.

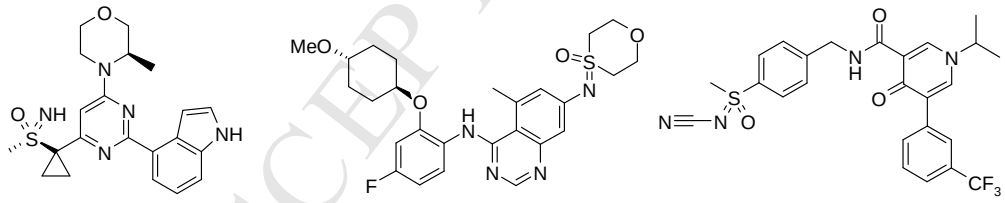
About a decade ago, the interest in sulfoximines began to grow along with intensified research activities in crop science and studies in the pharmaceutical industry. In 2005 Dow AgroSciences reported *N*-cyano sulfoximine **8** (Sulfoxaflor) as a new insecticide, [14] which was later approved for field applications in several countries. [15] Around the same time, Bayer Pharma (formerly Schering) began developing pan-CDK inhibitor BAY 1000394 (**9**), [16] which has entered clinical trials. More recently, other sulfoximines with potential medical applications have been made public, such as Amgen's GKRP disruptor **10**, [17] Astra Zeneca's ATR inhibitor **11**, [18] and the MNK inhibitor **12 [**19**]** and human neutrophile elastase inhibitor **13**, [20] both disclosed by Boehringer Ingelheim.



Sulfoxaflor (**8**)
(Dow AgroSciences)

BAY 1000394 (**9**)
(Bayer Pharma)

10
(Amgen)



AZD6378 (**11**)
(Astra Zeneca)

12
(Boehringer Ingelheim)

13
(Boehringer Ingelheim)

Figure 2. Bioactive sulfoximines - recent discoveries.

In addition to sulfoximines, other sulfur-containing compounds with related core structures such as sulfonimidamides [21] and sulfondiimides [22] have also recently garnered increased attention (Figure 3).

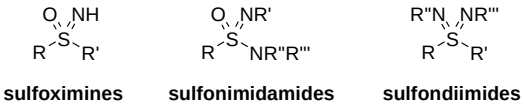


Figure 3. General scaffolds of sulfoximines and their congeners: sulfonimidamides and sulfondiimides.

Although there is an increasing interest in sulfoximines and their chemistry, we felt that the routine application of sulfoximines in drug discovery projects is still hampered by synthetic considerations or uncertainty about their chemical stability, and also due to limited experience about their physicochemical and in vitro parameters. Although a few scattered data can be found in the literature, [21c,23] a comprehensive picture is still missing.

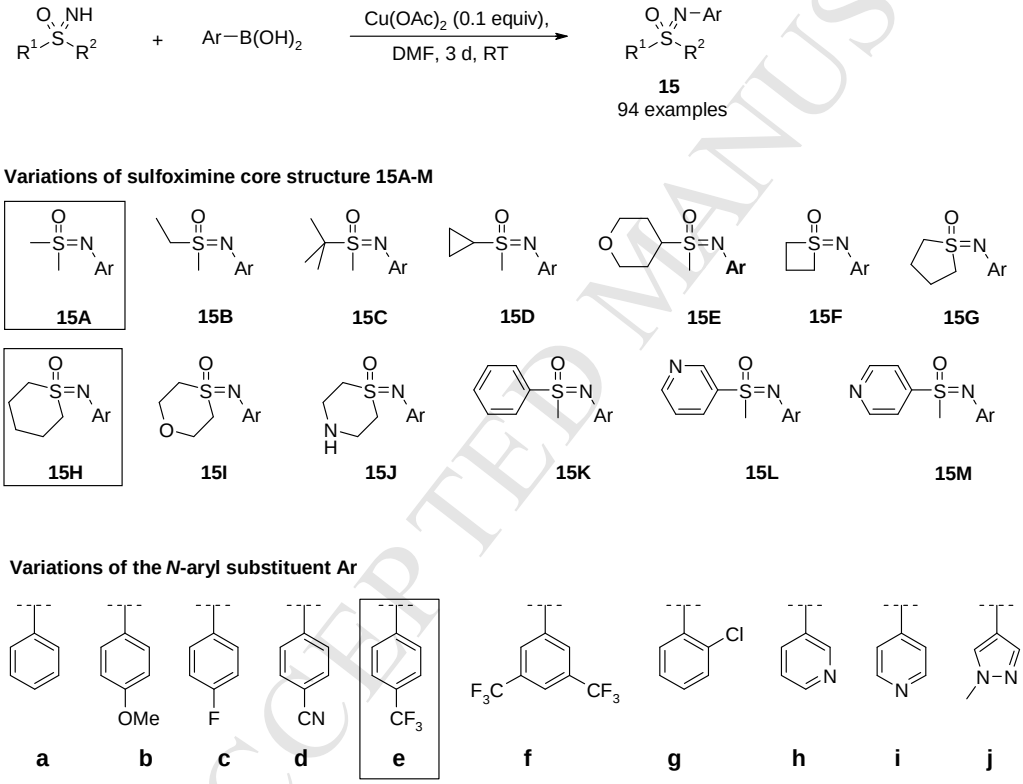
We sought to analyze from a medicinal chemist's perspective whether sulfoximines and related molecules implicate any principal flaws or if it could be recommended to employ them systematically in drug discovery projects like any other functional group. In this study, we report the physicochemical and in vitro properties of selected custom-made sulfoximines and compare them with related analogs and isosteres. Furthermore, we present an analysis of compounds from drug discovery projects within Boehringer Ingelheim.

2. Results and discussion

2.1 Selection, design and synthesis of matric compounds 15

At the outset of our studies, we defined a matrix of *N*-arylated sulfoximines **15** which could be synthesized from the *N*H- ("free") sulfoximines and arylboronic acids by Chan-Lam coupling reactions (Scheme 1). [24] For the sulfoximine cores **15A-M**, aliphatic residues covering a range

of lipophilicity (**15A-E**), cyclic sulfoximines (**15F-J**) and derivatives with (hetero)aromatic residues (**15K-M**) were selected. For the *N*-aryl group both neutral (**a**), electron rich (**b**) and electron poor (**c-g**) aromatics as well as heteroaromatic moieties (**h-j**) were chosen. From this matrix of 130 possible compounds **15Aa** to **15Mj** a total of 94 sulfoximines could be prepared in satisfactory yields, utilizing the aforementioned method (for details see the Supporting Information). With the exception of (*R*)-**15Ke** and (*S*)-**15Ke**, all chiral sulfoximines were used as racemates.



Scheme 1. Initial matrix of sulfoximines **15** (rectangles emphasize the structural elements of the subsequent template compounds **15Ae** and **15He**; see text for further explanation).

All synthesized compounds **15** were tested for metabolic stability in human liver microsomes and aqueous solubility (high-throughput HPLC assay, data not shown). The *N*-[4-(trifluoro-

methyl)phenyl]sulfoximines **15Ae** and **15He** were picked as reference structures, as they exhibited suitable intermediate values allowing for the observation of trends in subsequent measurements of analogs. To broaden the scope of our study, we intended not only to explore the properties of the sulfoximines **15**, but also to compare their properties with those of isosteres and further analogs bearing more common structural elements. To this end, the selected sulfoximines **15Ae** and **15He** served as templates for the design of series **16** comprising of various isosteres and of closely related analogs (Chart 1). The depicted spectrum of compounds covers not only structural motifs commonly found in small molecule drugs, such as carboxamides, sulfoxides, sulfones, sulfonates and sulfonamides (**16a-16g**), but also less common ones such as sulfondiimides (**16h**, **16i**), sulfonimidamides (**16j-16l**), sulfilimines (**16o**, **16q**) and sulfoximines (**16m**, **16n**). Since series **16** is mainly focused on 4-(trifluoromethyl)phenyl as the nitrogen substituent, a related series was designed in which the 4-(trifluoromethyl)phenyl group is attached to sulfur. Thus, sulfoximine **17c** served as template for the respective isosteres and analogs **17** (Chart 2). Additionally, sulfoximines **18d** and **19d** with a *N*-aroyl or a *N*-carbamoyl motif, respectively, served as reference structures for series of isosteres and analogs **18** and **19** (Chart 3).

Chart 1. Sulfoximines **15Ae** and **15He** together with isosteres and analogous compounds **16a-16q** (reference structures are highlighted).

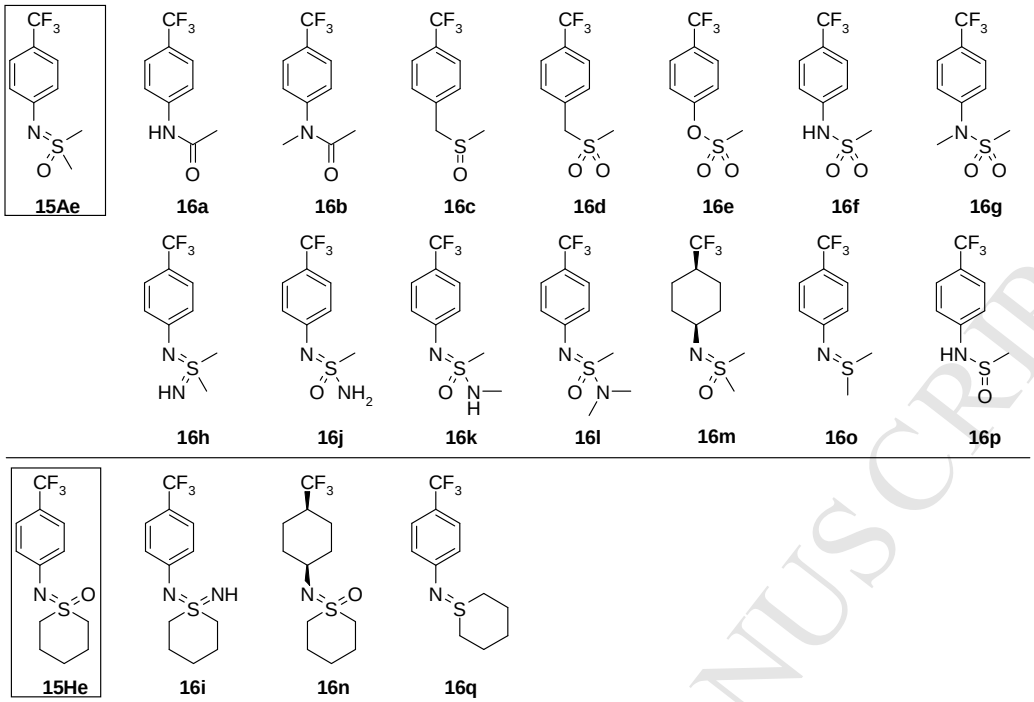


Chart 2. Sulfoximine **17c** together with isosteres and analogous compounds **17a-17n** (reference structures are highlighted).

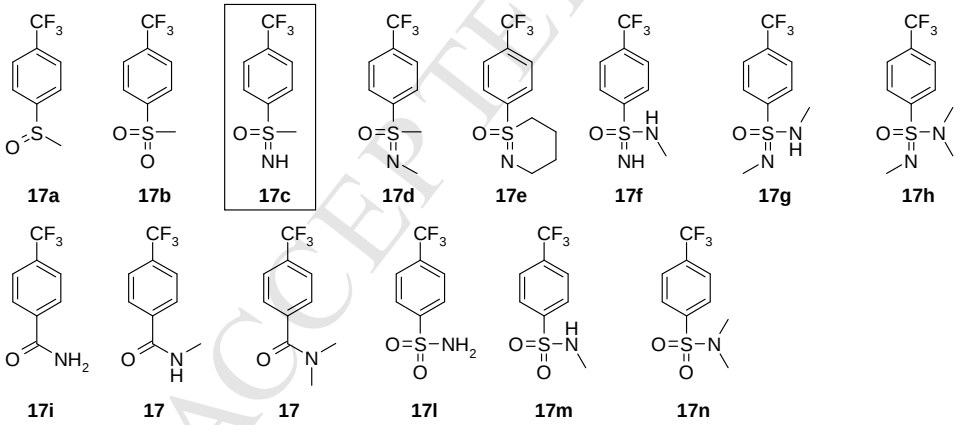
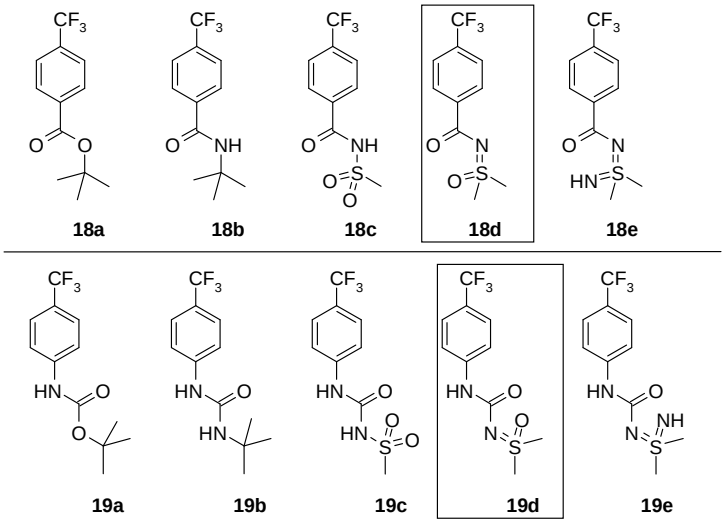


Chart 3. Sulfoximines **18d** and **19d** together with isosteres and analogous compounds **18a-18e** and **19a-19e** (reference structures are highlighted).



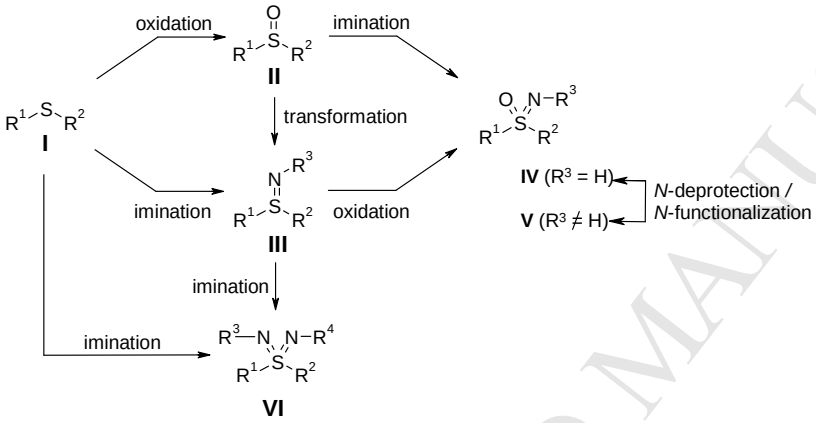
2.2 Chemistry

2.2.1 General synthetic routes

Whilst some of the abovementioned molecules were available from commercial suppliers [25a] or accessible using standard chemistry, [25b] the majority of the envisaged compounds and their synthetic precursors were unprecedented and thus required facile access. Most of them could be synthesized following established routes, which are schematically depicted in Schemes 2 and 3.

Typically, the synthesis of sulfoximines starts by oxidation of commercially available or easily accessible sulfides **I** and subsequent imination of the resulting sulfoxides **II** (Scheme 2). [26] While Rhodium-catalyzed iminations usually result in *N*-protected sulfoximines **V** (R^3 = protecting group) which are then deprotected, [27] iminations using in situ generated hydrazoic acid, [28] activated reagents such as MSH [29] or DPH [30] or ammonium carbamate in the presence of diacetoxyiodobenzene, [31] lead directly to the free sulfoximines **IV** (R^3 = H).

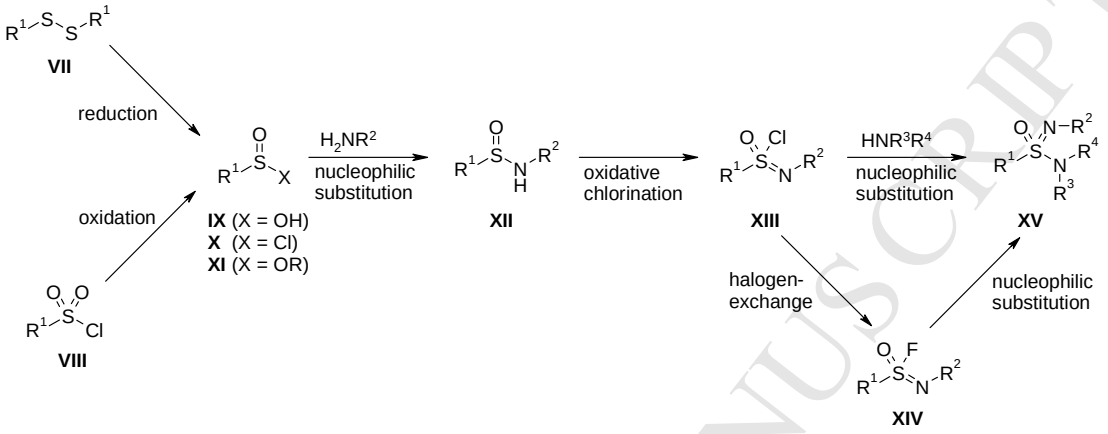
N-Functionalized sulfoximines **V** ($R^3 \neq H$) can be prepared from the free *N*H-sulfoximines **IV** ($R^3 = H$) by methods such as Cu-catalyzed arylations (Scheme 1), nucleophilic substitutions or reductive alkylations (see next section). Alternatively, sulfoximines **V** ($R^3 \neq H$) can also be obtained by oxidation of sulfilimines **III**, [32] which are accessible by imination of sulfides **I** or transformation of sulfoxides **II**. [33] Sulfondiimides **VI** can be synthesized by imination of sulfides **I** [34] or sulfilimines **III**. [22a]



Scheme 2. General synthetic routes for the preparation of sulfoximines **IV/V** and sulfondiimides **VI**.

As opposed to sulfoximines or sulfondiimides, the synthesis of sulfonimidamides often requires more steps, as the necessary sulfinamide precursors are usually not commercially available (Scheme 3). Hence, the sulfinamides **XII** have to be prepared from sulfinic acids **IX**, sulfinyl chlorides **X** or sulfinate esters **XI**, which themselves are accessible from more readily available starting materials such as disulfides **VII** or sulfonyl chlorides **VIII**. [35] Sulfonimidamides **XV** are typically prepared by oxidative chlorination of the parent sulfinamides **XII** and subsequent reaction of the intermediate sulfonimidoyl chlorides **XIII** with amines (Scheme 3). [21,36] Alternatively, the usually unstable sulfonimidoyl chlorides **XIII** can be

converted into the more stable sulfonimidoyl fluorides **XIV** which are easier to handle and less susceptible to reduction, e.g. by hydrazine nucleophiles. [37] Recently some of us reported that sulfonimidamides **XV** can also be prepared directly from *N*H-sulfoximines **IV**. [38]

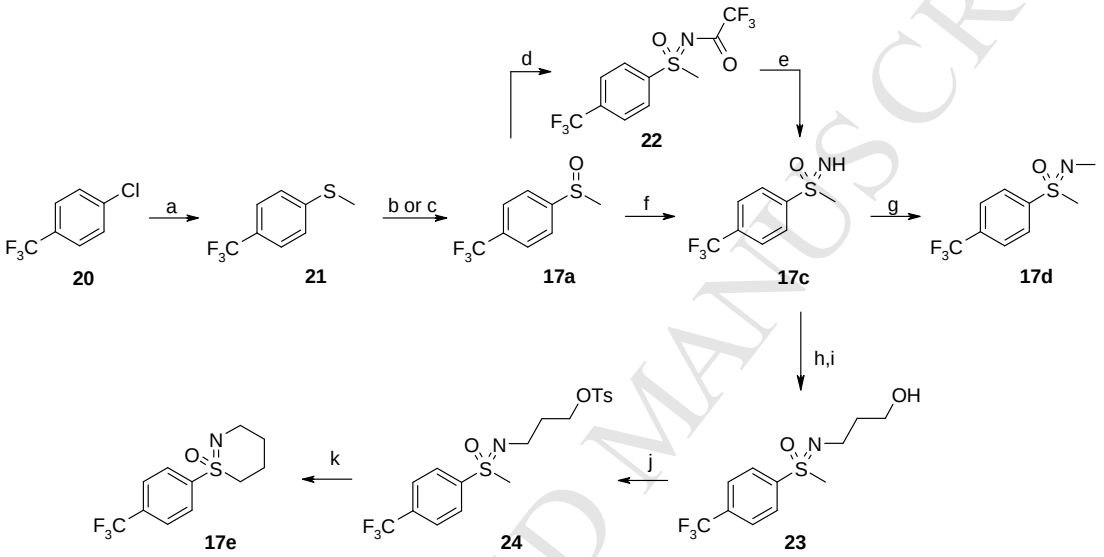


Scheme 3. General synthetic routes for the preparation of sulfonimidamides **XV**.

2.2.2 Synthesis of derivatives 16-19

To illustrate the abovementioned general synthetic routes, some of the syntheses that were carried out will be described below. For example, sulfoxide **17a** was prepared from sulfide **21** **[**39**]** by oxidation with *m*-CPBA or on larger scale using in situ prepared peracetic acid (Scheme 4). Mild imination under rhodium catalysis furnished *N*-trifluoroacetyl sulfoximine **22** which could readily be deprotected to give the desired *N*H-sulfoximine **17c**. [27] Alternatively, the latter compound could be prepared in one step on gram scale by imination of **22** with in situ generated hydrazoic acid. [28b] Methylation of sulfoximine **17c** was accomplished under Eschweiler-Clarke conditions to give target compound **17d**. [40] For the synthesis of cyclic sulfoximine **17e**, a ring closure by intramolecular nucleophilic substitution of tosylate **24** was envisaged. To this end, sulfoximine **17c** was alkylated with 2-(3-chloropropoxy)tetrahydro-2*H*-

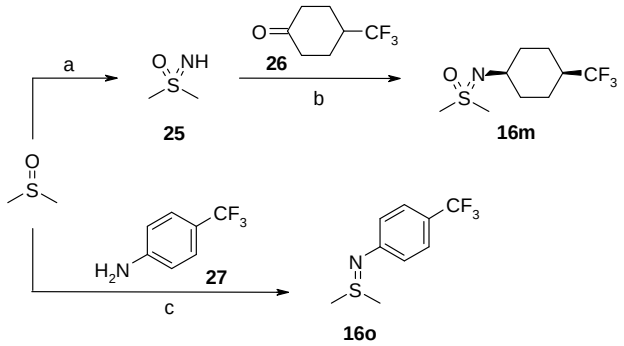
pyran using KOH as base in DMSO at room temperature. [22d, 41] Removal of the THP protecting group under acidic conditions and tosylation of the resulting alcohol delivered substrate **24**, which was now ready to be cyclized in the next step. While deprotonation of **24** with Schlosser's base under reported conditions [41] led only to incomplete ring closure, employing *n*-butyllithium afforded the desired 1,2-thiazine-1-oxide **17e** in good yield.



Scheme 4. Reagents and conditions: (a) NaSMe, DMF, 50 °C, 20 h (94%); (b) *m*-CPBA, CH_2Cl_2, 0 °C, 2 h (94%); (c) H_2O_2, AcOH, –5 °C to rt, 22 h (98%); (d) $Rh_2(OAc)_4$, $PhI(OAc)_2$, CF_3CONH_2, MgO, CH_2Cl_2, rt, 1.5 d (79%); (e) K_2CO_3, MeOH, rt, 1 h (quant.); (f) NaN_3, H_2SO_4, $CHCl_3$, –10 °C to 50 °C, 5 d (67%); (g) paraformaldehyde, formic acid, 130 °C, 4 d (75%); (h) 2-(3-chloropropoxy)tetrahydro-2*H*-pyran, KOH, DMSO, rt, 11 h; (i) aq. HCl (90%, two steps); (j) Et_3N, TsCl, CH_2Cl_2, 0 °C to rt, 14 h (78%); (k) *n*-BuLi, THF, –78 °C to rt, 45 h (58%).

For the synthesis of sulfoximine **16m**, *S*,*S*-dimethylsulfoximine (**25**) was prepared firstly by imination of DMSO (Scheme 5). [42] While reductive alkylations of *N*H-sulfoximines with aldehydes and, in particular, ketones had proven challenging for a long time, we were delighted to find that under adapted conditions [23,43] the reaction of sulfoximine **25** with 4-(trifluoro-

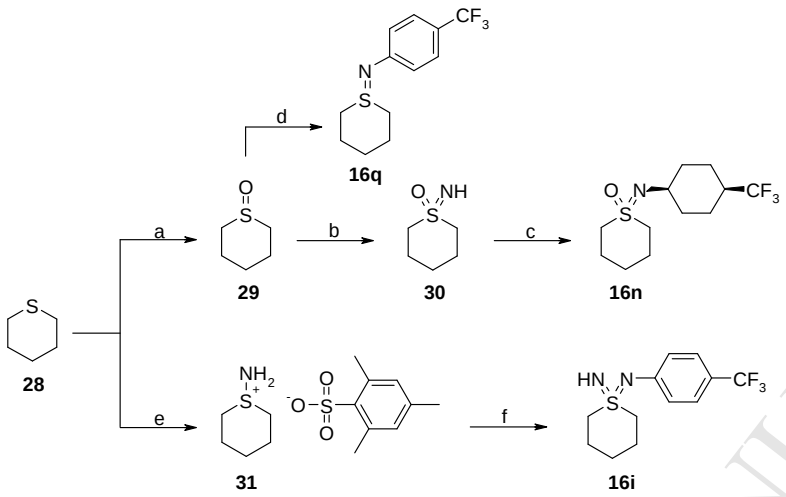
methyl)cyclohexanone (**26**) proceeded smoothly and furnished the target compound **16m** as a single *cis*-stereoisomer in acceptable yield. [44] The imination of DMSO with 4-(trifluoromethyl)aniline (**27**) failed when using either TFAA [33a] or sulfur trioxide-pyridine complex, [45] but could successfully be achieved when switching to phosphorus pentoxide as activator to give sulfilimine **16o**. [33b]



Scheme 5. Reagents and conditions: (a) NaN_3, H_2SO_4, CH_2Cl_2, 0 °C to 42 °C, 18 h (27%); (b) 4-(trifluoromethyl)cyclohexanone (**26**), $NaBH(OAc)_3$, DCE, 42 °C, 43 h (42%); (c) 4-(trifluoromethyl)aniline (**27**), P_4O_{10}, Et_3N, $CHCl_3$, 12 °C to rt, over night (56%).

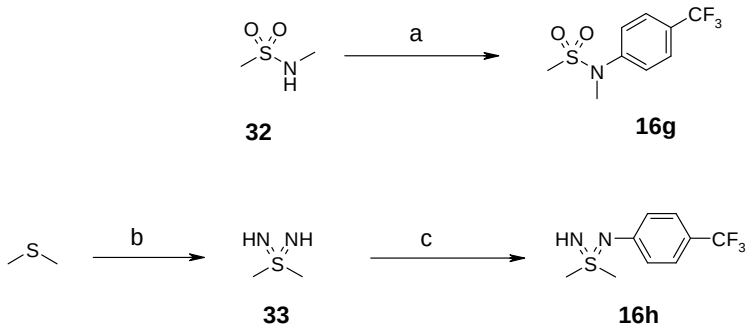
The synthesis of the cyclic representatives **16n** and **16q** started from tetrahydrothiopyran (**28**) and is depicted in Scheme 6. Oxidation of **28** gave sulfoxide **29**, which was then converted into sulfilimine **16q** and sulfoximine **16n**, respectively, in analogous fashion as described before. Once again, the reductive amination with cyclohexanone **26** delivered **16n** as a single *cis*-configured stereoisomer. [44] For the preparation of sulfondiimide **16i**, thioether **28** was iminated with MSH [29] to give sulfiliminium salt **31**. Although extensive experimentation was carried out, the following second imination under modified conditions [22a] with NCS and aniline **27** remained troublesome and sulfondiimide **16i** was isolated only in low yield. Since

control reactions with unsubstituted aniline or 4-iodoaniline resulted in much higher yields, the poor yield is likely due to the low nucleophilicity of **27**.



Scheme 6. Reagents and conditions: (a) $NaIO_4$, $MeOH/H_2O$, –20 °C to rt, 6.5 h (94%); (b) MSH, CH_2Cl_2, 0 °C, 20 min, then rt, 1.5 d, then aq. NaOH, rt, 1 h (81%); (c) **26**, $NaBH(OAc)_3$, DCE, 42 °C, 40 h (45%); (d) **27**, P_4O_{10}, Et_3N, $CHCl_3$, 0 °C to rt, over night (50%); (e) MSH, DCE, 0 °C to rt, 2.5 h (72%); (f) **27**, NCS, Na_2CO_3, DMF, 0 °C to rt, over night (12%).

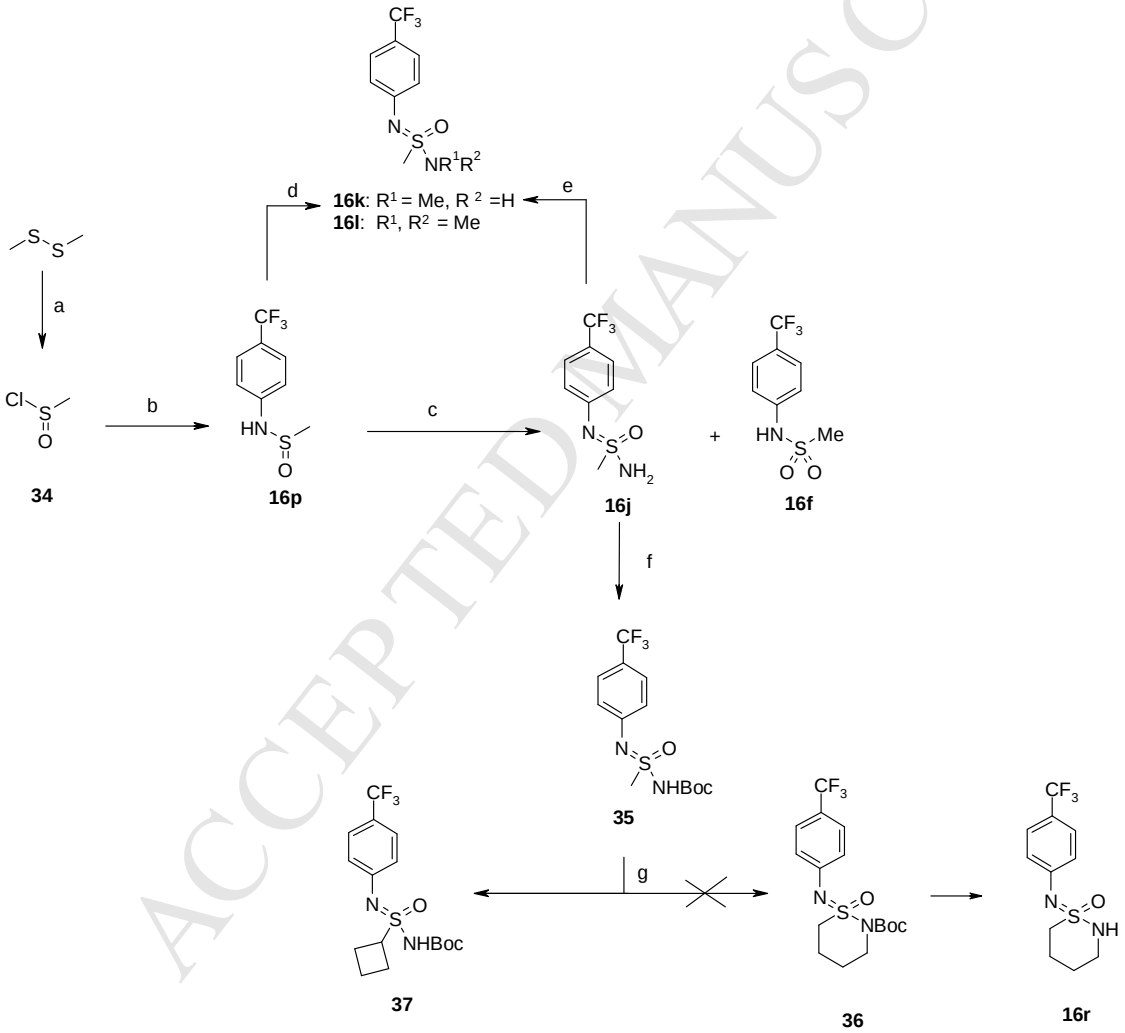
The synthesis of *N*-arylated derivatives **16g** and **16h** relied on palladium catalyzed arylation chemistry (Scheme 7). Thus, commercially available methyl(methylsulfonyl)amine (**32**) and *S*,*S*-dimethylsulfondiimide (**33**), which was prepared by double imination of dimethylsulfide according to Haake's procedure, [34] were arylated with appropriate aryl halides using palladium catalysts to give the desired products **16g** and **16h** in acceptable yield. The solid state structure of sulfondiimide **16h** was confirmed by X-ray crystal structure analysis. [46]



Scheme 7. Reagents and conditions: (a) 4-bromobenzotrifluoride, Pd_2dba_3, Xantphos, K_3PO_4, 1,4-dioxane, 100 °C, over night (36%); (b) *t*-BuOCl, MeCN, NH_3, –20 °C to rt, 48 h (30%); (c) 4-iodobenzotrifluoride, Pd_2dba_3, JohnPhos, NaO*t*-Bu, 1,4-dioxane, 80 °C, 4 h (16%).

Exemplary syntheses of sulfonimidamides are depicted in Scheme 8. Methanesulfinyl chloride (**34**) was freshly prepared by oxidative chlorination of dimethyl disulfide and treated with aniline **27** to give sulfinamide **16p**, which was found to be sensitive towards acidic conditions (traces of acid in $CDCl_3$, decomposition on silica gel). While this compound could be handled as an intermediate for further syntheses, its instability prevented any further physicochemical characterization. Next, sulfinamide **16p** was oxidized in situ with *tert*-butyl hypochlorite to the sulfonimidoyl chloride (as in Scheme 3) which was not isolated but directly treated with aqueous ammonia leading to sulfonimidamide **16j** as the main product and sulfonamide **16f** as a side product. Furthermore, sulfinamide **16p** was easily converted to the analogous *N*-methyl sulfonimidamide **16k** in the presence of NCS, methylamine and KO*t*-Bu. The corresponding *N*,*N*-dimethyl derivative **16l** was obtained by double alkylation of the unsubstituted sulfonimidamide **16j** with an excess of iodomethane and Cs_2CO_3.

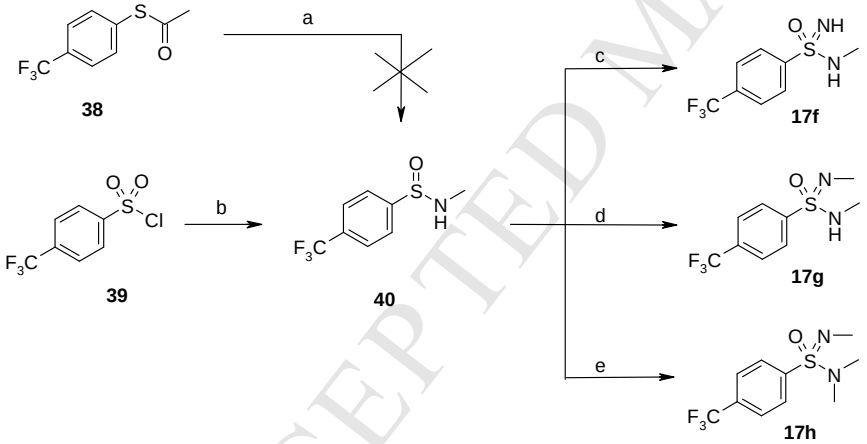
It was also planned to prepare cyclic sulfonimidamide **16r** by double alkylation of intermediate **35** with 1,3-dibromopropane. However, the envisaged double deprotonation and alkylation of Boc-protected compound **35** failed to furnish compound **36**, but rather resulted in the isolation of *S*-cyclobutyl derivative **37**. Since further attempts with other protecting groups and different alkylation conditions remained unsuccessful, the synthesis of target compound **16r** was abandoned.



Scheme 8. Reagents and conditions: (a) AcOH, SO_2Cl_2, –20 °C, over night, then 2 h, rt (79%); (b) **27**, Et_3N, CH_2Cl_2, –10 °C to 0 °C, 3.5 h (84%); (c) *t*-BuOCl, aq. NH_3, THF, 0 °C to rt, 5 h

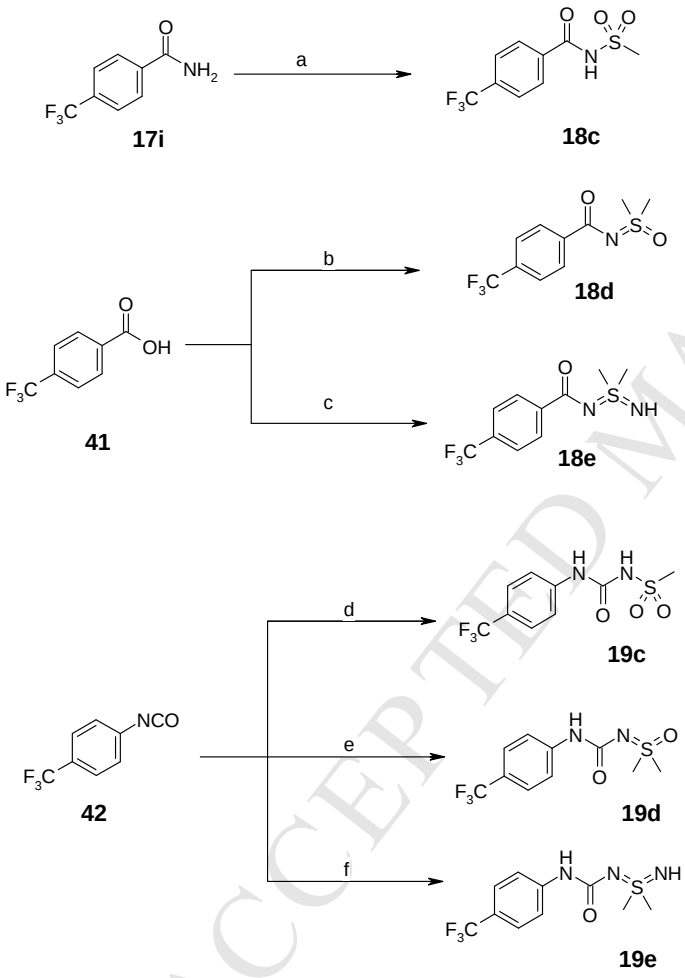
(**16j**: 68%, **16f**: 15%); (d) NCS, $MeNH_2$, KO*t*-Bu, MeCN, rt, over night (62%); (e) MeI, Cs_2CO_3, DMF, rt, 19 h (68%); (f) Boc_2O, Et_3N, DMAP, THF, rt, 18 h (66%); (g) *n*-BuLi, $Br(CH_2)_3Br$, THF, –78 °C to rt, over night (34%).

The synthesis of sulfonimidamide derivatives **17f-h** is described in Scheme 9. For the preparation of central sulfinamide **40**, the known synthetic route by oxidative chlorination of thiophenol acetate **38** to the sulfinyl chloride [47] and subsequent reaction with methylamine was attempted first, but the desired product **40** could not be detected. [48] Following the protocol reported by Harmata employing sulfonyl chloride **39** as starting material and PPh_3 as reducing agent, the preparation of the desired sulfinamide **40** proceeded smoothly, [49] and sulfonimidamides **17f-h** were prepared from this intermediate in serviceable yields. [50,51]



Scheme 9. Reagents and conditions: (a) SO_2Cl_2, Ac_2O, CH_2Cl_2, –20 °C to rt, then $MeNH_2$, CH_2Cl_2, 0 °C to rt (0%); (b) PPh_3, $MeNH_2$, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h (35%); (c) *t*-BuOCl, NH_3, MeCN, 30 min, 0 °C to rt (13%); (d) *t*-BuOCl, $MeNH_2$, MeCN, 30 min, 0 °C to rt (45%); (e) *t*-BuOCl, Me_2NH, MeCN, 30 min, 0 °C to rt (72%).

The synthesis of the acylated derivatives **18** was straightforward and relied on established methods such as sulfonylation (**18c**) or acylations (**18d**, **18e**) (Scheme 10). The structure of benzoylated sulfondiimide **18e** was determined by X-ray structure analysis. [46] For the synthesis of urea derivatives **19**, isocyanate **42** was treated with the appropriate nucleophiles, which provided the desired compounds in low (**19c**) to good yields (**19d** and **19e**).



Scheme 10. Reagents and conditions: (a) NaH, $MeSO_2Cl$, THF, 2 h, rt (30%); (b) **25**, HATU, DIPEA, DMF, over night, rt (61%); (c) **33**, HATU, DIPEA, DMF, over night, rt (38%); (d)

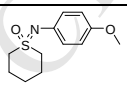
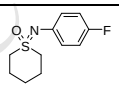
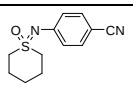
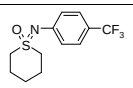
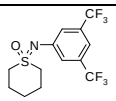
$MeSO_2NH_2$, aq. NaOH (1 M), acetone, reflux, 3 h (7%); (e) **25**, DIPEA, 1,4-dioxane, over night, rt (96%); (f) **33**, DIPEA, 1,4-dioxane, over night, rt (73%).

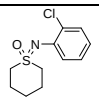
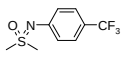
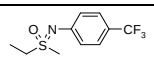
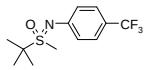
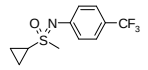
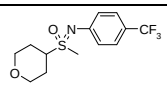
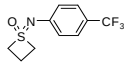
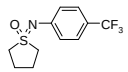
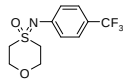
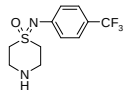
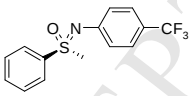
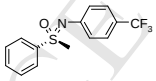
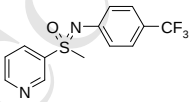
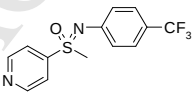
2.3 Analysis of physicochemical and in vitro properties

2.3.1 Physicochemical and in vitro properties for matrix compounds 15

For a subset of the obtained 94 matrix compounds **15**, basic physicochemical and in vitro pharmacokinetic parameters such as lipophilicity (logP), [52] stability in human liver microsomes, aqueous solubility (high-throughput HPLC assay) [53] and permeability (PAMPA) were measured (Table 1). For selected compounds, the dissociation constant (pK_a/pK_b) and aqueous solubility from solid material (shake flask assay) were also determined. [53]

Table 1. Physicochemical and in vitro pharmacokinetic parameters of selected compounds.[a]

Entry	Compound	Structure	logP [52]	pK_a/pK_b	Stability in human liver microsomes		Aqueous Solubility [µg/mL] [53]		Permeability (PAMPA) P_{app} [10^{-6} cm/s]
					$T_{½}$ [min]	$\%Q_H$	HPLC-Assay	Shake flask assay	
1	15Ha		–0.1	n.d.	>130	<23	37	n.d.	9.5
2	15Hb		–0.1	n.d.	>130	<23	>51	900	9.1
3	15Hc		0.7	n.d.	120	25	>46	>1,000	9.5
4	15Hd		1.1	n.d.	>130	<23	45	n.d.	7.9
5	15He		2.8	n.d.	46	46	51	70	7.7
6	15Hf		4.0	n.d.	6	87	<1	n.d.	3.3

7	**15Hg**		2.0	n.d.	28	58	>50	500	12.0
8	**15Hh**		–2.7	pK_b 4.8[b]	8	82	>75	n.d.	5.8
9	**15Hi**		–2.6	pK_b 7.2[b]	>130	<23	42	n.d.	5.7
10	**15Hj**		–3.9	n.d.	>130	<23	39	n.d.	3.2
11	**15Ae**		1.4	no pK_a/pK_b[c]	>130	<23	>50	900	8.2
12	**15Be**		2.0	n.d.	>130	<23	>51	n.d.	7.7
13	**15Ce**		3.1	n.d.	-[d]	-[d]	22	n.d.	-[d]
14	**15De**		2.3	n.d.	>130	<23	40	n.d.	7.8
15	**15Ee**		2.5	n.d.	>130	<23	46	n.d.	9.6
16	**15Fe**		2.5	n.d.	>130	<23	48	n.d.	9.6
17	**15Ge**		2.4	n.d.	110	26	50	6,000	8.7
18	**15Ie**		2.7	n.d.	>130	<23	>57	300	8.0
19	**15Je**		0.9	pK_b 5.2[e]	110	25	>57	2,300	8.3
20	**(*R*)-15Ke**		3.7	n.d.	>130	<23	20	n.d.	2.5
21	**(*S*)-15Ke**		3.7	n.d.	>130	<23	17	n.d.	3.5
22	**15Le**		2.5	no pK_a/pK_b[c]	>130	<23	47	n.d.	8.4
23	**15Me**		2.6	no pK_a/pK_b[c]	56	41	44	n.d.	6.2

[a] For assay details see the Supporting Information; n.d.: not determined.
[b] Protonation on the pyridine nitrogen.
[c] No pK_a/pK_b was detected within the measurement range of the assay (pH 2-12).
[d] No valid results were obtained.
[e] Protonation on the secondary amine.

As expected, variation of the *N*-aryl substituent has a significant impact on the lipophilicity of the compounds represented by the measured partition-coefficient (logP) of the compounds that covers a wide range between –3.9 for **15Hj** up to 4.0 for **15Hf** (Table 1, entries 1-10). Surprisingly, varying the substituents at the sulfur atom modulated logP only from 0.9 (thiomorpholine sulfoximine **15Je**) to 3.7 (*S*-phenyl sulfoximines **15Ke**, entries 5, 11-23). Amongst the cyclic sulfoximines (entries 5, 16-19), thietane and thiolane derivatives **15Fe** and **15Ge** show comparable lipophilicity and the tetrahydrothiopyran **15He** is only slightly more lipophilic. Interestingly, the oxathiane sulfoximine **15Ie** and its carbon analogue **15He** are equally lipophilic, whereas thiomorpholine sulfoximine **15Je** is significantly more polar.

The basicity of most of the sulfoximines **15** is outside the scope of the assay (pK_a/pK_b 2-12) and could therefore not be determined. Thus, only the pK_b of additional basic nitrogens could be measured. For 3-pyridyl and 4-pyridyl sulfoximines **15Hh** and **15Hi**, the measured pK_b values of 4.8 and 7.2, respectively, are comparable to those of the corresponding 3-methoxypyridine (pK_b = 4.9) [54] and 4-methoxypyridines (pK_b = 6.7), [55] thus indicating a similar electronic influence of the sulfoximine substituent. The basicity of *S*-pyridyl sulfoximines **15Le** and **15Me** was too low to be determined which is in line with the pK_b values for the corresponding sulfones as calculated using the Hammet equation (pK_b = 1.7 for 3-methylsulfonylpyridine and pK_b = 1.2 for 4-methylsulfonpyridine), [56] implicating a similar electronic effect of the sulfoximine substituent. The pK_b of the thiomorpholine derivative **15Je** of 5.2 is in good agreement with reported pK_b of the corresponding 1,4-thiazinane-1,1-dioxide (pK_b = 5.4). [57]

Most of the compounds **15** exhibit very desirable microsomal stability in human liver microsomes beyond the scope of the assay ($T_{½}$ > 130 min). This indicates that the sulfoximine moiety per se is not intrinsically metabolically unstable. [58]

Only limited conclusions can be drawn from the solubility data from the high-throughput HPLC assay, as many of the compounds are soluble beyond the upper detection limit of the assay (≈200 µM). As anticipated, representatives with high lipophilicity (**15Hf**, **15Ce**) or additional phenyl substituents (**15Ke**) exhibit significantly reduced solubility. For some of the compounds, aqueous equilibrium solubility from solid material was determined. In most of these cases, aqueous equilibrium solubility was found to be very high, for compounds **15Hc**, **15Ge** and **15Je** even higher than 1 mg/mL.

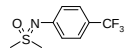
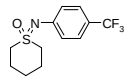
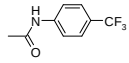
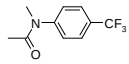
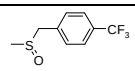
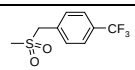
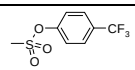
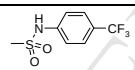
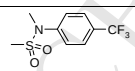
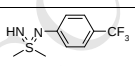
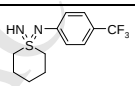
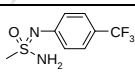
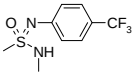
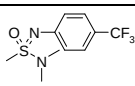
As assumed for such small molecules, the passive permeability of the compounds is generally very high (PAMPA). Reduced permeability is detected for the pyridyl derivatives **15Hh** and **15Hi** as well as the pyrazole **15Hj**, which is in agreement with their comparatively high polarity. The reduced permeability of the most lipophilic derivatives **15Hf** and **15Ke** may be an artefact caused by low solubility.

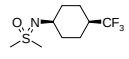
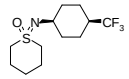
2.3.2 Physicochemical and in vitro properties of isosteres and compounds with related functional groups

Apart from exploring the physicochemical and in vitro properties of sulfoximines, we also envisaged to compare their properties with those of isosteres and analogs with more common structural elements. Hence, using sulfoximines **15Ae** and **15He** as templates, a series of *N*-aryl sulfoximine isosteres and congeners **16a-16n** (Table 2) was synthesized. Additionally, *S*-aryl

sulfoximines **17a-17n,** *N*-acyl sulfoximines **18a-18e** and *N*-carbamoyl sulfoximines **19a-19e** were prepared (Tables 3 and 4).

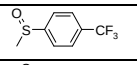
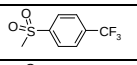
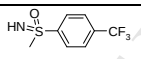
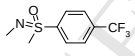
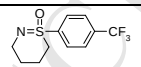
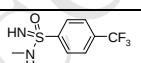
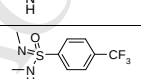
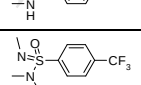
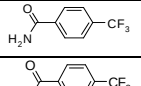
Table 2. *N*-Aryl sulfoximines and related compounds.[a]

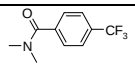
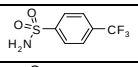
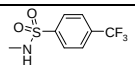
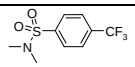
Entry	Compound	Structure	logP [52]		pK_a/pK_b	Stability in human liver microsomes		Aqueous Solubility [µg/mL] [53]		Permeability (PAMPA) P_{app} [10^{-6} cm/s]
			HPLC assay	Potentio-metric assay		$T_{½}$ [min]	$\%Q_H$	HPLC-Assay	Shake flask assay	
1	**15Ae**		1.4	n.d.	no pK_a/pK_b [b]	>130	<23	>50	900	8.2
2	**15He**		2.8	n.d.	n.d.	46	46	51	70	7.7
3	**16a**		1.8	n.d.	n.d.	60	39	10	100	6.0
4	**16b**		0.8	n.d.	n.d.	-[c]	-[c]	>52	1,300	9.7
5	**16c**		–0.5	n.d.	n.d.	110	25	>51	4,300	6.3
6	**16d**		1.3	n.d.	n.d.	-[c]	-[c]	n.d.	400	-[c]
7	**16e**		4.3	n.d.	n.d.	-[c]	-[c]	n.d.	300	-[c]
8	**16f**		n.d.	2.0[d]	pK_a 8.0[e]	>130	<23	47	600	5.1
9	**16g**		2.5	n.d.	n.d.	-[c]	-[c]	46	200	-[c]
10	**16h**		–0.5	1.8[f]	pK_b 4.0[g]	>130	<23	>51	8,400	5.6
11	**16i**		1.3	n.d.	pK_b 4.0	110	25	44	500	7.3
12	**16j**		n.d.	1.6[h]	pK_a 10.3[i]	>130	<23	31	<1	5.3
13	**16k**		1.6	n.d.	no pK_a/pK_b [b]	>130	<23	>54	800	5.0
14	**16l**		2.4	n.d.	no pK_a/pK_b [b]	42	48	41	70	7.6

15	**16m**		n.d.	2.4[f]	pK_b 4.2	>130	<23	n.d.	300	7.8
16	**16n**		n.d.	3.5[f]	pK_b 5.0	52	43	n.d.	<50	10.0

[a] For assay details see the Supporting Information; n.d.: not determined.
[b] No pK_a/pK_b was detected within the measurement range of the assay (pH 2-12).
[c] No valid results were obtained.
[d] Measured at pH 3.
[e] Deprotonation of the sulfonamide NH.
[f] Measured at pH 12.
[g] Protonation sulfoximine.
[h] Measured at pH 3.
[i] Deprotonation of the sulfonimidamide NH.
[j] Measured at pH 12.

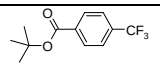
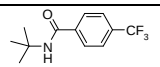
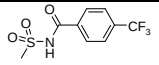
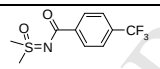
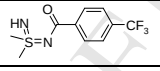
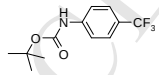
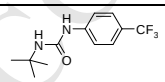
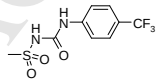
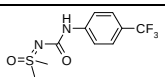
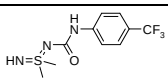
Table 3. *S*-Aryl sulfoximines and related compounds.[a]

Entry	**Compound**	**Structure**	**logP [52]**		**pK_a/pK_b**	**Stability in human liver microsomes**		**Aqueous Solubility [µg/mL] [53]**		**Permeability (PAMPA) P_{app} [10^{-6} cm/s]**
			HPLC assay	**Potentio-metric assay**		**$T_{½}$ [min]**	**$\%Q_H$**	**HPLC-Assay**	**Shake flask assay**	
1	**17a**		–0.3	n.d.	n.d.	-[b]	-[b]	>46	11,100	-[b]
2	**17b**		1.5	n.d.	n.d.	-[b]	-[b]	>47	300	-[b]
3	**17c**		-[b]	2.0[c]	pK_b 2.5	>130	<23	>50	9,100	6.9
4	**17d**		0.1	n.d.	no pK_a/pK_b[d]	>130	<23	>54	2,400	11.0
5	**17e**		0.2	n.d.	pK_b 3.8	>130	<23	>59	4,700	9.2
6	**17f**		–0.5	0.9[c]	pK_b 2.4	47	45	n.d.	6,900	5.7
7	**17g**		0.4	n.d.	no pK_a/pK_b[d]	>130	<23	n.d.	1,200	9.8
8	**17h**		1.5	n.d.	no pK_a/pK_b[d]	>130	<23	n.d.	1,200	9.5
9	**17i**		0.3	n.d.	n.d.	-[b]	-[b]	>44	300	-[b]
10	**17j**		0.5	n.d.	n.d.	>130	<23	n.d.	200	5.7

11	**17k**		0.2	n.d.	n.d.	>130	<23	n.d.	700	11.0
12	**17l**		n.d.	1.4[e]	pK_a 9.4	>130	<23	>48	800	4.1
13	**17m**		n.d.	2.3[e]	pK_a 10.7	>130	<23	>49	900	6.3
14	**17n**		2.7	n.d.	n.d.	-[b]	-[b]	47	90	-[b]

[a] For assay details see the Supporting Information; n.d.: not determined.
[b] No valid results were obtained.
[c] Measured at pH 12.
[d] No pK_a/pK_b was detected within the measurement range of the assay (pH 2-12).
[e] Measured at pH 2.

Table 4. Acylated and carbamoylated sulfoximines and related compounds.[a]

Entry	**Compound**	**Structure**	**logP [52]**		**pK_a/pK_b**	**Stability in human liver microsomes**		**Aqueous Solubility [µg/mL] [53]**		**Permeability (PAMPA) P_{app} [10^{-6} cm/s]**
			HPLC assay	**Potentio-metric assay**		**$T_{½}$ [min]**	**%Q_H**	**HPLC-Assay**	**Shake flask assay**	
1	**18a**		4.8	n.d.	n.d.	-[b]	-[b]	7	20	-[b]
2	**18b**		2.6	n.d.	n.d.	>130	<23	14	10	7.1
3	**18c**		n.d.	1.7[c]	pK_a 3.2	>130	<23	>62	>20,000	0.01
4	**18d**		1.8	n.d.	no pK_a/pK_b[d]	62	39	>53	300	11.0
5	**18e**		0.4	n.d.	no pK_a/pK_b[d]	>130	<23	n.d.	8,100	9.2
6	**19a**		4.4	n.d.	n.d.	-[b]	-[b]	<1	<1	0.8
7	**19b**		3.4	n.d.	n.d.	>130	<23	<1	20	5.1
8	**19c**		n.d.	1.9[c]	pK_a 4.2	>130	<23	55	11,100	0.04
9	**19d**		1.6	n.d.	no pK_a/pK_b[d]	>130	<23	44	40	4.3
10	**19e**		0.4	n.d.	pK_b 3.3[e]	-[b]	-[b]	>68	500	3.3

[a] For assay details see the Supporting Information; n.d.: not determined.
[b] No valid results were obtained.

[c] Measured at pH 2.
[d] No pK_a/pK_b was detected within the measurement range of the assay (pH 2-12).
[e] Protonation of S=N.

2.3.2.1 logP [52]

Within the series of *N*-[4-(trifluoromethyl)phenyl]sulfoximines and isosteric and related compounds **16**, the measured partition coefficients (HPLC assay) indicate that sulfoximines and related sulfondiimides and sulfonimidamides are relatively polar functional groups with the following order of logP: sulfondiimide (**16h**) ≈ sulfoxide (**16c**) << *N*-methylamide (**16b**) < sulfone (**16d**) ≈ sulfoximine (**15Ae**) < *N*-methylsulfonimidamide (**16k**) < amide (**16a**) < *N*,*N*-dimethylsulfonimidamide (**16l**) ≈ *N*-methylsulfonamide (**16g**) << sulfonate (**16e**). This suggests that as a rule of thumb for lipophilicity, sulfondiimides are comparable to sulfoxides and sulfoximines are comparable to sulfones and amides. *N*H-Sulfondiimides **16h** and **16i** were found to be more polar than their respective sulfoximine counterparts **1Ea** and **1Eh** by 1.5 to 2 logP units.

Within the series of *S*-[4-(trifluoromethyl)phenyl]sulfoximines **17**, unfortunately, no valid data could be obtained for *N*H-sulfoximine **17c** in the HPLC assay. Analyzing the available data from this assay, the following trend for logP is obtained: *N*-methylsulfonimidamide (**17f**) ≈ sulfoxide (**17a**) < *N*-alkylsulfoximines (**17d**, **17e**) ≈ *N*,*N*-dimethylamide (**17k**) ≈ amide (**17i**) < *N*,*N*'-dimethylsulfonimidamide (**17g**) < *N*-methylamide (**17j**) << sulfone (**17b**) ≈ *N*,*N*',*N*'-trimethylsulfonimidamide (**17h**). Based on the available data from the potentiometric assay, the sulfonimidamide **17f** and the sulfonamide **17l** are ranked as more polar than sulfoximine **17c**, which is slightly less polar than methylsulfonamide **17m**.

For the series of *N*-acyl and *N*-carbamoylsulfoximines **18** and **19**, and their isosteres the trends for lipophilicity as expressed by logP are comparable to the series of compounds **16**: sulfon-

diimides (**18e**, **19e**) << sulfoximines (**18d**, **19d**) ≈ sulfones (**18c**, **19c**) << *tert*-butyl amide (**18b**) < *tert*-butyl urea (**19b**) < *tert*-butyl carbamate (**19a**) < *tert*-butyl ester (**18a**).

2.3.2.2 Dissociation constants (pK_a/pK_b)

In accordance to literature data of related compounds, measurements of the dissociation constants confirmed that the sulfoximines **17c**, **17e**, **16m** and **16n** are weak bases [59] whereas the basicity of the *N*-[4-(trifluoromethyl)phenyl]sulfoximine **15Ae** was too low to be detected within the assay window (pK_a/pK_b 2-12). *S*-(4-Trifluoromethylphenyl)sulfoximines **17c** (pK_b = 2.5) and **17e** (pK_b = 3.8) are less basic than *S*-alkyl derivatives **16m** (pK_b = 4.2) and **16n** (pK_b = 5.0), the latter of which is approximately as basic as pyridine. Interestingly, no dissociation constant could be measured for *N*-methylsulfoximine **17d** within the assay window, and remarkably, sulfondiimide **16h** is significantly more basic (pK_b = 4.0) than its sulfoximine analogue **15Ae** (pK_b < 2). While sulfonimidamides **16k**, **16l**, **17g** and **17h** did not exhibit a pK_a/pK_b value within the scope of the assay, derivatives **16j** was found to be weakly acidic in the range of ethyl acetoacetate (pK_a = 10.3) and **17f** was determined to be a weak base (pK_b = 2.4). Within the series **18** and **19** of acyl- and carbamoyl derivatives, carbamoylsulfondiimide **19e** was detected as weak base (pK_b = 3.3), acyl- and carbamoylsulfonamides **18c** and **19c** were found to be acidic in the range of carboxylic acids (pK_a = 3.2 and 4.2, respectively), and *N*-arylated methanesulfonamide **16f** was weakly acidic (pK_a = 8.0).

2.3.2.3 Microsomal stability

As already observed for series **15**, the majority of the sulfoximines, sulfondiimides and sulfonimidamides from series **16**, **17**, **18** and **19** exhibited very high microsomal stability, often beyond

the scope of the assay ($T_{1/2}$ > 130 min). This underlines that sulfoximines and related functional groups have favorable metabolic stability.

2.3.2.4 Aqueous solubility

The solubility data from the HPLC assay for the compounds **17**, **18** and **19** cannot be fully analyzed, as many of the compounds are too soluble (>200 µM) to be precisely measured in this assay. The only clear trend is that the most lipophilic compounds **18a**, **19a** and **19b** are poorly soluble.

The data from the aqueous equilibrium solubility (shake flask assay) confirm that for most of the compounds, the solubility is high, often greater than 1 mg/mL. The solubility of the sulfoximines is usually high (**15Ae**, **16m**) or very high (**17c**, **17d**, **17e**) and only two examples show moderate solubility (**16n**, **19d**). Interestingly, the solubility of *S*-aryl sulfoximine **17c** is tenfold higher than for the corresponding *N*-aryl derivative **15Ae**. It is noteworthy, that *S*-aryl sulfoximine **17c** exhibits a very high solubility, comparable to sulfoxide **17a**, but a much higher (10-100 fold) solubility than sulfone **17b** or the corresponding amides (**17i**, **17j**, **17k**) or sulfonamides (**17l**, **17m**, **17n**).

For *N*-aryl sulfoximine **15Ae**, the solubility is inferior to the isosteric sulfoxide **16c**, comparable to *N*-methylamide **16b** and superior to amide **16a**, sulfone **16d**, sulfonate **16e** and sulfonamide **16g**. The sulfondiimides revealed high (**16i**, **19e**) or very high solubility (**16h**, **18e**). Interestingly, sulfondiimides **16h** and **18e** are by far more soluble than their sulfoximine analogs **15Ea** and **18d**. Within the class of sulfonimidamides, the solubilities are more diverse: while the *N*-arylated sulfonimidamides demonstrate a low (**16j**) or medium solubility (**16l**), *S*-arylated

analogs **17f**, **17g** and **17h** display a very high solubility, also higher than the corresponding sulfones **17l**, **17m** and **17n**.

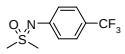
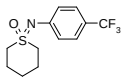
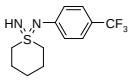
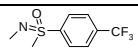
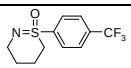
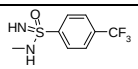
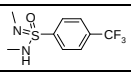
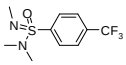
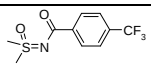
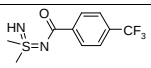
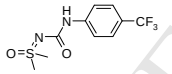
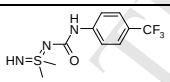
2.3.2.5 Permeability

As expected for such small molecules, the permeability of the compounds **16a-16n** and **17a-17n** is very high. Amongst the acylated compounds **18a-18e**, the acidic sulfonamide **18c** exhibits very low solubility, presumably caused by ionization as indicated by pH dependant permeability measurements (data not shown). For the carbamoyl derivatives **19a-19e**, permeability is generally slightly lower compared to compounds **16a-16e**, **17a-17e** and **18a-18e**, acidic sulfonamide **19c** showing again the lowest permeability.

2.3.2.6 Chemical stability

To assess the chemical stability of the functional groups, the degradation of a number of representative compounds was studied for seven days in aqueous solution at pH <1 and pH >10. [60] Generally, only minor decomposition was observed. Only benzoyl derivatives **18d** and **18e** completely decomposed under acidic conditions, however, this instability was not observed in the synthesis, purification and routine handling of this compound type. [61] Overall, the observations indicate that chemical stability in the range usually relevant for drug discovery is not problematic. Notably, only for the compounds **16i** and **19e** traces of the corresponding aniline as the decomposition product could be detected. Sulfilimines **16o** and **16q** as well as sulfinamide **16p** (Chart 2) were synthesized and could spectroscopically be characterized by NMR, however, their limited chemical stability impeded the determination of any further physicochemical data.

Table 5. Chemical stability of selected compounds.[a]

Entry	Compound	Structure	Decomposition pH <1	Decomposition pH >10
1	**15Ae**		13%	20%
2	**15He**		< 10%	< 10%
3	**16i**		13%	< 10%
4	**17d**		< 10%	< 10%
5	**17e**		< 10%	34%
6	**17f**		ca. 10%	< 10%
7	**17g**		< 10%	< 10%
8	**17h**		< 10%	ca. 10%
9	**18d**		> 90%	< 10%
10	**18e**		> 90%	34%
11	**19d**		< 10%	14%
12	**19e**		< 10%	< 10%

[a] For assay details see the Supporting Information.

Based on our results from this chapter, sulfoximines and the related sulfondiimides and sulfonimidamides do not show any intrinsic flaw. In comparison to other functional groups commonly used by medicinal chemists, they often exhibit favorable properties. As the small size of the model compounds investigated sometimes resulted in properties that were outside the range of the routine high-throughput assays, the analysis of molecules from drug discovery projects within BI was envisaged.

2.4 Physicochemical and in vitro pharmacokinetic analysis of molecules from drug discovery projects

In order to overcome the limitations of analyzing small and fragment-like sulfoximines and to gain knowledge based on molecules from drug discovery projects, we decided to analyze the data available from the Boehringer Ingelheim Corporate Database (CDB). To this end, we utilized a substructure search to identify matched molecular pairs or series of sulfoximines and related functional groups as well as more common structural motifs. [62] The functional groups of interest covered, amongst others, carboxylic acids, esters, amides, sulfoxides, sulfones, sulfonamides, sulfoximines, sulfondiimides, sulfonimidamides, amines, ureas and carbamates. Applying a filter for the molecular weight ($250 < MW < 750$) resulted in the identification of roughly 37,000 matched molecular pairs of compounds, where only the functional group of interest was changed, while the rest of the molecule remained constant.

For each matched molecular pair it was checked whether data for both compounds was available for at least one of the following assays: microsomal stability in human liver microsomes, aqueous solubility (high-throughput HPLC assay, pH 6.8) and Caco-2 permeability. [60] This resulted in a final dataset of transformations and associated experimental data comprising about 13,000 datapoints for microsomal stability, about 8,400 datapoints for aqueous solubility and about 2,800 datapoints for Caco-2 permeability. Given the fact that many of these datapoints obtained from routine assays are reported with an operator and considering the biological assay variability, it was not feasible to analyze in a statistically reliable manner the data based on ratios of two values and, for example, defining an improved microsomal stability by an n-fold increase of $t_{1/2}$. To identify trends within the dataset, an alternative approach was

chosen in which the data for these three assays were then classified into the three categories "desirable", "acceptable" and "undesirable" according to the criteria depicted in Table 6.

Table 6. Categories employed for the rating of experimental data.

Molecular property	**Unit**	**Definition "Desirable"**	**Definition "Acceptable"**	**Definition "Undesirable"**
Stability in human liver microsomes $T_{½}$	[min]	> 120 (< 25 % Q_H)	25-120 (25-75 % Q_H)	< 25 (>75% Q_H)
Aqueous Solubility	[µg / mL]	> 100	10-100	< 10
Caco-2 Permeability P_{app} a→b	10^{-6} cm/s	> 5	0.5 – 5	< 0.5

Next, it was determined for each matched molecular pair and separately for each assay, how the category for the respective result changed through the transformation: An improved rating is colored in green, an unchanged rating in grey and a worsened rating in red, according to the possible scenarios depicted in Table 7. [63]

Table 7. Rating of transformations.

Rating	**Possible scenarios resulting in this rating for the transformation**	**Coloring**
Improvement	undesirable → desirable acceptable → desirable undesirable → acceptable	green
No change	undesirable → undesirable acceptable → acceptable desirable → desirable	grey
Worsening	desirable → acceptable desirable → undesirable acceptable → undesirable	red

Finally, the processed data were plotted as pie charts in matrices, considering only those transformations where at least three datapoints were found. To illustrate the use of these matrices, the transformations of carboxylic acids, esters and primary and secondary amides are shown for stability in human liver microsomes in Figure 4.

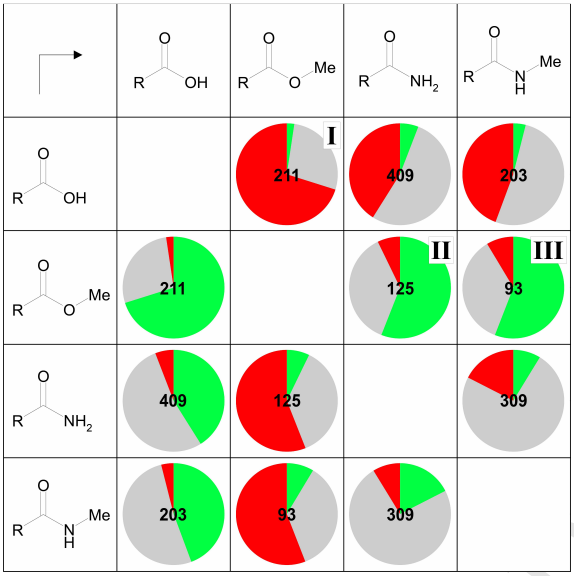


Figure 4. Stability in human liver microsomes of carboxylic acid derivatives. Numbers indicate dataset size.

The data in Figure **4** shows that the replacement of a carboxylic acid with a methyl ester worsens the stability in human liver microsomes in approximately two thirds of all cases and results in no change in approximately one third of all cases (**I**), while it rarely leads to an improvement. Changing a methyl ester into a primary amide (**II**) or into a methylamide (**III**) has a greater than 50% likelihood of improving microsomal stability and only a low probability of worsening it. In other words: switching towards an acid likely improves, switching to a methyl ester likely worsens microsomal stability.

2.4.1 Analysis of matrix data for microsomal stability, Caco-2 permeability and solubility

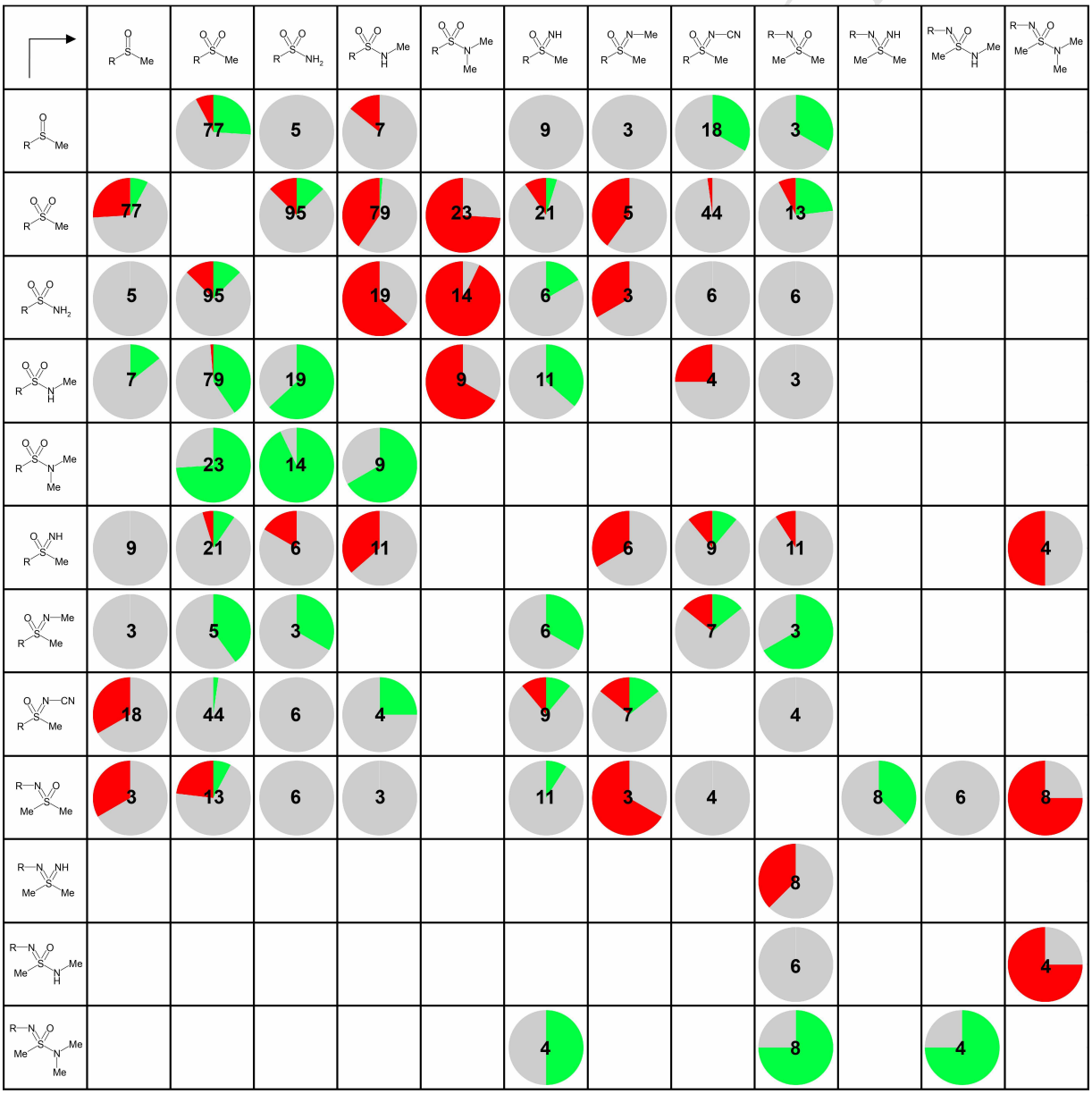
Figures **5**, **6** and **7** summarize the data for microsomal stability in human liver microsomes, Caco-2 permeability, and aqueous solubility at pH = 6.8 for selected transformations of sulfoximines and related functional groups. [60,64]

2.4.1.1 Microsomal stability in human liver microsomes (Figure 5)

As hypothesized, substituting a methylsulfoxide with a methylsulfone is beneficial for microsomal stability in a quarter of all cases and neutral in most other cases. In general, switching to a methylsulfone is likely to be neutral or beneficial with one remarkable exception: *N*-linked dimethylsulfoximines show even higher microsomal stability in one fourth of all cases. For sulfonamides, microsomal stability was found to improve along with increasing polarity in the order dimethylsulfonamide < methylsulfonamide < primary sulfonamide. Switching to a *N*H-sulfoximine was usually neutral (when substituting a methylsulfoxide or a methylsulfone) or beneficial (when replacing sulfonamides). Methylation of a *N*H-sulfoximine resulted in decreased microsomal stability in one third of all cases, while cyanation was most often neutral. Similarly, substitutions of methylsulfones or sulfonamides with *N*-methylsulfoximines were often detrimental for microsomal stability. *N*-Linked dimethylsulfoximines showed improved microsomal stability when replacing methylsulfoxides, methylsulfones or *N*-methylsulfoximines, and were outperformed only by the corresponding dimethylsulfondiimides in one third of all cases. The introduction of *N*-linked *S*,*N*,*N*-trimethylsulfonimidamides was found to worsen microsomal stability in most cases. As all other transformations including sulfondiimides or sulfonimidamides were only scarcely populated (n<3), they were not included in the matrix

analysis. However, as an overall trend we found that while exchanges towards sulfondiimides were usually neutral or beneficial for microsomal stability, exchanges towards sulfonimidamides were mostly neutral or detrimental for microsomal stability (data not shown).

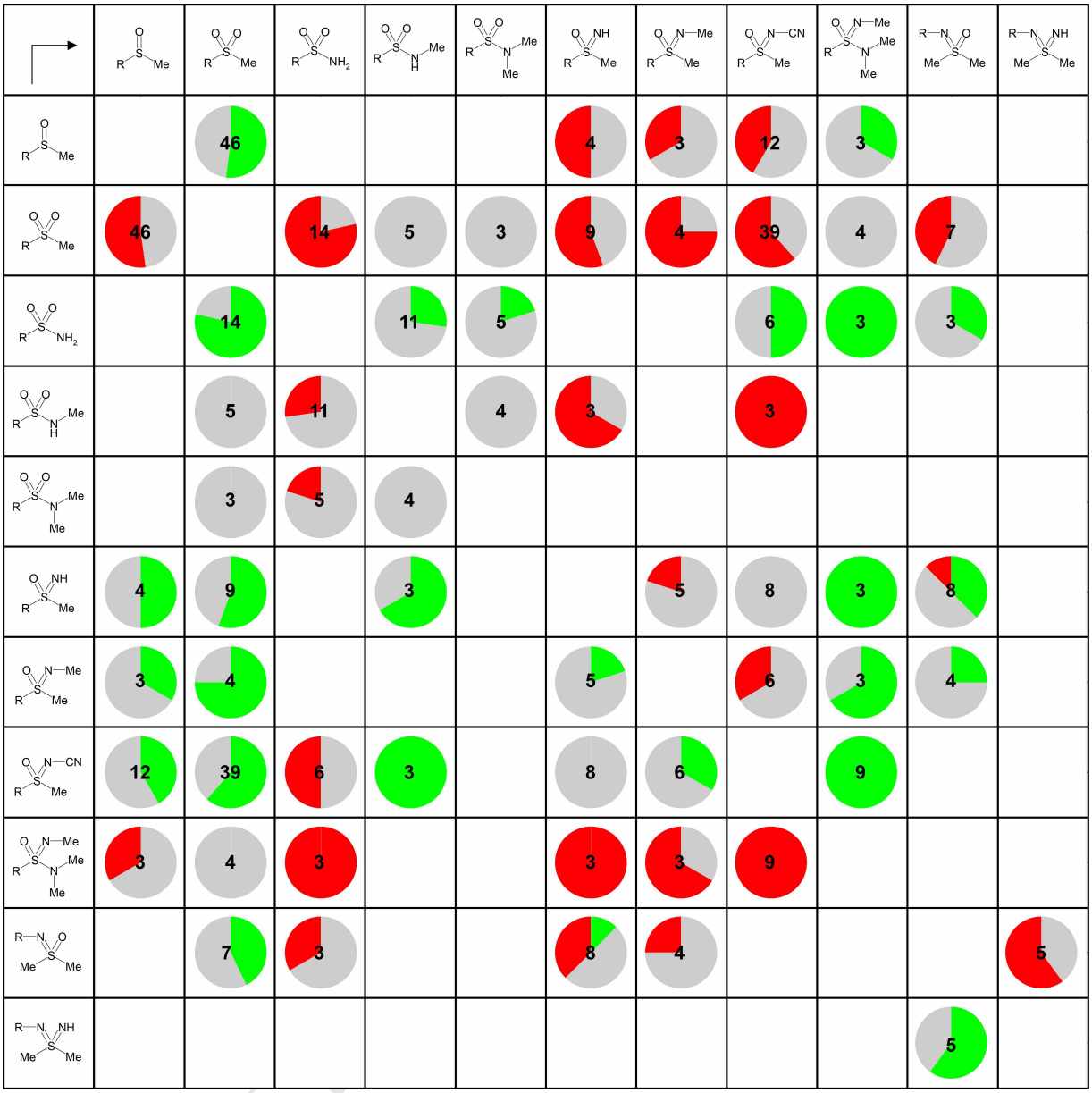
Figure 5. Microsomal stability data in human liver microsomes for selected transformations of sulfoximines and related functional groups. Numbers indicate dataset size.



2.4.1.2 Caco-2 permeability (Figure 6)

As expected, the substitution of methylsulfoxides with methylsulfones was observed to be beneficial for permeability in half of the cases and neutral in all other cases. In general, switching to a methylsulfone was never found to be detrimental for permeability but beneficial in many cases when replacing primary sulfonamides or sulfoximines. For sulfonamides, it was measured that permeability increased in some cases when switching from a primary sulfonamide to methyl- or dimethylsulfonamide, reflecting that permeability usually enhances with decreasing polarity. Generally, exchanging a primary sulfonamide never decreased, but often increased permeability. Substitutions with *S*-linked sulfoximines often reduced permeability or were at best neutral, but rarely beneficial. Interestingly, the methylation of *N*H-sulfoximines was not found to increase permeability. In contrast to their *S*-linked congeners, the introduction of *N*-linked dimethylsulfoximines was beneficial in many cases. Switching to a trimethylsulfonimidamide improved permeability in most cases and was never detrimental, also when replacing corresponding sulfoximine derivatives.

Figure 6. Caco-2 permeability data for selected transformations of sulfoximines and related functional groups. Numbers indicate dataset size.

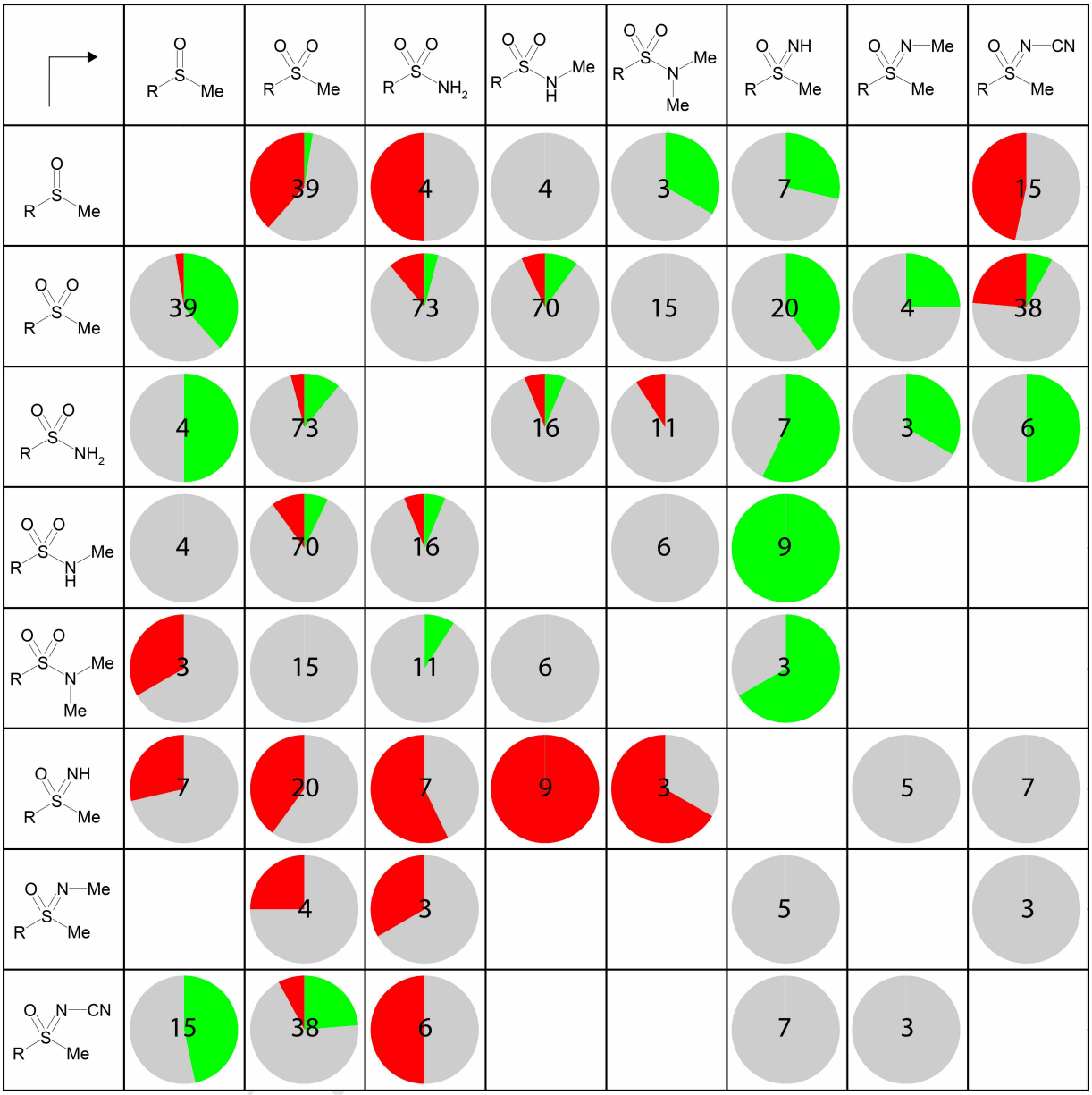


2.4.1.3 Aqueous solubility (Figure 7)

As aqueous solubility strongly depends on the pH, opposing trends are observed when analyzing solubility at different pH values. [60] As solubility at neutral pH was considered to be most relevant from a medicinal chemistry perspective, only data for solubility at pH = 6.8 are shown and discussed.

As expected, replacing methylsulfones with more polar methylsulfoxides led to an improved solubility in one third of the cases while being neutral in most other cases. Solubility decreased in half of the cases when methylsulfoxides were replaced with primary sulfonamides, but increased in one third of the cases when replaced with dimethylsulfonamides. Exchanges within primary, secondary or tertiary sulfonamides left solubility unchanged in most cases. Remarkably, we found that substitutions of methylsulfoxides, methylsulfones or sulfonamides with *N*H- or *N*-methylsulfoximines never decreased, but in many cases increased solubility.

Figure 7. Aqueous solubility at pH = 6.8 data for selected transformations of sulfoximines and related functional groups. Numbers indicate dataset size.



3. Conclusions

In summary, we have synthesized several series of tool compounds comprising sulfoximines, sulfondiimides and sulfonimidamides as well as their corresponding isosteres and analogous compounds with more common structural motifs, and explored their physicochemical properties

(logP, dissociation constant, aqueous solubility, chemical stability) and behavior in selected in vitro assays (permeability, microsomal stability).

As a rule of thumb for lipophilicity, we found that sulfoximines and sulfones have similar polarities and are less polar than sulfondiimides, which are comparable to sulfoxides. Sulfoximines were confirmed as weak bases, and sulfondiimides were observed to be significantly more basic than their sulfoximine analogues. Sulfoximines usually possessed high or very high aqueous solubility and higher solubility than the corresponding sulfones or other common functional groups such as amides or sulfonamides. Sulfondiimides often exceeded the solubility of their sulfoximine congeners, but showed decreased permeability. In most cases, sulfoximines and compounds with related functional groups showed high or very high microsomal stability. For some representative compounds the chemical stability was measured and assessed to be not problematic in the range that is usually relevant for drug discovery.

Furthermore, a matched molecular pair analysis of sulfoximines and related molecules from drug discovery projects within Boehringer Ingelheim was conducted. In this analysis, we found that the introduction of *S*-linked NH-sulfoximines often increased microsomal stability and solubility, but decreased permeability. Introduction of the corresponding NMe-sulfoximines reduced microsomal stability and permeability, but increased solubility. Finally, *N*-linked *S*,*S*-dimethylsulfoximines often improved permeability and sometimes microsomal stability.

The results from our study demonstrate that sulfoximines and the related sulfondiimides and sulfonimidamides do not have any intrinsic flaw. Instead, they often exhibit favorable properties compared to other more established functional groups. Moreover, their additional vectors at nitrogen enable simple chemical modifications and thus facilitate exploration and fine tuning of the molecular properties. Sulfoximines therefore do not deserve to be treated with reservations

and skepticism, but should be employed as routinely as established functional groups like sulfones or amides. We conclude that sulfoximines and their congeners significantly enrich the toolbox of medicinal chemists.

Appendix A. Supplementary data

Synthetic procedures and spectroscopic data for new compounds, descriptions of the physicochemical an in vitro assays, experimental data for the x-ray analyses and supplementary information on the matrix analyses can be found at http://.....

Appendix B. Accession Codes

CCDC-1483367 and CCDC-1483370 contain the supplementary crystallographic data for compound **16h** and **18e**, respectively. This data is available free of charge from The Cambridge Crystallographic Data Centre via https://summary.ccdc.cam.ac.uk/structure-summary-form.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

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Abbreviations

ADME, absorption, distribution, metabolism, excretion; ATR, ataxia-telangiectasia and Rad3 related; BSO, buthionine sulfoximine; CDB, Boehringer Ingelheim Corporate database; CDK, cyclin dependent kinase; dba, dibenzylideneacetone; DCE, 1,2-dichloroethane, DIPEA, *N*,*N*-diisopropylethylamine; DMAP, 4-dimethylaminopyridine; DMF, N,N-dimethylformamide; DMSO, dimethylsulfoxide; DPH, *O*-(2,4-dinitrophenyl)-hydroxylamine; GKRP, glucokinase regulatory protein; GSH, γ-L-glutamyl-L-cysteinylglycine (glutathione); HATU, *N*,*N*,*N*',*N*'-tetramethyl-*O*-(benzotriazol-1-yl)uronium hexafluorophosphate; JohnPhos, 2-(di-*tert*-butylphosphino)biphenyl; HIV, human immunodeficiency virus; HPLC; high performance liquid chromatography; MSH, *O*-mesitylenesulfonyl hydroxylamine; MNK, MAP kinase-interacting serine/theronine-protein kinase; n.d., not determined; NMR; nuclear magnetic resonance; PAMPA, parallel artificial membrane permeability assay; PYK, proline-rich tyrosine kinase; TFAA, trifluoroacetic anhydride; THF, tetrahydrofuran; THP, tetrahydropyran; Xantphos, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

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[50] Notably, in the reaction with methylamine (step d), sulfonamide **17m** was isolated separately as a side product in addition to the target substance **17g**.

[51] As depicted in Scheme 9, compound **17f** was present as the R–S(=O)(=NH)–NHMe and not the R–S(=O)(=NMe)–NH_2 tautomer. For details see the Supporting Information.

[52] As the partition-coefficient (logP) is pH-independent, we used these values to experimentally quantify the lipophilicity of the products. For those compounds that were measured in the potentiometric assay, experimental $logD_{7.4}$ values were also determined and found to be in excellent agreement with the logP values (see the supporting information). The acidic compounds **18c** and **19c** are the only exceptions and show significantly lower $logD_{7.4}$ values of –1.0 and –0.3, respectively.

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[64] For the sake of simplicity, the analysis shown here was limited to one variable residue R per functional group, and the remaining valences were saturated with hydrogen or methyl groups as shown. The analysis was also conducted for the case of multiple variable residues R per functional groups which then included cases where the functional group of interest was a central linker within the molecule: the results obtained here led to similar conclusions (data not shown).

HIGHLIGHTS

- Novel sulfoximines, sulfondiimides and sulfonimidamides have been synthesized.
- The physicochemical and in vitro properties of sulfoximines are analyzed.
- A matched molecular pair analysis of sulfoximines from a corporate database is shown.
- Sulfoximines are demonstrated to be free of any intrinsic flaws.