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Research Article

Designing of Heterocyclic Compounds as Promising VEGFR2 Tyrosine Kinase Inhibitors: An *In silico* Analysis

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ABSTRACT

Cancer is the most dangerous disease a human race battle with. Due to which, it is necessity of medicinal chemist to evaluate possible scenario to fight against this disease. The heterocyclic compounds have shown to possess intrinsic diversity and several physicochemical properties. Thus, investigation of newer and potential compounds for their activity to resist several malignancies. The present study aims to derivatize four different heterocyclic compounds. The number of members present in the ring has importance in heterocyclic compounds. Thus, the six-member ring containing pyrimidine, six-member ring fused with five-member ring in indole, bi-penta membered ring containing thiadiazole, and one six-member and a penta membered ring containing triazoles have been used in the present study. In search of potential anticancer drugs, several molecules were evaluated and checked for their potency to interact with a cancer target enzyme Vascular endothelial growth factor receptor 2 (VEGFR2). This study involves detailed *in-silico* analysis of several compounds and indicates compounds having the potential ability to resist these enzymes and hence the anticancer agent.

Introduction

In medicinal chemistry, heterocyclic-containing compounds are used due to their versatile nature and different physicochemical properties, which is a demand in the pharmaceutical world. Also in the organic compounds, large part contains heterocyclic fragments. In the drug prospective, drugs like atropine, quinine, morphine, codeine, which are natural drugs, have heterocyclic part. Most synthetic drugs, which have a market value, such as amoxicillin, Estazolam, azidothymidine, and many more, are heterocyclic compounds. The heterocyclic compounds have played a vital role because they had shown properties to resist bacterial, fungal or viral disease[1-3] and had involved in the development of antitumor drugs.[4-6] In the anticancer research, the target to develop drugs to target the pathways leading to cancer progression. Due to their efficiency in interaction, size variation, and numerous structure generation, the heterocyclic compounds are prime components for the initiation of anticancer study.

The heterocyclic compounds are mainly structured or identified based on heteroatoms present or attached to ring structure. The previous studies had shed light on such classifications based on the presence of oxygen, nitrogen, or sulphur.[7] In the present study, to incorporate such a diverse group of compounds, four compounds were selected, including pyrimidine, indole, thiadiazole, and thiazole-based compounds. The derivatization of these four category compounds has been performed to study their anticancer activity. The pyrimidine has two nitrogen present at positions 1 and 3 similar to benzene, i.e., six-membered rings. This heterocyclic compound has been used in different drug preparations such as Uramustine, Metioprim, Flucytosine, Idoxuridine, Piribedil, etc.

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Additionally, it has been reported that pyrimidine derivative shows pyrimidine properties.[8] Hence, pyrimidine-based derivatization has been performed in the current study. Further, the indole is the heterocyclic compound with five-membered pyrrole rings fused with benzene rings. The indole based compounds had been ranked in the top 10 compounds approved by USFDA.[9] Indole derivatives occurs under heterocyclic compounds, which are nitrogen-based. The interesting property of indole-based compounds is that they could be found naturally in plants, microbial hormones, etc.[10] These compounds have been shown to have various pharmacological activities including anticancer.[11] Another class of drugs that have an important biological impact is sulfur-based heterocycles. The thiadiazoles and thiazole have been found to have clinical value and used in various drug development to cure infectious diseases, allergies, chronic pain, and other diseases, including cancer.[12-15] These compounds have been shown to have DNA-cleaving,[16] antiproliferative[17] antitumor,[18] and such anticancer-based properties. Thus, these four different classes of compounds, i.e., pyrimidine, indole, thiadiazole, and thiazoles have been used for our search in finding anticancer drug molecules.

The present study has evaluated the derivatives of previously mentioned classes of compounds. The cancer target enzyme chosen in this study is Vascular endothelial growth factor receptor 2 (VEGFR2). It is a type V receptor falls under tyrosine kinase category. It is encoded by KDR gene. Its expression was found in vascular endothelial cells and some tumors. This receptor is responsible for signaling vascular endothelial growth and is essential in cancer studies. Several reports could be found regarding its expression in lung non-small cell,[19] mammary[20] and also in diffuse large B-cell lymphoma,[21] malignant melanoma.[22] Hence, VEGFR2 tyrosine kinase is selected as the target enzyme.

Material and Methods

The molecule formation for the anticancer activity profile was performed for five categories of drugs. The derivative formation of five heterocyclic compounds was chosen. The candidate from Indole, pyrimidine, thiazole and thiadiazole compounds was selected.

Lead Molecule Selection

In developing an anticancer molecule, the essential and most important step is the select lead molecule for derivatization. The pyrimidine is found in the base molecule in the building blocks of DNA and RNA. Also, it has been reported that the pyrimidine-based molecules has shown anticancer property.[23] The indole compounds are heterocyclic compounds showing anticancer activity.[24] In the case of thiazole, the thiazole structural diversity has been responsible for anticancer activity.[25] Several years ago, Thiadiazole was checked for anticancer activity and has shown different pharmacological activities.[26] It had also been tested in human cell lines.[27] Thus, after such investigations, the four compounds presented in Fig. 1 were used for derivatization.

Derivatives Library Preparation

The combinatorial library enumeration was performed using Library Enumeration model of Schrodinger software, Maestro (Schrodinger Inc.).[28] The enumeration was done by selecting R-Group Enumeration panel, which provides the synthetically trackable analogs. The R-Groups were chosen from the Schrodinger in-built dataset. It has various functional groups. The structures have been mentioned in the results. The place for enumeration, i.e., R, was incorporated for each molecule, as shown in Fig. 2.

Filtration of Ligand Molecules

The resulting molecules from ligand library generated need to be filtered before using it for enzyme interaction. The molecular weight criteria <500 was selected. Then

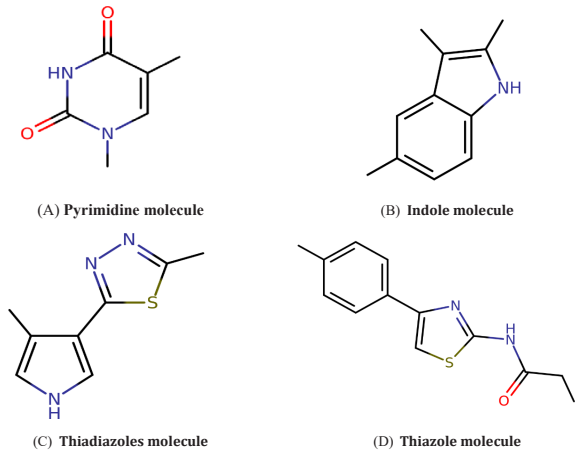


Fig. 1: The molecules chosen as a lead molecule.

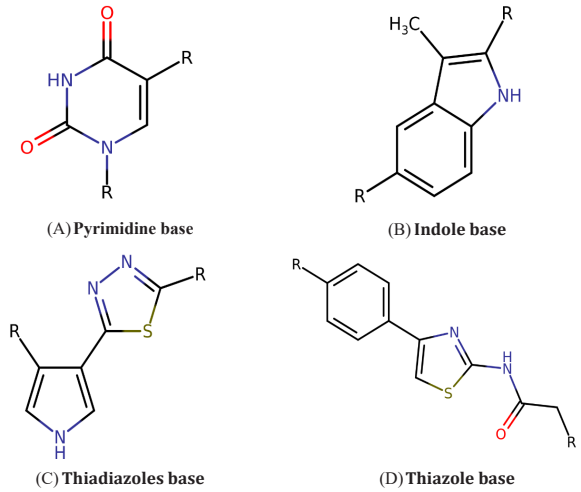


Fig. 2: The base molecules used for enumeration and the R-Group binding sites were presented by R in each structure.

the molecules were filtered using FAF-Drugs4 online web tool[29] for absorption, distribution, metabolism, excretion, and toxicity (ADME-Tox). The drug-like soft filtration was chosen to evaluate the physicochemical properties. This filtration includes different descriptor values designed from several articles and the in-house statistical analysis incorporated by the FAF-Drugs4 server. The pan assay interference compounds (PAINS) criteria[30] filtered toxicity-containing compounds.

Molecular Docking Based Virtual Screening

The molecules resulting were compatible with being drug molecules. However, finding the potential anticancer drug is important to find their interaction with target enzymes. The multiple ligand based pharmacophore model was created. The VEGFR2 Kinase, reported as a clinically validated drug, targets at renal cell cancer (RCC) and other cancers. Thus, the three-dimensional structure, having PDB id 4AG8,[31] was extracted from the RCSB databank.[32] The structure was complexed with the drug AXITINIB. The PDB file had several missing residues. Thus, the mode was developed for it using SWISS MODEL.[33] The RMSD of it with the 4AG8 structure was 0.157 Å. Thus, the energy minimization of the protein-only structure was performed using GROMACS,[34] a Linux based, open-source tool. The GROMOS96 54a7 force field[35] was used for this. Then the enzyme and ligands were prepared using AutoDock Tools scripts. The grid was set using the inhibitor complex 4AG8 structure as a template. The AutoDock Vina[36] based virtual screening was performed and based 20 lowest binding energy structures were extracted as a potential drug molecule. These steps were performed for all the fours molecules selected before.

Molecular Dynamics Simulation

The simulation was performed for the given complex using GROMACS v2018.3. For this, the protein only, i.e., modified 4AG8 structure and complexes with compounds having lowest binding energy from Indole, pyrimidine, thiazole, and thiadiazole compounds set, were selected for simulation. A total of 10 ns run had been carried out. For the simulation, the protein topology was generated using the pdb2gmx tool of GROMACS. The ligand topology was generated using PRODRG.[37] which is compatible with GROMOS force field. In GROMACS, GROMOS96 54a7 force field was chosen for simulation with the SPC water model. The box was defined as a dodecahedron unit cell with 1-nm. The system was soluted by adding the required water molecules. Then chlorine ions were added to neutralize the system. The energy minimization was performed using the steepest descent and conjugate gradient method for force < 10.0 kJ/mol. Then, the NVT and NPT equilibration was performed for 50000 steps at 300K temperature and 1 bar pressure. Finally, the 10ns md run was carried out with a protein-ligand temperature compiling group with water and ions. The analysis was carried out using the in-built tools of GROMACS. The MM/PBSA calculation was carried out by g_mmpbsa package.[38]

Results and Discussion

Structure Generation

The library generation of R-Group enumeration using Schrodinger software and by applying molecular weight threshold resulted in a generation of 1849 structures for each molecule, i.e., pyrimidine derivatives (supplementary 1), indole derivatives (supplementary 2), thiazole derivatives (supplementary 3), and thiadiazole derivatives (supplementary 4).

Druggability and Toxicity Filtration

All the 1849 molecules of each lead molecule were filtered before performing *in-silico* study of their derivatives. This was an essential step towards finding potential drug molecules. The Drug-Like Soft was applied to all the derivatives of each molecule. For pyrimidine derivatives, the total structures found suitable were 1212. The range variation for logP, molecular weight (MW), topological Polar Surface Area (tPSA), Hydrogen Bond Acceptor (HBA), Hydrogen Bond Donor (HBD), and rotatable bond (rotatable B) for all derivatives of pyrimidine has been produced in Fig. 3. There were 490 compounds rejected from physicochemical criteria. Also, 62 compounds were found as intermediate compounds and 42 as covalent inhibitors, and they were not included in the final file. PAINS-toxicity criteria had found no compound to fall under it.

Similarly, in the case of the indole derivatives, the 1059 molecules were fit to the ADMET evaluation and physicochemical descriptors data is represented in Fig. 4. There were 117 compounds were rejected from physicochemical criteria. Also, 588 compounds were found as intermediate compounds and 42 as covalent inhibitors and they were not included in the final file. PAINS-toxicity

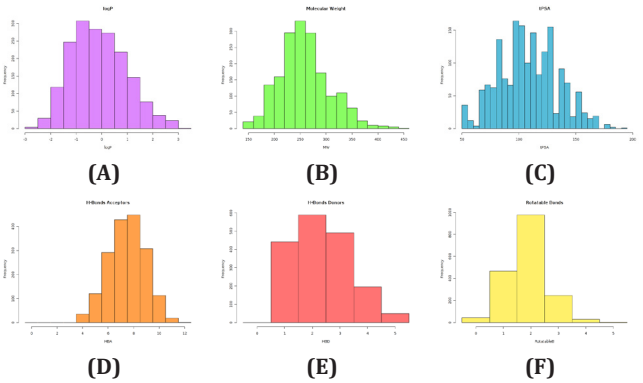


Fig. 3: The plot of different physicochemical descriptors for pyrimidine derivatives. The x-axis describes the frequency of compounds for the descriptor values plotted on the y-axis. Plots are for A) logP B) molecular weight, C) topological Polar Surface Area, D) Hydrogen Bond Acceptor, E) Hydrogen Bond Donor and F) rotatable bonds.

criteria found 462 compounds with higher toxicity value; hence, they were excluded.

Further, the thiadiazole derivatives had 1351 accepted molecules after the ADMET filtration and the physiochemical descriptor range and molecule frequency had been podcasted in Fig. 5. There were 281 compounds rejected from physicochemical criteria. Also, 132 compounds were found as intermediate compounds and 83 as covalent inhibitors and they were not included in the final file. PAINS-toxicity criteria had found no compounds.

Additionally, the thiazole derivative had resulted in 1623 structures after ADMET screening and has been represented in Fig. 6. There were 57 compounds rejected from physicochemical criteria. Also, 84 compounds were found as intermediate compounds and no covalent inhibitors and they were not included in the final file. PAINS-toxicity criteria found 84 compounds with higher toxicity value; hence, they were excluded.

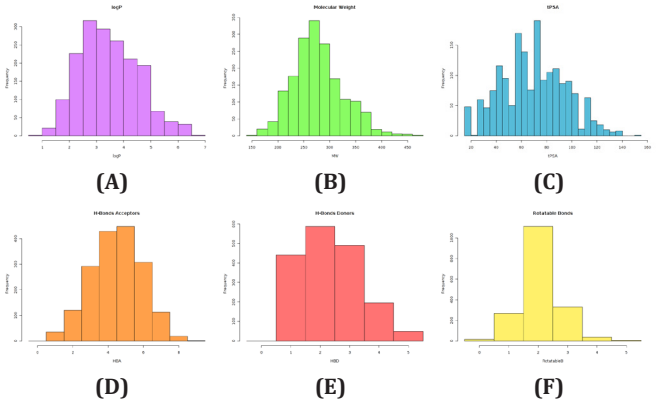


Fig. 4: The plot of different physicochemical descriptors for indole derivatives. The x-axis describes the frequency of compounds for the descriptor values plotted on the y-axis. Plots are for A) logP B) molecular weight, C) topological Polar Surface Area, D) Hydrogen Bond Acceptor, E) Hydrogen Bond Donor and F) rotatable bonds.

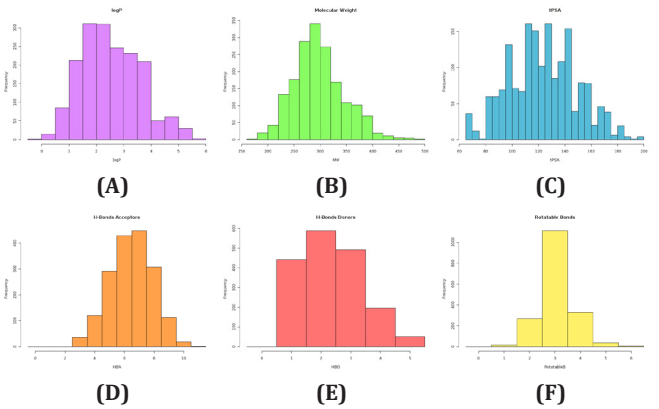


Fig. 5: The plot of different physicochemical descriptors for thiadiazole derivatives. The x-axis describes the frequency of compounds for the descriptor values plotted on the y-axis. Plots are for A) logP B) molecular weight, C) topological Polar Surface Area, D) Hydrogen Bond Acceptor, E) Hydrogen Bond Donor and F) rotatable bonds.

Virtual Screening through Molecular Docking

The ADMET screening provides the set of acceptable molecules to consider as a drug in the drug development study. Thus, virtual screening of molecules with the target enzyme structure is a key step to ensure the possible drug activity with the enzyme. The energy minimization of an enzyme, i.e., VEGFR2 Kinase, in a protein-only form was performed. The final potential energy of the system was -9.5 x 105 kJ/mol and the three-dimensional structure has been presented in Fig. 7.

The active site was extracted from literature (Fig. 8) and the grid for docking to this enzyme was selected around it, with a center of the box at (42.05, 44.14, 51.30) Å. The docking of 1764 derivatives of each molecule was taken place using AutoDock vina.

The docking of each molecule has provided binding energy, which ranged from -10 to -4.9 kcal/mol for pyrimidine derivatives, -11.5 to -9 kcal/mol for indole derivatives, -10.4 to -9 kcal/mol to thiadiazole derivatives, and -11. to -6.9 kcal/mol for thiazole derivatives. The binding energy cutoff of -9 kcal/mol was applied, resulting in 26, 436, 59 and 571 molecules for pyrimidine, indole,

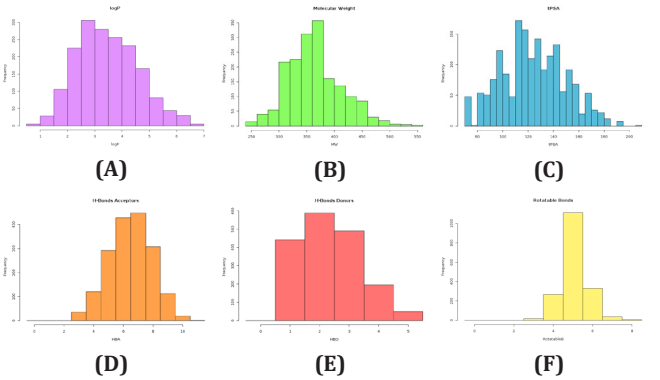


Fig. 6: The plot of different physicochemical descriptors for thiazole derivatives. The x-axis describes the frequency of compounds for the descriptor values plotted on the y-axis. Plots are for A) logP B) molecular weight, C) topological Polar Surface Area, D) Hydrogen Bond Acceptor, E) Hydrogen Bond Donor and F) rotatable bonds.

Fig. 7: The energy minimized the three-dimensional structure of VEGFR2 Kinase in the protein only form.

thiazole, and thiadiazole derivatives, respectively. The binding energy of all of these compounds has been incorporated in supplementary 5. Further, to study the interaction profile with enzyme, top 20 molecules were selected from each derivative class (Table 1). The indole and thiazole had shown higher binding affinity than pyrimidine and thiadiazole.

After extracting the 20 molecules of each derivative lead molecule, the binding orientation was analyzed. In its result, the binding occurred in the active site represented in Fig. 8. The important thing to observe here is that each class's orientation of derivatives was found to be in a similar fashion i.e., the base moiety has not changed its position. It represents that the docking occurred in the active site area with a perfect pose. This is an important evaluation to determine if there are any discrepancies in the binding. Also, it motivated us to look the binding pattern with the enzyme.

Binding of Selected Compounds to Target Enzyme

The target enzyme VEGFR2 kinase activity is dependent on the residues present in its active site (shown in Fig. 9). The

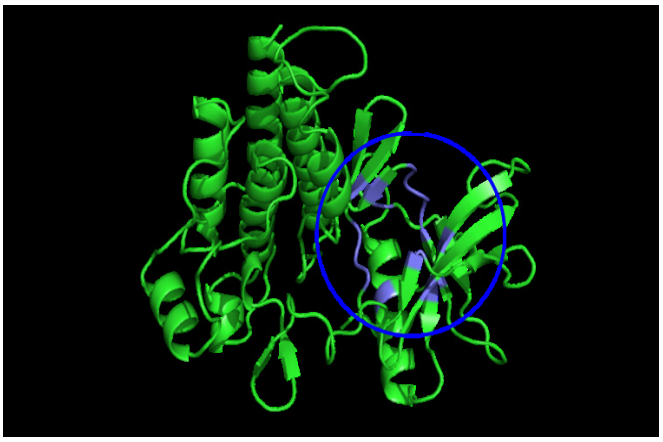


Fig. 8: The active site representation of VEGFR2 Kinase enzyme.

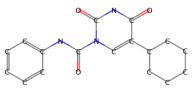
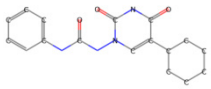
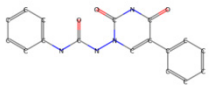
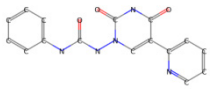
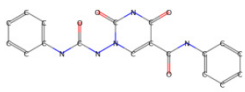
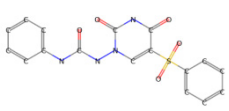
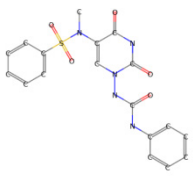
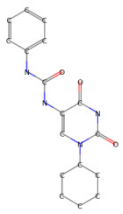
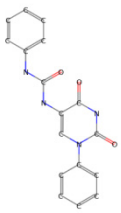
Table 1: The top 20 molecules, having the lowest binding affinity obtained from derivatives molecular docking.

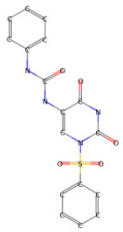
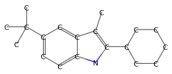
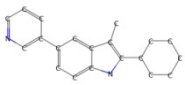
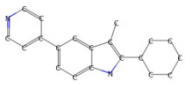
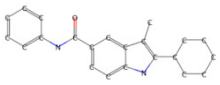
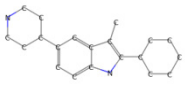
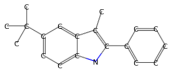
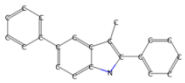
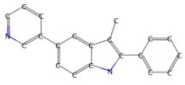
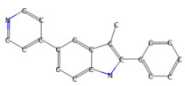
Pyridine		*Indole*		*Thiadiazole*		*Thiazole*	
Compound no	*B.E. (in kcal/mol)*	*Compound no*	*B.E. (in kcal/mol)*	*Compound no*	*B.E. (in kcal/mol)*	*Compound no*	*B.E. (in kcal/ mol)*
1_0154	-10	2_0115	-11.5	3_1239	-10.4	4_ac_0213	-11
1_0195	-10	2_0102	-11.3	3_1157	-10.3	4_ac_1393	-11
1_0865	-9.8	2_0136	-11.3	3_0153	-10.2	4_ac_1401	-11
1_0236	-9.6	2_0081	-11.2	3_0192	-10.1	4_ac_0292	-10.9
1_1025	-9.6	2_0083	-11.2	3_1120	-10.1	4_ac_1371	-10.9
1_1097	-9.6	2_0084	-11.2	3_1269	-10.1	4_ac_1373	-10.9
1_1098	-9.6	2_0111	-11.2	3_1240	-10	4_ac_0252	-10.8
1_1129	-9.6	2_0114	-11.2	3_1267	-10	4_ac_0190	-10.7
1_1066	-9.5	2_0117	-11.2	3_1194	-9.9	4_ac_0191	-10.7
1_0143	-9.4	2_0118	-11.2	3_0188	-9.8	4_ac_0332	-10.7
1_0184	-9.4	2_0146	-11.2	3_0149	-9.7	4_ac_0158	-10.6
1_0854	-9.4	2_0082	-11.1	3_0151	-9.7	4_ac_0268	-10.6
1_1130	-9.4	2_0116	-11.1	3_0190	-9.7	4_ac_1369	-10.6
1_1132	-9.4	2_0150	-11.1	3_0554	-9.7	4_ac_1510	-10.6
1_0139	-9.3	2_0151	-11.1	3_1196	-9.7	4_ac_1534	-10.6
1_0277	-9.3	2_0189	-11	3_1238	-9.7	4_ac_1610	-10.6
1_0849	-9.3	2_0190	-11	3_0004	-9.6	4_ac_0228	-10.5
1_0863	-9.3	2_1024	-11	3_0229	-9.6	4_ac_0229	-10.5
1_0984	-9.3	2_1025	-11	3_0767	-9.6	4_ac_0269	-10.5
1_0180	-9.2	2_0080	-10.9	3_0768	-9.6	4_ac_1426	-10.5

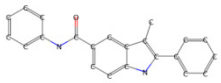
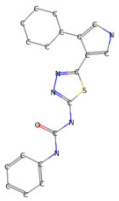
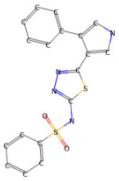
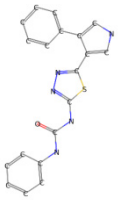
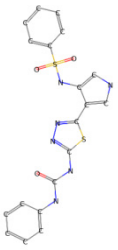
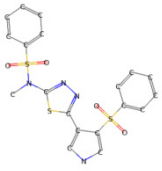
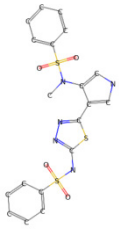
Table 2: Drug ability and toxicity filtration criteria

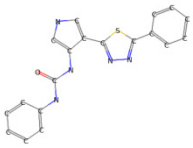
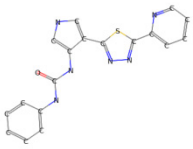
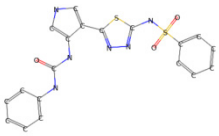
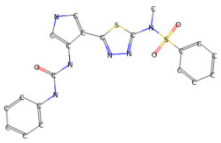
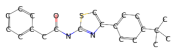
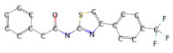
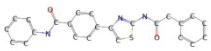
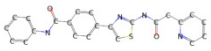
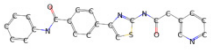
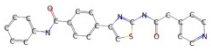
S.N.	*Derivative type*	*Total derivatives for study*	*Derivatives rejected in physicochemical criteria*	*Intermediate compound rejected*	*Covalent inhibitors rejected*	*Higher toxicity*	*Total*
1	Pyrimidine	1212	490	62	42	Nil	1806
2	Indole	1059	117	588	42	Nil	1806
3	Thiadiazole	1351	281	132	83	Nil	1847
4	Thiazole	1623	57	84	Nil	84	1848

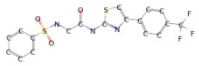
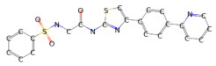
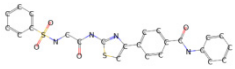
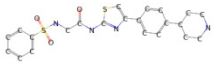
Table 3: The molecular and structural information 10 molecules, having the lowest binding affinity obtained from derivatives molecular docking.

Ligand ID	*Structure*	*MW (g/mol)*	*Solubility (mg/l)*	*HBD+ HBA*	*logP*	*logD*	*logSw*	*tPSA*
1_0143		313.35	8675.42	8	2.7375	3.04	-3.59	83.96
1_0154		328.37	10336.96	10	2.5059	2.45	-3.46	95.99
1_0195		322.32	11539.37	10	2.1252	2.12	-3.33	95.99
1_0236		323.31	16682.76	11	1.5202	1.28	-2.96	108.88
1_0865		365.34	13721.49	13	1.7835	1.46	-3.28	125.09
1_1025		386.38	8724.6	12	2.3718	1.42	-3.79	138.51
1_1066		415.42	8155.77	13	2.3641	1.17	-3.93	141.75
1_1097		328.37	8418.3	10	2.8318	2	-3.66	95.99
1_1098		322.32	10233.7	10	2.3158	1.83	-3.45	95.99

Ligand ID	*Structure*	*MW (g/mol)*	*Solubility (mg/l)*	*HBD+ HBA*	*logP*	*logD*	*logSw*	*tPSA*
1_1129		386.38	6878.55	12	2.6444	1.56	-4.03	138.51
2_0081		269.42	1504.72	2	5.8215	6.09	-5.19	15.79
2_0083		290.4	1478.93	3	5.586	4.97	-5.28	28.68
2_0084		290.4	1478.93	3	5.586	4.97	-5.28	28.68
2_0102		332.44	1211.36	5	5.8493	5.63	-5.61	44.89
2_0111		296.45	1937.15	4	5.3198	2.09	-5.03	32.4
2_0114		263.38	1706.11	2	5.4408	5.7	-5.04	15.79
2_0115		283.37	1130.79	2	5.8103	5.8	-5.52	15.79
2_0117		284.35	1633.85	3	5.2053	4.58	-5.16	28.68
2_0118		284.35	1633.85	3	5.2053	4.58	-5.16	28.68

Ligand ID	*Structure*	*MW (g/mol)*	*Solubility (mg/l)*	*HBD+ HBA*	*logP*	*logD*	*logSw*	*tPSA*
2_0136		250.3	4231.99	6	3.9425	3	-4.08	58.88
3_0153		367.47	1541.1	9	5.3709	4.8	-5.47	110.94
3_0188		382.46	1438.14	8	5.1548	2.76	-5.58	127.93
3_0192		361.42	1733.92	9	4.9902	4.33	-5.34	110.94
3_1120		440.5	1201.99	13	5.2778	2.74	-5.9	169.06
3_1157		460.55	1058.64	9	5.3527	3.2	-6.08	158.09
3_1194		475.56	1051.5	11	5.3937	1.82	-6.11	173.69

Ligand ID	*Structure*	*MW (g/mol)*	*Solubility (mg/l)*	*HBD+ HBA*	*logP*	*logD*	*logSw*	*tPSA*
3_1239		361.42	1733.92	9	4.9902	4.02	-5.34	110.94
3_1240		362.41	2505.94	10	4.3852	3.19	-4.97	123.83
3_1267		440.5	1201.99	13	5.2778	2.26	-5.9	169.06
3_1269		454.53	1196.88	12	5.2291	3.39	-5.94	156.7
4_0190		350.48	1727.18	4	5.3618	5.97	-5.31	70.23
4_0191		362.37	1862.73	4	5.0831	5.3	-5.27	70.23
4_0213		413.49	1335.49	7	5.3896	5.51	-5.74	99.33
4_0252		414.48	1934.38	8	4.7846	4.68	-5.37	112.22
4_0292		414.48	1934.38	8	4.7846	4.29	-5.37	112.22
4_0332		414.48	1934.38	8	4.7846	4.29	-5.37	112.22

Ligand ID	*Structure*	*MW (g/mol)*	*Solubility (mg/l)*	*HBD+ HBA*	*logP*	*logD*	*logSw*	*tPSA*
4_1371		441.45	1350.75	8	5.2906	3.97	-5.79	124.78
4_1373		450.53	1197.92	9	5.3338	3.91	-5.93	137.67
4_1393		492.57	941.81	11	5.5971	4.18	-6.26	153.88
4_1401		456.58	1554.42	10	5.0676	0.64	-5.68	141.39

main interacting residues were obtained by studying the tyrosine kinase inhibitor bound structure (PDB id- 4AG8). It showed that the residues Glu885, Asp1046 and Cys919 formed hydrogen bond with the inhibitor AXITINIB(AXI). The binding cavity also has different other residues near the active site as shown in Fig. 10, which must be responsible for the binding of derivative molecules.

The binding energy shades light on the interacting affinity of a molecule with the compound. However, residue interaction gives the idea of ligand binding sites. According to Table 2, the indole and thiazole derivatives have a higher binding affinity as compared to others. Later, the compounds were looked for interaction with target enzyme residues. This had provided a vibrant landscape of interaction. The data of molecule having the lowest binding energy has been presented here. The rest interaction tables data of all 20 selected molecules of pyrimidine, indole, thiadiazole, and thiazole have been presented in supplementary files (supplementary 6, supplementary 7, supplementary 8, and supplementary 9, respectively).

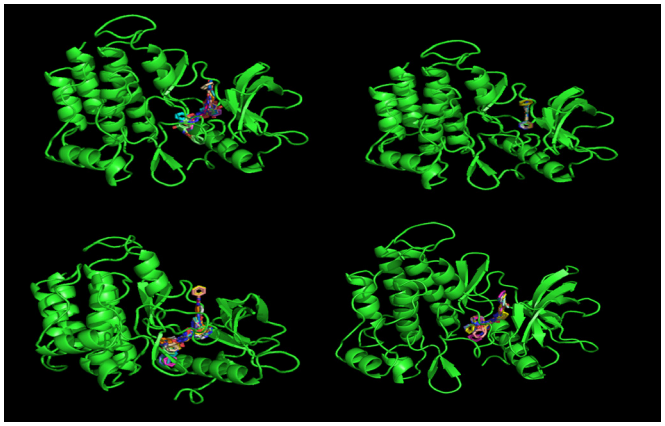


Fig. 9: The molecular docking of top 20 compounds with the VEGFR2 Kinase. A) pyrimidine derivatives, B) indole derivatives, C) thiadiazole derivatives D) thiazole derivatives.

The representative of each class of compounds has been represented in Fig. 11. It provides the idea of binding each molecule to the binding cleft and the interaction profile.

Hence, the detained information of compounds from each of four classes have been summarized in Table 3. It provides the structures and the other physicochemical properties.

This virtual screening-based study clearly provides the possible compounds with higher affinity towards binding the targeted VEGFR2 kinase enzyme. The provided information inferred that the top 20 compounds, whose interaction, binding affinity data have been provided, are important drugs that have resistance to this enzyme. It implies that these are potential anti-bacterial candidates.

Molecular Dynamics of Screened Compounds

From the screened compounds, complex structures from Indole, pyrimidine, thiazole, and thiadiazole compounds were chosen for simulation. The compounds which showed

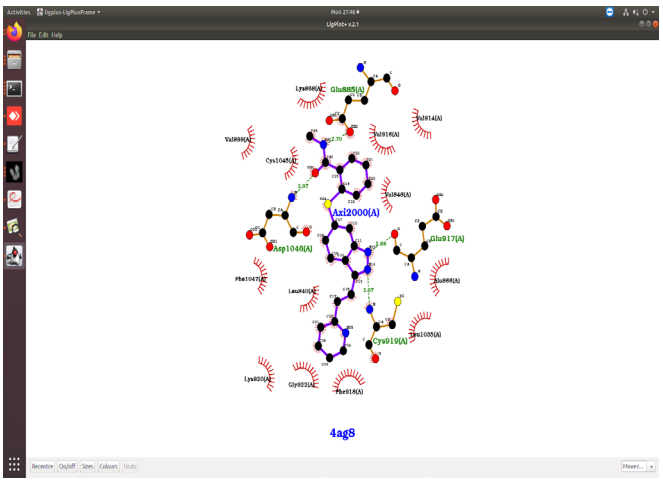


Fig. 10: The interaction plot, LIG plot, of inhibitor bound structure of VEGFR2 Kinase.