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Review Article

Sulfoximine Derivatives — Their Pharmacochemical Properties, Synthesis, and Potential in Drug Discovery

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ABSTRACT

Currently, pharmaceutical chemists focus on investigating an increasingly wide range of compounds as potential new drugs, including substances of natural origin and those obtained by chemical synthesis. Due to the advancements in the experimental techniques, modern science possesses numerous tools for discovering new types of biologically active molecules. For example, the development of chemical synthesis methods has created a possibility to reach completely new arrays of compounds, as potential candidates of some new drugs. In this context, sulfoximines have quite recently emerged as a promising and versatile class of organosulfur compounds with interesting pharmacological properties. In this article, we present an overview of the key features of sulfoximine functional group, including its unique pharmacochemical profile, that may elevate its potential in medicinal chemistry. We also briefly discuss examples of synthetic approaches to obtain new derivatives containing this functional group, with particular attention to both classical and modern synthetic protocols. Finally, selected examples of biologically active sulfoximines developed by various research groups are highlighted, demonstrating their potential applications in drug discovery.

KEYWORDS: sulfoximine derivatives; new drug candidates; chemical space; drug discovery; organosulfur compounds.

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1. Introduction

The rapid development of chemical synthesis methods has created a possibility of obtaining new arrays of compounds as potential drug candidates. An interesting group of compounds, which in recent years has begun to attract attention in the field of drug discovery are sulfoximine derivatives. Although they were first identified in 1940, for several reasons they were disregarded as molecules with biological potential. For example, they were wrongfully considered unstable [1]. In the years that followed, the pharmacological significance of sulfoximines was reacknowledged. This was mainly a result of investigations undertaken for example by major pharmaceutical industry, including Pfizer and AstraZeneca. These studies have greatly contributed to the renewed interest in sulfoximines and their potential in therapeutic applications, shaping one of the possible new directions in medicinal chemistry.

One of the earliest discovered sulfoximine compounds was methionine sulfoximine (MSI) (Fig. 1). It was identified as a toxic byproduct formed during the bleaching of wheat flour with nitrogen trichloride (NCl_3). MSI was found to produce epileptic seizures in dogs (canine epilepsy) which might have occurred due to the high structural similarity to glutamate. In order to investigate the potential use of MSI in therapy, it must have been determined beforehand whether it had some similar biological effects to glutamine [2]. The studies have shown the MSI to be an irreversible glutamine synthetase inhibitor. Other studies showed the weak antiseptic effect of this compound. These discoveries have marked the beginning of research on sulfoximines as chemically stable compounds with potential biological activity. Simultaneously, they became investigated in other fields related to medicinal chemistry, such as organic synthesis, catalysis and peptidomimetics design [1-4].

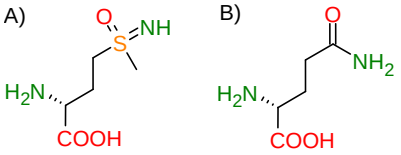


Fig. 1. Structure of MSI (A) and glutamine (B).

2. General properties of sulfoximines

Sulfoximines are a class of compounds characterized by a central, tetrahedral sulfur atom bonded to a weakly basic nitrogen, an oxygen atom, and two additional residues — typically alkyl or aryl groups. Such arrangement of substituents makes the sulfur atom a stereogenic center, giving rise to existence of stable stereoisomers [5-7].

The simplest sulfoximine is (*S*-methanesulfonimidoyl)-methane. Modifying the sulfur substituents can influence both the acid-base properties of the sulfoximine and the nucleophilicity of the nitrogen (Fig. 2). The nitrogen atom can act as a hydrogen bond donor or acceptor due to its lone pair of electrons. In addition, the presence of a weakly basic imine nitrogen allows sulfoximines to coordinate metal ions and form salts with strong acids, which can have a pharmacological relevance [5-7]. The high polarity and structural features of sulfoximines contribute to their excellent solubility in protic solvents such as water and alcohols and makes them highly functionalized, hydrophilic moieties useful for medicinal chemistry and drug design [8-12].

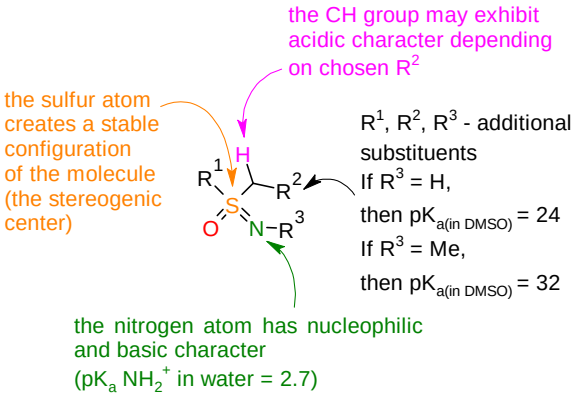


Fig. 2. A summary of the structural features of sulfoximine functional group and the influence of individual elements on its chemical properties.

As shown in Fig. 3 sulfoximines share structural features with other sulfur-functional groups: sulfones, sulfonamides, sulfoximines, sulfonimidamides and sulfondiimines to which they may be considered bioisosteric [8]. Compared to sulfones and sulfonamides, sulfoximines offer several distinct advantages: they enhance the solubility of compounds in protic solvents, improve hydrogen bond donor-acceptor characteristics, and increase both chemical and metabolic stability. These features can be fine-tuned by applying chemical modifications within the sulfur substituents, making sulfoximines particularly valuable in drug discovery [8-12]. Furthermore, cyclic sulfoximines can be formed by connecting substituents within this functional group.

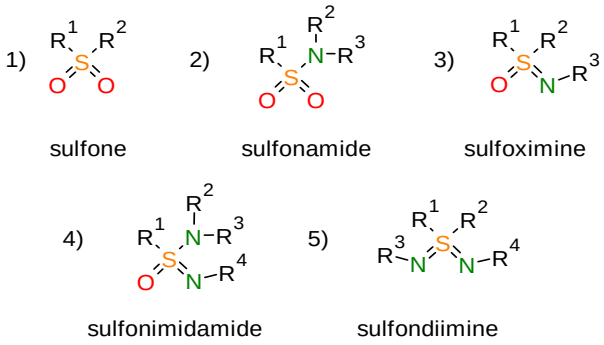


Fig. 3. Examples of various sulfur-containing functional groups.

3. Synthesis of *NH*-sulfoximines

The basic principle of the classical synthesis of sulfoximines consists in an initial introduction of either oxygen or nitrogen species into the sulfur atom of a sulfide (Fig. 4A and B, respectively). As a result, an intermediary sulfoxide (Fig. 4A) or sulfilimine (Fig. 4B) is obtained. In the next step, either an *N*-R group is added to a sulfoxide or a sulfilimine is being oxidized, which provides a final sulfoximine [7].

However, no matter which of the two pathways is followed, the formed sulfoximine is *N*-protected and requires an additional deprotection step to provide the desired *NH*-sulfoximine [7, 12-18].

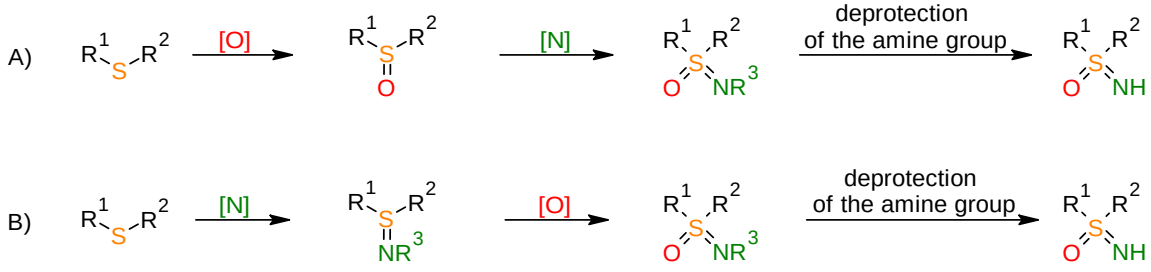


Fig. 4. Typical methods of sulfoximine synthesis by introducing either oxygen (oxidation, A) or nitrogen (amination, B) into the sulfide in the initial step.

Other interesting variant of the classical synthesis of *NH*-sulfoximines was proposed in 2004 by Bolm and Okamura [13]. The authors described its direct synthesis from sulfoxides. It was a two-step process, which begins with the reaction of trifluoroacetamide with iodobenzene diacetate and magnesium oxide, in the presence of a rhodium catalyst. The obtained product, *N*-trifluoroacetylsulfoximine, then underwent deprotection of the sulfoximine group mediated by potassium carbonate in methanol (Fig. 5).

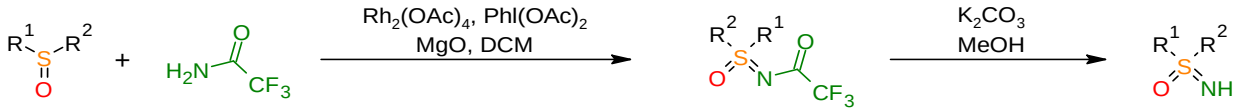


Fig. 5. A method of obtaining *NH*-sulfoximines from sulfoxides.

The yields acquired by the proposed method were very high and the sulfoximines obtained in this way were relatively pure, with almost a single product that was readily isolated from the post-reaction mixture. Under the proposed conditions, the imination reaction was stereospecific and occurred with the retention of the configuration on the sulfur stereocenter to which two different substituents were attached. The additional significant advantages of this synthesis were: the use of a rhodium catalyst, which shows high stability in the presence of oxygen and the use of $PhI(OAc)_2$ as an oxidant, which eliminated the need to use the hazardous imination reagents, such as azides and derivatives or explosive *O*-(mesitylenesulfonyl) hydroxylamine (MSH) [7, 12-18].

Many other methods for sulfoximine synthesis have been developed overtime [13]. For example, an interesting study conducted by Yu Din and Siu showed that *NH*-sulfoximines can be obtained in a safe manner, without the need to use metal catalysts and hazardous oxidants. The synthesis was carried out entirely using electrolysis. The reaction involved *N*-phthalimidosulfoximine as the amination reagent. The subsequent removal of the phthalimide moiety was achieved *via* a cathodic process mediated by Bu_4NBF_4. This variant of sulfoximine synthesis also allowed to obtain dialkylsulfoximines and diarylsulfoximines with high yields and complete conversion of substrates (Fig. 6) [7, 12-18]. This example shows that alternative, more sustainable and safer chemistry methods may be employed in sulfoximine synthesis.

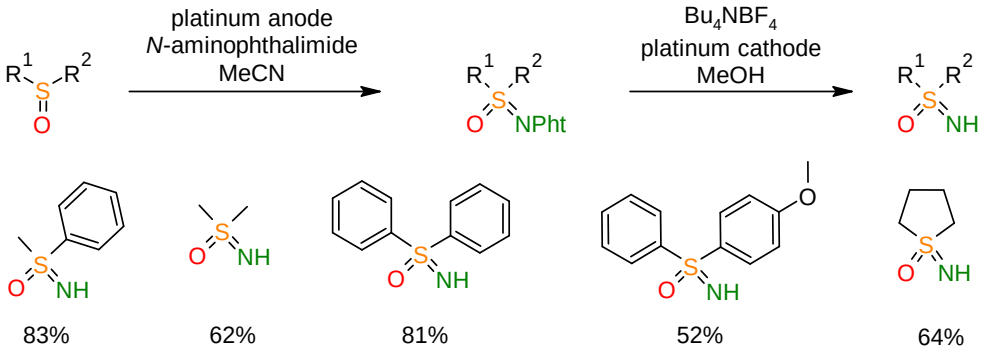


Fig. 6. General process of obtaining sulfoximines by electrolysis and examples of compounds obtained by this method, together with the respective yields.

4. A review of biologically active sulfoximine derivatives

As mentioned, owing to their desirable pharmacochemical properties, sulfoximines have recently attracted considerable attention in the field of medicinal chemistry. Here we present several examples of successful use of this moiety in drug discovery process. Perhaps the most prominent results were to date seen in the area of a kinase inhibition [19], in which sulfoximines were employed as bioisosteres for other sulfur-containing functional groups.

4.1. Ataxia telangiectasia and Rad3-related (ATR) kinase inhibitors

ATR kinase inhibitors contribute to the inhibition of DNA repair pathways. In the normal cells ATR kinase is responsible for maintaining the stability of genetic material, but in cancer cells, where the pathological, increased proliferation of cells occurs, the process of DNA damage and the associated replication stress occur commonly. The idea of inhibiting repair processes in such cells by using an ATR kinase inhibitor was therefore considered a promising perspective for anticancer therapy [5, 8, 10, 12, 20].

Over the years, numerous compounds targeting ATR kinase have been evaluated both as standalone therapeutic agents and as potential candidates for combination therapy. AstraZeneca emerged as a pioneering company in this field, developing a sulfone AZ20 (Fig. 7). It was assumed that this compound selectively inhibits ATR kinase, thereby impairing the ability of cancer cells to respond to stalled replication forks and DNA damage. Although AZ20 demonstrated a potential for studying ATR kinase inhibition, it was ultimately not advanced into clinical development due to two significant drawbacks: the limited water solubility and the time-dependent inhibition (TDI) of the CYP3A4 enzyme [8]. The poor solubility in water was reported to reduce compound's oral absorption and made subsequent formulation into a final dosage form challenging. Structural studies showed that methyl sulfone groups from AZ20 are engaged in strong intermolecular interactions, forming tightly packed crystal lattice. Additionally, these centrosymmetric sulfone-sulfone interactions led to a high melting point of 204°C, further indicating its low solubility and poor dissolution rate. Another major concern was AZ20's inhibitory effect on CYP3A4, a liver enzyme that plays a crucial role in the metabolism of many drugs. The mentioned pharmacokinetics and safety issues outweigh its biochemical advantages, preventing this lead compound from progressing as a clinical drug candidate [8, 20, 21].

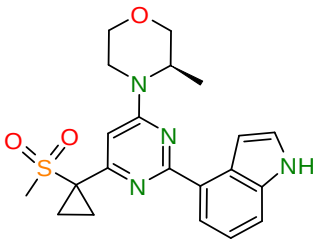


Fig. 7. Structure of ATR kinase inhibitor AZ20, which exhibits anticancer activity, a preclinical lead developed by AstraZeneca (currently discontinued).

To address the limitations of AZ20, researchers attempted to modify the sulfone group, which was associated with the mentioned poor solid-state properties and unfavorable metabolic behavior. The introduction of a sulfoximine group as a bioisosteric replacement was a major breakthrough. This significantly improved the aqueous solubility and reduced the lipophilicity of the resulting compound AZD6738 — later named ceralasertib (Fig. 8), while decreasing its potential for metabolic liabilities at the same time. Ceralasertib retained the strong ATR kinase inhibitory activity of the parent compound and demonstrated the markedly enhanced pharmacochemical and pharmacokinetic properties, including improved solubility and oral bioavailability. Importantly, unlike AZ20, ceralasertib did not exhibit significant TDI of CYP3A4, reducing the risk of drug-drug interactions [8]. Additionally, it showed a lower potential for cardiotoxicity, as evidenced by the reduced hERG channel activity compared to the sulfone-based counterpart. While the melting point of ceralasertib remained relatively high (222°C), its crystal structure was more favorable, lacking the dense sulfone-sulfone interactions that had contributed to AZ20's poor solubility [8, 20, 21]. Importantly, the sulfone-sulfoximide switch supported better formulation potential [18, 20]. Overall, ceralasertib was tested in various phase II and III clinical trials [22] and a III phase study is expected to be completed soon [23]. Therefore, development of ceralasertib from AZ20 to date remains one of the most prominent examples of benefits from bioisosteric replacement of sulfone by sulfoximine.

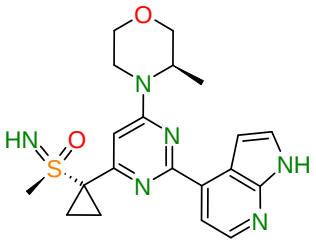


Fig. 8. Structure of ATR kinase inhibitor ceralasertib, a phase III clinical trial (ongoing) candidate, which exhibits anticancer activity and has been developed by AstraZeneca.

As the described ATR kinase inhibitors were considered therapeutically useful, the research on AZ20 and ceralasertib derivatives continued to advance. Scientists at Jiangsu Hengrui Pharmaceuticals successfully cyclized the sulfoximine fragment of AZ20. The results of this experiment led to the formation of a novel cyclic derivative, which has been tested in phase I clinical trials. (Fig. 9) [18, 20, 24].

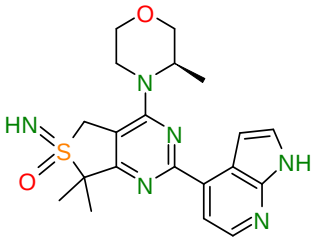


Fig. 9. Structure of the cyclized AZ20 analogue with a sulfoximine group, an ATR kinase inhibitor and a phase I clinical trial (ongoing) candidate, which exhibits anticancer activity and has been developed by scientists from Jiangsu Hengrui Pharmaceuticals.

This cyclization was achieved at the early stage of the synthesis, where a bond was formed between the sulfur and carbon of ethyl 2-((3-ethoxy-3-oxopropyl)sulfanyl)-2-methylpropanoate. In the subsequent synthetic steps, a stable AZ20 analogue was obtained which revealed a superior biological activity, both in terms of enzyme inhibition potency and selectivity toward cancer cells. (Fig. 10) [18, 20, 24].

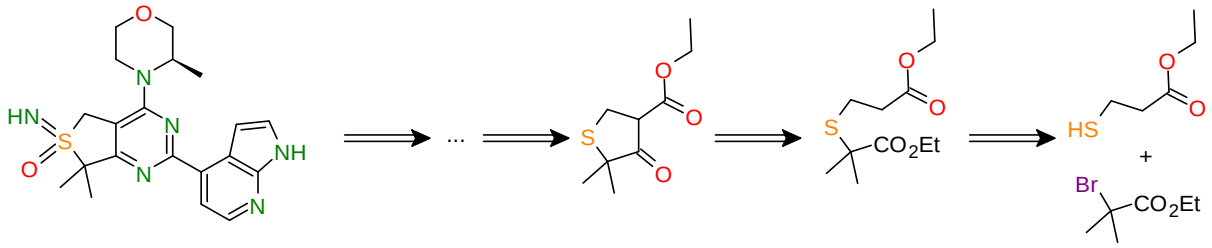


Fig. 10. The ring formation leading to an example of ATR kinase inhibitor developed at Jiangsu Hengrui Pharmaceuticals.

In another attempt to improve the pre-clinical profile of AZ20, scientists from the University of Texas designed its derivative, in which the sulfoximine group was directly connected to the aromatic core of the compound *via* a nitrogen atom. The cyclized sulfoximine analogue from Hengrui has been tested in preclinical trials and demonstrated significantly improved biological activity compared to other synthesized AZ20 derivatives, including enhanced stability, cellular potency, and selectivity in DNA repair-deficient cells (Fig. 11) [18, 20].

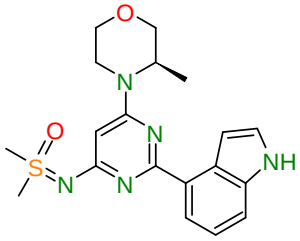


Fig. 11. Structure of the analogue of AZ20 with a sulfoximine group attached directly to the main chain of the compound *via* a nitrogen atom, an ATR kinase inhibitor and a preclinical trial (ongoing) candidate, which exhibits anticancer activity and has been developed by scientists from University of Texas.

4.2. Cyclin-Dependent Kinase 9 (CDK9) inhibitors

Following the clinical failure of pan-CDK kinase inhibitors, which lacked sufficient specificity and often caused dose-limiting toxicities, the researchers at Bayer shifted their focus to a more targeted approach—selective inhibition of CDK9 kinase. CDK9 is a cyclin-dependent kinase involved in transcriptional regulation, particularly in controlling transcription elongation *via* phosphorylation of RNA polymerase II. Because transcriptional addiction is common in many cancers, CDK9 kinase emerged as a promising therapeutic target, potentially suitable for treatment of oncological patients [8-12, 19, 24].

The first lead compound — BAY-958 (Fig. 12), demonstrated a strong inhibitory activity against CDK9 kinase and exhibited high selectivity over other cyclin-dependent kinases.

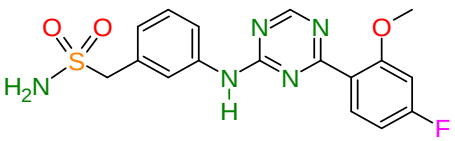


Fig. 12. Structure of BAY958, a CDK9 kinase inhibitor, a preclinical lead, which exhibits anticancer activity and has been developed by scientists from Bayer (currently discontinued).

Despite its excellent pharmacodynamic properties, BAY-958 showed poor pharmacokinetic properties, such as low aqueous solubility in water, limited cellular permeability, a high efflux ratio, and low oral bioavailability in rats (10%). To overcome these limitations, further optimization efforts were undertaken. In one attempt, the sulfonamide group of BAY-958 was replaced with a sulfoximine group, leading to the discovery of atuveciclib (Fig. 13).

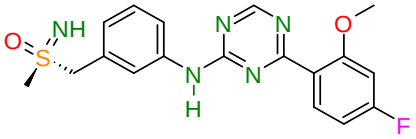


Fig. 13. Structure of atuveciclib, a CDK9 kinase inhibitor, a phase I (discontinued) clinical candidate, which exhibits anticancer activity and has been developed by scientists from Bayer.

Atuveciclib retained similar potency and selectivity to its predecessor but demonstrated significant improvements in other pharmacological properties, particularly oral bioavailability, which increased to 54%. Additionally, the sulfoximine modification eliminated the risk of CYP enzyme induction observed with the sulfonamide-containing compound BAY-958. Atuveciclib advanced to phase 1 clinical trials, showing promising oral pharmacokinetics. However, daily oral dosing led to neutropenia as a dose-limiting toxicity, and for strategic reasons, its development was ultimately discontinued [8-12, 19, 24].

To expand treatment options and to improve the therapeutic window of CDK9 kinase inhibitors, Bayer redirected its efforts toward the development of selective compounds suitable for intermittent intravenous (IV) administration. This led to the discovery of BAY-332 (Fig. 14), which exhibited good activity and selectivity. Due to these properties, the phase I clinical trials were conducted in patients with advanced cancers and leukemia, but both studies were discontinued early due to the occurrence of serious adverse events, such as neutropenia, and the absence of meaningful clinical responses. The further attempt to replace the sulfoximine group with another nitrogen-containing group attached to sulfur specifically, a sulfondiimine group, failed. This was mostly to improve its water solubility, however this came at the cost of a reduced biological activity — the cellular IC_{50} of analogue was approximately three times higher than that of the original BAY-332 [8-12, 19, 24].

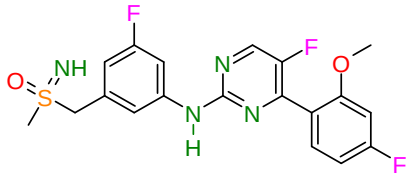


Fig. 14. Structure of BAY332, a CDK9 kinase inhibitor and a preclinical trial (discontinued) candidate, which

exhibits anticancer activity and has been developed by scientists from Bayer.

Continued research resulted in the discovery of enitociclib (Fig. 15), a compound with enhanced potency, high selectivity and excellent solubility. Enitociclib demonstrated a favorable safety profile and therapeutic window in phase I of clinical trials using a once-weekly IV dosing regimen, showing a potential clinical benefit in patients with advanced hematologic and solid tumors [8-12, 19, 24]. Interestingly, it has a reverse absolute configuration on sulfur atom, when compared to the related atuveciclib.

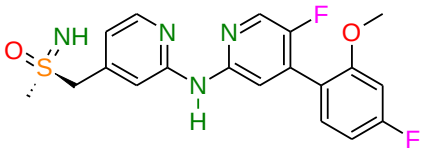


Fig. 15. Structure of enitociclib, a CDK9 kinase inhibitor and a phase I clinical (ongoing) candidate, which exhibits anticancer activity and has been developed by scientists from Bayer.

Encouraged by this success, researchers continued to explore and evaluate various structural analogues of enitociclib. To stabilize the bioactive conformation of the compound a series of macrocyclic derivatives was developed. The introduction of a cyclic structure was found to improve cell permeability, which contributed to the enhanced antiproliferative activity of these analogues. These macrocyclic compounds demonstrated not only stronger antiproliferative effects but also significantly prolonged target residence time on CDK9 kinase, further increasing their therapeutic potential [19, 24]. An example of such a compound is shown below (Fig. 16).

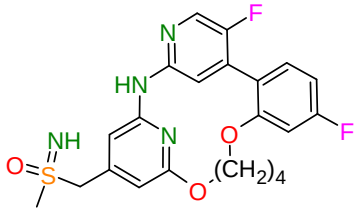


Fig. 16. Structure of an exemplary cyclic selective CDK9 kinase inhibitor, preclinical lead which exhibits anticancer activity, developed by scientists from Bayer.

4.3. Further research on kinase inhibitors

Despite the earlier clinical failures of pan-CDK kinase inhibitors, there is now a renewed interest in developing such compounds, as recent insights and new experimental procedures offer fresh possibilities for improving their selectivity and therapeutic potential. The scientists at Bayer are currently working on the synthesis of a pan cyclin-dependent kinase CDK kinase inhibitor, a sulfoximine derivative with an acronym BAY1000394 (Fig. 17). AstraZeneca, on the other hand, continues research on ATR kinase inhibitors and is currently working on a new ATR kinase inhibitor named AZD 6378 (Fig. 18) The structures of these molecules are shown below [25-27].

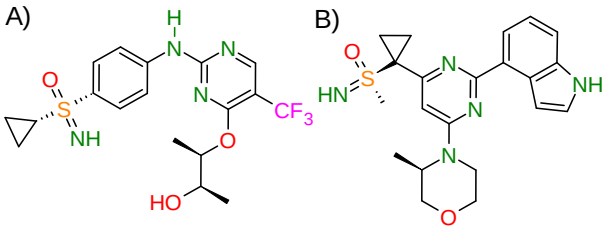


Fig. 17. Structure of phase II clinical (ongoing) candidates, which exhibits anticancer activity: BAY1000394 (A) a pan-CDK kinase inhibitor currently developed by scientists from Bayer, AZD 6378 (B) an ATR kinase inhibitor currently developed by scientists from AstraZeneca.

While AstraZeneca and Bayer are recognized as leaders in development of sulfoximine-based kinase inhibitors, numerous other well-known institutions and companies are also actively contributing to advancements in this area. For example, scientists at Pfizer have been working on the synthesis of a protein tyrosine kinase-2 (PYK2) inhibitor (Fig. 18), which may find its application in the treatment of osteoporosis. Numerous derivatives have been obtained in course of these studies, but one of them shown much greater activity in relation to other types of compounds. In addition, it was characterized by high bioavailability in studies on rats, and the low-toxicity profile [25-27].

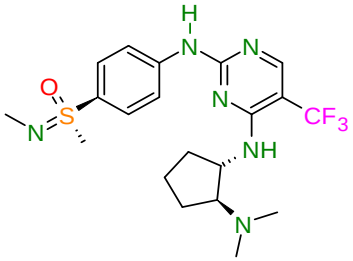


Fig. 18. Structure of PYK2 kinase inhibitor, a phase I (ongoing) clinical candidate, which exhibits anticancer activity and currently has been developed by scientists from Pfizer.

5. The potential of the sulfoximine functional group in other therapeutic areas — further opportunities in medicinal chemistry

The successful development of sulfoximine-containing kinase inhibitors has encouraged researchers to expand investigations of this functional group in drug discovery. Current studies extend beyond kinases and include for example various types of viral proteases. An example of application of sulfoximines in antiviral research is the work of Lu and Vince from the department of Medicinal Chemistry at the University of Minnesota, who synthesized a sulfoximine derivative of a Human Immunodeficiency Virus-1 (HIV-1) protease inhibitor (Fig. 19) [8, 28].

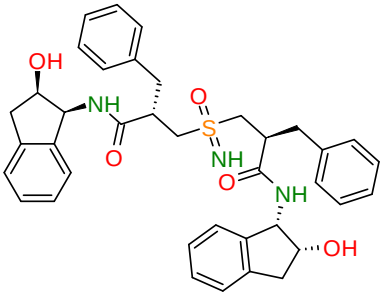
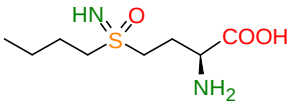


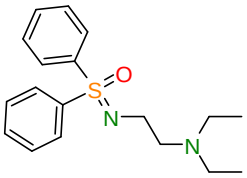
Fig. 19. Structure of HIV-1, a HIV protease inhibitor, a phase III (ongoing) clinical candidate, which exhibits anticancer activity and currently has been developed by scientists from the department of Medicinal Chemistry of University of Minnesota.

However, antiviral research is not the only area of active investigation, as interest in sulfoximine-containing compounds continues to grow across multiple therapeutic fields. Ongoing efforts are evaluating sulfoximine-containing compounds in a wide range of therapeutic areas, including potential drug candidates targeting a variety of conditions such as asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis or bronchiectasis.

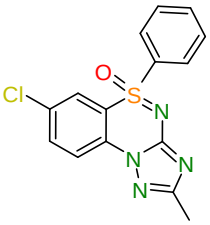
In addition, sulfoximine-containing compounds are still being considered for applications in oncology, especially in chemotherapy and radiotherapy, and in metabolic disorders including diabetes [8, 20]. Their confirmed ability to reduce inflammation and prevent tissue degradation has contributed to the increasing interest in exploring diverse therapeutic applications. It is also interesting that investigations of environmental stability and transformation of sulfoximine derivatives have led to discovery of their potential as biocidal agents for crop protection [27]. Continued research on sulfoximines has led to the development of libraries of compounds with promising biological activity. Below are the collected examples of sulfoximinederiviates, divided into early and latest discoveries, where sulfoximines are presented as bioactive agents (Fig. 20 and 21) [8, 9, 20, 21, 27, 28].



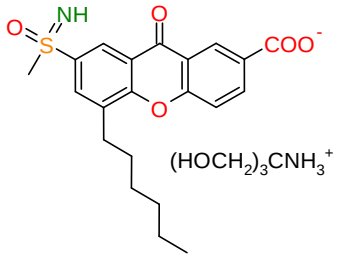
BSO (L-Buthionine-(*S*,*R*)-sulfoximine)
selective inhibitor of
γ-glutamylcysteine synthetase (*γ*-GCS)
(Cornell Research Foundation Inc.)



Suloxifen,
potential bronchodilator
for treatment of asthma and COPD
(Godecke AG, currently
part of the Pfizer)

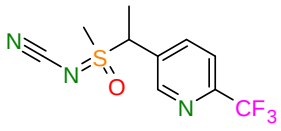


Go4962,
potential bronchodilator
for treatment of asthma and COPD
(Godecke AG - currently
part of the Pfizer)

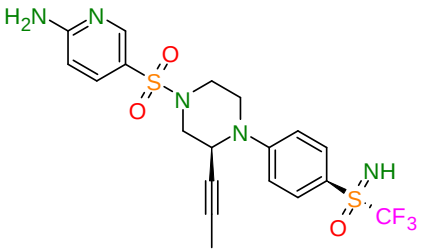


RU31156 - Sudexanox -
sulfoximine-modified xanthone scaffold,
potential candidate for treating allergic
asthma and asthmatic bronchitis
(Roussel Uclaf - currently part of Sanofi)

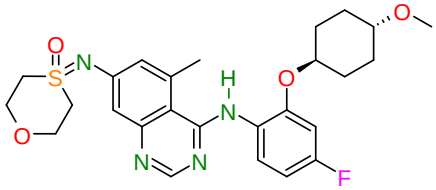
Fig. 20. Bioactive sulfoximines – examples of early discoveries of compounds that were published as bioactive agents, but hasn't been approved for a therapeutic application.



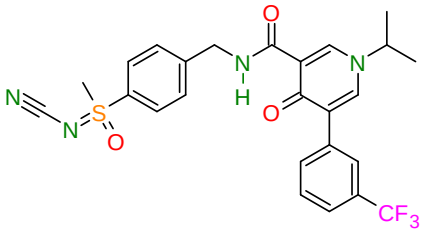
Slufoxaflor,
potential systemic insecticide - neurotoxin binder
of insect nicotinic acetylcholine receptors
(nAChRs).
(Dow AgroSciences)



Glucokinase-regulatory protein
(GKRP) disruptor,
a preclinical candidate
(Amgen)



Mitogen-activated protein
kinase (MAPK) interacting kinase (MNK)
inhibitor - a candidate to suppress
oncogenic protein synthesis,
phase I clinical candidate
in ongoing trial
(Boehringer Ingelheim)



Human neutrophil elastase (HNE)
inhibitor, phase II clinical candidate
in ongoing trial
(Boehringer Ingelheim)

Fig. 21. Bioactive sulfoximines –examples of latest discoveries and currently ongoing experimental research.

6. Limitations and Future Directions

As demonstrated in the previous sections, sulfoximines have potential as tools in medicinal chemistry and drug discovery. However, there are several factors that may limit their roles in this fileds. These issues are mostly linked with their non-obvious chemistry. Despite the recent, significant advances in sulfoximine synthesis, it still faces key limitations. Many current synthetic routes, particularly those based on C–H activation using transition-metal catalysts like Rh(III) or Ru(II), are challenging and rely on expensive, non-sustainable metals, which restricts their large-scale application**.** On the other hand, more affordable alternative of catalyst such as Co(III), have shown limited efficiency and narrower substrate compatibility [13]. Metal-free synthesis protocols, though more sustainable, are usually restricted to intramolecular transformations and generally have limited success when applied to substrates with diverse functional groups. Hence, the synthetic feasibility of sulfoximines may be a limiting factor for their widespread use in medicinal chemistry and in large-scale synthesis. In addition, presence of a sulfoximine group with non-equal substituents results in the introduction of additional stereocentre into a target molecule. Since there are not many stereoselective syntheses of sulfoximines described, this may pose challenges in drug discovery and development, where access to pure enantiomers is highly desired or even necessary. Finally, although sulfoximines are generally stable, their decomposition may also be a concern, especially under harsh conditions or during late-stage modifications of compounds. However, as the field of sulfoximine chemistry is evolving, many efforts are being made to overcome these issues [9, 12, 25, 26].

In addition to their potential chemistry-related issues, it is important to note that not too much is known about long-term safety of sulfoximines in patients. Although some of their derivatives have already been in clinics, the full validation of e.g., their chronic toxicity, adverse effects, drug-drug interactions potential and idiosyncratic risk will only be possible after their approval for use in general population [30-32].

7. Conclusion

In this this article, we have shown that sulfoximines have a unique chemical structure and pharmacochemical properties. We have also shown examples of how incorporating sulfoximine group into drug candidates can improve, *inter alia*, their target selectivity, solubility, and bioavailability. Therefore, “the sulfoximine story” is not only a revival of an underexplored functional class but also a chance for groundbreaking drug innovation, paving the way for the development of safer, more effective, and highly targeted therapies in the future.

Importantly, scientists at major pharmaceutical companies such as Pfizer and AstraZeneca have already recognized and demonstrated the practical viability of sulfoximine-containing compounds in advanced clinical trials, highlighting their growing role in pipeline development. Looking forward, the adaptability of the sulfoximine moiety can expand the chemical space available for drug discovery, supporting the design of next-generation therapeutics in various areas.

Additionally, ongoing research into asymmetric synthesis and late-stage functionalization of sulfoximines will likely

lead to further structural diversification and fine-tuning of biological activity.

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