Sulfoximines in Medicinal Chemistry: Emerging Trends and Opportunities from the Drug Designer's Perspective

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Abstract: Extension of the medicinal chemistry toolbox is in the vital interest of drug designers who are confronted with the task of finding molecular solutions for an ever-increasing biological target space. However, the diffusion of an innovation can be a lengthy process even within the drug discovery community which faces enormous pressure to formulate effective solutions for patients in a timely manner. Along these lines, it took almost 70 years before the use of the sulfoximine group reached a critical mass in medicinal chemistry. Even though interest in this versatile functional group has increased exponentially in recent years, there is ample room for further innovative applications. This minireview highlights emerging trends and opportunities for drug designers for the utilization of the sulfoximine group in medicinal chemistry, such as in the construction of complex molecules, proteolysis targeting chimeras (PROTACs), antibody–drug conjugates (ADCs) and novel warheads for covalent inhibition.

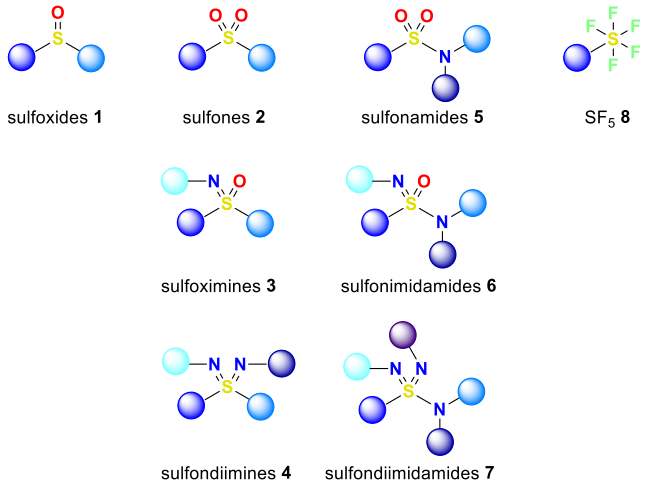


Figure 1. Established and underexplored sulfur-based functional groups in drug discovery.

1. Introduction

Sulfur-based functional groups offer drug designers an exceptional structural diversity.[1] While sulfonamides **5** in particular, and to a lesser extent sulfones **2** and sulfoxides **1** (Figure 1), are found in many approved drugs,[1,2] a large variety of sulfur-based functional groups has historically been neglected in drug discovery. However, in recent years underexplored functional groups such as sulfoximines **3**,[3] sulfondiimines **4**,[3b] sulfonimidamides **6**,[3b,4] sulfondiimidamides **7**[5] and sulfur fluorides like the pentafluorosulfanyl group (SF_5) **8**[6] have started to attract an increasing interest from drug designers.

My 2013 minireview suggested, for the first time, adding the sulfoximine group,[7] the monoaza analogue of the sulfone group, to the medicinal chemist's toolbox.[3a] Over the intervening 10 years, sulfoximines have indeed become much more popular and several novel drug candidates containing a sulfoximine group have entered clinical trials. Important drivers for this development have been successful case studies, an improved understanding of the properties of sulfoximines relevant to medicinal chemistry, and a remarkable evolution of the synthetic methodology along with a significantly increased commercial availability of sulfoximine building blocks.[3b] The 2013 minireview more or less listed every literature example for which the concept for the use of the sulfoximine group and the outcome were available. Due to the exponential growth of sulfoximine compounds reported over the last 10 years (Figure 2), this would no longer be feasible today. Moreover, several novel articles have reviewed the use of the sulfoximine group in medicinal chemistry.[3b,8]

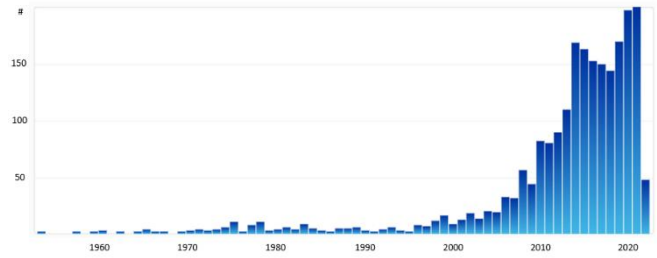
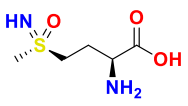


Figure 2. Number of patent applications exemplifying sulfoximine compounds versus publication year.[9]

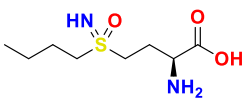
Nevertheless, more than 70 years after the discovery of the sulfoximine group in 1949, the full potential of this versatile functional group still remains to be fully leveraged. By means of selected examples, this minireview highlights emerging trends and opportunities for the utilization of sulfoximines in medicinal chemistry from the drug designer's perspective. Some background aspects, for instance the key criteria for the selection of recent clinical candidates containing a sulfoximine group, are featured in an historical context. Interestingly, all recently reported candidates are NH sulfoximines. However, the opportunity to functionalize the sulfoximine nitrogen, which was the original driving force to start evaluating this unusual functional group in medicinal chemistry, still offers diverse opportunities to drug designers including compound property tuning and the construction of complex molecules and new modalities. Moreover, the bioisosteric exchange of sulfones and sulfonamides for sulfoximines has been well exemplified in the literature by now, but selected examples will illustrate that the replacement of non-sulfur-based functional groups such as alcohols and amines is a worthwhile consideration. Last but not least, vinyl sulfoximines could offer novel opportunities, for instance for the design of covalent inhibitors or macrocyclic peptides.

2. Late Discovery of the Sulfoximine Group and Early Clinical Candidates

From the beginning of the 20th century an industrial bleaching process which employed nitrogen trichloride ('agene') was used to commercially improve the baking properties of freshly milled wheat. However, in 1946 it was reported that dogs fed a diet rich in wheat from this 'agene process' were subject to epileptiform fits and eventual death.[10] A few years later, the toxic factor was identified as methionine sulfoximine (MSO), the first reported sulfoximine compound.[11] Administration of the single stereoisomer L-methionine (*S*)-sulfoximine (**9**, Figure 3) to animals was later shown to induce decreased tissue levels of glutamine and glutathione (GSH).[12]



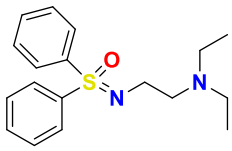
L-Methionine (*S*)-sulfoximine (**9**)



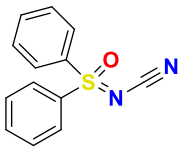
L-Buthionine sulfoximine (BSO, **10**)

Figure 3. Chemical structures of L-methionine (*S*)-sulfoximine (**9**) and L-buthionine sulfoximine (BSO, **10**).

Even though the identification of this very first sulfoximine compound was triggered by its profound biological effects, for about two decades the newly discovered functional group did not elicit much attention in the life sciences. The use of the sulfoximine group in medicinal chemistry was pioneered in the 1970s by Satzinger and Stoss at Gödecke AG who were attracted to this underexplored functional group by its chemical stability and the possibility to functionalize the sulfoximine nitrogen.[13] The utilization of the sulfoximine group in a bioisosteric approach to identify novel antiasthmatic agents finally led to the discovery of suloxifen (**11**, Figure 4),[14] which was subsequently evaluated in advanced clinical trials.[13] The promising results for suloxifen triggered additional medicinal chemistry efforts at Gödecke AG. Studies to utilize the sulfoximine group for the construction of novel heterocycles,[15] for example, led to the partial benzodiazepine receptor agonist Gö 4962 (**14**)[13,16] and a reverse transcriptase inhibitor **13** for the treatment of HIV[13,17] (Figure 4). Moreover, Satzinger and Stoss were the first to report a compound containing an *N*-cyano sulfoximine group (**12**, Figure 4).[18] This structural motif is found in the only marketed sulfoximine compound to date, the insecticide sulfoxaflor (**16**, Figure 5).[19]



suloxifen (**11**)



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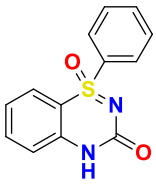

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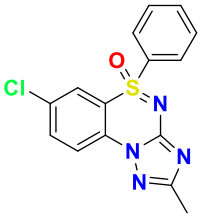


Gö 4962 (**14**)

Figure 4. Chemical structures of sulfoximines discovered at Gödecke AG: suloxifen (**11**), *N*-cyano sulfoximine **12**, reverse transcriptase inhibitor **13** and Gö 4962 (**14**).

Using MSO as a starting point, Griffith and Meister introduced L-buthionine sulfoximine (BSO, **10**; Figure 3), a specific inhibitor of γ-glutamylcysteine synthetase which is crucially involved in GSH biosynthesis, in the late 1970s.[12a] Based on the observation that intracellular GSH depletion increases drug sensitivity to a variety of cytotoxic agents, BSO was evaluated in advanced clinical trials for the combination treatment of tumors that overexpress GSH.[20] Around the same time, Taylor and co-workers at Roussel Laboratories reported another clinical candidate containing a sulfoximine group, namely the oral, prophylactic antiasthmatic sudexanox (**15**, Figure 5). This compound resulted from a program utilizing the sulfoximine group for bioisosteric replacements.[21] However, during the 1980s and 1990s only a few applications of sulfoximines in medicinal chemistry were reported.[3a]

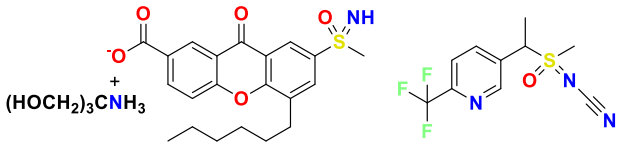


Figure 5. Chemical structures of sudexanox (**15**) and commercial insecticide sulfoxaflor (**16**).

In the early 2000s, Schering AG started to evaluate sulfoximines in their pan-CDK inhibitor program after the first candidate ZK 304709 (**17**, see Figure 7)[22] had failed in the clinic. A phase 1 dose-escalation study with ZK 304709 in patients had been terminated before the maximum tolerated dose was determined due to dose-limited absorption at high doses which was mainly attributed to the limited aqueous solubility of ZK 304709 (S_w pH 7.4: 8 mg/L). Moreover, ZK 304709 was found to accumulate in the erythrocytes of patients due to an off-target activity against carbonic anhydrases (CAs) mediated by its primary sulfonamide group.[23] Therefore a follow-up approach aimed to reduce the required therapeutic dose by improving cellular potency and increasing aqueous solubility, as well as eliminating CA inhibitory activity. However, options for structural modifications of the lead series were rather limited by the highly competitive IP landscape. Against this background, the promising, general properties of the sulfoximine group (Figure 6) as described in a review by Reggelin and Zur[7b] triggered the decision to evaluate such an unusual functional group in the pan-CDK inhibitor lead series. In the review,[7b] sulfoximines were described as being stable compounds that can be handled without special care. While isoelectronic with sulfones, the introduction of the nitrogen creates asymmetry and offers an additional point for substitution. The substituent at the sulfoximine nitrogen can modify the properties substantially as exemplified, for instance, by the pK_a values of analogues with R^3 = Me or Ts (Figure 6). Furthermore, the nitrogen is basic enough to allow metal ion coordination or salt formation. The heteroatoms bound to the sulfur are hydrogen-bond acceptors and in the case of NH sulfoximines (R^3 = H) the group has dual hydrogen-bond donor/acceptor functionality. Last but not least, sulfoximines were described as being readily soluble in protic solvents.[7b]

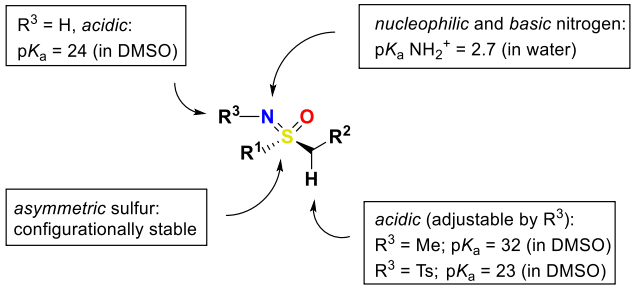


Figure 6. General properties of the sulfoximine group.

The utilization of the unusual sulfoximine group not only generated IP in the highly competitive aminopyrimidine series, but was also found to be crucial to overcome all lead optimization hurdles, culminating in the identification of the clinical candidate roniciclib (**18**, Figure 7).[24] In comparison to ZK 304709, roniciclib revealed significantly improved antiproliferative activities in vitro [IC_{50} MCF7: 266 nM (ZK 304709) vs 15 nM (roniciclib)] which translated to very promising activities in animal models at a much reduced therapeutic dose (roniciclib: 2 mg/kg vs ZK 304709: 100 mg/kg). Roniciclib also displayed significantly improved aqueous solubility [S_w pH 7.4: 182 mg/L (roniciclib) vs 8 mg/L (ZK 304709)], yet further improved permeability in the Caco-2 model [P_{app} A–B: 79 nm/s (roniciclib) vs 56 nm/s (ZK 304709)]. Moreover, sulfoximine roniciclib did not inhibit CAs. In phase 1 clinical trials, roniciclib also revealed promising pharmacokinetic properties in cancer patients but trials were finally terminated in phase 2 due to a safety signal. In this context it is noteworthy that a pan-CDK inhibitor has yet to make it to the market. Nevertheless, the initial success of roniciclib triggered the evaluation of the sulfoximine group across drug discovery programs at Bayer AG in the following years.

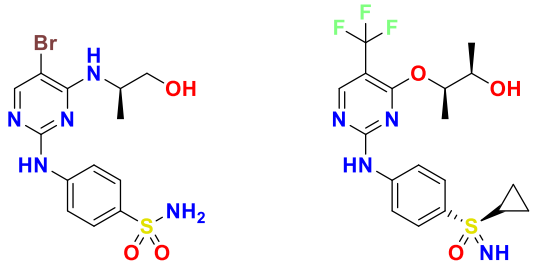


Figure 7. Chemical structures of pan-CDK inhibitors ZK 304709 (**17**, Schering AG) and roniciclib (**18**, Bayer AG).

3. Recent Clinical Candidates

3.1. CDK9 Inhibitors

After failing with pan-CDK inhibitors in the clinic, scientists at Bayer AG turned their attention to the selective inhibition of exclusively transcription regulating CDK9 as a promising new approach for cancer therapy.[25] The lead structure of this novel project, BAY-958 (**19**, Figure 8), revealed good activity against CDK9 (IC_{50} CDK9: 11 nM) and high kinase selectivity, including the CDK family (IC_{50} CDK2: 1078 nM).[26] On the downside, lead structure BAY-958 displayed limited aqueous solubility (S_w pH 6.5: 11 mg/L), low permeability (P_{app} A–B: 22 nm/s) and high efflux (efflux ratio: 15), resulting in low bioavailability [*F*, po (rat): 10%]. Lead optimization efforts finally led to the sulfoximine atuveciclib (**20**, Figure 8) with similar in vitro potency (IC_{50} CDK9: 13 nM) and selectivity (IC_{50} CDK2: 1300 nM) but remarkably improved aqueous solubility (S_w pH 6.5: 479 mg/L), increased permeability (P_{app} A–B: 35 nm/s) and reduced efflux (efflux ratio: 6), resulting in significantly improved bioavailability [*F*, po (rat): 54%]. Furthermore, the switch from sulfonamide to sulfoximine removed a potential CYP induction liability.[26] Atuveciclib also revealed promising oral pharmacokinetics in humans in phase 1 trials; however, daily oral application of this selective CDK9 inhibitor led to neutropenia as a dose-limiting toxicity and atuveciclib studies were finally stopped for strategic reasons.

To fully explore treatment options using selective CDK9 inhibitors, a follow-up program aimed at the identification of novel selective CDK9 inhibitors suitable for intermittent, intravenous (iv) administration in patients in order to improve the therapeutic

window. The novel lead structure BAY-332 (**21**, Figure 8) revealed good activity against CDK9 (IC_{50} CDK9, high ATP: 37 nM) and also good selectivity (IC_{50} CDK2, high ATP: 3960 nM) but aqueous solubility (S_w pH 4: 30 mg/L) was not sufficient to enable the formulation of the predicted human dose for iv administration.[27] To improve the aqueous solubility, various structural alternatives to the sulfoximine group directed to the exit of the ATP binding pocket were evaluated but none of the resulting compounds revealed a promising overall profile. Thus, the sulfoximine moiety was retained at this position and a scaffold hop finally led to the identification of enitociclib (**22**, Figure 8) which displayed significantly improved potency (IC_{50} CDK9, high ATP: 3 nM) and selectivity (IC_{50} CDK2, high ATP: 3100 nM). Moreover, the high aqueous solubility of enitociclib (S_w pH 4: 699 mg/L) enabled the formulation of the predicted human dose for iv administration.[27] Encouragingly, enitociclib monotherapy recently demonstrated an acceptable therapeutic window and a favorable safety profile along with evidence of clinical benefit in patients with advanced hematologic and solid tumors after once weekly iv administration.[28]

The idea to stabilize the bioactive conformation of enitociclib by macrocyclization led to an additional series of highly potent CDK9 inhibitors like macrocycle **23** (Figure 8) with significantly improved antiproliferative activities in various cell lines [IC_{50} HeLa: 108 nM (enitociclib) vs 11 nM (**23**)].[29] Furthermore, macrocyclic inhibitors such as **23** revealed a significantly differentiated in vivo pharmacokinetic profile [$t_{1/2}$ (rat): 0.73 h (enitociclib) vs 4.8 h (**23**)] and prolonged target residence time [TRT CDK9, 25 °C: 3 min (enitociclib) vs >333 min (**23**)].

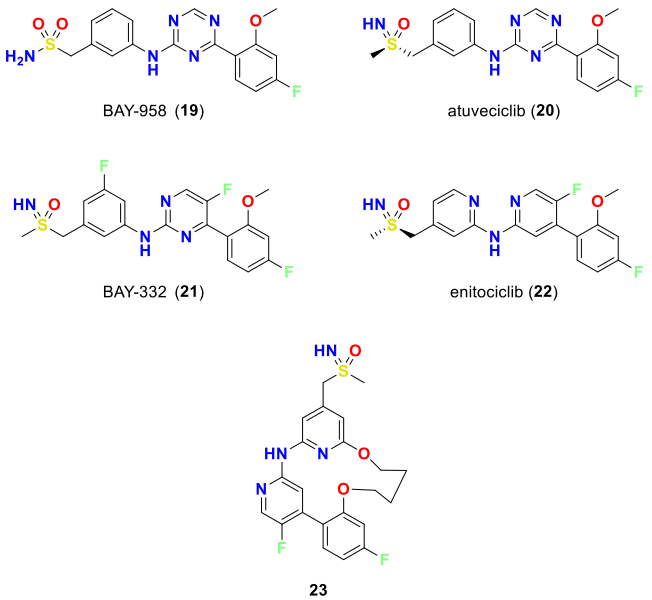


Figure 8. Chemical structures of selective CDK9 inhibitors reported by Bayer AG: BAY-958 (**19**), atuveciclib (**20**), BAY-332 (**21**), enitociclib (**22**) and macrocycle **23**.

3.2. ATR Inhibitors

The serine/threonine kinase ATR plays a key role in the DNA damage response by activating essential signaling pathways of DNA damage repair, especially in response to replication stress. Because DNA damage and replication stress are major sources of genomic instability in cancer, selective ATR inhibition has been recognized as a promising new approach in cancer therapy. Several ATR inhibitors were recently reported to have entered clinical trials as single agents and in combination therapy.[30] AstraZeneca's clinical candidate ceralasertib (**25**, Figure 9)[31] originated from tool compound AZ20 (**24**)[32] which is a potent and selective ATR inhibitor (IC_{50} ATR cellular: 61 nM). However, sulfone AZ20 was not considered for clinical development due to low aqueous solubility (S_w pH 7.4: 10 μM), which limits the maximum absorbable dose,[33] and high risk of drug–drug interactions resulting from CYP3A4 time-dependent inhibition (TDI).[31] A small-molecule crystal structure of AZ20 displayed a centrosymmetric methyl sulfone to methyl sulfone contact associated with high melting points and low solubility. To disrupt the observed solid-state contacts, structural changes to the sulfone were investigated, including replacing the sulfone moiety by a sulfoximine group. These efforts finally led to the discovery of the potent (IC_{50} ATR cellular: 74 nM) and selective sulfoximine ATR inhibitor ceralasertib, which has significantly improved aqueous solubility (S_w pH 7.4: 661 μM). While showing a different small-molecule crystal structure, the melting point of ceralasertib (mp 222 °C) is similar to that of AZ20 (mp 204 °C), which suggests that the significantly reduced lipophilicity of ceralasertib [logD pH 7.4: 1.9 (ceralasertib) vs 2.5 (AZ20)] is the main driver for the increased solubility. A further lipophilicity-related benefit of the sulfoximine group in this series of ATR inhibitors was realized in reduced hERG activity compared to the matched sulfones. Moreover, ceralasertib revealed no CYP3A4 TDI activity when incubated with human liver microsomes. In preclinical studies, ceralasertib demonstrated profound antitumor activity and associated pharmacodynamics combined with a favorable dose estimate and pharmaceutical properties.

The success of ceralasertib inspired a number of follow-up approaches from competitors, some nicely exemplifying the versatility of the sulfoximine group for drug design. Jiangsu Hengrui Medicine, for example, has recently claimed a series of potent annulated ATR inhibitors like **27** (Figure 9) in which the second α-carbon of the sulfoximine group is utilized to form an additional bond to the scaffold.[34] Moreover, the University of Texas has claimed a series of potent ATR inhibitors in which the sulfoximine group is inverted so that the nitrogen is directly attached to the central scaffold (**26**, Figure 9).[35] The syntheses of the test compounds relied on a palladium-catalyzed arylation of the sulfoximine nitrogen. Indeed, as advantage can be taken of the significantly increased commercial availability of NH sulfoximine building blocks, the palladium-catalyzed C–N bond coupling reaction between NH sulfoximines and aryl halides or aryl sulfonates[36] is being increasingly used in medicinal chemistry for the late-stage decoration of scaffolds.[37]

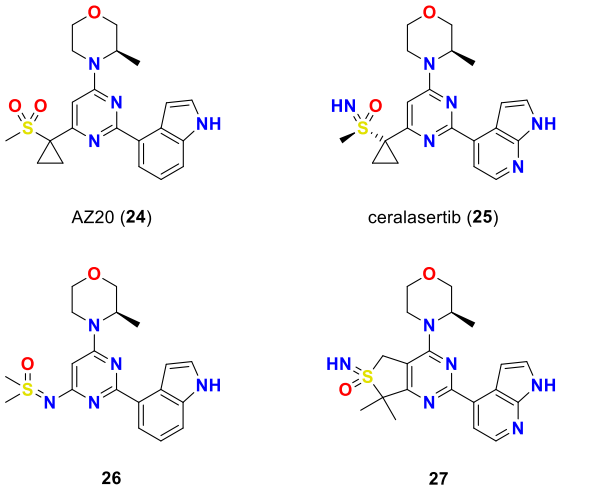


Figure 9. Chemical structures of selective ATR inhibitors: AZ20 (**24**, AstraZeneca), ceralasertib (**25**, AstraZeneca), inverted sulfoximine **26** (University of Texas) and annulated analogue **27** (Jiangsu Hengrui Medicine).

3.3. Herpes Simplex Virus Helicase-Primase Inhibitors

The current therapy for herpes simplex virus (HSV) infections targeting the viral polymerase with nucleoside analogues such as acyclovir is somewhat effective but limited by poor central nervous system (CNS) exposure. Moreover, latent infections are not affected by this therapy and for nucleoside-resistant HSVs, treatment options are limited.[38] Helicase-primase inhibitors offer a novel mode of action, but the clinical development of front-runner compound pritelivir (**28**, Figure 10) has been hampered by CA off-target activity, aromatic, primary sulfonamide class-related side effects and limited CNS exposure.[39] Using pritelivir as a starting point, Kleymann and co-workers at Innovative Molecules reduced the topological polar surface area (TPSA) in order to improve the CNS exposure, for instance by replacing the pyridyl group by a difluorophenyl moiety. This modification also resulted in a significantly increased lipophilicity. To eliminate the off-target CA activity and the sulfonamide-related side effects, the primary sulfonamide was exchanged for an NH sulfoximine group, which led to a further decrease in TPSA. In comparison to pritelivir, the resulting compound, IM-250 (**29**, Figure 10), revealed similar in vitro potency [IC_{50} HSV-1: 20 nM (pritelivir) vs 19 nM (IM-250)] but significantly reduced TPSA [106 Å^2 (pritelivir) vs 74 Å^2 (IM-250)] and increased lipophilicity [clogD pH 7.4: 2.0 (pritelivir) vs 3.3 (IM-250)].[39] In preclinical evaluation, IM-250 displayed a long half-life, high exposure, good bioavailability and high CNS exposure in various species, which translated into superior in vivo activity in animal models compared to pritelivir. Innovative Molecules has subsequently announced the closing of a series A financing round in which 20 million euro was raised for the clinical evaluation of IM-250.

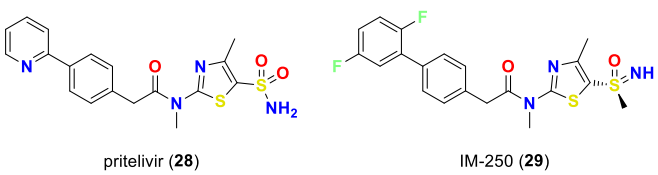


Figure 10. Chemical structures of helicase-primase inhibitors pritelivir (**28**) and IM-250 (**29**).

4. Bioisosteric Replacement of Non-sulfur-Based Functional Groups

The bioisosteric replacement of sulfones and sulfonamides for sulfoximines has recently elicited much interest in medicinal chemistry. The discoveries of the clinical candidates roniciclib (**18**), atuveciclib (**20**), enitociclib (**22**) and IM-250 (**29**) all included the switch from a primary sulfonamide group to a sulfoximine during lead optimization. The replacement of a sulfone for a sulfoximine was also crucial for the identification of ceralasertib (**25**). However, recent studies indicate that the replacement of non-sulfur-based functional groups such as alcohols and amines for sulfoximines offers additional opportunities for drug designers.

4.1. RORγ Inverse Agonists

The orphan nuclear receptor RORγ has emerged as an interesting therapeutic target due to its broad influence in human regulation processes.[40] The main focus of recent drug discovery efforts has been directed at the identification of selective RORγ inverse agonists to reduce interleukin-17 production for the treatment of autoimmune diseases. However, the identification of suitable clinical candidates with promising physicochemical properties has been hampered by the high lipophilicity which is required for high potency against this nuclear receptor. Inverse agonist **30** (Figure 11) from GSK, which is characterized by a hydrophilic hydroxymethyl group, suggested that the RORγ ligand binding domain can tolerate a certain amount of hydrophilicity in this region, and inspired a team at Nestlé Skin Health to screen polar structural alternatives at this position.[41] Based on the comparable pK_a values, NH sulfoximines have been suggested as bioisosteres of alcohols.[42] Introduction of a sulfoximine group to the RORγ lead series, exemplified by compound **31** (Figure 11), was indeed found to maintain good potency in a cellular in vitro assay [IC_{50} RORγ: 17 nM (**30**) vs 26 nM (**31**)] but strongly reduced lipophilicity [logD pH 6.5: 5.9 (**30**) vs 4.6 (**31**)], resulting in significantly improved lipophilic efficiency [1.9 (**30**) vs 3.0 (**31**)]. Due to high turnover in human hepatocytes, sulfoximine **31** was not considered suitable for oral application, but metabolic instability can be an advantage for topical application as this could allow local action, for example in the skin, while preventing potential systemic side effects. Sulfoximine **31** revealed robust results after topical application in a preclinical mouse model of psoriasis. A scale-up route to deliver the first 100 g of RORγ inverse agonist **31** has been published,[43] suggesting that the compound has been evaluated for IND-enabling studies.

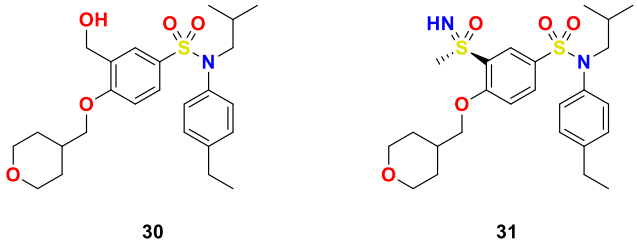


Figure 11. Chemical structures of RORγ inverse agonists: **30** (GSK) and **31** (Nestlé Skin Health).

4.2. PDE5 Inhibitors

Amines are ubiquitous in drug discovery and cover a wide range of therapeutic applications. However, the amine group is not only capable of interactions with the target protein but, for instance, also with membrane phospholipids, transporter proteins and drug-metabolizing enzymes. Therefore, the amine functionality is often pivotal to the metabolism of the corresponding drug.[44] Based on the rationale that under physiological conditions most amines are predominantly protonated and therefore tetrahedral, a study investigated if weakly basic, tetrahedral sulfoximines could serve as bioisosteres for amines in a series of sulfoximine analogues of marketed drugs and advanced clinical candidates.[8b] The sulfoximine analogue **33** (Figure 12) of PDE5 inhibitor vardenafil (**32**), for instance, revealed at least equipotent activity against the target in vitro [IC_{50} PDE5: 0.029 nm (vardenafil) vs 0.025 nM (**33**)]. Vardenafil has higher aqueous solubility [S_w pH 6.5: 220 mg/L (vardenafil) vs 52 mg/L (**33**)] but sulfoximine analogue **33** revealed reduced lipophilicity [logD pH 7.5: 2.6 (vardenafil) vs 2.0 (**33**)] and increased metabolic stability in rat hepatocytes [CL_b (rHep): 3.0 L/h/kg (vardenafil) vs 2.1 L/h/kg (**33**)]. Interestingly, vardenafil showed high permeability and no efflux, whereas sulfoximine analogue **33** was characterized by poor permeability properties [P_{app} A–B: 206 nm/s (vardenafil) vs 0.7 nm/s (**33**); efflux ratio: 0.87 (vardenafil) vs 288 (**33**)]. In the light of the profiles of recently reported clinical candidates, as outlined in Section 3., the poor permeability properties of **33** seem surprising. However, reduced permeability/increased efflux was also pointed out as a potential liability of NH sulfoximines by Gnamm, Bolm and co-workers in their comprehensive study of sulfoximines from the medicinal chemist's perspective.[8a]

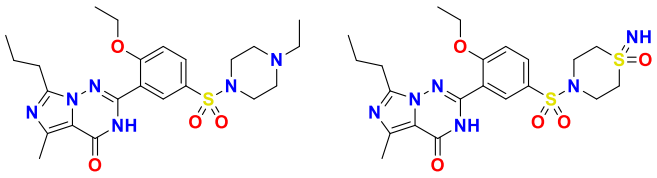


Figure 12. Chemical structures of PDE5 inhibitors vardenafil (**32**) and sulfoximine analogue **33**.

5. N-Functionalized Sulfoximines

Chemical stability and the possibility to functionalize the imine position originally attracted Satzinger and Stoss at Gödecke AG to the underexplored sulfoximine group in the 1970s, finally leading to the identification of the clinical candidate suloxifen.[13,14] In contrast, all recent sulfoximine clinical candidates are characterized by an NH sulfoximine group. Nevertheless, developments of late indicate that the N-functionalization of sulfoximines is being increasingly utilized for the design of complex molecules and novel modalities such as proteolysis targeting chimeras (PROTACS) and antibody–drug conjugates (ADCs), as well as to tune the overall properties of target molecules.

5.1. Five- to Seven-Membered Cyclic Sulfoximines

Elimination of the hydrogen-bond donor at the sulfoximine nitrogen of PDE5 inhibitor **33**, for example by alkylation of the imine position, could be a potential strategy to improve the permeability properties. However, N-alkylated sulfoximines often display decreased metabolic stability.[8a] In this context, a study at Bayer AG investigated if saturated, cyclic sulfoximines could combine high permeability, low efflux and high metabolic stability with favorable aqueous solubility. Based on a novel synthetic approach to saturated five- to seven-membered cyclic sulfoximines,[45] the in vitro properties of NH sulfoximine roniciclib (**18**, see Figure 7) were compared with those of the *N*-ethyl and the five-membered cyclic sulfoximine analogues (**34**, **35**; Figure 13).[46] Roniciclib was tested as a single stereoisomer whereas the two analogues **34** and **35** were synthesized without stereocontrol at the sulfoximine position and tested as 1:1 mixtures of two diastereoisomers. *N*-Ethyl derivative **34** revealed significantly improved permeability [P_{app} A–B: 231 nm/s (**34**) vs 79 nm/s (roniciclib)] and reduced efflux [efflux ratio: 0.95 (**34**) vs 2.60 (roniciclib)] but a trend for reduced inhibitory activity [IC_{50} CDK2: 17 nM (**34**) vs 9 nM (roniciclib)], reduced metabolic stability in rat hepatocytes [F_{max}: 44% (**34**) vs 80% (roniciclib)], slightly increased lipophilicity [logD pH 7.4: 2.4 (**34**) vs 2.3 (roniciclib)] and reduced aqueous solubility [S_w pH 6.5: 282 mg/L (**34**) vs 385 mg/L (roniciclib)]. In contrast, cyclo-roniciclib (**35**) showed a clear trend for improved potency [IC_{50} CDK2: 5 nM (**35**) vs 9 nM (roniciclib)], comparable metabolic stability [F_{max}: 79% (**35**) vs 80% (roniciclib)] and solubility [S_w pH 6.5: 337 mg/L (**35**) vs 385 mg/L (roniciclib)], improved permeability [P_{app} A–B: 148 nm/s (**35**) vs 79 nm/s (roniciclib)] and reduced efflux [efflux ratio: 1.71 (**35**) vs 2.60 (roniciclib)]. Surprisingly, cyclo-roniciclib (**35**) also revealed slightly reduced lipophilicity [logD pH 7.4: 2.2 (**35**) vs 2.3 (roniciclib)]. These results indicate that saturated cyclic sulfoximines could serve as very interesting building blocks for medicinal chemistry.[47]

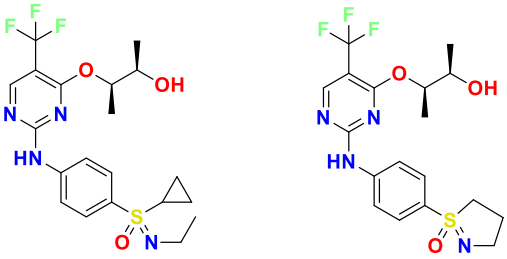


Figure 13. Chemical structures of *N*-ethylroniciclib (**34**) and cyclo-roniciclib (**35**).

5.2. BACE1 Inhibitors

Alzheimer's disease (AD) is characterized by two major pathological features in the brain of patients, the occurrence of neurofibrillary tangles and amyloid plaques. The principal component of amyloid plaques are Aβ-peptides, which are generated from the amyloid precursor protein (APP) by the sequential action of two proteases termed β- and γ-secretase.[48] Because β-secretase activity is exerted by the β-site APP-cleaving enzyme (BACE1), it has been presumed that inhibitors of BACE1 activity can be useful agents for therapeutic intervention of AD. Several BACE1 inhibitors, originating from diverse companies, have been evaluated in clinical trials; however, a majority of these trials has been terminated for various reasons.[49] The early, phase 3 BACE1 inhibitor verubecestat (**36**, Figure 14) provided inspiration for intense modifications of its

chemical structure in this highly competitive area of research. Sulfonylguanidines like verubecestat are among the most-explored structural motifs of BACE1 inhibitors as the electronegative sulfonyl group allows modulation of the basicity of the mandatory (for inhibitory activity) guanidine or amidine moiety, but at the cost of a high TPSA, high efflux and poor CNS penetration.[49] In this context, Merck and Roche have filed several patent applications in which utilization of the sulfoximine group is described.[50] Unfortunately, there are no scientific publications which compare the overall profiles of these highly complex molecules with verubecestat. However, cyclic sulfoximine **37** (Figure 14), for instance, revealed high cellular activity (IC_{50} BACE1 cellular: 0.09 nM) and in vivo potency in a rat model (86% Aβ reduction).[50b]

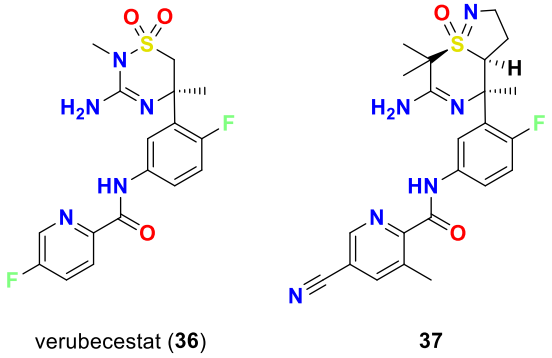


Figure 14. Chemical structures of BACE1 inhibitors verubecestat (**36**, Merck) and **37** (Roche).

5.3. CDK9 Inhibitor Antibody–Drug Conjugates

Antibody–drug conjugates (ADCs) are one of the fastest growing classes of anticancer therapeutics. The primary goal of ADCs is to improve the therapeutic index of antitumor agents by restricting systemic delivery to cells that express the target antigen of interest.[51] For the construction of an ADC, a humanized or human monoclonal antibody which targets a suitable antigen expressed on the cancer cell surface is conjugated with a highly cytotoxic small molecule (toxophore) via a linker. Following the introduction of the ADC into the tumor cell and subsequent dissociation of the conjugate, either the cytotoxic agent itself or a cytotoxic metabolite formed therefrom is released within the tumor cell and can unfold its action therein directly and selectively. Triggered by the significantly improved antiproliferative activity of macrocyclic CDK9 inhibitors like compound **23** (see Figure 8), related macrocycles were utilized as toxophores for the construction of ADCs.[52] In the CDK9/enitociclib complex, the sulfoximine group is directed to the exit of the CDK9 binding pocket.[27] Therefore, the NH sulfoximine group is well positioned for the introduction of a linker to the monoclonal antibody. Moreover, NH sulfoximines can be conveniently functionalized via a broad variety of reactions including, for example, N-alkylation, N-arylation, N-acylation, N-carbamylation, N-carbamoylation and N-sulfonylation (Figure 15).[53] The resulting structural diversity could transpire to be beneficial with respect to the release of the toxophore by dissociation of the conjugate in the cell. CDK9 ADC **38** (Figure 15) utilizing the EGFR antibody cetuximab, for instance, revealed subnanomolar antiproliferative activity against NCI-H292 cells in vitro (IC_{50}: 0.7 nM).[52]

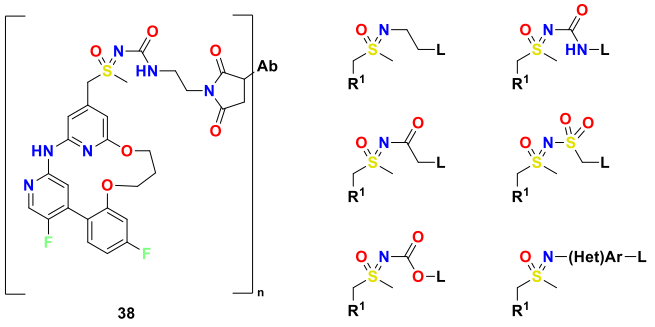


Figure 15. Chemical structure of CDK9 ADC **38** utilizing the EGFR antibody (Ab) cetuximab and structural variations for the introduction of the linker (L) via the sulfoximine nitrogen of the macrocyclic toxophore (Bayer AG).[52]

5.4. CDK9 Proteolysis Targeting Chimeras

Targeted protein degradation using proteolysis targeting chimeras (PROTACs) has gained considerable momentum as a novel therapeutic modality in drug discovery.[54] PROTACs are heterobifunctional molecules which consist of three parts: a ligand to bind to an E3 ubiquitin ligase and a second ligand to bind to the protein of interest, connected by a chemical linker.[55] Selective CDK9 inhibitor atuveciclib (**20**, see Figure 8) was recently utilized for the development of a series of selective CDK9 degraders with enhanced antiproliferative activity.[56] In the CDK9/atuveciclib complex, the sulfoximine group is directed to the exit of the ATP binding pocket[26] enabling the utilization of the sulfoximine NH for the introduction of various linkers to the E3 ligase binding moiety, similar to the design strategy of the CDK9 ADCs at Bayer AG (vide supra). Lead optimization efforts led to PROTAC **39** (Figure 16) which was shown to completely degrade CDK9 in cancer cells such as MV4-11 with high degradation efficiency (DC_{50}: 7.6 nM). PROTAC **39** revealed slightly increased CDK9 inhibitory activity in vitro compared to atuveciclib [IC_{50} CDK9: 8.7 nM (**39**) vs 13.1 nM (atuveciclib)] and retained high kinase selectivity in the DiscoverX kinase panel. Compared with atuveciclib, degrader **39** displayed significantly improved antiproliferative activity against MV4-11 cells in vitro [IC_{50} MV4-11: 25 nM (**39**) vs 560 nM (atuveciclib)]. Furthermore, CDK9 PROTAC **39** was shown to degrade CDK in vivo in a mouse model.

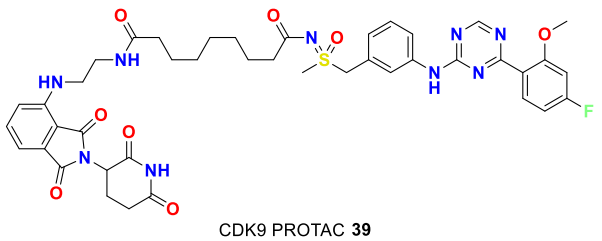


Figure 16. Chemical structure of CDK9 PROTAC **39**.

Considering that the sulfoximine moiety of the complexed ATR inhibitor ceralasertib (**25**) is also directed to the exit of the ATP binding pocket of ATR,[57] a similar strategy might be successful for the development of ATR degraders.

5.5. TMTH-Sulfoximine (TMTHSI) Click Reagent

Click chemistry reactions are an important part of the medicinal chemistry toolbox. Among all the click reactions, the 1,3-dipolar cycloaddition of alkynes and azides is the most popular and has been utilized, for instance, for the development of diverse pharmaceutical and biomedical imaging agents.[58] Nevertheless, applications in the biological sciences have been somewhat limited by the requirement for copper catalysis in the click reaction[59] which thus triggered the development of a variety of alternative click reagents relying on strained triple bonds which do not require copper catalysis. However, several of these newly developed click reagents are characterized by reduced reactivity, high molecular weight and low aqueous solubility. To overcome these limitations, Liskamp and co-workers recently introduced TMTH-sulfoximine (TMTHSI, **41**; Figure 17).[60] Strained thiacycloheptynes such as TMTH (**40**) had been previously recognized as a promising new class of reagents for copper-free click chemistry but low stability and the lack of a convenient point of attachment to which different types of ligands could be connected posed major hurdles for their practical applications. In contrast, the sulfoximine analogue TMTHSI, which is stable on the bench for more than a year, was shown to be a highly reactive click reagent which can be conveniently functionalized, for instance, via N-alkylation, N-sulfonylation, N-acylation and N-carbamoylation of the sulfoximine moiety.[60] Moreover, in comparison to other strained click reagents, TMTHSI is characterized by low molecular weight and low lipophilicity contributing to improved aqueous solubility. TMTHSI was, for example, utilized successfully for the preparation of folic acid functionalized core cross-linked polymeric micellar nanoparticles (**42**, Figure 17).

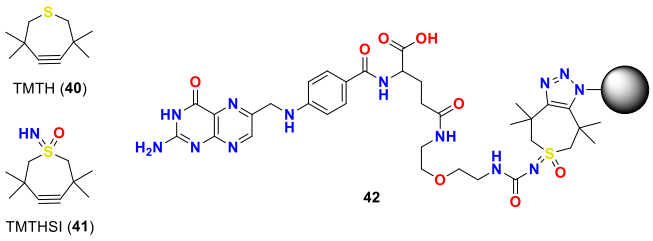


Figure 17. Chemical structures of TMTH (**40**), TMTHSI (**41**) and folic acid functionalized core cross-linked polymeric micellar nanoparticles (**42**).

6. Vinyl Sulfoximines

6.1. Covalent Inhibition

Targeted covalent inhibition (TCI), wherein a reactive group (warhead) is strategically incorporated onto a reversible ligand of the target protein to facilitate specific covalent engagement, is being increasingly recognized as a powerful concept for drug discovery.[61] Vinyl sulfones and sulfonamides have been often utilized as warheads for covalent inhibition.[62] Given the prior examples of the successful replacement of sulfones and sulfonamides for sulfoximines in the discovery of reversible inhibitors (vide supra), it seems obvious to evaluate vinyl sulfoximines for covalent inhibition, too. In contrast to sulfones and sulfonamides, the imine position of the sulfoximine group could, for instance, be utilized to tune the reactivity of the warhead via a substituent at the nitrogen. The concept of applying vinyl sulfoximines for the development of covalent inhibitors was recently highlighted by Armstrong, Bull and co-workers in a publication describing various synthetic approaches to vinyl sulfoximines.[63] However, the only case study reported so far is a recent series of vinyl sulfoximines which activate the transcription factor Nrf2.[64] While Nrf2 is considered the main target of the multiple sclerosis drug dimethyl fumarate (**43**, Figure 18), exploration of additional Nrf2-activating compounds is motivated by its significant off-target effects and low CNS penetration. Against this backdrop, vinyl sulfones like VSC2 (**44**, Figure 18) were recently shown to increase Nrf2 levels via covalent interaction with certain cysteines in Keap1, leading to Nrf2 activation.[65] Carlström and co-workers have evaluated a series of VSC2 sulfoximine analogues employing a broad variety of substituents at the sulfoximine nitrogen.[64] The *N*-methyl analogue CH-3 (**45**, Figure 18) and dimethyl fumarate displayed comparable activation of Nrf2 in vitro, but *N*-methyl sulfoximine **45** revealed less off-target effects in vitro and in vivo. Unfortunately, the publication does not provide any insights into the mode of action of vinyl sulfoximine CH-3, but studies with structurally related chalcones and vinyl sulfones suggest that the compound is acting as a covalent inhibitor.[65b]

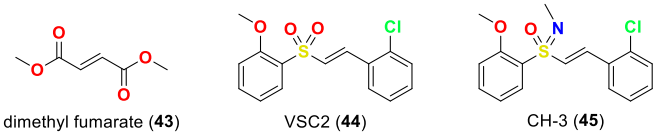
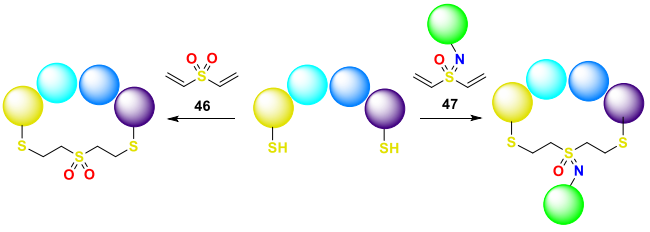


Figure 18. Chemical structures of Nrf2 activators dimethyl fumarate (**43**), VSC2 (**44**) and CH-3 (**45**).

6.2. Cyclic Peptides

Based on their ability to bind with high affinity and selectivity to protein targets, as well as their low inherent toxicity, cyclic peptides are gaining considerable attention in drug discovery.[66] One strategy to transform therapeutically active peptides into orally available drugs is to convert them into cyclic peptides, for example by using bis-electrophile cyclization reagents such as divinyl sulfone (**46**, Scheme 1).[67] In this regard, it is envisaged that the use of divinyl sulfoximines **47** could offer novel opportunities for the design and application of cyclic peptides as the sulfoximine nitrogen would offer an additional point for diversification.[68]



Scheme 1. Possible use of divinyl sulfoximines **47** as bis-electrophile cyclization reagents for the construction of cyclic peptides.

7. Summary

The sulfoximine group has emerged from a 'lab oddity'[24] to become a 'rising star in modern drug discovery'.[8c] After its late discovery in 1949 in the form of the toxic side product MSO of the

'agene process', the initial interest in sulfoximines for drug discovery was driven by the stability of this functional group and the possibility to functionalize the sulfoximine nitrogen. These early efforts, pioneered by Satzinger and Stoss in the 1970s, led to only a few clinical candidates, such as the antiasthmatic suloxifen (**11**).[14] The next wave of clinical candidates containing a sulfoximine group, starting in the 2000s, was heralded by pan-CDK inhibitor roniciclib (**18**), which exemplified the utilization of an NH sulfoximine group as a bioisostere for a sulfonamide group to overcome the main project hurdles of aqueous solubility, sulfonamide-mediated off-target activity and IP.[24] The introduction of NH sulfoximines as bioisosteres for sulfonamides and sulfones was also successfully utilized in the discoveries of recent clinical candidates, including the CDK9 inhibitors atuveciclib (**20**)[26] and enitociclib (**22**)[27], ATR inhibitor ceralasertib (**25**)[31] and helicase-primase inhibitor IM-250 (**29**).[39] The high stability and polarity of the sulfoximine group, resulting in superior physicochemical and ADME properties, were key criteria for the selection of these sulfoximine compounds as clinical candidates.

However, rather than sulfoximines only being diminished to their now popular use as sulfonamide/sulfone bioisosteres with good stability and ADME properties and potentially promising IP, recent developments indicate that the versatile sulfoximine group offers many more opportunities to drug designers. RORγ inverse agonist **31**[41] and PDE5 inhibitor **33**[8b] illustrate that it is also worthwhile considering sulfoximines for the replacement of non-sulfur-based functional groups such as alcohols and amines. Moreover, the utilization of all three exit vectors of the tetrahedral sulfoximine group via the structurally diverse options for N-functionalization offers access to novel chemical space. N-Alkylation, for instance, allows access to complex cyclic structures, exemplified by BACE1 inhibitor **37**[50b] and cyclo-roniciclib (**35**), the latter displaying a significantly modulated overall profile compared to its NH analogue roniciclib (**18**). Moreover, early work at Gödecke AG in the 1970s already outlined the potential of utilizing sulfoximines for the construction of novel heterocycles such as partial benzodiazepine receptor agonist Gö 4962 (**14**)[16] or reverse transcriptase inhibitor **13**.[17] In addition, scattered reports indicate the potential of NH sulfoximines as convenient points of linker attachment for the construction of ADCs (e.g., **38**)[52] and PROTACs (e.g., **39**)[56] or as a click reagent (i.e., **41**)[60] for pharmaceutical or biomedical imaging applications. The versatile chemistry available for the N-functionalization of the sulfoximine group offers multiple options to adjust the overall properties of a target molecule in accordance to the desired target profile. In this context, the possibility to tune the reactivity of vinyl sulfoximines via N-functionalization could also prove to offer novel opportunities for the development of covalent inhibitors.[64] Moreover, divinyl sulfoximines **47** could be useful bis-electrophile reagents, for example for the construction of cyclic peptides.

From the drug designer's perspective it is obvious that the initially surprising success story of sulfoximines in drug discovery not only has offered many more options in medicinal chemistry, but has also helped pave the way for the use of additional sulfur-based 'lab oddities' such as sulfondiimines, sulfonimidamides, sulfondiimidamides and sulfur fluorides to tackle an ever-increasing biological target space in an even more multifaceted manner.

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Keywords: drug design • innovation • life sciences • medicinal chemistry • sulfoximines

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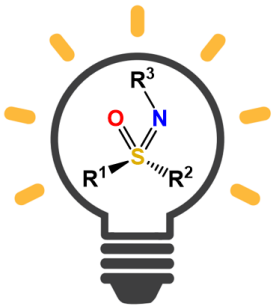

The sulfoximine group has emerged from a ‘lab oddity’ to become a ‘rising star in modern drug discovery’. Even though the increasing interest in this versatile functional group in recent years has resulted in several sulfoximine clinical candidates, there is ample room for further innovative applications. This minireview highlights emerging trends and opportunities for drug designers for the utilization of the sulfoximine group, such as in the construction of complex molecules, PROTACs, ADCs and novel warheads for covalent inhibition.