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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

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