Integrative Framework for Developing Innovative SIRT2 Inhibitors

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Sirtuin 2 inhibitors (SIRT2i) represent a promising class of potential drugs in the therapy of age-related disorders, including malignant diseases. Recent studies demonstrated potential of SIRT2i in advancing tumour immunotherapy by activating tumour-infiltrating lymphocytes. [1,2] Some of the key obstacles in the development of new SIRT2 inhibitors include the complex conformational dynamics of the sirtuin 2 (SIRT2) binding site, a lack of a clear correlation between structure and activity, and insufficient exploration of the pharmacological context of SIRT2 inhibition. [1,2] The main goal of this work was to establish a framework to support future rational design of new SIRT2 inhibitors through the integration of molecular modelling, cheminformatics, and bioinformatics approaches.

In the first phase of the framework development, a protocol for structure-based virtual screening (SBVS) was established, relying on enhanced sampling of the conformational dynamics of the SIRT2 binding site. Improved sampling was achieved through metadynamics simulations using a set of collective variables derived from the time-independent component analysis. The application of enhanced sampling identified, for the first time, the existence of the cryptic pocket within the SIRT2 binding site and demonstrated significant expansion of known chemical space of SIRT2i through prospective screening study. [1] In the second phase of the framework development, a set of four highly validated quantitative structure-activity relationship (QSAR) models were developed by incorporating all SIRT2i data available to date. The models were trained on a large dataset comprising a total of 1797 compounds, utilizing five leading machine learning algorithms. The models were employed to create a tool for rational design of SIRT2 inhibitors, named SIRT2i_Predictor. [2] In the third phase of framework development, leveraging the data on chemical sensitivity of pancreatic adenocarcinoma cell lines, a bioinformatics protocol was developed to predict a synergistic combinations of histone deacetylase inhibitors (including sirtuins) and other bioactive molecules in order to prioritize targets for development of novel dual acting SIRT2i. [3]

The framework discovered novel SIRT2i from unexplored portions of chemical space, guided the design and synthesis of novel SIRT2i, and identified potential targets for development of dual-acting SIRT2i. Additionally, it demonstrated utility in repurposing studies by designing dual SIRT2/AURKA and SIRT2/PD-L1 inhibitors as novel antineoplastic for advancing cancer immunotherapeutic approaches.

Bibliography:

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