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FULL PAPER

Increasing Complexity: A Practical Synthetic Approach to Three-Dimensional, Cyclic Sulfoximines and First Insights into Their in vitro Properties

Emilie Boulard,[b] Vivien Zibulski,[a] Luisa Oertel,[a] Philip Lienau,[a] Martina Schäfer,[a] Ursula Ganzer,[a] and Ulrich Lücking*[a]

Abstract: A short synthetic approach with broad scope to access five- to seven-membered cyclic sulfoximines in only 2–3 steps from readily available thiophenols is reported. Thus, simple building blocks were converted into complex molecular structures by a sequence of S-alkylation and one-pot sulfoximine formation, followed by intramolecular cyclization. 17 structurally diverse cyclic sulfoximines were prepared in high overall yields. In vitro evaluation of these underrepresented, three-dimensional, cyclic sulfoximines with respect to properties relevant to medicinal chemistry did not reveal any intrinsic flaw for application in drug discovery.

Introduction

Sulfoximines **2**,[1] the mono-aza analogues of sulfones **1**, have only recently been the subject of growing interest in drug discovery (Figure 1).[2] Nevertheless, four sulfoximine compounds (roniciclib,[3] atuveciclib,[4] BAY 1251152,[5] AZD6738[6]) have entered clinical evaluation for the treatment of cancer of late and their promising physicochemical and DMPK properties were important triggers for their selection as clinical candidates. Sulfoximines **2** are isoelectronic with sulfones **1** but the introduction of the nitrogen atom creates asymmetry at the tetrahedral sulfur atom in the case where the two carbon substituents R^1 and R^2 are not identical. In contrast to sulfones **1**, sulfoximines **2** offer an additional point for substitution, the mildly basic nitrogen atom, which can also be utilized for the construction of cyclic sulfoximines **3** (Figure 1), for example by connecting the substituents R^2 and R^3. Recent reports have suggested that the introduction of NH-sulfoximines **2** (R^3 = H) into certain lead structures can result in reduced Caco2 permeability and increased efflux.[2b,2c] In principle, masking of the hydrogen-bond donor function[7] of the sulfoximine NH (**2**, R^3 = H) by N-alkylation (**2**, R^3 = alkyl) should be a means to improve membrane permeability, but there are only scattered reports. However, in a recent study by Gnamm, Bolm, and co-workers, N-methylation did not improve permeability properties significantly.[2b] Moreover, N-methylated sulfoximine analogues **2** (R^3 = CH_3) can suffer from reduced metabolic stability and solubility relative to the matched NH-sulfoximines **2** (R^3 = H).[2b] Against this background, we wondered if cyclic sulfoximines of general structure **3** could combine high permeability, low efflux, and high metabolic stability with favorable solubility. Furthermore, we were attracted to these underrepresented, three-dimensional heterocycles as novel building blocks for drug discovery efforts, fragment-based screening, and library syntheses.[8]

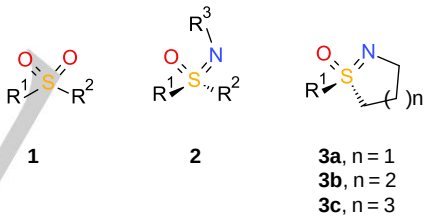

Figure 1. General structures of sulfones **1**, sulfoximines **2**, and cyclic sulfoximines **3**.

Currently, only limited literature on the synthesis of cyclic sulfoximines is available. The first example of a cyclic sulfoximine **3** was reported in 1973 by Johnson and Janiga.[9] The synthetic approach to their intended target compound **6** started with alkylation of the sodium salt of *p*-thiocresol (**4**) with 1-bromo-3-chloropropane (Scheme 1). The resulting thioether **5** was converted into the corresponding sulfoxide, which was followed by sulfoximine **6** formation using concentrated sulfuric acid and sodium azide. Upon removal of the volatiles, a partial, 'slow, spontaneous cyclization' of (chloropropyl)sulfoximine **6** to the undesired cyclic sulfoximine **3aa** occurred.[9] No additional examples of cyclic sulfoximines prepared by this route were reported in this study.

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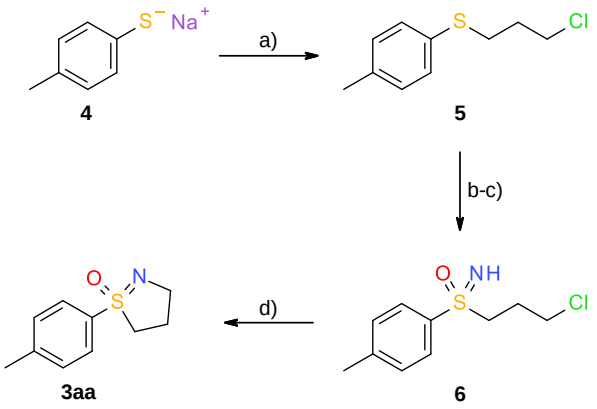
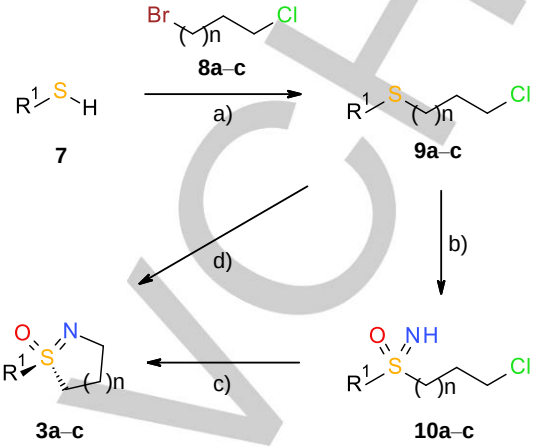


Scheme 1. Unexpected synthesis of cyclic sulfoximine **3aa** by Johnson and Janiga:[9] a) 1-bromo-3-chloropropane, dioxane, H_2O, 86%; b) sodium periodate, H_2O, 99%; c) NaN_3, H_2SO_4, $CHCl_3$, 89%; d) precipitate (insoluble in DCM) was dissolved in H_2O and neutralized with aqueous NaOH, yield not reported.

Some 25 years later, Boßhammer and Gais disclosed a novel approach for the synthesis of cyclic sulfoximine **3ab** (see Table 1).[10] Starting from *S*-methyl-*S*-phenylsulfoximine, alkylation of the NH position with a protected 2-haloethanol led to the corresponding *N*-(hydroxyethyl)sulfoximine, which was converted into the tosylate. Finally, treatment with BuOK/BuLi afforded the cyclized product **3ab**. The six-membered cyclic homologue **3bb** (see Table 1) was prepared in a similar manner. Recently, Bolm and co-workers reported a novel approach, with broad functional group tolerance, to five- and six-membered cyclic sulfoximines **3** via intramolecular imidation of azido-containing sulfoxides using a commercially available iron(II) phthalocyanine as catalyst.[11] Moreover, Maruoka and co-workers have outlined a novel procedure for the synthesis of unsaturated five-membered cyclic sulfoximines from *N*-propargylsulfinamides via sulfur–carbon bond formation.[12]

The development of significantly improved methodologies for the synthesis of sulfoximines **2** has been an important trigger for the increased interest in this functional group by the drug discovery community in recent years.[2d] A late example is a novel one-pot procedure which allows the direct conversion of thioethers into NH-sulfoximines **2** (R^3 = H), first reported by Bull, Luisi, and co-workers.[13] This reaction is mediated by commercially available (diacetoxyiodo)benzene and ammonium carbamate in methanol at room temperature and tolerates a wide range of functional groups. From our perspective, the major drawback of the early synthetic route to cyclic sulfoximine **3aa** by Johnson and Janiga[9] is the use of sodium azide and concentrated sulfuric acid, due to safety concerns.[2a,2d] In this context, we contemplated whether it would be possible to apply the novel, safe, one-pot methodology of Bull, Luisi, and co-workers to the synthesis of cyclic sulfoximines **3**. Relying on readily available thiols **7**, our strategy envisaged the preparation of thioethers **9a–c** with variable carbon chain length and a suitable chloro leaving group in place (Scheme 2). One-pot sulfoximine formation would afford the cyclization precursors **10a–c** for the final intramolecular alkylation of the NH position, resulting in cyclic sulfoximines **3a–c** of various ring sizes.

Possibly, the one-pot sulfoximine formation step could also afford the direct conversion of thioethers **9** into cyclic sulfoximines **3** in one step.



Scheme 2. Novel synthetic approach to cyclic sulfoximines **3**: a) NEt_3 (2 equiv), THF, RT; b) $PhI(OAc)_2$ (2.5 equiv), $H_2NCO_2NH_4$ (2–2.5 equiv), MeOH, RT; c) aqueous 0.1% NH_3, 80 °C; d) $PhI(OAc)_2$ (2.5 equiv), $H_2NCO_2NH_4$ (2 equiv), MeOH, RT until full conversion of **9** into **10**, then stirring of the mixture in a closed vial at 80 °C; **a**: n = 1, **b**: n = 2, **c**: n = 3.

Results and Discussion

To evaluate the feasibility, the planned synthetic steps were tested for the synthesis of model compound **3ab**. Using standard S-alkylation conditions,[14] the reaction of thiophenol (**7a**) with commercial 1-bromo-3-chloropropane (**8a**) in the presence of triethylamine gave thioether **9ab** in 78% yield. One-pot sulfoximine formation with (diacetoxyiodo)benzene and ammonium carbamate in methanol[13a] afforded acyclic sulfoximine **10ab** in a clean reaction with no sign of cyclized product **3ab**, as indicated by TLC and UPLC-MS analysis. However, initial attempts to isolate the novel product **10ab** by preparative HPLC resulted in a mixture of acyclic sulfoximine **10ab** and cyclized **3ab** in a ca. 2:1 ratio. Further analysis revealed that this mixture of products was formed in a clean reaction during rotary evaporation, at elevated temperatures, of the HPLC solvent (water + 0.1% NH_3) from the relevant fractions after preparative HPLC separation. This unexpected result led to the idea of employing similar conditions for the desired intramolecular cyclization reaction. Thus, a stirred solution of cyclization precursor **10ab** in aqueous 0.1% NH_3 at 80 °C in a closed microwave vial for 1 hour afforded the desired product **3ab** in a very clean reaction and 77% isolated yield (Table 1). The originally intended use of KOH in DMSO[15] for the final intramolecular alkylation also gave the cyclization product **3ab** in good yield (63%). Moreover, the reaction of **10ab** with NaH in DMF also provided product **3ab** in comparable yield (68%). The isolated yields using the last two methods did not reflect the very clean reactions indicated by UPLC-MS; product **3ab** was also found in the aqueous phase from the corresponding workup

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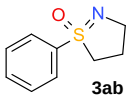
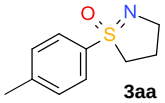
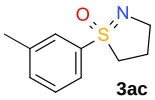
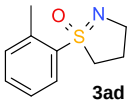
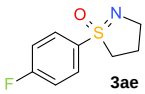
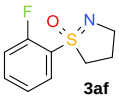
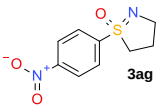
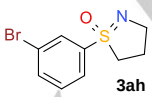
procedures, probably due to its high aqueous solubility. However, since the use of aqueous 0.1% NH_3 gave the best isolated yield of **3ab** and was also most attractive from an environmental[16] and economic point of view, we elected to use these unusual conditions for the final cyclization step when evaluating the scope of our novel synthetic approach to the three-dimensional, cyclic sulfoximines **3**. In the series of five-membered cyclic sulfoximines **3aa**–**ao**, a wide range of substituents at the aryl ortho, meta, and/or para position was tolerated and generally good to excellent yields were recorded for all three synthetic steps a) to c) (Table 1).

Table 1. Yields of steps a)–d) in the synthesis of cyclic sulfoximines according to Scheme 2 and comparison of the in vitro properties of compounds **3aa**–**3cb** with acyclic sulfoximines **2a** and **2b**.

Compound	Yield [%] steps a), b), c), unless otherwise indicated	S_w[a] [mg/L] pH 6.5	F_{max}[b] [%] (h/r/m)LMs	F_{max}[b] [%] rHep	P_{app} A–B[c] [nm/s]	Efflux ratio[c]	log*D* pH 7.5[d]
 **3ab**	78 80 77 91 (step d)	492	100 (h) 99 (r) 100 (m)	100	256	0.77	0.60
 **3aa**	quantitative 90 73	510	100 (h) 98 (r) 100 (m)	100	345	0.69	1.00
 **3ac**	88 72 94	>195	100 (h) 100 (r) 100 (m)	100	284	0.62	1.05
 **3ad**	76 71 78	148	100 (h) 95 (r) 99 (m)	99	363	0.45	0.95
 **3ae**	84 80 65	>199	100 (h) 100 (r) 100 (m)	100	305	0.57	0.70
 **3af**	88 61 80	>199	100 (h) 84 (r) 91 (m)	100	417	0.58	0.70
 **3ag**	– 97 89	>226	100 (h) 100 (r) 100 (m)	79	201	0.72	0.75
 **3ah**	83 95 55	207	82 (h) 93 (r) 100 (m)	80	462	0.57	1.20

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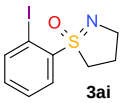
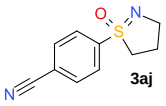
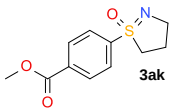
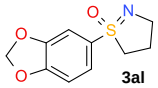
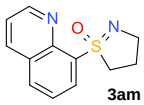
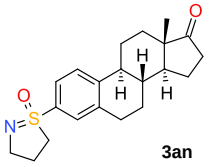
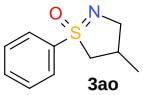
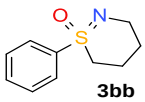
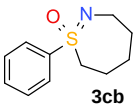
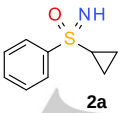
 3ai	82 40 98	279	94 (h) 100 (r) 92 (m)	84	369	0.74	1.30
 3aj	89 66 71	159	100 (h) 97 (r) 87 (m)	100	514	0.53	0.50
 3ak	95 65 81	229	99 (h) 28 (r) 99 (m)	26	125	0.4	0.90
 3al	87 95 80	>225	86 (h) 98 (r) 95 (m)	21	390	0.64	0.60
 3am	40 61 73	126	100 (h) 97 (r) 81 (m)	79	405	0.65	0.90
 3an	97 88 73	142	51 (h) 47 (r) 49 (m)	41	382	0.65	2.20
 3ao	69 not determined not determined 77 (step d)	–[e]	80 (h) 99 (r) 97 (m)	97	422	0.63	0.95
 3bb	89 53 83	128	78 (h) 93 (r) 84 (m)	89	373	0.65	0.85
 3cb	95 96 76[f]	–[e]	94 (h) 93 (r) 100 (m)	57	479	0.58	1.35
 2a	not applicable	135	100 (h) 100 (r) 100 (m)	84	374	0.60	0.80

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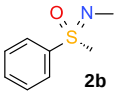 **2b**	not applicable	–[e]	71 (h) 70 (r) 98 (m)	100	467	0.55	0.70

[a] Determined by a high-throughput screening method using 1 mM DMSO stock solutions.[17] [b] Predicted hepatic metabolic first pass given as the maximum oral bioavailability F_{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).[18] [c] P_{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 P_{app} B–A/P_{app} A–B.[18] [d] Determined by reversed-phase HPLC.[19] [e] No valid results were obtained. [f] Cyclization of **10cb** using NaH in DMF at 50 °C overnight.

The majority of the final sulfoximine products were isolated as oils, but in the case of nitro derivative **3ag** crystals were obtained and the cyclic structure was confirmed by X-ray diffraction analysis (Figure 2, see the Supporting Information for details).

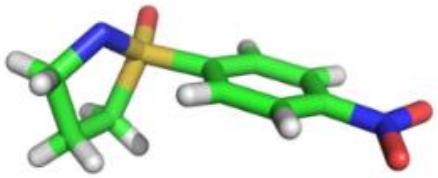

Figure 2. X-ray structure of the five-membered cyclic sulfoximine **3ag**.

The synthetic applicability of bromo-substituted products like **3ah** for metal-catalyzed cross-coupling reactions has already been demonstrated by Bolm and co-workers.[11] *ortho*-Iodo derivative **3ai** was envisaged to allow access to a novel class of P,N-ligands[20] by cross-coupling with suitable phosphines.[21] Preparation of the matched pyridyl analogues of phenyl derivative **3ab** proved to be difficult due to very high polarity and solubility of the corresponding products, which hampered preparative isolation. However, the feasibility of heterocyclic substituents R^1 is displayed in products **3al** and **3am**. Moreover, starting from 3-sulfanylestra-1(10),2,4-trien-17-one,[22] the applicability of the three-step procedure for complex, drug-like molecules is demonstrated by the formation of **3an** (1:1 mixture of diastereomers), in high overall yield.

In the attempted synthesis of methyl-substituted analogue **3ao**, one-pot sulfoximine formation from **9ao** using (diacetoxyiodo)-benzene and ammonium carbamate gave the desired cyclization precursor **10ao** in a clean reaction, as indicated by UPLC-MS analysis. However, upon removal of solvent (hexane/EtOAc) from the isolated fractions after flash chromatography, we noted partial cyclization of the acyclic precursor **10ao** to the cyclic sulfoximine **3ao**. This result rekindled our idea of achieving sulfoximine formation and intramolecular cyclization in one step. We repeated the conversion of [(3-chloro-2-methylpropyl)sulfanyl]benzene (**9ao**) into the corresponding acyclic sulfoximine **10ao** under the standard conditions. After full conversion of the starting material, as indicated by UPLC-MS, the mixture was heated to 80 °C in a closed vessel overnight. To our delight, there was full conversion of **10ao** in a clean reaction which gave cyclic product **3ao** as a 1:1 mixture of diastereomers in 77% isolated yield. Moreover, thioether **9ab** was first reacted with (diacetoxyiodo)benzene and ammonium carbamate on a gram scale to give cyclization precursor **10ab**, as indicated by UPLC-MS. Subsequent heating of the reaction mixture at 80 °C in a closed vessel for 5 hours led to the formation of the cyclic product **3ab**, which was isolated in 91% yield.

Using the standard three-step procedure, the six-membered cyclic sulfoximine **3bb** was also synthesized, in comparable yield to the five-membered homologue **3ab** (Table 1). To our surprise, the attempted cyclization of acyclic sulfoximine **10cb** to the seven-membered product **3cb** in aqueous 0.1% NH_3 at 80 °C resulted in a very low yield. Full conversion of the acyclic precursor **10cb** was only recorded after 4 days at 80 °C with stirring, and resulted in the formation of cyclic product **3cb** and an acyclic alcohol, resulting from hydrolysis at the chloro position, in a ca. 1:1 ratio. The separation of these two products by flash chromatography proved to be difficult, but was finally achieved by preparative HPLC. The formation of the alcohol side product and the repeated isolation attempts contributed to the low, unoptimized yield of 11% for sulfoximine **3cb** by this method. In contrast, cyclization of **10cb** with NaH in DMF at 50 °C gave the cyclized product **3cb** in a good yield of 76%. Moreover, the use of KOH in DMSO[15] for the final intramolecular alkylation also provided seven-membered cyclic sulfoximine **3cb** in 53% isolated yield.

To gain further knowledge of the medicinal chemistry properties of the cyclic sulfoximines synthesized in this study, the behavior of compounds **3aa**–**cb** was compared to acyclic sulfoximines **2a** and **2b** in selected in vitro assays (Table 1). The majority of the cyclic sulfoximines **3** displayed high aqueous solubility at pH 6.5, including the drug-like, steroidal product **3an** (S_w = 142 mg/L). There was no significant difference in aqueous solubility of the cyclic sulfoximines relative to acyclic NH-sulfoximine **2a** (S_w = 135 mg/L); unfortunately, a valid solubility measurement could not be obtained in the case of N-methylated sulfoximine **2b**. It should be taken into account, however, that most products were isolated as oils and that aqueous solubility was determined by a high-throughput screening method using 1 mM DMSO stock solutions of test compounds. Ring size and the nature of substituents significantly influence the lipophilicity of the cyclic compounds (Table 1). The most polar compound of this study was the cyano-substituted sulfoximine **3aj**, with a log*D* value of 0.5. Five-membered cyclic sulfoximine **3ab** revealed a log*D* value of 0.6, surprisingly slightly lower than that of acyclic NH-sulfoximine **2a** (log*D* = 0.8) and of N-methylated sulfoximine **2b** (log*D* = 0.7).[23]

Depending on the nature of the substituent, log*D* values in the range of 0.50 (**3aj**) to 1.35 (**3cb**) were recorded for the fragment-like compounds, while drug-like molecule **3an** displayed a log*D* value of 2.2. All compounds were tested in a Caco2 screening assay and demonstrated high permeability coefficients (P_{app} A–B) and no evidence of drug efflux (Table 1). These results can be attributed to the low molecular weight and the good solubility of these small and fragment-like compounds. However, steroid derivative **3an** also exhibited high permeability (382 nm/s) and no efflux (ER = 0.65).

In vitro pharmacokinetic studies in liver microsomes of human, rat, and mouse origin with the cyclic sulfoximines of this study usually demonstrated very high stability, assessed as maximum oral bioavailability F_{max}[24] (Table 1). One exception is steroidal compound **3an** which displayed moderate metabolic stability in human, rat, and mouse liver microsomes. Furthermore, ester **3ak** also exhibited low metabolic stability in rat liver microsomes. However, it is noteworthy that the main sites of metabolism and the involved metabolic enzymes were not determined for any of the test compounds. In the in vitro studies with rat hepatocytes, very high metabolic stabilities were observed for the majority of the tested cyclic sulfoximines, again with compounds **3an** and **3ak**, along with acetal **3al**, being exceptions. In comparison to acyclic compounds **2a** and **2b**, five-membered cyclic model compound **3ab** shows a trend for increased metabolic stability in vitro in rat hepatocytes [F_{max}: 100% (**3ab**) vs 84% (**2a**)] and human and rat liver microsomes [human F_{max}: 100% (**3ab**) vs 71% (**2b**); rat F_{max}: 99% (**3ab**) vs 70% (**2b**)]. Moreover, the homologous cyclic sulfoximines **3ab**, **3bb**, and **3cb** show a trend for decreased metabolic stability in rat hepatocytes with increased ring size, with F_{max} values of 100% (**3ab**), 89% (**3bb**), and 57% (**3cb**). However, this trend can also be correlated with increased lipophilicity of these compounds.

Conclusions

In summary, we have developed a practical, safe approach for the synthesis of five- to seven-membered cyclic sulfoximines **3**, which are currently underrepresented in drug discovery, to broaden the chemical repertoire in small molecule drug discovery. Starting from readily available thiophenols **7**, a sequence of S-alkylation (**9**), one-pot sulfoximine formation (**10**), and intramolecular cyclization afforded 17 cyclized products **3** in high yields and broad scope. The intramolecular cyclization of acyclic sulfoximines **10** to five- and seven-membered cyclic products **3** can be achieved with a variety of methods. Moreover, the direct conversion of thioethers **9** into cyclic sulfoximines **3** in high yields has also been demonstrated. In vitro evaluation of the compounds prepared in this study has not revealed any intrinsic flaw of the five- to seven-membered cyclic sulfoximines **3** with respect to their application as versatile building blocks for drug discovery.

Experimental Section

For general methods and materials, see the Supporting Information.

Synthesis of thioethers 9: General procedure A

A mixture of thiol **7** (1.0 equiv), the corresponding bromochloroalkane **8** (1.1 equiv), and NEt_3 (2.0 equiv) in THF was stirred at RT overnight. Then, the reaction mixture was diluted with H_2O. The organic layer was separated and the aqueous layer was extracted with DCM (3 ×). The combined organic layers were filtered through water-repellent filter paper. The volatiles were removed under reduced pressure and the crude product was purified by flash column chromatography to afford the desired thioether **9**.

[(3-Chloropropyl)sulfanyl]benzene (9ab)

Prepared according to general procedure A, by reacting benzenethiol (1.00 g, 9.08 mmol) with 1-bromo-3-chloropropane (0.99 mL, 9.98 mmol) and NEt_3 (2.53 mL, 18.15 mmol) in THF (20 mL); crude purified by flash column chromatography (0–10% EtOAc in hexane) to give **9ab** as a colorless oil (1.32 g, 7.07 mmol, 78%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.30–7.37 (m, 4H; Ar-H), 7.17–7.24 (m, 1H; Ar-H), 3.73 (t, J = 6.34 Hz, 2H; CH_2), 3.07 (t, J = 7.10 Hz, 2H; CH_2), 1.94–2.02 ppm (m, 2H; CH_2); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 135.5, 129.1, 128.3, 125.9, 43.8, 31.5, 29.2 ppm.

1-[(3-Chloropropyl)sulfanyl]-4-methylbenzene (9aa)

Prepared according to general procedure A, by reacting 4-methyl-benzenethiol (1.00 g, 8.05 mmol) with 1-bromo-3-chloropropane (0.88 mL, 8.86 mmol) and NEt_3 (2.24 mL, 16.1 mmol) in THF (15 mL); crude purified by flash column chromatography (0–10% EtOAc in hexane) to give **9aa** as a colorless liquid (1.62 g, 8.08 mmol, quantitative): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.24–7.28 (m, 2H; Ar-H), 7.15 (d, J = 7.86 Hz, 2H; Ar-H), 3.72 (t, J = 6.34 Hz, 2H; CH_2), 3.01 (t, J = 7.10 Hz, 2H; CH_2), 2.27 (s, 3H; CH_3), 1.91–1.98 ppm (m, 2H; CH_2); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 135.6, 131.6, 129.8, 129.2, 43.8, 31.5, 29.9, 20.6 ppm.

1-[(3-Chloropropyl)sulfanyl]-3-methylbenzene (9ac)

Prepared according to general procedure A, by reacting 3-methyl-benzenethiol (1.00 g, 8.05 mmol) with 1-bromo-3-chloropropane (0.88 mL, 8.86 mmol) and NEt_3 (2.24 mL, 16.1 mmol) in THF (15 mL); crude purified by flash column chromatography (0–10% EtOAc in hexane) to give **9ac** as a colorless liquid (1.43 g, 7.12 mmol, 88%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.10–7.33 (m, 3H; Ar-H), 7.01 (d, J = 7.35 Hz; Ar-H), 3.73 (t, J = 6.34 Hz, 2H; CH_2), 3.06 (t, J = 7.10 Hz, 2H; CH_2), 2.28 (s, 3H; CH_3), 1.94–2.01 ppm (m, 2H; CH_2); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 138.5, 135.3, 129.0, 128.8, 126.7, 125.3, 43.9, 31.5, 29.1, 20.9 ppm.

1-[(3-Chloropropyl)sulfanyl]-2-methylbenzene (9ad)

Prepared according to general procedure A, by reacting 2-methyl-benzenethiol (1.00 g, 8.05 mmol) with 1-bromo-3-chloropropane (0.88 mL, 8.86 mmol) and NEt_3 (2.24 mL, 16.1 mmol) in THF (15 mL); crude purified by flash column chromatography (0–10% EtOAc in hexane) to give **9ad** as a colorless liquid (1.23 g, 6.13 mmol, 76%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.09–7.35 (m, 4H; Ar-H), 3.75 (t, J = 6.34 Hz, 2H; CH_2), 3.05 (t, J = 7.35 Hz, 2H; CH_2), 2.28 (s, 3H; CH_3), 1.96–2.03 ppm (m, 2H; CH_2); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 136.4, 134.8, 130.1, 127.0, 126.7, 125.5, 43.9, 31.4, 28.6, 19.9 ppm.

1-[(3-Chloropropyl)sulfanyl]-4-fluorobenzene (9ae)

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Prepared according to general procedure A, by reacting 4-fluorobenzenethiol (1.00 g, 7.80 mmol) with 1-bromo-3-chloropropane (0.85 mL, 8.58 mmol) and NEt_3 (2.18 mL, 15.6 mmol) in THF (25 mL); crude purified by flash column chromatography (0–10% EtOAc in hexane) to give **9ae** as a colorless liquid (1.34 g, 6.56 mmol, 84%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.42 (t, J = 6.41 Hz, 2H; Ar-H), 7.19 (t, J = 8.28 Hz, 2H; Ar-H), 3.72 (t, J = 6.46 Hz, 2H; CH_2), 3.04 (t, J = 7.1 Hz, 2H; CH_2), 1.91–1.98 ppm (m, 2H; CH_2); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 162.2, 159.8, 131.5, 131.4, 130.8, 130.8, 116.3, 116.1, 43.7, 31.4, 30.3 ppm.

1-[(3-Chloropropyl)sulfanyl]-2-fluorobenzene (9af)

Prepared according to general procedure A, by reacting 2-fluorobenzenethiol (1.00 g, 7.80 mmol) with 1-bromo-3-chloropropane (0.85 mL, 8.58 mmol) and NEt_3 (2.18 mL, 15.6 mmol) in THF (25 mL); crude purified by flash column chromatography (0–10% EtOAc in hexane) to give **9af** as a colorless liquid (1.40 g, 6.86 mmol, 88%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.48 (td, J = 7.79, 1.65 Hz, 1H; Ar-H), 7.19–7.33 (m, 3H; Ar-H), 3.74 (t, J = 6.34 Hz, 2H; CH_2), 3.07 (t, J = 7.10 Hz, 2H; CH_2), 1.97 ppm (quin, J = 6.78 Hz, 2H; CH_2); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 161.4, 159.0, 130.7, 130.7, 128.4, 128.3, 125.2, 125.2, 122.3, 122.2, 115.7, 115.5, 43.7, 31.5, 28.8, 28.8 ppm.

1-Bromo-3-[(3-chloropropyl)sulfanyl]benzene (9ah)

Prepared according to general procedure A, by reacting 3-bromobenzenethiol (1.00 g, 5.29 mmol) with 1-bromo-3-chloropropane (0.58 mL, 5.82 mmol) and NEt_3 (1.34 mL, 9.62 mmol) in THF (15 mL); crude purified by flash column chromatography (0–10% EtOAc in hexane) to give **9ah** as a colorless liquid (1.17 g, 4.41 mmol, 83%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.52 (t, J = 1.77 Hz, 1H; Ar-H), 7.25–7.40 (m, 3H; Ar-H), 3.73 (t, J = 6.34 Hz, 2H; CH_2), 3.12 (t, J = 7.22 Hz, 2H; CH_2), 1.99 ppm (quin, J = 6.78 Hz, 2H; CH_2); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 138.6, 130.9, 129.7, 128.5, 126.8, 122.3, 43.7, 31.3, 28.8 ppm.

1-[(3-Chloropropyl)sulfanyl]-2-iodobenzene (9ai)

Prepared according to general procedure A, by reacting 2-iodobenzenethiol (250 mg, 1.06 mmol) with 1-bromo-3-chloropropane (0.12 mL, 1.16 mmol) and NEt_3 (0.30 mL, 2.11 mmol) in THF (3.4 mL); crude purified by flash column chromatography (0–10% EtOAc in hexane) to give **9ai** as a colorless liquid (270 mg, 0.86 mmol, 82%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.84 (dd, J = 1.39, 7.73 Hz, 1H; Ar-H), 7.29–7.54 (m, 2H; Ar-H), 6.93 (dt, J = 1.65, 7.54 Hz, 1H; Ar-H), 3.70–3.78 (m, 2H; CH_2), 3.04–3.15 (m, 2H; CH_2), 1.95–2.07 ppm (m, 2H; CH_2); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 140.6, 139.3, 129.0, 126.9, 126.6, 99.0, 44.0, 30.9, 29.8 ppm.

4-[(3-Chloropropyl)sulfanyl]benzonitrile (9aj)

Prepared according to general procedure A, by reacting 4-sulfanylbenzonitrile (1.00 g, 7.40 mmol) with 1-bromo-3-chloropropane (0.81 mL, 8.14 mmol) and NEt_3 (2.06 mL, 14.79 mmol) in THF (24 mL); crude purified by flash column chromatography (0–10% EtOAc in hexane) to give **9aj** as a colorless liquid (1.40 g, 6.61 mmol, 89%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.71–7.78 (m, 2H; Ar-H), 7.43–7.54 (m, 2H; Ar-H), 3.75 (t, J = 6.46 Hz, 2H; CH_2), 3.16–3.20 (m, 2H; CH_2), 1.99–2.08 ppm (m, 2H; CH_2); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 143.9, 132.6, 126.8, 118.9, 107.2, 43.8, 31.1, 27.7 ppm.

Methyl 4-[(3-chloropropyl)sulfanyl]benzoate (9ak)

Prepared according to general procedure A, by reacting methyl 4-sulfanylbenzoate (500 mg, 2.97 mmol) with 1-bromo-3-chloropropane (0.32 mL, 3.27 mmol) and NEt_3 (0.83 mL, 5.94 mmol) in THF (10 mL); crude purified by flash column chromatography (0–10% EtOAc in hexane) to give **9ak** as a colorless liquid (690 mg, 2.82 mmol, 95%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.80–7.96 (m, 2H; Ar-H), 7.36–7.47 (m, 2H; Ar-H), 3.83 (s, 3H; OMe), 3.72–3.81 (m, 2H; CH_2), 3.15–3.21 (m, 2H; CH_2), 1.86–2.08 ppm (m, 2H; CH_2); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 165.9, 143.3, 129.7, 126.3, 126.2, 52.1, 43.8, 31.2, 27.9 ppm.

5-[(3-Chloropropyl)sulfanyl]-1,3-benzodioxole (9al)

Prepared according to general procedure A, by reacting 1,3-benzodioxole-5-thiol (1.00 g, 6.48 mmol) with 1-bromo-3-chloropropane (0.71 mL, 7.13 mmol) and NEt_3 (1.81 mL, 12.97 mmol) in THF (20 mL); crude purified by flash column chromatography (0–10% EtOAc in hexane) to give **9al** as a colorless oil (1.30 g, 5.63 mmol, 87%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.02 (t, J = 1.01 Hz, 1H; Ar-H), 6.88 (d, J = 1.01 Hz, 2H; Ar-H), 6.02 (s, 2H; OCH_2O), 3.71 (t, J = 6.34 Hz, 2H; CH_2), 2.96 (t, J = 7.10 Hz, 2H; CH_2), 1.87–1.99 ppm (m, 2H; CH_2); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 147.9, 146.6, 126.9, 124.4, 111.0, 108.8, 101.4, 43.7, 31.5, 31.3 ppm.

8-[(3-Chloropropyl)sulfanyl]quinoline (9am)

Prepared according to general procedure A, by reacting quinoline-8-thiol hydrochloride (1:1) (1.00 g, 5.06 mmol) with 1-bromo-3-chloropropane (0.55 mL, 5.56 mmol) and NEt_3 (1.41 mL, 10.12 mmol) in THF (16 mL); crude purified by flash column chromatography (0–10% EtOAc in hexane) to give **9am** as a colorless oil (480 mg, 2.02 mmol, 40%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.89 (dd, J = 1.77, 4.06 Hz, 1H; Ar-H), 8.36 (dd, J = 1.65, 8.24 Hz, 1H; Ar-H), 7.73 (dd, J = 2.15, 7.22 Hz, 1H; Ar-H), 7.53–7.60 (m, 3H; Ar-H), 3.82 (t, J = 6.34 Hz, 2H; CH_2), 3.17 (t, J = 7.22 Hz, 2H; CH_2), 2.14 ppm (quin, J = 6.84 Hz, 2H; CH_2); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 149.3, 144.7, 137.7, 136.5, 127.9, 126.8, 123.9, 123.7, 122.1, 44.2, 31.0, 26.6 ppm.

3-[(3-Chloropropyl)sulfanyl]estra-1(10),2,4-trien-17-one (9an)

Prepared according to general procedure A, by reacting 3-sulfanylestra-1(10),2,4-trien-17-one (500 mg, 1.75 mmol) with 1-bromo-3-chloropropane (0.19 mL, 1.92 mmol) and NEt_3 (0.49 mL, 3.49 mmol) in THF (6 mL); crude purified by flash column chromatography (0–10% EtOAc in hexane) to give **9an** as a colorless oil (615 mg, 1.70 mmol, 97%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.24 (d, J = 8.11 Hz, 1H), 7.11 (d, J = 8.50 Hz, 1H), 7.06 (s, 1H), 3.73 (t, J = 6.34 Hz, 2H), 3.02 (t, J = 7.10 Hz, 2H), 2.83 (br dd, J = 3.68, 8.49 Hz, 2H), 2.32–2.48 (m, 2H), 2.22 (br s, 1H), 1.91–2.11 (m, 5H), 1.72–1.81 (m, 1H), 1.33–1.62 (m, 6H), 0.83 ppm (s, 3H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 219.6, 137.8, 137.3, 131.9, 129.1, 126.2, 126.2, 49.6, 47.3, 43.9, 43.7, 37.5, 35.4, 31.6, 29.5, 28.8, 25.9, 25.2, 21.2, 13.5 ppm.

[(3-Chloro-2-methylpropyl)sulfanyl]benzene (9ao)

Prepared according to general procedure A, by reacting benzenethiol (1.00 g, 9.08 mmol) with 1-bromo-3-chloro-2-methylpropane (1.59 mL, 13.61 mmol) and NEt_3 (2.53 mL, 18.15 mmol) in THF (15 mL); crude purified by flash column chromatography (0–10% EtOAc in hexane) to give **9ao** as a colorless oil (1.25 g, 6.23 mmol, 69%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.28–7.42 (m, 4H; Ar-H), 7.15–7.24 (m, 1H; Ar-H), 3.70 (dd, J = 1.65, 5.45 Hz, 2H; CH_2), 3.07 (dd, J = 6.46, 13.31 Hz, 1H), 2.91 (dd, J = 7.10, 13.43 Hz, 1H), 1.96–2.07 (m, 1H), 1.06 ppm (d, J = 6.84 Hz, 3H; CH_3); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 135.9, 129.2, 128.3, 125.9, 49.7, 36.0, 34.7, 16.9 ppm.

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[(4-Chlorobutyl)sulfanyl]benzene (9bb)

Prepared according to general procedure A, by reacting benzenethiol (1.00 g, 9.08 mmol) with 1-bromo-4-chlorobutane (1.15 mL, 9.98 mmol) and NEt_3 (2.53 mL, 18.15 mmol) in THF (15 mL); crude purified by flash column chromatography (0–10% EtOAc in hexane) to give **9bb** as a colorless oil (1.63 g, 8.12 mmol, 89%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.29–7.34 (m, 4H; Ar-H), 7.11–7.21 (m, 1H; Ar-H), 3.66 (t, J = 6.46 Hz, 2H; CH_2), 2.99 (t, J = 7.35 Hz, 2H; CH_2), 1.80–1.88 (m, 2H; CH_2), 1.63–1.74 ppm (m, 2H; CH_2); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 136.1, 129.1, 128.0, 125.6, 44.9, 31.1, 31.1, 25.9 ppm.

[(5-Chloropentyl)sulfanyl]benzene (9cb)

Prepared according to general procedure A, by reacting benzenethiol (1.00 g, 9.08 mmol) with 1-bromo-5-chloropentane (1.32 mL, 9.98 mmol) and NEt_3 (2.53 mL, 18.15 mmol) in THF (15 mL); crude purified by flash column chromatography (0–10% EtOAc in hexane) to give **9cb** as a colorless oil (1.85 g, 8.67 mmol, 95%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.28–7.41 (m, 4H; Ar-H), 7.10–7.20 (m, 1H; Ar-H), 3.58–3.66 (m, 2H; CH_2), 2.96 (t, J = 7.10 Hz, 2H; CH_2), 1.68–1.86 (m, 2H; CH_2), 1.46–1.63 ppm (m, 4H; 2×CH_2); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 136.4, 129.0, 127.9, 125.5, 45.3, 31.8, 31.6, 27.8, 25.5 ppm.

Synthesis of acyclic sulfoximines 10 from thioethers 9: General procedure B

In an open flask, MeOH was added to thioether **9** (1.0 equiv), (diacetoxyiodo)benzene [$PhI(OAc)_2$] (2.5 equiv), and ammonium carbamate ($H_2NCO_2NH_4$) (2.0–2.5 equiv). The mixture was stirred at RT for 2 h. When all starting material had been consumed (monitored by TLC and UPLC-MS), saturated aqueous $NaHCO_3$ and EtOAc were added, and the mixture was stirred for 5 min. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 ×). The organic phases were combined and dried by filtration through water-repellent filter paper. The volatiles were removed under reduced pressure and the crude product was purified by flash column chromatography to afford the desired acyclic sulfoximine **10**.

[*S*-(3-Chloropropyl)sulfonimidoyl]benzene (10ab)

Prepared according to general procedure B, by reacting thioether **9ab** (500 mg, 2.68 mmol) with $PhI(OAc)_2$ (2.16 g, 6.70 mmol) and $H_2NCO_2NH_4$ (418 mg, 5.36 mmol) in MeOH (4.3 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **10ab** as a yellow oil (468 mg, 2.15 mmol, 80%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.84–7.91 (m, 2H), 7.60–7.73 (m, 3H), 3.78–3.82 (m, 1H), 3.58–3.70 (m, 1H), 3.35–3.43 (m, 2H), 2.15–2.33 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 140.3, 133.3, 129.3, 128.9, 55.9, 55.4, 25.7 ppm; LC-MS (+ESI) *m*/*z*: 218.1 $[M+H]^+$.

1-[*S*-(3-Chloropropyl)sulfonimidoyl]-4-methylbenzene (10aa)

Prepared according to general procedure B, by reacting thioether **9aa** (500 mg, 2.49 mmol) with $PhI(OAc)_2$ (2.01 g, 6.23 mmol) and $H_2NCO_2NH_4$ (389 mg, 4.98 mmol) in MeOH (4.0 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **10aa** as an orange oil (521 mg, 2.25 mmol, 90%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.69–7.84 (m, 2H), 7.35–7.57 (m, 2H), 4.45 (br s, 1H), 3.58–3.71 (m, 2H), 3.14–3.27 (m, 2H), 2.40 (s, 3H), 1.89–2.02 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 143.3, 138.8, 129.7, 129.3, 128.1, 54.3, 43.3, 26.9, 21.0 ppm; HRMS (+ESI): *m*/*z* calcd for $C_{10}H_{15}ClNOS$ $[M+H]^+$: 232.0563, found: 232.0565.

1-[*S*-(3-Chloropropyl)sulfonimidoyl]-3-methylbenzene (10ac)

Prepared according to general procedure B, by reacting thioether **9ac** (500 mg, 2.49 mmol) with $PhI(OAc)_2$ (2.01 g, 6.23 mmol) and $H_2NCO_2NH_4$ (486 mg, 6.23 mmol) in MeOH (4.0 mL); crude purified by flash column chromatography (0–50% EtOAc in hexane) to give **10ac** as a colorless oil (418 mg, 1.80 mmol, 72%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.66–7.74 (m, 2H), 7.47–7.58 (m, 2H), 4.46 (br s, 1H), 3.67 (t, J = 6.59 Hz, 2H), 3.16–3.32 (m, 2H), 2.41 (s, 3H), 1.90–2.01 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 141.7, 138.9, 133.5, 129.0, 128.2, 125.2, 54.2, 43.4, 26.7, 20.9 ppm; LC-MS (+ESI) *m*/*z*: 232.1 $[M+H]^+$.

1-[*S*-(3-Chloropropyl)sulfonimidoyl]-2-methylbenzene (10ad)

Prepared according to general procedure B, by reacting thioether **9ad** (500 mg, 2.49 mmol) with $PhI(OAc)_2$ (2.01 g, 6.23 mmol) and $H_2NCO_2NH_4$ (486 mg, 6.23 mmol) in MeOH (4.0 mL); crude purified by flash column chromatography (0–50% EtOAc in hexane) to give **10ad** as a yellow oil (409 mg, 1.77 mmol, 71%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.93–7.95 (m, 1H), 7.50–7.58 (m, 1H), 7.38–7.47 (m, 2H), 3.69 (t, J = 6.59 Hz, 2H), 3.23–3.30 (m, 2H), 2.67 (s, 3H), 1.91–1.99 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 139.7, 137.6, 133.0, 132.9, 129.9, 126.5, 52.4, 43.4, 26.6, 20.3 ppm; LC-MS (+ESI) *m*/*z*: 232.1 $[M+H]^+$.

1-[*S*-(3-Chloropropyl)sulfonimidoyl]-4-fluorobenzene (10ae)

Prepared according to general procedure B, by reacting thioether **9ae** (500 mg, 2.44 mmol) with $PhI(OAc)_2$ (1.97 g, 6.11 mmol) and $H_2NCO_2NH_4$ (479 mg, 6.11 mmol) in MeOH (4.0 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **10ae** as a yellow oil (460 mg, 1.95 mmol, 80%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.93–7.99 (m, 2H), 7.43–7.50 (m, 2H), 3.62–3.71 (m, 2H), 3.21–3.37 (m, 2H), 1.91–2.02 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 165.9, 163.4, 137.8, 131.3, 131.2, 116.4, 116.2, 54.2, 43.3, 26.7 ppm; LC-MS (+ESI) *m*/*z*: 236.1 $[M+H]^+$.

1-[*S*-(3-Chloropropyl)sulfonimidoyl]-2-fluorobenzene (10af)

Prepared according to general procedure B, by reacting thioether **9af** (500 mg, 2.44 mmol) with $PhI(OAc)_2$ (1.97 g, 6.11 mmol) and $H_2NCO_2NH_4$ (479 mg, 6.11 mmol) in MeOH (4.00 mL); crude purified by flash column chromatography (0–50% EtOAc in hexane) to give **10af** as a colorless oil (352 mg, 1.49 mmol, 61%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.85 (t, J = 7.69 Hz, 1H), 7.69–7.78 (m, 1H), 7.40–7.50 (m, 2H), 4.90 (br s, 1H), 3.71 (t, J = 6.59 Hz, 2H), 3.30–3.45 (m, 2H), 1.95–2.05 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 160.0, 157.5, 135.8, 135.7, 130.5, 130.0, 129.9, 125.0, 124.9, 117.4, 117.2, 53.1, 53.1, 43.3, 26.5 ppm; LC-MS (+ESI) *m*/*z*: 236.1 $[M+H]^+$.

1-[*S*-(3-Chloropropyl)sulfonimidoyl]-4-nitrobenzene (10ag)

Prepared according to general procedure B, by reacting commercially available 1-[(3-chloropropyl)sulfanyl]-4-nitrobenzene (**9ag**; 2.00 g, 8.63 mmol) with $PhI(OAc)_2$ (6.95 g, 21.58 mmol) and $H_2NCO_2NH_4$ (1.35 g, 17.26 mmol) in MeOH (17.2 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **10ag** as a yellow solid (2.20 g, 8.37 mmol, 97%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.36–8.52 (m, 2H), 8.04–8.24 (m, 2H), 4.80 (br s, 1H), 3.68 (t, J = 6.59 Hz, 2H), 3.28–3.40 (m, 2H), 1.91–2.07 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 150.0, 147.8, 129.7, 124.4, 53.8, 43.2, 26.6 ppm; LC-MS (+ESI) *m*/*z*: 263.1 $[M+H]^+$.

1-Bromo-3-[*S*-(3-chloropropyl)sulfonimidoyl]benzene (10ah)

Prepared according to general procedure B, by reacting thioether **9ah** (500 mg, 1.88 mmol) with $PhI(OAc)_2$ (1.52 g, 4.71 mmol) and $H_2NCO_2NH_4$ (294 mg, 3.77 mmol) in MeOH (3.2 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **10ah** as a yellow oil (531 mg, 1.80 mmol, 95%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.02 (t, *J* = 1.77 Hz, 1H), 7.85–7.93 (m, 2H), 7.59 (t, *J* = 7.86 Hz, 1H), 4.60 (br s, 1H), 3.68 (t, *J* = 6.59 Hz, 2H), 3.25–3.33 (m, 2H), 1.90–2.03 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 144.3, 135.7, 131.4, 130.5, 127.1, 122.1, 53.8, 43.3, 26.6 ppm; LC-MS (+ESI) *m*/*z*: 297.9 [*M*+H]$^+$.

1-[*S*-(3-Chloropropyl)sulfonimidoyl]-2-iodobenzene (10ai)

Prepared according to general procedure B, by reacting thioether **9ai** (270 mg, 0.86 mmol) with $PhI(OAc)_2$ (696 mg, 2.16 mmol) and $H_2NCO_2NH_4$ (135 mg, 1.73 mmol) in MeOH (1.5 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **10ai** as a yellow oil (120 mg, 0.35 mmol, 40%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.10–8.21 (m, 2H), 7.64 (dt, *J* = 1.14, 7.67 Hz, 1H), 7.33 (dt, *J* = 1.65, 7.54 Hz, 1H), 3.70 (t, *J* = 6.34 Hz, 2H), 3.44–3.58 (m, 2H), 1.91–2.01 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 143.7, 142.8, 133.9, 131.0, 128.8, 95.0, 50.3, 43.5, 26.4 ppm; LC-MS (+ESI) *m*/*z*: 344.0 [*M*+H]$^+$.

4-[*S*-(3-Chloropropyl)sulfonimidoyl]benzonitrile (10aj)

Prepared according to general procedure B, by reacting thioether **9aj** (500 mg, 2.36 mmol) with $PhI(OAc)_2$ (1.90 g, 5.90 mmol) and $H_2NCO_2NH_4$ (369 mg, 4.72 mmol) in MeOH (4.0 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **10aj** as a yellow oil (370 mg, 1.55 mmol, 66%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.04–8.18 (m, 4H), 3.59–3.71 (m, 2H), 3.29–3.43 (m, 2H), 1.91–2.01 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 146.3, 133.3, 128.9, 117.9, 115.3, 53.6, 43.2, 26.5 ppm; LC-MS (+ESI) *m*/*z*: 243.1 [*M*+H]$^+$.

Methyl 4-[*S*-(3-chloropropyl)sulfonimidoyl]benzoate (10ak)

Prepared according to general procedure B, by reacting thioether **9ak** (500 mg, 2.04 mmol) with $PhI(OAc)_2$ (1.75 g, 5.42 mmol) and $H_2NCO_2NH_4$ (338 mg, 4.33 mmol) in MeOH (3.6 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **10ak** as a yellow oil (390 mg, 1.41 mmol, 69%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.12–8.20 (m, 2H), 8.02–8.07 (m, 2H), 4.60 (br s, 1H), 3.83–3.91 (s, 3H), 3.67 (t, *J* = 6.59 Hz, 2H), 3.20–3.34 (m, 2H), 1.91–2.02 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 165.3, 146.0, 133.3, 129.9, 128.6, 53.9, 52.7, 43.3, 26.6 ppm; LC-MS (+ESI) *m*/*z*: 276.0 [*M*+H]$^+$.

5-[*S*-(3-Chloropropyl)sulfonimidoyl]-1,3-benzodioxole (10al)

Prepared according to general procedure B, by reacting thioether **9al** (500 mg, 2.17 mmol) with $PhI(OAc)_2$ (1.75 g, 5.42 mmol) and $H_2NCO_2NH_4$ (338 mg, 4.33 mmol) in MeOH (3.6 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **10al** as a yellow oil (540 mg, 2.06 mmol, 95%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.42 (dd, *J* = 1.77, 8.11 Hz, 1H), 7.33 (d, *J* = 1.77 Hz, 1H), 7.11 (d, *J* = 8.11 Hz, 1H), 6.18 (s, 2H), 4.28 (s, 1H), 3.67 (t, *J* = 6.59 Hz, 2H), 3.17–3.26 (m, 2H), 1.90–1.99 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 152.4, 148.3, 130.6, 124.9, 108.7, 108.2, 103.0, 53.4, 43.0, 26.3 ppm; LC-MS (+ESI) *m*/*z*: 262.0 [*M*+H]$^+$.

8-[*S*-(3-Chloropropyl)sulfonimidoyl]quinoline (10am)

Prepared according to general procedure B, by reacting thioether **9am** (480 mg, 2.02 mmol) with $PhI(OAc)_2$ (1.63 g, 5.05 mmol) and $H_2NCO_2NH_4$ (315 mg, 4.04 mmol) in MeOH (3.4 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **10am** as a yellow oil (331 mg, 1.23 mmol, 61%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.08 (dd, *J* = 1.77, 4.06 Hz, 1H), 8.56 (dd, *J* = 1.77, 8.36 Hz, 1H), 8.41 (dd, *J* = 1.52, 7.35 Hz, 1H), 8.31 (dd, *J* = 1.39, 8.24 Hz, 1H), 7.80 (t, *J* = 7.73 Hz, 1H), 7.69–7.74 (m, 1H), 4.52 (s, 1H), 3.92 (t, *J* = 7.60 Hz, 2H), 3.67 (t, *J* = 6.46 Hz, 2H), 1.90–2.08 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 151.3, 143.2, 138.3, 137.2, 134.1, 130.9, 128.7, 125.8, 122.5, 53.1, 43.6, 26.5 ppm; LC-MS (+ESI) *m*/*z*: 269.0 [*M*+H]$^+$.

3-[*S*-(3-Chloropropyl)sulfonimidoyl]estra-1(10),2,4-trien-17-one (1:1 mixture of diastereomers) (10an)

Prepared according to general procedure B, by reacting thioether **9an** (660 mg, 1.82 mmol) with $PhI(OAc)_2$ (1.46 g, 4.55 mmol) and $H_2NCO_2NH_4$ (284 mg, 3.64 mmol) in MeOH (3.1 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give a 1:1 diastereomeric mixture of **10an** as a yellow solid (630 mg, 1.60 mmol, 88%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.58–7.65 (m, 2H), 7.50–7.55 (m, 1H), 3.68 (t, *J* = 6.59 Hz, 2H), 3.22–3.30 (m, 2H), 2.91–2.99 (m, 2H), 2.30–2.47 (m, 3H), 1.90–2.12 (m, 5H), 1.71–1.88 (m, 1H), 1.36–1.64 (m, 6H), 0.84 ppm (s, 3H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 219.5, 145.1, 138.6, 137.6, 128.3, 126.2, 125.3, 54.1, 49.6, 47.3, 44.0, 43.4, 37.1, 35.4, 31.3, 28.9, 26.7, 25.6, 25.2, 21.2, 13.5 ppm; LC-MS (+ESI) *m*/*z*: 394.2 [*M*+H]$^+$.

[*S*-(4-Chlorobutyl)sulfonimidoyl]benzene (10bb)

Prepared according to general procedure B, by reacting thioether **9bb** (500 mg, 2.49 mmol) with $PhI(OAc)_2$ (2.00 g, 6.23 mmol) and $H_2NCO_2NH_4$ (486 mg, 6.23 mmol) in MeOH (4.3 mL); crude purified by flash column chromatography (0–50% EtOAc in hexane) to give **10bb** as a yellow oil (305 mg, 1.32 mmol, 53%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.89 (d, *J* = 7.70 Hz, 2H), 7.58–7.69 (m, 3H), 4.24 (br s, 1H), 3.60 (t, *J* = 6.34 Hz, 2H), 3.13–3.22 (m, 2H), 1.59–1.77 ppm (m, 4H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 142.2, 132.7, 129.1, 128.0, 55.7, 44.8, 30.3, 20.6 ppm; LC-MS (+ESI) *m*/*z*: 232.1 [*M*+H]$^+$.

[*S*-(5-Chloropentyl)sulfonimidoyl]benzene (10cb)

Prepared according to general procedure B, by reacting thioether **9cb** (1.00 g, 4.66 mmol) with $PhI(OAc)_2$ (3.75 g, 11.64 mmol) and $H_2NCO_2NH_4$ (727 mg, 9.31 mmol) in MeOH (7.5 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **10cb** as a yellow oil (1.10 g, 4.48 mmol, 96%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.89 (d, *J* = 7.33 Hz, 2H), 7.58–7.69 (m, 3H), 4.20 (s, 1H), 3.55 (t, *J* = 6.59 Hz, 2H), 3.10–3.17 (m, 2H), 1.48–1.68 (m, 4H), 1.33–1.43 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 142.2, 132.6, 129.0, 128.0, 56.4, 45.1, 31.5, 24.9, 22.4 ppm; LC-MS (+ESI) *m*/*z*: 246.1 [*M*+H]$^+$.

Synthesis of cyclic sulfoximines 3 by the cyclization of acyclic sulfoximines 10 in aqueous NH_3: General procedure C

The acyclic sulfoximine **10** was dissolved in aqueous 0.1% NH_3. The mixture was stirred for 1–2 h at 80 °C in a sealed microwave vial. The cooled reaction mixture was neutralized by the addition of saturated aqueous $NaHCO_3$ and then concentrated to dryness under reduced pressure. The residue was purified by flash column chromatography to afford the desired cyclic sulfoximine **3**.

1-Phenyl-4,5-dihydro-3*H*-1λ^4,2-thiazole 1-oxide (3ab)

Prepared according to general procedure C, from acyclic sulfoximine **10ab** (100 mg, 0.46 mmol) in aqueous 0.1% NH_3 (2 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **3ab** as a yellow oil

(64 mg, 0.35 mmol, 77%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.84–7.88 (m, 2H), 7.59–7.74 (m, 3H), 3.78–3.84 (m, 1H), 3.65–3.69 (m, 1H), 3.35–3.43 (m, 2H), 2.16–2.33 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 140.4, 133.3, 129.3, 128.8, 55.9, 55.5, 25.8 ppm; IR (ATR): ν = 3062, 2937, 2860, 1447, 1332, 1205, 1105, 902 cm^{-1}; HRMS (+ESI): *m*/*z* calcd for $C_9H_{12}NOS$ [*M*+H]$^+$: 182.0640, found: 182.0638.

1-(4-Methylphenyl)-4,5-dihydro-3*H*-1λ^4,2-thiazole 1-oxide (3aa)

Prepared according to general procedure C, from acyclic sulfoximine **10aa** (100 mg, 0.43 mmol) in aqueous 0.1% NH_3 (2 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **3aa** as a yellow oil (61 mg, 0.31 mmol, 73%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.73 (d, *J* = 7.84 Hz, 2H), 7.43 (d, *J* = 7.77 Hz, 2H), 3.78 (ddd, *J* = 5.32, 6.65, 10.33 Hz, 1H), 3.60–3.71 (m, 1H), 3.31–3.40 (m, 2H), 2.41 (s, 3H), 2.13–2.30 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 143.7, 137.4, 129.7, 128.9, 56.0, 55.4, 25.8, 21.0 ppm; IR (ATR): ν = 3572, 3060, 2923, 2854, 1595, 1201, 1101, 900, 812 cm^{-1}; HRMS (+ESI): *m*/*z* calcd for $C_{10}H_{14}NOS$ [*M*+H]$^+$: 196.0796, found: 196.0793.

1-(3-Methylphenyl)-4,5-dihydro-3*H*-1λ^4,2-thiazole 1-oxide (3ac)

Prepared according to general procedure C, from acyclic sulfoximine **10ac** (100 mg, 0.43 mmol) in aqueous 0.1% NH_3 (2 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **3ac** as a yellow oil (80 mg, 0.41 mmol, 94%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.63–7.72 (m, 2H), 7.49–7.53 (m, 2H), 3.80 (ddd, *J* = 5.20, 6.59, 10.27 Hz, 1H), 3.66 (td, *J* = 6.56, 10.20 Hz, 1H), 3.31–3.39 (m, 2H), 2.41 (s, 3H), 2.14–2.34 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 140.3, 139.0, 133.9, 129.1, 129.0, 126.0, 55.9, 55.4, 25.7, 20.8 ppm; IR (ATR): ν = 3666, 2773, 1595, 1197, 1095, 900, 707 cm^{-1}; HRMS (+ESI): *m*/*z* calcd for $C_{10}H_{14}NOS$ [*M*+H]$^+$: 196.0796, found: 196.0791.

1-(2-Methylphenyl)-4,5-dihydro-3*H*-1λ^4,2-thiazole 1-oxide (3ad)

Prepared according to general procedure C, from acyclic sulfoximine **10ad** (100 mg, 0.43 mmol) in aqueous 0.1% NH_3 (2 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **3ad** as a yellow oil (66 mg, 0.34 mmol, 78%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.86–8.01 (m, 1H), 7.50–7.64 (m, 1H), 7.43 (s, 2H), 3.76–3.91 (m, 1H), 3.42 (s, 3H), 2.59 (s, 3H), 1.96–2.35 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 139.4, 137.7, 133.0, 132.5, 128.6, 126.3, 54.2, 54.0, 25.3, 20.1 ppm; IR (ATR): ν = 2927, 2852, 1458, 1205, 1095, 904, 763 cm^{-1}; HRMS (+ESI): *m*/*z* calcd for $C_{10}H_{14}NOS$ [*M*+H]$^+$: 196.0796, found: 196.0791.

1-(4-Fluorophenyl)-4,5-dihydro-3*H*-1λ^4,2-thiazole 1-oxide (3ae)

Prepared according to general procedure C, from acyclic sulfoximine **10ae** (100 mg, 0.42 mmol) in aqueous 0.1% NH_3 (2 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **3ae** as a yellow oil (55 mg, 0.28 mmol, 65%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.82–8.04 (m, 2H), 7.46 (t, *J* = 8.87 Hz, 2H), 3.73–3.89 (m, 1H), 3.58–3.71 (m, 1H), 3.34–3.48 (m, 2H), 2.11–2.33 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 166.2, 163.7, 136.6, 136.5, 132.1, 132.0, 116.5, 116.3, 55.9, 55.3, 25.7 ppm; IR (ATR): ν = 2814, 1575, 1479, 1199, 1101, 808, 682 cm^{-1}; HRMS (+ESI): *m*/*z* calcd for $C_9H_{11}FNOS$ [*M*+H]$^+$: 200.0545, found: 200.0542.

1-(2-Fluorophenyl)-4,5-dihydro-3*H*-1λ^4,2-thiazole 1-oxide (3af)

Prepared according to general procedure C, from acyclic sulfoximine **10af** (100 mg, 0.42 mmol) in aqueous 0.1% NH_3 (2 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **3af** as a yellow oil (68 mg, 0.34 mmol, 80%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.88 (dt, *J* = 1.77, 7.60 Hz, 1H), 7.75 (dddd, *J* = 1.90, 5.32, 7.32, 8.27 Hz, 1H), 7.25–7.57 (m, 2H), 3.73–3.90 (m, 1H), 3.58 (br d, *J* = 1.27 Hz, 1H), 3.38–3.51 (m, 2H), 2.10–2.29 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 160.1, 157.6, 135.9, 135.8, 129.9, 129.3, 129.1, 124.9, 124.9, 117.4, 117.2, 54.5, 54.5, 25.2 ppm; IR (ATR): ν = 2922, 2862, 1597, 1469, 1205, 1095, 761 cm^{-1}; HRMS (+ESI): *m*/*z* calcd for $C_9H_{11}FNOS$ [*M*+H]$^+$: 200.0545, found: 200.0545.

1-(4-Nitrophenyl)-4,5-dihydro-3*H*-1λ^4,2-thiazole 1-oxide (3ag)

Prepared according to general procedure C, from acyclic sulfoximine **10ag** (100 mg, 0.38 mmol) in aqueous 0.1% NH_3 (2 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **3ag** as a colorless solid (77 mg, 0.34 mmol, 89%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.35–8.48 (m, 2H), 8.12 (d, *J* = 9.12 Hz, 2H), 3.78–3.95 (m, 1H), 3.62–3.74 (m, 1H), 3.41–3.59 (m, 2H), 2.14–2.39 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 150.3, 146.6, 130.4, 124.4, 55.7, 55.6, 25.7 ppm; IR (ATR): ν = 3099, 2934, 2874, 1514, 1339, 1204, 1097, 905 cm^{-1}; HRMS (+ESI): *m*/*z* calcd for $C_9H_{11}N_2O_3S$ [*M*+H]$^+$: 227.0490, found: 227.0487.

1-(3-Bromophenyl)-4,5-dihydro-3*H*-1λ^4,2-thiazole 1-oxide (3ah)

Prepared according to general procedure C, from acyclic sulfoximine **10ah** (520 mg, 1.75 mmol) in aqueous 0.1% NH_3 (8 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **3ah** as a yellow oil (250 mg, 0.96 mmol, 55%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.79–8.06 (m, 3H), 7.51–7.66 (m, 1H), 3.76–3.90 (m, 1H), 3.59–3.72 (m, 1H), 3.34–3.57 (m, 2H), 2.02–2.30 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 142.8, 136.1, 131.4, 131.1, 128.0, 122.1, 55.7, 55.5, 25.6 ppm; IR (ATR): ν = 2933, 2854, 1568, 1402, 1203, 1103, 902, 765 cm^{-1}; HRMS (+ESI): *m*/*z* calcd for $C_9H_{11}BrNOS$ [*M*+H]$^+$: 259.9745, found: 259.9757.

1-(2-Iodophenyl)-4,5-dihydro-3*H*-1λ^4,2-thiazole 1-oxide (3ai)

Prepared according to general procedure C, from acyclic sulfoximine **10ai** (120 mg, 0.35 mmol) in aqueous 0.1% NH_3 (2 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **3ai** as a yellow oil (105 mg, 0.34 mmol, 98%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.14 (ddd, *J* = 1.39, 7.79, 15.91 Hz, 2H), 7.54–7.70 (m, 1H), 7.26–7.43 (m, 1H), 3.86–3.99 (m, 1H), 3.44–3.64 (m, 3H), 2.10–2.37 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 143.3, 142.2, 134.1, 130.5, 128.6, 95.7, 54.3, 53.1, 25.1 ppm; IR (ATR): ν = 2922, 2866, 1562, 1201, 1095, 904, 763 cm^{-1}; HRMS (+ESI): *m*/*z* calcd for $C_9H_{11}INOS$ [*M*+H]$^+$: 307.9606, found: 307.9602.

4-(1-Oxido-4,5-dihydro-3*H*-1λ^4,2-thiazol-1-yl)benzonitrile (3aj)

Prepared according to general procedure C, from acyclic sulfoximine **10aj** (100 mg, 0.41 mmol) in aqueous 0.1% NH_3 (2 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **3aj** as a colorless oil (60 mg, 0.29 mmol, 71%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.81–8.04 (m, 3H), 7.59 (t, *J* = 7.86 Hz, 1H), 3.75–3.90 (m, 1H), 3.59–3.73 (m, 1H), 3.37–3.54 (m, 2H), 2.06–2.32 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 145.3, 133.3, 129.5, 117.8, 115.6, 55.6, 55.5, 25.7 ppm; IR (ATR): ν = 2853, 2233, 1201, 1097, 929, 692 cm^{-1}; HRMS (+ESI): *m*/*z* calcd for $C_{10}H_{11}N_2OS$ [*M*+H]$^+$: 207.0592, found: 207.0597.

Methyl 4-(1-oxido-4,5-dihydro-3*H*-1λ^4,2-thiazol-1-yl)benzoate (3ak)

Prepared according to general procedure C, from acyclic sulfoximine **10ak** (100 mg, 0.36 mmol) in aqueous 0.1% NH_3 (2 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **3ak** as a yellow oil

(70 mg, 0.29 mmol, 81%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.10–8.24 (m, 2H), 7.87–8.05 (m, 2H), 3.90 (s, 3H), 3.79–3.88 (m, 1H), 3.59–3.74 (m, 1H), 3.36–3.56 (m, 2H), 2.16–2.36 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 165.3, 144.9, 133.6, 129.9, 129.2, 55.7, 55.6, 52.7, 25.7 ppm; IR (ATR): ν = 2949, 2860, 1720, 1434, 1274, 1203, 902 cm^{-1}; HRMS (+ESI): *m*/*z* calcd for $C_{11}H_{14}NO_3S$ [*M*+H]$^+$: 240.0694, found: 240.0696.

1-(1,3-Benzodioxol-5-yl)-4,5-dihydro-3*H*-1λ^4,2-thiazole 1-oxide (3al)

Prepared according to general procedure C, from acyclic sulfoximine **10al** (190 mg, 0.73 mmol) in aqueous 0.1% NH_3 (4 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **3al** as a colorless oil (130 mg, 0.58 mmol, 80%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.41 (dd, *J* = 1.90, 8.24 Hz, 1H), 7.27 (d, *J* = 1.77 Hz, 1H), 7.11 (d, *J* = 8.36 Hz, 1H), 6.18 (s, 2H), 3.70–3.83 (m, 1H), 3.58–3.68 (m, 1H), 3.22–3.42 (m, 2H), 2.07–2.34 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 151.6, 148.0, 133.3, 124.8, 108.5, 108.3, 102.7, 56.0, 55.2, 25.7 ppm; IR (ATR): ν = 2841, 1477, 1190, 1068, 1039, 858, 730 cm^{-1}; HRMS (+ESI): *m*/*z* calcd for $C_{10}H_{12}NO_3S$ [*M*+H]$^+$: 226.0538, found: 226.0537.

8-(1-Oxido-4,5-dihydro-3*H*-1λ^4,2-thiazol-1-yl)quinoline (3am)

Prepared according to general procedure C, from acyclic sulfoximine **10am** (110 mg, 0.41 mmol) in aqueous 0.1% NH_3 (2 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **3am** as a yellow oil (70 mg, 0.30 mmol, 73%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.07 (dd, *J* = 1.65, 4.18 Hz, 1H), 8.55 (dd, *J* = 1.52, 8.36 Hz, 1H), 8.43 (dd, *J* = 1.27, 7.35 Hz, 1H), 8.31 (dd, *J* = 1.14, 8.24 Hz, 1H), 7.78 (t, *J* = 7.68 Hz, 1H), 7.69–7.74 (m, 1H), 3.83–3.93 (m, 2H), 3.46–3.62 (m, 2H), 2.17–2.42 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 151.3, 143.3, 138.8, 137.0, 133.7, 130.4, 128.8, 125.8, 122.5, 54.7, 54.1, 25.1 ppm; IR (ATR): ν = 3572, 2937, 2862, 1490, 1191, 1085, 902, 786 cm^{-1}; HRMS (+ESI): *m*/*z* calcd for $C_{12}H_{13}N_2OS$ [*M*+H]$^+$: 233.0749, found: 233.0750.

3-(1-Oxido-4,5-dihydro-3*H*-1λ^4,2-thiazol-1-yl)estra-1(10),2,4-trien-17-one (1:1 mixture of diastereomers) (3an)

Prepared according to general procedure C, from acyclic sulfoximine **10an** (130 mg, 0.33 mmol) in aqueous 0.1% NH_3 (2 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give a 1:1 diastereomeric mixture of **3an** as a colorless solid (87 mg, 0.24 mmol, 73%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.51–7.63 (m, 3H), 3.74–3.81 (m, 1H), 3.62–3.70 (m, 1H), 3.15–3.31 (m, 2H), 2.91–2.99 (m, 2H), 2.40–2.48 (m, 2H), 2.30–2.38 (m, 1H), 2.03–2.28 (m, 3H), 1.94–2.01 (m, 2H), 1.71–1.86 (m, 1H), 1.23–1.63 (m, 6H), 0.83 ppm (s, 3H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 219.6, 145.5, 145.5, 137.8, 137.3, 129.1, 129.1, 128.4, 126.1, 126.1, 56.0, 55.4, 49.6, 47.3, 44.0, 37.1, 35.4, 31.3, 28.8, 25.8, 25.6, 25.2, 25.2, 21.2, 13.5 ppm; IR (ATR): ν = 2926, 2856, 1732, 1404, 1203, 1082, 902 cm^{-1}; HRMS (+ESI): *m*/*z* calcd for $C_{21}H_{28}NO_2S$ [*M*+H]$^+$: 358.1841, found: 358.1845.

1-Phenyl-3,4,5,6-tetrahydro-1λ^4,2-thiazine 1-oxide (3bb)

Prepared according to general procedure C, from acyclic sulfoximine **10bb** (100 mg, 0.43 mmol) in aqueous 0.1% NH_3 (2 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **3bb** as a yellow oil (70 mg, 0.36 mmol, 83%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.93–8.03 (m, 2H), 7.68–7.76 (m, 1H), 7.58–7.66 (m, 2H), 3.37–3.48 (m, 1H), 3.24–3.32 (m, 1H), 3.11–3.21 (m, 1H), 2.99–3.10 (m, 1H), 2.19–2.37 (m, 1H), 2.05–2.17 (m, 1H), 1.57–1.75 ppm (m, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 139.8, 133.2, 129.2, 127.8, 50.6, 43.2, 23.1, 21.2 ppm; IR (ATR): ν = 2925, 2862, 1440, 1217, 1116, 730, 599 cm^{-1}; HRMS (+ESI): *m*/*z* calcd for $C_{10}H_{14}NOS$ [*M*+H]$^+$: 196.0796, found: 196.0794.

Synthesis of cyclic sulfoximines 3 from thioethers 9 (one-pot method): General procedure D

In an open flask, MeOH was added to thioether **9** (1.0 equiv), PhI(OAc)$_2$ (2.5 equiv), and $H_2NCO_2NH_4$ (2.0 equiv). The mixture was stirred at RT for 2 h. When all starting material had been consumed (monitored by TLC and UPLC-MS), the reaction mixture was stirred at 80 °C in a closed microwave vial. After full conversion of the intermediate acyclic sulfoximine **10** (monitored by TLC and UPLC-MS), the reaction mixture was cooled to RT and saturated aqueous $NaHCO_3$ and EtOAc were added. The mixture was stirred for 5 min. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 ×). The organic phases were combined and dried by filtration through water-repellent filter paper. The volatiles were removed under reduced pressure and the crude product was purified by flash column chromatography to afford the desired cyclic sulfoximine **3**.

4-Methyl-1-phenyl-4,5-dihydro-3*H*-1λ^4,2-thiazole 1-oxide (1:1 mixture of diastereomers) (3ao)

Prepared according to general procedure D, by reacting thioether **9ao** (200 mg, 1.00 mmol) with PhI(OAc)$_2$ (802 mg, 2.49 mmol) and $H_2NCO_2NH_4$ (156 mg, 1.99 mmol) in MeOH (2 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give a 1:1 diastereomeric mixture of **3ao** as a yellow oil (150 mg, 0.77 mmol, 77%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.80–7.95 (m, 4H), 7.54–7.77 (m, 6H), 3.85–3.98 (m, 1H), 3.72–3.85 (m, 1H), 3.60–3.71 (m, 1H), 3.46–3.60 (m, 1H), 3.37–3.46 (m, 1H), 3.16–3.27 (m, 1H), 2.98–3.14 (m, 2H), 2.66–2.83 (m, 1H), 2.54–2.66 (m, 1H), 1.04–1.20 ppm (m, 6H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 141.0, 140.5, 133.2, 129.3, 129.2, 128.8, 128.7, 62.8, 62.6, 62.3, 62.2, 35.6, 33.7, 17.3, 17.0 ppm; IR (ATR): ν = 2960, 2850, 1446, 1211, 1105, 893, 734, 628 cm^{-1}; HRMS (+ESI): *m*/*z* calcd for $C_{10}H_{14}NOS$ [*M*+H]$^+$: 196.0796, found: 196.0795.

1-Phenyl-4,5-dihydro-3*H*-1λ^4,2-thiazole 1-oxide (3ab)

Prepared according to general procedure D, by reacting thioether **9ab** (1.32 g, 7.07 mmol) with PhI(OAc)$_2$ (5.69 g, 17.67 mmol) and $H_2NCO_2NH_4$ (1.10 g, 14.14 mmol) in MeOH (11.4 mL); crude purified by flash column chromatography (0–10% EtOH in DCM) to give **3ab** as a yellow oil (1.17 g, 6.43 mmol, 91%). NMR data consistent with the data listed for **3ab** prepared from **10ab** according to general procedure C.

Synthesis of cyclic sulfoximines 3 by the cyclization of acyclic sulfoximines 10: Alternative procedures

1-Phenyl-4,5-dihydro-3*H*-1λ^4,2-thiazole 1-oxide (3ab)

Under argon, NaH (13 mg, 0.55 mmol) was added to a solution of acyclic sulfoximine **10ab** (100 mg, 0.46 mmol) in DMF (1.9 mL) at RT. The reaction mixture was stirred at RT for 2 h, then quenched with H_2O and extracted with EtOAc (3 ×). The organic phases were combined and dried by filtration through water-repellent filter paper. The volatiles were removed under reduced pressure and the crude product was purified by flash column chromatography (0–10% EtOH in DCM) to afford **3ab** as a yellow oil (57 mg, 0.32 mmol, 68%). NMR data consistent with the data listed for **3ab** prepared from **10ab** according to general procedure C.

1-Phenyl-4,5-dihydro-3*H*-1λ^4,2-thiazole 1-oxide (3ab)

Under argon, KOH (52 mg, 0.92 mmol) was added to a solution of acyclic sulfoximine **10ab** (100 mg, 0.46 mmol) in DMSO (1.9 mL) at RT. The reaction mixture was stirred at RT for 2 h, then diluted with H_2O and extracted with EtOAc (3 ×). The organic phases were combined and dried

by filtration through water-repellent filter paper. The volatiles were removed under reduced pressure and the crude product was purified by flash column chromatography (0–10% EtOH in DCM) to afford **3ab** as a yellow oil (52 mg, 0.29 mmol, 63%). NMR data consistent with the data listed for **3ab** prepared from **10ab** according to general procedure C.

1-Phenyl-4,5,6,7-tetrahydro-3*H*-1λ^4,2-thiazepine 1-oxide (3cb)

Under argon, NaH (23 mg, 0.98 mmol) was added to a solution of acyclic sulfoximine **10cb** (200 mg, 0.81 mmol) in DMF (4 mL) at RT. The reaction mixture was stirred at 50 °C overnight. After cooling, the reaction mixture was quenched with H_2O and extracted with EtOAc (3 ×). The organic phases were combined and dried by filtration through water-repellent filter paper. The volatiles were removed under reduced pressure and the crude product was purified by flash column chromatography (0–5% EtOH in DCM) to afford **3cb** as a yellow oil (130 mg, 0.62 mmol, 76%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.93–8.07 (m, 2H), 7.55–7.74 (m, 3H), 3.44–3.60 (m, 2H), 3.35–3.43 (m, 1H), 3.09–3.28 (m, 1H), 1.76–1.92 (m, 2H), 1.38–1.76 ppm (m, 4H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 139.9, 132.8, 129.1, 128.4, 58.8, 44.1, 32.4, 29.9, 22.5 ppm; IR (ATR): ν = 2916, 2844, 1444, 1276, 1126, 908, 752, 688 cm^{-1}; HRMS (+ESI): *m/z* calcd for $C_{11}H_{16}NOS$ [*M*+H]$^+$: 210.0953, found: 210.0952.

1-Phenyl-4,5,6,7-tetrahydro-3*H*-1λ^4,2-thiazepine 1-oxide (3cb)

Under argon, KOH (91 mg, 1.63 mmol) was added to a solution of acyclic sulfoximine **10cb** (200 mg, 0.81 mmol) in DMSO (3.8 mL) at RT. The reaction mixture was stirred at RT overnight, then diluted with H_2O and extracted with EtOAc (3 ×). The organic phases were combined and dried by filtration through water-repellent filter paper. The volatiles were removed under reduced pressure and the crude product was purified by flash column chromatography (0–5% EtOH in DCM) to afford **3cb** as a yellow oil (90 mg, 0.43 mmol, 53%). NMR data consistent with the data listed above for **3cb** prepared from **10cb** with NaH in DMF.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cyclic sulfoximines • cyclization • drug design • medicinal chemistry • structure diversity

[1] a) C. R. Johnson, *Aldrichimica Acta* **1985**, *18*, 3; b) M. Reggelin, C. Zur, *Synthesis* **2000**, 1.

[2] a) U. Lücking, *Angew. Chem. Int. Ed.* **2013**, *52*, 9399; *Angew. Chem.* **2013**, *125*, 9570; b) M. Frings, C. Bolm, A. Blum, C. Gnamm, *Eur. J. Med. Chem.* **2017**, *126*, 225; c) J. A. Sirvent, U. Lücking, *ChemMedChem* **2017**, *12*, 487; d) U. Lücking, *Org. Chem. Front.* **2019**, *6*, 1319.

[3] U. Lücking, R. Jautelat, M. Krüger, T. Brumby, P. Lienau, M. Schäfer, H. Briem, J. Schulze, A. Hillisch, A. Reichel, A. M. Wengner, G. Siemeister, *ChemMedChem* **2013**, *8*, 1067.

[4] U. Lücking, A. Scholz, P. Lienau, G. Siemeister, D. Kosemund, R. Bohlmann, H. Briem, I. Terebesi, K. Meyer, K. Prelle, K. Denner, U. Bömer, M. Schäfer, K. Eis, R. Valencia, S. Ince, F. von Nussbaum, D. Mumberg, K. Ziegelbauer, B. Klebl, A. Choidas, P. Nussbaumer, M. Baumann, C. Schultz-Fademrecht, G. Rühter, J. Eickhoff, M. Brands, *ChemMedChem* **2017**, *12*, 1776.

[5] U. T. Luecking, A. Scholz, D. Kosemund, R. Bohlmann, H. Briem, P. Lienau, G. Siemeister, I. Terebesi, K. Meyer, K. Prelle, R. Valencia, S. Ince, F. von Nussbaum, D. Mumberg, K. Ziegelbauer, M. Brands, AACR Annual Meeting, Washington, DC, April, **2017**, MS.CH01.01 #984.

[6] K. M. Foote, J. W. M. Nissink, T. McGuire, P. Turner, S. Guichard, J. W. T. Yates, A. Lau, K. Blades, D. Heathcote, R. Odedra, G. Wilkinson, Z. Wilson, C. M. Wood, P. J. Jewsbury, *J. Med. Chem.* **2018**, *61*, 9889.

[7] S. B. Rafi, B. R. Hearn, P. Vedantham, M. P. Jacobson, A. R. Renslo, *J. Med. Chem.* **2012**, *55*, 3163.

[8] F. W. Goldberg, J. G. Kettle, T. Kogej, M. W. D. Perry, N. P. Tomkinson, *Drug Discovery Today* **2015**, *20*, 11.

[9] C. R. Johnson, E. R. Janiga, *J. Am. Chem. Soc.* **1973**, *95*, 7692.

[10] S. Boßhammer, H.-J. Gais, *Synthesis* **1998**, 919.

[11] H. Yu, Z. Li, C. Bolm, *Angew. Chem. Int. Ed.* **2018**, *57*, 12053; *Angew. Chem.* **2018**, *130*, 12229.

[12] Y. Aota, Y. Maeda, T. Kano, K. Maruoka, *Chem. Eur. J.* **2019**, *25*, 15755.

[13] a) A. Tota, M. Zenzola, S. J. Chawner, S. St. John-Campbell, C. Carlucci, G. Romanazzi, L. Degennaro, J. A. Bull, R. Luisi, *Chem. Commun.* **2017**, *53*, 348. For additional publications on the synthesis of sulfoximines using hypervalent iodine reagents, see: b) M. Zenzola, R. Doran, L. Degennaro, R. Luisi, J. A. Bull, *Angew. Chem. Int. Ed.* **2016**, *55*, 7203; *Angew. Chem.* **2016**, *128*, 7319; c) J.-F. Lohier, T. Glachet, H. Marzag, A.-C. Gaumont, V. Reboul, *Chem. Commun.* **2017**, *53*, 2064; d) Y. Xie, B. Zhou, S. Zhou, S. Zhou, W. Wei, J. Liu, Y. Zhan, D. Cheng, M. Chen, Y. Li, B. Wang, X.-S. Xue, Z. Li, *ChemistrySelect* **2017**, *2*, 1620; e) J. A. Bull, L. Degennaro, R. Luisi, *Synlett* **2017**, *28*, 2525; f) A. Tota, S. St John-Campbell, E. L. Briggs, G. Ogalla Estévez, M. Afonso, L. Degennaro, R. Luisi, J. A. Bull, *Org. Lett.* **2018**, *20*, 2599.

[14] M. R. Marzabadi, J. Wetzel, J. E. DeLeon, Y. Jiang, C.-A. Chen, K. Lu (Synaptic Pharmaceutical Corporation), US 6727264B1, **2004**.

[15] C. M. M. Hendriks, R. A. Bohmann, M. Bohlem, C. Bolm, *Adv. Synth. Catal.* **2014**, *356*, 1847.

[16] C. J. Clarke, W.-C. Tu, O. Levers, A. Bröhl, J. P. Hallett, *Chem. Rev.* **2018**, *118*, 747.

[17] For the assay description, see: T. Onofrey, G. Kazan, Millipore Corporation Application Note AN1731EN00, **2003**.

[18] For the assay description, see: U. Lücking, P. Wasnaire, A. Scholz, P. Lienau, G. Siemeister, C. Stegmann, U. Bömer, K. Zheng, P. Gao, G. Chen, J. Xi (Bayer Schering Pharma Aktiengesellschaft), WO 2015155197, **2015**.

[19] For the assay description, see: D. J. Minick, J. H. Frenz, M. A. Patrick, D. A. Brent, *J. Med. Chem.* **1988**, *31*, 1923.

[20] M. P. Carroll, P. J. Guiry, *Chem. Soc. Rev.* **2014**, *43*, 819.

[21] See, for example: C. Korff, G. Helmchen, *Chem. Commun.* **2004**, 530.

[22] U. Bothe, Y. Cancho Grande, H. Irlbacher, N. C. Ray (Bayer Pharma Aktiengesellschaft), WO 2016037956, **2016**.

[23] The standard deviation of this assay is usually less than 0.018.

[24] L. Z. Benet, P. Zia-Amirhosseini, *Toxicol. Pathol.* **1995**, *23*, 115.

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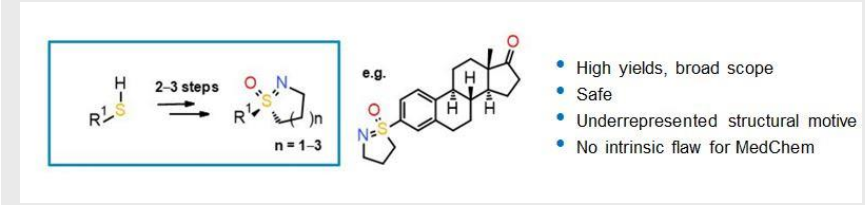

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Increasing Complexity: A Practical Synthetic Approach to Three-Dimensional, Cyclic Sulfoximines and First Insights into Their in vitro Properties

An underrepresented structural motive in the life sciences is now accessible by a practical and safe synthetic approach. Five- to seven-membered cyclic sulfoximines were prepared in 2–3 steps in high yields and broad scope (17 examples). In vitro evaluation of properties relevant to medicinal chemistry of these three-dimensional, cyclic sulfoximines did not reveal any intrinsic flaw for drug discovery.