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Original Article

IN SILICO STUDIES ON NEW INDAZOLE DERIVATIVES AS GSK-3β INHIBITORS

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ABSTRACT

Objective: *In silico* studies were conducted on newly proposed Indazole derivatives as GSK-3β inhibitors to select the best possible drug candidates based on drug properties and bioactivity score of the compounds.

Methods: 31 Indazole derivatives and active GSK-3β Indazole inhibitor 3-(5-chloro-1-methyl-indol-3-yl)-4-[1-[3-(triazol-1-yl)propyl]indazol-3-yl]pyrrole-2,5-dione(IC_{50} of 0.003 μM) were subjected to predict the mutagenic, tumorigenic, irritant, reproductive risks, and drug-relevant properties using OSIRIS Property Explorer. Further bioactivity scores were determined using Molinspiration online tools.

Results: The results of new GSK-3β inhibitors were compared with potent GSK-3β Indazole inhibitor to examine the prospective of the optimized compounds. The best possible drug candidates were reported after comprehensive analysis on predicted cLogP, solubility, molecular weight, topological molecular polar surface area (TPSA), drug- likeness, drug score properties and bioactivity score for different human targets like GPCR, ion channel, kinase, nuclear receptor, protease and enzymes.

Conclusion: Five compounds 282, 141, 161, 108 and 456 were reported as the best drug like candidates for GSK-3β regulation.

Keywords: Physiochemical properties, GSK-3β, Bioactivity score, Indazole.

INTRODUCTION

Drug discovery and development processes are expensive and time consuming [1], so the various computational methods are being used across the research communities from academy and pharmaceutical industry to make quicker decisions before starting experimentation on lead compounds. The computational studies are also being applied to select the possible best lead candidates based on the assessments of various important drug-relevant and biological properties of compounds through *In silico* methods to reduce the failure rate during the drug discovery process. Three decades ago, the Glycogen Synthase Kinase-3(GSK-3) was discovered which exists in two isoforms namely GSK-3α and GSK-3β but each isomer functionality is different and involves in the phosphorylation process. Glycogen Synthase Kinase-3β (GSK-3β) is a serine/threonine kinase that playsa key role in the regulation of numerous signaling pathways. As GSK-3β plays a crucial role in several human diseases, it is being considered as one of the potential therapeutic targets for diseases such as cancer, diabetes, cardiac, Alzheimer's and other central nervous system disorders [2]. Various researches on GSK-3β have reported different inhibitors to treat different disease conditions. In addition to that, 5-substituted Indazole derivatives were reported as potent GSK-3β inhibitors [3, 4]. In a previous report, based on 2D/3D QSAR studies on a series of 42 Indazole derivatives [3, 4] 450 new compounds were generated and validated through docking studies. Further, reported 31 new optimized Indazole compounds were possible potent GSK-3β inhibitors [14].

In order to select the best drug candidates for the next level of research, the newly proposed 31 Indazole derivatives were subjected to predict toxicity risks, drug properties and bioactivity score using online OSIRIS property explorer and Mol inspiration tools. The predicted results were compared with the results of active Indazole containing GSK-3β inhibitor 3-(5-chloro-1-methyl-indol-3-yl)-4-[1-[3-(triazol-1-yl)propyl]indazol-3-yl]pyrrole-2,5-dione (See Figure1) which has been reported with the excellent inhibition (IC50 0.003μM)[19] for GSK-3β.

MATERIALS AND METHODS

In drug discovery, many potential drugs have failed in clinical studies or late drug discovery process due to poor drug-like properties and adverse side-effects. The prediction of different properties of molecules in the early stage is a vital step in the drug discovery and development process. In the current investigation all the optimized potential Indazole derivatives were subjected to *Insilico* studies to make sure the toxicity risks and drug-relevant properties of molecules which are key factors to determine drug-likeness of lead molecules. 2D structures of Indazole derivative were sketched in a web based tool OSIRIS Property Explorer [15] from Actelion's in-house substance registration system [6]. Toxicity like mutagenic, tumorigenic, irritant, reproductive risks and drug-relevant properties such as cLogP, solubility, molecular weight (MW), topological molecular polar surface area (TPSA), drug-likeness and drug score for all new inhibitors were predicted using OSIRIS Property Explorer. OSIRIS rightly predicted the toxicity for 86% of known substances. Conversely, OSIRIS was indicated that only 12% of tested commercial drugs were potentially harmful [12]. The OSIRIS program calculates the drug-likeliness based on a list of around 5,300 distinct substructure fragments created by 3,300 traded drugs as well as 15,000 commercially available chemicals yielding a complete list of all available fragments with associated drug-likeliness. The drug score is calculated using the drug-likeliness, cLogP, logS, MW, and toxicity risks [15]. In the same manner 2D structures were sketched in Molinspiration online tool [5] to predict the bioactivity score for all the compounds against various human therapeutic targets such as GPCR, ion channel, kinase, nuclear receptor, protease and enzymes.

Toxicity

The toxicity risk assessment is mandatory to avoid destructive substances for further processing of the drug discovery and development. The mutagenic, tumorigenic, irritant and reproductive toxicity risks were measured by means of pre-computed set of structural fragment which was created based on the classification of compounds from the Registry of Toxic Effects of Chemical Substances (RTECS) database. The toxicity risks are estimated with color code. The un desired (toxic risks) effects of molecule are displayed in red and while the green color indicates the desired effects of compound [8].

cLogP

cLogP is a partition coefficient between n-octanol and water. It indicates the hydrophobicity of drug molecules and influences the