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Molecular Docking and ADME Study of Quinoline and Chalcone based Derivatives for Anti-Cancer Activity

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ABSTRACT

Cancer is a big issue that affects people all over the world. It develops as a result of uncontrolled cell growth. The interaction between developed ligands and thymine phosphorylation was investigated in this study, which was computationally optimized. The aim of this study was to examine the anticancerous activity of designed ligands in thymine phosphorylation (PDB ID: 1UOU) in order to minimize the cost and time required to develop a novel anticancer drug with minimal side effects. All the designed ligands showed mild to excellent binding with proteins. Most of the ligands exhibited better interaction compared to reference compound Tamoxifen with pdb files. Some of the designed ligands among (1-7) in qunoline derivatives and (1-5) in Chalcone derivatives showed excellent docking scores with PDB file (1UOU) of thymine phosphorylation. All the designed ligands and Zinc databases were docked with 1UOU PDB files of protein, and it was found that out of twenty-five designed ligands in Qunoline series, ligand 25 showed the best binding (docking score −8.268) with 1UOU PDB of protein thymine phosphorylation. And that out of ten designed ligands in Chalcone series, ligand K1 showed the best binding (docking score −9.433) with 1UOU PDB of protein thymine phosphorylation. Docked ligand cavity of ligand ku 25 in qunoline series and K 9 in Chalcone series showed important hydrophobic/non-polar residues such as Ile199, Ile316, Trp119, Phe168, Ile198, Cys172, Tyr188, Tyr398, Tyr435, Phe343, Tyr60, Leu328, Leu171, and showed pi-pi interaction with Tyr326. Further wet laboratory studies are continued in our laboratory to confirm and find out the efficiency and activity of target compounds.

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INTRODUCTION

Despite the development of several cancer drugs in recent years, cancer remains the leading cause of death in humans. In a cell screen study, Tamoxifene had the strongest tumor inhibition effect. Tamoxifene markedly increased intracellular ROS and induced apoptosis in human cancer cells, as well as suppressing the proliferation of the xenografted tumor. Thymidine phosphorylase (TP) is a nucleoside metabolic enzyme involved in the pathway of pyrimidine salvage (El-Karim *et al.*, 2015). Thymi-

dine phosphorylase is a protein dimer with similar subunits that aids in the recovery of nucleosides after the degradation of DNA or RNA. It assists in the maintenance of blood vessel integrity, promotes endothelial cell growth and has angiogenic and chemotactic activity. It is overexpressed in many solid tumors like lungs, breast, cervix etc. (Balakumar *et al.*, 2010).

Molecular docking is an application of molecular modeling and drug design, which gives the most possible and stable orientation of a molecule which interact with a biologically relevant molecule such as proteins, enzymes, carbohydrate, nuclear material like DNA, RNA and lipids and from a stable complex (Kitchen, 2004). Docking is frequently used to predict the binding orientation of small molecule drug-like candidates to their protein targets in order to, in turn, predict the affinity and activity of the small molecule. Hence, docking plays an important role in the rational design of drugs (Olivieri *et al.*, 2008). Docking protocols can be described as a combination of two components a search strategy and a scoring function. The search algorithm should generate an optimum number of configurations that include the experimentally determined binding mode (Taylor, 2010). A rigorous search algorithm would exhaustively elucidate all possible binding modes between the ligand and receptor. All six degrees of translational and rotational freedom of the ligand would be explored along with the internal conformational degrees of freedom of both the ligand and protein (Yongye *et al.*, 2010). A common approach in modelling molecular flexibility is to consider only the conformational space of the ligand, assuming a rigid receptor throughout the docking protocol. The docking accuracy in a rigid-body approach is much greater for bound complexes than uncomplexed molecules (Kim *et al.*, 2011). Even though the observed structural changes between the bound and free forms are small, the difference in accuracy implies that the assumption of rigidity is not fully warranted (Berry *et al.*, 2008). Also, the difference between the near-native structures and others far from native cannot be distinguished, even with simple scoring functions such as measures of surface complementarity (solvent accessible surface area (SASA) burial, solvation free energy, electrostatic interaction energy, or the total molecular mechanic's energy. Hence, the docking procedures were improved by several groups by allowing for receptor and ligand flexibility. (Redecker *et al.*, 2011). Feher and Williams continued studying the variability of docking outcomes as a function of input ligand conformations. Using GOLD, Glide, FlexX, and Surflex, they deconstructed this variability into two independent effects (Feher and Williams, 2010). The inadequacy of the conformational search during docking (major) and random chaotic effects due to sensitivity to (small) input perturbations (minor but significant). To assess the effects of such perturbations, they used the 0.1, 1, and 10 torsional grid ensembles for ligand input. The authors further elaborated their earlier recommendation about the use of multiple conformations as input (Yuriev and Ramsland, 2013). The interaction of a drug molecule with its receptor protein is a complex event encompassing the interplay in entropy and enthalpy of many forces: conformational flexibility, and electrostatic, hydrophobic, and vanderwaal's interactions (Goldman and Wipke, 2000). The docking algorithms suggest possible structures for molecular complexes. They are used to model biological function and to discover potential ligands (Wang, 2018; Welsh *et al.*, 2008).

ADME is an abbreviation in pharmacokinetics and pharmacology for "absorption, distribution, metabolism, and excretion" and also define the disposition of a drug within an organism. The SwissADME (http://www.swissadme.ch/) is an online website that allows you to compute physicochemical descriptors and to predict ADME parameters, drug-like nature and pharmacokinetic properties for multiple small molecules to support drug discovery (Daina *et al.*, 2017).

METHODS

Ligand preparation

All 25 compounds in Qunoline series, 10 compounds in Chalcone series and the Zinc database were imported in the molecular area of the Schrödinger module maestro (v5.2). Which converted into the 3D structure, than molecules were minimize using Ligand preparation (lig-prep) panel by sets the following parameter, pH of 7.0+/-2.0, force field used OPLS3e and RMSD cut-off of 0.01Å. Before the minimization and finally, run the lig-prep tool for minimization of energies. The minimized structures were saved as a lig-prep file into the working directory with the name as we given. (Table 1).

Protein preparation

The protein structures were imported into a molecular area and open the protein preparation wizard window, and analyze the workspace of the Schrödinger window (Chou *et al.*, 2018). Choose the preprocessing option and did for the selected protein structure. Whenever preprocess was done, deleted all the water molecules from the protein, except those which play an important role in the

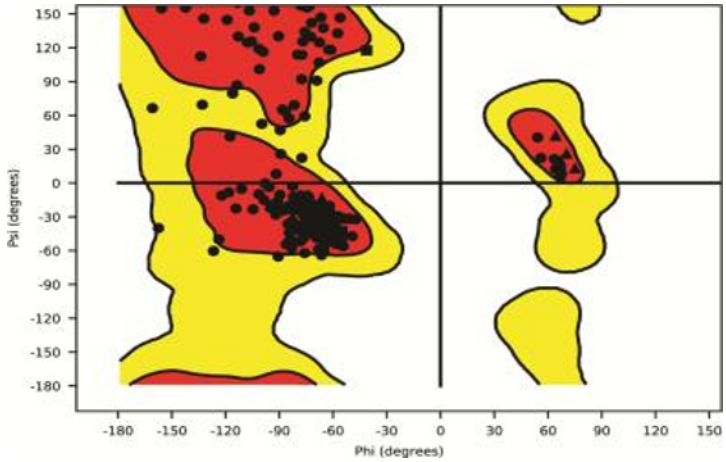

Figure 1: Ramachandran plot: red colour shows beta-sheet; yellow colour shows alpha helix Thymidine Phosphorylase receptor

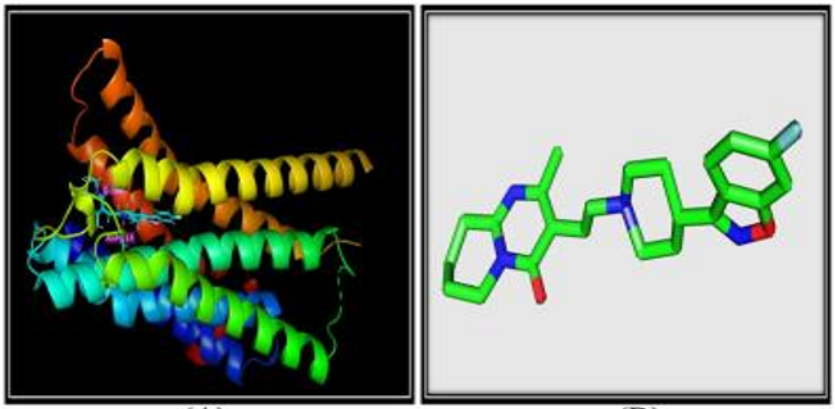

Figure 2: 3D view of fully prepared protein: Thymidine Phosphorylase (A); 3D view of co-crystallized ligand risperidone(B).

binding of ligand molecule (Farid *et al.*, 2006). After that, checked the problem box of the protein preparation wizard window and solve the problem by removing unwanted material like a solvent, chains, molecule etc. important water molecules are still remaining through optimizing the H-bond network in the refinement tab, at the last minimize the protein structure to achieve stabilization. The fully prepared Thymidine Phosphorylase protein structure (Figure 2) was validated through the Ramachandran plot (Figure 1). Here, the red area zone is allowed for beta-sheet and yellow for alpha-helix, but the white region of this plot are a strictly disallowed region except for the amino acid residue glycine due to the lacks of the side chain (Gilad and Senderowitz, 2014).

Receptor grid generation

A receptor grid was generated in the binding site of both the receptors. Receptor grid generation was carried by a selection of co-crystallized ligand into the protein structure (Vijesh *et al.*, 2013). In the receptor grid generation process, the tool of receptor grid generation automatically remove the co-crystallized ligand from its binding site and free the space for new docking of ligands. The receptor grid generated file saved in grid.zip format into the working directory (Oshiro *et al.*, 2004).

Molecular docking studies

Docking studies were performed on the data set by using software Schrödinger (v5.2). The target protein selected for molecular docking study is Thymidine Phosphorylase receptors. Protein structures were collected from protein data bank PDB ID: 1UOU for thymine phosphorylase receptor with co-crystallized ligand Tamoxifene (Wang *et al.*, 2018).

The validation of docking analysis was carried out using two scoring functions one is docking score, and another is glide score. The fully prepared protein structure and chemical structure of co-crystallized ligand Tamoxifene with the polar contacts (ASP155 and ASP114) are given in Figure 2.

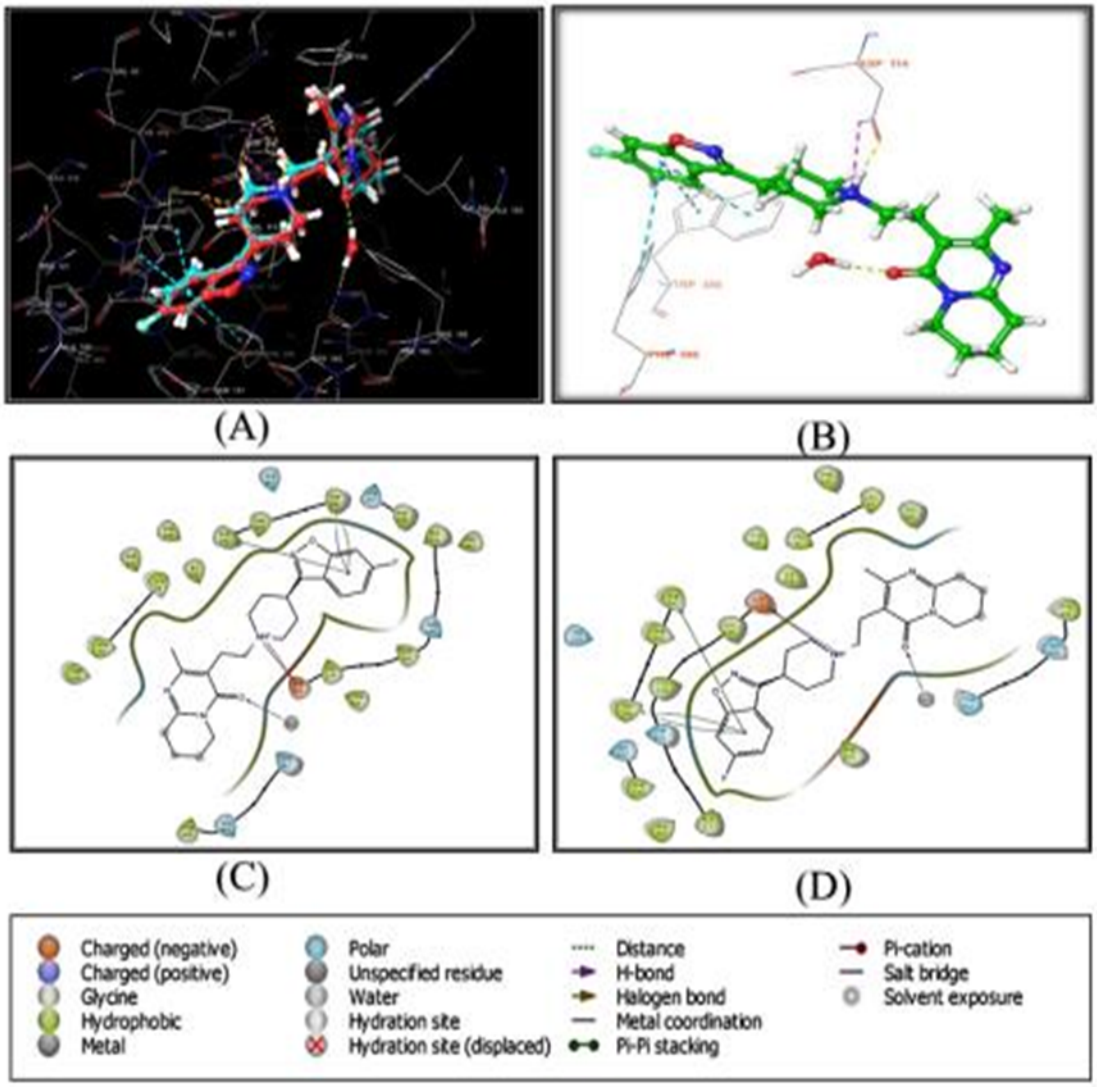

Figure 3: Bonding interactions of thymine phosphorylase receptor (PDB ID: 1UOU) R: Red colour,co-crystallized ligand, sky blue colour, re-docked ligand thymine phosphorylation (A); Interaction of re-docked reference ligand (B); 2Dinteractions diagram of co-crystallized ligand and re-docked ligand (C), (D).

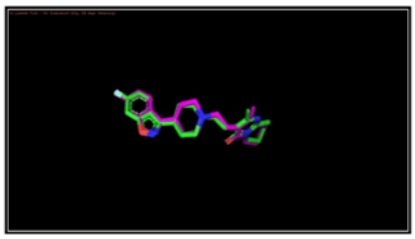

Figure 4: RMSD calculation: Green colour reference ligand risperidone another sky blue colour re-docked ligand thymine phosphorylation, Green colour reference ligand risperidone another magenta colour re-docked ligand thymine phosphorylase receptor(PDB ID: 1UOU);the calculated RMSD value is 0.24

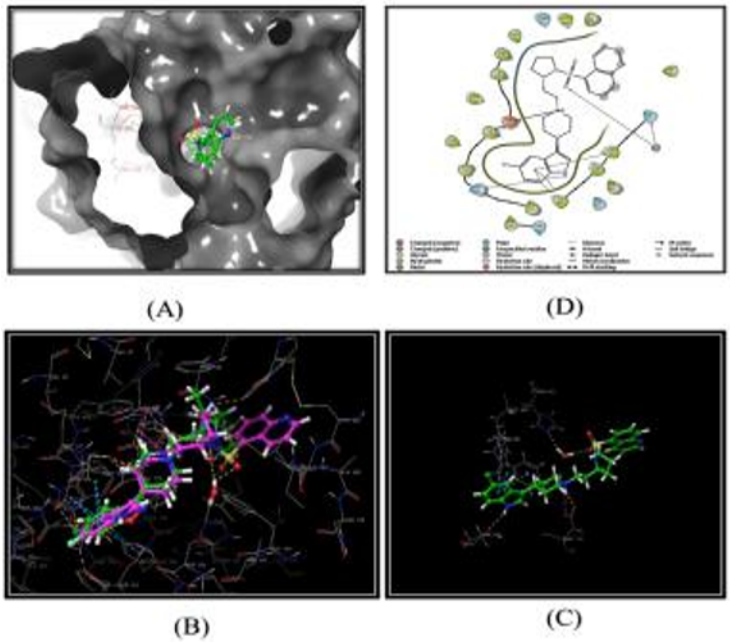

Figure 5: Molecular surface of the thymine phosphorylase receptor (PDB ID: 1UOU): Docked ligand with cavity1h (A); Co-crystallized ligand (green colour), docked ligand (pinkcolour) (B); Amino acid residue involved (1h) in bonding, (C); 2D interaction diagram,1h (D).

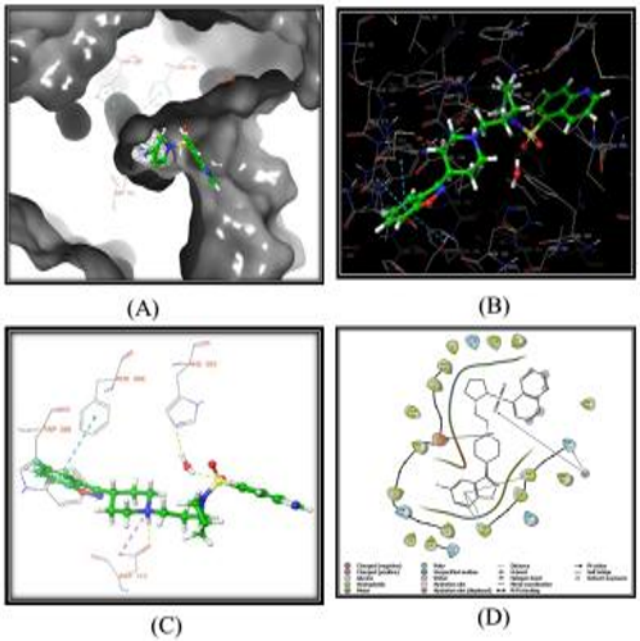

Figure 6: Molecular surface of the thymine phosphorylase receptor (PDB ID: 1UOU): Docked ligand with cavity KU 25 (A), (B); Amino acid residue.

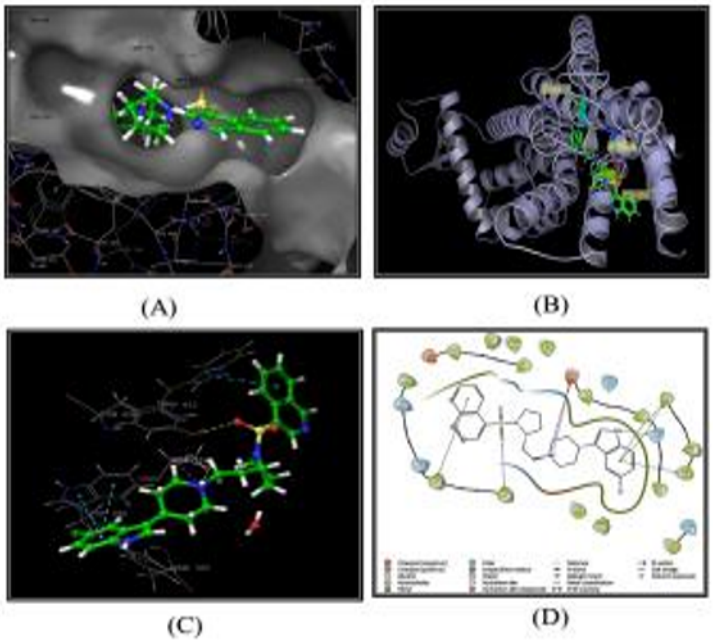

Figure 7: Molecular surface of the thymine phosphorylase receptor (PDB ID: 1UOU): Docked ligand with cavity K Q (A), (B); Amino acid residue involved (K 1) in bonding, (C); 2D interaction diagram, K 1 (D).

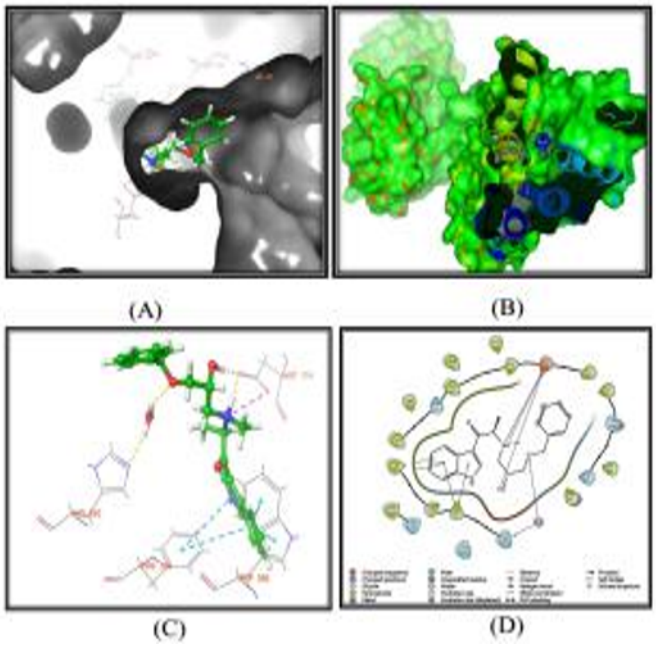

Figure 8: Molecular surface of the thymine phosphorylase receptor (PDB ID:1UOU): Docked ligand with binding cavity ZINC74289318 (A), (B); Amino acid residue involved (ZINC74289318) in bonding, (C); 2D interaction diagram, ZINC74289318 (D)

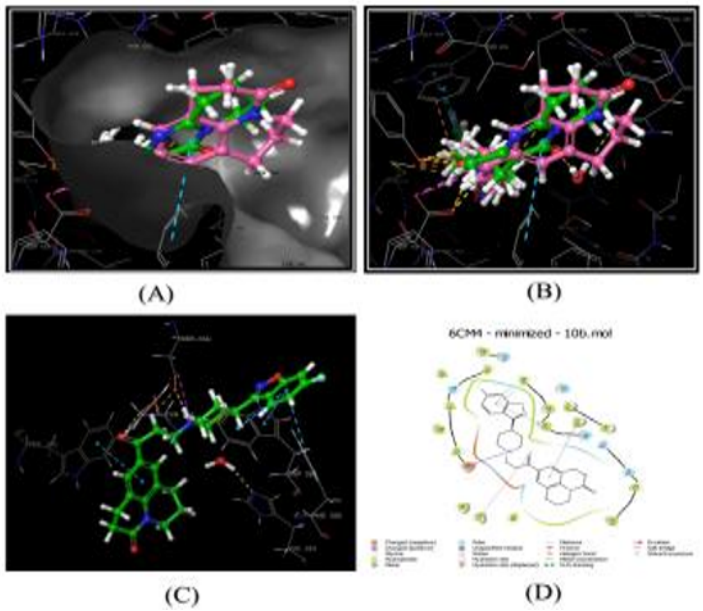

Figure 9: Molecular surface of the protein thymine phosphorylase (PDB ID: 1UOU); Co-crystallized ligand (greencolour) and docked ligand Ku 14 (pink colour) (A), (B); Amino acid residue involved (Ku 14) in bonding, (C); 2D interaction diagram Ku 14(D).

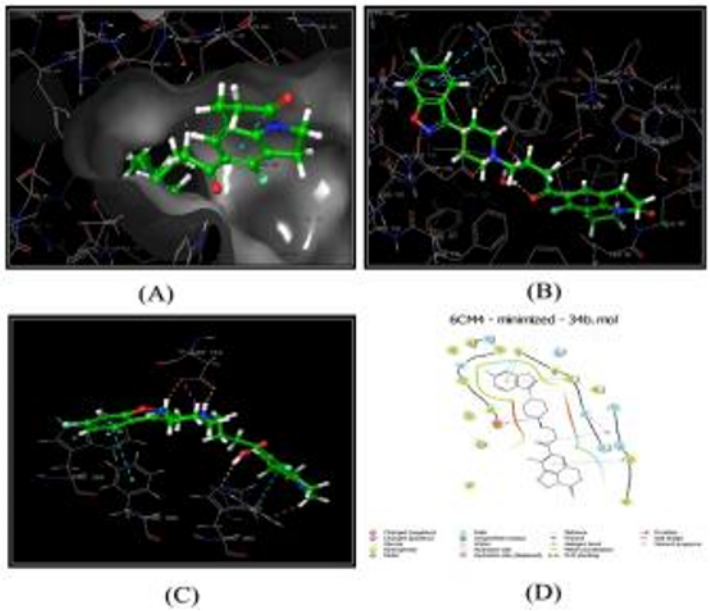

Figure 10: Molecular surface of the protein thymine phosphorylase (PDB ID: 1UOU); docked ligand K 3 (A), (B); Amino acid residue involved (K 3) in bonding, (C); 2D interaction diagram K 3 (D).

Table 1: List of compounds having best docking score and interactions on thymine phosphorylase receptor (PDB ID: 1UOU) series 1

Ligand	Docking Score	Glide Score
Ku-25	-8.268	-8.268
Ku-14	-7.921	-7.921
Ku-9	-7.976	-7.976
Ku-7	-7.643	-7.643
ZINC74289318	-11.388	-11.388
Tamoxifen	-10.086	-10.086

Table 2: Docking score results of docked Quniline series1 ligands, into the binding pocket of thymine phosphorylase receptor type.

S.No.	Compound name	Docking score	Glide score	Glide emodel
1	KU 25	-8.424	-8.424	76.488
2	KU 14	-8.268	-8.268	-76.488
3	KU 9	-7.976	-7.976	-83.137
4	KU 4	-7.921	-7.921	-73.752
5	KU 24	-7.79	-7.79	-74.26
6	KU 21	-7.775	-7.775	-71.207
7	KU 8	-7.722	-7.722	-44.168
8	KU 11	-7.643	-7.643	-79.548
10	KU 5	-7.569	-7.569	-73.419
11	KU 13	-7.51	-7.51	-73.637
12	KU 3	-7.385	-7.385	-65.206
13	KU 12	-7.218	-7.218	-55.433
14	KU 10	-7.145	-7.145	-65.76
15	KU 6	-7.068	-7.068	-64.275
16	KU 1	-6.954	-6.954	-57.215
17	KU 2	-6.936	-6.936	-59.884
18	KU 16	-6.916	-6.916	-56.99
19	KU 9	-6.904	-6.904	-62.13
20	KU 17	-6.798	-6.798	-41.923
21	KU 20	-6.402	-6.402	-66.019
22	KU 22	-6.251	-6.251	-51.12
23	KU 23	-5.864	-5.864	-60.883
24	KU 15	-5.741	-5.741	-56.591
25	KU 18	-5.623	-5.623	-51.085
26	KU 7	-5.442	-5.442	-59.236
27	ZINC74289318*	-11.388	-11.388	-92.66
28	Tamoxifen	-10.086	-10.086	-96.846

Ligand docking

The molecular docking was done using grade based ligand docking energetics (GLIDE) ligand docking panel. Glide's docking algorithm approximates a complete systematic search over ligand positions, orientation, and conformations in the receptor site (Pang and Kozikowski, 1994). A glide grid.zip file of the receptor was used in ligand docking panel, then choose prepared ligand file, used scaling factor 0.80 and partial charge cutoff 0.15, set standard docking precision method, dielectric constant 2.0, force field used OPLS3e, set number of pose per ligand set 2 and set rest of the all parameter as default. Finally, run the docking process and observe in run task option maestro (Bhosale *et al.*, 2020).

Validation of docking

Validation of docking procedure is performed to assure that the processes is accurate or not to validate the docking procedure, co-crystallized ligand Tamoxifene with thymine phosphorylase receptor (PDB ID: 1UOU) was re-docked with the same receptor at the same binding site. The interaction 2D diagram and pose (conformation) of the re-docked ligand are shown in Figure 3 respectively (Ricci and Netz, 2009). The docked conformation of both the ligand were re-align or superimpose to each other and calculated the rout mean square deviation (RMSD > 0.3), using PyMOL protein-ligand visualizer (v2.3.3), shown in Figures 4 and 3.

ADME Study

In this study, molecules were taken from series 1-3 on the basis of their binding interaction, docking scores and pharmacophore fitness results, and evaluate their ADME properties with Swissadme along with standard drug Tamoxifene. All compounds showed good pharmacokinetic properties. The software predicts different parameters like physicochemical properties, lipophilicity, a drug like nature,

Table 3: Docking scores of Chalcone series 2 ligands against thymine phosphorylase receptors.

S.NO.	Compound name	Docking score	Glide score	Glide emodel
1. 1.	K1	-9.533	-9.539	-93.155
1. 2.	K2	-9.324	-9.329	-89.884
1. 3.	K3	-9.304	-9.317	-82.381
1. 4.	K4	-9.299	-9.31	-88.717
1. 5.	K5	-9.299	-9.304	-89.796
1. 6.	K6	-9.296	-9.302	-89.764
1. 7.	K7	-9.254	-9.318	-90.879
1. 8.	K8	-9.156	-9.159	-76.905
1. 9.	K9	-9.052	-9.057	-81.357
1. 10.	K10	-9.011	-9.023	-84.539

water solubility, and permeability through BBB, pharmacokinetic and synthetic accessibility of the compounds (Bora-Tatar *et al.*, 2009).

The 2D structure of selected compounds were imported one by one and converted them into smile format using the Swissadme tool and run the panel to predict structural ADME features of compounds **(**http://www.swissadme.ch/).

RESULTS AND DISCUSSION

The file containing a list of best docking results of all the compounds against both the receptors with their glide Score, docking score and glide emodel scores listed in Table 1 for Qunoline series and Table 2 for Chalcone series along with Zinc database, docking interaction with crucial amino acid play an important role in receptor affinity were given in Table 3. Docking results of all the ligands shown in Table 1 and Table 2 against the thymine phosphorylase receptors. Among all compounds, ZINC74289318 showed promising interaction and binding scores for the receptor, which is greater than reference ligand Tamoxifene.

Among these all compounds, sometimes, the docking scores of a compound was good but poor the binding interactions Table 4 with protein in that situation we have to choose ligand having good docking scores as well binding interaction. The toped ranked molecules with the docking scores for the targets, listed in Table 1. The binding pocket of the ligands is given in Table 3.

Docking pose of thymine phosphorylase ligands

The binding of different ligands with its thymine phosphorylase receptor (PDB ID: 1UOU), in Figures 5, 6, 7 and 8, among of these ZINC74289318 showed good results and considered as a proto-type ligand for further study.

Table 4: Binding interaction of top scored compounds on thymine phosphorylase (1UOU) Series 1

Ligand	Amino acid residue	H-bond	Pi-Pi stacking	Pi-cation	Salt bridge
KU 25	ASP114	+	-	-	+
	THR119	+	-	-	-
	TRP386	-	+	-	-
	PHE390	-	+	-	-
	HID393-H2O	+	-	-	-
KU 14	ASP114	+	-	-	+
	TRP386	-	+	-	-
	PHE390	-	+	-	-
	HID393-H2O	+	-	-	-
KU 9	ASP114	+	-	-	+
	TRP386	-	+	-	-
	PHE390	-	+	-	-
	HID393-H2O	+	-	-	-
ZINC74289318	ASP114	++	-	-	+
	TRP386	-	+	-	-
	PHE390	-	+	-	-
	HID393-H2O	+	-	-	-
Tamoxifen	ASP114	+	-	-	+
	TRP386	-	+	-	-
	PHE390	-	+	-	-
	H2O	+	-	-	-

Table 5: Pharmacokinetic results

S. No.	Compound name	GI absorp-tion	BBB perme-ant	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4	Pgp sub-strate
1	Ku 25	High	Yes	No	No	Yes	Yes	Yes	Yes
2	Ku14	High	Yes	No	No	Yes	Yes	Yes	Yes
3	Ku9	High	No	Yes	Yes	Yes	Yes	Yes	Yes
4	Ku7	High	Yes	No	No	Yes	Yes	Yes	Yes
5	K1	High	No	No	Yes	Yes	Yes	Yes	Yes
6	K3	High	No	No	Yes	Yes	Yes	Yes	Yes
7	K7	High	No	No	Yes	Yes	Yes	Yes	Yes
8	ZINC74289318	High	Yes	No	No	No	No	No	No
9	ZINC385355656	High	Yes	Yes	Yes	Yes	Yes	Yes	yes
19	Tamoxifen	High	Yes	No	Yes	Yes	Yes	Yes	Yes

Molecular docking studies on series

Docking results of all the compounds of series 1 and 2oagainst the receptor are listed in Table 2 , the best docking scores possessing ligand were given in Tables 5 and 6, and the binding interaction of topped ranked molecules with the scores reference ligand Tamoxifen. Thymine phosphorylase receptor molecules Ku 25, Ku 14 shown good binding scores with -8.427, -8.268 in series 1 and k3, k1 in series 2 shown good binding scores with -9.564, -9.433 (docking score), which little bit lower than reference but the binding interaction residues of these ligands shown promising results than Tamoxifene (Figures 9 and 10).

ADME Study

The results were presented in terms of different pharmacokinetic profiles such as oral absorption, Lipinski's rule of five, permeability through blood-

Table 6: Results of ADME study. Physicochemical properties. (Kuseries of Qunolines ligands and K series of Chalcone ligands)

S. No.	Compound name	No. rot. bonds	No. H-bond donors	No. H-bond acceptor	Molar refractivity
1	Ku 25	6	1	5	153.65
2	Ku 14	6	1	7	149.74
3	Ku 9	6	0	5	154.73
4	Ku 7	6	1	5	153.65
5	Ku 13	5	0	5	129.62
6	Ku 20	7	0	6	139.65
7	K 1	5	0	6	134.85
8	K 3	7	0	7	134.07
9	K 7	6	0	8	144.31
10	K 9	6	0	8	144.31
11	ZINC74289318	9	2	3	108.93
12	ZINC385355656	6	1	4	138.8
13	Tamoxifen	4	0	6	117.71

brain barrier, octanol/water partitions coefficient, other cells permeability etc. (Qin *et al.*, 2015). The physicochemical properties of molecules shown in Table 6 indicated the most of the compounds showed molecular weight >500, number of hydrogen bond acceptors 1-8, number of hydrogen bond donor 0-2 and rotatable bonds between 4-9. Lipophilicity and synthetic accessibility of compounds reported water solubility parameter is shown in Table 6, some compounds like Ku 25, ZINC74289318, Ku 9, Tamoxifene showed moderate solubility in water, and others showed poor solubility. All the compounds had high GI absorption, and only a few compounds have BBB permeability. The overall results predicted with Swissadme, the compound ZINC74289318 found through pharmacophore-based vertual screening and 38b showed very good drug-likeness pharmacokinetic as well pharmacodynamics profile comparable with reference drug (Tamoxifene) Swissadme profile.

Docking of compounds found via virtual screening study of Zinc database based on pharmacophore models

Docking based virtual screening was carried out using ligands of a zinc data base. The pharmacophore hypothesis AHPRR_1 (series-one and two) and compound 1h was used for ligands screening, 40000 molecules were screen using Lipinski rule of five and collected from zinc database, and again filter by selected pharmacophore model, out 4000 molecules have drug-like properties, which further put for HTVS, standard precision and extra precision docking methods. The topped best glide docking score and binding interaction showed by ligand ZINC74289318, the docking scores and binding interaction was shown in Tables 1 and 3.

CONCLUSION

All the compounds in the dataset were docked in the same binding pocket as the binding pocket of co-crystallized ligand Tamoxifene to understand the binding interaction of these compounds with the thymine phosphorylase receptor. The compounds showed promising binding interactions desirable for inhibitory activity against the receptors. One of zinc database screened compound ZINC74289318 showed very promising results in terms of binding interaction and docking pocket binding energies scores towards the receptors.

The compound ZINC74289318 further showed promising results against the thymine phosphorylase receptor, the compound showed two hydrogen bonds with ASP114 and HID393, and two pi-pi stacking with PHE390 and TRP386. The docking scores were compared with Tamoxifene, and ZINC74289318 was showed higher scores against both targets, shown in Tables 1 and 3.

Further, we concluded that some compounds of series one and two not showed greater docking scores, but they showed greater and equivalent binding interaction like reference drug Tamoxifene. The compounds are ku25, Ku 9, ku14 (series one) and k 1, k 6 (series two).

The overall ADME profile studies of nine compounds suggested that the high GI absorption for all molecules in which only three compounds were

actively cross the blood-brain barrier, having soluble or moderately water-soluble profile. The synthetic accessibility of compounds and lipophilicity profile also showed good results. Some compounds like Ku 1, Ku 7 did not follow the Lipinski rule as because of the unsatisfactory ADME parameter. Only four compounds (Ku 25, ZINC74289318, ZINC385355656,) including reference compound Tamoxifene were showed drug-like properties and followed the rules of Swissadme. Among these molecules, ZINC74289318 and ku25,k1 have higher blood-brain barrier permeability, should not inhibit many cytochrome P-50 enzymes. It also have a -3.93 **(ESOL)** moderate-soluble profile in the water**,** followed Lipinski rule of five with little volition or no violation. These molecules can be considered as lead molecules for further studies.

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Authors Contribution

Did the literature survey from standard databases, carried out the synthesis, conducted the compound characterization, performed the anti-cancer activity and wrote this manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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