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Research Article

MOLECULAR DOCKING ANALYSIS OF NATRIURETIC PEPTIDE RECEPTOR-C TOWARDS THE DESIGN OF POTENTIAL ATRIAL FIBRILLATION INHIBITORS

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ABSTRACT

Atrial fibrillation (AF) stands the most widely recognized kind of clinical arrhythmia. Right now accessible anti-Atrial Fibrillation drugs are restricted by just moderate adequacy and an unfavorable safety profile. There is a perceived requirement for enhanced antiarrhythmic agents including activities that are specific for the fibrillating atrium. Therefore, it is of interest to design an appropriate medication for the disease Atrial Fibrillation using Molecular Docking techniques through protein-ligand interaction analysis. Hence, we document the Molecular docking analysis of natriuretic peptide receptor-C towards the design of potential Atrial Fibrillation inhibitors (Aprindine, Inclacumab, and Budiodarone) with the most favorable binding features for further consideration. This study centers around the process for drug discovery finding appropriate medication for the disease Atrial Fibrillation by Molecular Docking technique through protein-ligand interaction. The examination uncovered that out of a couple of molecules that were chosen as target, three of them were seen as most reasonable having the least energies compared to the other molecules. Aprindine, which is utilized in arrhythmia patients as a cardiac depressant. Inclacumab, which is an investigational sedate utilized in trials to look at the treatment and evasion of Myocardial Infarction, Peripheral Arterial Disease (PAD), and Coronary Heart Disease. Budiodarone, which is an antiarrhythmic drug at present in clinical preliminaries identified with amiodarone.

INTRODUCTIION

Atrial fibrillation (AF) is a highly prevalent form of arrhythmia seen by the cardiologists. Over 33 million people worldwide are affected by it [1] which makes it the number one cause of hospitalization for arrhythmias [2-4]. The rate of prevalence increases as the age advances and so does its associated effects, like cardiac arrest [5]. AF is connected with poor lifestyle and increased mortality along with morbidity [6]. Antiarrhythmic drugs have been in use to treat AF for a long period [7], but these antiarrhythmic agents have limited drug efficacy and have a high risk of serious difficulties such as ventricular pro-arrhythmia [8-10]. Many drugs have shown limited success in persistent AF patients [11]. AF is often related to cardiac disease and cardiac/non-cardiac comorbidity. The most common comorbidities are high blood pressure, cardiac arrest, diabetes, and obesity [12-14]. It is observed that one in three patients have no less than three related comorbidities, along with a low percentage of AF patients experiencing presumably no heart-related disease or comorbidities, although the studies in practice do not offer any information on the degree of diagnostic testing to eliminate all risk factors and comorbidities that are associated with AF at present [15].

Therefore, it is of interest to design an appropriate medication for the disease Atrial Fibrillation using Molecular Docking techniques through protein-ligand interaction analysis.

METHOD

Selection of Target Protein

The process of Target-identification plays a vital function in drug discovery. The identification of targets can be performed by direct genetic interactions, biochemical methods, and computational interpretation. Computational interpretation was used in this case by finding a target protein based on its stability and sequence length. 1YK0 (natriuretic peptide receptor-C

complexed with atrial natriuretic peptide) was selected. The target has Resolution: 2.40 Å, R-Value Free: 0.284, R-Value Work: 0.240, R-Value Observed: 0.242 by X-Ray Diffraction. The file for the 3D structure was downloaded in PDB format from RCSB PDB for usage in molecular docking later.

Selection of Drug Target Molecules

The target molecules were selected by finding out the ongoing investigational drugs for Atrial Fibrillation from Drug Bank and Pub Chem. Drug Bank is a richly annotated resource that blends extensive drug statistics with thorough drug target information with comprehensive drug action information. Drug Bank has been broadly used to encourage drug interaction prediction, in silico drug target discovery, drug docking or screening, drug design, general pharmaceutical instruction, and metabolism prediction. Pub Chem is a chemical data asset at the U.S. National Center for Biotechnology Information (NCBI). Since its dispatch in 2004, Pub Chem has developed into a key information base that serves the biomedical exploration networks in numerous territories, including chem-informatics, synthetic biology, drug discovery, and medicinal chemistry. The two stages permit to scan for drug molecules that are either affirmed, investigational, pulled back, or in test stages. A list of various drug molecules was made and their 3D structural file was downloaded in PDB format for interaction with target protein while molecular docking procedure.

Target Protein-Ligand Docking

Docking is generally utilized for the investigation of bio-molecular associations and components, and it is applied to structure-based drug design. The techniques are sufficiently quick to allow virtual screening of ligand libraries containing countless compounds. Molegro Virtual Docker is used to execute interactions. Molegro Virtual Docker is used in protein-ligand docking that permits us to complete docking simulations in a completely coordinated computational package. MVD requires a three-dimensional structure of both protein and ligand (normally got from X-Ray/NMR examinations or homology modeling). MVD performs adaptable docking of ligands, so the perfect geometry of the given ligand is resolved during the docking.

After opening MVD the structure of the protein was retrieved from the saved PDB file followed by selecting File and Importing Molecules from the MVD window. MVD supports SDF, PDB, Mol2, and MVDML. Some structures have explicit hydrogens assigned and contain information about bond types and bond orders. The last tab in the import dialog (Warnings (0)) shows potential problems with the structure file. In this case, no warnings were reported. After clicking on the Import button the protein and the ligand appeared in the Visualization Window. The protein category was hidden to inspect the imported ligand in the Workspace Explorer. The potential binding site for the protein was narrowed down by selecting Preparation then Detect Cavities. After pressing the OK button, the system predicted a binding site in the center of the protein. The Docking Wizard was invoked by selecting Docking Wizard. The docking progress was observed in the Batch job dialog of Molegro Virtual Docker. The total number of poses were studied and noted. After the completion of the docking process, the poses were visualized one by one and the residues were recorded.

Forming Tabular Data

The molecules were all docked one by one and the poses along with the hydrogen bonds and residues were recorded in a tabular form. Below is the data obtained,

Name- Aprindine

Drug Bank Accession number- DB01429

Table 1 Aprindine (DrugBank Accession Number-DB01429)

Name	Energy	H-Bonds	Residues
Aprindine	-260.879	1	Arg 166
	-234.813	0	NA
	-234.485	0	NA
	-233.32	0	NA
	-227.034	0	NA

Name- Melperone

DrugBank Accession number- DB09224

Table 2 Melperone (DrugBank Accession number- DB09224)

Name	Energy	H-Bonds	Residues
Melperone	-68.0672	0	NA
	-57.2653	0	NA
	-56.3162	0	NA
	-55.7485	2	Glu 193, Lys 195
	-53.0174	3	Glu 193, Lys 195, Thr 194

Name- Inclacumab

DrugBank Accession number- DB12246

Table 3 Inclacumab (DrugBank Accession Number-DB12246)

Name	Energy	H-Bonds	Residues
Inclacumab	-243.473	3	Thr 171, Cys 168, Asn 167
	-239.176	1	Glu 165
	-228.791	1	Gln 16
	-223.863	1	Thr 171
	-219.994	1	Thr 171

Name- Bopindolol
DrugBank Accession number- DB08807

Table 4 Bopindolol (DrugBank Accession Number-DB08807)

Name	Energy	H-Bonds	Residues
Bopindolol	-83.0177	3	Ser 224, Thr 221, Arg 223
	-81.2383	1	Arg 223
	-78.8256	2	Thr 221, Ser 218
	-75.9807	2	Arg 223, Ser 224
	-75.3	5	Arg 223, Ser 224, Ser 224, Ser 218, Thr 221

Name- Idraparinux
DrugBank Accession number- DB06406

Table 5 Idraparinux (DrugBank Accession Number-DB06406)

Name	Energy	H-Bonds	Residues
Idraparinux	-64.2783	4	Ser 224, Arg 223, Arg 223, Asp 220
	-58.1842	3	Ser 224, Arg 223, Arg 223
	-55.8842	4	Thr 221, Ser 218, Ser 218,Glu 193
	-54.7673	1	Ser 218
	-52.9268	4	Arg 223, Ser 224, Ser 224, Asp 220

Name- Budiodarone
DrugBank Accession number- DB05519

Table 6 Budiodarone (DrugBank Accession Number-DB05519)

Name	Energy	H-Bonds	Residues
Budiodarone	-186.271	9	Asp 261, Arg 223, Asp 220, Asp 220, Ser 219, Ser 251, Arg 259, Arg 259, Val 90
	-181.933	4	Gly 260, Arg 259, Asp 220, Asp 220
	-172.325	13	Arg 259, Ser 251, Ser 250, Ser 250, Ser 250, Asn 248, Asn 248, Asn 248, Asn 248, Glu 306, Glu 306, Glu 306,Arg 26
	-169.754	9	Arg 26, Ser 19, Glu 306, Glu 306, Asn 248, Asn 248, Asn 248, Ser 250, Ser 251
	-166.306	7	Arg 259, Arg 259, Arg 259, Ser 219, Ser 251, Ser 251, Asn 248

Name- Odiparcil
DrugBank Accession number- DB06609

Table 7 Odiparcil (DrugBank Accession Number- DB06609)

Name	Energy	H-Bonds	Residues
Odiparcil	-70.4151	2	Ser 224, Ser 218
	-72.7168	1	Ser 218
	-63.5936	2	Ser 224, Ser 218
	-62.9752	2	Asp 261, Arg 223
	-68.6841	3	Arg 223, Thr 221, Ser 218

Name- Tecadenoson
DrugBank Accession number- DB04954

Table 8 Tecadenoson (DrugBank Accession Number-DB04954)

Name	Energy	H-Bonds	Residues
Tecadenoson	-73.2797	1	Arg 223
	-72.0901	2	Ser 224, Thr 221
	-71.2974	2	Ser 218, Thr 221
	-66.5489	4	Ser 218, Ser 224, Thr 221, Thr 221
	-65.4846	2	Arg 223, Ser 224

Name- Danegaptide
DrugBank Accession number- DB11821

Table 9 Danegaptide (DrugBank Accession Number-DB11821)

Name	Energy	H-Bonds	Residues
Danegaptide	-77.6317	2	Ser 224, Asp 261
	-69.1495	1	Thr 221
	-72.1915	2	Ser 218, Thr 221
	-70.1611	2	Leu 197, Thr 194
	-70.0766	2	Arg 259, Asp 220

Name- Piboserod
DrugBank Accession number- DB04873

Table 10 Piboserod (DrugBank Accession Number-DB04873)

Name	Energy	H-Bonds	Residues
Piboserod	-68.0613	2	Thr 221, Ser 218
	-66.7869	2	Glu 193, Thr 194
	-66.3479	3	Lys 195, Thr 194, Glu 193
	-66.0444	4	Thr 194, Glu 193, Lys 195, Thr 221
	-65.315	1	Thr 221

Name- Azimilide
DrugBank Accession number- DB04957
Table 11 Azimilide (DrugBank Accession Number-DB04957)

Name	Energy	H-Bonds	Residues
Azimilide	-91.9381	3	Leu 197, Ser 218, Thr 221
	-86.5544	3	Thr 221, Arg 223, Ser 218
	-81.4192	1	Ser 224
	-83.5602	2	Thr 221, Ser 218
	-77.3429	3	Arg 223, Thr 221, Ser 218

Name- Tedisamil
DrugBank Accession number- DB06200
Table 12 Tedisamil (DrugBank Accession Number-DB06200)

Name	Energy	H-Bonds	Residues
Tedisamil	-101.651	7	Ser 128, Ser 128, Thr 221, Thr 221, Arg 223, Ser 224, Ser 224
	-96.8298	2	Arg 223, Arg 223
	-89.8778	7	Thr 221, Thr 221, Thr 221, Ser 224, Ser 224, Ser 218, Ser 218
	-87.083	4	Ser 224, Ser 224, Thr 221, Thr 221
	-81.3887	3	Ser 224, Arg 223, Arg 223

Name- Indobufen
DrugBank Accession number- DB12545
Table 13 Indobufen (DrugBank Accession Number-DB12545)

Name	Energy	H-Bonds	Residues
Indobufen	-63.9552	4	Arg 259, Arg 259, Ser 218, Ser 224,
	-65.3497	1	Arg 223
	-63.8802	3	Ser 224, Ser 218, Thr 221,
	-67.1712	0	NA
	-59.5297	1	Asp 220

Name- Pilsicainide
DrugBank Accession number- DB12712
Table 14 Pilsicainide (DrugBank Accession Number-DB12712)

Name	Energy	H-Bonds	Residues
Pilsicainide	-98.1289	4	Ser 224, Asp 220, Thr 221, Ser 218
	-94.7741	4	Ser 224, Thr 221, Glu 193, Glu 193
	-89.7436	1	Thr 221
	-85.7309	4	Thr 221, Ser 218, Glu 193, Lys 195
	-77.4761	4	Asp 261, Asp 261,
			Arg 223, Ser 224

Name- Fimasartan
DrugBank Accession number- DB09279
Table 15 Fimasartan (DrugBank Accession Number-DB09279)

Name	Energy	H-Bonds	Residues
Fimasartan	-60.3297	0	NA
	-55.8163	0	NA
	-58.1977	3	Thr 221, Ser 218, Ser 218
	-53.1962	0	NA
	-51.0384	0	NA

Name- Mibenratide
DrugBank Accession number- DB15195
Table 16 Mibenratide (DrugBank Accession Number-DB15195)

Name	Energy	H-Bonds	Residues
Mibenratide	-90.2693	3	Thr 221, Thr 221, Ser 218
	-88.0874	3	Thr 221, Thr 221, Ser 218
	-84.0519	3	Thr 221, Thr 221, Ser 218
	-80.2662	3	Thr 221, Thr 221, Ser 218
	-73.1078	3	Thr 221, Thr 221, Ser 218

Name- Quinacrine
DrugBank Accession number- DB01103
Table 17 Quinacrine (DrugBank Accession Number-DB01103)

Name	Energy	H-Bonds	Residues
Quinacrine	-65.384	2	Thr 221, Ser 224
	-65.9906	4	Thr 221, Thr 221, Ser 218, Ser 224
	-61.9212	2	Thr 221, Glu 193
	-61.9364	0	NA
	-58.8375	3	Thr 221, Thr 221, Ser 218

Name- Amrubicin
DrugBank Accession number- DB06263
Table 18 Amrubicin (DrugBank Accession Number-DB06263)

Name	Energy	H-Bonds	Residues
Amrubicin	-70.8786	2	Arg 223, Ser 224
	-72.5829	3	Arg 259, Ser 224, Asp 220
	-68.4329	1	Ser 224
	-68.2113	2	Arg 259, Ser 224
	-69.3214	1	Ser 224

Name- Benzbromarone
DrugBank Accession number- DB12319

Table 19 Benzbromarone (DrugBank Accession Number-DB12319)

Name	Energy	H-Bonds	Residues
Benz-bromarone	-68.8526	3	Lys 262, Ser 251, Arg 259
	-68.0469	2	Ser 224, Thr 221
	-64.9393	1	Ser 224
	-66.7262	6	Ser 219, Ser 219, Ser 218, Asp 220, Thr 221, Leu 197
	-62.7049	6	Thr 221, Thr 221, Ser 218, Ser 224, Ser 224, Arg 223

Name- Saprisartan
DrugBank Accession number- DB01347

Table 20 Sapisartan (DrugBank Accession Number-DB01347)

Name	Energy	H-Bonds	Residues
Saprisartan	-67.3354	4	Thr 221, Thr 276, Ser 224, Ser 218
	-61.27	1	Ser 224
	-60.4604	3	Ser 218, Ser 224, Thr 221
	-59.7673	5	Arg 223, Ser 224, Thr 221, Thr 221, Ser 218
	-57.4187	1	Ser 224

Name- Tasosartan
DrugBank Accession number- DB01349

Table 21 Tasosartan (DrugBank Accession Number-DB01349)

Name	Energy	H-Bonds	Residues
Tasosartan	-96.5906	2	Ser 224, Arg 223
	-88.9027	2	Ser 224, Arg 223
	-85.0993	0	NA
	-85.6825	3	Asp 220, His 121, Ser 218
	-86.8098	2	Thr 221, Ser 218

RESULTS

The molecules with the lowest energies obtained after docking indicates of no or least protein-ligand clashes or other structural anomalies, such as high conformational strain. The energies obtained a little higher show that clashes are present between a drug molecule and protein target and hence, cannot be termed fit for usage by Atrial Fibrillation patients. According to the energies given the top three most suitable molecules/ drugs from the above-stated molecules for Atrial Fibrillation were found to be Aprindine which is used in arrhythmia patients as a cardiac depressant. Inclacumab is an investigational drug used in trials to examine the treatment and avoidance of Myocardial Infarction, Peripheral Arterial Disease (PAD), and Coronary Heart Disease. Budiodarone is an antiarrhythmic drug currently in clinical trials related to amiodarone.

DISCUSSION AND CONCLUSION

Upcoming proof suggests that antioxidants, oxidative stress, and paraoxonase may also play a part in cardiovascular diseases.[16] Similarly, atherosclerotic heart disease can also result in a heart attack or angina. The frequency and burden of Atrial Fibrillation on a global level calls for an urgent rise for investment in basic and translational research within industries, government, and academia. Important developments in research and newer translation methods are required, so that indispensable scientific challenges can be conquered, which include growing the grasp of AF mechanisms, figuring out and validating targets, creating predictive biologic and computational models, recognizing dependable biomarkers for affected person stratification and as endpoints for medical trials, preventing arrhythmia towards clearing regulatory pathways, and ensuring the reliability and reproducibility of posted data, as properly as information sharing and collaboration. We document the Molecular docking analysis of natriuretic peptide receptor-C towards the design of potential Atrial Fibrillation inhibitors (Aprindine, Inclacumab, and Budiodarone) having optimal binding features for further consideration.

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