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Docking analysis for identification of lead compound and 3d pharmacophore generation against gsk-3β involved in bipolar disorder

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Abstract: Bipolar disorder is a psychiatric illness that strikes between mania and depression, caused by both genetic and environmental factors. It is the sixth leading cause of disability worldwide and 3% of the global population suffers from this disorder. Focusing on the drugs used for psychotherapy and their associated side effects, there is a need to design and develop new anti-bipolar drugs with lesser side effects and improved efficacy. Molecular docking and pharmacophore modeling were performed to identify lead and the construction of pharmacophore triangle. One compound demonstrated best docking results that fit appropriately in the pocket of protein. In this study, an efficient compound for GSK-3B involved in bipolar disorder was identified through docking analysis. Distances were calculated among pharmacophore features like Aromatic Ring, Hydrophobic, HBD and HBA. Pharmacophore triangle was designed for three different classes that are Aromatic, HBD and HBA. This pharmacophore modeling can be useful for designing of novel drugs because this 3D pharmacophore showed best merging properties.

Keywords: GSK-3β, bipolar, docking, pharmacophore, pharmacophore triangle.

INTRODUCTION

The term bipolar signifies the polar opposites of mania and depression (Raymond 2016). Bipolar Disorder (also known as manic depressive illness) is a complex mental disorder in which the core feature is an episodic pathological mood disturbance ranging from extreme elation to severe depression marked by thinking and behavioral disturbances along with hallucinations and grandiose delusions (Craddock and Sklar 2013). Bipolar Disorder is divided into four types: Bipolar Disorder type I, Bipolar Disorder type II, Cyclothymic Disorder and Bipolar Disorder not otherwise definite. Symptoms of Mania are -euphoria, less need for sleep, talkativeness, bad-tempered, increased energy level, increased motor activity and sexual activity, aggressive nature, bad judgment. Genetic, neurochemical and environmental factors are interacting at different levels to play important role in the development of bipolar disorder (Perreira 2015). The lifetime prevalence of Bipolar disorder is 2.4% (Boland and Alloy 2013, Schmitt *et al*., 2014). The annual average suicide rate is 0.4 (Sadock and KAPLAN 2007). Males and females are equally affected by disorder, with the first episode in men usually being mania and in women usually being depression (Janney *et al*. 2014). The overall heritability of bipolar disorder is estimated to be 0.71 (Edvardsen *et al*., 2008). The risk of bipolar disorder in relatives of bipolar proband are: unrelated member have chances to get disorder is 0.5-1.5%, first degree relative 5 to 10%, and co twin 40 to 60%. Estimates of inheritance in twins are very high approximately 89% was reported in UK in 67 twin pairs (Kieseppä *et al*. 2014).

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Glycogen Synthase Kinase-3 Beta also known as GSK-3β is a therapeutic target protein involved in treating Bipolar Disorder (Rowe *et al*., 2007). GSK-3β protein is a serine-threonine kinase, belongs to a glycogen synthase kinase family. GSK-3β is a key regulator in the range of cellular processes like differentiation, growth, motility and apoptosis (Benedetti *et al*., 2013). Abnormal regulation and expression of GSK-3β leads to Bipolar Disorder (Luykx *et al*., 2010). Over expression also leads to increased apoptosis in neuronal cells that causes inflammation in cellular processes. Inhibition of GSK-3β provides neuroprotective effects.

The basic mechanism of medication involves psychotherapy, mood stabilizers like lithium and anticonvulsants. Lithium causes inhibition of GSK-3β activity directly or indirectly by competing with magnesium and by increasing phosphorylation by inhibition of protein phosphatase but lithium also causes renal failure (Benedetti *et al*., 2013).

Thus the hunt for new effective compounds is vital to minimize the effects. In the reflection of past studies, Protein-ligand docking studies were performed for Bipolar Disorder. Docking approach can be used to model interactions between a small molecule and protein at atomic level which describes the behavior of small molecule in binding site of target protein (Meng *et al*., 2011).

In drug designing, pharmacophore is considered as the largest denominator of molecular interaction features shared by active molecules. Pharmacophore features like hydrogen bond donor, hydrophobic centers, hydrogen

bond acceptor and aromatic ring centers are responsible for biological effect. A three dimensional pharmacophore specifies the spatial relationship between the group of compounds, expressed as distance ranges, angles and planes (Qing *et al*., 2014). In this study we performed molecular docking, pharmacophore modeling and pharmacophore triangle generation for the discovery of effective drugs to treat bipolar disorder.

MATERIALS AND METHODS

D structure retrieval

Retrieval of the 3D structure of GSK-3β was done through PDB (Protein Data Bank) (http://www.rcsb.org/) under accession ID 4DIT. As the structure of protein was already determined, physiochemical properties of GSK-3β including molecular weight, amino acid composition and atomic composition of GSK-3β were analyzed through ProtParam (Irshad *et al*., 2017) (http://web.expasy.org/protparam/). The 3D structure of protein was visualized and purified by using Chimera. On the basis of previous studies, various antibipolar compounds were identified, 19 ligands were chosen for docking analysis for GSK-3β. Their chemical structures are shown in table 2. PubChem (https://pubchem.ncbi.nlm.nih.gov/) was the source of deriving ligands in SDF (Spatial Data File) is the file format that is well recognized format to read, open and analyze the Chemical Structures through conventional metrics (Hood *et al*., 2015).

Molecular docking

Selected compounds were docked with GSK -3β protein using Pyrx (Dallakyan *et al*., 2015) (https://pyrx.sourceforge.io/) under the (AutoDock Vina). Protein Ligand Interaction Profiler (PLIP: https://projects.biotec.tu-dresden.de/plip-web/plip/index) was used to identify interactions of docked compounds. Different amino acids were found to be engaged in interaction of GSK-3β. Toxicity of lead compound was determined through ametSAR (Gleeson, Bravi *et al*. 2009).

Generation of Pharmacophore triangle

In present study, ligand-based pharmacophore approach was used. Pharmacophore was modeled by using Ligand Scout (http://en.bio-soft.net/3d/LigandScout.html) Software proposed in the study by (Seidel *et al*., 2017) for selected dataset compounds of GSK-3β. It created a shared feature pharmacophore using selected dataset compounds, calculated alignment and valid feature overlapping and combined all features overlapping into a shared feature pharmacophore. 3D Pharmacophore was designed to get better understanding of interaction between the receptor and ligand. Pharmacophore triangle was created to get distance between features from minimum to maximum range. Features include hydrogen bond donor, hydrophobic, aromatic ring, hydrogen bond acceptor, positively and negatively ionizable groups.

RESULTS

In this study, computer aided drug designing approach was used to design an efficient inhibitor for GSK-3β. To identify an efficient compound, docking approach was used on selected data set, identified protein-ligand interactions, generated pharmacophore; pharmacophore triangle was constructed on the basis of measured distances between pharmacophore features. Pharmacophore contained the best merging features; it can be used for future studies. Physiochemical properties of GSK-3β protein determined by ProtParam are shown in table (table 1).

Table 1: Physical properties of GSK-3β

Property	Value
Molecular Weight	43190.60
No. of amino acid residues	382
Isoelectric point(pI)	8.59
Extinction Co-efficient	38320-37820 M-1 cm -1
Instability Index	27.50
Aliphatic Index	87.54
GRAVY	-0.299

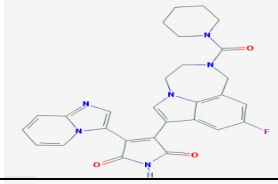
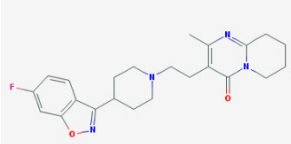
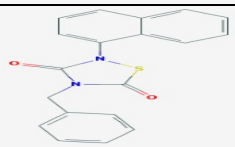
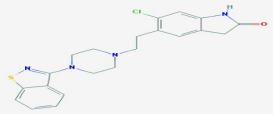
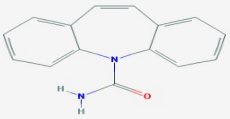
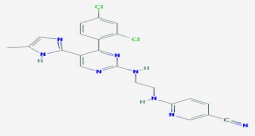
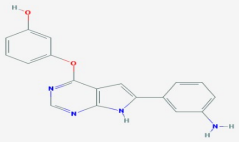
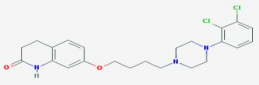
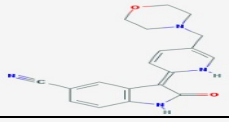
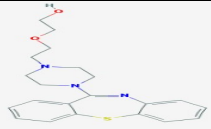
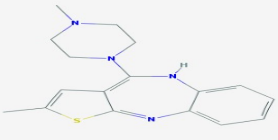
Ligands that were selected for GSK-3β were filtered according to Lipinski Rule of Five. 2D chemical structures of compounds, their molecular weight are shown in table (table 2).

Docking results are shown graphically in fig 1. Lead compound having minimum binding energy-13.1. Amino Acid residues involved in binding interactions of GSK-3βb can give us a strong structural insight about its mechanism of action and enable us to trace important target residues for designing drugs against the GSK-3β. Acute toxicity involves harmful effects in an organism through short term exposure. Chronic toxicity effects over an extended period sometimes for the whole life. Toxicity of lead compound determined through ametSAR showed less toxic effects are shown in table 3.

Ligand based pharmacophore was designed that is an ensemble of steric and electronic features to ensure supramolecular interactions of ligands with a specific biological target fig. 2.

By 3D pharmacophore discovered minimum and maximum distances of pharmacophore features like aromatic ring, hydrogen bond acceptor and hydrogen bond donor through Ligand Scout. Compounds showed acceptor to aromatic values ranging from 1.000A° to 5.602A° fig. 3. Compounds showed aromatic to donor values ranging from 1.000A to 5.292A. From Donor to Acceptor, Compounds showed values ranging from 1.000A to 5.718A. Pharmacophore triangle was generated on the basis of distances calculated among pharmacophore features. Triangle constructed is shown fig. 4.

Table 2: Pharmacophoric features of GSK-3β Inhibitors

S. No	Compounds	2D Structures	Aromatic Ring	Hydrogen Bond Acceptor	Hydrogen Bond Donor	Hydrophobic	Fitness
1	LY2090314		1	2	1	1	50.6200
2	Rizperidone		1	2	0	1	42.3300
3	Tideglusib		1	2	0	1	43.3700
4	Zipradisone		1	1	1	1	43.4200
5	Carbamazepine		1	1	1	1	44.3100
6	CHIR-99021		1	2	1	1	49.4100
7	TIWS119		1	1	0	1	37.1600
8	Arapiparazole		1	2	1	1	49.8900
9	AZD1080		1	2	1	1	48.9300
10	Quitapine		1	1	1	1	41.0700
11	Olanzapine		1	1	1	1	43.1700

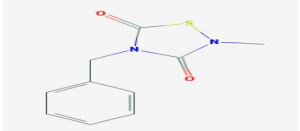
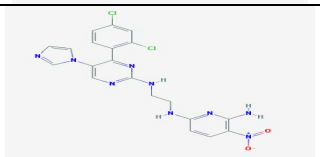
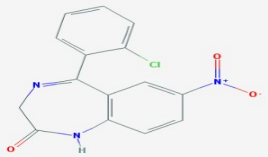
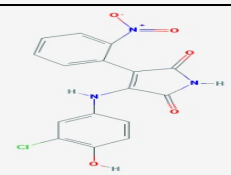
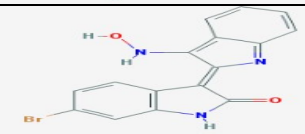
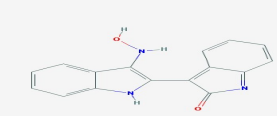
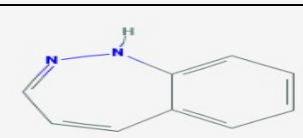
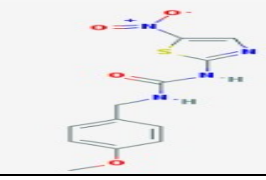
12	TDZD-8		1	2	0	1	43.3700
13	CHIR-98014		1	1	1	1	43.4100
14	Colanzepam		1	2	0	1	43.0100
15	SB-415286		1	2	1	1	49.3700
16	6BIO		1	1	1	1	50.0300
17	Indirubin-3'-monoxime		1	2	1	1	49.5200
18	Benzodiazepine		1	1	1	1	44.5100
19	AR-A014418		1	1	1	1	44.3200

Table 3: Toxicity Analysis of lead compound

Compound name	Blood Brain Barrier	Human Intestinal Absorption	Caco2-permeability	Carcinogens	Fish Toxicity	Acute Oral Toxicity	Aqueous Solubility	Rat Acute Toxicity
LY2090314	0.9669	1.0000	0.5740	0.9005	0.9706	0.5677	-3.7725	2.5286

DISCUSSION

Bipolar disorder is a psychiatric illness composed of episodes ranging from extreme elation to depression. GSK-3β is a therapeutic target involved in treating bipolar disorder. The whole methodology was designed to get a lead compound for GSK-3β through docking and pharmacophore modeling. GSK-3 plays significant roles in developing the metabolic homeostasis as well as neuronal growth and differentiation (Hur & Zhon, 2010), with the expression of cell polarity, cell fate and apoptosis. GSK-3 has been recognized as conserved protein kinase associated to the CMGC family of serine/threonine protein kinases, the responsible gene coding enzymes haves been also identified in the genome of eukaryote that has been investigated, for Dictyostelium

discoideum (Kim *et al*., 1999), Xenopus laevis (Itoh *et al*., 1995), Drosophila melanogaster (Ruel *et al*., 1993) including some parasites as Plasmodium falciparum, Trypanosoma brucei and Leishmania donovani (Osolodkin *et al*., 2011).

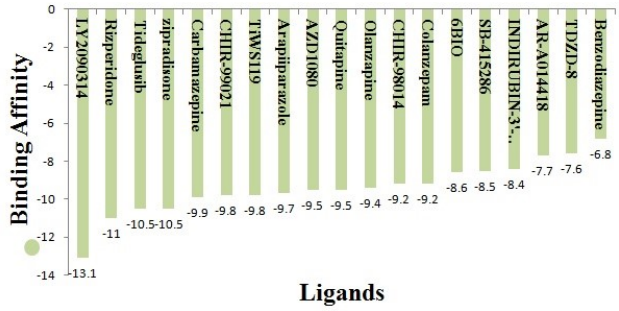


Fig. 1: The graphical docking results

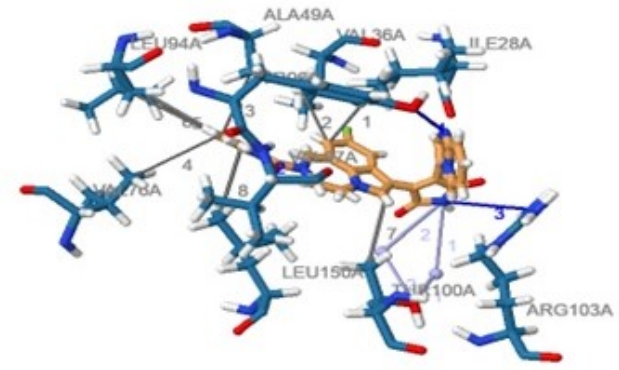


Fig. 2: Protein-Ligand Interactions of Lead Compound

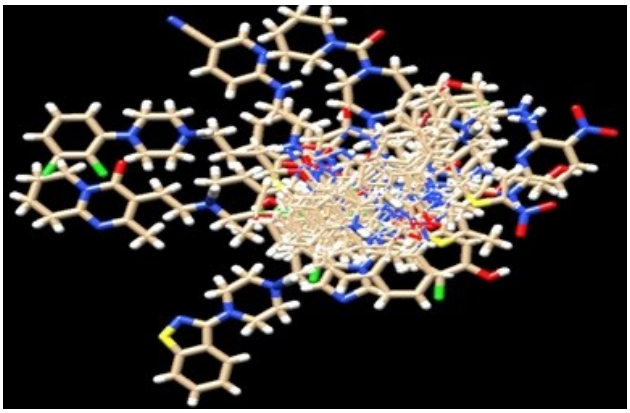


Fig. 3: Structure of Pharmacophore

The goal of protein-ligand docking is to predict the predominant binding mode of ligand with 3D structure of protein. Different amino acids of ligands were involved in interactions of GSK-3β. Edvardsen *et al*., 2008 have completely performed the bipolar spectrum with each specific constraint under the concept of heterogeneity. Lead compound was selected on the basis of best interactions and lowest binding affinity and toxicity of lead compound was checked. Luykx *et al*., 2010 compared the different genetic studies for the conventional involvement of GSK3β in bipolar disorder. *In silico* approach always reduce the time and energies for the experimental evidences thus a ligand based pharmacophore study may specifies the spatial relationship between the functional groups that are expressed as distance ranges and angles, leading to the construction of 3D pharmacophore.

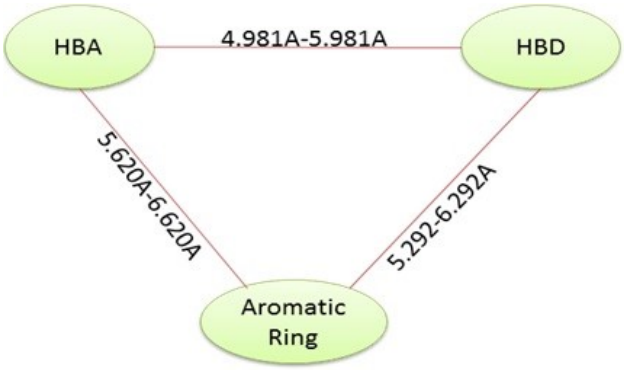


Fig. 4: Pharmacophore Triangle

CONCLUSION

In this study, an efficient compound for GSK-3B involved in Bipolar disorder was identified through docking analysis. Toxicity analysis was performed to calculate how much this compound will be toxic. 3D pharmacophore was designed to merge the features of selected dataset compounds for GSK-3B. Distances were calculated among pharmacophore features like Aromatic Ring, Hydrophobic, HBD and HBA. Pharmacophore triangle was designed for three different classes that are Aromatic, HBD and HBA. This pharmacophore modeling will be useful for designing of novel drugs in because this 3D pharmacophore showed best merging properties.

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