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Docking and ADMET prediction of few GSK-3 inhibitors divulges 6-bromoindirubin-3-oxime as a potential inhibitor

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ABSTRACT

GSK-3 is a member of cellular kinases with diversified functions such as cellular differentiation, metabolic signaling, neuronal functions and apoptosis. It has been validated as an important therapeutic target in Alzheimer's disease and type 2 diabetes. Few molecules targeting GSK-3 are currently in clinical trials. In this study, we have compared certain docking and computational ADME (Absorption, Distribution, Metabolism, Excretion) parameters of a few GSK-3 targeted ligands (Indirubin, Hymenialdisine, Meridianins, 6-bromoindirubin-3-oxime) against two control molecules (Tideglusib and LY-2090314) to derive and analyze the basic drug-like properties of the test compounds. Docking between the GSK-3 and various ligands was done using AutoDock while ADME parameters were derived from ADMET server PreADMET and admetSAR. Various docked images were retrieved from docking, indicating the docking sites in the target protein. Out of four compounds tested, 6-bromoindirubin-3-oxime (6-BIO) was found as the best docking and ADME parameters, followed by Hymenialdisine (HMD). The LigPlot interaction results show two residues Leu (188) and Thr (138) to be common at the interaction site. The LD_{50} of 6-BIO is better than one of the control ligands while very similar to the other. Some of the parameters were very similar to the control ligands, thus, making it a suitable candidate among the test ligands. From this *in-silico* study, we concluded that 6-BIO is a potent drug candidate which could be further tested *in vitro* and *in vivo* to establish a drug molecule. Since, 6-BIO is a chemically modified form of the basic molecule Indirubin, we can hypothesize that certain other modified indirubins could be tested as GSK-3 targeted ligands.
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1. Introduction

Glycogen Synthase Kinase-3 (GSK-3; EC No: 2.7.11.1) has been named for its initial determined function of phosphorylating the target downstream enzyme glycogen synthase (GS), rendering the later inactive. GSK-3, a serine/threonine kinase, is currently found to have multiple actions, apart from the above mentioned initial activity, such as insulin signaling, glycogen metabolism, cellular proliferation, neuronal functions, apoptosis, embryonic development and oncogenesis to name a few. Thus, some of the GSK-3 targets involved in the above mentioned functions are glycogen synthase, tau protein (microtubule protein) and β-catenin. Due to these multivariant actions, the enzyme has been implicated in multiple diseases like Non Insulin Dependent Diabetes Mellitus (NIDDM), also known as Type 2 diabetes mellitus (T2DM), Alzheimer's Disease (AD), certain Cancers and others [1,2].

Physiologically, there are two mammalian isoforms of the enzyme GSK-3, namely GSK-3α (mol. wt. 51 kDa) and GSK-3β (mol. wt. 47 kDa). Among these isoforms, GSK-3β (EC No: 2.7.11.26), a 420 residue long enzyme, is the primary isoform regulating the GS activity and insulin signaling in muscle. (Fig. 1) One of the primary actions of insulin is conversion of blood glucose to glycogen and storage into the muscle cells. Insulin, on binding to insulin receptor, inhibits GSK-3β which in turn prevents phosphorylation and increases dephosphorylation of GS, keeping it active. The basic process involves activation of phosphoionositide-3 kinase (PI-3K), which activates its target PKB (or Akt) which in turn phosphorylates and inactivates GSK-3β. The enzyme GS plays the most crucial role in the synthesis of storage polysaccharide glycogen, muscle being the major storage site. Thus, conversion of blood glucose to muscle glycogen keeps the blood glucose level in control [3,4]. It was demonstrated in animal model that tissue specific inhibition of GSK-3β (in liver and skeletal muscle) delivered different effects.

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MSGRPRTTSF	AESCKPVQQP	SAFGSMKVSR	DKDGSKVTTV	VATPGQGPDR	PQEVSYTDTK
VIGNGSFGVV	YQAKLCDSGE	LVAIKKVLQD	KRFKNRELQI	MRKLDHCNIV	RLRYFFYSSG
EKKDEVYLNL	VLDYVPETVY	RVARHYSRAK	QTLPVIYVKL	YMYQLFRSLA	YIHSFGICHR
DIKPQNLLLD	PDTAVLKLCD	FGSAKQLVRG	EPNVSYICSR	YYRAPELIFG	ATDYTSSIDV
WSAGCVLAEL	LLGQPIFPGD	SGVDQLVEII	KVLGTPTREQ	IREMNPNYTE	FKFPQIKAHP
WTKVFRPRTP	PEAIALCSRL	LEYTPTARLT	PLEACAHSFF	DELRDPNVKL	PNGRDTPALF
NFITQELSSN	PPLATILIPP	HARIQAAAST	PTNATAASDA	NTGDRGQTNN	AASASASNST

Fig. 1. Amino acid residues in GSK-3 beta.

While liver specific GSK-3β knockout (KO) mice showed normal metabolic features with no effect on glucose regulation, skeletal muscle GSK-3β KO mice showed improved glucose tolerance and better GS activation and glycogen storage [4]. Mussman et al. have shown that inhibition of GSK-3β also promotes proliferation and replication of pancreatic β-cells and preventing hyperglycemia and free fatty acid (FFA) induced cell death [5]. GSK-3 inhibition is primarily based on four preferred sites: ATP binding domain, Mg^{2+} binding domain, scaffold binding region and substrate binding domain. Most of the GSK-3 inhibitors being tested work by binding the ATP binding domain [6].

Among the GSK-3 inhibitors available in market, lithium is probably the only example and the oldest one. Some molecules, both natural and synthetic, such as maleimide derivatives, staurosporine (from the bacterium *Streptomyces storosporeus*), indole derivatives such as indirubin (used since long in traditional chinese medicine for leukemia), paullone derivatives, pyrazolamide derivatives, pyrimidine derivatives, oxadiazole derivatives, hymenialdisine and many more are in experimental (or clinical trial) stage as inhibitors of GSK-3 [7]. Indirubins (IND) are natural indole derivatives basically extracted from a purple dye from a mollusk *Hexaplex trunculus* and certain Chinese herbal plants. Indirubin derivatives and analogs have been shown to be potent inhibitors of GSK-3 [8,9]. Hymenialdisine (HMD) is a molecule derived from a marine sponge such as *Agelaside, Halichondriidae, Hymeniasidon aldis* and a few more families. HMD has been shown to be potent inhibitor of GSK-3 [7,10]. LY2090314 is a GSK-3 inhibitor which is currently in oncology trial from Eli Lilly (IN, USA) [11]. Tideglusib is another GSK-3β inhibitor under clinical trial against Alzheiemr's disease [12,13]. 6-Bromoindirubin-3-oxime (BIO), a derivative of indirubin, is a very potent inhibitor of GSK-3 [14]. Meridianins, which are brominated 3-(2-aminopyrimidines)-indoles, are naturally found and isolated from *Aplidium meridianum* (an ascidian, marine invertebrate) [15,16].

In this article, we have compared the docking aspects and the related ADME and toxicity profiles of various candidate drugs such as Indirubin, BIO, Hymenialdesine and Meridianin as compared to the controls Tideglusib and LY-2090314. Tideglusib and LY-2090314 have been used as controls, since they are already being tested as potent medicine in various clinical trials.These kinase inhibitors are being viewed as potent therapeutic molecules against type 2 diabetes, Alzheimer's Disease and a few types of cancers also.

2. Materials and methods

2.1. Retrieval of 3D structure of GSK-3β

The 3D structure of the receptor binding sites of human GSK-3β isoform (PDB: 1I09; DOI: 10.2210/pdb1i09/pdb) was retrieved from the Protein Data Bank (http://www.rcsb.org/pdb/home/home.do). (Fig. 2)

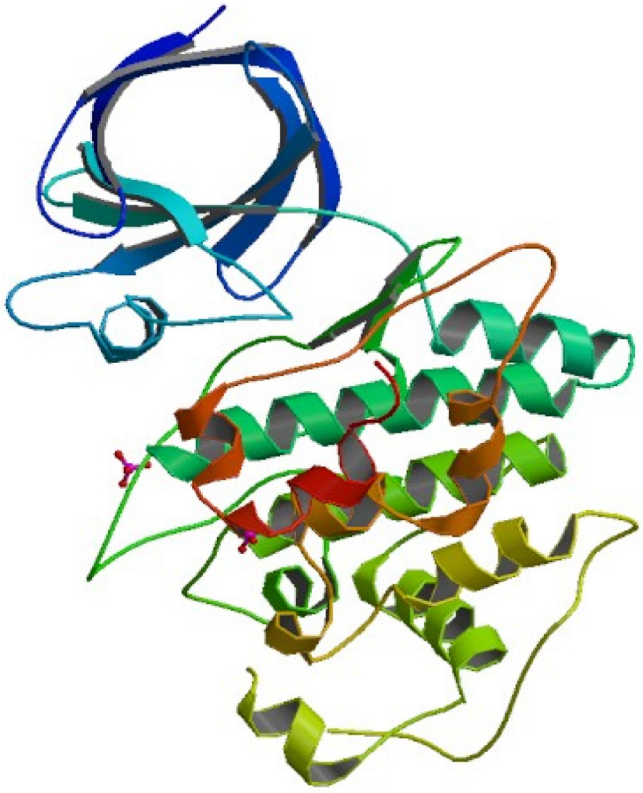

Fig. 2. The structure of the target protein GSK-3, retrieved from PDB.

2.2. Ligand selection

A few selective/non-selective GSK-3α/β inhibitors like Indirubin, Tideglusib, LY-2090314, 6-bromoindirubin-3-oxime (6-BIO), Meridianin and Hymenialdesine some of which are in clinical trials (Phase I/II), were chosen for the study through wide literature survey. The ligand molecules were retrieved in Structure Date File (SDF) format and then converted to Protein Data Bank (PDB) coordinates using the Open Babel (http://openbabel.org) converter which is available freely [17]. The chemical structures of ligands used in the study are shown in (Fig. 3).

2.3. Docking

The docking analyses of the candidate molecules with GSK-3 were carried out using AutoDock Tools (ADT v1.5.6) and AutoDock Vina, available from the Scripps Research Institute (http://www.scripps.edu/mb/olson/doc/autodock) [18]. AutoDock was run using a searching grid extended over ligand molecules. Gasteiger-type polar hydrogen charges were assigned and the torsions were set. It was followed by assigning the Kollman charges and addition of

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