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Machine learning based approach to develop potential dual inhibitors of Neprilysin and Dipeptidyl peptidase-4: Implications in the treatment of type 2 diabetes

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INTRODUCTION & AIM

Diabetes mellitus (DM) is a chronic metabolic disease characterized by elevated levels of blood glucose. Neutral endopeptidase (NEP or neprilysin) is a key enzyme associated with the metabolic inactivation of numerous bioactive natriuretic peptides (NP). Among these, bradykinin, endothelin, angiotensin II, amyloid β protein, substance P, and glucagon-like peptide 1 (GLP-1) are the key NPs that affect the heart, kidney, and other organs. Among these, GLP-1, an essential stimulator of insulin secretion, is frequently found to be impaired or downregulated in the case of diabetes, particularly type 2 diabetes. The level of GLP-1 is also diminished by another serine protease, Dipeptidyl peptidase-4 (DPP-4). . DPP4 inhibitors increase insulin secretion and reduce glucagon secretion in a glucose-dependent manner by inhibiting the degradation of two gastrointestinal hormones (GLP-1 and gastric inhibitory polypeptide (GIP)Combination therapy of Dipeptidyl peptidase-4 and NEP inhibitors could offer an alternative regimen for treating type 2 diabetes.

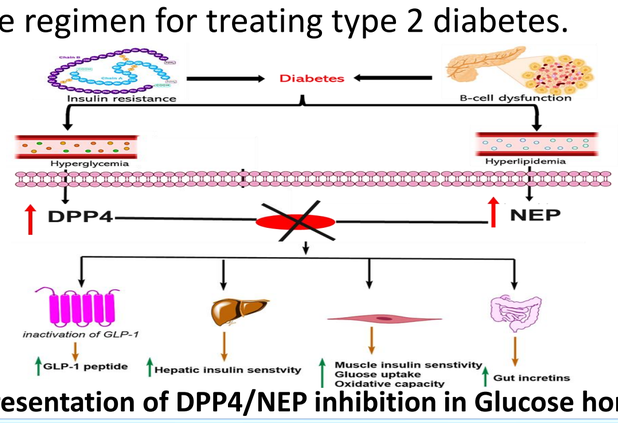

Figure 1. Representation of DPP4/NEP inhibition in Glucose homeostasis

METHOD

- ✓ Machine learning plays a crucial role in drug lead identification. It allows researchers to analyze vast amounts of data and identify patterns that may not be immediately apparent to the human eye.
- ✓ We have developed a machine learning predictive model for DPP-4 and NEP, which helps us to predict the possible lead for dual NEP/DPP4i.

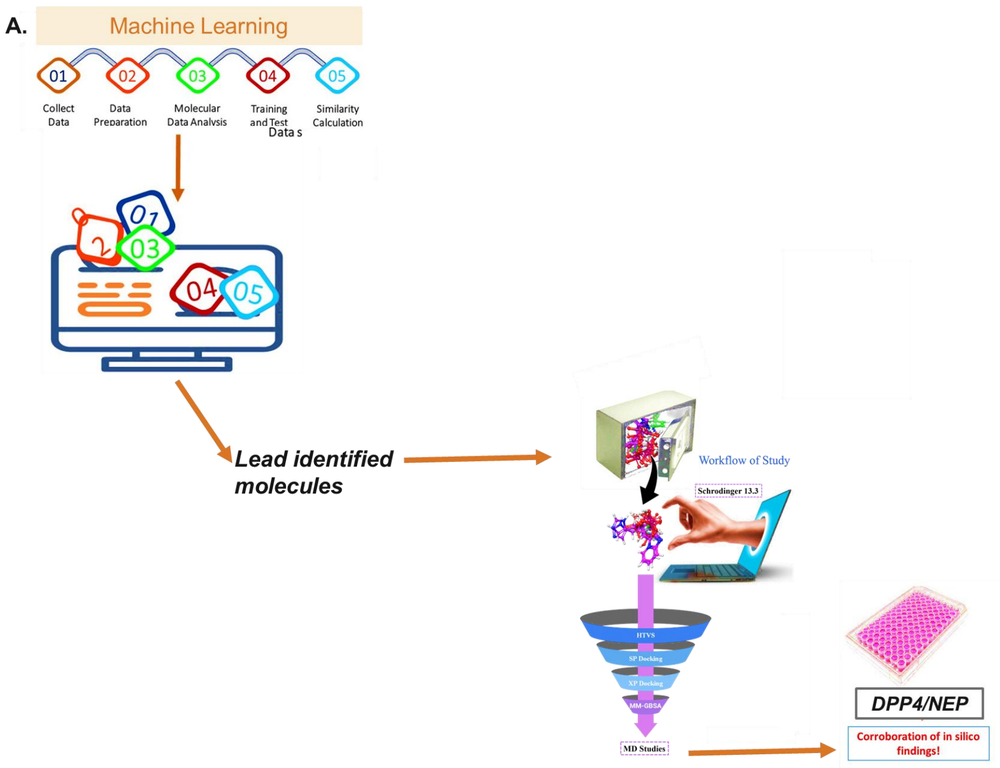

Figure 2. Workflow of the present Work

Further lead identified molecules subjected to High throughput virtual screenin followed by Molecualr dynamics simulations.The X-ray crystal structure of NEP (PDB ID: 5JMY) reveals that the catalytic site comprises a zinc ion, a zinc-binding residue Glu-646, and the conserved zinc metalloprotease His-583 and His-587 complete the zinc-binding, while Glu-584 is a catalytic residue. S1, S1', and S2' are the three subsites of the metalloproteases. Thus proposed prototypes are further screened by in silico screening by using Schrodinger software, Mastero version 13.3.For X-ray crystal structure of DPP4 (PDB ID: 3G0B) revealed presence of catalytic amino acids 206 Glu in the β-propeller region, 630Ser, 708Asp and 747His cataytic triad, and 547Tyr present in hydrolyase domain.

RESULTS & DISCUSSION

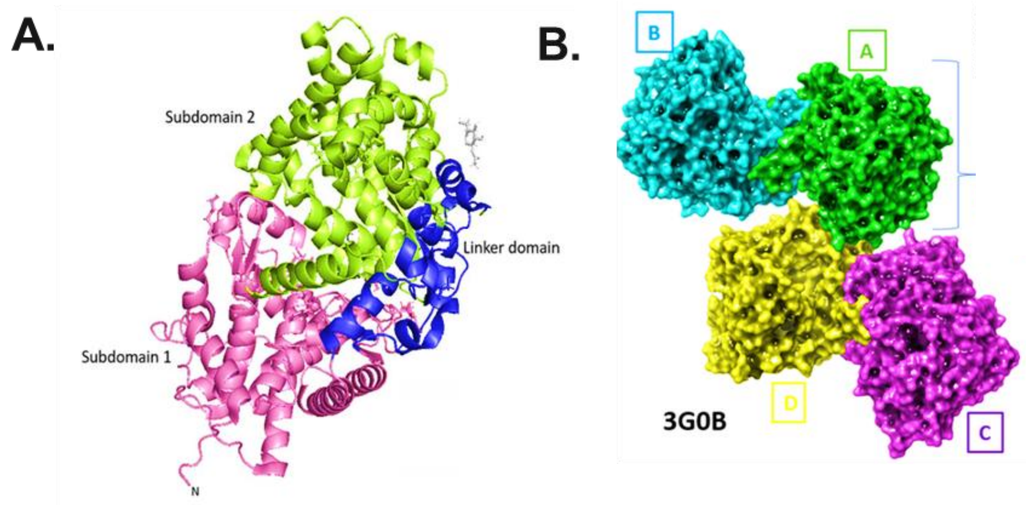

Figure 3. (A.) Protein structures of Neutral endopeptidase (NEP) PDB ID: 5JMY; (B.) Dipeptidyl peptidase 4 (DPP4) PDB ID: 3G0B

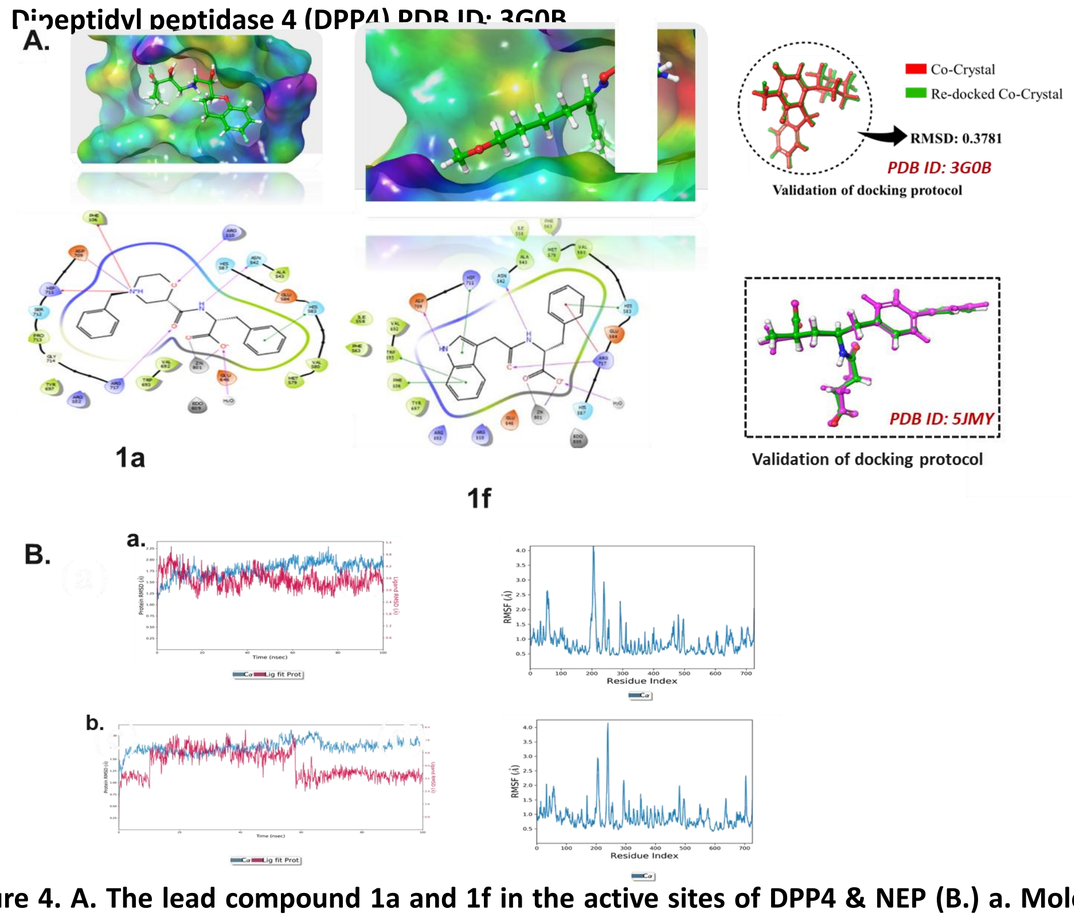

Figure 4. A. The lead compound 1a and 1f in the active sites of DPP4 & NEP (B.) a. Molecular Dynamics Protein-Ligand RMSD 1a and protein RMSF graph b. Protein-Ligand RMSD 1f and protein RMSF graph.

Table 1. In vitro activity and dock score of lead compounds

S. No.	Compound code	Inhibitory concentration DPP4 (IC50) ± SD (μM)	Inhibitory concentration NEP (IC50) ± SD (μM	Docking score (kcal/mol)	Docking score (kcal/mol)
1.	1a	11.92 ± 0.21 μM	4.72 ± 0.05 μM	− 7.61	− 9.61
2.	1f	10.92 ± 0.19 μM	4.72 ± 0.05 μM	− 6.71	− 7.71
3.	Sitagliptin	8.72 ± 0.22 μM	-	− 5.61	
4.	Thiorphan	-	4.72 ± 0.05 μM		− 8.61

In the present study, we have developed a machine learning (ML) based prediction model considering the pharmacophoric features of both NEP and DPP-4.

CONCLUSION

The present study, we report a dual inhibitors of DPP4 and NEP (1a & 1f), which are recognized targets in diabetes. The model was tested against an array of in-house developed and newly designed and synthesized NCEs as training sets with the reported inhibitors against the enzyme. The work was further validated and standardized with molecular docking and dynamics studies and corroborated with numerous biological studies. The cumulative analysis yielded **1a** and **1f** as the best lead molecules with potent dual inhibition of NEP and DPP-4 with anti-diabetic potential.

FUTURE WORK / REFERENCES

Further lead-identified molecules (1a & 1f) from in vitro studies open up the avenue for in vivo studies in clinical translations.

1. Ibrahim, N.E., et al., *Effect of Neprilysin Inhibition on Various Natriuretic Peptide Assays.* J Am Coll Cardiol, 2019. **73**(11): p. 1273-1284.

2. Roques, B.P., et al., *Neutral endopeptidase 24.11: structure, inhibition, and experimental and clinical pharmacology.* Pharmacol Rev, 1993. **45**(1): p. 87-146.