The Inhibition of the Glycogen Synthase Kinase 3β (GSK3β) via Computational Drug Screening

Nada Mohamed[(a)], Mostafa Youssef[(b)], Anwar Abdelnasser [(c)]

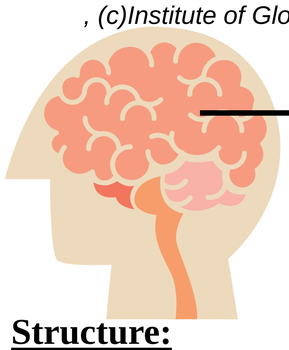
(a)Biotechnology Department.

(b)Department of Mechanical Engineering, The American university in Cairo, AUC Avenue, P.O. Box 74, New Cairo 11835, Egypt

, (c)Institute of Global Public Health, The American university in Cairo, AUC Avenue, P.O. Box 74, New Cairo 11835, Egypt

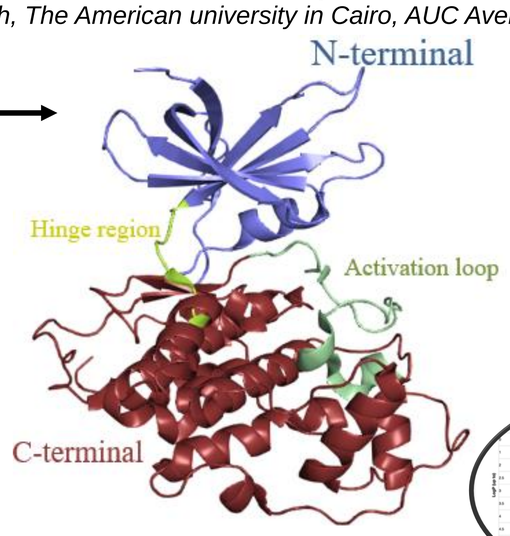
Introduction:

Abnormal phosphorylation of kinases such as GSK3, causes the initiation of neurodegenerative diseases. Once onset of the symptoms , it can not be reversed. Not only neurodegenerative disorders, However, malignant tumors and diabetes.GSK3β was highly implicated in the processes , and our target is its inhibition.



Structure:

- Serine/threonine kinase.
- Has two main isoforms, alpha and beta.
- 420 Residues.

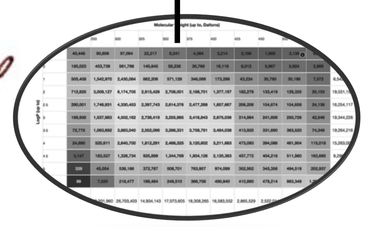


GSK3β

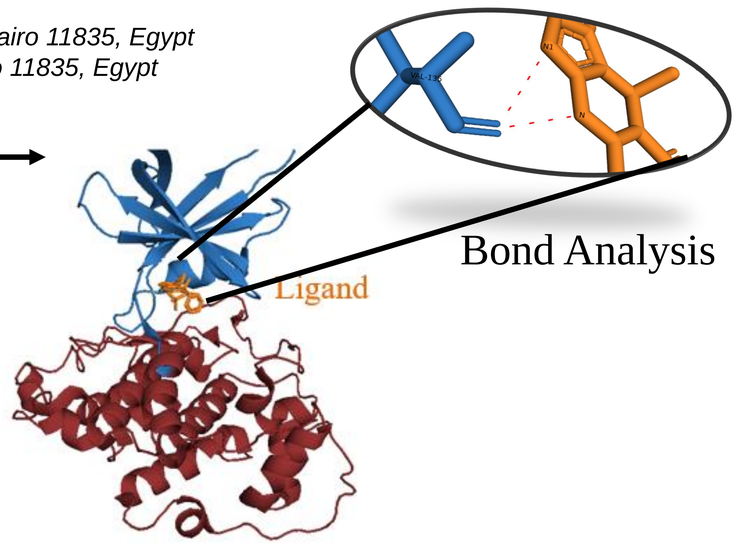
Choosing the Best protein

Protein preparation

Streamlining using inhouse Python utilities



ZINC 15 drug Library



Molecular Docking of Ligands with GSK3β

Bond Analysis

Molecular Docking

Protein Preparation:

The Protein itself is a Dimer of A and B chains. Before molecular docking potential binding pockets are searched using a F pocket software . Each monomer contained 25 binding pocket while both dimers together showed 60 binding pockets.

Each pocket should be tested for its activity whether agonist or antagonist to determine the activity.

Benchmarking:

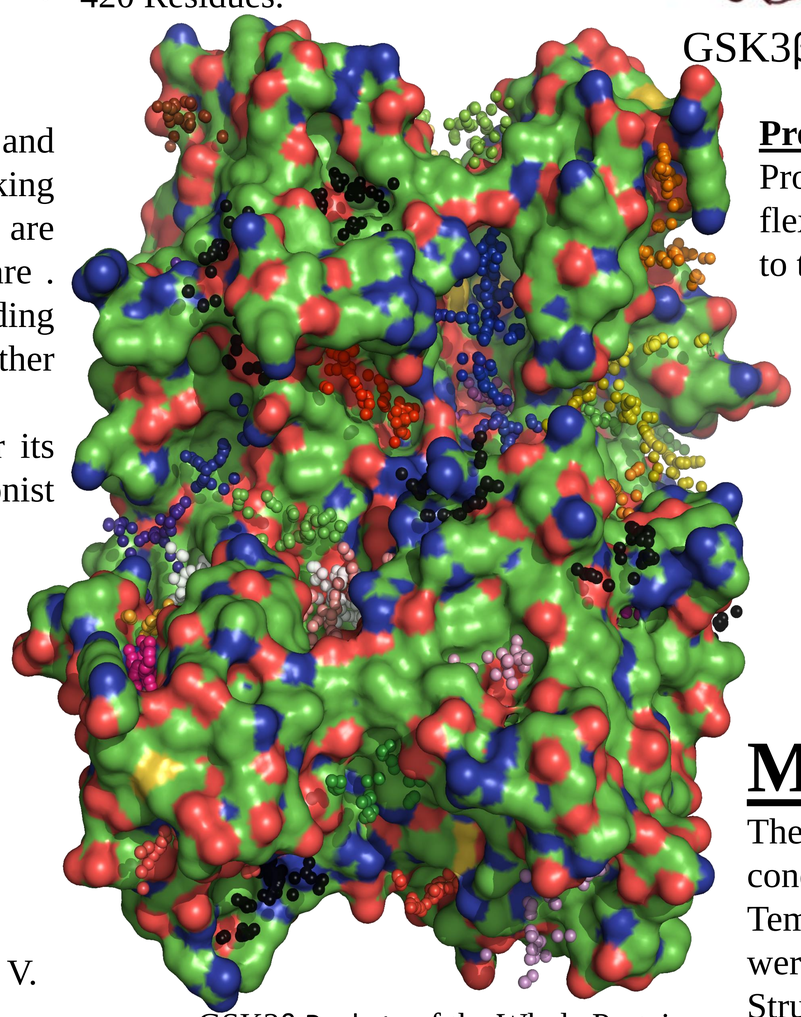
- Of Software and docking study using different software and previously reported inhibitors.

Computational Model:

- GSK3β – form PDB.
- ZINC 15 & chEMBL libraries.
- GROMACS
- VMD

Software:

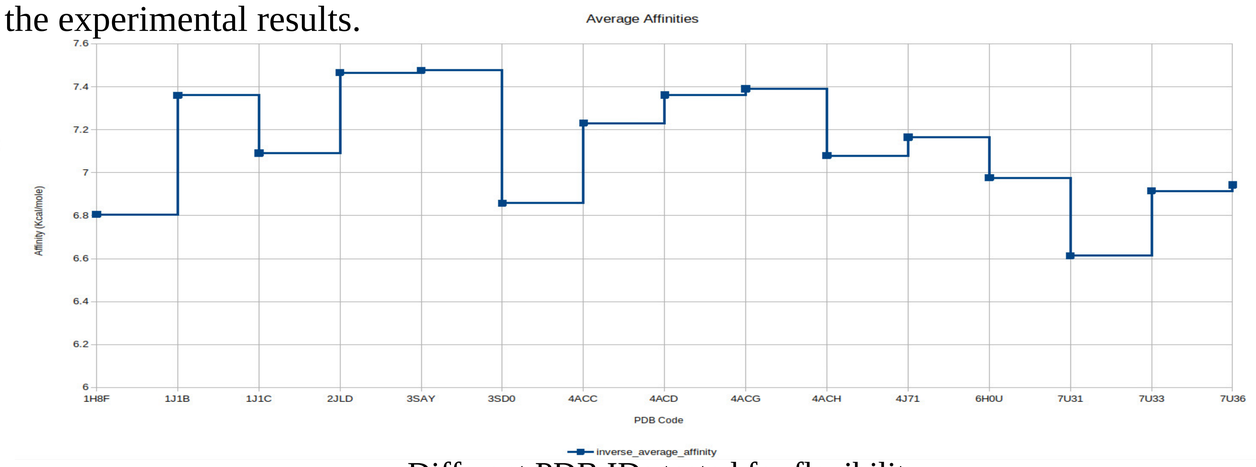
- Docking Using Autodock Vina V. 1.5.7. *(1,2)*
- Visualization Pymol *(3)*,.



GSK3β Pockets of the Whole Protein

Protein Selection:

Protein selection criteria was strictly done to ensure the selection of the most flexible and complete protein in order to get the most accurate results compared to the experimental results.



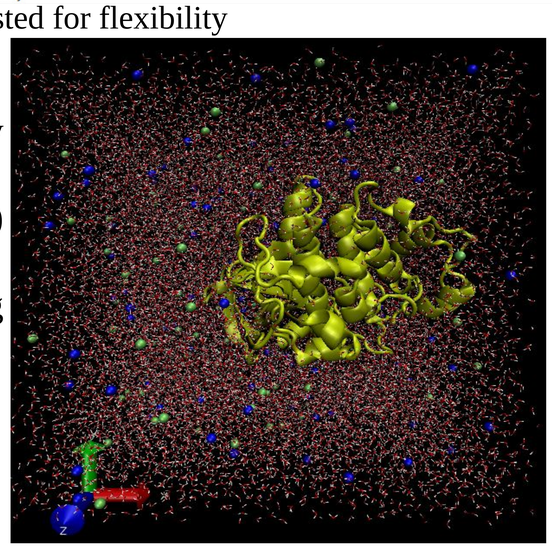
Different PDB IDs tested for flexibility

Molecular Dynamics

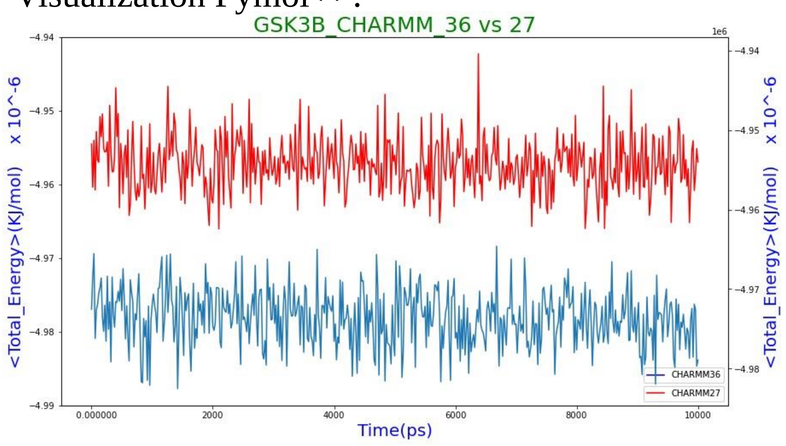
The Structure stability under normal body conditions of

Temperature (300K) and salt concentration (0.15) were tested.

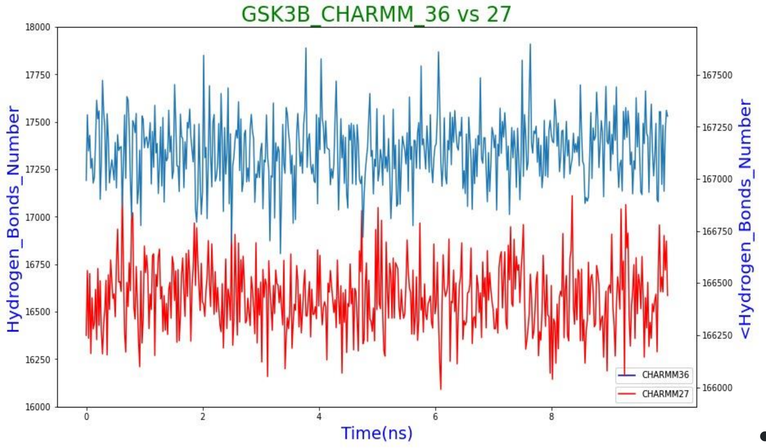
Structure showed perfect stability using CHARMM 36 Force Field package.



GSK3β within normal salt conc. And normal temp. pictured using GROMACS



Total Energy Analysis under different salt conc.



Hydrogen Bonds Analysis under different salt conc

Model Strength:

- Our model is successfully able to reproduce same results as the previously published inhibitors.

Protein Stability:

Upon changing salt concentration protein showed good stability via testing both total energy and hydrogen bonds.

Future Trend:

- Top hits will then be filtered to find the best possible **Leads** which will be then tested for Molecular Dynamics and further enter clinical studies in order to find the best possible drugs commercially available for patients to use.

Acknowledgment

- SSE Dean`s Graduate research Grant.

•References:

1.J. Eberhardt, D. Santos-Martins, A. F. Tillack, and S. Forli. (2021). AutoDock Vina 1.2.0: New Docking Methods, Expanded Force Field, and Python Bindings. Journal of Chemical Information and Modeling.

2.O. Trott, A. J. Olson, AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading, Journal of Computational Chemistry 31 (2010) 455-461

3.The PyMOL Molecular Graphics System, Version 2.0 Schrödinger, LLC.

4. Sivaprakasam P, Han X, Civiello RL, Jacutin-Porte S, Kish K, Pokross M, Lewis HA, Ahmed N, Szapiel N, Newitt JA, Baldwin ET, Xiao H, Krause CM, Park H, Nophsker M, Lippy JS, Burton CR, Langley DR, Macor JE, Dubowchik GM. Discovery of new acylaminopyridines as GSK-3 inhibitors by a structure guided in-depth exploration of chemical space around a pyrrolopyridinone core. Bioorg Med Chem Lett. 2015 May 1;25(9):1856-63. doi: 10.1016/j.bmcl.2015.03.046. Epub 2015 Mar 24. PMID: 25845281.