INHIBITORS OF HISTONE DEACETYLASE (HDAC) – PROSPECTIVE EPIGENETIC DRUGS. RATIONAL DESIGN OF NEW HDAC INHIBITORS WITH 2-OXINDOLE NUCLEI AND THE FRAGMENTS OF A DICARBOXYLIC ACID USING METHODS CHEMINFORMATICS

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Histone deacetylase (HDAC) inhibitors are a prospective class of therapeutics with potential as anticancer drugs. The rationale for developing and de novo design HDAC inhibitors as anticancer therapies arose from the understanding that in addition to contribute to neoplastic growth. The family of HDAC inhibitors includes a range of naturally occurring and synthetic compounds. HDAC inhibitors have multiple cell type-specific effects *in vitro* and *in vivo*, such as growth arrest, cell differentiation, and apoptosis in malignant cells. Currently, there are two HDAC inhibitors that have received approval from the US FDA for the treatment of cutaneous T-cell lymphoma: vorinostat (suberoylanilide hydroxamic acid, Zolinza) and depsipeptide (romidepsin, Istodax). The aim of our work is the rational design of new HDAC inhibitors with the nuclei of 2-oxindole and dicarboxylic acid residues using techniques Cheminformatics, in particular the design of computer platforms Molinspiration Cheminformatics (University of Bratislava, Slovakia). As a promising class for the construction of new HDAC inhibitors us consider hydroxamates (e.g. suberoylanilide hydroxamic acid, Zolinza). Pharmacofore based approach as potential HDAC inhibitors we have proposed structure based on 3-N-acyl (suberoyl-, glutaroyl-, succinoyl-) hydrazones of 2-oxindole hydroxamic acid (I) and spiropyrrolidino-2-oxindoles (II). In the first stage, we studied the QSAR for a known set of hydroxamates using computational platform Molinspiration Cheminformatics, which allowed us to construct the correlation model to a number of molecular descriptors. In the second phase, two focus screening libraries I, II in silico, showed high sensitivity to compounds II. Thus, the proposed structures deserve attention for further research for potential HDAC inhibitors.