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MOLECULAR DOCKING AND VIRTUAL SCREENING

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and insufficient insulin secretion, leading to hyperglycemica and various associated complications such as cardiovascular disease, neuropathy, and nephropathy. Current therapeutic approaches aim to manage blood glucose levels, enhance insulin sensitivity, and reduce resistance, yet there remains an ongoing need for novel therapeutic agents. Advances in bioinformatics and computational drug discovery methods, including molecular docking and virtual screening, have become integral in accelerating the identification and optimization of potential drug candidates for T2DM.

Molecular Docking in Drug Discovery for Type 2 Diabetes

Molecular docking is a powerful computational technique that predicts the preferred orientation of a ligand as it binds to a specific receptor or enzyme target. This approach plays a crucial role in understanding the binding affinity and molecular interactions between drug candidates and their respective biological targets.

The docking process involves simulating the molecular structure of the drug candidate and the target protein and calculating the binding interactions to determine the most favorable binding conformation. The strength of these interactions, represented as binding affinity scores, allows researchers to prioritize compounds with potential therapeutic activity. Docking algorithms typically use scoring functions to estimate binding affinity and rank compounds based on their predicted efficacy. This process can help filter out weak candidates and focus experimental efforts on high-potential compounds

Virtual Screening for Type 2 Diabetes Drug Candidates

Virtual screening is a computational approach that screens vast libraries of compounds to identify potential drug candidates by simulating their interactions with biological targets. There are two main types of virtual screening: ligand-based and structure-based screening. Ligand-based virtual screening relies on known active compounds to identify molecules with similar chemical structures or properties. Structure-based virtual screening, which includes molecular docking, directly models the interaction between a library of compounds and the target protein.

In T2DM research, virtual screening can be used to identify compounds that modulate targets involved in glucose uptake, insulin sensitivity, and pancreatic beta-cell function. For instance, using virtual screening against the DPP-4 enzyme has led to the discovery of potential inhibitors that can prolong the action of incretin hormones, thereby enhancing insulin secretion and improving glucose control in diabetic patients. Similarly, screening compounds against PPARγ has contributed to the development of drugs that enhance insulin sensitivity by promoting adipocyte differentiation and lipid storage.

Combined Approaches for Efficient Drug Discovery

The combination of molecular docking and virtual screening is increasingly used in T2DM drug discovery due to its efficiency and cost-effectiveness. High-throughput virtual screening enables the evaluation of large compound libraries, while molecular docking refines the selection by providing detailed insights into binding interactions. This combined approach accelerates the drug discovery process, reduces the time and resources required for initial testing, and helps identify promising candidates for further development. In recent years, artificial intelligence and machine learning techniques have further enhanced the accuracy of these approaches, improving the prediction of drug efficacy and safety profiles.

Challenges and Future Directions

Despite its advantages, computational drug discovery also faces challenges. The accuracy of docking and screening results depends heavily on the quality of protein structures and the parameters used in simulations. In T2DM, target proteins often undergo conformational changes upon ligand binding, which can complicate docking accuracy. Furthermore, the physiological complexity of diabetes and the multi-target nature of its pathology make it necessary to consider polypharmacology – the simultaneous modulation of multiple targets.

Future directions in T2DM drug discovery may involve integrating molecular docking and virtual screening with experimental validation to improve accuracy and drug efficacy. Advances in structural biology, such as cryo-electron microscopy, are also expected to provide more accurate target structures, improving the reliability of docking results. Additionally, the development of next-generation algorithms and AI-driven models holds promise for identifying novel, multi-targeted therapies that can address the multifaceted nature of T2DM.

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GLUT4 vesicles, Akt appears to participate in the pathway by phosphorylating glycogen synthase kinase 3 (GSK3) to promote glycogen synthesis via glycogen synthase (GS) [Moule, SK1997]. GSK3 is constitutively active and phosphorylates GS to inactivate this enzyme, which is required for the incorporation of glucose (in the form of UDPglucose) in to glycogen. Phosphorylation of GSK3 by Akt inactivates the kinase and relieves its block on GS. In addition to the above pathway, a PI3-Kindependent pathway appears to be required for insulindependent glucose uptake into cells. This c-Cblassociated protein (CAP)/Cbldependent pathway apparently provides a second signal that influences GLUT4 vesicle translocation via lipid rafts to effect glucose uptake [Bickel, PE2002].

MOLECULAR DOCKING

Molecular docking is a computational technique widely used in drug discovery to predict the interaction between a small molecule (ligand) and a protein (target). This interaction prediction is crucial because it provides insights into how a potential drug might bind to its target in the body and affect its biological function. By simulating this binding process, molecular docking helps researchers evaluate the potential efficacy, specificity, and safety of a drug candidate early in the drug development pipeline.

1. Principle of Molecular Docking

The main purpose of molecular docking is to find the most suitable orientation and position of a ligand within the binding site of a target protein. Docking simulates the ligand's "fit" into the protein's active site to form a stable complex. The strength of the interaction, known as the binding affinity, is influenced by various forces, including hydrogen bonding, hydrophobic interactions, van der Waals forces, and electrostatic interactions. A strong binding affinity generally suggests that the ligand may effectively interact with the protein, potentially altering its function in a desired way to produce therapeutic effects.

- Docking Simulation: In this step, the molecular docking software performs simulations to predict how the ligand can orient itself within the binding site. During the simulation, numerous poses or orientations are generated to explore how the ligand can fit within the site. Each pose represents a different potential binding configuration between the ligand and protein.
- Scoring and Ranking: Once the docking poses are generated, each pose is evaluated based on a scoring function that estimates the binding affinity or energy. This score is a numerical value that reflects how well the ligand might bind to the protein. Typically, a lower binding energy and tetrazoles and protonating most aliphatic amines.

Molecules in ZINC are annotated by molecular property. These include molecular weight, number of rotatable bonds, calculated log P (OpenEye's wang's algorithm) number of hydrogenbon d acceptors, number of hydrogenbond donors, number of chiral double bonds(E/Z isomerism), polar and a polar desolvation energy (in kcal/mol), net charge and number of rigid fragments. Each molecule is also an notated with the vendor and original catalog number of each commercial source of that compound. Molecul es are available for download in SMILES, mol2, sdf and DOCK flexibase formats.

Subset name	Log P	Molecular weight	Hydrogen-bond donor	Hydrogen-bond acceptor
Lead-like	< 4 > -2	< 350 > 150	≤ 3	≤ 6
Drug-like	≤ 5	≤ 500	≤ 5	≤ 10
Fragment-like	< 3 > -2	≤ 250	< 3	< 6
Greasy-leads	< 6 > 2	< 350	-	-

The following classes of ligands are downloaded from ZINC database for virtual screening:

Class of chemicals	Number of Molecules
Drug like	25,29,908
Lead like	7,51,695
Greasy	8,29,114
Fragment like	56,526
Total	41,67,243

Virtual screening was carried out for finding novel ligands of PTP1B with over 4.1 millions ligands of vario us chemical properties. Top 10 molecules from all chemical class except are presented here along with their energy score of both van der Waals and electrostatic components.

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- Greasy top 10 Ligands

1)

Name	ZINC00969372
RMSD	0
Energy Score	-56.777107
vdw:	-35.822250
es:	-20.954855

2- [4-oxo-2-(4-tert-butylcyclohexylidene)aminoimino-thiazolidin-5-yl]acetic

2)

Name	**ZINC02136559**
RMSD	0
Energy Score	50.638535
vdw:	-33.773861
es:	-16.864672

3-[4-(4-methoxyphenyl)phenyl]-2-oxo-propanoic

3)

Name	**ZINC02433415**
RMSD	0
Energy Score	-50.438122
vdw:	-34.422985
es:	-16.015137

[No name assigned by Zinc]

4)

Name	**ZINC02066448**
RMSD	0
Energy Score	-50. 314754
vdw:	-34. 562346
es:	19.752409

2-[4-[(2-methyl-4-oxo-3Hquinazolin-3yl)iminomethyl]phenoxy]acetic

5)

Name	**ZINC01521756**
RMSD	0
Energy Score	-49.210175
vdw:	-35. 411560
es:	-13.798615

3-hydroxy-2-[4-(4-isobutylphenyl)thiazol-2yl]amino-propanoic

- Drug like top 10 ligands:

1)

Name	ZINC01001250
RMSD	0
Energy Score	-59. 343987
vdw:	- 30.486544
es:	-28.857441

4-[[4-[(2-carboxymethyloxyphenyl)methylidene]-3methyl-5-oxo-1H-pyrazolyl]]benzoic

2)

Name	ZINC00969372
RMSD	0
Energy Score	-56.777107
vdw:	- 35.822250
es:	-20.954855

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2-[4-oxo-2-(4-tert-butylcyclohexylidene)aminoimino-thiazolidin-5-yl]acetic

3)

Name	ZINC01257923
RMSD	0
Energy Score	-56. 659447
vdw:	- 31. 582424
es:	-25. 077021

2-[4-(3-hydroxyaminocarbonylphenyl)phenyl]aminoacetic

4)

Name	ZINC02912978
RMSD	0
Energy Score	-55. 980484
vdw:	- 23.972197
es:	-32.008289

2-[3-carboxy-4-(3- carboxypropylamino)phenyl]sulfonylaminobenzoic

5)

Name	ZINC02788645
RMSD	0
Energy Score	-54. 718060
vdw:	- 28.874233
es:	-25.843826

2-[4-(carboxymethoxy)phenyl]thiazolidine-4-carboxylic

- Lead like top 10 ligands

1)

Name	ZINC00969372
RMSD	0
Energy Score	-56.777107
vdw:	- 35.822250
es:	-20.954855

2-[4-oxo-2-(4-tert-butylcyclohexylidene)aminoimino-thiazolidin-5-yl]acetic

2)

Name	ZINC00537457
RMSD	0
Energy Score	-52.217987
vdw:	- 34.037426
es:	-18.180559

2-(4-styrylpiperazinyl)carbonylaminopropanoic

3)

Name	ZINC01521178
RMSD	0
Energy Score	-50.931358
vdw:	- 31.497229
es:	-19.434132

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3-hydroxy-2-BLAHylamino-propanoic

4)

Name	ZINC00215106
RMSD	0
Energy Score	-50.759781
vdw:	- 26.026064
es:	-24.733717

5-[(3-carbamoyl-4-ethyl-5-methyl-2-thienyl)amino]-5-oxo-pentanoic

5)

Name	ZINC01068949
RMSD	0
Energy Score	-50.670303
vdw:	- 30.232044
es:	-20.438257

2-[4-(3-amino-2-cyano-3-thioxo-prop-1-enyl)phenoxy]acetic

- Fragment like top 10 ligands

1)

Name	ZINC02458587
RMSD	0
Energy Score	-47.771179
vdw:	- 26.791307
es:	-20.979874

5-[(5-amino-3-pyridyl)]thiophene-2-carboxylic

2)

Name	ZINC00874633
RMSD	0
Energy Score	-47.692165
vdw:	- 27.364004
es:	-20.328161

5-(4-chlorophenyl)isoxazole-3-carboxylic

3)

Name	ZINC00173374
RMSD	0
Energy Score	-46.571960
vdw:	- 26.905027
es:	-19.666931

5-(4-chlorophenyl)-2-Hpyrazole-3-carboxylic

4)

Name	ZINC01034281
RMSD	0
Energy Score	-46.357246
vdw:	- 27.482958
es:	-18.874289

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4-BLAHylbenzoic

5)

Name	ZINC02237034
RMSD	0
Energy Score	-46.113373
vdw:	- 20.564249
es:	-25.549124

2-(sulfanylmethyl)-1H-benzoimidazole-5-carboxylic

- DOCK result of inhibitor (5phenyl1,2,5thiadiazolidin3 ONE 1,1dioxide) with PTP1B:

Name	Inhibitor.pdb
RMSD	4.87387
Energy Score	-31.339895
vdw:	- 31.339895
es:	0.000000

- Top 5 ligands from all classes of ligands

1)

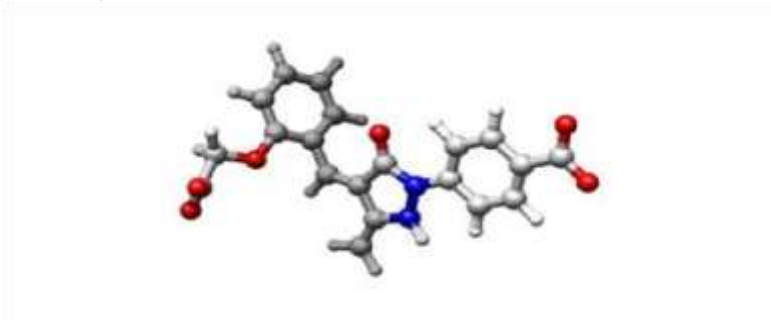


Figure 6 ZINC01001250

Name	ZINC01001250
RMSD	0
Energy Score	-59.343987
vdw:	-30.486544
es:	-28.857441

4-[[4-[(2-carboxymethyloxyphenyl)methylidene]-3-methyl-5-oxo-1H-pyrazolyl]]benzoic

2)

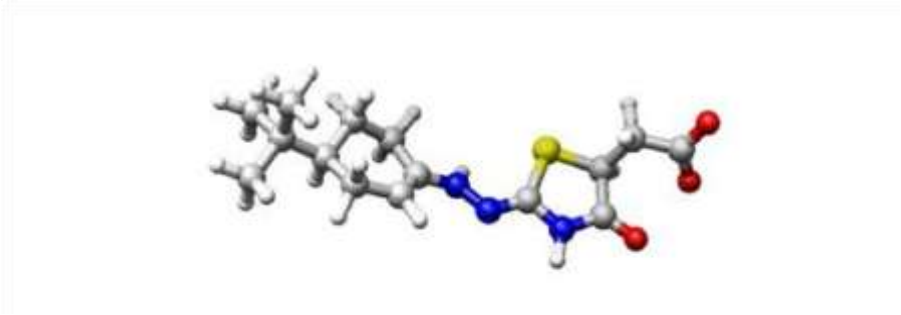


Figure 7 ZINC00969372

Name	ZINC00969372
RMSD	0
Energy Score	-56.777107
vdw:	-35.822250
es:	-20.954855

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2-[4-oxo-2-(4-tert-butylcyclohexylidene)aminoimino-thiazolidin-5-yl]acetic

3)

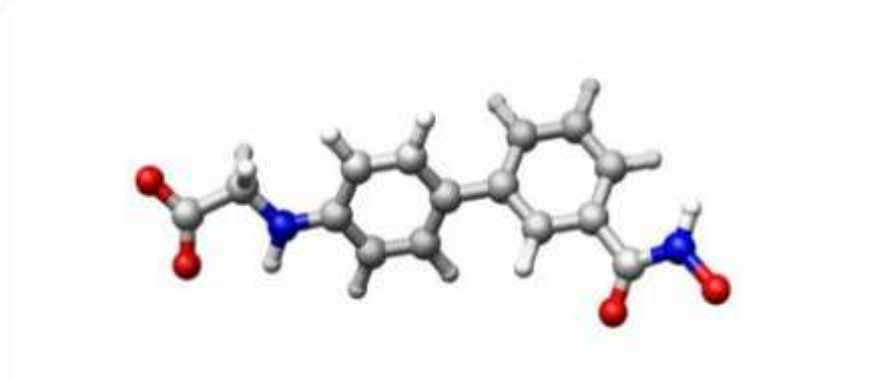


Figure 8 ZINC01257923

Name	ZINC01257923
RMSD	0
Energy Score	-56.659447
vdw:	-31.582424
es:	-25.077021

2-[4-(3-hydroxyaminocarbonylphenyl)phenyl]aminoacetic

4)

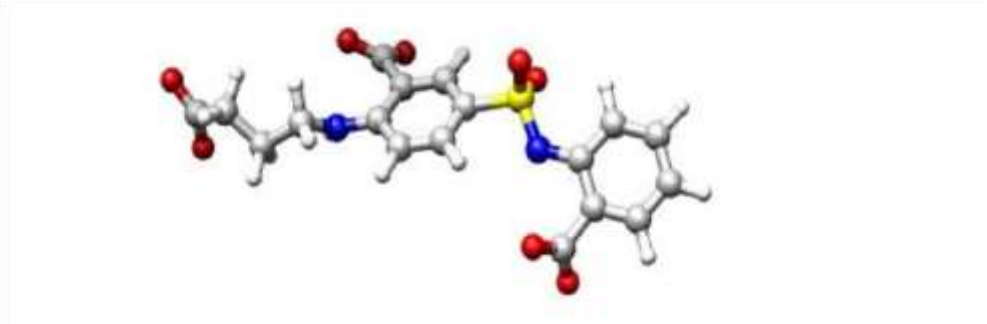


Figure 9 ZINC02912978

Name	ZINC02912978
RMSD	0
Energy Score	-55.980484
vdw:	-23.972197
es:	-32.008289

2-[3-carboxy-4-(3-carboxypropylamino)phenyl]sulfonylaminobenzoic

5)

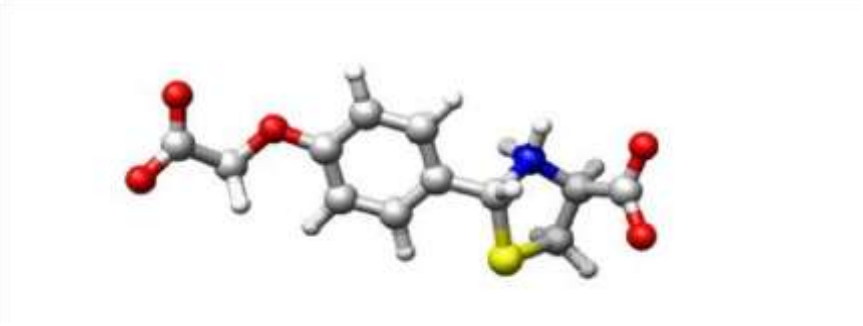


Figure 10 ZINC02788645

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Name	ZINC02788645
RMSD	0
Energy Score	-54.718060
vdw:	-54.718060
es:	-25.843826

2-[4-(carboxymethoxy)phenyl]thiazolidine-4-carboxylic

AbouT 41,67,243 ligand molecules of various chemical properties were screened by DOCK program and there are quite good number of ligand molecules were surpassing the specific competitive inhibitor 5-PHENYL-1,2,5-THIADIAZOLIDIN-3-ONE 1,1DIOXIDE in terms of energy score consisting of van der Waals and electrostatic components. These ligands, especially belonging to drug like, chemical class of Zinc database are putatively better ligands for PTP1B inhibition, th ough biochemical experimental confirmation of them is must.

This project was aimed at finding novel lead molecules for the selective competitive inhibition of PTP1B pro tein, an important protein that plays crucial role in the insulin resistance and obesity. The X ray crystal str ucture (resolution 1.80 Angstrom) of PTP1B along with specific inhibitor (5 phenyl1,2,5thiadiazolidin3ONE 1,1dioxide) (PDB code 2BGE) was considered as receptor molecule after removing all water molecules and 5phenyl1,2,5thiadiazolidin3ONE 1,1dioxide.

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