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Molecular Docking Study of Natural Compounds against Non Receptor Protein Tyrosine Kinases Src

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ABSTRACT

Non-receptor tyrosine kinases Src family plays an important role in signal transduction induced by diverse extracellular stimulus, including cytokine, and growth factors. Overactivity or overexpression of the non-receptor tyrosine kinase Src is involved in the growth, development and progression of various human cancers and their inhibitors are under intensive investigations as novel anti-cancer agents. Therefore, we studied receptor-based molecular docking of src against natural compounds. Each Selected compounds docked with the X-ray crystal structure of Src (PDB; 3EL7). The best-docked compounds have been elected for target by optimal energy value, types of interactions, and conformations. STOCK1N-75795, STOCK1N-80087, STOCK1N-72227, STOCK1N-79428, STOCK1N-72232, STOCK1N-72129, and STOCK1N-72552 compound have a better binding energy as well as binding conformation against src. Foremost, STOCK1N-80087, STOCK1N-72227, and STOCK1N-72232 are their excellent QPlogPo/w, CIQPlogS, QPlog HERG K^+ channels, QPPCaco, QPlogBB, QPPMDCK, QPlogKP, QPlogKhsa and percentage of human oral absorption values which satisfy the Lipinski's Rule of Five. This molecular docking study recapitulates docking free energy, protein ligands interaction profile, pharmacokinetic, and pharmacodynamic parameter of lead molecules, which are tremendously helpful to improve activity of natural compounds against src.

Keywords: Src kinase, InterBioScreen natural compound library, Lipinski's Rule of Five, Maestro 9.3

INTRODUCTION

Non-receptor protein tyrosine kinase (nRTKs) c-Src proto-oncogene is cytoplasmic enzymes that oversee for catalysing the transfer of a phosphate group from a nucleoside triphosphate, to tyrosine residues in proteins [1]. c-Src plays a decisive role in the signal transduction pathways involved in cell division and cell survival of cancer cells by regulation of the immune system [2-4]. nRTKs play an indispensable role in signal transduction in activated T and B cells in the immune system [5]. Src family kinases (SFKs) are activated in an array of cancers, but detailed mechanisms for the progression of tumors remain to be defined. Src is the largest family of non-receptor protein tyrosine kinases, known as the SFKs and 32 others non-receptor tyrosine kinases found in human cells led to diverse biological homeostasis [6, 7]. Constitutively active proto-oncogene Src, encoding a receptor tyrosine kinase discovered by J. Michael for which they were awarded the 1989 Nobel Prize in Physiology or Medicine. c-Src can be activated by various transmembrane proteins such as adhesion receptors; G-protein coupled receptors, cytokine receptors, and receptor tyrosine kinases including, Insulin Receptor (IR), Insulin-like Growth Factor (IGF), Epidermal Growth Factor (EGF), and Vascular Endothelial Growth Factor (VEGF) [8, 9]. Among these factors, most studies receptor tyrosine kinases are platelet-derived growth-factor receptor (PDGFR) pathway and EGFR. Overexpression of receptor tyrosine kinases such as EGFR, HER2, PDGFR, Fibroblast Growth Factor Receptor (FGFR), VEGFR, ephrins, and integrin led to activation of Src activity [10, 11]. Elevated Src expression has been seen in multiple solid tumors including breast cancer, and

colon cancer [12, 13]. Moreover, Src signaling cross-talk between growth-promoting pathways, such as the ER and tyrosine kinase family including IR, IGFR, EGFR, and VEGFR, known to be over-activated in different types of cancer. Interestingly c-Src play an important role in osteoclast function and one is the primary metastatic site of patients with different types of cancer [14, 15]. In this context, Src is a novel target for this obstacle in malignancies. Blocking Src activation may slow down cancer progression thus potentially play a chemopreventive role in cancer disease recurrence and the development of metastases [15, 16]. Src inhibition decreases the development of destructive bone metastases [17]. c-Src inhibitor dasatinib inhibited proliferation of primary mouse osteoblasts [2, 18]. A mutation in a gene for nRTKs can results an aberrant activity of this enzyme led to the induction of drug-resistance, formation of metastasis and tumor neovascularization [19].

A number of low molecular weight ATP-competitive Src inhibitors have been investigated including a dasatinib, bosutinib, and saracatinib. A dasatinib an oral, potent cancer drug and used for the particular type of chronic myeloid leukemia remedy [20, 21]. Bosutinib is a tyrosine kinase inhibitor selected for phase II clinical trials for treatment of glioblastoma and advanced breast cancer [22]. Further, Saracatinib a selective Src kinase inhibitor currently under phase II clinical trials in patients with advanced solid malignancies including breast cancer, head and neck squamous cell carcinoma [23-25].

Inhibitors of Src signaling are currently being tested in cancer clinical trials, however, clinical trials of the non-receptor tyrosine kinases c-Src inhibitors were discouraging because of cross-talk between receptor tyrosine kinases and non-receptor tyrosine kinases at downstream signaling led to drug resistance and poor prognosis in various myelomas. In this context, molecular docking of c-Src against IBS compounds has been carried out. All selected natural product compounds were docked with the X-ray crystal structure of Src (PDB; 3EL7) retrieved from the protein data bank by using Maestro 9.3. This study aims to screen novel, potent, and selective slow binding energy Src inhibitor by using molecular docking approach.

METHODOLOGY

Selection and Preparation of Ligands: InterBioScreen natural compound library (IBS) as ligand molecules were selected in our study. IBS is a collection of one of the world's largest natural compound library, and in March 2013, it has grown to include over 49000 compounds. Of the whole natural compound library, 60-65% is compounds of plant origin; 5-10% was isolated from microorganisms, about 5% of marine species and the rest from other natural sources. These ligand molecules were subjected to ligand preparation by Ligprep wizard application of the Maestro 9.3, and that performs amendment on the ligands, such as the addition of hydrogens, 2D to 3D conversion, corrected bond lengths and bond angles, low energy structure, stereochemistries and ring conformation. After preparation of ligands, energy minimization, optimization, and molecular dynamics was done by using Optimized Potential for Liquid Simulations (OPLS_2005) force field [26-28], and finally, one conformation for each ligand was preceded. Supplementary others parameter such as ionization do not change, tautomers not generated and retain specific chiraties generate at most one per ligands were used as a default restriction in Maestro 9.3.

Preparation of protein molecules, Receptor grid formation, and GLIDE molecular docking: *In silico* molecular docking procedure adapted from our previous published literature [17, 29]. The X-ray crystal structure of non-receptor protein tyrosine kinases, Src (PDB; 3EL7) retrieved from the protein data bank with 2.8Å resolution [30]. Protein is prepared using the Schrodinger 9.3 protein preparation wizard by addition of hydrogen atoms, assigning bond orders, creation of zero-order bonds to metal, creation of disulphide bonds, fixing of the charges, and orientation of groups was incorporated. Moreover, water and sulphate molecules were removed by using protein preparation wizard. After preparing protein molecules minimization and optimization, was done using OPLS_2005force field of Schrodinger Glide. Active site of protein molecules was determined by using receptor grid generation option of Schrodinger. We have generated the grid that covers the entire active residues cavity. Receptor grid was scaled by van der Waal's radii of 1.0A0 with partial atomic charge less than 0.25A0. Others parameter such as sites, constraints, and excluded volume are default setting of the Maestro 9.3 are used [31, 32]. Using GLIDE molecular docking, IBS compounds docked with the X-ray crystal structure of Src (PDB; 3EL7). The best fit compounds have been selected for the target on the basis of optimal energy value (Gscore), types of interactions, potential of bonding, and conformations [33, 34]. The Gscore is calculated in Kcal/mol and it is an accumulative energy of a number of parameters such as Hydrogen bond, hydrophobic, Vander-Waals, columbic, Polar interactions in the binding site, metal binding term and penalty for buried polar group and freezing rotatable bonds.

ADME properties studies: Absorption, Distribution, Metabolism, Excretion and Toxicity (ADME/T) possessions of selected best-docked ligands molecules were foreseen by using QikProp tools of Schrodinger 2012. It predicts properties such as logBB, overall CNS activity, Caco-2, MDCK cell permeability, and logKhsa for human serum albumin binding [35, 36].

RESULT AND DISCUSSION

Molecular docking outcome based on Gscore and protein ligands interactions are summarized in table 1. Ten best lead (lowest Gscore) IBS natural compounds with Src (PDB; 3EL7) protein molecules, was the screen by the GLIDE molecular docking protocol. Protein ligands interaction discloses an abundance of information accentuate the irrefutable role portrayed by numerously molecular bonds such as hydrogen bonds, salt bridges, metal interactions, lipophilic interactions, π-π and π-cation interactions. The crystal structure of c-Src in complex with pyrazolopyrimidine five has been determined with 2.8Å resolutions. Crystal structure of c-Src in complex with pyrazolopyrimidine five revealed that hydrogen bonds, salt bridges, metal, and hydrophobic interactions are involved in protein-ligand interaction. Amino acids Glu339 and Met341 comprise in the hydrogen bonds, salt bridges, and metal interactions, Nevertheless, amino acids Leu393 and Ala403 are involved in hydrophobic interactions [37]. Dasatinib is a novel, potent, multitargeted kinase, ATP-competitive, and orally bioavailable synthetic small molecule SRC/ABL inhibitor. Dasatinib inhibits tyrosine phosphorylation of Src that led to inhibition of downstream Signal Transducer and Activator of Transcription 5 (STAT5) signaling including the down-regulation of gene expression of Bcl-x, and cyclin D1 [24, 38]. Another drug Bosutinib is a 7-alkoxy-3-quinolinecarbonitrile; synthetic quinolone derivative and potent dual kinase inhibitor led to reducing cell proliferation. Furthermore, it has been demonstrated for the treatment of chronic or blast phase Philadelphia chromosome positive chronic myelogenous leukemia (CML) with resistance and others solid tumors [39-42]. Our molecular docking studies have shown that STOCK1N-75795, STOCK1N-80087, STOCK1N-72227, STOCK1N-79428, STOCK1N-72232, STOCK1N-72129, and STOCK1N-72552 have lowest Gscore in addition to better or with similar binding conformation with Src (PDB; 3EL7) than any other Src specific inhibitors as listed in Table 1. Furthermore, these compounds were docked into the ATP binding site of the Src kinase and our drug compounds (control) also docked in the same as our lead molecules, and these integrity validate our docking protocol. To validate the docking result, all compounds control as well as lead molecules amino acids Thr338, Met341, and Ser 345 involved in the protein-ligans interactions at the ATP-binding site of the Src kinase. Physicochemical properties such as Molecular weight (MW), Dipole, Solvent Accessible Surface Area (SASA), FOSA (Hydrophobic component of the SASA), FISA (Hydrophilic component of the SASA), PISA (π component of the SASA), hydrogen bond donors, and hydrogen bond acceptors are a prerequisite for the drug-likeness. Thus, these properties are calculated for leads compounds. (Figure 1)

STOCK1N-75795 has been shown better binding energy with c-Src with Gscore of -12.09 kcal/Mol, and even better than previously available c-Src inhibitors represented in table 1. Protein-ligands interactions are mainly dominated by hydrogen bonding (backbone and side chain hydrogen bond) of STOCK1N-75795 with c-Src. Protein-Ligand interactions underlined that amino acid Thr338, Glu339, Met341, and Asp404 are involved in hydrogen bond interactions. Moreover, our docked results also divulge the presence of large hydrophobic pocket surrounded by Leu 273, Ala 293, Met314, Leu325, Ile336, Tyr 340, and Met341 amino acids. Physicochemical properties of STOCK1N-75795 such as molecular weight (MW), Dipole, solvent-accessible surface area (SASA), FOSA (Hydrophobic component of the SASA) FISA (Hydrophilic component of the SASA), PISA (π component of the SASA), hydrogen bond donors , and hydrogen bond acceptors are 269.259, 3.034, 498.51, 75.943, 221.33, 201.24, 3, and 4.75 respectively. STOCK1N-80087 has been shown better binding energy with c-Src with Gscore of -11.28 kcal/Mol, and even better than previously available c-Src inhibitors. STOCK1N-80087 with c-Src protein-ligand interactions underlined that amino acid Thr338, Met341, and Asp404 are involved in hydrogen bond interactions. Physicochemical properties such as SASA are the surface area of a biomolecule that is attainable to a solvent and described in units of square ångstroms. Foremost, physicochemical properties of STOCK1N-80087 such as molecular weight (MW), dipole, SASA, FOSA, FISA, PISA, hydrogen bond donors, and hydrogen bond acceptors are 350.45, 4.908, 621.56, 238.58, 177.37, 114.25, 2, and 6.5 respectively. Foremost, STOCK1N-72227 and STOCK1N-72232 has better binding energy with c-Src with Gscore of -10.75 and -10.02 kcal/Mol. Interestingly, many physicochemical properties of these compounds conformity with the drug-likeness.

ADME properties: Pharmacokinetic and pharmacodynamic properties of lead IBS natural compounds were appraised by using the Qikprop application of Maestro 9.3. Lead IBS natural compounds STOCK1N-80087, STOCK1N-72227, and STOCK1N-72232 were found to be most promising based on their docking free energy score as well as percent bioavailability. Most fascinating aspect of STOCK1N-80087, STOCK1N-72227, and STOCK1N-72232 are their admirable QPlogPo/w, CIQPlogS, QPlogHERGK^{+} channels, QPPCaco, QPlogBB, QPPMDCK, QPlogKP, QPlog Khsa and percentage of human oral absorption values which satisfy the Lipinski's Rule of Five (Table 2). Polar surface area, high oral bioavailability, H-bond donors, and acceptors are imperative criteria for the development of therapeutic agents. Daniel F. Veber et al. 2002 reported that compounds having ten or fewer rotatable bonds and polar surface area equal to or less than 140 Å (or 12 or fewer H-bond donors and acceptors) can be high probability of good oral bioavailability in the rat. Furthermore, it is also reported that polar surface area inverse proposal to permeation rate [43]. Our best leads molecules STOCK1N-80087, STOCK1N-72227, and STOCK1N-72232 have lesser SASA than control compounds. These results indicate that these compounds will have better permeation rate.

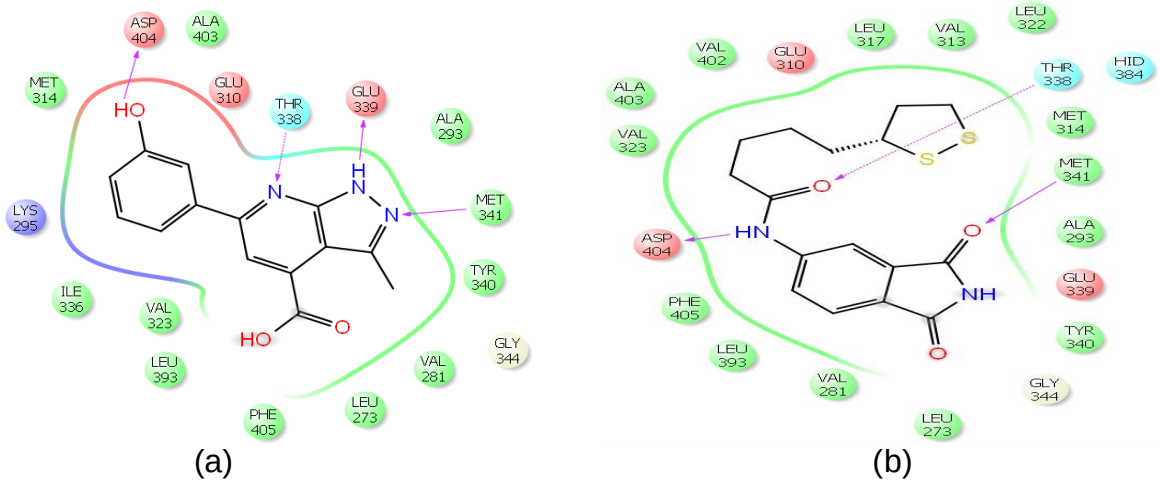

Figure 1 Protein-ligands interactions profile of Src (PDB; 3EL7) protein molecule with (a) STOCK1N-75795, (b) STOCK1N-80087,

Table 1 Lowest binding energy for the ligand- Src (PDB; 3EL7) protein interaction as detected by GLIDE molecular docking

	Molecule	GScore	Lipop EvdW	PhobEn	Phob EnHB	HBond	Electro	Protein-ligands interaction
Control	CID3062316	-9.32	-5.48	0	-1.5	-1.68	-0.68	Thr338, Met341, and Ser 345
	CID10302451	-8.98	-7.56	-0.3	-1.5	-0.44	-0.35	Met341, and Lys 295
	CID5328940	-7.31	-5.75	-0.24	-1.5	-0.77	-0.1	Thr338, and Met341
IBS	STOCK1N-75795	-12.09	-4.3	-0.75	-3	-2.39	-0.74	Thr338, Glu339, Met341, and Asp404
	STOCK1N-80087	-11.28	-5.21	-0.42	-2.5	-1.84	-0.41	Thr338, Met341, and Asp404
	STOCK1N-72227	-10.75	-6.7	-0.36	-1.43	-1.67	-0.47	Thr338, Met341, and Asp404
	STOCK1N-79428	-10.39	-5.84	-0.65	0	-2.96	-0.89	Glu310, Thr338, Met341, and Asp404
	STOCK1N-72232	-10.02	-7.39	-0.51	-1.5	-1.04	-0.38	Thr338, and Asp404
	STOCK1N-72129	-9.88	-7.01	-0.44	-1.5	-1.61	-0.42	Thr338, Met341, and Asp404
	STOCK1N-72552	-9.81	-6.61	-0.42	-1	-1.33	-0.5	Thr338, and Met341
	STOCK1N-72314	-9.34	-6.31	-0.35	-1	-1.32	-0.54	Thr338, and Met341
	STOCK1N-26287	-9.27	-6.31	-0.47	-1	-1.33	-0.42	Thr338, and Met341

STOCK1N-71839	-9.1	-5.64	-0.44	-1.5	-1.65	-0.5	Thr338, Met341, and Asp404

Molecule CID; Pubchem IDs
Molecule STOCK, InterBioScreen's library (IBS)
GScore; Glide extra precision scores (kcal/mol)
Lipophilic E Vdw; Chemscore lipophilic pair term and fraction of the total protein-ligand vdw energy
HBond; Hydrogen-bonding term
Electro; Electrostatic rewards
Protein ligands interaction; π-π stacking, π –cat interaction and hydrogen bond between the ligands and protein

Table 2 Evaluation of drug-like properties of the lead molecules by Qikprop Maestro 9.3 molecular docking suite

	Molecule	QPlog Po/w	CIQPlog S	QPlog HERG	QPPCaco	QPlog BB	QPPM DCK	QPlog Kp	QPlog Khsa	PHOA
Control	CID3062316	2.615	-4.859	-7.142	68.63	-1.154	82.27	-5.182	0.13	75.13
	CID10302451	3.539	-4.804	-7.788	256.3	0.55	270.278	-4.882	0.25	77.822
	CID5328940	4.241	-6.233	-7.589	111.7	0.199	300.382	-5.495	0.524	75.479
IBS	STOCK1N-75795	1.476	-3.618	-2.956	19.98	-1.614	9.161	-4.602	-0.358	58.865
	STOCK1N-80087	2.428	-4.377	-5.079	206.0	-1.356	283.917	-3.81	0.006	82.576
	STOCK1N-72227	3.62	-6.188	-6.673	1143.	-0.632	572.044	-1.577	0.334	100
	STOCK1N-79428	0.355	-4.744	-4.921	9.226	-2.983	7.344	-5.211	-0.552	46.294
	STOCK1N-72232	4.329	-6.576	-7.447	981.003	-0.76	484.559	-1.371	0.627	100
	STOCK1N-72129	4.29	-6.093	-7.217	1130.332	-0.765	564.754	-1.388	0.574	100
	STOCK1N-72552	3.275	-5.508	-6.826	637.785	-1.018	304.247	-2.043	0.208	96.318
	STOCK1N-72314	4.155	-5.786	-7.293	1153.554	-0.671	577.306	-1.31	0.555	100
	STOCK1N-26287	5.677	-6.884	-6.743	2080.244	-0.361	1091.92	-1.087	1.182	100
	STOCK1N-71839	2.69	-4.184	-5.794	840.764	-0.673	410.139	-2.396	0.13	95.042

Molecule CID, Pubchem IDs

Molecule STOCK, InterBioScreen's library (IBS)

QPlog Poct; was predicted partition coefficient of octanol/gas, (8.0 to 35.0)

QPlogPw; was predicted partition coefficient of water/gas (4.0 to 45.0)

PlogPw; was Predicted octanol/water partition co-efficient log p (recommended range: -2.0 to 6.5)

QPlogS; was Predicted aqueous solubility; S in mol/L (acceptable range: -6.5 to 0.5)

Predicted IC_{50} value for blockage of HERG K+ channels; (acceptable range: above -5.0)

QPP Caco-Predicted apparent Caco-2 cell permeability in nm/sec. Caco-2 cells is a model for the gut blood barrier; (nm/sec) <25-poor >500- great

QPlog BB- Predicted brain/blood partition coefficient

QPPMDCK -Predicted apparent MDCK cell permeability in nm/sec. MDCK cells are considered to be a good mimic for the blood-brain barrier; (nm/sec) <25-poor >500- great

QPlog KP- Predicted skin permeability; Q P log K_{hsa-} Prediction of binding to human serum albumin; (acceptable range: -1.5 to 1.5)

Percentage of Human Oral Absorption; (<25% is poor and >80% is high)

CONCLUSION

In this study, we aimed to identify Src kinase inhibitors by using Maestro 9.3 molecular docking suite. STOCK1N-75795, STOCK1N-80087, STOCK1N-72227, STOCK1N-79428, STOCK1N-72232, STOCK1N-72129, and STOCK1N-72552 compound containing quinazoline and aminothiazole as a structural Skelton have a better binding energy as well as binding conformation. Protein-ligands interactions are disclosed that amino acids Met341 and Glu339 intricate in the hydrogen bonds, salt bridges, and metal interactions. Nevertheless, amino acids Leu393 and Ala403 are convoluted, in hydrophobic interactions. Foremost, STOCK1N-80087, STOCK1N-72227, and STOCK1N-72232 are their excellent QPlogPo/w, CIQPlogS, QPlogHERGK^+ channels, QPPCaco, QPlogBB, QPPMDCK, QPlogKP, QPlogKhsa and percentage of human oral absorption values which satisfy the Lipinski's Rule of Five. Further *in vitro* and *in vivo* experimental work is required for validation of our *in silico* results, as well as identification of c-Src inhibitor.

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Conflict of interest- None

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