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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

absorption, bioavailability, metabolism and toxicity risks of a drug. cLogP is a key parameter in drug discovery and in the environmental toxicity studies. The calculated values of cLogP is >3000 drugs in the market are indicating that the high logP value causes poor absorption or permeation. The clogP value must not be greater than 5.0 [17].

Molecular weight and solubility (logS)

As the absorption of a drug molecule is linked with molecular weight, increasing the molecular weight will decrease the absorption. Keeping less molecular weight is an essential one in the drug development process. Analysis of molecular weight of the available drugs has pointed out that the 80% of drugs have <450 molecular weight.

Solubility (logS) property of a drug in aqueous solution affect absorption and distribution characteristics. The solubility of a compound is predicted using OSIRIS tool to identify the low solubility behavior and eliminate from the study based on logS value. The preferred value is greater than -4 [10].

Topological polar surface area (TPSA)

TPSA is molecular polar surface area and it characterizes the transport properties of a drug. This property is defined by polar atoms and predicted using different methods of classical 3D PSA and summation of tabulated surface contributions of polar fragments. OSIRIS Property Explorer predicts the property based on the summation of surface contributions of polar fragments as mentioned in Ertl. et al [6]. TPSA of drug molecules <160A^0 [11, 18].

Drug-likeness

The drug-likeness is defined based on the structural features of a compound with structural features of marketed drugs. Drug-likeness of a compound is predicted based on 5300 distinct substructure fragments with associated drug-likeness scores. The substructure fragments were created from 3300 marketed drugs and 15000 commercially available chemicals (Fluka) yielded a complete list of all available fragments. The drug-likeness is sum of the score values of the fragments present in the molecule. Positive value in drug-likeness indicates that the tested molecule mainly contains fragments which are frequently present in marketed drugs.

Drug score

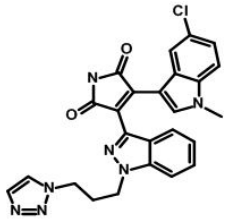
Drug score value indicates overall potential of a compound to be a drug candidate. OSIRIS Property explorer considers toxicity risks, cLogP, logS, Molecular weight and drug-likeness parameters to derive this value [12].

Molinspiration

Mol inspiration is a web based tool which was used to predict the bioactivity score of new Indazole derivatives against regular human receptors such as GPCR, ion channel, kinase, nuclear receptor, protease and enzyme [13].

The bioactivity scores were predicted for different human targets for all newly designed Indazole compounds and the predicted results of compounds were compared with the result of a potent GSK-3β inhibitor containing Indazole fragment, which is shown in fig. 1, to know the effectiveness of new compounds.

Bioactivity activity of a compound was decided based on the bioactivity score. If bioactivity score is >0, it is an active compound while <-5.0 is an inactive compound and range between -5.0 to 0.0 is moderately active compounds.



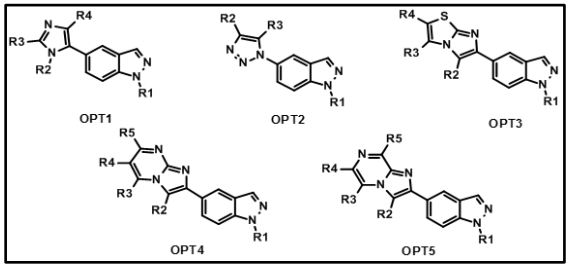
Cpd2

Fig. 1: Potent GSK-3β inhibitor (Cpd2) as reference compound contains Indazole

Cpd2 was reported with excellent inhibition for GSK-3β [19]. Cpd2 was one of the active GSK-3β inhibitors containing Indazole fragment; the reported IC50 value was 0.003μM. The drug properties and bioactivity scores were predicted for Cpd2, the sepredicted results were considered as baseline to select best drug candidates from the newly designed Indazole compounds.

The reference compound Cpd2 was claimed as a potential GSK-3β inhibitor that would be useful in treating cardiovascular diseases, diabetes, inflammatory diseases, immunological disorders, on cological disorders and CNS disorders [19].

Table 1: Optimized compounds



Cpd_ID	Core	R1	R2	R3	R4	R5
416	OPT1	n-propyl	6-oxo-2-piperidyl	H	H	-
397	OPT1	ethyl	6-oxo-2-piperidyl	H	H	-
308	OPT3	n-propyl	pyrimidine-4-yl	H	H	-
46	OPT4	n-propyl	H	3-OH-pyridin-4-yl	H	H
107	OPT4	H	3-OH-pyridin-4-yl	H	H	H
468	OPT2	n-propyl	H	6-oxo-2-piperidyl	-	-
282	OPT3	H	1H-imidazol-4-yl	H	H	-
453	OPT1	n-propyl	H	3-OH-pyridin-4-yl	H	-
141	OPT5	H	Pyrimidine-4-yl	H	H	H
435	OPT1	ethyl	H	6-oxo-2-piperidyl	H	-
134	OPT4	ethyl	6-oxo-2-piperidyl	H	H	H
434	OPT1	ethyl	H	3-OH-pyridin-4-yl	H	-
126	OPT4	methyl	3-OH-pyridin-4-yl	H	H	H

118	OPT4	n-propyl	1H-imidazol-4-yl	H	H	H
71	OPT4	H	H	H	6-oxo-2-piperidyl	H
68	OPT4	H	H	H	acetylamino	H
139	OPT5	H	acetylamino	H	H	H
514	OPT2	ethyl	3-OH-pyridin-4-yl	H	-	-
78	OPT4	n-propyl	H	H	cyclohexylamino	
471	OPT2	n-propyl	H	cyclohexylamino	-	-
36	OPT4	H	H	6-oxo-2-piperidyl	H	H
160	OPT5	methyl	6-oxo-2-piperidyl	H	H	H
210	OPT5	H	H	H	acetylamino	H
161	OPT5	methyl	3-OH-pyridin-4-yl	H	H	H
152	OPT5	n-propyl	3-OH-pyridin-4-yl	H	H	H
108	OPT4	H	1H-imidazol-4-yl	H	H	H
456	OPT1	n-propyl	H	pyrimidine-4-yl	H	-
100	OPT4	ethyl	H	H	1H-imidazol-4-yl	H
347	OPT3	n-propyl	H	6-oxo-2-piperidyl	H	-
55	OPT4	methyl	H	3-OH-pyridin-4-yl	H	H
10	OPT2	ethyl	6-oxo-2-piperidyl	H	-	-

RESULTS AND DISCUSSION

Toxicity and drug-like properties were predicted using OSIRIS property explorer tool. The3-(5-chloro-1-methyl-indol-3-yl)-4-[1-[3-(triazol-1-yl)propyl]indazol-3-yl]pyrrole-2,5-dione is a potent GSK-3β Indazole inhibitor. The predicted parameters and their corresponding values are shown in Table 2. The predicted toxicity risks and drug-like properties of new optimized Indazole derivatives are shown in table 4.

Bioactivity scores for potent GSK-3β Indazole inhibitor and optimized compounds were predicted. GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor, enzyme inhibitor score values were predicted using Molnspiration. The predicted bioactivity scores for potent GSK-3βinhibitorare given in table 3 and for optimized compounds in table 5.

Table 2: Toxicity and Drug-relevant properties prediction for potent GSK-3β Indazole inhibitor

Toxicity				**Physico-chemical properties**					
Mu	Tu	Ir	Re	cLogP	Solubility	M. Wt	TPSA	Drug-likeness	Drug score
G	G	G	R	1.07	-3.39	485	99.63	3.31	0.41

G = Green (No toxic); R = Red (toxic); Mu = Mutagenic; Tu =Tumorigenic; Ir = Irritant; Re = Reproductive

The drug-relevant properties cLogP, Solubility, Molecular Weight and TPSA showed promising value. Drug-likeness and drug score is 3.31 and 0.41respectively indicate the overall potential of the compound and were calculated considering drug-relevant properties. The potent GSK-3β Indazole inhibitor was predicted that would have the reproductive risk. The predicted physico-chemical properties cLogP, Solubility and TPSA values are 1.07, -3.39 and 99.63 respectively, these parameters meet the basic criteria to be a potent inhibitor.

Table 3: Bioactivity scores for potent GSK-3β Indazole inhibitor

GPCR Ligand	**Ion channel modulator**	**Kinase inhibitor**	**Nuclear receptor ligand**	**Protease inhibitor**	**Enzyme inhibitor**
0.27	0.03	1.07	0.02	0.05	0.53

The predicted values of reference compound Cpd2 showed highest bioactivity score 1.07 for Kinase inhibition. It was also predicted that moderately active as Ion channel modulator, nuclear receptor ligand, Protease Inhibitor, Enzyme Inhibitor and GPCR ligand.

Table 4: Toxicity and Drug-relevant properties prediction for optimized compounds

Cpd ID	**Toxicity**				**Drug-relevant properties**					
	Mu	**Tu**	**Ir**	**Re**	**cLogP**	**Solubility**	**M. weight**	**TPSA**	**Drug-likeness**	**Drug score**
416	G	G	G	G	2.21	-3.85	323	64.74	2.29	0.77
397	G	G	G	G	1.75	-3.58	309	64.74	1.92	0.79
308	G	G	G	G	2.57	-2.97	348	92.04	5.78	0.84
46	G	G	G	G	2.1	-3.21	370	81.13	5.67	0.82
107	G	G	G	G	1.22	-2.74	329	91.99	4.36	0.88
468	G	G	G	G	0.65	-2.49	324	77.63	-4.82	0.46
282	G	G	G	G	1.69	-2.5	306	102.9	4.63	0.9
453	G	G	G	G	1.96	-3.81	319	79.62	4.85	0.82
141	G	G	G	G	0.84	-4.42	313	84.65	3.88	0.77
435	G	G	G	G	1.13	-2.36	309	75.00	1.66	0.84
134	G	G	G	G	1.33	-2.86	360	77.11	2.41	0.83
434	G	G	G	G	1.5	-3.64	305	79.62	4.45	0.85
126	G	G	G	G	1.39	-2.94	342	81.13	5.24	0.87
118	G	G	G	G	1.7	-2.81	343	76.69	6.09	0.87
71	G	G	G	G	0.86	-2.64	332	87.97	1.86	0.83
68	G	G	G	G	0.52	-2.4	292	87.97	3.93	0.91
139	G	G	G	G	0.62	-4.82	292	87.97	4.8	0.74
514	G	G	G	G	0.51	-2.3	306	81.65	-2.51	0.49
78	G	G	G	G	2.9	-4.16	374	60.04	0.55	0.6

471	G	G	G	G	2.12	-4.04	324	60.56	-7.1	0.40
36	G	G	G	G	0.91	-2.67	332	87.97	1.81	0.83
160	G	G	G	G	0.82	-4.76	346	77.11	1.96	0.68
210	G	G	G	G	0.62	-4.82	292	87.97	4.8	0.74
161	G	G	G	G	1.13	-4.84	342	81.13	4.69	0.71
152	G	G	G	G	1.84	-5.11	370	81.13	5.01	0.66
108	G	G	G	G	0.82	-2.34	301	87.55	4.98	0.92
456	G	G	G	G	1.83	-3.58	304	72.28	4.92	0.84
100	G	G	G	G	1.16	-2.85	329	76.69	5.9	0.88
347	G	G	G	G	2.66	-3.3	379	92.46	2.52	0.77
55	G	G	G	G	1.39	-2.94	342	81.13	5.37	0.87
10	G	G	G	G	0.2	-2.22	310	77.63	-5.19	0.46

G = Green (No toxic); R = Red (toxic); Mu = Mutagenic; Tu =Tumorigenic; Ir = Irritant; Re = Reproductive

New Indazole derivative molecules were projected that these molecules were toxic free whereas the reference compound (Cpd2) was predicted with reproductive risk. All optimized compounds were predicted with favorable values for cLogP, solubility, M. Weight, TPSA like reference compound; however compound 152 showed poor solubility. The compound 468, 514, 471 and 10 molecules exhibited with negative drug-likeness score even though the drug score of these compounds are better than the reference compound. Hence, compounds 152, 468, 514, 471 and 10 could not be appropriate for next level of investigation.

The predicted drug-likeness and drug score for compounds 308, 46, 107, 282, 453, 141, 434, 126, 118, 68, 139, 210, 161, 108, 456, 100 and 55 were more than potent GSK-3β inhibitor with favorable values for cLogP, solubility, M. Weight, TPSA. In the case of compound 416, 397, 435, 134, 71, 78, 36, 160 and 347 drug-likeness and drug score was less than the reference compound which showed 3.31 drug-likeness score. On comparing the drug-likeness and solubility value of new Indazole derivatives with reference compound which a potent GSK-3β inhibitor, eighteen molecules specifically 308, 46, 107, 282, 453, 141, 434, 126, 118, 68, 139, 210, 161, 108, 456, 100, 347 and 55were selected for further investigation.

For different human receptors GPCR, Ion Channel, kinase, nuclear receptor, protease and enzymes bioactivity scores were calculated for the reference compound and new Indazole compounds. The new Indazole compounds bioactivity score in the case of kinase inhibition is more than 0.00 which indicates that these compounds are active in kinase inhibition.

All these optimized compounds showed good bioactivity score in the case of kinase inhibition. The predicted bioactivity score of these compounds in kinase inhibition compared with the predicted kinase inhibitor score of reference compound Cpd2 which showed highest bioactivity score 1.07 in kinase inhibition to select the best possible drug candidates. The molecules 46, 453, 126, 68, 139, 100, 347 and 55 exhibited promising drug-relevant properties and toxic free but bioactivity score as kinase inhibitor less than the reference compound. The other molecules 308, 107, 434, 118 and 210 were also predicted as good kinase inhibitor whereas their values are less than reference compound Cpd2. On comparing the kinase inhibition score of reference Cpd2, the new molecules 282, 141, 161, 108 and 456 showed higher bioactivity score as kinase inhibitor 1.33, 1.59, 1.11, 1.31 and 1.15 respectively, these five compounds could be the best drug candidates than other Indazole molecules.

Table 5: Predicted bioactivity scores for optimized compounds

Cpd ID	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
416	0.25	0.12	0.58	-0.22	-0.15	0.24
397	0.19	0.09	0.63	-0.28	0.23	0.26
308	0.37	0.24	1.04	-0.73	-0.53	0.40
46	0.30	0.31	0.66	-0.43	-0.08	0.01
107	0.24	0.51	0.97	-0.21	-0.18	0.09
468	0.36	0.02	0.02	-0.39	-0.08	0.11
282	0.32	0.41	1.33	-0.72	-0.51	0.48
453	0.51	0.41	0.89	-0.12	-0.08	0.49
141	0.50	0.56	1.59	-0.11	-0.32	0.42
435	0.39	0.07	0.34	-0.49	-0.05	0.41
134	0.27	0.16	0.28	-0.64	-0.21	-0.27
434	0.45	0.38	0.96	-0.18	-0.17	0.51
126	0.24	0.43	0.84	-0.39	-0.36	0.07
118	0.54	0.59	1.01	-0.51	-0.13	0.23
71	0.27	0.30	0.34	-0.79	-0.11	-0.12
68	0.24	0.30	0.70	-0.81	-0.23	-0.24
139	0.13	-0.12	0.64	-0.65	-0.63	-0.11
514	0.49	0.20	0.80	-0.10	-0.05	0.43
78	0.42	0.26	0.53	-0.58	-0.12	-0.10
471	0.38	0.11	0.32	-0.21	-0.03	0.08
36	0.23	0.42	0.40	-0.77	-0.07	-0.06
160	0.38	0.18	0.56	-0.56	-0.14	0.15
210	0.30	0.20	0.94	-0.70	-0.31	0.09
161	0.38	0.35	1.11	-0.06	-0.51	0.34
152	0.40	0.27	0.96	0.02	-0.42	0.29
108	0.52	0.80	1.31	-0.46	-0.03	0.29
456	0.66	0.55	1.15	-0.40	-0.02	0.58
100	0.44	0.50	0.86	-0.78	-0.12	0.21
347	0.08	-0.13	0.11	-0.98	-0.53	0.05
55	0.27	0.40	0.78	-0.58	-0.15	0.03
10	0.32	-0.06	0.11	-0.38	-0.12	0.14

CONCLUSION

In silico studies on drug-like properties and bioactivity score on different human targets like GPCR, ion channel, kinase, nuclear receptor, protease and enzyme were predicted for newly proposed Indazole derivatives GSK-3β inhibitors using OSIRIS Property Explorer and Molinspiration online tools to select best possible drug candidates. 31 Indazole derivatives and active GSK-3β Indazole inhibitor3-(5-chloro-1-methyl-indol-3-yl)-4-[1-[3-(triazol-1-yl) propyl] indazol-3-yl]pyrrole-2,5-dione(IC50 of 0.003 μM) were subjected to predict the mutagenic, tumorigenic, irritant, reproductive risks, and drug-relevant properties and bioactivity score. The predicted results of new GSK-3β inhibitors were compared with potent GSK-3β Indazole containing inhibitor. The reported five compounds 282, 141, 161, 108 and 456 are possible best drug candidates for next level of research.

CONFLICT OF INTERESTS

Declared None

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