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2.1 Aim and objective

The global market for DPP-4 inhibitors is forecast to reach US$14.8 billion up to 2022. The increased interest of the pharmaceutical industry in DPP-4 inhibitors reflects their market attractiveness and patent application. It is worth developing a faster and more accurate system to discover DPP-4 inhibitors with better therapeutic profiles.

QSAR studies are mathematical methodologies, statistically validated and mostly used to correlate experimental or calculated properties derived from chemical structures with biological activities. With the advent of 3D molecular space modeling, a pharmacophore hypothesis can visualize the potential interaction between the ligand and the receptor. A pharmacophore is a set of functional groups/fragment types in a 3D spatial arrangement that represents the interaction made in a common scaffold by a set of small molecular ligands with a protein receptor. The pharmacophore concept is based on the kinds of interaction observed in molecular recognition and alternatively can be used as a query in a 3D database virtual screening to identify new structural classes of potential lead compounds; and it can serve as a template for generating alignment for 3D QSAR analysis. The main goal of a virtual screen is to come up with hits of novel chemical structure that yields a unique pharmacological profile. Thus, the success of a virtual screen is defined in terms of finding interesting new scaffolds rather than many hits. VS methods are often divided into structure based VS (SBVS) and ligand-based VS (LBVS). A combination of LBVS and SBVS methods are used where LBVS techniques measuring compound similarity to known potent molecules outperforms molecular docking, a more computationally intensive SBVS technique that generate sand scores putative protein–ligand complexes according to their calculated binding affinities.

The development of selective DPP-4 inhibitors is a big task due to another member of dpp family like DPP-2, DPP-8, DPP-9, etc. which may produce side effect as severe toxic reaction, alopecia, thrombocytopenia, anemia and increased mortality. To discover potent and selective and safer drugs in a shorter time frame and with reduced cost it requires using an innovative approach for designing novel inhibitors. The utilization of CADD solutions and mathematical models like QSAR can help with future development of more selective DPP-4 agents. We have applied pharmacophore mapping 3D-QSAR and virtual screening technique in the present work for the discovery of new DPP-4 inhibitors, and optimize lead with higher inhibitory potencies.

2.2 Plan of Work

1. Design of α-series peptidomimetcis inhibitors

A. Fragment based HQSAR modeling to design selective DDP-4 inhibitors

B. Pharmacophore modelling, 3D-QSAR virtual screening and lead optimization

C. Synthesis of substrate like peptidomimetic inhibitors

D. Characterization of synthesized compounds by analytical techniques

2. Design of β-series peptidomimetcis inhibitors

A. Pharmacophore modelling, 3D-QSAR virtual screening and lead optimization

B. Synthesis of substrate like peptidomimetic inhibitors

C. Characterization of synthesized compounds by analytical techniques

3. Biological Evaluation

A. Assessment of inhibitory potency against DPP-4 target

B. Investigation of the effects on blood glucose, plasma insulin and HbA1C levels after oral glucose loading in streptozotocin induced diabetic Rat,

C. Investigation of lipid profile and effect on hepatic function

D. Histopathology

E. Cytotoxicity study