



Molecular docking analysis of curcumin analogues against kinase domain of ALK5

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Abstract

During metastasis, cancer cells transcend from primary site to normal cells area upon attaining epithelial to mesenchymal transition (EMT) causing malignant cancer disease. Increased expression of TGF- β and its receptor ALK5 is an important hallmark of malignant cancer. In the present study, efficacy of curcumin and its analogues as inhibitors of ALK5 (TGF β R-I) receptor was evaluated using in silico approaches. A total of 142 curcumin analogues and curcumin were retrieved from peer reviewed literature and constructed a combinatorial library. Further their drug-likeness was assessed using Molinspiration, cheminformatics and preADMET online servers. The interaction of 142 curcumin analogues and curcumin with ALK5 receptor was studied using Autodock Vina. This study revealed six curcumin analogues as promising ALK5 inhibitors with significant binding energy and H-bonding interaction.

Keywords EMT · Metastasis · TGF- β · ALK5 · Autodock Vina · Curcumin · Curcumin analogues

Background

Transforming growth factor- β (TGF- β) emerged as a potent cytokine that play a critical role in several biological process, such as immune response, inflammation, wound healing, extracellular matrix (ECM) formation and remodeling, embryonic development through EMT (Massagué Joan 2012; Dijke Peter et al. 1997) and regulate key cellular functions such as differentiation, migration and death during normal development. Excessive production/activation of TGF- β implicated in wide spectrum of pathological conditions such as cancer, fibrotic disorders, myelodysplastic syndrome, autoimmune diseases and Marfan syndrome (Masagué 2008, 2000; Akhurst and Derynck 2001).

TGF- β signals through two serine/threonine kinase receptors, the type I (TGF β R-I) and type II (TGF β R-II) receptors. The type I receptor is inactive in the absence of ligand while type II receptor is constitutively active. (Massagué 1998; Wrana 1994). The binding of TGF- β to its receptors induces the oligomeric receptor-ligand complex formation which enables the type II receptor to phosphorylate the type I receptor, known as Acting Receptor-like Kinase 5 (ALK5) in the GS domain (Wrana 1994a; Shi 2003). Activated T β RI with the help of SARA (Smad Anchor for Receptor Activation) recruits and phosphorylates Smad2/Smad3 (R-Smads) (Tsukazaki 1998). Phosphorylation of R-Smads leads to the dissociation from SARA to form a homo-oligomeric complexes with Smad4, which eventually translocating the complex into the nucleus involved in regulating the target gene transcription process. Deregulation of TGF- β signaling implicated in many human disease including cancer cells to flee from primary site through the induction of EMT that ultimately leads to cancer metastasis. During EMT, epithelial cells acquire mesenchymal phenotype, leading to enhanced motility and invasion property (Xu 2009).

Several small molecules of LY2109761 (Melisi et al. 2008), Galunisertib (LY2157299) (Phase 2/3) (Liu et al. 2009), LY364947 (Li et al. 2006), SB505124 (DaCosta et al. 2004) that bind ALK5 were reported. Among ALK5

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inhibitors only Galunisertib was proven to be safe and passed phase I and phase II clinical trials against hepatocellular carcinoma (HCC) and pancreatic cancer (Jin et al. 2014) and EW-7197 is under phase I clinical trial against advanced stage solid tumors research (Son et al. 2014). ALK5 inhibitors specifically occupying the ATP binding site of ALK5 kinase domain, which phosphorylates SMAD2 and SMAD3 and ultimately inhibit SMAD signaling pathway. Hence, new ALK5 inhibitors are propinquity need for the treatment of cancer and related diseases.

Curcumin, the main active component of turmeric, is a polyphenol derived from the rhizomes of *Curcuma Longa* Linn. It has been used for centuries in folk medicinal remedies, daily dietary spice and as a coloring agent in Asian countries (Ammon and Martin 1991; Gupta et al. 2012). Numerous evidences point that the pleiotropic nature of curcumin is having anti-inflammatory (Gupta et al. 2012), antioxidant (Sharma 1976), anti-microbial (Negi et al. 1999) as well as anticancer activities (Kuttan et al. 1985). While some of the experimental evidence authenticate non-toxic effect in high dose (Senft et al. 2010). Nevertheless, poor stability and bioavailability of curcumin prevents its potency as selective cancer drug and to overcome this property, researchers have been focusing on the synthesis of new curcumin analogues. Several curcumin-analogues proved to be effective in preclinical studies (Allegra et al. 2017) and several reports have been unveiled reduced expression of TGF- β receptor type I (T β R-I) and TGF- β receptor type II (T β R II) expression in several epithelial cells and inhibited TGF- β induced EMT during fibrosis and cancer (Li et al. 2013; Gaedeke et al. 2004).

In the present study, we investigate the potential of curcumin and its analogues (curcuminoids) against TGF- β receptor type I (ALK5) by molecular docking studies.

Methods

Preparation of ligands

The IUPAC name of curcumin and its analogues were procured from peer reviewed literature (Ahmed et al. 2013) and using OPSIN (Open Parser for Systematic IUPAC nomenclature) (<http://opsin.ch.cam.ac.uk/>) 'SMILES' of curcumin and its analogues were fetched (Lowe et al. 2011). They are used as an input to identify the 2D structure of curcumin and its analogues in ChemSpider database (<http://chemspider.com/>) and the PDB file of ligand were generated using Open Babel software (Pence and Williams 2010; O'Boyle et al. 2011). The known inhibitors of ALK5 such as Ly364947, SB431543 and SD-408 were reaped through ChemSpider database (Li et al. 2006; Callahan et al. 2002). Energy minimization was carried out using PRODRG server and PDB

file of curcumin and its analogues with known inhibitors were converted into PDBQT file format using Auto Dock Tool (ADT) for further analysis (Morris et al. 1998).

Preparation of receptor

The atomic coordinates of ALK5 kinase domain was retrieved from the RCSB PDB (<https://www.rcsb.org/pdb/home/home.do>). The co-crystallized structure of ALK5 (PDB ID: 1RW8, resolution: 2.4 Å) was retrieved and selected for docking study (Sawyer et al. 2004). Prior to docking analysis, the structure was emended by removing co-crystallized heteroatoms and water molecules using SPDBV software, followed by addition of polarhydrogen and Gasteiger charges using Auto Dock Tool (ADT). Then structures were saved in PDBQT files, for further analysis.

Drug-likeness prediction

Drug likeness provides whether the molecule of interest is similar to known drug based on the molecular and structural features of drug molecule. The important properties of drug likeness are hydrophobicity, hydrogen bonding, electron distribution, molecular size and other pharmacophore features influence the behaviour of a molecule in terms of bioavailability, transportation, toxicity, reactivity and other properties on living organism. In the present work the molecular properties and bioactivity of curcumin analogues was evaluated using Molinspiration cheminformatics server (<http://www.molinspiration.com/>). The server supports wide range of tools for the processing and manipulation of molecules including generation of tautomer, molecule fragmentation, normalization of molecules, calculation of various molecular properties needed in QSAR study as well supports fragment based virtual screening. The server calculate the molecular properties based on Lipinski Rule of five (Lipinski 2004) and predicts bioactivity score for the most important therapeutic targets like GPCR receptors kinase inhibitors, ion channel modulators, enzymes and nuclear receptors (Ertl et al. 2000).

Molecular docking studies

Binding mode and interaction of ALK5 with Curcumin and its analogues was performed using Autodock Vina platform (Trott and Olson 2010). This Program require pre-calculated grid box, Serves as frontier of active pocket amino acids in the receptor by attaining XYZ co-ordinates. The active pocket amino acid residues were identified using PoSSuM server (<http://possum.cbrc.jp/PoSSuM/>) by comparing the ALK5 (PDB ID: 1RW8) with other ALK5 crystallographic structure present within PDB. PoSSuM predicts the specific ligand for unbound structures and also enables rapid

exploration of similar binding sites among structures with different global folds as well as similar folds (Ito et al. 2015). The grid optimization was carried out using Autogrid program and the grid box was centered at region covering all the identified active pocket amino acid residues (ILE 211, LYS213, VAL219, ALA230, VAL231, LYS232, GLU245, TYR249, LEU260, PHE262, LEU278, VAL279, SER280, ASP281, TYR282, HIS283, LYS337, ASN338, LEU340, ALA350, ASP351). The grid box size was set at 16, 16 and 16 and centered on mass center 3.753, 15.918 and 9.96 for x, y and z co-ordinates respectively with space separated by 1.0 Å (grid-point spacing). The exhaustiveness was set to the value of 10 for all docking analysis. Docking was accomplished under AutoDock program, and ten different mode of confirmations were generated with their respective binding energy/affinity. Lowest binding energy results were considered for further post docking analysis. Docked complex of ALK5 protein and curcumin and its analogues with good binding affinity were visualized in Pymol viewer, then LigPlot 1.4.5 was used to generate two dimensional docking for the analysis of hydrogen bond and hydrophobic interaction (Wallace et al. 1995).

ADMET prediction

PreADMET is a web-based application used to predict ADMET (absorption, distribution, metabolism, excretion and toxicity) (<http://preadmet.bmdrc.kr/>) of curcumin and its analogues possessing good binding affinity with receptor protein based on lowest binding energy. The ADMET is the most important parameter in drug discovery studies and is considered before designing drug as attributes of the molecules play decisive role in pre-clinical and clinical phase. The Caco2 cell (human colon adenocarcinoma) and MDCK (Madin-Darby Canine Kidney) cell models are important in the prediction of oral absorption and Human intestinal absorption (HIA) of drugs. Plasma protein binding (PPB) and blood brain barrier (BBB) are critical factor in distribution phase of the drugs. PreADMET predicts percentage of drug bound in plasma protein to emulate in vitro data on human and envisage in vivo data based on the value of BBB penetration. The drug action depends on its interaction with plasma proteins, generally unbound drug molecule shows better interaction with target molecules, which influence directly/indirectly on dissemination and efficacy of the drug molecule.

PreADMET predicts toxicity value based on Ames test and the value of the prediction results would be decided either as “positive” or “negative”. Finally carcinogenicity was speculated using preADMET, based on NTP (National Toxicology Program) and which comprise results of the in vivo carcinogenicity tests in mice and rats during 2 years (Yamashita et al. 2000).

Metabolic site prediction

MetaPrint 2D server was used to predict the sites of metabolism of the best docked compounds, that are most likely undergo phase I metabolism (Carlsson et al. 2010). This software was used on the web platform (<http://www-metaprint2d.ch.cam.ac.uk/metaprint2d/>), by uploading the SMILES string of compounds.

Results and discussions

A total of 143 Curcumin analogues (including curcumin) were collected from the literature with their complete information including PubChem Id as furnished in the supplementary Table 1.

Drug-likeness properties

The drug-likeness properties of 143 Curcumin analogues obtained from Molinspiration server are framed in Supplementary Table 2. It deduce that only 139 molecules possess molecular weight in the acceptable range ($MWT \leq 500$), and four molecules violated the Lipinski's rule of five thereby excluded for further analysis, as an important phenomenon which determines directly the discovery of drug effecting the target function. The number of hydrogen bond donors (OH and NH atoms) and acceptors (O and N atoms) in Curcumin analogues were found to be 0 to 8 and 0 to 5 respectively, which establishes Lipinski's limit range less than 10 and 5 respectively (Lipinski 2004). Lipophilicity and Hydrophobicity of the molecule play an important role in distribution phase of drug molecule and is evaluated under the MLogP value (octanol/water partition co efficient) (Clark 1999). The MLogP of all the curcumin analogues were within the acceptable range (< 5 Lipinski's rule).

TPSA (Topological Polar Surface Area) is another important physicochemical property used to predict drug distribution attributes based on sum of all polar atoms such as oxygen, nitrogen and attached hydrogen. TPSA is a good descriptor illustrating intestinal absorption, hydrogen bonding potential, bioavailability, blood brain barrier penetration (BBB) and Caco-2 cell permeability. The TPSA value ≤ 140 Å and number of rotatable bonds (≤ 10) indicate good bioavailability (Clark 1999). The number of rotatable bonds found to be ≤ 10 in 119 curcumin analogues excluding 20 molecules. Rotatable polar atomic bonds increase the flexibility of molecules for more adaptable and efficient interaction with the enzyme active site and the value of TPSA of all curcumin analogues found to be in the range of 0.00–140 Å explicitly showing good oral bioavailability.

Biological activity of the curcumin analogues were evaluated against GPCR ligand, kinase inhibitor, nuclear receptor

Table 1 Top curcumin analogues showing highest binding energy

Symbol	ChemSpider ID	IUPAC name of the compound
S4	4579943	(1E, 6E)-1-(3,4-dihydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene- 3,5-dione
S5	4579942	(1E,6E)-1,7-bis(3,4-dihydroxyphenyl)hepta-1,6-diene-3,5-dione
S6	24660343	(1E,6E)-1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl)hepta-1,6-diene-3,5-dione
S30	24676587	(1E,6E)-1-(4-hydroxy-3-methoxy-5-nitrophenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione
S57	–	(E)-7-(3,4-dihydroxyphenyl)-1-(4-hydroxy-3-methoxyphenyl) hept-4-en-3-one
S58	–	(E)-1-(3,4-dihydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl) hept-4-en-3-one

ligand, ion channel modulator, protease and enzyme inhibitory activity (Supplementary Table 3). The molecule having bioactivity score more than 0.00, is likely considerable biological activity, score between -0.50 and 0.0 indicate moderate activity and if the score less than -0.50 shows the inactive state. The present study illustrates that the curcumin analogues are biologically active and exhibit physiological effect with nuclear receptor ligands, inhibiting proteases, GPCR ligands and other enzymes. The bioactivity score for GPCR ligand, Ion channel modulator, Kinase inhibitor, Nuclear receptor ligand, protease inhibitor and enzyme inhibitor was found to be < -0.50 for all tested molecules excluding five molecules.

Taken together the results show that curcumin and its analogues having significant physicochemical properties in consonance with better biological activity.

Molecular docking studies

All 139 Curcumin analogues showing the good drug-like-ness properties were docked against kinase domain of ALK5 along with known inhibitors. Based on binding energy, the ligands were sorted and compared with known inhibitors. The results shows binding energy of S4, S5, S6, S30, S57 and S58 providing a decent antagonists based on docking energy above -10.0 kcal/mol. Among them binding energy

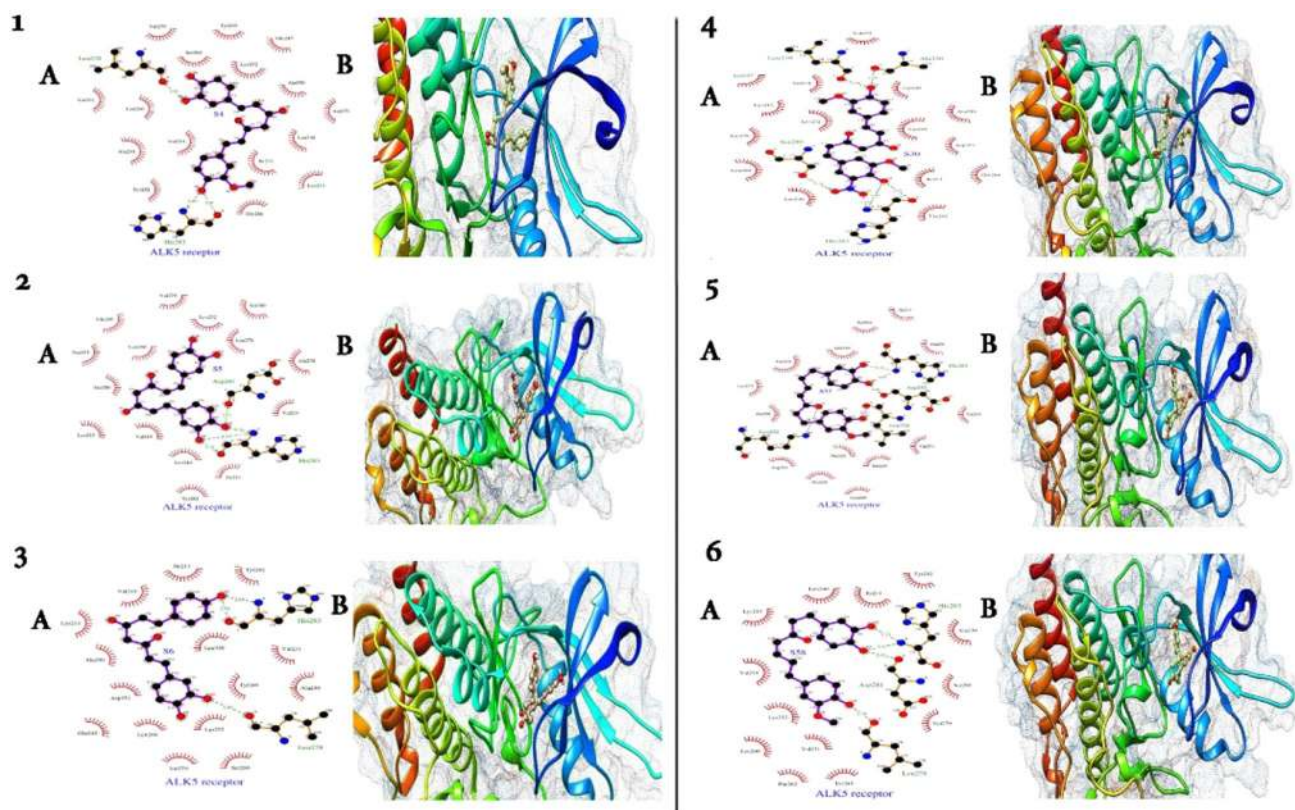


Fig. 1 Molecular docking study: Ligand as ball and stick (1B. S4; 2B. S5; 3B. S6; 4B. S30; 5B. S58; 6B.S59) at the binding pocket of ALK5 receptor

Table 2 Molecular docking results of curcumin analogues against ALK5 receptor

Compounds	Binding energy (kcal/mol)	Protein ligands interaction		
		No. of H bonds	Amino acid residues	Distance (Å)
S4	− 10.0	3	Leu278	2.91
			His283	2.80, 3.04
S5	− 10.2	4	Asp281	2.71
			His283	2.72, 3.33, 3.15
S6	− 10.2	3	Leu278	2.86
			His283	2.88, 2.92
S30	− 10.0	6	Leu278	2.70
			Ala230	2.89
			Ser280	3.11
			His283	3.18, 3.03, 2.97
S57	− 10.0	5	Lys232	3.16
			Leu278	2.87
			Asp281	2.86
			His283	3.05, 3.15
S58	− 10.0	4	Leu278	2.78
			Asp281	2.91
			His283	3.17, 3.24
Known Inhibitors				
LY364947	− 10.2	—	—	—
SD-208	− 10.0	—	—	—
SB505124	− 10.2	1	Ser280	2.88

of S5 and S6 are close to known inhibitors by exhibiting H-bonding (Table 1). The complete results were furnished in the Supplementary Table 4.

These Curcumin analogues were classified into four groups based on the middle-linear seven carbon linkage between phenyl rings and β -diketone, monoketone, pyrazole, and isoxazole group (Ahmed et al. 2013). The S4, S5,

S6 and S30 molecules belongs to β -diketone group and the remaining S57 and S58 belongs to monoketone.

Theoretically, all the six curcumin analogues exhibit good binding energy compared to the reference drugs LY364947, SD-208 and SB505124. The curcumin analogues S4, S5, S6, S30, S58 and S59 form hydrogen bond and the bond lengths ranging from 2.70 to 3.33 Å with the active pocket amino acid residues Leu278, His283, Asp281, Ala230, Ser280 and Lys232 of 1RW8 (Fig. 1). When compared with known inhibitors the curcumin analogues are having better hydrogen bonding potential with the active pocket amino acid residues of the receptor molecule (Table 2).

Pharmacokinetics and toxicity

Pharmacokinetics attributes of six curcumin analogues holding better binding energy were further evaluated using preADMET program. Molecules retaining weak pharmacokinetic and higher toxicity properties get failed in clinical trials. The physicochemical properties such as lipophilicity (clogP), polar surface area, molecular weight (MW) and aqueous solubility (logS) were earlier evaluated using molinspiration server, these properties affect absorption and bioavailability of drug molecule. When compared with known inhibitors (LY364947, SD-208 and SB50512), the curcumin analogues pertaining almost similar physicochemical properties are listed in the Table 3. Lipophilicity (log P) is important property for the calculation of oral availability of the molecules. The six Curcumin analogues have ideal log p value ranging from 1.62 to 3.02 (≤ 5). TPSA (Topological Polar Surface Area) of the curcumin analogues is found to be 140 Å indicating the good bioavailability (Veber et al. 2002). The number of rotatable bond in curcumin analogues is above 5 when compared with known inhibitors, which indicate that the curcumin analogues are more flexible than known inhibitors as a result of which it shows good binding potentials in docking studies. The number of hydrogen bond

Table 3 Comparison of physicochemical properties of top six curcumin analogues against known inhibitors

No	Compounds (chemspider ID)	Molecular properties						
		MW	miLogP	TPSA	nON	nOHNH	nrotb	Volume
S4	4579943	354.3533	2.00	104.06	6	3	7	314.65
S5	4579942	340.3268	1.69	115.05	6	4	6	297.13
S6	24660343	324.3273	2.18	94.83	5	3	6	289.11
S30	24676587	413.3775	2.42	138.89	9	2	9	355.52
S57	—	342.3856	3.02	86.99	5	3	8	318.66
S58	—	342.3856	3.02	86.99	5	3	8	318.66
S59	553011	328.3591	2.71	97.98	5	4	7	301.13
Known inhibitors								
1	394909 (LY364947)	272.31	2.81	54.47	4	1	2	243.37
2	8491497 (SD-208)	352.76	3.84	76.49	6	1	3	280.94
3	8034640 (SB505124)	335.41	3.88	60.04	5	1	3	310.21

acceptors and donors in the curcumin analogues are in the ideal range of 0–8 and 0–5 respectively.

The HIA (human intestinal absorption) value for all six curcumin analogues and known inhibitors are in the range of 80–100%. This indicates that all curcumin analogues can be well absorbed via intestinal tract. In addition, curcumin analogues show average permeability to Caco2 cell (4–70) and to MDCK cell model (predicted value in the range 4–70) except S57 and S58 (predicted value above 70). In the distribution phase, the PPB binding assessment of curcumin analogues exhibit strong binding energy with plasma proteins (predicted value above 90%) except S4 and S30(< 90%). Generally weak plasma protein binding compounds exist freely for transport across the cell membrane and also for interaction with target. In addition, BBB penetration revealed that the S4, S5, S6 and S30 curcumin analogues showed low absorption in CNS (predicted value less than 0.1), while S57 and S58 has shown middle absorption (predicted value between 2.0 and 1.0). On the other hand known inhibitors shows high absorption to CNS compared to curcumin analogues by illustrating minimal side effects of curcumin analogues. The skin permeability is an another important risk assessment factor of the compounds during accidental contact with the skin and all the six curcumin analogues had revealed least skin permeability compared with the known inhibitors (Singh and Singh 1993) as shown in the Table 4. In the toxicity phase, the carcinogenic and mutagenic effects of curcumin analogues were evaluated. Ames test is a simple method to test mutagenicity of six curcumin analogues, among them S30, S57 and S58 had shown positive result indicating that these analogues act as mutagens, and the remaining S4, S5 and S6 had shown negative property depicting non-mutagen type. Finally, The drug-likeness and ADMET values of curcumin analogues with known inhibitors connotes that the selected curcumin analogues S4, S5, S6, S30, S58 and S59 are having the potential to act as good inhibitors against ALK5 receptor.

Prediction of metabolic site curcumin analogues

MetaPrint 2D predictor is a fast, efficient and accurate predictor which uses circular fingerprints and substrate/product ratios for predicting the sites and products of metabolism in small molecules. The atoms indicated in orange color would be moderately active at metabolic site, green color atoms indicate low metabolic active site, whereas red color atoms indicate high metabolic active site and no color would be metabolically very less/nil active (Boyer et al. 2007).

All the selected compounds-metabolic sites have been shown in the Fig. 2, among them S5 compound has more metabolic site than other compounds. In the case of lead S5 compound, the carbon atom number two, three, eighteen

Table 4 Comparison of ADMET properties of top six curcumin analogues against known inhibitors

Name	ADMET	Toxicity							Rodent carcinogenicity	
							Ames test			
		Compounds (chemspider ID)	HIA (%)	PPB (%)	BBB (%)	Caco2 (nm/sec)	Skin-permeability	MDCK (nm/sec)	Carcino_Mouse	Carcino_Rat
S4	4579943	90.52	89.31	0.317	18.34	− 2.93	78.55	Non-mutagen	Negative	Positive
S5	4579942	83.96	95.62	0.479	18.89	− 3.15	53.37	Non-mutagen	Negative	Positive
S6	24660343	90.32	94.04	0.783	19.99	− 2.93	20.10	Non-mutagen	Negative	Positive
S30	24676587	85.47	89.19	0.070	12.09	− 2.36	15.99	Mutagen	Positive	Positive
S57	−	90.25	100.0	1.290	18.55	− 2.46	96.52	Mutagen	Negative	Positive
S58	−	90.25	100.0	1.217	19.45	− 2.46	96.52	Mutagen	Negative	Positive
Known inhibitors										
1	394909 (LY364947)	93.34	91.17	2.29	20.36	− 3.76	274.5	Mutagen	Negative	Negative
2	8491497 (SD-208)	96.39	100.0	0.17	27.67	− 3.79	31.05	Mutagen	Negative	Negative
3	8034640 (SB505124)	92.98	88.26	4.50	44.59	− 3.23	14.51	Non-mutagen	Negative	Positive

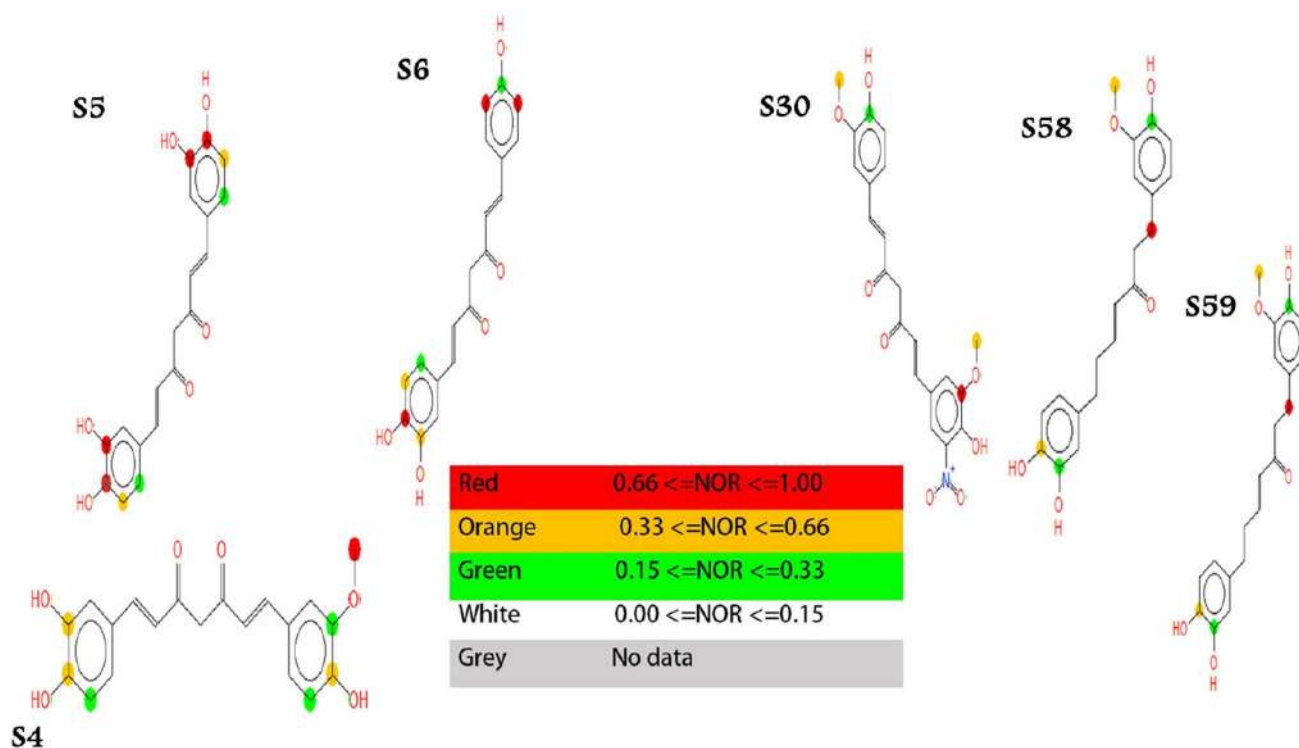


Fig. 2 Metabolic site of lead molecules: NOR indicates the Normalized Occurrence Ratio; a high NOR indicates a more commonly reported site of metabolism in the metabolite database. The atoms are

colored according to the chances of a metabolic site; No data: grey, Very low: Not colored, Low: green, Medium: orange and High: red

and nineteen showed high metabolic site. The carbon atom fourth and seventeenth exhibit moderate metabolic site and the carbon atom in five and sixteen shows low metabolic active site. Through molecular docking studies the Selectivity and steric information of the potential compounds studied, these helpful in predicting the site of metabolism and possible toxic metabolites.

Conclusion

In the present study, six curcumin analogues S4, S5, S6, S30, S58 and S59 have shown promising ALK5 inhibition with excellent binding affinity as well as drug-likeness. Among them, S5 and S6 have been validated in all the drug designing parameters by showing significant binding interaction with the conserved amino acids in the receptor molecule by depicting greater binding affinity compared to standard ALK5 inhibitors. With these results, the selected curcumin analogues were further explored for detailed investigations and structural modification to arrive possible newer potent agents with better therapeutic activity against ALK5 receptor.

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Authors' contributions SK and SBS carried out the literature survey and molecular docking studies. UH carried out Drug-likeness and ADMET analysis. Dr. BBR and Dr. MH have guided and supported in the preparation of manuscript. All authors have read and approved the final manuscript.

Competing interests All authors declared that they have no competing interest.

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