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KEYWORDS: sulfoximines, bridged bicyclic structures, bicyclic pyrazoles, heteroatom-substituted spiro [3.3]heptanes, library production, European Lead Factory

ABSTRACT: The design and synthesis of three novel polycyclic scaffolds containing sulfoximines is presented in this work which exemplifies that sulfoximines represent a real opportunity for the discovery of new drug candidates. Additionally, the structures present at least two points of diversification and contain a high level of sp^3-character, hence being very interesting 3D-scaffolds. The compounds synthesized were added to the compound collection of the European Lead Factory.

INTRODUCTION

Methioninesulfoximine (MSO) **1** (Figure **1a**) was the first sulfoximine to be discovered in the late 1940s.[1] MSO is a toxic compound, formed during the "agene process", a wheat bleaching method using nitrogen trichloride.[2] It was discovered in England, following a report indicating epileptic seizures in dogs fed with agenized flour.[3] Since then, the application of sulfoximines in organic chemistry (ligands and auxiliaries for asymmetric synthesis,[4,5,6] directing groups in C-H functionalization[7,8]) or agronomy[9] has continued to grow. However, until recently, sulfoximines were scarcely found in building blocks for medicinal chemistry.[10] This was partly due to the, rather odd, perceived nature of the functional group and the lack of efficient and safe synthetic procedures. The development of BAY 1000394 (**2**, Figure **1a**), a pan-CDK inhibitor, that entered phase 1 clinical trials for cancer in patients with advanced solid tumors,[11,12] really triggered the interest for sulfoximines in drug discovery programs. Following BAY 1000394, several compounds emerged, such as Amgen's GKRP disruptor **3**,[13] Astra Zeneca's serine/threonine-protein kinase ATR inhibitor **4**[14,15,16] and PYK2 inhibitor **5** (Figure **1a**).[17]

Sulfoximines possess very interesting features, which improve the physicochemical properties of potential drug candidates, when compared to their sulfone analogues. They are conformationally stable and possess a stereogenic sulfur, an acidic hydrogen and a nucleophilic nitrogen (hydrogen-bond acceptor/donor functionalities).[10] Moreover, compared to their isosteric sulfones, they present an additional point of substitution *via* the nitrogen, hence offering an opportunity for library production.[10,18,19]

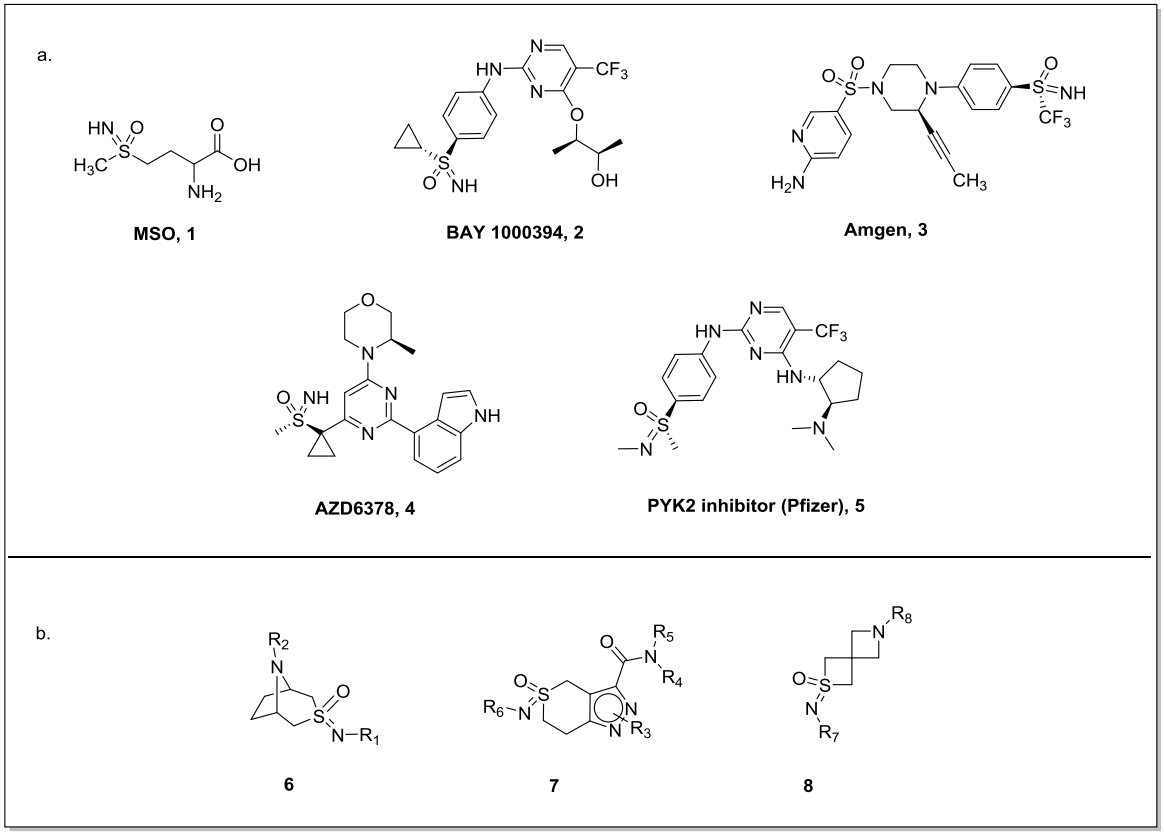


Figure 1. (a) Bioactive sulfoximines; (b) General scaffolds of polycyclic sulfoximines

The European Lead Factory (ELF)[20-24] is a public–private partnership acting in the field of early drug discovery. One of the aims is the construction of a Joint European Compound Library (JECL) containing half a million compounds, derived from new public and existing private company collections. Here we present our work towards the synthesis of three novel libraries of polycyclic structures (general scaffolds **6**, **7** and **8** are depicted in Figure **1**) which were added to the JECL. All three libraries exhibit a high level of sp^3-character and showcase the potential of sulfoximines in drug discovery. Interestingly, the sulfoximines presented are alkylated on both the sulphur and nitrogen atoms, a combination which is underrepresented with respect to *S*-alkyl building blocks in the medicinal chemistry literature.[18] The key functionality is introduced in two steps (oxidation and imination) from sulfides.[25] To cover the chemical space as much as possible,

the structures offer at least two points of diversification *via* functionalization of nitrogen atoms and/or carboxylic acids. For confidentiality reasons, the final structures are not depicted and general descriptors are used.

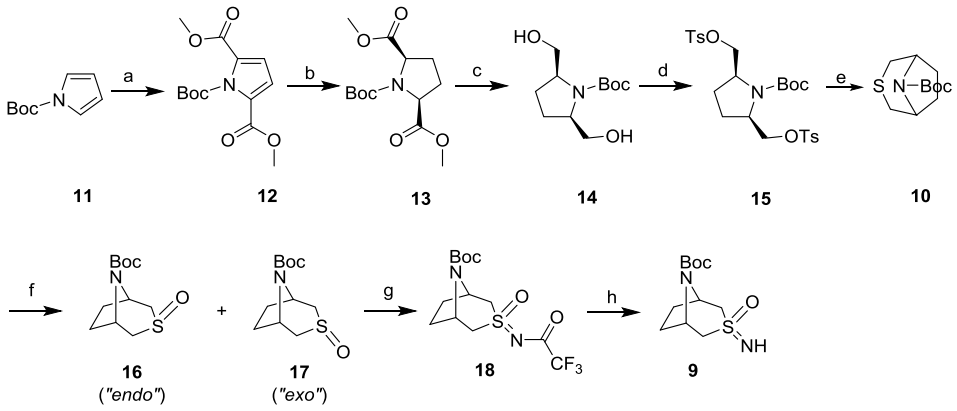
RESULTS AND DISCUSSION

Bridged bicyclic sulfoximines library

Rigid bicycles are relevant ring systems in medicinal chemistry.[26,27] Access to the bridged bicyclic sulfoximine skeleton **9** required the synthesis of the bridged bicyclic thiomorpholine **10** which was constructed according to a procedure described in the literature (Scheme **1**).[28] Starting with commercially available *N*-(*tert*-butoxycarbonyl)pyrrole **11**, bis-carbomethoxylation occurred under the conditions developed by Donohoe and co-workers and gave diester **12** in 53% yield. Diester **12** was subjected to catalytic hydrogenation with Rh/Al_2O_3 at 60 psi in acetic acid and pyrrolidine **13** was obtained as a single diastereoisomer in 94% yield. Sodium borohydride in combination with calcium chloride was used for reduction of both methyl carboxylate groups of **13** and afforded bis-alcohol **14** in 84% yield. Bis-alcohol **14** was finally converted into its corresponding bis-tosylate **15** (68% yield), which was reacted with sodium sulfide nonahydrate to afford bicyclic thiomorpholine **10** in 71% yield. Overall, the synthesis of thiepane **10** proceeded smoothly and the yields were comparable to the literature (20% over 5 steps obtained versus 25% in the literature).[28] With compound **10** in hand, the synthesis of building block **9** was pursued using a three-step sequence. Oxidation of **10** with an equimolar amount of $NaIO_4$ afforded **16** and **17** in an 8:2 mixture. Precipitation from hot cyclohexane allowed isolation of one single diastereoisomer. However, the absolute configuration could not be determined as the material was not crystalline. Sulfoximination occurred under the conditions originally described

by Bolm and co-workers[25] and protected sulfoximine **18** was obtained in 66% yield. Deprotection of **18** using potassium carbonate gave **9** quantitatively. The synthesis was scaled up to produce 23 g of sulfoximine **9** in a single batch, this supplied sufficient material to allow exploitation of the first point of diversification.

Scheme 1. Synthesis of bridged bicyclic sulfoximine building block **9**.

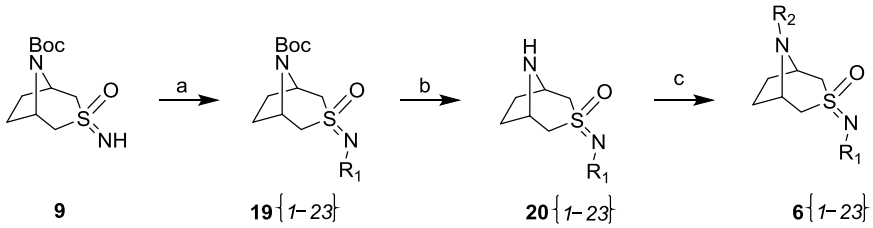


Reagents and conditions: a) LiTMP (2.5 equiv), THF, -78 °C, 3 h, $ClCO_2Me$ (3.0 equiv), -78 °C, 30 min, 53%; b) H_2 (60 psi), 5% Rh/Al_2O_3, AcOH, rt, 8 h, 94%; c) $CaCl_2$ (3.0 equiv), $NaBH_4$ (5.0equiv), EtOH-MeOH (9:1), rt, 5 h, 84%; d) *p*-TsCl, pyridine, 0 °C, 4 h, 68%; e) $Na_2S{\cdot}9H_2O$ (3.0 equiv), EtOH-H_2O (1:1), 90 °C, 2 h, 71%; f) $NaIO_4$ (1 eq), MeOH/H_2O, 0 °C to rt, 60%; g) CF_3CONH_2 (2 eq), $Rh_2(OAc)_4$ (0.03 eq), $PhI(OAc)_2$ (2 eq), MgO (6 eq), rt, overnight, 66%; h) K_2CO_3, MeOH, rt, overnight, quantitative.

Several type of reactions were performed to diversify compound **9** (Scheme **2**, Figure **2**: acylation, amidation, arylation, isocyanation) which gave access to compounds **19** {*1-23*}. Most of the reactions proceeded as expected. However, it should be noted that the amidation reaction with carboxylic acids containing tertiary amines *12* and *14* failed. Additionally, upon reaction with indole *13* side reactions took place (possibly Pictet-Spengler type). The material proved to be difficult to purify but a sufficient amount could be obtained. Finally, to complete the library, compounds **19**{*1-23*} were treated with HCl in dioxane. The deprotected amines **20**{*1-23*} were

functionalized in various ways to afford final compounds **6**{*1-23*}{**R2**} (Scheme **2**, reactions with chloroformates, amidation, sulfonylation, urea formation).

Scheme 2. Access to the bridged bicyclic sulfoximines library.



Reagents and conditions: a) Acylation: RCOCl (1.2 eq), NEt_3 (1.5 eq), DMAP (cat), DCM, 0 °C to rt, overnight; Amidation: RCO_2H (1.2 eq), DIPEA (4 eq), HATU (1.2 eq), DMF, rt, overnight; Isocyanation: RNCO (1.6 eq), NEt_3 (1.5 eq), DMAP (cat), DCE, rt, overnight; Arylation: $ArB(OH)_2$ (2.5 eq), $Cu(OAc)_2$ (0.6 eq), MeOH, rt, 6 days; b) HCl in dioxane (20 eq), rt, dioxane, 2 h; c) 2nd functionalization: reaction with chloroformates: chloroformate (1.3 eq), Et_3N (2 eq), rt, DCM, 16 h; Amidation: R′CO_2H (1.2 eq), DIPEA (4 eq), HATU (1.2 eq), DMF or DCM, rt, 16 h; Sulfonylation: R′SO_2Cl (3 eq), DBU (5 eq) DCE, rt, 16 h; Isocyanation: R′NCO (1-2 eq), DIPEA (1-4 eq), rt, DCM, DCE or DMF,16 h.

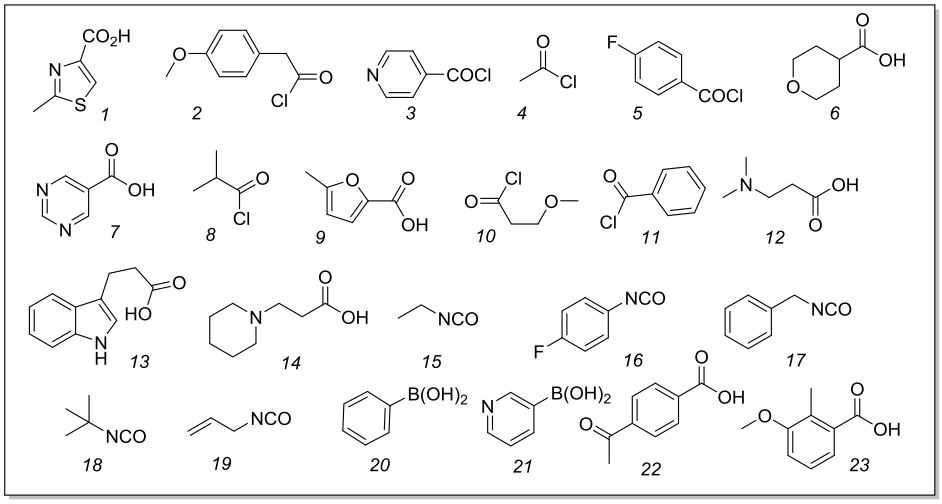
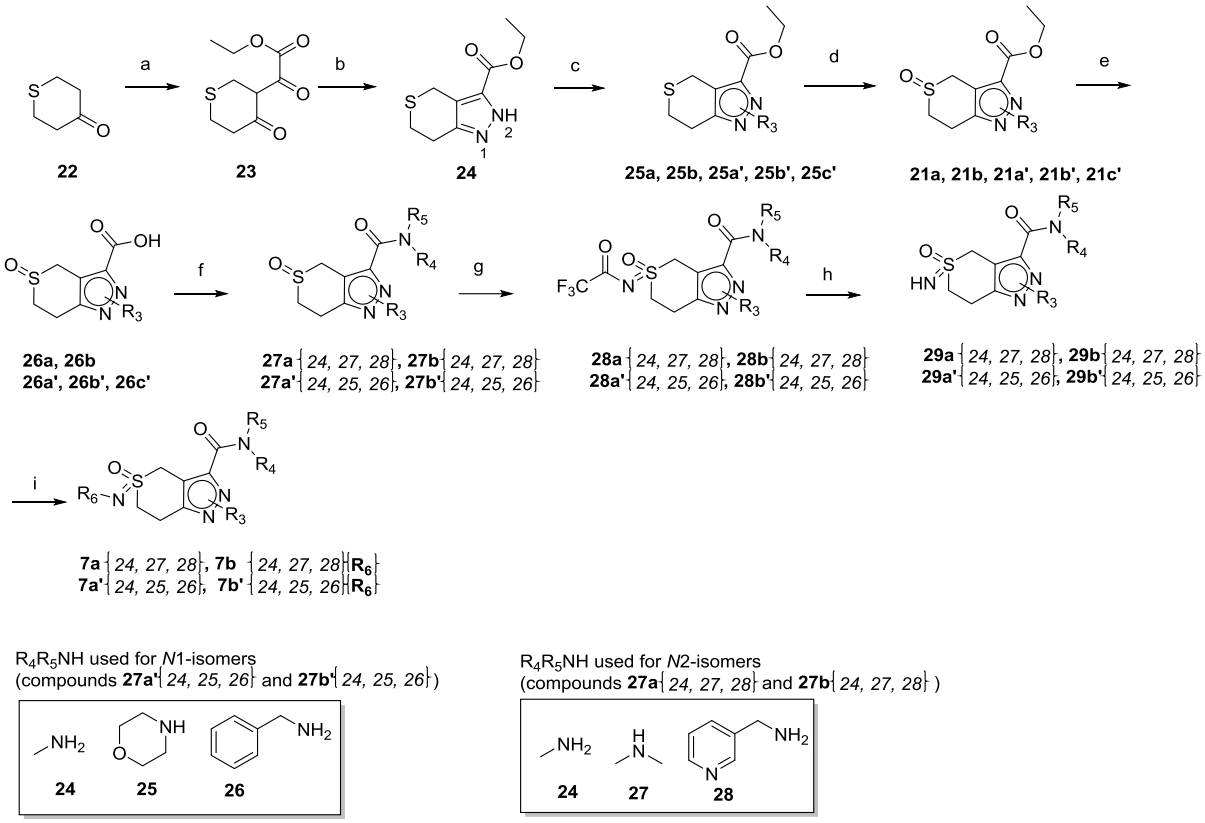


Figure 2. First diversification (R_1) for the bridged bicyclic sulfoximines library (compounds **19**{*1-23*}).

Bicyclic pyrazoles library

Bicyclic pyrazoles are also compounds which have been of particular interest for decades.[29] Synthesis of the building blocks **21a, 21b, 21a' 21b'**and **21c'** is outlined in Scheme **3** and began with tetrahydrothiopyran-4-one **22**. In a two-step procedure[30] **24** was obtained (66% yield, 41 g obtained) *via* **23**. Alkylation of **24** with methyl iodide or 2-iodopropane provided pyrazoles **25a, 25a'** and **25b, 25b'** respectively. In both cases, the two isomers (~ 1:1 mixture) could easily be separated by column chromatography. The compounds were isolated with an overall yield of 76% (with methyl iodide) and 93% (with iodopropane). Copper-catalyzed arylation of pyrazole **24** afforded only the *N*1-isomer **25c'**in moderate yield (34%). Each isomer was reacted with $NaIO_4$ to obtain sulfoxides **21a, 21b, 21a' 21b'**and **21c'** in 74% to quantitative yield.

Scheme 3. Synthesis of building blocks **21a, 21b, 21a' 21b'**and **21c'**and production of the first part of the bicyclic pyrazoles **7a{***24, 27, 28***}{R$_6$}**, **7b{***24, 27, 28***}{R$_6$}**, **7a'{***24, 25, 26***}{R$_6$}**, and **7b'{***24, 25, 26***}{R$_6$}** library. Descriptors **a** and **b** refer to the N2-isomer, descriptors **a'**, **b'** and **c'** refer to the N1-isomer.



Reagents and conditions: a) LiHMDS (1 eq), diethyloxalate (1 eq), Et_2O, -78 °C, 2.5 h; b) hydrazine.hydrate (1.3 eq), acetic acid, reflux, 3.5 h, 66% (2 steps); c) R_3X (1.2 eq), K_2CO_3 (3 eq), acetone, reflux, 76% (**25a/25a'**, R_3 = methyl), 93% (**25b/25b'** R_3 = isopropyl) or CuI (0.05 eq), iodobenzene (1.3 eq), K_2CO_3 (2.1 eq), trans-*N*,*N*'-dimethylcyclohexane-1,2,-diamine (0.2 eq), toluene, 110 °C, 20 h, 34% (**25c'**, R_3 = phenyl); d) $NaIO_4$ (1 eq), MeOH/H_2O, - 15 °C, 2 h then up to rt, overnight, 74% - quantitative; e) LiOH.H_2O (2.2 eq), H_2O/THF, rt, overnight; f) Amidation: R_4R_5NH (1.2 eq), DIPEA (4 eq), HATU (1.2 eq), DCM or DMF, rt, overnight; g) CF_3CONH_2 (2 eq), $Rh_2(OAc)_4$ (0.03 eq), $PhI(OAc)_2$ (2 eq), MgO (6 eq), rt, overnight; h) K_2CO_3, DCM/MeOH (1:10), rt, overnight; i) Acylation: RCOCl (1.2 eq), NEt_3 (1.5 eq), DMAP (cat), DCM, 0 °C to rt, 16 h or RCOOH (1.2 eq), DIPEA (4 eq), HATU (1.2 eq), DMF or DCM, rt, 16 h, overnight.

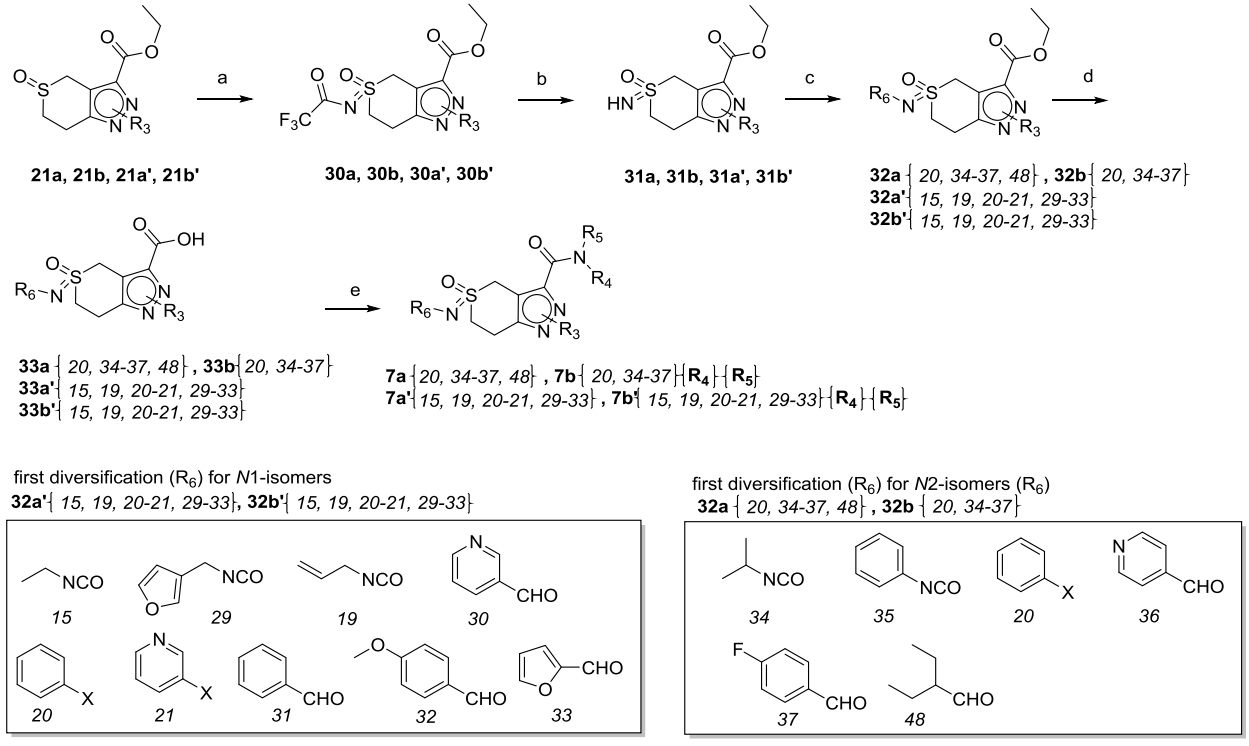
At this point, two separate pathways were followed because acylated sulfoximines proved to be unstable to several hydrolytic conditions. In the first case (Scheme **3**), the amide moiety was introduced prior to the introduction of the sulfoximine. Hydrolysis of compounds **21a, 21b, 21a'** and **21b'** gave the corresponding acids **26a, 26b, 26a'** and **26b'** in a quantitative manner. Crude mixtures were used for the amidations (Scheme **3**, **27a/27b**{*24,27-28*}**, 27a'/27b'**{*24-26*}). The reactions were low yielding for the Me-pyrazole derivatives because of the high polarity of the

amides and consequently the troublesome removal of DIPEA and TMU. The reaction towards sulfoximines **28a/28b{***24,27-28***}, 28a'/28b'{***24-26***}** gave mixed results. Often slow and incomplete conversion was observed. Addition of more of the various reagents and/or application of heating resulted in more conversion, but the yields remained moderate and ranged between 56% and 83%.[25] When pyridine-containing **27a{***28***}** or **27b{***28***}** was reacted in the sulfoximine synthesis step only very little conversion was observed and increased amounts of the catalyst were required, the product was isolated but in a low yield. Finally, the deprotection towards building blocks **29a/29b{***24,27-28***}, 29a'/29b'{***24-26***}** went in 82% to quantitative yield. The different sulfoximines could be used in the second diversification step to yield the final compounds **7a{***24, 27, 28***}{R$_6$}**, **7b{***24, 27, 28***}{R$_6$}**, **7a'{***24, 25, 26***}{R$_6$}**, and **7b'{***24, 25, 26***}{R$_6$}**. Initially, acid chlorides were used to functionalize the sulfoximine using Et_3N and catalytic DMAP as base but in most cases the conversion was moderate and complex reaction profiles were observed. Hence, an acid/HATU approach was used, which worked well enough, even though the yields were not as high as in ordinary amide couplings.

In the second case (Scheme **4**), the sulfoximine part was introduced prior to hydrolysis of the ester. In general, the synthesis of sulfoximines **30a, 30b, 30a'** and **30b'** resulted in a moderate 50% yield, even though NMR analysis of the crude material indicated a much higher conversion. For the removal of the trifluoroacetyl group (compounds **31a, 31b, 31a'** and **31b'**), it was noted that the presence of methanol accelerated the reaction, but at the same time resulted in transesterification of the ester. The sulfoximine was then decorated in various ways (Scheme **4, 32a/b{***20,34-37, 48***}, 32a'/b'{***15,19-21,29-33***}**). Reactions with isocyanates (DCE, Et_3N, DMAP (cat)) were successful when using alkyl isocyanates. When an excess of an aryl isocyanate was used, addition of a second isocyanate molecule was observed. Fortunately, the *bis*-product could

be converted to the desired product by treatment with strong alkaline conditions. Reductive amination of aldehydes, mediated by $NaBH(OAc)_3$, proceeded in moderate to good yields. Arylation using phenyl boronic acid using $Cu(OAc)_2$ worked well (60% isolated yield). However, using pyridyl boronic acid, hardly any conversion was observed. A different set of conditions (CuI, iodopyridine) did not work as well and the target was abandoned. After exploitation of the first diversification handle, ester hydrolysis was carried out (compounds **33a/b{***20, 34-37, 48***}, 33a'/b'{***15, 19, 20-21, 29-33***}**) which allowed the final functionalization of the library *via* amidations (compounds **7a/b{***20, 34-37, 48***}{R4}{R5}, 7a'/b'{***15, 19, 20-21, 29-33***}{R4}{R5}**).

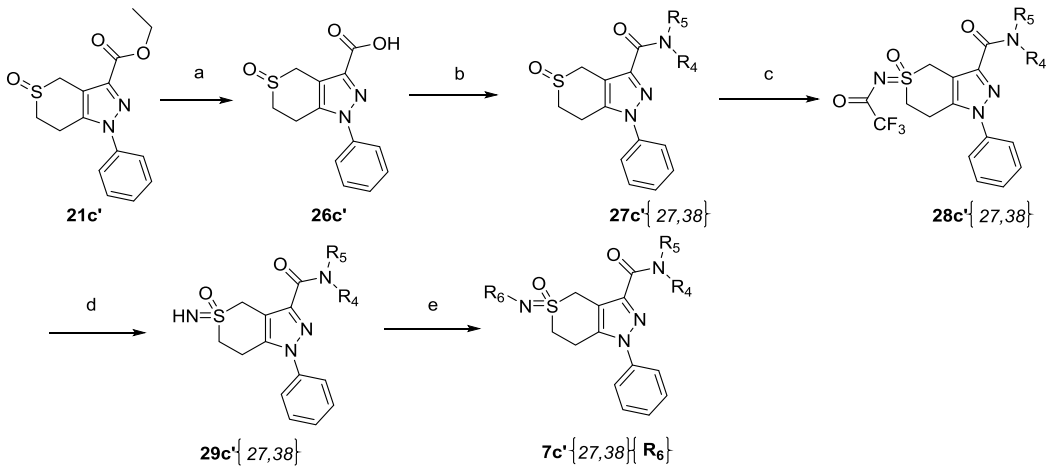
Scheme 4. Second part of the library production of bicyclic pyrazoles **7a/b{***20, 34-37, 48***}{R4}{R5}, 7a'/b'{***15, 19, 20-21, 29-33***}{R4}{R5}**.



Reagents and conditions: a) CF_3CONH_2 (2 eq), $Rh_2(OAc)_4$ (0.03 eq), $PhI(OAc)_2$ (2 eq), MgO (6 eq), rt, overnight, 47% - 55%; b) K_2CO_3, DCM/MeOH (1:10), rt, overnight, 92% - quantitative; c) Isocyanation: RNCO (1.6 eq), NEt_3 (1.5 eq), DMAP (cat), DCE, rt, overnight; Reductive amination: RCHO (1.5 eq), $NaBH(OAc)_3$ (2 eq), DCE, rt, overnight; Arylation $Cu(OAc)_2$ (0.6 eq), $ArB(OH)_2$ (2.5 eq), MeOH, rt, 6 days; d) $LiOH.H_2O$ (2.2 eq), H_2O/THF, rt, overnight; e) Amidation: R_3R_4NH (1.2 eq), DIPEA (4 eq), HATU (1.2 eq), DCM or DMF, rt, overnight.

N1-phenyl derivatives were also synthesized (Scheme **5**). After saponification of ester **21c'**, HATU coupling afforded **27c'**{*27*} and **27c'**{*38*} in high yields (88% and 92% respectively). Formation of the sulfoximine was clean with complete conversion in the case of **27c'**{*38*}, while the reaction towards **28c'**{*27*} was incomplete. However, after purification, the yield was modest in both cases (12% (**28c'**{*27*}) and 34% (**28c'**{*38*})). Removal of the trifluoroacetyl group proceeded without any trouble and the final diversification could be performed.

Scheme 5. Third part of the library production of bicyclic pyrazoles **7c'**{*27-38*}{$\mathbf{R_6}$}.



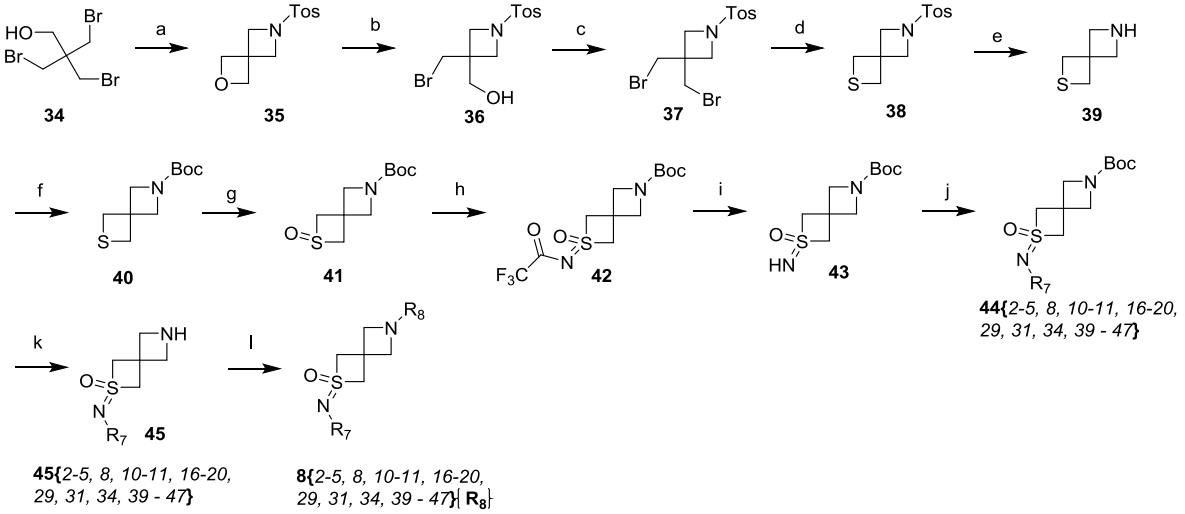
Reagents and conditions: a) $LiOH.H_2O$ (2.2 eq), H_2O/THF, rt, overnight (crude used as such); b) R_3R_4NH ({*27*} or {*38*}) (1.2 eq), DIPEA (4 eq), HATU (1.2 eq), DCM or DMF, rt, overnight, 88% (**27c'**{*27*}) and 92% (**27c'**{*38*}); c) CF_3CONH_2 (2 eq), $Rh_2(OAc)_4$ (0.03 eq), $PhI(OAc)_2$ (2 eq),

MgO (6 eq), rt, overnight, 12% (**28c'**{*27*}) and 34% (**28c'**{*38*}); d) K_2CO_3 (2 eq), MeOH, rt, overnight, quantitative (**29c'**{*27*}) and 84% (**29c'**{*38*}); e) Acylation: RCOCl (1.2 eq), NEt_3 (1.5 eq), DMAP (cat), DCM, 0 °C to rt overnight; Isocyanation: RNCO (1.6 eq), NEt_3 (1.5 eq), DMAP (cat), DCE, rt, overnight; Reductive amination: RCHO (1.5 eq), $NaBH(OAc)_3$ (2 eq), DCE, rt, overnight; Arylation $Cu(OAc)_2$ (0.6 eq), $ArB(OH)_2$ (2.5 eq), MeOH, rt, 6 days.

Sulfoximines-substituted spiro [3.3]heptanes Library

Our attention finally focused on the synthesis of a library of heteroatom-substituted spiro [3.3]heptanes which are important building blocks in drug discovery programs.[31,32] Specifically, azetidine-thietane spirocycle **40** first needed to be prepared. The synthesis relied on reactions known in the literature[33] and is depicted in Scheme **6**.

Scheme 6. Synthesis of spirocyclic sulfoximines library **8**{*2-5, 8, 10-11, 16-20, 29, 31, 34, 39-47*}{**R8**}.



Reagents and conditions: a) KOH (3.3 eq), *p*-tosylamide (1.2 eq), EtOH, reflux, 6 days, 56%; b) HBr/AcOH (1.3 eq), Et_2O, -3 °C/ 0 °C, 45 min, quantitative; c) CBr_4 (1.3 eq), PPh_3 (1.0 eq), DCM, 0 °C to rt, overnight, 52%; d) $Na_2S.3H_2O$ (2 eq), 5 h, CH_3CN/H_2O, 50 °C, 99%; e) Mg (8 eq), MeOH, sonication, 40 min; f) Boc_2O (1 eq), NEt_3 (1.2 eq), MeOH, rt, overnight, 87% (2 steps); g) $NaIO_4$ (1 eq), $MeOH/H_2O$, 0 °C to rt, overnight, 85%; h) CF_3CONH_2 (2 eq), $PhI(OAc)_2$ (1.4 eq), $Rh_2(OAc)_4$ (0.01 eq), DCM, reflux, 3 h, rt, overnight, quantitative; i) K_2CO_3 (4 eq), MeOH, rt, overnight, 88%; j) Acylation: RCOCl (1.2 eq), NEt_3 (1.5 eq), DMAP (cat), DCM, 0 °C to rt

overnight; Isocyanation: RNCO (1.6 eq), DIPEA (4 eq), DMF, rt, overnight; Arylation: $ArB(OH)_2$ (2.5 eq), $Cu(OAc)_2$ (0.6 eq), MeOH, rt, 6 days; Reductive amination: RCHO (1.5 eq), $NaBH(OAc)_3$ (2 eq), DCE, rt, overnight; k) TFA (40 eq) DCM, rt, overnight; l) 2nd functionalization; reaction with chloroformates: chloroformate (1.3 eq), Et_3N (2 eq), rt, DCM, 6 h; Amidation: $R'CO_2H$ (1.2 eq), DIPEA (4 eq), HATU (1.2 eq), DMF or DCM, rt, 16 h; Sulfonylation: $R'SO_2Cl$ (3 eq), DBU (5 eq), DCE, rt, 16 h; Isocyanation: R'NCO (1-2 eq), DIPEA (1-4 eq), rt, DCM, DCE or DMF, 16 h.

Cyclization of tribromide **34** with *p*-tosylamide in the presence of KOH and purification by crystallization from MeOH resulted in oxetane **35** in 56% yield.[34,35,36] Ring opening of the oxetane ring with HBr/HOAc in diethylether[37] afforded crude bromoalcohol **36**. This compound was not purified but further reacted with Ph_3P /CBr_4 to yield dibromide **37** in 52% yield. Ring-closure with sodium sulfide[33] in acetonitrile-water (1:1) followed by detosylation and Boc protection of the secondary amine afforded **40** in 86% yield over three steps. This compound was utilized for the three-step sequence previously described for the two other libraries and the desired 2-imino-2λ^6-thia-6-azaspiro[3.3]heptane 2-oxide scaffold **43** was prepared in 75% yield (three steps, largest scale: 27 g isolated). Several type of reactions could be carried out thanks to the first diversity handle as shown in Figure **3** (compounds **44**{*2-5, 8, 10-11, 16-20, 29, 31, 34, 39 - 47*}). For the arylated sulfoximines, Chan-Lam[38] conditions were chosen. The compounds, after careful removal of the Boc protective group using TFA, were finally derivatized through their nitrogen atom using the typical diversity reactions (reactions with chloroformates, amidation, sulfonylation, urea formation, Scheme **6**) and final compounds **8**{*2-5, 8, 10-11, 16-20, 29, 31, 34, 39-47*}{$\mathbf{R_8}$} were obtained.

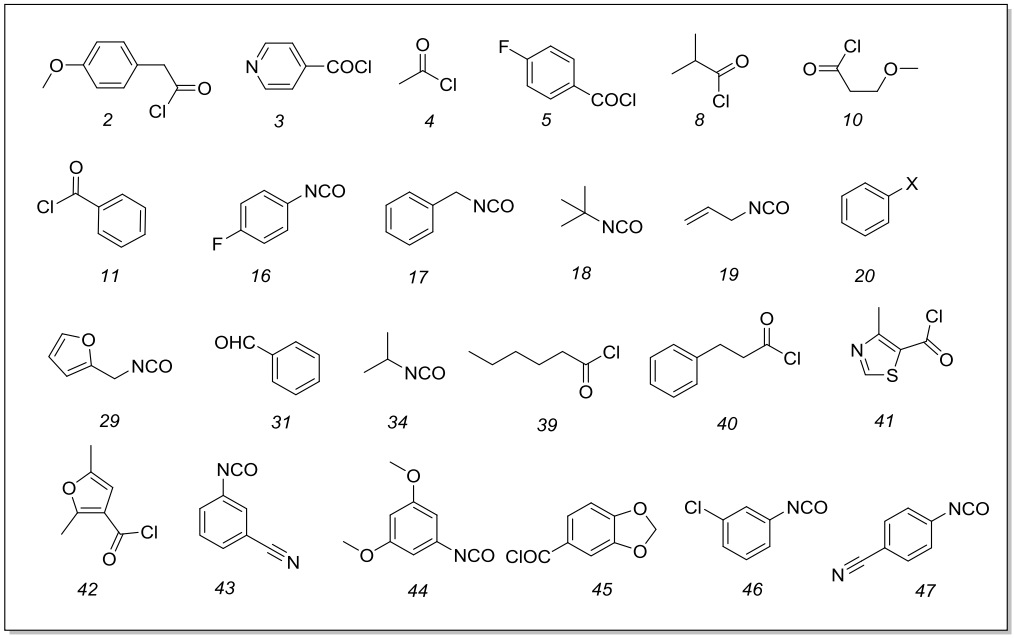


Figure 3. First diversification (R_7) for sulfoximines-substituted spiro [3.3]heptanes library

To conclude, 759 compounds were generated from the first library, with a success rate of 90% for the final reactions. For the second library, 616 compounds were prepared, with a success rate of 85%. Lastly, the third library contained 690 new entities, with a success rate of 96%. The difference of compounds within the library, guaranteed by the ELF library construction process, can be visualized with the logP/MW plots in Figure **4**[39]. One word of caution is necessary with respect to the calculated logP values of sulfoximines. In those cases, where sulfoxides and sulfoximines could be compared, the polarity of a sulfoximine (based on the retention time under UPLC conditions) is higher than that of the parent sulfoxide. Theoretical logP calculations predict it the other way around and hence underestimate the polarity of sulfoximines.

Stability studies (DMSO solutions at room temperature) were also carried out and revealed that no degradation occurred over time.

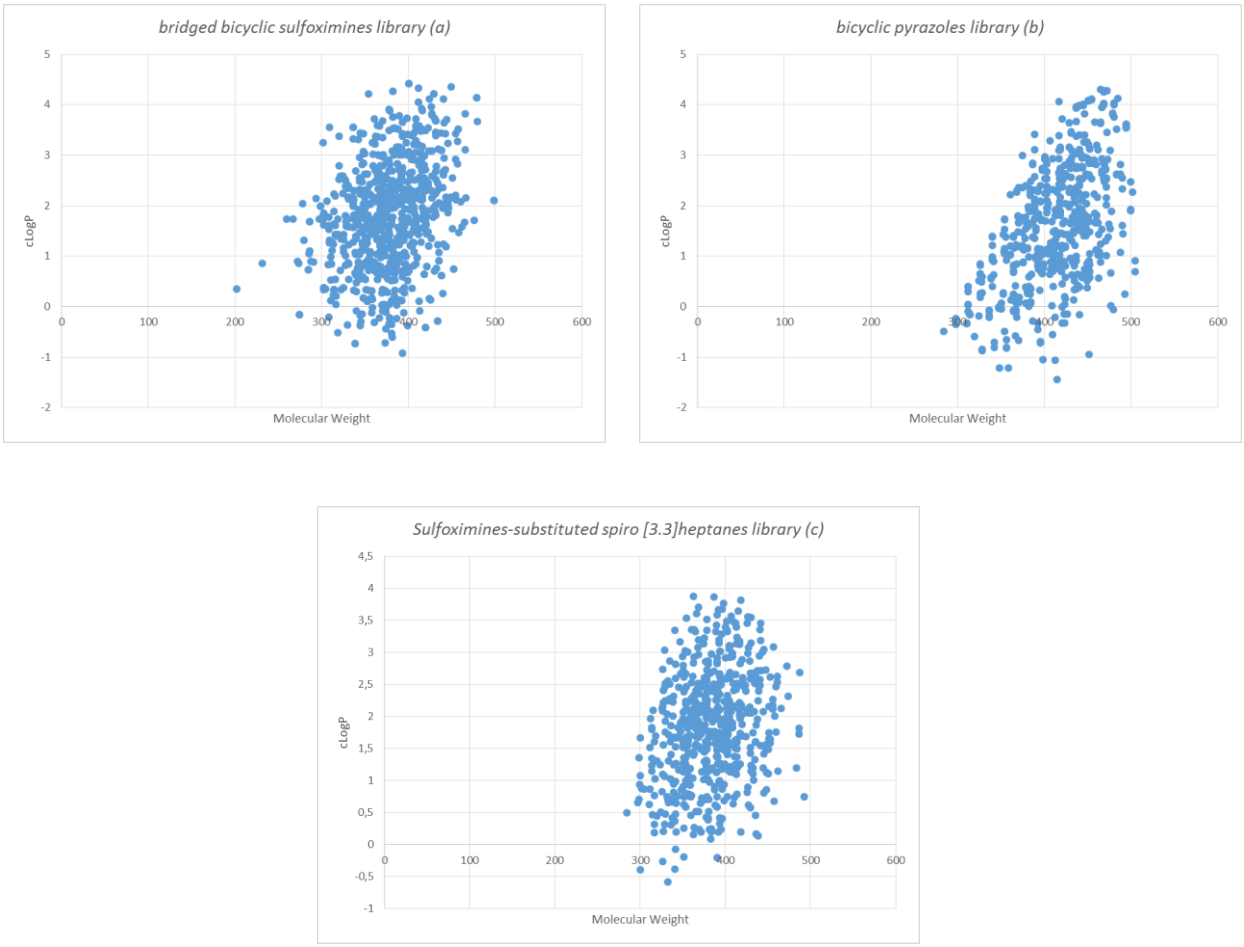


Figure 4. Physicochemical properties (calculated Log P (cLogP) and molecular weight) for the bridged bicyclic sulfoximines (a), bicyclic pyrazoles (b) and sulfoximines-substituted spiro [3.3]heptanes (c) libraries.

CONCLUSION

We have described the synthesis and the library production of three novel and original scaffolds based on sulfoximines. Sulfoximines are of growing interest in drug discovery programs thanks to their general properties (stability, tetrahedral sulfur atom, solubility, etc..). Additionally, the structures contain a high level of sp^3-character, representing very attractive 3D-scaffolds. Finally,

the presence of several diversification points permits easy expansion of the size of the libraries and their quality.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures for bridged bicyclic sulfoximines library, bicyclic pyrazoles library and sulfoximines-substituted spiro [3.3]heptanes library. General Procedure. Characterization of intermediates, building blocks and representative compounds of the different libraries. NMR spectra of intermediates and building blocks. HPLC of representative compounds of the new three libraries.

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Notes

The authors declare no competing financial interest.

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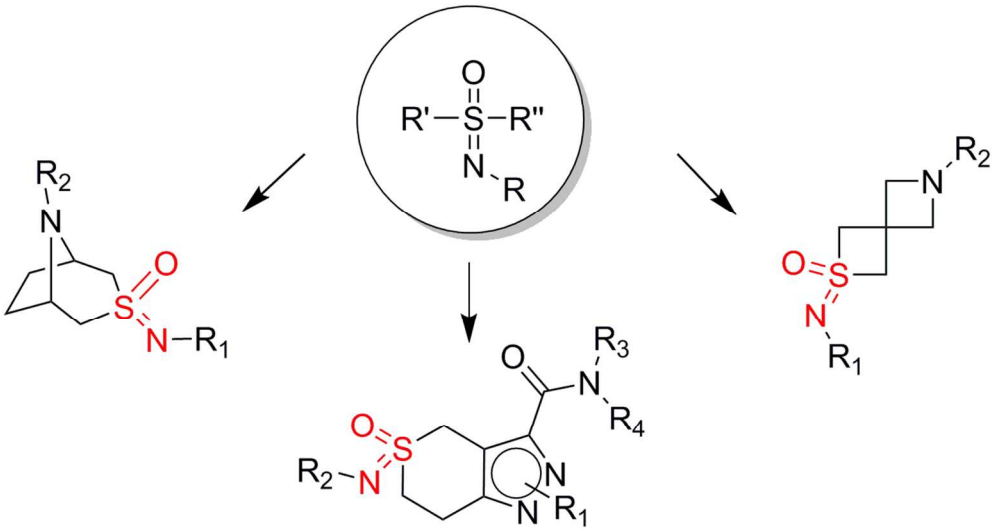

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