EFMC
International Symposium on Medicinal Chemistry

Ljubljana, Slovenia September 2-6, 2018

BOOK OF ABSTRACTS

Organised by:

Sekcija za Farmacevtsko Kemijo
Slovenskega Farmacevtskega Društva
Section for Medicinal Chemistry
of the Slovenian Pharmaceutical Society

Slovensko Farmacevtsko Društvo
SLOVENIAN PHARMACEUTICA L SOCIETY

On behalf of:

EFMC
European Federation
for Medicinal Chemistry

Ljubljana, Slovenia
September 2-6, 2018
www.efmc-ismc.org

RATIONAL DRUG DESIGN OF HISTONE DEACETYLASE 6 INHIBITORS

Dusan Ruzic (1), Katarina Nikolic (1), Milos Petkovic (2), A Ganesan (3), Danica Agbaba (1)

1) Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Belgrade, Vojvode Stepe 450, 11000 Belgrade, Serbia
2) Department of Organic Chemistry, Faculty of Pharmacy, University of Belgrade, Vojvode Stepe 450, 11000 Belgrade, Serbia
3) School of Pharmacy, University of East Anglia, Norwich Research Park, NR4 7TJ Norwich, United Kingdom

Activity of the histone deacetylases (HDACs) has an essential influence on histone posttranslational modifications. Therefore, alterations in the structure and expression of HDACs isoforms are strongly related to the pathogenesis of inflammation, cancer, and neurodegeneration. The HDACs became extensively examined targets in novel drug discovery. The HDAC6 isoform is a non-histone cytoplasmic deacetylase, manly involved in deacetylation of α-tubulin, cortactin, and heat shock protein 90 (Hsp90) [1]. Our rational drug design study was focused on identification of selective histone deacetylase 6 (HDAC6) inhibitors by use of combined ligand and structure based methodologies. Based on the 3D-QSAR (Quantitative Structure Activity Relationship) modeling of HDAC6 inhibitors were defined specific molecular determinants for selective HDAC6 inhibition and further applied for fragment based design of selective HDAC6 inhibitors. Recently resolved crystal structure of second human catalytic domain of HDAC-6 enzyme (5EDU) [2] was used in virtual docking study of the examined inhibitors.

References

1) Lee, J. H., Mahendran, A., Yao, Y., Ngo, L., Venta-Perez, G., Choy, M. L., Kim N., Ham WS, Breslow R. and Marks, P. A. (2013). Development of a histone deacetylase 6 inhibitor and its biological effects. Proceedings of the National Academy of Sciences, 110(39), 15704-15709.
2) Hai, Y., Christianson, D. W. (2016). Histone deacetylase 6 structure and molecular basis of catalysis and inhibition. Nature chemical biology, 12(9), 741.

COMBINED MOLECULAR DYNAMICS AND VIRTUAL SCREENING STUDIES TO IDENTIFY NOVEL SIRTUIN 2 INHIBITORS

Nemanja Djokovic (1), Katarina Nikolic (1), Maija Lahtela-Kakkonen (2), Danica Agbaba (1)

1) Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Belgrade, Vojvode Stepe 450, 11000 Belgrade, Serbia
2) School of Pharmacy (Pharmaceutical Chemistry) University of Eastern Finland, Kuopio, Finland

Sirtuins are highly conserved class of NAD+-dependent lysine deacetylases. Altered function of sirtuin 2 (Sirt2) is related to pathogenesis of cancer, inflammation and neurodegeneration, which makes Sirt2 very attractive drug target in novel epigenetic research [1]. A number of Sirt2 inhibitors have been recently developed, but for most of them are missing structural information of their interaction with the enzyme [2, 3]. Our molecular dynamic (MD) study was performed on recently resolved crystal structures of selective ligand-Sirt2 complexes [1]. In the MD study were defined significant interactions with novel inhibitors, one of key residues responsible for conformational stability of cofactor-binding pocket, and residue acting as gate-keeper for cofactor-binding loop. Some residues completely changed orientation after the MD simulation, compared to the starting crystal structures. This result indicates on the errors in the X-ray structures that may have influence on structure-based design of novel inhibitors. After clustering of MD trajectory, 20 conformations (centroids) from 20 clusters of Sirt2 have been selected as representative conformations for retrospective structure based virtual screening. The virtual screening performances were significantly improved by use of the ensemble of conformations, selected with this MD methodology, compared to screening against available X-ray structures.

References

1) Rumpf, T.; Schiedel, M.; Karaman, B.; Roessler, C.; North, B.J.; Lehotzky, A.; Oláh, J.; Ladwein, K.I.; Schmidtkunz, K.; Gajer, M.; Pannek, M.; Steegborn, C.; Sinclair, D.A.; Gerhardt, S.; Ovádi, J.; Schutkowski, M.; Sippl, W.; Einsle, O.; Jung, M. Selective Sirt2 inhibition by ligand-induced rearrangement of the active site. Nat Commun. 2015, 6, 6263.
2) Seifert, T.; Malo, M.; Kokkola, T.; Engen, K.; Fridén-Saxin, M.; Wallén, E.A.; Lahtela-Kakkonen, M.; Jarho, E.M.; Luthman, K. Chroman-4-one- and chromone-based sirtuin 2 inhibitors with antiproliferative properties in cancer cells. J Med Chem. 2014, 57, 9870-88.
3) Schiedel, M.; Rumpf, T.; Karaman, B.; Lehotzky, A.; Oláh, J.; Gerhardt, S.; Ovádi, J.; Sippl, W.; Einsle, O.; Jung, M. Aminothiazoles as Potent and Selective Sirt2 Inhibitors: A Structure-Activity Relationship Study. J Med Chem. 2016, 59, 1599-612.