Angewandte International Edition Chemie

Medicinal Chemistry

DOI: 10.1002/anie.201302209

Sulfoximines: A Neglected Opportunity in Medicinal Chemistry

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Dedicated to the Bayer company on the occasion of its 150th anniversary

drug design · medicinal chemistry · pharmacophores · sulfoximines

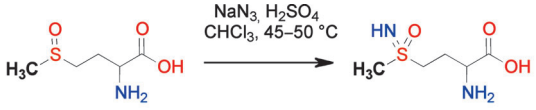
Innovation has frequently been described as the key to drug discovery. However, in the daily routine, medicinal chemists often tend to stick to the functional groups and structural elements they know and love. Blockbuster cancer drug Velcade (bortezomib), for example, was rejected by more than 50 companies, supposedly because of its unusual boronic acid function (as often repeated: "only a moron would put boron in a drug!"). Similarly, in the discovery process of the pan-CDK inhibitor BAY 1000394, the unconventional proposal to introduce a sulfoximine group into the lead series also led to sneers and raised eyebrows, since sulfoximines have seldom been used in medicinal chemistry. However, it was the introduction of the sulfoximine group that finally allowed the fundamental issues of the project to be overcome, culminating in the identification of the clinical sulfoximine pan-CDK inhibitor BAY 1000394. This Minireview provides an overview of a widely neglected opportunity in medicinal chemistry—the sulfoximine group.

1. Introduction

Sulfoximines, the monoaza analogues of sulfones, are stable compounds that offer a rich and versatile chemistry.[1] Considering that the identification of the very first sulfoximine compound, methionine sulfoximine (MSO), was triggered by its profound biological effects, it is surprising that this functional group has rarely been used in medicinal chemistry. Probably less than a handful of sulfoximine compounds have entered clinical trials, and there is no drug containing a sulfoximine group on the market. However, with the emergence of new, safe synthetic methods for the preparation of sulfoximines[2] and the recent example of sulfoximine pan-CDK inhibitor BAY 1000394 in Phase I studies,[3] it is time to (re)consider this functional group for drug discovery. This Minireview provides an overview of the rather limited history of the sulfoximine group in medicinal chemistry approaches (Table 1), focusing on selected examples where the concept for its use as a pharmacophore and the outcome are available. Although this Minireview is not focused on synthetic methods,[1,2,4] representative syntheses will be highlighted to demonstrate the use of standard transformations.

2. Late Discovery of the Sulfoximine Group

Various agents have been used to commercially improve freshly milled wheat, including nitrogen trichloride ("agene"). This method of bleaching, the "agene process", was in use from early in the 20th century; however, in 1946 it was reported that dogs fed a diet rich in agenized flour were subject to epileptiform fits and eventual death.[5] These findings became a matter of great concern, since at that time an estimated 90% of flour milled in England was treated with agene.[6] A few years later, the toxic factor was finally identified as the "sulfoximine" of methionine (MSO, **2**).[7] The compound was also prepared synthetically by the action of hydrazoic acid on methionine sulfoxide (**1**) in the presence of concentrated sulfuric acid (Scheme 1).[8] The sulfoximine moiety had previously been unknown. Needless to say, MSO (**2**) was not a natural product, since it was derived chemically from peptide-bound methionine in wheat; however, the same material was later reported to be isolated from *Cnestis palala*, a tropical woody



Scheme 1. Synthesis of methionine sulfoximine (MSO, **2**).

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Table 1: Overview of sulfoximines in medicinal chemistry approaches.

Compound	Mode of action	Rationale
5	γ-glutamylcysteine synthetase	better specificity
8	spasmolytic/antiasthmatic	opportunistic approach
9	spasmolytic	opportunistic approach
15	benzodiazepine receptor agonist	opportunistic approach
16	reverse transcriptase inhibitor	opportunistic approach
19–21	antiasthmatic	bioisoster for carboxylic acid with oral bioavailability
23	α-adrenergic receptor blocker	bioisoster for heterocyclic amidine
28	carboxypeptidase A inhibitor	stable transition-state analogue inhibitor
29, **30**	L-asparagine synthetase inhibitor	stable transition-state-analogue inhibitor
33	CYP24 inhibitor	bioisoster of sulfone
BAY 1000394	pan-CDK inhibitor	opportunistic approach to reduce CA inhibitory activities of arenesulfonamide lead structure
36, **37**, **39**	HIV-1 protease inhibitor	bioisoster of secondary alcohol/stable transition-state mimic
42, **43**	PYK2 inhibitor	opportunistic approach to reduce hERG activity of sulfone lead structure
45–47, **49**	COX-2 inhibitor	opportunistic approach to reduce hERG activity of sulfone lead
51, **52**	androgen receptor suppressor	opportunistic approach to investigate effect on AR activities compared to sulfone lead structure
55	HNE inhibitor	opportunistic approach
57–60	factor Xa inhibitor	bioisoster of amidine to improve oral bioavailability

plant of the family Connaraceae, species of which are known for their toxicity.[9]

Administration of MSO (**2**) to animals leads to decreased tissue levels of glutamine and glutathione (GSH).[10] Among the four stereoisomers of MSO, L-methionine (*S*)-sulfoximine (**2a**; Figure 1) was found to be the biologically active stereoisomer. It was shown that isomer **2a** inhibits both glutamine synthetase[11] and γ-glutamylcysteine synthetase,[12] the rate-limiting enzyme in GSH biosynthesis. L-Methionine (*S*)-sulfoximine (**2a**) serves as an analogue of the tetrahedral transition state formed in the reaction of enzyme-bound γ-glutamyl phosphate (**4**) with ammonia or cysteine. Thus, both synthetases interact with **2a** and ATP to give L-methionine (*S*)-sulfoximine phosphate (**3**), which binds tightly to the active sites of these enzymes, thereby producing inhibition.[10a]

The ability to increase drug sensitivity by decreasing intracellular GSH has been demonstrated in a number of cell lines exposed to a variety of cytotoxic agents.[13] To achieve better specificity, a series of MSO analogues were synthesized in which the methyl group was replaced by other alkyl units.[10a,14] Buthionine sulfoximine (BSO, **5**) was found to be a specific and competitive inhibitor of γ-glutamylcysteine synthetase. The ability of BSO-induced GSH depletion to enhance cytotoxicity has been demonstrated in vitro and in vivo.[13] Several research groups have undertaken clinical studies with BSO to evaluate whether modulation of GSH could be clinically useful in treating tumors that overexpress GSH (e.g. hepatocarcinoma). In these preliminary studies, the drug proved to be well-tolerated and safe.[15] To date, BSO (**5**) has been the most prominent sulfoximine compound in the literature,[1b] since it has also found wide application for inducing experimental GSH deficiency in investigations of the role of GSH in cellular processes.

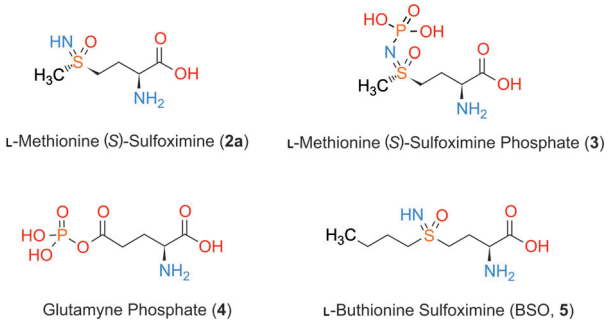


Figure 1. Structures of L-methionine (*S*)-sulfoximine (**2a**) and related compounds.

Ulrich Lücking studied chemistry at the University of Hannover (Germany). As an Erasmus student and later for his diploma studies, he worked with Prof. Steven V. Ley at Cambridge University (UK). In 1999 he completed his PhD with Prof. Andreas Pfaltz at the MPI für Kohlenforschung, Mülheim an der Ruhr (Germany), and then carried out postdoctoral work with Prof. Julius Rebek at the Scripps Research Institute, La Jolla (USA). His industrial career began at the former Schering AG in 2001. He is currently a Senior Research Scientist at Bayer Pharma AG in Berlin. He has worked in many therapeutic areas, principally in lead-structure optimization.

3. General Properties of Sulfoximines

Sulfoximines are isoelectronic with sulfones; however, the introduction of the nitrogen atom creates asymmetry at the tetrahedral sulfur atom in the case where the two carbon substituents are not identical. In general, sulfoximines are constitutionally and configurationally stable compounds which can be manipulated without special care.[1] In contrast to sulfones, sulfoximines offer an additional point for substitution: the mildly basic nitrogen atom (Figure 2. N-Unsubstituted sulfoximines ($R^3 = H$, "free sulfoximines" are capable of being phosphorylated in vivo, as demonstrated for example with MSO (**2**). The nitrogen atom is also sufficiently basic to allow metal-ion coordination[16] and to form salts with

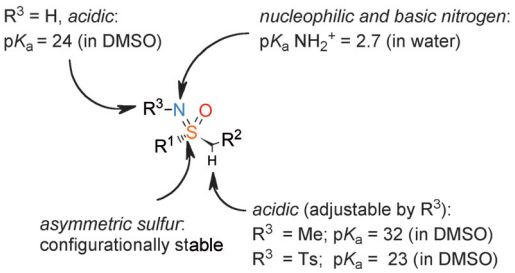


Figure 2. Features of sulfoximines that account for their unusual chemical versatility.[1b,18]

mineral acids. The nature of the substituent on the nitrogen atom dramatically influences the acid/base properties of the compound.[1,17] The sulfur-bound heteroatoms of sulfoximines are hydrogen-bond acceptors. Free sulfoximines offer dual functionality as a hydrogen donor (through the NH group) and an acceptor. NMR spectroscopic studies have indicated that the sulfoximine group is slightly more electron-withdrawing than the sulfone group. Furthermore, there is a marked difference between sulfoximines and the corresponding sulfones, in that simple sulfoximines with a low molecular weight are readily soluble in protic solvents, such as water and alcohols. This is probably due to special solvation around the sulfoximine group.[17b] This unique combination of properties makes the small, hydrophilic sulfoximine group very attractive for medicinal chemistry.

4. Sulfoximines as Pharmacophores: Pioneering Studies

Sulfoximines were still a chemical curiosity around 1970 and had not been used to construct drugs. Attracted by their chemical stability and the easily exchangeable imine proton, Satzinger and Stoss at Gödecke pioneered the use of the sulfoximine group in medicinal chemistry approaches.[19] In the search for a new basic structure for antiasthmatic agents with reduced side effects and a broader spectrum of action than classic anticholinergics, such as atropine (**6**) or oxyphenonium bromide (**7**; Figure 3) the team at Gödecke started to introduce (*S*,*S*)-diphenyl sulfoximine (**12**) as a new pharmacophore.[20] Lead optimization within this new class culminated in the identification of suloxifen (**8**), selected for clinical development as a polyvalent spasmolytic and antiasthmatic agent, which is effective both orally and parenterally. However, "the convincing clinical studies were terminated by company decree shortly before the product was ready for the market."[19] High spasmolytic activities were also recorded for a related series of *N*-aminomethylated (*S*,*S*)-diphenyl sulfoximine derivatives which were independently synthesized by Haake et al. and investigated at Heumann Pharma. In particular, HE-HK 52 (**9**) was identified as a potent spasmolytic.[21]

It is noteworthy that the scientists at Gödecke reported on safety issues in the synthesis of the required (*S*,*S*)-diphenyl sulfoximine (**12**) when employing hydrazoic acid that was formed in situ:[22] reaction of diphenyl sulfoxide (**10**) with

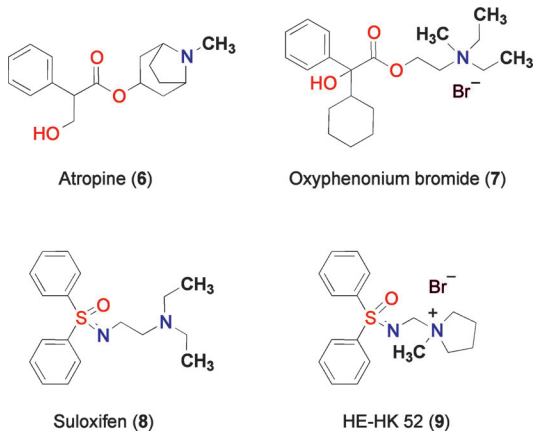
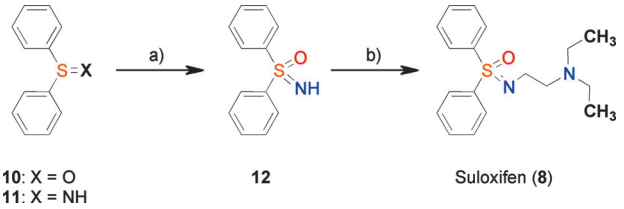


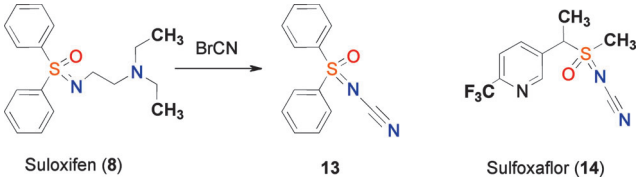
Figure 3. Structures of the classic anticholinergics atropine (**6**) and oxyphenonium bromide (**7**) compared to suloxifen (**8**) and HE-HK 52 (**9**).

sodium azide in polyphosphoric acid (PPA) at 80 °C on a multigram scale led in one case to an explosion.[20] This probably triggered the development of an alternative synthesis of (*S*,*S*)-diphenyl sulfoximine (**12**; Scheme 2), which relied on the oxidation of (*S*,*S*)-diphenyl sulfimide (**11**) and was considered to be "safe on technical scale".[23]



Scheme 2. Synthesis of suloxifen (**8**). Reagents and conditions: a) **10**, NaN_3, PPA, 80 °C; alternatively: **11**, $KMnO_4$, pyridine, RT; b) 2-chloro-*N*,*N*-diethylethanamine, NaH, toluene, reflux.

Additional studies with suloxifen (**8**) resulted in the isolation of the first *N*-cyano sulfoximine **13** (Scheme 3).[24] Almost 40 years later, this functional group found its way into the first sulfoximine insecticide, the commercially available sulfoxaflor (**14**).[25]



Scheme 3. Synthesis of *N*-cyano sulfoximine **13** and structure of the commercial insecticide sulfoxaflor (**14**).

5. Benzodiazepine Receptor Agonists and Reverse-Transcriptase Inhibitors

In the 1970s, sulfoximines were still an underrepresented pharmacophore in drug discovery approaches; however, encouraged by the promising results with suloxifen (**8**),

scientists at Gödecke proceeded to study synthetic routes for new heterocyclic sulfoximines.[26] From these efforts, Gö 4962 (**15**; Figure 4) was identified as a partial benzodiazepine receptor agonist with excellent anxiolytic and anticonvulsive

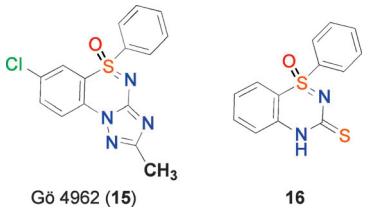


Figure 4. Heterocyclic sulfoximines synthesized at Gödecke.

activities.[19,27] Moreover, the heterocyclic sulfoximine **16** was shown to be a potential reverse transcriptase inhibitor with excellent lymphocyte protection against HIV.[19,28]

6. Oral, Prophylactic Antiasthmatics

As part of a program aimed at discovering new series of therapeutically active compounds, Taylor and co-workers at Roussel Laboratories started to "investigate the capacity of the sulfoximine group to modify the activity of parent structures with established activity".[29] Disodium chromoglycate (DSCG, **17**; Figure 5) prevents the release of inflammatory chemicals such as histamine from mast cells. It is mainly effective as a prophylaxis for allergy- and exercise-induced asthma; however, DSCG (**17**) is not active orally. Xanthone-2-carboxylic acid (**18**), which had been shown to possess DSCG-like activity on oral administration, was chosen as a lead structure with the aim to discover an oral, prophylactic antiasthmatic agent. The sulfoximine group was envisaged to serve as a bioisoster for the carboxylic acid group of **18**, but analogue **19** did not show activity in animal experiments. Nevertheless, the research group proceeded to investigate the sulfoximine group as a means to enhance activity within the series, and synthesized sulfoximine **20**, which was shown to be 30–40 times more potent than **17** after intravenous administration in animals. Unlike **17**, compound **20** also exhibited oral activity. Moreover, introduction of a hexyl substituent at the C-5 position produced a sixfold increase in activity after intravenous application and a 10-fold increase after per oral application in animals. RU 31156 (sudexanox, **21**) was finally selected for clinical testing.[30]

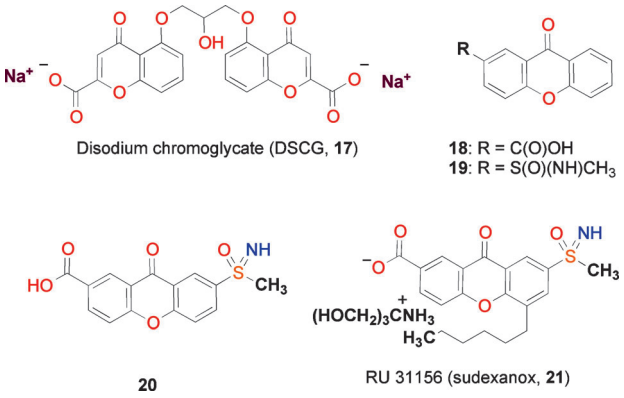


Figure 5. Compounds studied as oral, prophylactic antiasthmatics.

7. α-Adrenergic Receptor Blockers

Dillard et al. also investigated the sulfoximine group as a potential bioisoster to modify the activity of a parent structure with established activity, the α-adrenergic receptor blocker prazosin (**22**; Figure 6)[31] Thus, they designed a series of heterocyclic sulfoximines, replacing the amidine function of prazosin (**22**) by an (*S*)-methyl sulfoximine moiety.

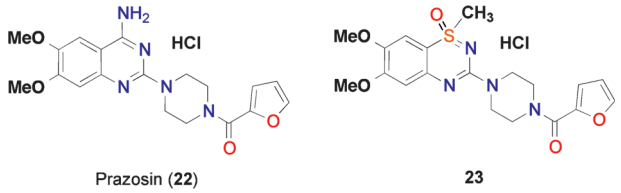
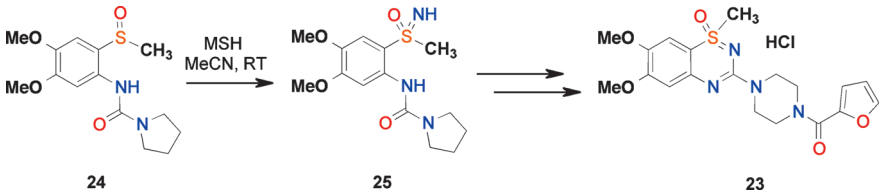


Figure 6. Prazosin (**22**) and the heterocyclic sulfoximine analogue **23**.

In the key synthetic reaction, sulfoxide **24** was converted into sulfoximine **25** with *O*-(mesitylenesulfonyl)hydroxylamine (MSH)[32] under neutral and mild conditions (Scheme 4); however, like hydrazoic acid, MSH has to be handled with extreme caution, since it can decompose with explosive violence.[31,33] Evaluation of the blood-pressure-lowering activity of prazosin (**22**) and its analogue **23** in two animal systems revealed superior results for **23**, thus indicating that the amidine moiety in prazosin (**22**) can be replaced by a sulfoximine group.

8. Transition-State-Analogue Inhibitors of Carboxypeptidase A

The metalloprotease carboxypeptidase A has been used as a prototype to illustrate the mechanistic theory suggesting that stable substrate analogues which resemble high-energy intermediates along the reaction path for an enzymatic reaction should function as potent inhibitors. Phosphonami-



Scheme 4. Synthesis of the heterocyclic sulfoximine analogue **23** of prazosin (**22**).

date **27** (Figure 7), which contains a phosphonyl group that occupies the location of the enzymically cleaved carboxamide linkage of model substrate **26**, was, for example, used successfully to demonstrate this theory of transition-state

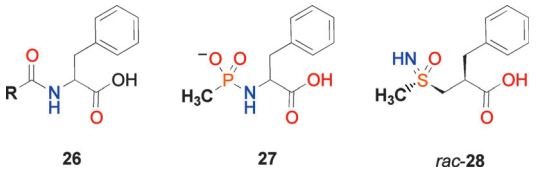


Figure 7. Transition-state-analogue inhibitors of carboxypeptidase A.

mimicry: the tetrahedral nature of the phosphonyl group provides an excellent fit to the active site, while anion coordination satisfies the electron deficiency of the zinc ion within carboxypeptidase A (**27**: $K_i = 0.12$ μM[34]). Since the tetrahedral sulfoximine group was known to be stable and to allow metal-ion coordination through its nitrogen atom (but not the oxygen atom), Mock and Tsay designed the sulfoximine transition-state analogue **28**.[35] In subsequent studies, *rac*-**28** (*R*,*R*/*S*,*S*) was shown to be a competitive inhibitor of carboxypeptidase A ($K_i = 2.7$ μM).[16]

9. Transition-State-Analogue Inhibitors of L-Asparagine Synthetase

The enzyme L-asparaginase (ASNase), which catalyzes the hydrolysis of L-asparagine, is a component of most therapeutic protocols for the treatment of acute lymphoblastic leukemia (ALL). L-Asparagine synthetase (ASNS) catalyzes the formation of L-asparagine from L-aspartate and ammonia. The question of whether upregulation of ASNS expression is a direct cause of ASNase resistance in patients remained unsolved, in part because of the absence of potent and selective ASNS inhibitors that prevent intracellular asparagine biosynthesis. Based on the proposed mechanism of the ASNS-catalyzed reaction, Hiratake et al. designed transition-state analogue **29** (Figure 8), where the carbonyl group to be attacked by ammonia is replaced by a tetrahedral sulfoximine sulfur atom.[36] Sulfoximine **29** was shown to inhibit human ASNS with nanomolar potencies. Furthermore, it was demonstrated that treatment of the ASNase-resistant leukemia cell line MOLT-4R with sulfoximine **29** had a cytostatic effect.[37] However, the antiproliferative effect of ASNS inhibitor **29** was only recorded at very high concentrations of 100–1000 μM. The need to use high concentrations of **29** to suppress cell proliferation was explained by ionizable groups on the molecule reducing the cell permeability. In an extension of the approach, sulfoximine **30**, which has no net charge at cellular pH values, indeed revealed improved ASNS inhibitory properties and was shown to suppress the proliferation of MOLT-4R cells at a 10-fold lower concentration.[33]

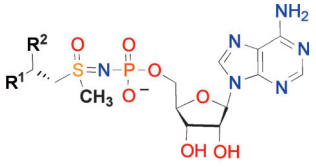


Figure 8. Transition-state-analogue inhibitors of ASNS.

10. Calcitriol Analogues

In the search for potent, selective, and low-calcemic inhibitors of CYP24 hydroxylase, Posner et al. investigated sulfoximine analogues of calcitriol (**31**; Figure 9)[38] Calcitriol

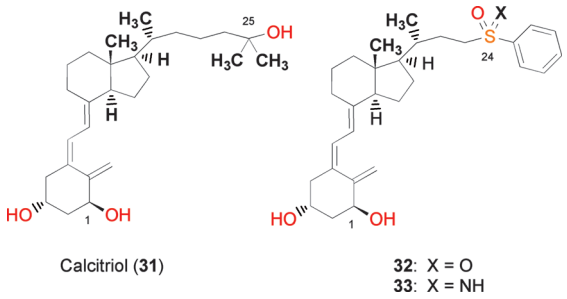


Figure 9. Sulfone and sulfoximine analogues of calcitriol (**31**).

has an important role in the antiproliferative and growth regulatory effects on normal and neoplastic cells. The biological effects of **31** and its synthetic analogues are mediated by the nuclear vitamin D receptor (VDR). VDR ligands have potential widespread clinical application; however, in many cases, hypercalcemia develops as a limiting side effect. Inhibiting the catabolism of calcitriol (**31**) and its analogues by the human cytochrome CYP24 is expected to lengthen the biological lifetime of the compounds, thus allowing smaller doses for effective human chemotherapy. Among a series of 24-sulfone calcitriol analogues, compound **32** was shown to be a very potent ($IC_{50} = 28$ nM), low-calcemic, and selective inhibitor of CYP24.[39] The approach was extended to a series of free sulfoximine analogues which also displayed promising properties.[38] The stereochemical configuration at the sulfur atom was shown to be very important, with the 24*S* diastereomers having higher CYP24 inhibitory properties than the 24*R* epimers. (24*S*)-Sulfoximine **33** revealed potent ($IC_{50} = 7.4$ nM) and selective CYP24 inhibitory properties and is approximately 40 times more potent than the commonly used CYP24 inhibitor ketoconazole ($IC_{50} = 312$ nM). To measure the toxicity and safety in animals, compound **33** was administered orally to rats daily for one week at a 20-fold higher dose than calcitriol (**31**), and revealed low calcemic activity.

11. CDK Inhibitors

At Bayer Pharma AG (formerly Schering AG), the sulfoximine group was investigated for the first time as

a pharmacophore in the pan-CDK inhibitor project. Since their discovery, cyclin-dependent kinases (CDKs) have been considered strong prospective targets for a new generation of anticancer drugs. Several low-molecular-weight inhibitors of CDKs have entered clinical trials; however, none has reached the market as yet.

In a Phase I dose-escalation study in patients, the potent pan-CDK inhibitor ZK 304709[40] (Figure 10) showed limited absorption at high oral doses, which was accompanied by high

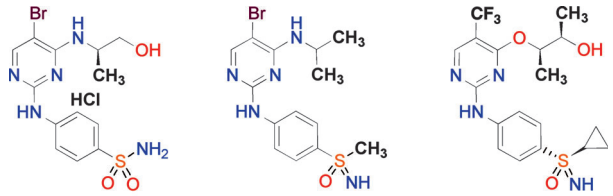


Figure 10. Clinical pan-CDK inhibitors ZK 304709 and BAY 1000394.

interpatient variability of exposures, and the trial was stopped before the maximum tolerated dose (MTD) was determined. This outcome was attributed to the rather limited solubility of the compound (thermodynamic solubility in water: 8 mg L^{-1} at pH 7.4). Another source of the observed variability was ascribed to the off-target activity of ZK 304709 against carbonic anhydrases (CAs), mediated by the sulfonamide group, which leads to an accumulation of the compound in erythrocytes.[41] The follow-up approach, therefore, focused on the following parameters: first, the limited absorption at high dose was to be addressed by reducing the dose size through significant improvement of the antitumor potency, as well as increased aqueous solubility; second, the follow-up compound was to be devoid of CA inhibitory properties. One idea to eliminate the undesired CA affinity while conserving inhibitory activity against CDKs was to exchange the sulfonamide for a sulfoximine group. The proposal was initially met with much skepticism, but sulfoximine model compound **34** revealed significant CDK inhibitory properties and moderate antiproliferative activity.[42] Moreover, the compound displayed no CA inhibitory properties. Extensive lead optimization within this new class of sulfoximine CDK inhibitors culminated in the identification of BAY 1000394 (Figure 10).[43] The compound is a nanomolar pan-CDK inhibitor with very potent antiproliferative activity, but shows no off-target inhibition of CAs. BAY 1000394, in contrast to many other ATP-competitive kinase inhibitors, has a comparatively high thermodynamic solubility in water (182 mg L^{-1}, 22-fold more than ZK 304709) and is generally stable with regard to hydrolysis. Moreover, BAY 1000394 shows potent antitumor efficacy in human tumor models xenografted onto nude mice at a low therapeutic dose (50-fold lower than ZK 304709). BAY 1000394 was selected as a development candidate and is currently being investigated in a Phase I clinical trial in patients with advanced solid tumors (ClinicalTrials.gov identifier: NCT01188252).[3]

BAY 1000394 is the first sulfoximine in clinical development for a long time. It is also noteworthy that the advent of the new and safe synthetic methods for the preparation of sulfoximines[2] was a key factor in the decision to select a sulfoximine as a development compound, since a large-scale synthesis of BAY 1000394[44] using potentially explosive reagents such as hydrazoic acid or MSH would not be possible. The success of BAY 1000394 triggered the investigation of the sulfoximine group as a pharmacophore in a variety of different drug discovery approaches across indications at Bayer Pharma AG.[45]

12. HIV-1 Protease Inhibitors

Lu and Vince have evaluated the sulfoximine group with some success as a bioisoster for secondary alcohols in inhibitors of HIV-1 protease, which has been one of the primary targets for antiviral drug development. Nine commercially available protease inhibitors contain a free hydroxy group that acts as a transition-state mimic (TSM) for the tetrahedrally hybridized amide linkage during catalytic cleavage. As a result of its tetrahedral structure and its potential hydrogen-bond donor/acceptor function, the sulfoximine group was evaluated as a TSM for HIV-1 protease inhibitors, with L700,417 (**35**, Merck) as a parent structure (Figure 11);[46] moreover, the acidity of the NH group of a free

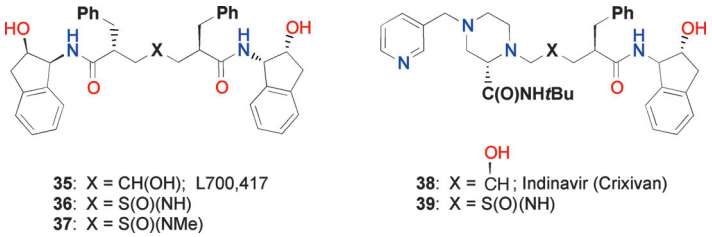


Figure 11. Sulfoximine analogues of L700,417 (**35**) and indinavir (**38**).

sulfoximine ($pK_a = 24$ in DMSO) also compares favorably with that of a secondary alcohol[18] (*i*PrOH; $pK_a = 30$). Indeed, it was demonstrated that the free sulfoximine is a novel moiety, potentially functioning as a TSM in HIV-1 protease inhibitors. In an in vitro HIV-1 protease inhibition assay, analogue **36** was shown to be only fourfold less potent than the parent compound (**36**: $IC_{50} = 2.5$ nM; **35**: $IC_{50} = 0.6$ nM). Furthermore, free sulfoximine **36** also displayed significant antiviral activity in a cell-based assay ($IC_{50} = 408$ nM). Introduction of an *N*-methyl substituent at the sulfoximine group led to significantly decreased enzymatic and antiviral activities (**37**: $IC_{50} = 460$ nM and > 10 μM, respectively).[47] However, in an extension of the concept, the introduction of a sulfoximine group into the commercial HIV-1 protease inhibitor indinavir (Crixivan, **38**; Merck) surprisingly afforded poor potency for in vitro activity against HIV-1 protease (**38**: $IC_{50} = 0.4$ nM; **39**: $IC_{50} = 100$ μM).[48]

13. Proline-Rich Tyrosine Kinase 2 (PYK2) Inhibitors

Researchers at Pfizer have investigated the sulfoximine group in the context of proline-rich tyrosine kinase 2 (PYK2) inhibitors, a target for treating osteoporosis.[49] The potent and selective PYK2 inhibitor **40** (Figure 12) was found to have high stability in human liver microsomes (HLMs). Furthermore, sulfone **40** tested negative in a high-throughput reactive metabolite assay (RMA), which assesses the bioactivation of drug candidates that can lead to toxicological liabilities. However, the significant activity of sulfone **40** in a dofetilide binding assay, an effective screening tool for assessing hERG blockade and proarrhythmia, raised safety concerns. To find a suitable surrogate for the sulfone moiety with reduced hERG activity, the Pfizer group first turned their attention to sulfonamides. *N*-Methyl sulfonamide **41** was shown to have PYK2 inhibitory properties similar to sulfone **40**, but was less stable than **40** in HLMs and revealed no improvement in the dofetilide binding assay. Next, a series of sulfoximine analogues were synthesized, which revealed comparable PYK2 enzyme activity. Except for the free sulfoximine **43**, all the sulfoximine analogues displayed good PYK2 cellular activity and moderate stability in HLMs. The (*S*)-sulfoximine diastereomer of *N*-methyl sulfoximine **42** was shown to be slightly more active than its epimer in the PYK2 cellular assay and also tested negative in the RMA. Unexpectedly, the sulfoximine analogues showed significantly less dofetilide binding than the corresponding sulfone or sulfonamide compounds. In line with these findings, sulfoximine (*S*)-**42** revealed a 4.3-fold improvement in a hERG patch-clamp K^+ channel assay. Furthermore, (*S*)-**42** was shown to have good oral exposure in a rat pharmacokinetic model.

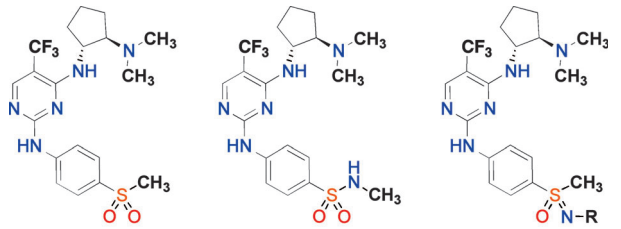


Figure 12. PYK2 inhibitors.

14. COX-2 Inhibitors

The Bolm research group, which has been the main source of new and safe synthetic methods for the synthesis of sulfoximines in recent years,[2] has also investigated bioactive sulfoximines. Traditional, nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit both isoforms of the enzyme cyclooxygenase, COX-1 and COX-2, which has a key role in inflammatory conditions. Comprehensive studies led to the conclusion that selective COX-2 inhibitors (COXIBs) would be potent anti-inflammatory agents that lacked the toxicities and negative effects associated with the inhibition of COX-1 (e.g. gastrointestinal ulceration, perforation, and hemorrhage); however, the long-term use of COXIBs has been reported to cause significant cardiovascular side effects, which finally led to the withdrawal of compounds such as rofecoxib (Vioxx, **44**; Figure 13). However, recent findings indicating that the long-term use of COXIBS led to a decrease in death rate from several cancers have revived the interest in selective COX-2 inhibitors. The switch from sulfone **40** to N-substituted sulfoximine **42** in the PYK2 inhibitor series (Figure 12), which resulted in an improved hERG profile, stimulated the Bolm group to investigate sulfoximine analogues of the selective COX-2 inhibitor rofecoxib (**44**).[50] Sulfoximines **45** and **46** were shown to have moderate COX inhibitory activities, although less active than rofecoxib (**44**; Figure 13). *N*-Methyl sulfoximine **46** displayed nonselective COX-1 and COX-2 inhibitory activities, while the free sulfoximine **45** showed some COX-2 selectivity. In whole-cell patch-clamp investigations, analogue **45** indeed revealed moderately reduced hERG activity compared to rofecoxib (**44**). Stimulated by the discovery of the *N*-cyano sulfoximine sulfoxaflor (**14**) as a new agent in crop protection, the bioactivity of *N*-cyano sulfoximine **47** was also investigated, and revealed significant, selective COX-2 inhibitory properties.[51] This sparked the synthesis of a series of *N*-cyano sulfoximine analogues of other known sulfone COX-2 inhibitors. The enantiomers of *N*-cyano sulfoximine **49**, which is an analogue of DuP697 (**48**; DuPont Merck), revealed profound differences: one enantiomer of **49** was shown to be a potent and selective COX-2 inhibitor, whereas the other enantiomer exhibited rather weak COX-1 and COX-2 inhibition. Moreover, the potent enantiomer of **49** was also tested with the cell panel of the US National Cancer Institute (NCI), and revealed good antiproliferative activity against various cancer cell lines.[52]

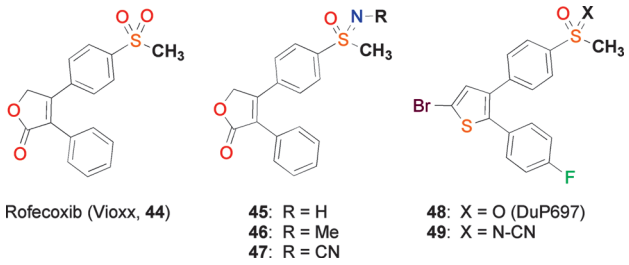
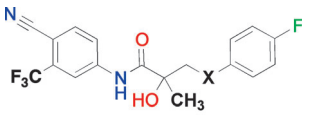


Figure 13. Structures of rofecoxib (**44**), DuP697 (**48**), and analogues.

15. Analogues of the Antiandrogen Bicalutamide

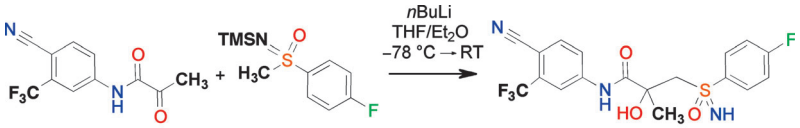
Hormone-dependent prostate cancer is treated with GnRH ligands and nonsteroidal antiandrogens such as bicalutamide (Casodex, **50**; Figure 14) for complete androgen blockade and prevention of androgen-dependent cell growth. Long-term treatment with antiandrogens is usually successful for about 18–24 months, after which resistance takes place. This is thought to arise from, among other mechanisms,



50: X = SO_2 (bicalutamide)
51: X = S(O)(NH)
52: X = S(O)(NCN)

Figure 14. Structures of the antiandrogen bicalutamide (**50**) and sulfoximine analogues.

mutations to several key residues in the androgen receptor (AR) ligand-binding domain. As a consequence, antiandrogen-resistant mutants may show varying agonism and reduced antagonism in the presence of antiandrogens. Recently, Duke et al. investigated a series of bicalutamide (**50**) analogues and found that observed differences in agonism and antagonism seem to be controlled by the size and orientation of the linker group X (Figure 14).[53] In an opportunistic approach, the effects of the structural exchange from a sulfone to a sulfoximine group on AR activities were investigated at Bayer Pharma AG. The free sulfoximine **51** was easily accessible as a mixture of four stereoisomers by treating ketone **53** with *N*-trimethylsilyl-protected sulfoximine **54** under basic conditions (Scheme 5).[54] Chromatographic purification gave the corresponding racemates **51a** and **51b** (stereochemistry not



53 **54** **51**

Scheme 5. Synthesis of sulfoximine analogue **51** of bicalutamide (**50**). TMS = trimethylsilyl.

assigned). The free sulfoximine racemates **51a** and **51b**, and also *N*-cyano sulfoximine **52** (as a mixture of four stereoisomers), were shown to have much reduced AR antagonistic activities ($IC_{50} > 10$ μM, 3.1 μM, and 7.5 μM, respectively) in a cellular assay[55] than bicalutamide (**50**: $IC_{50} = 0.2$ μM).[56] This clearly indicates that the sulfoximine group is not a suitable bioisoster for the sulfone group of bicalutamide.

55

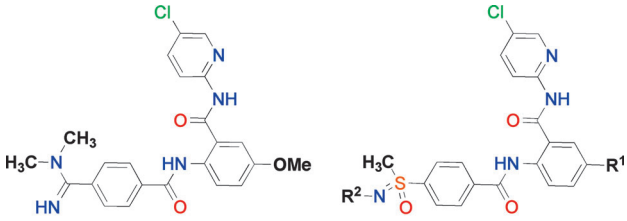
Figure 15. Sulfoximine inhibitor of HNE.

16. Inhibitors of Human Neutrophil Elastase

At Bayer Pharma AG, a series of sulfoximidoyl-substituted 1,4-diaryldihydropyrimidin-2-one derivatives were identified as selective inhibitors of human neutrophil elastase (HNE) for the treatment and/or prevention of pulmonary disorders and disorders of the cardiovascular system. Compound **55** (Figure 15), for example, revealed a low IC_{50} value of < 0.3 nM for the inhibition of HNE in vitro.[57]

17. Factor Xa Inhibitors

Compounds containing a highly basic amidine group are often characterized by poor oral bioavailabilities. Pandya et al. recently investigated the exchange of the highly basic amidine group of factor Xa (FXa) inhibitor betrixaban (**56**; Figure 16), which is currently being investigated as an oral



56: Betrixaban

57: R^1 = OMe, R^2 = H
58: R^1 = Cl, R^2 = H
59: R^1 = Cl, R^2 = $C(O)CH_2NEt_2$
60: R^1 = Cl, R^2 = $C(O)CH_2NHEt$

Figure 16. Sulfoximine analogues of betrixaban (**56**).

anticoagulant in Phase II studies, for a less-basic sulfoximine group.[58] The free sulfoximine analogues **57** and **58** demonstrated moderate inhibitory activity against human FXa in vitro (**57**: 42%, **58**: 76% inhibition at 0.1 μM). Further lead optimization culminated in the identification of N-substituted sulfoximine **59**, which displayed strong human FXa inhibitory activity ($IC_{50} =$ 2.1 nM) and anticoagulant activities in both rat and human plasma in vitro; moreover, sulfoximine **59** also revealed potent ex vivo anticoagulant activity in rat plasma. Evaluation of the pharmacokinetics in the same species, however, demonstrated that the activity is mainly attributed to the formation of active metabolite **60** after oral dosing. In vivo antithrombotic efficacy was determined by using arterial and venous thrombosis models in rats, which demonstrated dose-dependent reduction in thrombus weight with sulfoximine **59**.

18. Summary and Outlook

After its eventful, late discovery, triggered by the profound biological effects of MSO (**2**), the sulfoximine group has raised only moderate interest in medicinal chemistry to date. This is quite surprising, since this small, tetrahedral functional group offers a unique combination of properties that are relevant in many medicinal chemistry approaches, namely, high stability, favorable physicochemical properties, hydrogen-bond acceptor/donor functionalities, and structural diversity. It can be speculated that the long period of limited synthetic methods which relied on potentially explosive reagents was unattractive to medicinal chemists. This may especially be the case for industrial chemists, who also have to consider a possible large-scale production of the molecules

they design. However, it is quite striking that medicinal chemistry approaches employing the sulfoximine group have been rather limited to certain scientists and/or institutions. With the advent of new synthetic methods, safety concerns should no longer be an issue and, indeed, the number of publications and patents reporting the use of the sulfoximine functional group in medicinal chemistry is on the rise. Since its discovery, the sulfoximine group has been evaluated as a pharmacophore in a variety of molecular settings and indications with diverse rationales (Table 1). Sulfoximines have been used successfully to construct stable transition-state analogues that serve, for example, as molecular probes. Significant research has been conducted in which the sulfoximine group is used in opportunistic approaches and as a bioisoster for a surprising variety of functional groups, such as alcohols, acids, amidines, sulfones, and sulfonamides. In particular, the switch from sulfones and sulfonamides to sulfoximines has raised some interest; however, as shown in this Minireview, the results to be expected remain unpredictable. In some cases the corresponding sulfoximines indeed displayed similar or superior properties, whereas in others the exchange led to significant loss of activities. Drug discovery, however, still requires experimentation.[59] The underrepresented sulfoximine moiety certainly deserves to be added to the medicinal chemist's toolbox, thereby broadening the chemical repertoire in drug discovery to tackle an ever-increasing number of biological targets even more multifacetedly.

I thank F. von Nussbaum, I. Hartung, B. Händler, G. Siemeister, M. Bergmann, and M. Brands for fruitful discussions concerning the manuscript, and N. Heinrich for the design of the table of contents graphic.

Received: March 15, 2013
Published online: August 9, 2013

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