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In silico studies in the prediction of novel isoxazole derivatives as potentially active anticancer agents

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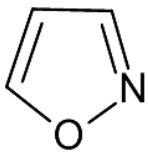
Abstract

Isoxazoles have engaged a distinctive position in heterocyclic chemistry and their derivatives have significant pharmacological effects. The active pharmacophores of various isoxazole analogs are accountable for antifungal, anticancer, antiviral, antidiabetic, analgesic, antitubercular, anti-inflammatory and other activities. In this research, all the designed compounds were subjected to various pharmacokinetic and pharmacodynamic properties by using *in silico* tools. Isoxazole derivatives were designed and their molecular properties and toxicity prediction studies were carried out to know the safety and efficacy by using molinspiration, molsoft and swissADME. Top lead molecules were identified and subjected to molecular docking. Docking studies were accomplished to find the probable protein-ligand interactions. The thirty designed compounds were docked against the target protein (Pdb ID: 3QAQ). Approximately, hundred diverse protein-ligand complex conformations for every docked complex were produced through MGL tools, the Autodock suite. Among the docked ligands, compounds 5,7,10,13,15,17 and 24 conveyed the lowest binding energy between – 9.5 to – 8.8 kcal/mol. The binding energy of all the compounds reached from – 7.1 to – 9.5 kcal/mol. The compounds 7,10,13 and 24 possess the same hydrogen bonds, each with ARG:849, ARG:690, amino acids are standard regorafenib. Finally, the docking results conclude that compounds 7 (– 9.5 kcal/mol) 10 (– 9 kcal/mol), and 17 (– 9 kcal/mol) possess two hydrogen bonds with the best binding energy values. Subsequently, an ADMET study was done for ligand appropriateness as a drug candidate. Thirty docked compounds were assessed for their biological properties and compared with the standard drug regorafenib.

1. Introduction

Heterocyclic compounds have captivated observable attention as they elucidate the relationship between chemical and life sciences (Kapubalu *et al*., 2011). Heterocycles that hold atoms like oxygen and nitrogen are recognized as a predominant class in medicinal chemistry. Isoxazole is a five-membered heterocyclic compound with O and N (Sagar *et al*., 2017).



The isoxazole ring was first synthesized by Dunstan and Dymand. The chemistry of isoxazole is developed in between 1930-1946.The study is contributed from Quilico's studies from nitrile oxides and un-saturated compounds. The common name for 5-membered unsaturated heterocycles as isoxazole was primitively put forwaded by Hantszch (Kuntal Manna *et al*., 2014). In the past decades, remarkable efforts were made to synthesize isoxazoles due to their properties (Nagajyothi *et al*., 2015). 1,3 dipolar cyclo-addition of alkenes and alkynes is the major method used for synthesis of isoxazole ring (Soumyadip Das *et al*., 2021). Isoxazoles are widely explored in therapeutics such as antibacterial, antitumour, antitubercular, anticancer, ulcerogenics, antileishmania, *etc*. (Sagar *et al*., 2017). Isoxazole ring is present in some of thetherapeutic drugs, including lactam antibiotics-cloxacillin, dicloxacillin, antibacterials-sulfamethoxazole, COX-Ï inhibitor-valdecoxib, DMARD (immmuno supressive disease modifying antirheumatic drug) leflunomide (Afzal Shaik *et al*., 2019). Isoxazoles have some industrial efficiency, reduced isoxazole derivatives such as antibiotic-cycloserine and MAO inhibitor-isocarboxazidis useful in psychotherapy and denazolanis a isoxazole steroid that exhibits anabolic activity. Isoxazole is best described as a resonance hybrid of many resonance structures. The heteroatoms present in the ring impact the rate of electrophilic substitution in the ring. It is unstable towards nucleophilic agents action that causes the cleavage of isoxazole ring that yields beta-keto nitriles as the end products (Leach *et al*., 2006). Isoxazole is also used in material science, such as photochromic, electrochemical probe for Cu^{+2} and also has optical properties in dye-sensitized solar cells, liquid crystal. Some of the marketed drugs with isoxazole nucleus are oxacillin, cycloserine, acivicin, broxaterol, isoxaflutole, sulfame-thoxazole, *etc*.

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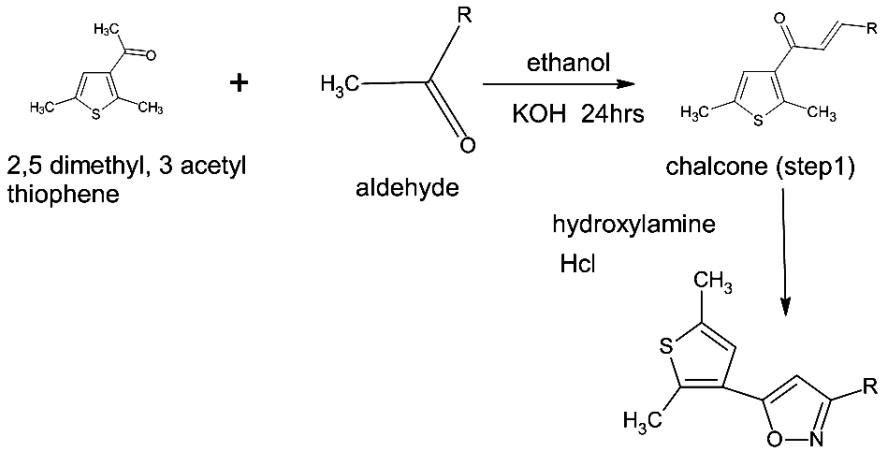
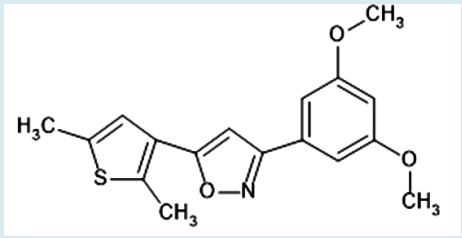
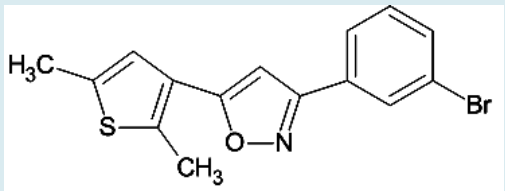
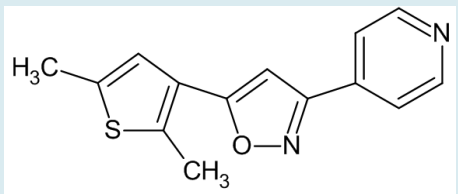
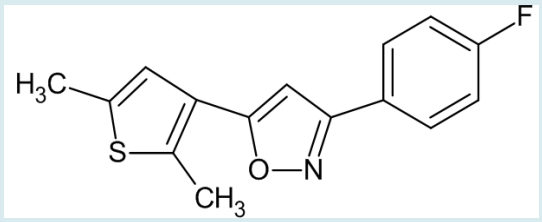
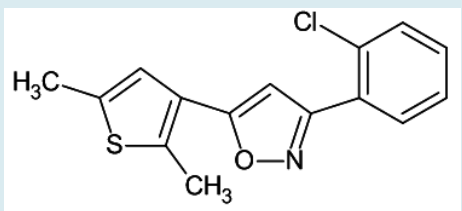
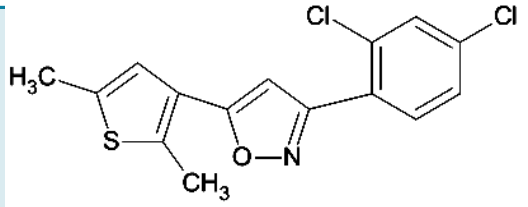
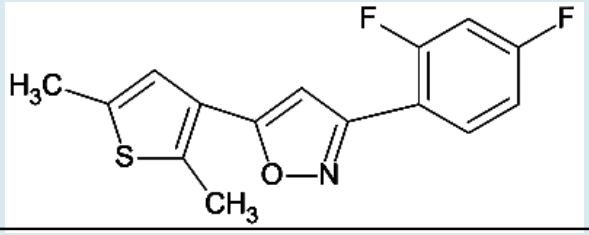
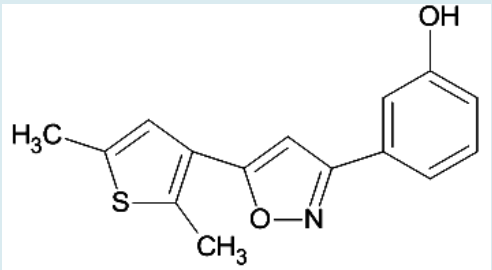
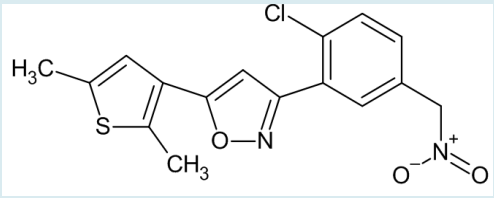
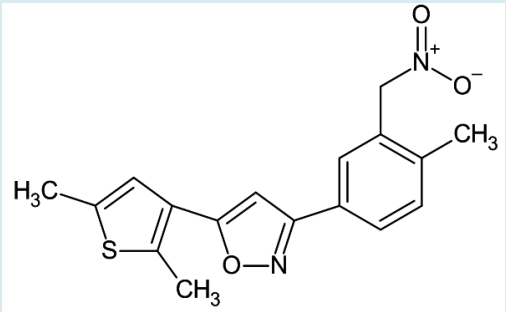
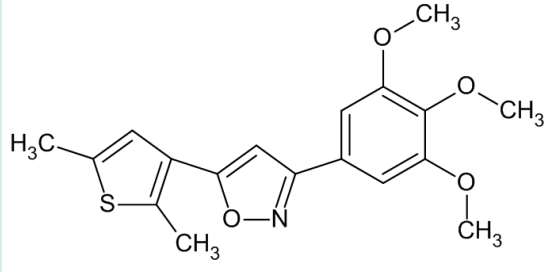
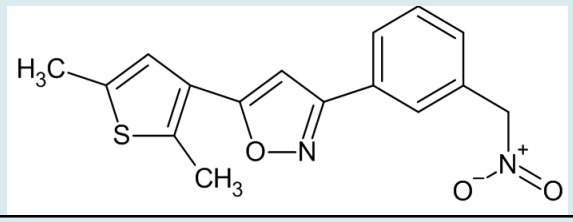
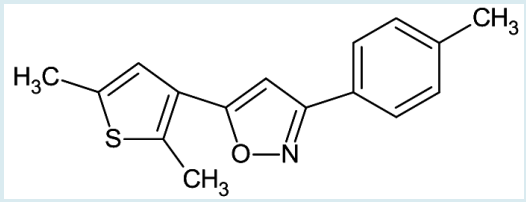
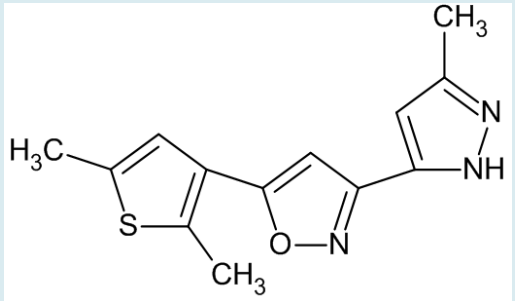
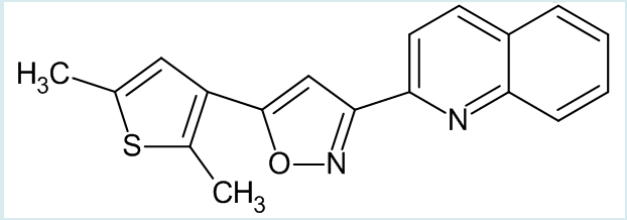
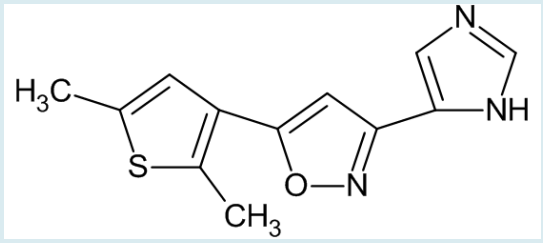
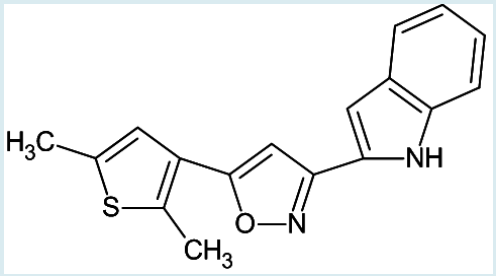
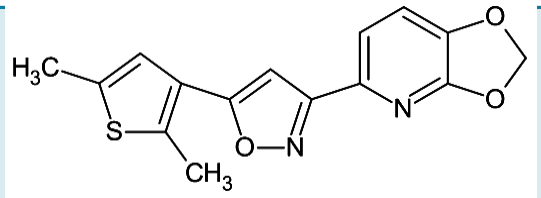
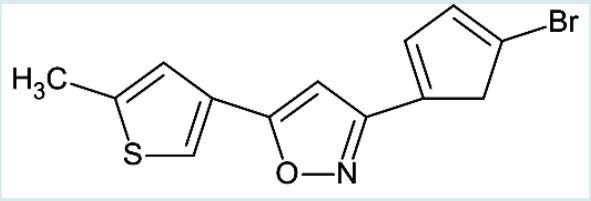
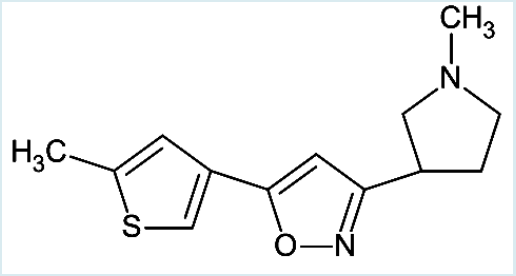
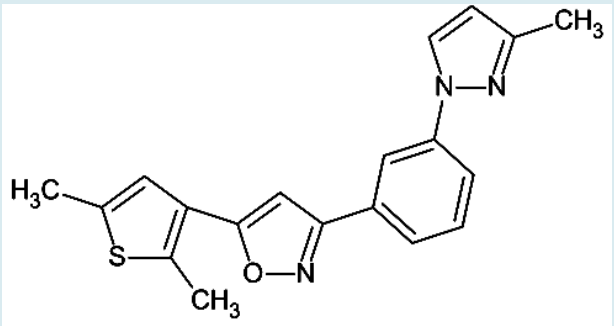
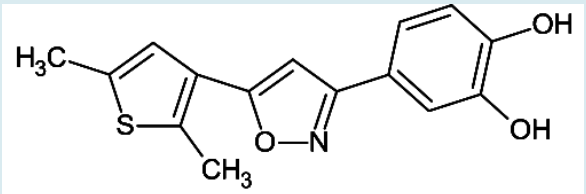
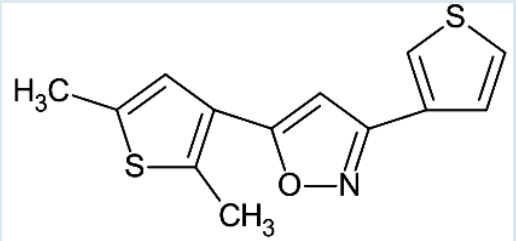
2. Materials and Methods

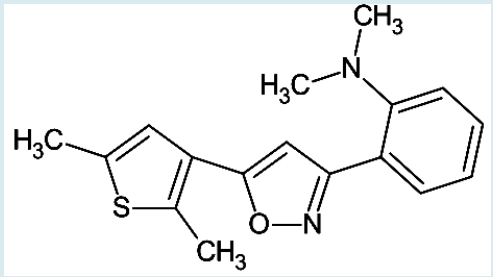
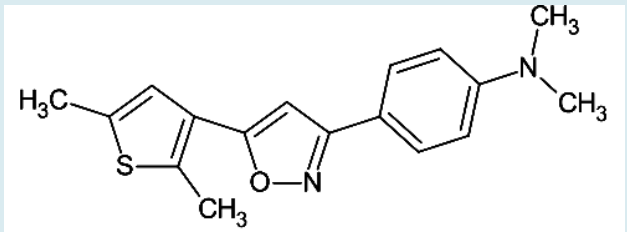
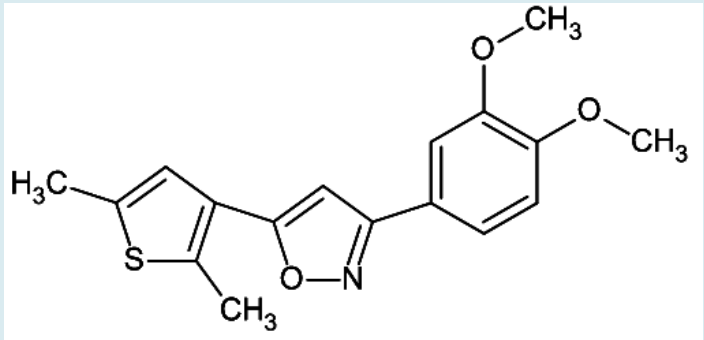
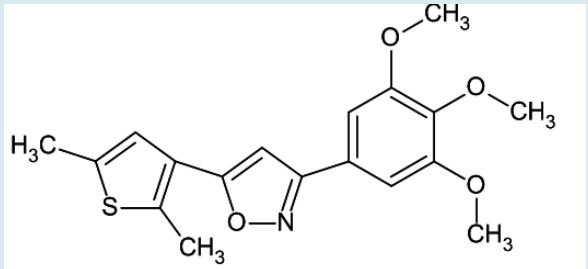
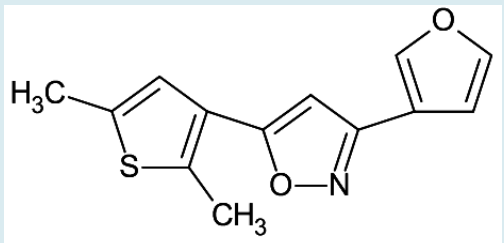


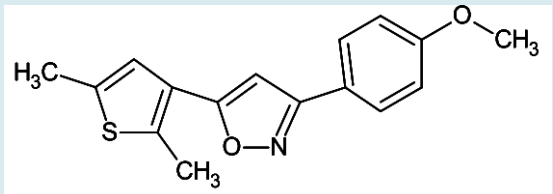
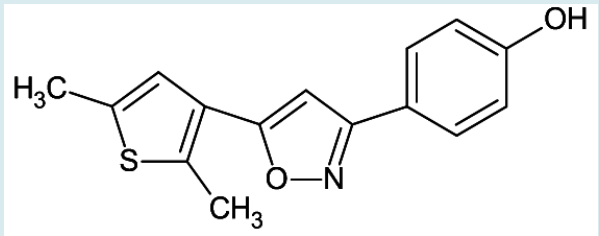
Compound	Structures
1.	
2.	
3.	
4.	
5.	

6.	
7.	
8.	
9.	
10.	
11.	

12.	
13.	
14.	
15.	
16.	
17.	

18.	
19.	
20.	
21.	
22.	
23.	

24.	
25.	
26.	
27.	
28.	

29.	
30.	

Molecular docking is a molecular modelling technique that is the interaction among a small molecule and target which shows the best-fit alignment of a ligand that binds to a specific protein of interest. The present study integrates the use of *in silico* molecular modelling tools like Autodock vina (Munisireesha *et al*., 2021). The grid that was produced will assist in finding the active site of a protein, clarify the design of potential drug candidates against pokeweed antiviral protein (Munisireesha *et al*., 2022).

2.1 Ligand selection and optimization

Using ACD/Chemsketch, the two dimentional structures of thirty designed compounds were created. 3D optimization of generated ligands was performed and saved in the MDL molfile format (Noel Boyle *et al*., 2011). With the help of open babel server, all the ligands were converted to PDBQT file format (Peterson *et al*., 2011).

2.2 Molecular docking studies

The 3D structure of phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma isoform (PI3K) protein (Pdb ID: 3QAQ) was downloaded from protein data bank (https://www.rcsb.org) and saved inpdb file format. The protein structure was optimized by removing water molecules, adding polar hydrogen atoms and Kollman and Gasteiger charges to satisfy the valences, and the whole structure energy was minimized by using AUTODOCK suite of MGL tools (Jocelyn Sunserii *et al*., 2016).

Molecular docking studies were accomplished using Autodock Vina. A grid was created around the co-crystallized ligand. The co-ordinates (x = 23.16, y = 15.21, z = 21.41) were produced with the help of MGL tools and pharmit (http://pharmit.csb.pitt.edu/) (Munisireesha *et al*., 2021). Later target protein (PDB id: 3QAQ) and ligands are saved in PDBQT (Sunghwan Kim *et al*., 2016). Based on the constraints that have been observed, the best protein-ligand complex is selected depend on its binding energy and were analysed in the discovery studio for the interactions with the active site (Tahmeena Khan *et al*., 2017). The binding efficiency and interactions of the binding were considered in terms of dock score, which is a blend of bonding and non-bonding interactions with the receptors (Shawshank *et al*., 2016).

2.3 Molecular properties prediction

2.3.1 Bioactivity prediction

Bioactivity score and drug-likeness of the synthesized compounds can be predicted opposed to regular human receptor including GPCRS, ion channels, kinase, nucleases, proteases enzymes, by using the web-tool molinspiration. Comprehensive potential of the compound can be indicated by drug score values. Drug likeness of the created compounds can be assessed based on Lipinski's rule of five, which is useful in relating molecular assets of drug compounds which are essential for determining the pharmacokinetic parameters such as absorption, distribution, metabolism and excretion. This rule is beneficial in drug design and development (Shawshank *et al*., 2016). Using the molinspiration computational technique possible new drug candidates can be identified by analyzing the chemical database (Antoine Daina *et al*., 2017).

Drug-likeness is a qualitatively chance for converting a molecule to an oral drug with respect to bioavailability. Drug-likeness was introduced for structural or physicochemical inspection and development of compounds (Douglass Eduardo *et al*., 2015).

2.3.2 PKCSM

Development of the new drug has become high affecting rate with high risks and with low pharmacokinetic and safety properties (Douglass *et al*., 2018). PKCSM (predicting pharmacokinetics of small molecules) computational technique is developed to reduce these risks. PKCSM is used to predict the ADMET properties of molecules for drug development. It is used to evaluate the pharmacokinetics and toxicity properties of small molecules. The interactivity between the pharmacokinetics, potency and toxicity is critical for efficient lead. The pharmacokinetics study of a molecule which describes itsabsorption, distribution, metabolism, excretion properties. PKCSM which uses the graph-based structural crosses to study and forecast the ADMET properties for novel chemical entities.

SMILES which are generated in swiss ADME, is widely used for representing the atomic conformation and structure of chemical entities. These SMILES of individual compound were introduced into the PKCSM prediction web tool. Choose the prediction mode, by connecting on their corresponding button, the estimates will be exhibited on the screen in a tabular format (Mabkhot *et al*., 2016).

2.3.3 Molinspiration

Molinspiration is a software which is used to evaluate and shows the important part and effect of substituents on biological activity and influence the unfavourable structural parameter in authentic drug design, more substituition with electron donar does not give assurance to active bioactivity. This molinspiration should enormously help in abright and a precise pharmacomodulation of compounds (Shashank Shekhar *et al*., 2016). Molinspiration cheminformatics server states numerous tools, supporting molecule handling and processing, along with SMILES and SD file conversion, molecules normalization, tautomer generation, fragmentation of molecule, calculation of several molecular properties. This tool also affords fragment based virtual screening, prediction of bioactivity and visualization of data. The bioactivity score of selected agents were also reported by using the tool molinspiration cheminformatics server. In computational chemistry techniques, huge chemical databases were estimated in order to define probable new drug candidates (James *et al*., 2015).

2.3.4 Molsoft

Molsoft is a main provider of tools, databases and accessing services in the part of structure prediction, cheminformatics, proteomics, bioinformatics, lead discovery, modelling and combine data management. Molsoft was used to clarify the situation disclosing the construction of the protein –DNA within the transcription complex (Patil *et al*., 2021). First, compounds were rescued from the pubchem databases and estimated for their drug likeliness using the molsoft webserver and compounds which were having drug-like property were evaluated for foremost adverse drug reaction. It is generally used for visualizing and data sharing. It is used for designing the proteins with needed properties and also to convert 2D to 3D conversion, as well as evaluating the compounds properties (Nawaz *et al*., 2022).

3. Results

3.1 Docking

Molecular docking was executed to recognize the possible protein-ligand interactions of the ligands. The possible active site amino acids of the 3QAQ complex were projected using CASTp. The protein target and ligands were geometrically optimized. All the thirty compounds were docked against the active site of target 3QAQ using Autodock Vina. Furthermore, these also aided in recognizing the conformational variations of the ligand in the protein location. Approximately, 100 different protein-ligand complex configurations for each docked complex were produced through MGL tools AUTODOCK suite.The lowest binding energy conformation was exhibited as the best binding energy. Binding energy of the designed ligands was shown in Table 1 along with the amino acid interaction.

Table 1: Binding energy scores of 30 designed molecules along with standard regorafenib

Compound id	Docking affinity in kcal per mol	Compound id	Docking affinity in kcal per mol
1	– 7.9	17	– 9
2	– 7.8	18	– 8.4
3	– 7.9	19	– 7.8
4	– 8.5	20	– 7.2
5	– 9	21	– 8.2
6	– 8.3	22	– 8.4
7	– 9.5	23	– 7.1
8	– 8.1	24	– 8.8
9	– 8.4	25	– 8.1
10	– 9	26	– 8
11	– 6.8	27	– 7.4
12	– 8.3	28	– 7.2
13	– 9.1	29	– 7.9
14	– 7.9	30	– 8.5
15	– 8.5	**Regorafenib**	**– 10.7**
16	– 7.6		

Among the docked ligands, compound 5,7,10,13,15,17 and 24 conveyed lowest binding energy between – 9.5 to – 8.8 kcal/mol. All the thirty compounds binding energy ranged from – 7.1 to – 9.5 kcal/mol. 7, 10, 13 and 24 possess same hydrogen bonds each with ARG:849, ARG:690, amino acids as standard regorafenib. Finally, we conclude that compound 7 (– 9.5 kcal/mol), 10 (– 9 kcal/mol) and 17(– 9 kcal/mol) possess two hydrogen bonds with best binding energy values.

Table 2: Binding energy scores and bonding interactions of top lead along with standard regorafenib

Compound No.	Binding energy (kcal/mol)	No of H-bonds	H-Bond interactions	H-bond lengths (Å)	Interacting amino acids
5	– 9	1	GLY:868	3.53	LEU:657, PHE:694, ARG:849, GLU:880
7	– 9.5	2	ARG:849	2.82,2.97	LEU:865, PHE:694 ARG:690, LEU:657
10	– 9	2	ARG:690	2.00,2.33	LEU:865, PHE:694 ARG:849, GLU:880
13	– 9.1	1	ARG:849	2.77	PHE:694, LEU:657 PHE:698, LEU:660
15	– 8.9	1	HIS:658	2.82	PHE:694, TRP:201 LEU:657, ARG:294 GLN:846
17	– 9	2	GLY:868 ARG:849	2.57,2.93	PHE:694, LEU:657 GLU:880
24	– 8.8	1	ARG:690	2.61	PHE:694, HIS:658 TRP:201, LEU:657
Regorafenib	**– 10.7**	**4**	**GLN:846 ARG:849 ARG:690**	**2.64,2.81 2.32,2.96**	**PHE:694, TRP:201 LEU:657, LYS:298 GLU:856, ARG:294**

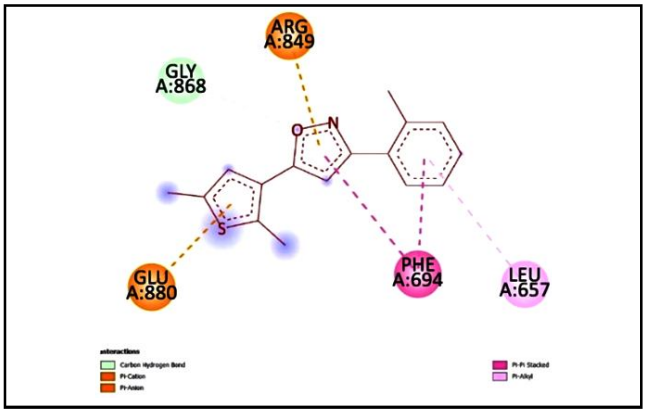


Figure 1: 2D representation of standard ligand regorafenib.

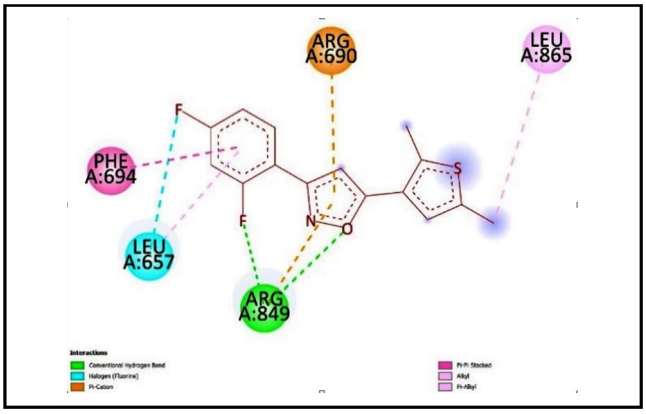


Figure 3: 2D representation of compound 7.

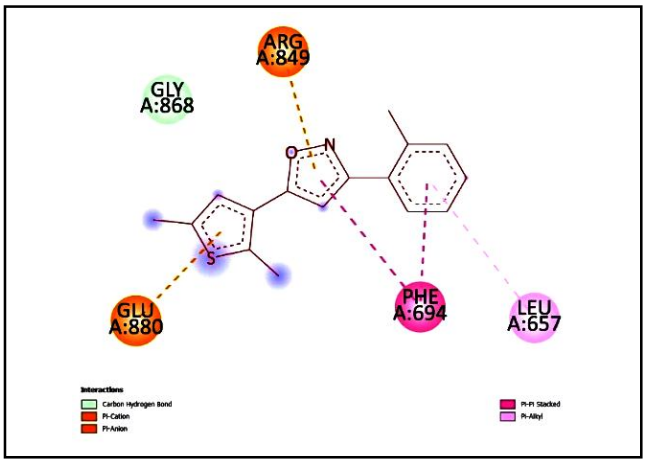


Figure 2: 2D representation of compound 5.

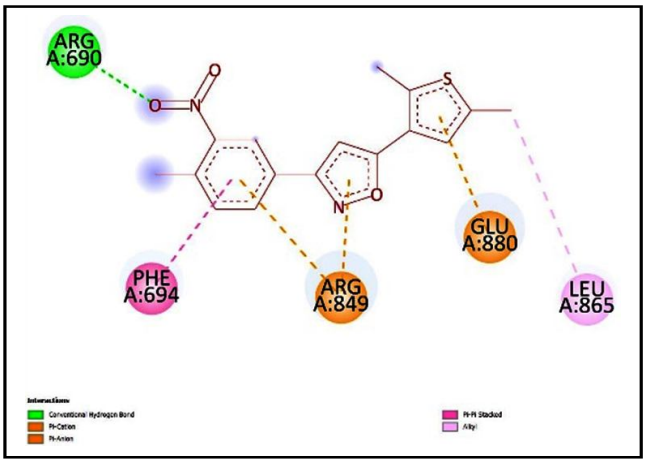


Figure 4: 2D representation of compound 10.

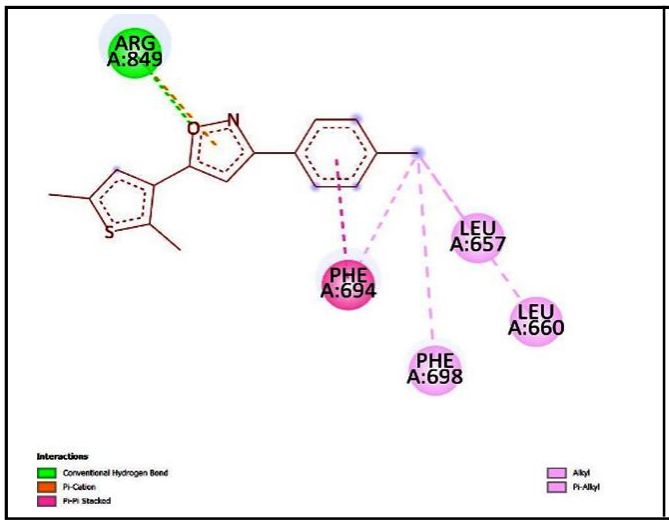


Figure 5: 2D representation of compound 13.

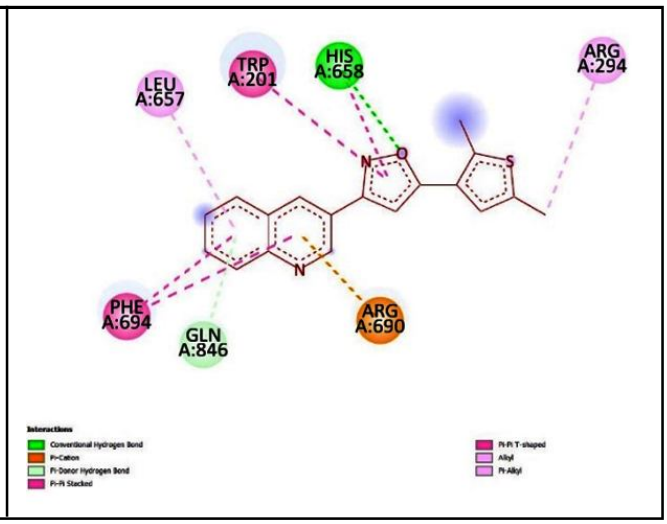


Figure 6: 2D representation of compound 15.

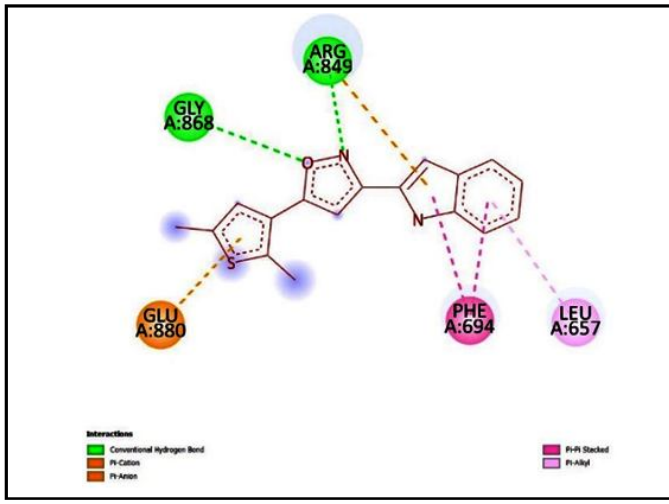


Figure 7: 2D representation of compound 17.

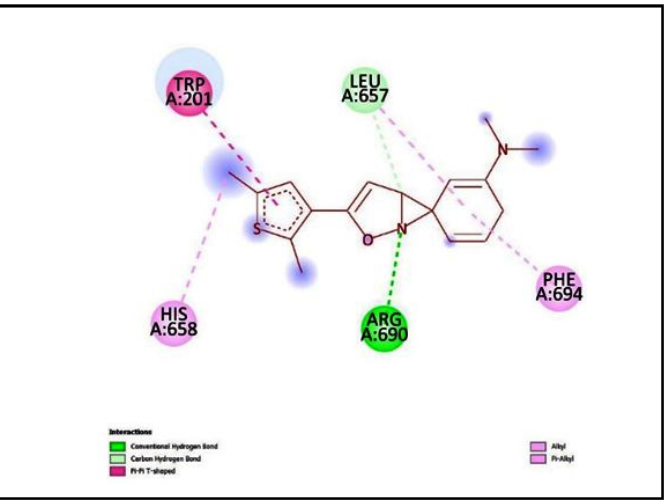


Figure 8: 2D representation of compound 24.

3.2 Predicted properties

3.2.1 Bioactivity

Bioactivity prediction is the software used to predict the drug likeness of the small molecules and gives various receptor binding activity. All the synthesized compounds bioactivity was predicted and all the compounds showed good activity against the receptors GPRC, ion channel, kinase, nuclease, proteases.

3.2.2 PKCSM

PKCSM is the online tool used to predict the pharmacokinetics properties of small molecules. Using this tool, the pharmacokinetic properties of all the synthesized compounds were predicted and all of them showed good ADME properties.

3.2.3 Molinspiration

All the derivatives were projected by using molecular property prediction. Molinspiration calculate the molecular possessions like (log P, molecular volume, molecular polar, surface area, molecular weight, Rule of 5 **prop** number of rotatable bonds and bioactivity) when log P altered hydrophobicity is also altered. Hydrophobicity is drug absorption, bioavailability and active of the compounds.

All the compounds obey the Lipinski rule of 5. The rule state, that most "drug like" molecule have <=5, molecule weight<=500, number of hydrogen bond acceptors<=10 and number of hydrogen bond donors<=5.

In the above table, among all the designed compounds, the compound 1 showed excellent activity when compound standard isoxazole and thiophene. Because it have log P (3.94), higher TPSA (55.47), higher hydrogen bond receptors (4). So, there is no violating one of these rules.

3.2.4 Molsoft

Molsoft online tool calculated the chemical properties like molecular formula, molecular weight, number of hydrogen bond acceptors, number of hydrogen bond donors, mol log P, mol log S, polar surface area, volume, number of stereo centers, drug likeness model score.

In the above table, all the compounds obey the Lipinski rule. Among the synthesized compound 1 showed potent activity and more bioavailability when compared to standard isoxazole and thiophene. Because this compound have HBA value(6), log P (4.63), log S(-4.4), PSA (50.97), higher the log P higher the bioavailability.

Table 3: Bioactivity scores of all thirty designed compounds

Compound	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	-0.45	-0.09	-0.06	-0.36	-0.51	-0.17
2	-0.25	-0.27	-0.26	-0.16	-0.59	-0.32
3	-0.21	-0.21	-0.17	-0.1	-0.58	-0.29
4	-0.22	-0.2	-0.24	-0.16	-0.6	-0.31
5	-0.12	-0.18	-0.16	-0.09	-0.49	-0.32
6	-0.13	-0.1	-0.04	-0.05	-0.5	-0.24
7	-0.17	-0.14	-0.12	0.06	-0.55	-0.19
8	-0.38	-0.1	0	-0.31	-0.46	-0.21
9	-0.41	-0.12	0.02	-0.3	-0.53	-0.16
10	-0.14	-0.25	-0.07	-0.11	-0.4	-0.25
11	-0.14	-0.3	-0.14	0.03	-0.46	-0.27
12	-0.36	-0.28	-0.28	-0.29	-0.72	-0.35
13	-0.22	-0.12	-0.1	-0.25	-0.6	-0.23
14	-0.08	-0.4	-0.08	-0.1	-0.41	-0.26
15	-0.03	-0.14	0.13	0.02	-0.32	-0.1
16	-0.13	-0.05	0.15	-0.49	-0.58	0.05
17	0.1	-0.23	0.31	0.21	-0.19	-0.01
18	-0.14	-0.28	-0.15	-0.12	-0.48	-0.25
19	-0.35	-0.55	-0.65	-0.98	-1.01	-0.67
20	-0.27	-0.3	-0.1	-0.03	-0.68	-0.14
21	-0.08	-0.43	-0.09	-0.31	-0.48	-0.42
22	-0.13	-0.14	-0.08	-0.06	-0.49	-0.17
23	-0.46	-0.46	-0.41	-0.32	-0.79	-0.38
24	-0.18	-0.17	-0.1	-0.2	-0.5	-0.25
25	-0.12	-0.21	-0.07	-0.03	-0.44	-0.25
26	-0.16	-0.26	-0.08	-0.06	-0.46	-0.26
27	-0.14	-0.25	-0.07	-0.11	-0.4	-0.25
28	-0.38	-0.5	-0.51	-0.47	-0.94	-0.48
29	-0.27	-0.3	-0.1	-0.03	-0.68	-0.14
30	-0.22	-0.28	-0.2	-0.1	-0.54	-0.13

Table 4: Pharmacokinetic properties of all the synthesized compounds

Compound	Human intestinal absorption (HIA, %)	*In vitro* $CaCO_2$ cell permeability (log Papp in 10 cm/s)	*In vitro* skin permeability (log kp)	*In vitro* VDss (human) (log l/kg)	*In vitro* BBB permeability (log BB)	Toxicity
1	94.314	0.582	-2.507	0.056	-0.61	Hepatotoxicity
2	95.32	1.108	-2.307	0.405	0.155	Non-toxicity
3	94.715	1.067	-2.44	0.313	0.137	Non-toxicity
4	93.431	1.272	-2.353	0.356	0.066	Non-toxicity
5	92.201	1.124	-2.396	0.428	0.047	Non-toxicity
6	88.6	0.489	-2.735	0.011	0.463	AMES toxicity
7	93.425	1.367	-2.746	0.302	0.539	Non-toxicity
8	91.399	1.52	-2.47	0.289	0.232	AMES toxicity
9	95.166	1.473	-2.433	0.433	0.145	AMES toxicity
10	95.981	1.366	-2.711	0.17	0.193	Hepatotoxicity
11	95.29	1.408	-2.556	0.262	0.48	Hepatotoxicity
12	94.353	1.247	-2.349	0.415	0.094	Non-toxicity
13	97.84	1.737	-2.28	0.19	0.683	Non-toxicity
14	94.439	1.504	-2.717	0.501	0.797	Non-toxicity
15	96.377	1.636	-2.606	0.585	0.867	Non-toxicity
16	90.611	1.351	-2.735	0.433	0.625	hepato toxicity
17	92.567	1.504	-2.731	0.526	0.632	Non-toxicity
18	96.106	1.424	-2.617	0.264	0.237	Hepatotoxicity
19	94.809	1.608	-2.338	0.156	0.524	Non-toxicity
20	96.61	1.501	-2.318	0.218	0.035	Hepatotoxicity
21	96.312	1.532	-2.649	0.589	0.713	Hepatotoxicity
22	93.103	1.001	-2.853	0.294	0.34	Non-toxicity
23	93.618	1.222	-2.278	0.28	0.061	Non-toxicity
24	96.261	1.464	-2.295	0.498	0.244	Hepatotoxicity
25	95.862	1.468	-2.283	0.494	0.239	Hepatotoxicity
26	93.18	1.12	-2.627	0.188	0.256	Hepatotoxicity
27	95.981	1.366	-2.711	0.17	0.193	Hepatotoxicity
28	96.602	1.698	-2.27	0.155	0.543	Non-toxicity
29	96.61	1.501	-2.318	0.218	0.035	Hepatotoxicity
30	93.443	1.367	-2.74	0.36	0.525	Non-toxicity

Table 5: The molecular properties with molinspiration

Compound	Log P	TPSA	n atoms	M.wt	Non	nOHNH	n - violations	nrotb	Volume
1	3.94	55.47	20	284.34	4	0	0	3	242.93
2	4.49	26.03	19	269.37	2	0	0	2	244.67
3	4.21	26.03	19	273.33	2	0	0	2	233.04
4	4.72	26.03	19	289.79	2	0	0	2	241.64
5	5.33	26.03	20	324.23	2	0	1	2	255.18
6	4.3	26.03	20	291.32	2	0	0	2	237.97
7	3.54	46.26	19	271.34	3	1	0	2	236.12
8	4.55	55.47	21	318.79	4	0	0	3	256.47
9	4.32	55.47	21	298.37	4	0	0	3	259.49
10	3.68	53.73	24	345.42	5	0	0	5	304.74
11	4.09	44.5	22	315.39	4	0	0	4	279.2
12	4.83	26.03	19	334.24	2	0	0	2	245.99
13	2.76	38.92	18	256.33	3	0	0	2	223.95
14	3.87	43.86	24	335.43	4	0	0	3	297.29
15	4.15	38.92	22	306.39	3	0	0	2	267.94
16	1.91	54.72	17	245.31	4	1	0	2	208.94
17	4.14	41.82	21	294.38	3	1	0	2	257.08
18	3.94	44.5	21	299.35	4	0	0	2	252.03
19	4.12	39.17	18	324.2	3	0	0	2	227.56
20	2.91	30.97	18	258.35	3	0	0	2	230.03
21	2.19	30.97	18	258.35	3	0	0	2	230.03
22	3.08	66.49	20	287.34	4	2	0	2	244.14
23	3.83	26.03	17	261.37	2	0	0	2	218.82
24	4.1	29.27	21	298.41	3	0	0	3	274.01
25	4.15	29.27	21	298.41	3	0	0	3	274.01
26	3.69	44.5	22	315.39	4	0	0	4	279.2
27	3.68	53.73	24	345.42	5	0	0	5	304.74
28	3.19	39.17	17	245.3	3	0	0	2	209.67
29	2.91	30.97	18	250.35	3	0	0	2	230.03
30	4.1	35.27	20	285.37	3	0	0	3	253.65

NON - Number of hydrogen acceptors, NOhnh - Number of hydrogen donors, Nrotb - Number of rotatable bonds. MW - molecular weight, TPA - total polar surface area.

Table 6: Chemical properties using molsoft

Compound	No. of HBA	No. of HBD	Mol Log P	Mol log S	Mol PSA	Mol volume	No.ofstereo centers	DLMS
1	6	2	4.63	-4.4	50.97	270.94	0	-0.82
2	3	0	5.51	-5.49	22.52	267.75	0	-1.03
3	3	0	5.13	-5.02	22.52	252.73	0	-0.8
4	3	0	5.31	-5.8	22.52	262.05	0	-0.9
5	3	0	6.02	-6.11	22.52	279.32	0	-0.84
6	3	0	4.62	-4.44	22.06	259.61	3	-0.59
7	4	1	4.59	-4.35	40.14	257.44	0	-0.77
8	3	2	4.71	-4.91	43.33	269.63	0	-0.96
9	5	0	5.04	-4.89	50.27	283.48	0	-1.2
10	6	0	4.6	-4.46	45.5	341.93	0	-0.64
11	5	0	4.55	-4.49	37.78	310.08	0	-0.67
12	3	0	5.81	-5.74	22.52	268.74	0	-1.29
13	4	0	3.76	-3.83	31.95	242.11	0	-0.75
14	4	0	4.66	-4.45	35.42	328.83	0	-1.25
15	4	0	5.09	-5.52	30.85	290.72	0	-1.13
16	4	1	3.14	-3.4	43.82	231.23	0	-1.3
17	3	1	5.63	-6.09	31.87	285.73	0	-1.72
18	5	0	4.9	-4.88	39.64	286.64	0	-1.21
19	4	0	4.76	-4.72	31.45	248.97	0	-1.26
20	3	0	5.13	-5	25.33	296.37	0	-0.98
21	4	0	4.77	-4.84	36.88	303.82	0	-0.98
22	5	2	4.01	-3.86	55.62	270.08	0	-0.6
23	4	0	4.64	-4.4	23.54	241.69	0	-1.31
24	3	0	4.35	-4.42	25.02	253.18	0	-1.26
25	3	0	5.13	-5	25.33	296.37	0	-0.98
26	5	0	4.55	-4.49	37.78	310.08	0	-0.67
27	6	0	4.6	-4.46	45.5	341.93	0	-0.64
28	4	0	3.97	-4.21	31.1	230.51	0	-1.31
29	3	0	4.57	-4.38	24.94	256.4	0	-1.11
30	3	0	5.51	-5.49	22.52	267.75	0	-1.03

HBA - hydrogen bond acceptors,
HBD- hydrogen bond donor,
Mlog P- mol log P,
Mlog S- mol log S,
MPSA - molecular polar surface area,
MV - molecular volume,
SC - no. of stereo centers,
DL - drug likeness.

4. Discussion

In the present study, 30 compounds are synthesized and are subjected to docking studies, Binding energy scores of 30 designed molecules are performed along with standard regorafenib. Among the docked ligands, compounds 5,7,10,13,15,17 and 24 conveyed lowest binding energy between – 9.5 to – 8.8 kcal/mol. All the 30 compounds binding energy ranged from – 7.1 to – 9.5 kcal/mol. 7,10,13 and 24 possess same hydrogen bonds each with ARG:849, ARG:690, amino acids as standard regorafenib. So, 7,10 and 17 possess best binding energy values. Molecular properties of all 30 compounds are predicted from that, bioactivity prediction is used to predict the druglikeliness of small molecules and gives the various receptor binding activity. All compounds showed good activity against the receptors like GPCR, ion channel, kinase, nuclease, proteases. PKCSM tool is used to predict the pharmacokinetic properties of small molecules and all the synthesized compounds showed good ADME properties. All the molecular properties like log P, molecular volume, molecular polar surface area, molecular weight are predicted using molinspiration. Among the 30 compounds the compound 1 showed excellent activity. Chemical properties are predicted using molsoft, all the 30 compounds, obeyed Lipinski rule of 5 and Compound 1 showed potent activity and more bioavailabity among all compounds because the compound 1 has high HBA value(6), log P (4.63), PSA (50.97) higher the log P, higher is the bioavailability.

5. Conclusion

Based on various literature surveys, a series of isoxazole derivatives were designed which have great potential for different pharmacological activities. The new isoxazole derivatives along with phosphatase and tensin homolog is selected for docking studies which shows great potential in tumor suppressor that acts as an anticancer agent. From the docking studies, we conclude that compounds 7 (– 9.5 kcal/mol), 10 (– 9 kcal/mol) and 17 (–9 kcal/mol) possess two hydrogen bonds with the best binding energy values. Subsequently, molecular properties of all newly designed derivatives are projected using various software like molinspiration, molsoft, PKCSM and bioactivity properties. These descriptors are useful in the general understanding of chemical interactions with the target. All derivatives showed good pharmacokinetic and pharmacody namic properties. All derivatives are non-toxic and shown good ADME properties.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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