*In-silico* Discovery of Dual inhibitors of Dipeptidyl Peptidase IV (DPP IV) and Neutral Endopeptidase (NEP)

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In 2014, 422 million of the world's population had diabetes. This number is expected to reach 642 million by 2040. Dipeptidyl Peptidase IV (DPP IV) enzyme cleaves an incretin based glucoregulatory hormone Glucagon Like Peptide -1 (GLP-1) from N-terminal where penultimate amino acid is either alanine or proline. Several DPP 4 inhibitors, “gliptins”, are approved for management of Type 2 Diabetes or under clinical trial. Neutral endopeptidase (NEP) also degrades GLP-1. Within the kidney, GLP-1 clearance is primarily due to NEP. NEP inhibitors are used in management of hypertension and chronic heart failure. Hence combined inhibition of DPP IV and NEP could efficiently control hyperglycemia. In present study, docking based virtual screening protocol was used for identification of new hits from the Specs Database, which would inhibit DPP IV and NEP enzymes. The entire computational studies were performed using the Discovery Studio v. 4.1 (Accelrys Inc.) and FRED v. 2.2.5 (OpenEye Scientific Software). The specs database was prefiltered based on drug-likeness and docked into active site of NEP (PDB- 2QPJ). Top ranking hits from the docking were further docked into active site of DPP IV (PDB- 2OGZ). Hits resulting from the end of docking were clustered based on fingerprint (ECFP). Hits were analyzed for interaction with DPP IV and NEP. Based on docking studies, virtual hits were predicted to form interaction with essential amino acid residues of DPP IV and NEP has almost similar binding orientation as that of reference molecule. Structures of such hits are disclosed here.

**Thrust Area:** Computational Chemistry

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