Exploration of Novel Chemical Space: Synthesis and in vitro Evaluation of N-Functionalized Tertiary Sulfonimidamides

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Abstract: An unprecedented set of structurally diverse sulfonimidamides (47 compounds) has been prepared by various N-functionalization reactions of tertiary -NH sulfonimidamide 2aa. These N-functionalization reactions of model compound 2aa include arylation, alkylation, trifluoromethylation, cyanation, sulfonation, alkoxylation, carbamate formation and aminocarbonylation (urea formation). Small molecule X-ray analyses of selected N-functionalized products are reported. To gain further insight into the properties of sulfonimidamides relevant to medicinal chemistry, a variety of structurally diverse reaction products were tested in selected in vitro assays. The described N-functionalization reactions provide a short and efficient approach to structurally diverse sulfonimidamides which have been the subject of recent, growing interest in the life sciences.

Introduction

The sulfonamide group 1 (Figure 1) is an important pharmacophore found in about 200 drugs currently on the market.[1] In contrast, sulfonimidamides 2, the mono-aza analogues of sulfonamides 1, have received little interest until recently, despite being first synthesized as early as 1962.[2] The infrequent take-up of the sulfonimidamide group as a pharmacophore is surprising since it seems to offer very interesting properties, including high stability, favorable physicochemical properties, multiple hydrogen-bond acceptor/donor functionalities and structural diversity.[3]

Possible reasons for the neglected use of the sulfonimidamide group are the lack of commercial availability and limited synthetic methods for its preparation,[4] as well as an incomplete understanding of its medicinal chemistry properties. However, as recently pointed out by Arvidsson and co-workers, the sulfonimidamide group is currently gaining popularity as a novel pharmacophore in the life sciences.[5] Examples include the sulfonimidamide analogues 5 and 6 of the clinical sulfonamide-containing anticancer agent tasisulam[6] and non-steroidal anti-inflammatory drug celecoxib,[7] respectively, as well as an increasing number of sulfonimidamides claimed in patent applications, for instance the sodium channel inhibitor 7 (Figure 2).[8] However, to the best of our knowledge, a sulfonimidamide candidate for clinical testing has yet to be disclosed.

This increasing interest in the life sciences is supported by the very recent advent of new and safe synthetic methods for the preparation of sulfonimidamides 2. Latest developments include the copper-catalyzed conversion of sulfonoximes 4 into sulfonimidamides 2,[9] the preparation of trifluoromethylated sulfonimidamides[10] and the one-pot de novo synthesis of sulfonimidamides relying on the stable reagent N-sulfanyltritylamine.[11]

Triggere...
The reaction is mediated by commercially available (diacetoxyiodo)benzene and ammonium carbamate in methanol at room temperature and tolerates a wide range of functional groups. Originally, these reaction conditions had been newly reported by Bull, Luisi and co-workers\cite{13} for the conversion of sulfoxides into sulfoximines 4. Moreover, we investigated a variety of in vitro properties, relevant to medicinal chemistry, of –NH sulfoximines 2aa in comparison to its matched sulfonamide analogue 1aa and did not identify any intrinsic flaw of the –NH sulfoximide group with respect to its application in the life sciences.\cite{12}

However, in contrast to sulfonamides 1, –NH sulfoximidamides 2a offer the possibility of exploration of novel chemical space via the introduction of substituents at the –NH position. Functionalization of this –NH position would also offer an additional handle to modulate the overall properties of the resulting molecules, for example with respect to conformational behavior, lipophilicity and physicochemical properties.

Therefore, we set course to investigate the N-functionalization of tertiary –NH sulfoximidamides 2a. To test the desired transformations, we selected –NH sulfoximidamide 2aa as a model compound, which had been prepared from the corresponding sulfonamide 3 on a gram scale by the one-pot NH-transfer method (Scheme 1).\cite{12}

With respect to the reactivity of the –NH position, we expected a certain similarity of sulfoximidamides and sulfoximines. Therefore, we elected to probe reaction conditions for the desired N-functionalizations of –NH sulfoximidamides that we had already successfully employed for the analogous reactions of –NH sulfoximines, even on complex, drug-like molecules.\cite{14}

### Results and Discussion

The palladium-catalyzed coupling of –NH sulfoximines with aryl bromides was first described in 1998 by Bolm and Hildebrand who used catalytic amounts of Pd(OAc)\(_2\) and a chelating bisphosphine (e.g., BINAP) in the presence of Cs\(_2\)CO\(_3\) as a base.\cite{15} In the meantime, a variety of modified reaction conditions and reagents have been described by both academic and industrial groups.\cite{16} In our drug discovery efforts, we had relied on the catalyst system Pd\(_2\)(dba)/BINAP\cite{14e,i} or Pd\(_2\)(dba)/Xantphos\cite{17} in toluene in the presence of Cs\(_2\)CO\(_3\) for this type of reaction. However, in an ongoing lead optimization approach, we recently switched to the combination of Pd(OAc)\(_2\) and Xantphos as a catalyst since the use of Pd\(_2\)(dba) resulted in purification issues.\cite{18} In contrast to the broad variety of N-arylation methods available for –NH sulfoximines, as far as we are aware there is only one report of the analogous palladium-catalyzed reaction of –NH sulfoximidamides. Thus, Arvidsson and co-workers used RuPhos and 2nd generation RuPhos precatalyst in THF in the presence of NaO\(_2\)Bu under microwave conditions; nevertheless, only four structurally simple products, having no substituents at the aryl group, were described.\cite{19} The same research group also successfully investigated the copper-catalyzed coupling of –NH sulfoximidamides with boronic acids.\cite{20} However, we were mainly interested in the N-arylation of –NH sulfoximidamides using aryl halides, due to better availability and reduced costs. Hence, conditions that we had successfully applied for the analogous functionalization of –NH sulfoximines were tested. As a model reaction, tertiary –NH sulfoximidamide 2aa (100 mg, 0.45 mmol, 1.1 equiv) was treated with bromobenzene (8a, 1 equiv) in the presence of catalytic amounts of Pd(OAc)\(_2\) (5 mol\%) and Xantphos (10 mol\%), along with Cs\(_2\)CO\(_3\) (1.5 equiv), in toluene at 100°C overnight. To our delight, the desired coupling product 2ba was isolated in 86% yield after column chromatography (Table 1). Given the clean reaction and very good yield, we then elected to explore the substrate scope of this new process. A variety of substituted aryl bromides 8b–l were subjected to the standard reaction conditions. Gratifyingly, the desired products 2bb–2bl were afforded in all cases, the majority in good to excellent yields.

**Figure 2.** Structures of the sulfonimidamide analogues 5 and 6 of the clinical sulfonamide-containing anticancer agent tasisulam\cite{20} and non-steroidal anti-inflammatory drug celecoxib,\cite{21} as well as of the sodium channel inhibitor 7\cite{21} disclosed in a recent patent application.

**Scheme 1.** Synthesis of N-functionalized tertiary sulfoximidamides by various methods using –NH sulfoximidamide 2aa as a model compound.
The exception was the reaction of 2-bromo-1,3,5-trimethylbenzene (8h) which gave the coupling product 2bh in very low yield (3%). This is probably due to steric hindrance resulting from the two methyl groups at the positions ortho to the bromine, since the monosubstituted bromotoluenes 8e–q all resulted in very good yields. Coupling product 2bk was successfully recrystallized and the structure confirmed by X-ray analysis (Figure 3) for additional X-ray analyses (compounds 2bg, 2bj and 2bm, see the Supporting Information). The reaction of various heteroaryl bromides 8m–q also gave the desired heteroaromatic products 2bm–2bq in good yields.

Figure 4. Examples of clinical and commercial sulfoximines: BAY 1251152, AZD 6738, suloxifen and sulfoxaflor.

Table 1. Exploration of the substrate scope of the palladium-catalyzed N-arylation of tertiary =NH sulfinimidamide 2aa: Variation of aryl bromide 8.

| Aryl bromide (R^1Br) | Isolated yield [%] |
|----------------------|-------------------|
| 8a: bromobenzene     | 2ba: 86           |
| 8b: 1-bromo-2-fluorobenzene | 2bb: 46       |
| 8c: 1-bromo-3-fluorobenzene | 2bc: 97       |
| 8d: 1-bromo-4-fluorobenzene | 2bd: 72       |
| 8e: 2-bromotoluene   | 2be: 97           |
| 8f: 3-bromotoluene   | 2bf: 84           |
| 8g: 4-bromotoluene   | 2bg: 99           |
| 8h: 2-bromo-1,3,5-trimethylbenzene | 2bh: 3       |
| 8i: 3-bromoanisole   | 2bi: 65           |
| 8j: 4-bromobenzonitrile | 2bj: 88       |
| 8k: methyl 4-bromobenzoate | 2bk: 99       |
| 8l: 4-bromobenzotri fluoride | 2bl: quant. |
| 8m: 2-bromopyridine  | 2bm: 71           |
| 8n: 3-bromopyridine  | 2bn: 77           |
| 8o: 4-bromopyridine  | 2bo: 72           |
| 8p: 2-bromopyrimidine| 2bp: 77           |
| 8q: 2-bromo-1,3-thiazole | 2bq: 45       |

(1.5 equiv) in DMSO in the presence of 2:1 -bromo-2-fluorobenzene 24 using alkyl bromides in the 2-bromopyridine 24 and 2-bromotoluene 4 -bromotoluene was successfully recrystallized and the structure confirmed by X-ray analysis (Figure 3) for additional X-ray analyses (compounds 2bg, 2bj and 2bm, see the Supporting Information). The reaction of various heteroaryl bromides 8m–q also gave the desired heteroaromatic products 2bm–2bq in good yields.

Figure 3. ORTEP plot (50% thermal ellipsoids) of the crystal structure of N-arylated sulfinimidamide 2bk.

Another important option for the N-functionalization of =NH sulfoximines and =NH sulfinimidamides is the corresponding N-alkylation reaction. It is noteworthy that all recent sulfoximine clinical candidates, the kinase inhibitors roniciclib (BAY 1000394)[11a,21] atveciclib (BAY 1143572)[22] AZD 6738 (Figure 4)[23] and BAY 1251152 (Figure 4)[24] contain an unsubstituted =NH group. However, since for instance low Caco2 permeability and high efflux can be an issue with =NH sulfoximines,10c,10d N-alkylation may be a means of improving the permeability properties.10d,10e Moreover, N-alkylation is an interesting option for drug design to explore novel chemical space. Satzinger and Stoss, who pioneered the use of the sulfoximine group in drug discovery, were originally attracted to this functional group by this possibility of introducing substituents at the =NH position. Their lead optimization efforts led to the identification of the first sulfoximine clinical candidate suloxifen, which is an N-alkylated diphenyl sulfoximine (Figure 4).10c,25

Direct N-alkylation of =NH sulfoximines is not a trivial task since the nucleophilicity of the nitrogen is dramatically reduced due to steric and electronic effects of the adjacent tetra-coordinated sulfur.26 N-Methylation of =NH sulfoximines has usually been achieved under Eschweiler–Clarke conditions or by the use of a strong methyl-transfer agent.27 Introduction of more complex alkyl groups, however, remained difficult until Bolm and co-workers introduced a new method employing alkyl bromides and KOH as a base in DMSO at room temperature.28

So far, there have been scant reports of the corresponding direct N-alkylation of =NH sulfinimidamides, the first from Johnson and Lavergne.33,34 They discovered that while Eschweiler–Clarke conditions resulted in degradation of the =NH sulfinimidamide starting materials, the use of primary alkyl bromides in combination with KH and the phase-transfer catalyst Bu4NBr in 1,2-dimethoxyethane gave the desired N-alkylation products in good to excellent yields. In contrast, secondary bromides did not provide the N-alkylated products under these conditions.

Along the lines of our concept to apply successful reaction conditions from our experience with =NH sulfoximines in drug discovery to =NH sulfinimidamides, we investigated the N-alkylation of model compound 2aa using alkyl bromides in the presence of KOH in DMSO. In the first reaction, tertiary =NH sulfinimidamide 2aa (100 mg, 0.45 mmol, 1 equiv) was treated with bromoethane (9a, 1.5 equiv) in DMSO in the presence of KOH (2 equiv) for 4 hours at room temperature, to give the desired N-ethyl derivative 2ca in 99% isolated yield (Table 2).
This radical process relies to isolate the methylated product. Exploration of the substrate scope of the N-alkylation of tertiary N-alkylation products, usually in good yields. 2018 thyl bromoacetate can be considered as a partially was isolated but none other compound. There is also one report by Gnam and co-workers with a variety of more complex alkyl bromides in 59% yield. Benzyl bromide (9n) under radical conditions also gave the desired product in 44% yield (Scheme 2) without further optimization.

After this initial success, the substrate scope of this new process was explored using alkyl bromides 9b–l. In contrast to Johnson and Lavergne’s method, reaction of the secondary alkyl bromide 2-bromopropane (9b) also gave the desired product 2cb, albeit in a significantly reduced yield of 38%. Reaction of 2aa with a variety of more complex alkyl bromides 9c–k gave the corresponding N-alkylation products, usually in good to moderate yields. Similar to the reported results of the N-alkylation of sulfoximines, the use of N-(2-bromomethyl)-N,N-diethyamine (9l) resulted in a low 13% yield. However, the corresponding product 2cl can be considered as a partially saturated sulfonylimidamide analogue of the potent spasmyloptic and antiasthmatic agent sulfoxifen (Figure 4). Since methyl bromide is a gas, we employed methyl iodide for the desired N-methylation reaction of 2aa to isolate the methylated product 2cm in 59% yield. Benzyl bromide (9n) reacted with 2aa in a similar yield of 57% (2cm), and product 2co was isolated from the reaction with heterocyclic 3-(bromomethyl)-5-methylisoxazole (9o) in good yield. Moreover, the reactions of allyl bromide (9p) and propargyl bromides 9q,r also gave the corresponding products 2cp–2cr in good yields.

Bolm and co-workers recently achieved the first N-trifluoromethylation of NH sulfoximines. This radical process relies on the use of TMSCF₃ as a trifluoromethylation agent and catalytic amounts of Ag₂CO₃ and 1,10-phenanthroline under an oxygen atmosphere. The introduction of trifluoromethyl substituents is now a well-accepted strategy in medicinal chemistry, since it can significantly alter the properties of the resulting compounds, for example with respect to lipophilicity, metabolic stability and conformational behavior. Since N-trifluoromethylation of NH sulfonylimidamides has not been reported, we were intrigued to apply the above conditions to model compound 2aa. To our delight, the desired product 2cs was formed and could be isolated in 44% yield (Scheme 2).

**Scheme 2.** Synthesis of N-trifluoromethylated tertiary sulfonylimidamide 2cs.

N-Cyanation of NH sulfoximines is another interesting design option in the life sciences. The resulting NH sulfoximine group is, for instance, present in the only marketed sulfoxime so far, the insecticide sulfoxaflor (Figure 4). In the past, we and others have relied on the reaction of NH sulfoximines with cyanogen bromide to prepare NH-CN sulfoximines. There is also one report by Gnam and co-workers of the successful application of this method for the preparation of an NH-CN sulfonylimidamide derivative. However, given the high toxicity of the required cyanogen bromide, a new, environmentally benign procedure caught our attention. Thus, Cheng and co-workers recently reported the direct copper-catalyzed N-cyanation of NH sulfoximines using AIBN as a safe cyanide source. Given the successful N-trifluoromethylation of NH sulfonylimidamide 2aa under radical conditions (Scheme 2), we elected to apply the new radical N-cyanation process of sulfoximines to NH sulfonylimidamide model compound 2aa and at once isolated the corresponding product 2da in 43% yield (Scheme 3).

**Scheme 3.** Synthesis of N-cyanated tertiary sulfonylimidamide 2da.

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**Scheme 3.** Synthesis of N-cyanated tertiary sulfonylimidamide 2da.
tained by the direct reaction of $\equiv\text{NH}$ sulfonimidamides with sulfonyl chlorides. Nevertheless, the reaction of model compound 2aa with sulfonyl chlorides 10a,b in pyridine at room temperature gave the desired coupling products in good yields (Table 3).

### Table 3. N-Sulfonylation of tertiary $\equiv\text{NH}$ sulfonimidamide 2aa with sulfonyl chlorides 10a,b.

| Sulfonyl chloride (RSO₂Cl) | Isolated yield [%] |
|---------------------------|-------------------|
| 10a: methanesulfonyl chloride |  2aa: 62 |
| 10b: p-toluenesulfonyl chloride |  2eb: 58 |

The carbamate group is a key structural motif in many approved drugs. Sulfoximes and sulfonimidamides also offer the opportunity to form carbamate-type products by employing the $\equiv\text{NH}$ position. The first N-(sulfoxylidene)carbamate was described in 1970 and products of this type are usually synthesized by the reaction of $\equiv\text{NH}$ sulfoximes with chloroformates. Carbamates based on sulfonimidamides were already described in 1963 but, to the best of our knowledge, there is only one literature example of a direct coupling of an $\equiv\text{NH}$ sulfonimidamide with a chloroformate. To gain further insight into this straightforward method, $\equiv\text{NH}$ sulfonimidamide model compound 2aa was reacted with chloroformates 11a,b in pyridine to give the coupling products in good yields (Table 4).

### Table 4. N-Alkoxy carbonylation of tertiary $\equiv\text{NH}$ sulfonimidamide 2aa with chloroformates 11a,b (carbamate formation).

| Chloroformate [R’OC(O)Cl] | Isolated yield [%] |
|---------------------------|-------------------|
| 11a: phenyl chloroformate |  2fa: 60 |
| 11b: ethyl chloroformate |  2fb: 69 |

Like the carbamate group, the urea moiety is a very important pharmacophore in the life sciences. The formation of N-(sulfoxylidene)urea derivatives via reaction of the $\equiv\text{NH}$ group of sulfoximes with isocyanates was described as early as 1965. We have also successfully applied this reaction in a variety of lead optimization programs. In comparison, very few sulfonimidamide-based ureas have been described as yet. As far as we are aware, none of these products was obtained by the direct reaction of an $\equiv\text{NH}$ sulfonimidamide with an isocyanate. However, the reaction of $\equiv\text{NH}$ sulfonimidamide model compound 2aa with isocyanates 12a-f in dichloromethane at room temperature gave the desired coupling products in good yields (Table 5).

### Table 5. N-Aminocarbonylation of tertiary $\equiv\text{NH}$ sulfonimidamide 2aa with isocyanates 12a-f (urea formation).

| Isocyanate (R’N = C=O) | Isolated yield [%] |
|--------------------------|-------------------|
| 12a: n-propyl isocyanate |  2ga: 65 |
| 12b: phenyl isocyanate |  2gb: 79 |
| 12c: 4-nitrophenyl isocyanate |  2gc: 82 |
| 12d: 2.5-dimethoxyphenyl isocyanate |  2gd: 75 |
| 12e: 4-methoxyphenyl isocyanate |  2ge: 82 |
| 12f: |  2gf: 49 |

In a recent, preliminary assessment of the medicinal chemistry properties of sulfonimidamides, the behavior of $\equiv\text{NH}$ sulfonimidamide 2aa was compared to the matched sulfonamide analogue 1aa in selected in vitro assays. The hydrolytic stability of both compounds at different pH values was investigated, along with the metabolic stability in liver microsomes (human, rat and mouse) and also rat hepatocytes in vitro. Furthermore, the Caco2 permeability and logD values were determined. In vitro, model compound 2aa did not reveal any intrinsic flaw of the sulfonimidamide group with respect to its application in the life sciences.

To gain further knowledge of the properties of the neglected sulfonimidamide group, selected N-functionalized sulfonimidamides were evaluated in the same in vitro panel (Table 6 contains selected examples; see the Supporting Information for additional examples). Similar to $\equiv\text{NH}$ sulfonimidamide 2aa, the tested N-functionalized sulfonimidamides revealed very high hydrolytic stabilities after 24 hours with stirring at pH 1, 7 and 10. The only exception was N-trifluoromethylated sulfonimidamide 2cs that revealed signs of hydrolysis at pH 1 and 10.

As expected, introduction of a substituent at the $\equiv\text{NH}$ position significantly influences the lipophilicity of the resulting compounds. Depending on the nature of the substituent, logD values in the range of 1.9 (2d) up to 4.3 (2bc) were recorded. Introduction of a methyl group at the $\equiv\text{NH}$ position, for instance, resulted in an increased logD value from 1.9 (2aa) to 2.4 (2cm), whereas the introduction of a trifluoromethyl group raised the logD value to 3.7 (2cs).

All compounds were tested in a Caco2 screening assay and revealed high permeability coefficients ($P_{app}$ A–B) and no evidence of drug efflux. This behavior can be attributed to the...
In vitro pharmacokinetic studies in liver microsomes of human, rat and mouse origin, and rat hepatocytes, with selected N-functionalized sulfonimidamides revealed a clear species dependence of the predicted metabolic stabilities, given as the maximum oral bioavailability \( F_{\text{max}} \) (Table 6 and Supporting Information). From the studies with rat hepatocytes, low metabolic stabilities \( (F_{\text{max}} < 30\%) \) were observed for all tested sulfonimidamides as well as sulfonamide \( 1\text{aa} \). Similar instabilities were also observed with rat liver microsomes, which is well in line with the unrestricted membrane permeability observed in Caco2 cells and hints at a major involvement of Phase I metabolism for these compounds in rats. Based on liver microsomes from humans, however, the metabolic stabilities cover the whole range, from high \( (F_{\text{max}} > 70\%) \) to low \( (F_{\text{max}} < 30\%) \). This range of metabolic stabilities in human liver microsomes correlates nicely with the corresponding log\(D\) values of the test compounds (see the Supporting Information), which is in line with the general trend for many chemical series in the life sciences.\(^{[27]}\) However, it is noteworthy that the main sites of metabolism and the involved metabolic enzymes were not determined in these in vitro studies.

Conclusions

Although overlooked in the life sciences for a long time, the sulfonimidamide functional group has recently been the subject of a growing interest as a versatile pharmacophore. Based on the premise that the \( \equiv\text{NH} \) position of tertiary sulfonimidamides should show a similar reactivity as the \( \equiv\text{NH} \) position of sulfoximines, we have successfully applied various reported re-

### Table 6. Comparison of the in vitro properties of sulfonamide \( 1\text{aa} \) and the analogous \( \equiv\text{NH} \) sulfonimidamide \( 2\text{aa} \) with a structural variety of N-functionalized sulfonimidamides.

| Compound | Recovery \([\%]^{[a]}\) | \( F_{\text{max}} \) \( (\text{h}/\text{m}) \) | \( P_{\text{app}} \) A-B | Efflux log\(D\) | pH 7.5 | log\(D\) |
|----------|-----------------|-----------------|-----------------|-----------------|-------|-------|
| \( 1\text{aa} \) | 100 (1) | 69 (h) | 10 (1) | 26 (m) | 4.3 | 393 | 0.64 | 2.6 |
| \( 2\text{aa} \) | 100 (1) | 97 (h) | 30 (1) | 79 (m) | 14 | 378 | 0.59 | 1.9 |
| \( 2\text{cl} \) | 100 (1) | 100 (h) | 3.4 (1) | 164 (m) | 8.2 | 11 | 26 | 1.5 | 1.9 |
| \( 2\text{ea} \) | 100 (1) | 100 (h) | 33 (1) | 20 Tal 83 (m) | 83 (m) | 87 (h) | 11 (1) | 47 (m) | 7.8 | 256 | 0.73 | 2.2 |
| \( 2\text{da} \) | 100 (1) | 84 (h) | 18 (1) | 19 (m) | 40 (1) | 84 (h) | 18 (1) | 47 (m) | 19 | 26 | 0.57 | 2.4 |
| \( 2\text{cm} \) | 100 (1) | 82 (h) | 18 (1) | 67 (m) | 40 (1) | 82 (h) | 18 (1) | 47 (m) | 26 | 0.61 | 2.6 |
| \( 2\text{bo} \) | 100 (1) | 65 (h) | 26 (1) | 11 (m) | 40 (1) | 65 (h) | 26 (1) | 28 (m) | 11 | 404 | 0.57 | 3.0 |
| \( 2\text{gb} \) | 100 (1) | 56 (1) | 19 (1) | 9.3 (m) | 6.8 | 192 | 0.70 | 3.7 |

\[ ^a \] Hydrolytic stability measured as recovery of test compound after 24 hours with stirring at pH \( 1 \) (HCl buffer), pH \( 7 \) (phosphate-buffered saline) and pH \( 10 \) (sodium borate buffer).\(^{[48]}\) Predicted hepatic metabolic first pass given as the maximum oral bioavailability \( F_{\text{max}} \) based on a metabolic stability assay using (i) pooled human liver microsomes (hLMs), (ii) pooled rat liver microsomes (rLMs), (iii) pooled mouse liver microsomes (mLMs) and (iv) freshly harvested rat hepatocytes (rHep).\(^{[49]}\) [c] \( P_{\text{app}} \) A-B (apical to basolateral) and efflux ratio (ER) data were generated in a bidirectionally performed Caco2 permeability assay in a 24-well format; ER was calculated as \( \text{P}_{\text{app}}\text{B}/\text{P}_{\text{app}}\text{A} \).\(^{[46]}\) [d] Determined by reversed-phase HPLC.\(^{[50]}\)
action conditions for the N-functionalization of sulfoximines to the tertiary \(\equiv\text{NH} \) sulfonimidamide model compound 2aa. Using this methodology, we have synthesized an unprecedented set of structurally diverse sulfonimidamides (47 compounds). The described N-functionalization reactions include arylation, alkylation, trifluoromethylation, cyanation, sulfonylation, alkoxy carbonylation (carbamate formation) and aminocarbonylation (urea formation). Generally, only isolated examples of these transformations have been reported previously, and we have utilized many of the described reactions for the first time for the N-functionalization of \(\equiv\text{NH} \) sulfonimidamides. In vitro studies of selected, structurally diverse N-functionalized sulfonimidamides from our set of compounds have not revealed any intrinsic flaw of the sulfonimidamide group with respect to its application as a versatile pharmacophore in drug discovery. The combination of our recently reported one-pot synthesis of tertiary \(\equiv\text{NH} \) sulfonimidamides by \(\equiv\text{NH} \) transfer to simple sulfinamides and the subsequent N-functionalization of the newly formed \(\equiv\text{NH} \) position employing the now-outlined set of reactions offers rapid access to highly complex and structurally diverse molecules, addressing novel chemical space with properties suitable for application in the life sciences.

Experimental Section

N-Arylation of sulfonimidamide 2aa: General procedure A

In a dry MW vial flushed with Ar, sulfonimidamide 2aa (100 mg, 0.45 mmol, 1.1 equiv) and an aryl bromide (0.40 mmol, 1.0 equiv) were dissolved in toluene (6.8 mL). The mixture was then degassed for 10 min and Pd(OAc)\(_2\) (4.44 mL, 2.22 mmol, 5.0 equiv; 0.5 m solution in THF) was added. Then, a balloon charged with O\(_2\) was attached to the MW vial and the solution was degassed for 10 min. The mixture was stirred and heated in an oil bath at 60°C for 16 h. Then, the solution was cooled, solvent removed in vacuo and the crude product was purified by flash column chromatography.

1-(N-Ethyl-S-phenylsulfonylimidoyl)piperidine (2ca)

In a MW vial charged with sulfonimidamide 2aa (100 mg, 0.45 mmol, 1.0 equiv), TMSCF\(_3\) (4.44 mL, 22.0 mmol, 5.0 equiv; 0.5 m solution in THF), Ag\(_2\)CO (24 mg, 0.09 mmol, 0.2 equiv), 1,10-phenanthroline (32 mg, 0.18 mmol, 0.4 equiv) and 1,4-dioxane (8.9 mL) were added. Then, a balloon charged with O\(_2\) was attached to the MW vial and the solution was degassed for 10 min. The mixture was stirred and heated in an oil bath at 75°C for 16 h. Then, the solution was cooled, solvent removed in vacuo and the crude product was purified by flash column chromatography (KP-SiO\(_2\), 0–50% EtOAc in PE) to give 2ca as a colorless oil (111 mg, 99%). \(\delta\)\(_{\text{H}}\) NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.66–7.63\) (m, 2H), 7.33–7.24 (m, 3H), 3.10 (dq, \(J = 12.3, 7.2\) Hz, 1H), 2.93 (dq, \(J = 12.3, 7.2\) Hz, 1H), 2.71 (qt, \(J = 11.7, 5.4\) Hz, 4H), 1.39 (quin, \(J = 6.6\) Hz, 4H), 1.17 (tt, \(J = 8.3, 4.7\) Hz, 2H), 1.06 ppm (t, \(J = 7.2\) Hz, 3H); \(\delta\)\(_{\text{C}}\) NMR (101 MHz, CDCl\(_3\)): \(\delta = 136.1, 131.8, 128.5, 127.7, 47.7, 36.8, 25.5, 23.7, 18.3\) ppm; IR (KBr): \(\nu = 3063, 2934, 2853, 1524, 1153, 914\) cm\(^{-1}\); HRMS (ESI-TOF) \(m/z\) [\(\text{M} + \text{H}\)^+] calcd for C\(_{15}\)H\(_{22}\)N\(_2\)O\(_2\): 253.1375, found: 253.1379.

N-Trifluoromethylation of sulfonimidamide 2aa\(^{[2a]}\)

In a MW vial charged with sulfonimidamide 2aa (100 mg, 0.45 mmol, 1.0 equiv), CuI (16 mg, 0.09 mmol, 0.2 equiv), KSCN (122 mg, 0.88 mmol, 2.0 equiv) and MeCN (6.7 mL) were added. Then, a balloon charged with O\(_2\) was attached to the MW vial and the solution was degassed for 10 min. The mixture was stirred and heated in an oil bath at 75°C for 16 h. Then, the solution was cooled, filtered and the solids washed with MeCN. The liquid phase was collected, solvent removed in vacuo and the crude product was purified by flash column chromatography (KP-SiO\(_2\), 0–50% EtOAc in PE) to give 2da as a yellow oil (57 mg, 44%). \(\delta\)\(_{\text{H}}\) NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.89–7.86\) (m, 2H), 7.65–7.60 (m, 1H), 7.57–7.53 (m, 2H), 3.11–3.00 (m, 4H), 1.68–1.62 (m, 4H), 1.48–1.42 ppm (m, 2H); \(\delta\)\(_{\text{C}}\) NMR (101 MHz, CDCl\(_3\)): \(\delta = 135.6, 133.3, 129.2, 127.5, 121.6\) (\(J = 75.5\) Hz), 47.5, 25.3, 23.7 ppm; IR (neat): \(\nu = 3069, 2944, 2856, 1256, 1077, 921\) cm\(^{-1}\); HRMS (ESI-TOF) \(m/z\) [\(\text{M} + \text{H}\)^+] calcd for C\(_{14}\)H\(_{24}\)N\(_2\)OS: 293.0930, found: 293.0935.

N-Cyanation of sulfonimidamide 2aa\(^{[3b]}\)

N-[Oxo(phenyl)piperidin-1-yl]-\(\lambda^5\)-sulfanylidene)cyanamide (2da)

In a MW vial charged with sulfonimidamide 2aa (100 mg, 0.45 mmol, 1.0 equiv), AIBN (108 mg, 0.66 mmol, 1.5 equiv), Cul (16 mg, 0.09 mmol, 0.2 equiv), \(\text{K}_2\text{CO}_3\) (122 mg, 0.88 mmol, 2.0 equiv) and MeCN (6.7 mL) were added. Then, a balloon charged with O\(_2\) was attached to the MW vial and the solution was degassed for 10 min. The mixture was stirred and heated in an oil bath at 75°C for 16 h. Then, the solution was cooled, filtered and the solids washed with MeCN. The liquid phase was collected, solvent removed in vacuo and the crude product purified by flash column chromatography (KP-SiO\(_2\), 0–100% EtOAc in PE) to give 2da as a brown oil (47 mg, 43%). \(\delta\)\(_{\text{H}}\) NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.87–7.84\) (m, 2H), 7.72–7.67 (m, 1H), 7.62–7.57 (m, 2H), 3.14 (td, \(J = 5.6, 2.2\) Hz, 4H), 1.77–1.63 ppm (m, 4H), 1.54–1.46 ppm (m, 2H); \(\delta\)\(_{\text{C}}\) NMR (101 MHz, CDCl\(_3\)): \(\delta = 134.4, 133.6, 129.7, 127.8, 111.2, 47.4, 25.1, 23.4\) ppm; IR (neat): \(\nu = 3063, 2924, 2853, 2511, 1268, 1200, 924\) cm\(^{-1}\); HRMS (ESI-TOF) \(m/z\) [\(\text{M} + \text{H}\)^+] calcd for C\(_{15}\)H\(_{25}\)N\(_2\)O\(_2\): 250.1009, found: 250.1011.
N-Sulfonylation of sulfonimidamide 2aa: General procedure C
Sulfonimidamide 2aa (100 mg, 0.45 mmol, 1.0 equiv) was dissolved in pyridine (3.0 mL) under Ar atmosphere; then, the appropriate sulfonyl chloride (0.71 mmol, 1.6 equiv) was added. The reaction mixture was stirred at RT overnight; then, the reaction was quenched with aqueous NaHCO₃ and diluted with EtOAc (3 mL). The mixture was transferred to a separating funnel, the aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed with brine (3 × 10 mL) then, filtered through water-repellent filter paper. Solvent was removed in vacuo and the crude product purified (when needed).

Phenyl [oxo(phenyl)(piperidin-1-yl)-N,S-sulfanylidene]methanesulfonamide (2 ga)
Prepared according to general procedure C, from methanesulfonyl chloride; crude purified by preparative HPLC to give 2 ga as a white solid (83 mg, 62%); m.p. 93–95 °C; ¹H NMR (400 MHz, CDCl₃): δ = 7.92–7.90 (m, 2H), 7.67–7.63 (m, 1H), 7.59–7.54 (m, 2H), 3.23 (dd, J = 11.4, 7.1, 4.0 Hz, 2H), 3.18 (s, 3H), 3.10 (dd, J = 11.5, 6.9, 3.9 Hz, 2H), 1.74–1.60 (m, 4H), 1.49 ppm (quin, J = 5.9 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃): δ = 136.1, 133.7, 129.4, 127.6, 47.2, 45.0, 25.1, 23.5 ppm; IR (KBr): ν = 2939, 2856, 2311, 1246, 1099, 918 cm⁻¹; HRMS (ESI-TOF) m/z [M+H]+ calcd for C₁₇H₁₃N₂O₅S: 303.0837, found: 303.0838.

N-Alkoxycarbonylation of sulfonimidamide 2aa (carbamate formation): General procedure D[51]
To a solution of sulfonimidamide 2aa (100 mg, 0.45 mmol, 1.0 equiv) and pyridine (54 μL, 0.67 mmol, 1.5 equiv) was added. As soon as the chloroformate was in solution, a white precipitate formed. The temperature was allowed to rise to RT and the mixture was stirred overnight. The reaction was quenched with H₂O₂ and diluted with EtO (3 mL). The mixture was transferred to a separating funnel, the aqueous layer was extracted with EtO (3 × 10 mL) and the combined organic phases were washed with 1 M HCl (3 × 10 mL) and brine (3 × 10 mL), then filtered through water-repellent filter paper. Solvent was removed in vacuo and the crude product purified (when needed).

N-Aminocarbonylation of sulfonimidamide 2aa (urea formation): General procedure E[52]
To a solution of sulfonimidamide 2aa (100 mg, 0.45 mmol, 1.0 equiv) in anhydrous DCM (0.9 mL), the corresponding isocyanate (0.66 mmol, 1.5 equiv) was added dropwise at RT under Ar atmosphere. The reaction mixture was stirred until a precipitate formed (3–16 h) and starting material had been consumed (TLC analysis). Et₂O was added, and the precipitate was collected by filtration under reduced pressure and washed with Et₂O. The solid was purified by flash column chromatography (when needed).

Phenyl [oxo(phenyl)(piperidin-1-yl)-N,S-sulfanylidene]-3-propylurea (2 ga)
Prepared according to general procedure E, from n-propyl isocyanate; crude purified by flash column chromatography (KP-Sil, 0–100% EtOAC in PE) to give 2 ga as a colorless oil (89 mg, 65%); ¹H NMR (400 MHz, CDCl₃): δ = 7.87 (dt, J = 8.4, 1.3 Hz, 2H), 7.59–7.55 (m, 1H), 7.51 (dd, J = 8.3, 6.5, 1.2 Hz, 2H), 5.16 (brs, 1H), 3.17–3.06 (m, 6H), 1.63 (quin, J = 5.4 Hz, 4H), 1.55–1.42 (m, 4H), 0.92–0.88 ppm (m, 3H); ¹³C NMR (101 MHz, CDCl₃): δ = 158.4, 137.1, 132.7, 129.0, 127.7, 46.9, 42.4, 25.4, 23.7, 23.3, 11.5 ppm; IR (neat): ν = 3252, 2931, 2855, 1617, 1520, 1244, 931 cm⁻¹; HRMS (ESI-TOF) m/z [M+H]+ calcd for C₁₃H₁₃N₂O₅S: 310.1584, found: 310.1602.

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Conflict of interest
The authors declare no conflict of interest.

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