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UNVEILING A PROMISING DIPEPTIDYL PEPTIDASE-4 INHIBITOR FOR TYPE 2 DIABETES: A COMPUTATIONAL AND ARTIFICIAL INTELLIGENCE-BASED APPROACH

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I-Introduction

Type 2 diabetes (T2D) is a substantial global health problem [1]. Dipeptidyl peptidase-4 (DPP-4) inhibitors, known as gliptins, have significantly impacted T2D treatment [2-3]. However, the development of novel, more potent DPP-4 inhibitors with reduced side effects remains crucial.

II-Methods

Using artificial intelligence (AI) tools, ChEMBL and Zinc15 databases, and machine learning protocls, we searched for gliptin molecule that has enhanced DPP-4 affinity and favorable pharmacokinetics properties.

III-FINDINGS

Results: We identified a standout gliptin exhibiting significantly higher binding affinity (pKi) for DPP-4 compared to other structurally similar drugs. In addition, it displayed favorable pharmacokinetic properties, including optimal human intestinal absorption (HIA), lack of brain-blood barrier (BBB) penetration, unlike sitagliptin, and non-substrate status for the efflux pump P-glycoprotein (PGP), unlike both sitagliptin and linagliptin. This molecule demonstrated oral bioavailability and LD50 similar to linagliptin. While its oral bioavailability was similar to sitagliptin, its LD50 was slightly lower. Additionally, unlike the other two drugs, it undergoes minimal biotransformation, with N-acetylation being the only predicted pathway.

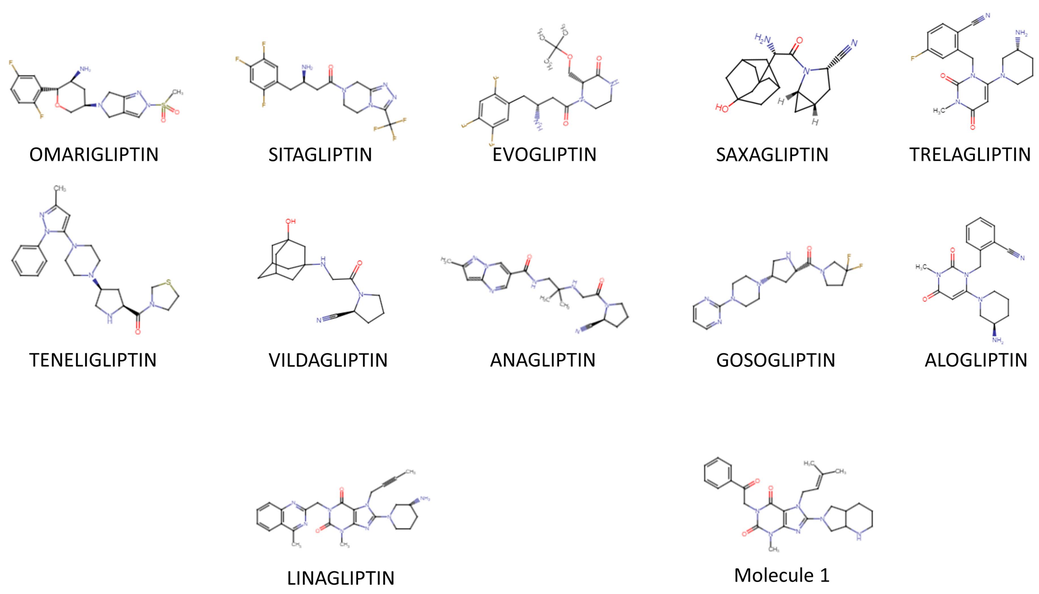

Figure 1: Structure of DPP-4 inhibitors

Table 2 : Lipinski descriptors and binding affinity of the selected DPP-4 inhibitors

Parent Molecule Name	pKi	MW	LogP	Number of H Donors	Number of H Acceptors
OMARIGLIPTIN	9,1	398,435	1,1421	1	7
SITAGLIPTIN	8,46	407,318	2,0165	1	5
EVOGLIPTIN	9,05	401,429	1,5059	2	4
SAXAGLIPTIN	9,22	315,417	1,15798	2	4
TRELAGLIPTIN	8,4	357,389	0,53358	1	7
TENELIGLIPTIN	9,54	426,59	1,56612	1	7
VILDAGLIPTIN	9,24	303,406	1,17428	2	4
ANAGLIPTIN	8,42	383,456	0,6503	2	7
GOSOGLIPTIN	7,95	366,416	0,1967	1	6
ALOGLIPTIN	9	339,399	0,39448	1	7
LINAGLIPTIN	10	472,553	1,14742	1	10
Molecule 1	10,32	476,581	1,934	1	9

Table 3 : AD Gastrointestinal Absorption, Blood-Brain Barrier Permeability, and P-glycoprotein Substrate Status

Parent Molecule Name	GI absorption	BBB permeant	P-gp Substrate
OMARIGLIPTIN	High	No	Yes
SITAGLIPTIN	High	Yes	Yes
EVOGLIPTIN	High	No	Yes
SAXAGLIPTIN	High	No	Yes
TRELAGLIPTIN	High	No	No
TENELIGLIPTIN	High	No	No
VILDAGLIPTIN	High	No	Yes
ANAGLIPTIN	High	No	Yes
GOSOGLIPTIN	High	No	Yes
ALOGLIPTIN	High	No	No
LINAGLIPTIN	High	No	Yes
Molecule 1	High	No	No

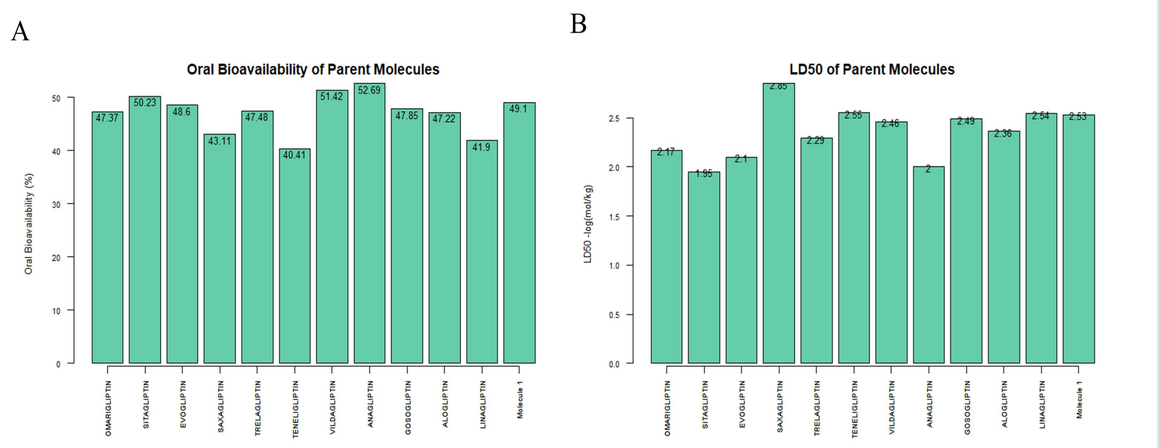

Figure 2: Oral bioavailability and toxicity assessment

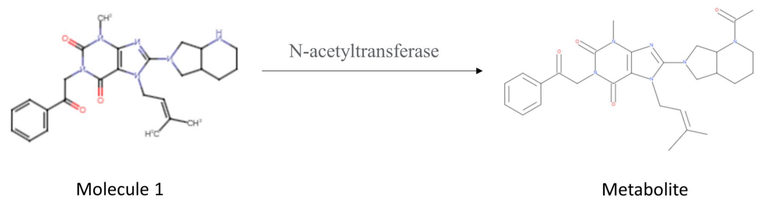

Figure 3: Predicted metabolism reaction and metabolite structure

IV-Conclusion:

This study highlights the potential of the identified molecule as a promising DPP-4 inhibitor for T2D management. Its superior DPP-4 affinity, favorable pharmacokinetic profile, few metabolites and reduced side effects warrant further investigation and development.

References

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3. Gamble, J.-M., et al., *Comparative Safety of Dipeptidyl Peptidase-4 Inhibitors Versus Sulfonylureas and Other Glucose-lowering Therapies for Three Acute Outcomes.* Scientific Reports, 2018. **8**(1): p. 15142.