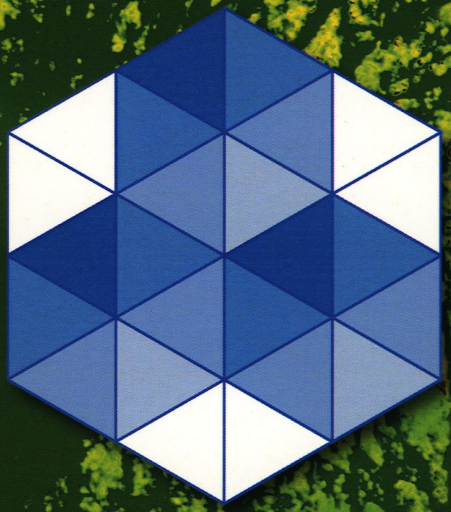
The Eighth Multidisciplinary Conference on Drug Research

BOOK OF ABSTRACTS



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COMMITTEE OF THERAPY AND DRUG RESEARCH POLISH ACADEMY OF SCIENCE

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17:00 Poster 117

Microbiologically active Mannich bases derived from 1,2,4-triazoles. The effect of C-5 substituent on antibacterial activity.

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In the recent years, there has been a significant tendency in organic chemistry to imitate chemical phenomena occurring in the nature. The so-called biomimetic reactions consist in transformation of simple substrates into complex products, usually at mild conditions [1]. One of such reactions is the aminomethylation reaction, discovered and described by Carl Mannich [2]. This reaction makes it possible to introduce amine fragment into the different chemical scaffolds which can increase the affinity of the obtained molecule towards appropriate molecular target. 1,2,4-Triazole-3-thione derivatives known for their antibacterial activity [3,4] were used by many researchers as substrates for the Mannich reaction.

Our research proved that chemical character of the C-5 substituent significantly determines the antibacterial activity of the Mannich bases derived from 4,5-disubstituted 1,2,4-triazole-3-thiones. This activity was considerably increased by an introduction of a chlorine atom to the phenyl ring. Furthermore, the disparities in the activity of appropriate *ortho-*, *meta-*, and *para-* derivatives were analysed. The obtained compounds were particularly active against opportunistic bacteria (*Bacillus subtilis*, *Bacilluscereus*). The antibacterial activity of some Mannich bases was similar or higher than the activity of commonly used antibiotics such as ampicillin and cefuroxime.

References

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[3] Turan-Zitouni, G.; Kaplancıklı, Z.A.; Yıldız, M.T.; Chevallet, P.; Kaya, D. *Eur. J. Med.Chem.***2005**, 40, 607-613.

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17:00 Poster 118

The multiobjective based design, synthesis and evaluation of the arylsulfonamide/amide derivatives of arylxyethyl- and arylthioethyl- piperidines and pyrrolidines as a novel class of potent 5-HT$_7$ receptor antagonists

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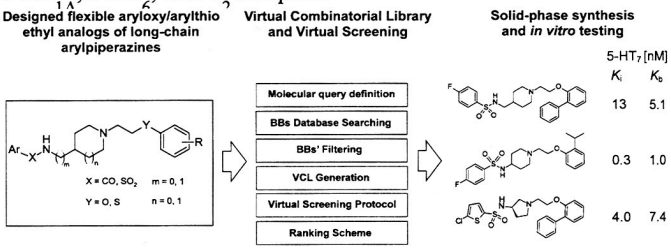
An analysis of the virtual combinatorial library was used for refining a pilot set of 34 derivatives and designing a targeted 38-member library of the arylamide and arylsulfonamide derivatives of aryloxyethyl- and arylthioethyl- piperidines and pyrrolidines. All compounds were synthesized according to an elaborated parallel solid-phase method and were biologically evaluated for their affinity for 5-HT$_7$. Additionally, the targeted library members were tested for 5-HT$_{1A}$, 5-HT$_2$, and D$_2$ receptors.



Selected compounds of particular interest were examined for their intrinsic activity at 5-HT$_7$R in vitro employing a cAMP assay. The study allowed us to identify compound **68** (4-fluoro-*N*-(1-{2-[(propan-2-yl)phenoxy]ethyl}piperidin-4-yl) benzenesulfonamide) as a potent 5-HT$_7$R ligand (K_i = 0.3 nM) with strong antagonistic properties (K_b = 1 nM) and a 1450-fold selectivity over 5-HT$_{1A}$Rs.

This study was partly supported by the Polish Ministry of Science and Higher Education (MNiSW), Grant No. N N405 671540 and Funds for Statutory Activity of Jagiellonian University Medical College. Radioligand binding experiments were financially supported by the Norwegian Financial Mechanism as part of the Polish-Norwegian Research Fund, Grant No. PNRF–103–AI-1/07.