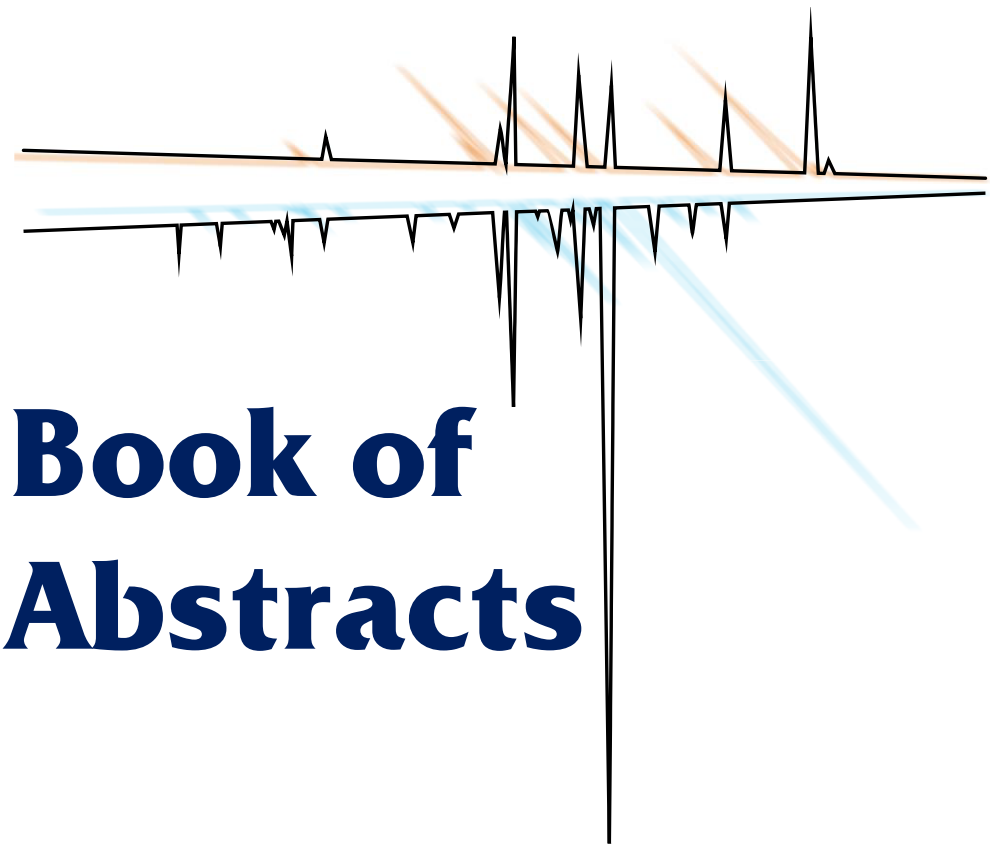
10th IAPC Meeting

Tenth World Conference on Physico-Chemical Methods in Drug Discovery & Sixth World Conference on ADMET and DMPK



Book of Abstracts

10th IAPC Meeting

Tenth World Conference on Physico-Chemical Methods in Drug Discovery
&
Sixth World Conference on ADMET and DMPK
Belgrade, Serbia, September 4-6, 2023

Book of Abstracts

Organized by
International Association of Physical Chemists
&
Faculty of Chemistry, University of Belgrade, Serbia

Published by
International Association of Physical Chemists
E-mail: office@iapchem.org, URL: http://www.iapchem.org

For Publisher
Zoran Mandić

Editor
Tatjana Verbić & **Zoran Mandić**

Design, page making and computer layout
Aleksandar Dekanski

On Line version only

The Scientific and Organizing Committee:

Tatjana Verbić, Conference Chair
University of Belgrade, Serbia,

Alex Avdeef
ADME Research, New York, USA

Kiyohiko Sugano
Ritsumeikan University, Osaka, Japan

Kin Tam
University of Macau, Macau

Zoran Mandić
University of Zagreb, Croatia

Klara Valko
Biomimetic chromatography Ltd. UK

Godefridus J. Peters
Amsterdam University Medical Centers, The Netherlands

Hong Wan
WHDeX Consultng AB, Sweden

Local Organizing Committee

Tatjana Verbić, Conference Chair
University of Belgrade, Faculty of Chemistry, Serbia

Goran Roglić
University of Belgrade, Faculty of Chemistry, Serbia

Ilija Cvijetić
University of Belgrade, Faculty of Chemistry, Serbia

Miloš Pešić
University of Belgrade, Faculty of Chemistry, Serbia

Olivera Marković
University of Belgrade, Institute of Chemistry, Technology and Metallurgy, Serbia

Aleksandar Dekanski
University of Belgrade, Institute of Chemistry, Technology and Metallurgy, Serbia

Marija Popović Nikolić
University of Belgrade, Faculty of Pharmacy, Serbia

P 05

Virtual docking and design of novel Histone deacetylase and Rho-associated protein kinases dual inhibitors (HDAC/ROCKs)

Milan Beljkaš[1], Miloš Petković[2], Katarina Nikolić[1], Slavica Oljačić[1]

[1]*Department of Pharmaceutical Chemsitry, Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia*
[2]*Department of Organic Chemistry, Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia*

Histone deacetylases (HDACs) belong to a family of epigenetic enzymes that has 18 different isoforms and play an important role in the development and progression of various tumors. To date, five histone deacetylase inhibitors have been approved by the FDA, and are used to treat multiple myeloma, cutaneous T-cell lymphoma, peripheral T-cell lymphoma, and breast cancer (estrogen and/or progesterone positive) [1]. All of them are non-selective. Therefore, their safety profile is poor and their efficacy is low in single therapy. One of our previous research projects demonstrated the synergistic effect of HDAC inhibitors and inhibitors of Rho-associated protein kinases (ROCK) in the treatment of pancreatic ductal adenocarcinoma (PDAC) [2]. This finding led us to design of the dual HDAC/ROCK inhibitors with potential effects on PDAC by using structure-based molecular docking method.

Molecular docking study was performed using GOLD software. The crystal structures of ROCK1 (PDB: 6E9W), ROCK2 (PDB: 7JNT), HDAC1 (PDB: 5ICN), and HDAC6 (PDB: 5EDU) enzymes were downloaded from the Protein Data Bank (PDB). The enzymes were prepared for docking study using the online software Play Molecule-ProteinPrepare. The structures of the ROCK1, ROCK2, HDAC1 and HDAC6 inhibitors with their pIC50 values were obtained from the ChEMBL database. The dominant microspecies of all compounds at physiological pH were selected by Marvin Sketch Sketch 6.1.0 program and their further geometrical optimization were performed using the PM3 semi-empirical method and the Hartree-Fock method with 3-21G basis set.

The virtual docking procedures for all four enzymes were validated and the calculated RMSD values were below 2Å. The critical parts of the structures that establish the interactions crucial for the inhibition of HDAC1, HDAC6, ROCK1, and ROCK2 were identified. Based on the obtained resultsdual HDAC/ROCK inhibitors were designed and evaluated by validated docking procedures and *in silico* ADMET profiling.

Taking into account all these findings, the most active compounds are selected and will be further synthesized and evaluated using *in vitro* enzyme and cell tests.

References

[1] Aldana-Masangkay, G. I., & Sakamoto, K. M. (2010). The role of HDAC6 in cancer. Journal of Biomedicine and Biotechnology, volume 2011

[2] Djokovic, N., Djuric, A., Ruzic, D., Srdic-Rajic, T., & Nikolic, K. (2023). Correlating basal gene expression across chemical sensitivity data to screen for novel synergistic interactors of HDAC inhibitors in pancreatic carcinoma. Pharmaceuticals, 16(2), 294.