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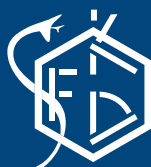
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BOOK OF ABSTRACTS



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RATIONAL DRUG DESIGN OF HISTONE DEACETYLASE 6 INHIBITORS

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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, mainly 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.

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

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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

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