POLISH SOCIETY OF MEDICINAL CHEMISTRY

ACCORD INTERDISCIPLINARY CONFERENCE ON DRUG SCIENCES

*„Pharmaceutical innovations across the borders“*

Warsaw, May 23-25th, 2024

# POSTER AWARDS

# FOCUSED ON MEDICINAL CHEMISTRY

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# BEST POSTER
# FOCUSED ON MEDICINAL CHEMISTRY

*To*

***Nadiia Diyuk***

*in recognition of the presentation entitled*

*Sonidegib bioisosteres: activity and ADME properties*

On behalf of Award Committee,

Prof. dr hab. Jadwiga Turło
Prof. dr hab. Monika Wujec
Prof. dr hab. Paweł Zajdel
*Polish Society of Medicinal Chemistry*

Abstract No. PSP.16

## Sonidegib bioisosteres: activity and ADME properties

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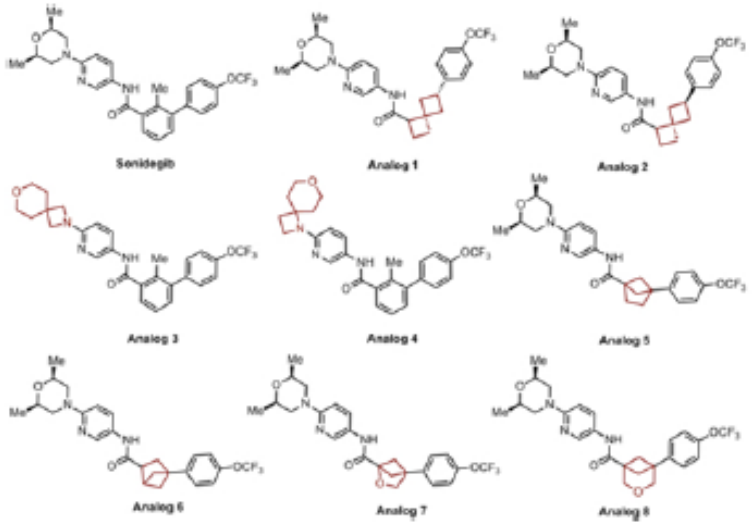
**Objectives:** Sonidegib is a patented drug used for skin cancer therapy, which is characterized by low solubility and high logD.

**Methods:** We synthesized spiro[3.3]heptane, 7-oxa-azaspiro[3.5]nonane, bicyclo[2.1.1]hexane and oxabicyclo[2.1.1]hexane analogs of Sonidegib (Fig. 1). ADME parameters and inhibition of the Hedgehog signalling pathway in the Gli-Luc NIH3T3 reporter cell line were tested for all analogs.




**Results:** Replacing the meta-substituted phenyl ring in Sonidegib structure with spiro[3.3]heptane (analogs 1 and 2) has virtually no effect on logD, plasma protein binding and solubility in PBS. At the same time, the metabolic stability of both analogs was lower and differed significantly between trans- and cis- isomers. Spiro[3.3]heptane analogs were less active inhibitors of Hedgehog signaling pathway but more cytotoxic on NIH3T3 cells compared to Sonidegib. Replacement of the 2,6-dimethylmorpholine with 7-oxa-2-azaspiro[3.5]nonane and 7-oxa-1-azaspiro[3.5]nonane (analogs 3 and 4) resulted in slightly increased solubility but decreased metabolic stability (for analog 4 only). Both analogs were less cytotoxic on NIH3T3 cells and analog 3 retained nanomolar inhibition of the Hedgehog signaling. Analogs 5-8 were less active but more cytotoxic (5, 6, 8) compared to Sonidegib. ADME parameters do not differ significantly, only analog 8 exhibited slightly higher solubility.

**Conclusions:** Thus, these structures can be useful structural elements in drug discovery projects

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# DISTINGUISHED POSTER FOCUSED ON MEDICINAL CHEMISTRY

*To*

***Marta Splandesci***

*in recognition of the presentation entitled*

*Exploring new classes of sulfoximine derivatives of potential biological activity*

On behalf of Award Committee,

Prof. dr hab. Jadwiga Turło
Prof. dr hab. Monika Wujec
Prof. dr hab. Paweł Zajdel
*Polish Society of Medicinal Chemistry*

Abstract No. PSP.08

# Exploring new classes of sulfoximine derivatives of potential biological activity

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**Objectives:** Sulfoximines constitute a chemical group that is of increasing interest in drug discovery. This moiety is considered a bioisosteric to e.g.sulfone, sulfonamide, secondary amine, hydroxyl, and carbonyls. It has interesting reactivity and desired pharmaco(chemical) properties, such as high aqueous solubility and stability[(1)]. Consequently, sulfoximines are considered promising leads and first compounds bearing this functional group are currently in clinical trials[(1)]. Considering the desired properties of sulfoximines and the rich possibility of exploring novel chemistries around them, we investigate their possible use in obtaining biologically interesting derivatives through multicomponent reactions (MCRs), particularly the UGI reaction[(2)]. We focus on the optimization of reaction conditions and obtaining compound libraries of sulfoximine derivatives to demonstrate the usefulness of the applied synthetic methodology in medicinal chemistry and chemical biology. The results obtained may provide useful for the pharmaceutical industry and researchers in the field of drug discovery.

**Methods:** The Ugi reaction was conducted in 1 mmol scale. Each Ugi product was separated and purified using preparative chromatography in automatic and manual methods. Characterisation of the each product was performed using spectroscopic techniques (NMR, HRMS, LC/MS).

**Results:** The Ugi reaction was successfully used to obtain sulfoximine derivatives that could have potential applications as building blocks in drug discovery. In this research, we obtained a significant change in yields, between 13% and 96%. Lower yields between 13% and 38% were observed using ketones as starting materials instead of aldehydes (11% and 96%), besides longer reaction conditions.

**Conclusions:** This result shows the possibility of obtaining different sulfoximines derivatives using the Ugi multicomponent reaction, and it is a good starting point for construction of libraries of small- molecular scaffolds and peptidomimetics synthesis.

**References:**

1) Mäder P, et al. *J. Med. Chem.* 2020, 63, 14243−75

2) Cores A, et al. Pharmaceuticals 2022, 15, 1009

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# DISTINGUISHED POSTER FOCUSED ON MEDICINAL CHEMISTRY

*To*

***Oleg Demchuk***

*in recognition of the presentation entitled*

*Development of novel family of antifungal agents based on a quinone methide oxime framework*

On behalf of Award Committee,

Prof. dr hab. Jadwiga Turło
Prof. dr hab. Monika Wujec
Prof. dr hab. Paweł Zajdel
*Polish Society of Medicinal Chemistry*

Abstract No. PPP.42

# Development of a novel family of antifungal agents based on a quinone methide oxime framework

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Objectives: Fungal infections are a global problem and are consistently associated with high morbidity and mortality in immunocompromised patients. Here we propose the quinone methide oxime as a framework for development of a novel class of antifungal agents. From series testes quinone methide oximes showing antifungal activity against Candida albicans and non-albicans Candida, we chose one which appeared to be the most promising for further in-depth analysis. The molecular docking studies and quantitative quantumchemical calculations were performed to understand the mechanism of the biological interactions.

Methods: According to the docking model, interactions involving the aryl and the nitrile groups of quinone methide oximes within the active site of DYRK1A kinase facilitated the stabilization of the resultant complexes more then interaction of the hydroxyl group or it derivatives. The chemical synthesis furnished a series of quinone methide derivatives with altered functionality at the oxime hydroxide, aryl ring, and quinone moiety. The elucidation of stereo configuration of most active isomers was achieved applying the XRD analysis. Both in vitro and in silico investigations revealed that the synthesized compounds demonstrated notable inhibition of protein kinases, particularly exhibiting a robust affinity for the active site of DYRK1A kinase.

Results

The incorporation of an acyl group into compound phenylcyanomethylenequinone oxime resulted in a significant enhancement in the activity of syn- isomer of compound formed. Despite the positively passed safety test towards to the human calls, this acetylated derivative effectively suppresses the growth of C. albicans hyphae, eradicates mature biofilms, and demonstrates efficacy against several clinical fungal isolates, including those resistant to systemic drugs.

Figure 1. Presentation of electrostatic potential, natural atomic charges, and molecular docking into protein kinase DYRK1A.

Conclusions: Our research has revealed that some of the acquired compounds effectively hinder the growth of Candida albicans fungi. This characteristic positions them as promising contenders in combatting fungal infections, with enhanced antifungal properties, capacity to eradicate biofilms, and advantageous safety profile compared to normal human cells.

The financial support from the Polish National Science Centre grant number 2019/33/B/NZ7/01608 is gratefully acknowledged. We gratefully acknowledge the Polish high-performance computing infrastructure PLGrid for providing computer facilities and support within computational grant no. PLG/2023/016326.