ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 12, Dec 2022

Mitogen and Stress Triggered Protein Kinase Inhibitor Molecular Docking Studies for Cardiovascular Disease

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Abstract
The term "cardiovascular disease" covers a wide range of illnesses, from peripheral vascular disease to coronary artery disease, that have an impact on the heart and blood arteries of the body. The growth factor-stimulated serine/threonine kinase known as MSK1 is involved in the control of gene transcription and the activation of pro-inflammatory cytokines. One polypeptide, MSK1, has two distinct protein kinase domains, making it a dual kinase. at 2.0 A and 2.5 A resolutions, we report the active conformation of the crystal structures of its C-terminal kinase domain in apo form and in association with a nonhydrolyzable ATP analogue. In this ework the ligand Phospho amino phosphoric acid adenylate ester has been chosen to conduct the docking investigations. These substances have the ability to slow the progression of cardiovascular disease, and the structures of their ligands have been identified and reduced. This reduced structure was placed through high-throughput virtual screening against the protein from PDB (3KN5), and the best-scoring ligands were chosen for induce fit docking. For various postures, the interactions between the ligands and proteins were seen. It was investigated how well the protein interacted with the final docking score. Computer-based analysis this protein is used to prevent cardiovascular disease.

Keywords: Cardiovascular disease; Molecular docking; Virtual screening; Ligand

Introduction

The term "cardiovascular disease" covers a wide range of illnesses, from peripheral vascular disease to coronary artery disease, that have an impact on the heart and blood arteries of the body [1, 2, 3]. By depositing on inflamed portions of the inner wall of the artery, persistently elevated cholesterol levels may contribute to the development of cardiovascular disease [4, 5]. When cholesterol and other lipids accumulate, blood flow to the afflicted parts of the body may ultimately be restricted or blocked [6, 7, 8, 9]. For instance, the development of a plaque in the inner walls of an artery in the legs may result in peripheral vascular disease, but a heart attack may result from the same condition [10, 11, 12]. Many people consider chest discomfort to be a typical sign of cardiovascular illness. Cough, exhaustion, light-headedness,

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 12, Dec 2022

backache, and/or an indigestion-like sensation are other symptoms [13, 14]. Cyanosis, palpitations, altered levels of awareness, perspiration, and shortness of breath, chills, nausea, and vomiting [15, 16, 17].

Inhibitor of P38-Mitogen-And Stress-Activated Protein Kinase Extracellular Signal, Regulated Kinase Has Four Different Families [18, 19, 20]. P38 MSAPK, ERK5 Kinase, and C-Jun N-Terminal Kinase. Proline-direct serine threonine-specific protein kinase, or MSAPK, is a class of enzyme [21, 22]. The Mitogen- and Stress-Activated Protein Kinase (MSAPK) Kinase Family is essential for the regulation and transmission of intracellular signals. Chains A and B have the PDB (Protein Data Bank) number 3KN5. Natural ligand is phosphoaminophosphonic acid adenylate, according to Resolution 2.40[23, 24, 25].

This work examines the use of the MASPK inhibitor, a protein kinase that is activated by mitogens and stress, to dock various compounds and analyse ligand binding.

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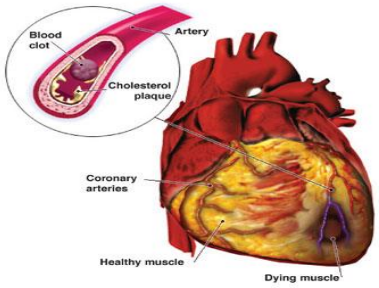

Fig.1 Cardiovascular disease

Materials and methods

Retrieve protein

The native ligand for Mitogen-And Stress Activated Protein Kinase Inhibitor (MASPK) is phosphoamino phosphonic acid adenylate easter. Its PDB (Protein Data Bank) ID is 3KN5,Chains A,B, Resolution 2.40.A file in PDB format was downloaded.

Ligand choice

The pubchem database is used to download the ligand structures. Several ligands are chosen.

Molecular Docking

Preparation of proteins

The capability for making proteins has two parts: preparation and refining. Preparation that guarantees chemical accuracy. Neutralizes side chains that are far from the binding cavity and don't take part in salt bridges by adding hydrogen to them. The co-crystallized complex's refining influence is minimized, reorienting side-chain hydroxyl groups and preventing possible steric collisions.

Preparation of ligands

Two techniques are used to decrease the ligand structures. Impact minimization employs two methods for minimizing: steepest descent and conjugate gradient, which run for 500–1000

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 12, Dec 2022

cycles in ligprep minimization and ligprep create tautomers and conformers for single ligands. Both techniques minimize the structures using the OPLS force field.

Screening and fit docking-induced

To find the unique lead molecule to treat cardiovascular disease, 20 compounds were screened against 3KN5.The relevant ligand is used as a guide to bind the target 3KN5 protein in the active site. Compounds are chosen for Induced Fit Docking based on the Glide energy and Docking Score from HTVS results.

Induced fit docking

The induced fit docking procedure is automated via a Python script that Schrodinger has created. The Maestro interface for this Python script allows one to define the structures and provide parameters for many options. Restricted receptor reduction. For each protein-ligand complex pose, the receptor and ligand are minimized in the first place. Each pose of the receptor now exhibits an induced fit to the structure and conformation of the ligand. Each protein or ligand complex structure should be redocked smoothly within a certain energy range of the lowest-energy structure. Using default Glide parameters, the ligand is now carefully docked into the induced-fit receptor shape.

Results and discussion

Protein selection

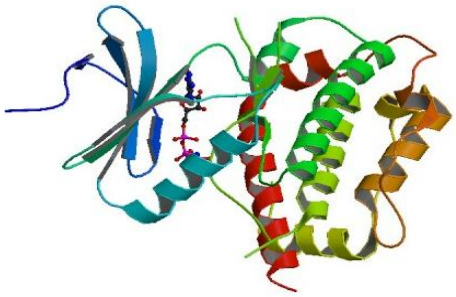

Fig.2 Mitogen and Stress Induced Protein Kinase Structure from PDB (3KN5)

Ligand structure utilized in docking studies

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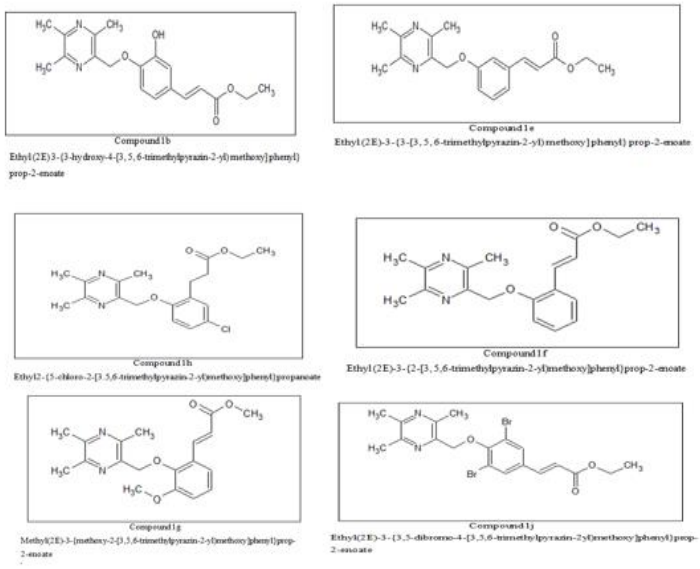

Fig.3 Several chemical structures were found in the pubchem database

Table.1 Inhibitors of Mitogen Stress Activated Protein Kinase High throughput Virtual Screening Findings

S.No	Ligands	Amino acid residues	Hydrogen bond Interaction	Distance	Docking score	Glide energy
1	1b	ASP565	O-H..N	1.70	-10.198	-75.92
2	1e	ASP544	O-H..N	1.70	-9.642	-74.64
3	1f	ASP549	O-H..N	1.95	-9.906	-74.05
4	1g	LYS546	O-H..N	2.91	-9.980	-72.77
5	1h	GLU499	O-H..N	1.76	-8.057	-70.57
6	1j	LEU501	O-H..N	3.10	-9.312	-69.65

The best docking score, 10.198, was achieved by the ligand 1b Ethyl (2e) 3-3-Hydroxy-4-[3, 5, 6-Trimethylpyrazin-2-Yl) Methoxy] Phenyl Prop-2-Enoate. Mitogen Stress Activated Protein Kinase is inhibited.

Visualization of a protein ligand in pymol

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 UGC CARE Listed (Group -I) Journal Volume 11, Iss 12, Dec 2022

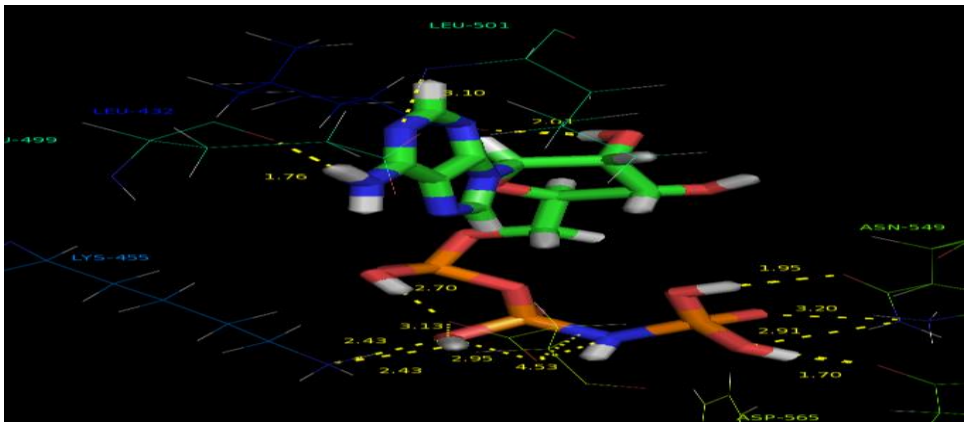

Fig.4 Mitogen Stress Induced Protein Kinase Interactions with the Original Ligand Ethyl (2e) (2e) 4-[3, 5, 6-Trimethylpyrazin-2-Yl) Methoxy]-3,3,3-Hydroxy-4-[3, 3, 3] Phenyl Prop-2-Enoat

Conclusion

The original ligand present in MSAPK has a docking score of -10.1983 kcal/mol in a comparative docking investigation between other similar series of phosphoamino phosphoric acid adenylate ester. Ethyl(2E)-3,5,6-trimethylpyrazin-2yl)methoxy]phenylprop-2-enoate has a docking score of -7.2173 kcal/mol and a glide energy of -55.0576 kcal/mol. The active site residue ASP 565 is the single point of contact between the protein and its initial ligand. The original ligand, which is present in the Mitogen and Stress Activated Protein Kinase, and the docking score are both better in this interaction. The current research thus proposes that more in vivo and in vitro testing for the compounds might be done to demonstrate that it is an effective inhibitor.

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