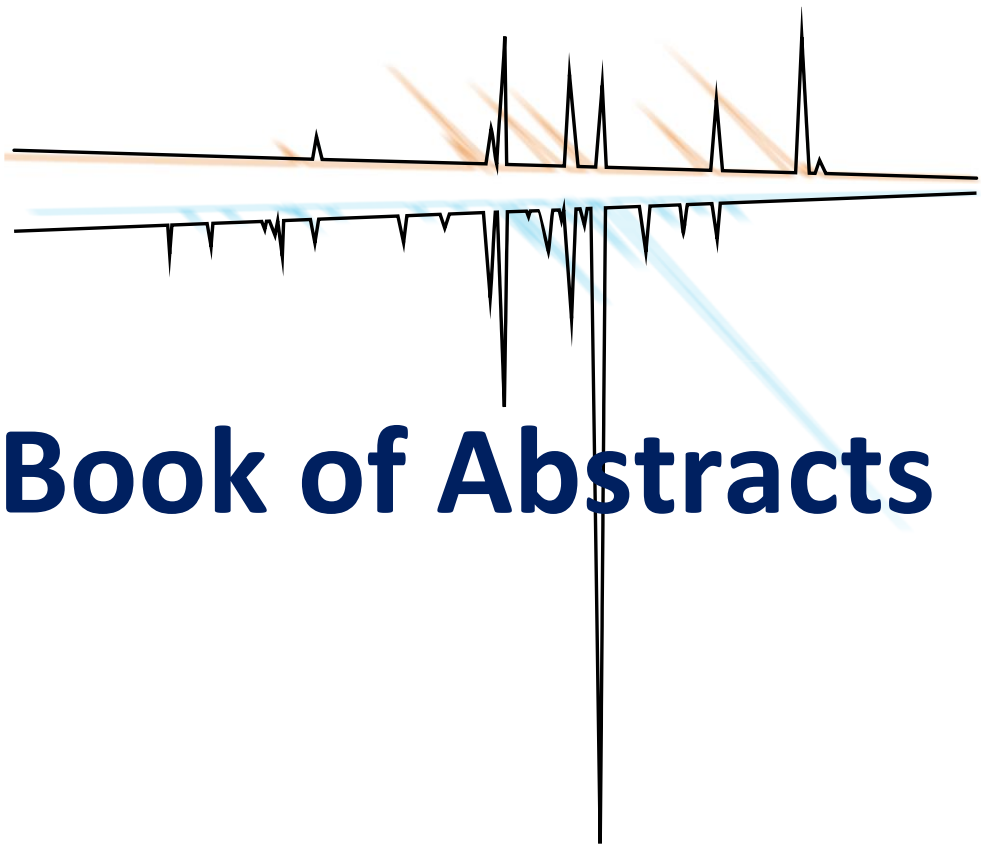
10th IAPC Meeting

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



Book of Abstracts

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&
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~~Withdrawn~~

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Towards the multitarget HDAC Inhibitors for the treatment of pancreatic carcinoma by joining the drug synergy predictions and the molecular modeling

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Pancreatic ductal adenocarcinoma (PDAC) ranks among the most formidable and deadly types of cancer. The emergence of chemoresistance in PDAC plays a significant role in the unfavorable survival rates, making it imperative to swiftly develop new pharmaceutical strategies to address this issue and improve treatment outcomes for PDAC (*1*). Considering the numerous epigenetic changes observed in PDAC, the utilization of epigenetic drugs, such as histone deacetylase (HDAC) inhibitors, holds a great promise as a transformative approach, particularly when used in combination therapy settings (*2*).

In this study, we investigated the potential of utilizing drug sensitivity data and the basal gene expression of pancreatic carcinoma cell lines to develop a bioinformatics screening protocol for prediction of the combinatorial options available for HDAC inhibitors, including sirtuin (SIRT) inhibitors. Experimental validation of the protocol performed on the two pancreatic carcinoma cell lines (MIA PaCa-2 cells and PANC-1) confirmed the identified synergisms between HDAC inhibitors and sphingosine 1-phosphate (S1P) receptor agonist – fingolimod, or HDAC inhibitors and Rho-associated protein kinase (ROCK) inhibitor – RKI-1447 (*3*).

Developed bioinformatics screening protocol for predictions of synergistic drug combinations in PDAC identified several previously unreported interaction partners of HDAC inhibitors. Predicted interaction partners of HDAC inhibitors including Aurora Kinase A (AURKA) inhibitor, glutaminase (GLS) inhibitor, and WEE1 kinase inhibitor were selected for the design of novel classes of dual-acting HDAC inhibitors by the means of structure-based molecular modeling. Novel dual inhibitors (SIRT/AURKA, HDAC/GLS and HDAC/WEE1) were designed relying on the known pharmacophoric features and molecular docking models developed for each of the targets of interest. The docking scores of the designed inhibitors revealed a notable affinity towards the specific targets. Additionally, when combined with predictions of drug synergy, these designed molecules exhibit great potential as promising structures for subsequent experimental evaluation.

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