In silico drug design of some Novel diarylurea derivatives as Antiproliferative Agent

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Abstract:

Aromatase catalyzes the final and crucial step in the synthesis of estrogen biosynthesis and was identified as attractive target for selective inhibition for the treatment of breast cancer. we have designed some *1-(4-(benzamido)phenyl)-3-arylureas* derivatives through molecular docking studies. The entire molecules are examined through molecular docking studies. From present investigation, we have concluded that compound **19 [**1-(4-(benzamido)phenyl)-3-o-tolylurea] is most potent and exhibited -8.6 kcal/mol binding affinity. It has formed conventional hydrogen bonds with ALA306 and THR310. Results obtained from this study pointed out that **compound 19** showed most promising activity. From present investigation it is concluded that the designed molecules had potential to be developed as broad spectrum anticancer agents.

Keywords: Aromatase inhibitors, Molecular docking, Diaryl Urea, Antiproliferative Agent, Breast cancer.

INTRODUCTION

Cancer is second leading cause of death worldwide behind cardiovascular diseases worldwide.[1] Aromatase enzyme catalyzed the key step that is conversion of androgen to estrogen and it is highly expressed in or near breast tumor sites.[2] Elevated expressions of estrogen and aromatase in breast cancer tissues than non-cancerous have been reported by several studies.[3] Although several aromatase inhibitors have been developed for the treatment of breast cancer, they are not suitable for everyone and show several side effects. The molecular docking approach can be used to examine general pattern of molecular atomic interaction between small molecule and protein. It characterizes the binding interaction between small molecules and target protein sites. Protein binds selectively to small molecule target called ligands, binding affect enzyme activity elucidate the behavioral activity of small molecules. Molecular docking analyses the conformation and orientation of novel compounds for therapeutic interest at molecular level. Many novel series of compounds have been

synthesized and evaluated for anticancer activity using sorafenib as parent structure.[4] The diaryl urea is a prominent pharmacophore in building anticancer moiety.[5] This activity due to pharmacophore screening shows it's near perfect binding with certain acceptors.[6] For drug design and development molecular hybridization is an attractive area in medicinal chemistry that aims to combine two or more pharmacophore for development of single compound with improved efficacy.[7] From a synthetic view it was of interest to combine heterocycles to Benzamide through urea linker bridge to develop more potent antiproliferative agents.[8], [9] Amide derivatives were associated with variety of biological activities like anticonvulsant, anti-tuberculosis, insecticidal, antifungal, anti-microbial, anti-HCV, anti-proliferative properties.[10]–[12] The intermolecular forces have increased importance in medicinal chemistry and allow them to interact with variety of enzyme and receptor due to their high solubility, ease and efficiency to reach to target sites.[13]–[15]

MATERIAL AND METHODS

Molecular docking was performed on Lenovo ThinkPad with 64-bit operating system, Processor: Intel(R) Core(TM) i5-4300M CPU @2.60 GHz 2.59 GHz, RAM: 4GB by using PyRx-Virtual Screening Tool. The structures of all the designed novel derivatives (1-20) and native ligand (mole. File format) were drawn in ChemDraw Ultra 8.0. The energy minimization (optimization) was performed by Universal Force Field (UFF)[16].

EXPERIMENTAL WORK

In silico Study

The elucidated crystal structure of human placental aromatase complexed with breast cancer drug exemestane was obtained from the RCSB Protein Data Bank (PDB) as entry 3S7S (https://www.rcsb.org/structure/3S7S). The native ligand present in 3S7S was exemestane (PubChem ID: 60198). Autodock vina 1.1.2 in PyRx 0.8 was used to perform the docking studies of all the designed novel derivatives and the native ligand against the crystal structure of aromatase enzyme [17]. The enzyme structure was optimized, purified and prepared for docking with the help of Discovery Studio Visualizer 2019[18].

The binding affinity studies were performed by using Vina Wizard Tool in PyRx 0.8. Molecules (PDBQT Files), both ligands as well as target (aromatase enzyme) were selected for docking study. For molecular docking simulation, the three-dimensional grid box (size_x = 51.602628352A^o; size_y = 62.2935613655A^o; size_z = 41.7297385081A^o) was designed using Autodock tool 1.5.6 with exhaustiveness value of 8[[17]]. The active amino acid

residues in the protein were identified and noted using BIOVIA Discovery Studio Visualizer (version-19.1.0.18287) [18]. The identified cavity of the enzyme with co-crystallize ligand molecule is represented in fig. 1.

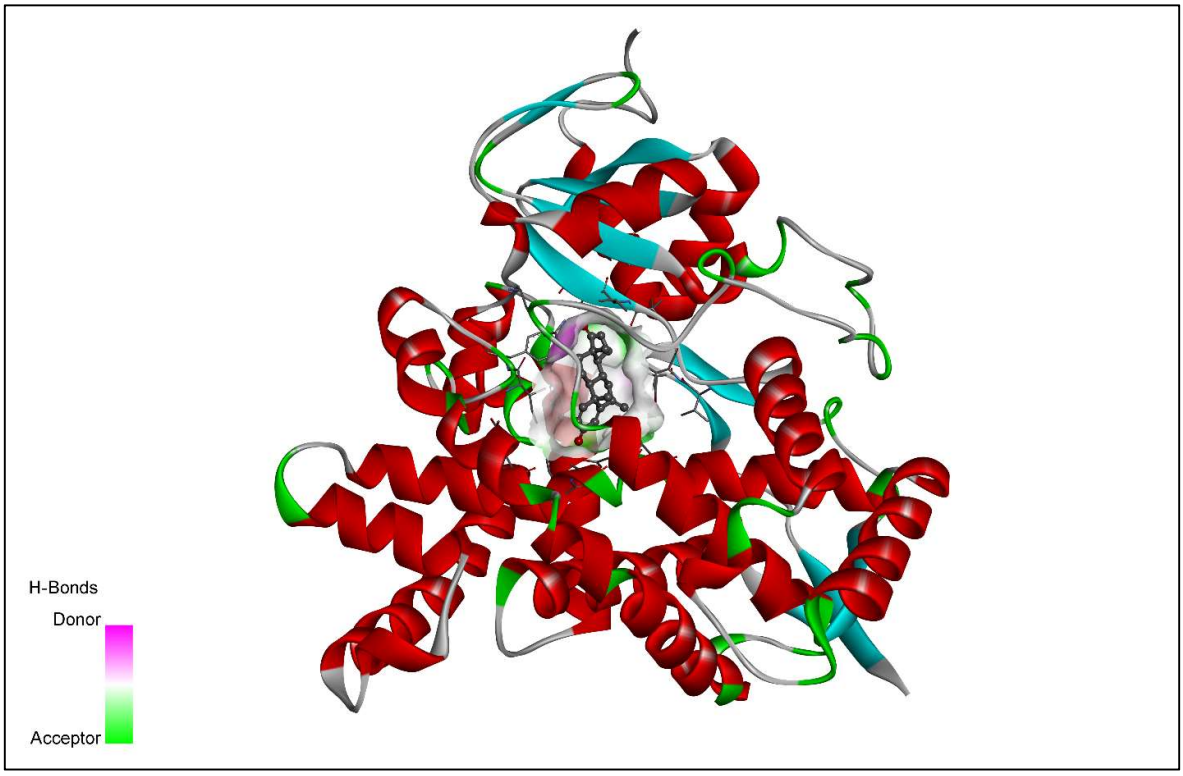


Fig. 1. The identified active cavity with native ligand present in human aromatase enzyme

The docking scores of all the derivatives and native ligand is tabulated in table 1. The active amino acid residues, bond length (A^0), bond type and bond category involved in the interactions are illustrated in table 2.

Table 1. The docking scores of native ligand and novel derivatives with aromatase enzyme

Compound Code	Ligand Energy (kcal/mol)	Binding Affinity (kcal/mol)	rmsd/ub	rmsd/lb
Native Ligand	1113.62	-8.9	0	0
		-8.8	3.765	2.54
		-8.8	6.864	1.751
		-8.7	5.027	3.134
		-8.7	6.537	1.282
		-8.7	6.557	1.519
		-8.2	7.204	4.375

		-7.8	6.447	2.492
		-7.6	18.619	16.842
1	250.47	-8.4	0	0
		-8.3	2.304	1.876
		-7.8	10.72	1.767
		-7.4	19.8	18.345
		-7.1	24.381	18.503
		-7	22.241	18.557
		-6.7	24.457	22.368
		-6.7	25.452	19.957
		-6.6	24.166	20.094
2	277.44	-8.4	0	0
		-8.2	10.689	1.336
		-8.2	10.814	1.941
		-8.1	2.303	1.633
		-7.3	21.399	18.674
		-7.2	18.727	16.332
		-7.1	24.172	18.663
		-6.9	22.569	19.257
		-6.9	26.972	22.353
3	287.84	-8.2	0	0
		-7.2	22.603	18.82
		-7.2	20.674	19.006
		-7.1	21.194	19.308
		-7.1	20.902	19.717
		-6.9	21.297	20.229
		-6.8	24.83	19.862
		-6.7	23.984	19.451
		-6.6	21.957	20.155
4	275.03	-8	0	0
		-7.9	10.801	2.172
		-7.9	19.154	13.894

		-7.8	2.333	2.109
		-7.2	10.711	1.722
		-7.2	20.74	19.516
		-7.1	20.906	19.589
		-7.1	6.461	5.216
		-7	22.74	19.232
5	458.41	-8	0	0
		-7.7	10.566	3.42
		-7.3	19.374	14.45
		-7.3	19.355	16.393
		-7	20.809	19.544
		-7	16.296	14.836
		-6.8	25.115	22.859
		-6.8	22.589	19.141
		-6.7	20.96	19.247
6	575.4	-7.2	0	0
		-7.1	12.602	4.131
		-7	40.393	39.872
		-7	29.199	27.281
		-6.9	40.584	39.852
		-6.9	19.892	17.711
		-6.9	8.695	5.519
		-6.8	7.773	4.861
		-6.7	22.856	20.769
7	402.26	-8.1	0	0
		-7.9	2.286	2.102
		-7.7	10.592	3.314
		-7.3	10.346	2.939
		-7.2	20.58	19.428
		-7.1	20.378	18.959
		-6.5	23.688	19.474
		-6.5	20.759	18.756

		-6.4	25.548	23.804
8	420.02	-8.3	0	0
		-8.2	10.24	1.61
		-7.6	19.302	14.387
		-7.5	20.366	18.943
		-7.5	10.411	2.324
		-7.1	21.3	19.535
		-7.1	20.766	19.352
		-7.1	20.834	18.352
		-7	20.292	17.322
9	514.81	-7.9	0	0
		-7.7	26.911	22.644
		-7.6	20.553	18.832
		-7.6	18.179	14.673
		-7.5	37.06	32.877
		-7.5	32.162	30.301
		-7.3	20.07	16.226
		-7.3	24.679	22.528
		-7.2	18.587	14.365
10	528.5	-7.9	0	0
		-7.7	22.503	19.843
		-7.6	23.813	19.079
		-7.5	12.06	2.386
		-7.5	30.251	28.76
		-7.5	15.595	14.786
		-7.4	26.682	24.898
		-7.2	26.249	23.68
		-7.2	41.226	39.692
11	175.12	-7.8	0	0
		-7.5	9.553	5.698
		-7.5	8.72	4.79
		-7.4	6.825	6.016

		-7.2	24.659	22.792
		-7.1	5.347	4.766
		-7	5.778	4.846
		-6.9	8.952	4.601
		-6.9	14.612	12.003
12	174.28	-7.4	0	0
		-7.1	2.761	2.007
		-7	2.33	1.699
		-7	9.584	2.255
		-6.9	2.581	2.11
		-6.8	19.439	18.763
		-6.6	16.176	14.997
		-6.4	20.52	19.093
		-6.3	3.159	2.862
13	172.5	-6.4	0	0
		-6.4	24.434	19.909
		-6.3	10.324	4.165
		-6.1	28.169	26.124
		-6	22.707	18.682
		-6	9.638	1.426
		-5.9	20.669	18.877
		-5.9	17.591	15.4
		-5.8	50.408	49.202
14	177.15	-7.9	0	0
		-7.2	9.686	1.948
		-7.1	9.38	1.245
		-6.7	19.059	14.96
		-6.7	1.908	1.656
		-6.7	9.46	1.856
		-6.6	19.667	18.187
		-6.3	22.288	18.368
		-6.1	2.904	1.93

15	274.78	-7.9	0	0
		-7.9	15.961	13.92
		-7.2	39.269	33.961
		-7.1	37.415	31.546
		-7.1	32.608	30.701
		-7.1	41.767	37.631
		-7	37.195	32.464
		-6.7	38.521	34.046
		-6.6	29.459	24.572
16	284.12	-8.6	0	0
		-8.4	10.979	1.642
		-8.2	2.275	1.861
		-7.3	20.235	18.843
		-7.2	22.241	21.138
		-7.1	21.702	20.314
		-7.1	22.496	18.821
		-7.1	24.277	20.133
		-6.8	6.579	5.905
17	300.1	-8.3	0	0
		-8	2.309	1.881
		-7.4	22.416	18.825
		-7.2	21.904	20.505
		-7.2	20.799	18.921
		-7.1	22.719	21.65
		-7	24.465	22.414
		-6.8	25.3	19.649
		-6.8	22.332	19.648
18	276.5	-8.7	0	0
		-8.3	10.719	1.268
		-7.6	20.11	18.239
		-7.4	22.199	18.458
		-6.9	24.976	19.417

		-6.9	24.276	22.259
		-6.9	20.396	19.101
		-6.9	22.375	20.75
		-6.8	20.54	18.712
19	275.96	-8.6	0	0
		-8.2	10.683	0.992
		-8.1	2.227	1.636
		-8	19.124	13.728
		-7.2	21.15	19.111
		-7.2	19.663	14.623
		-7.2	10.807	1.696
		-7.1	21.301	19.403
		-7	7.15	5.169
20	227.72	-8.6	0	0
		-8.4	3.013	2.467
		-8.3	1.699	1.362
		-7.8	10.744	1.543
		-7.4	21.898	20.411
		-7.3	10.279	1.891
		-7.3	21.079	19.93
		-7.3	19.509	18.169
		-7.1	19.801	18.133

Table 2. The interaction involved in the molecular docking

Active Amino Acid Residue	Atom from Ligand	Bond Length (A^0)	Bond Category	Bond Type
Native Ligand				
A:ILE133	Alkyl	4.78318	Hydrophobic	Alkyl
A:CYS437	Alkyl	3.59788	Hydrophobic	Alkyl
A:VAL370	Alkyl	3.9176	Hydrophobic	Alkyl
A:ALA306	Alkyl	4.12208	Hydrophobic	Alkyl
A:ILE133	Alkyl	4.00864	Hydrophobic	Alkyl
A:ALA306	Alkyl	5.2502	Hydrophobic	Alkyl
A:TRP224	Pi-Orbitals	5.23612	Hydrophobic	Pi-Alkyl
1				

A:LEU152	C-H	3.59141	Hydrophobic	Pi-Sigma
A:MET374	Sulfur	5.18676	Other	Pi-Sulfur
A:MET446	Sulfur	5.7763	Other	Pi-Sulfur
A:ILE133	Pi-Orbitals	4.73032	Hydrophobic	Pi-Alkyl
A:CYS437	Pi-Orbitals	5.02222	Hydrophobic	Pi-Alkyl
A:ALA306	Pi-Orbitals	4.43544	Hydrophobic	Pi-Alkyl
A:ALA307	Pi-Orbitals	4.86199	Hydrophobic	Pi-Alkyl
2				
A:LEU152	C-H	3.60212	Hydrophobic	Pi-Sigma
A:MET446	Sulfur	5.69567	Other	Pi-Sulfur
A:MET374	Alkyl	4.95459	Hydrophobic	Alkyl
A:ILE133	Pi-Orbitals	5.07191	Hydrophobic	Pi-Alkyl
A:ALA306	Pi-Orbitals	4.81635	Hydrophobic	Pi-Alkyl
A:CYS437	Pi-Orbitals	5.02515	Hydrophobic	Pi-Alkyl
A:ALA306	Pi-Orbitals	4.47315	Hydrophobic	Pi-Alkyl
A:ALA307	Pi-Orbitals	4.8061	Hydrophobic	Pi-Alkyl
A:PHE134	Pi-Orbitals	5.08734	Hydrophobic	Pi-Alkyl
3				
A:THR310	H	2.998	Hydrogen Bond	Conventional Hydrogen Bond
A:ALA306	H	2.52969	Hydrogen Bond	Conventional Hydrogen Bond
A:THR310	H	2.00243	Hydrogen Bond	Conventional Hydrogen Bond
A:THR310	C-H	3.71566	Hydrophobic	Pi-Sigma
A:MET374	Sulfur	5.1018	Other	Pi-Sulfur
A:VAL370	Pi-Orbitals	5.23308	Hydrophobic	Pi-Alkyl
4				
A:ALA306	H	2.58921	Hydrogen Bond	Conventional Hydrogen Bond
A:THR310	H	1.99588	Hydrogen Bond	Conventional Hydrogen Bond
A:THR310	C-H	3.76289	Hydrophobic	Pi-Sigma
A:MET446	C-H	3.82147	Hydrophobic	Pi-Sigma
A:MET374	Sulfur	5.15429	Other	Pi-Sulfur
A:VAL370	Pi-Orbitals	5.34159	Hydrophobic	Pi-Alkyl
A:LEU152	Pi-Orbitals	5.1788	Hydrophobic	Pi-Alkyl
A:ALA306	Pi-Orbitals	4.76943	Hydrophobic	Pi-Alkyl
A:ALA307	Pi-Orbitals	4.29899	Hydrophobic	Pi-Alkyl
A:ILE442	Pi-Orbitals	5.36139	Hydrophobic	Pi-Alkyl
5				
A:THR310	H	2.90166	Hydrogen Bond	Conventional Hydrogen Bond
A:ALA306	H	2.73553	Hydrogen Bond	Conventional Hydrogen

				Bond
A:THR310	H	1.95289	Hydrogen Bond	Conventional Hydrogen Bond
A:THR310	C-H	3.83414	Hydrophobic	Pi-Sigma
A:MET446	C-H	3.96889	Hydrophobic	Pi-Sigma
A:MET374	Sulfur	5.05165	Other	Pi-Sulfur
A:VAL370	Pi-Orbitals	5.24051	Hydrophobic	Pi-Alkyl
A:LEU152	Pi-Orbitals	5.3237	Hydrophobic	Pi-Alkyl
A:ALA306	Pi-Orbitals	4.51771	Hydrophobic	Pi-Alkyl
A:ALA307	Pi-Orbitals	4.24055	Hydrophobic	Pi-Alkyl
6				
A:GLY117	O	2.46014	Hydrogen Bond	Conventional Hydrogen Bond
A:LYS376	O	2.27727	Hydrogen Bond	Conventional Hydrogen Bond
A:LYS376	Positive	4.13478	Electrostatic	Pi-Cation
A:GLU92	Negative	3.5594	Electrostatic	Pi-Anion
A:GLY117; SER118	Amide	3.63876	Hydrophobic	Amide-Pi Stacked
A:LYS376	Pi-Orbitals	5.48565	Hydrophobic	Pi-Alkyl
A:PRO138	Pi-Orbitals	4.01776	Hydrophobic	Pi-Alkyl
7				
A:THR310	H	2.96757	Hydrogen Bond	Conventional Hydrogen Bond
A:ALA306	H	2.62519	Hydrogen Bond	Conventional Hydrogen Bond
A:THR310	H	1.87699	Hydrogen Bond	Conventional Hydrogen Bond
A:THR310	C-H	3.89798	Hydrophobic	Pi-Sigma
A:MET446	C-H	3.92962	Hydrophobic	Pi-Sigma
A:MET374	Sulfur	5.11903	Other	Pi-Sulfur
A:VAL370	Pi-Orbitals	5.38799	Hydrophobic	Pi-Alkyl
A:LEU152	Pi-Orbitals	5.23351	Hydrophobic	Pi-Alkyl
A:ALA306	Pi-Orbitals	4.61904	Hydrophobic	Pi-Alkyl
A:ALA307	Pi-Orbitals	4.30702	Hydrophobic	Pi-Alkyl
8				
A:ALA306	H	3.07047	Hydrogen Bond	Conventional Hydrogen Bond
A:THR310	H	2.12731	Hydrogen Bond	Conventional Hydrogen Bond
A:THR310	C-H	3.72459	Hydrophobic	Pi-Sigma
A:MET374	Sulfur	5.14288	Other	Pi-Sulfur
A:MET446	Sulfur	5.48999	Other	Pi-Sulfur
A:VAL370	Pi-Orbitals	5.16372	Hydrophobic	Pi-Alkyl
A:LEU152	Pi-Orbitals	5.28988	Hydrophobic	Pi-Alkyl

A:ALA306	Pi-Orbitals	4.17509	Hydrophobic	Pi-Alkyl
A:ALA307	Pi-Orbitals	4.22316	Hydrophobic	Pi-Alkyl
9				
A:CYS124	H	2.62578	Hydrogen Bond	Conventional Hydrogen Bond
A:CYS124	H	1.96848	Hydrogen Bond	Conventional Hydrogen Bond
A:TYR241	HH	2.54449	Hydrogen Bond	Conventional Hydrogen Bond
A:CYS124	Sulfur	5.56438	Other	Pi-Sulfur
A:TYR241	Pi-Orbitals	5.34825	Hydrophobic	Pi-Pi Stacked
A:PHE235; LYS236	Amide	3.85212	Hydrophobic	Amide-Pi Stacked
A:VAL248	Pi-Orbitals	5.46931	Hydrophobic	Pi-Alkyl
A:LYS249	Pi-Orbitals	4.6032	Hydrophobic	Pi-Alkyl
A:LYS236	Pi-Orbitals	4.92931	Hydrophobic	Pi-Alkyl
10				
A:GLY117	H	2.0319	Hydrogen Bond	Conventional Hydrogen Bond
A:GLY117	H	2.67471	Hydrogen Bond	Conventional Hydrogen Bond
A:GLU129	NH	2.5366	Hydrogen Bond	Conventional Hydrogen Bond
A:ASN136	H	2.55066	Hydrogen Bond	Conventional Hydrogen Bond
A:GLU92	Negative	4.05003	Electrostatic	Pi-Anion
A:LYS119	NH	3.08756	Hydrogen Bond	Pi-Donor Hydrogen Bond
11				
A:THR310	H	2.73917	Hydrogen Bond	Conventional Hydrogen Bond
A:PRO429	H	2.16876	Hydrogen Bond	Conventional Hydrogen Bond
A:PRO429	H	2.33609	Hydrogen Bond	Conventional Hydrogen Bond
A:VAL370	O	2.77996	Hydrogen Bond	Conventional Hydrogen Bond
A:ALA306	C-H	3.89756	Hydrophobic	Pi-Sigma
A:MET303	Sulfur	5.44002	Other	Pi-Sulfur
A:VAL370	Pi-Orbitals	5.31721	Hydrophobic	Pi-Alkyl
A:CYS437	Pi-Orbitals	4.78236	Hydrophobic	Pi-Alkyl
A:ALA443	Pi-Orbitals	5.36601	Hydrophobic	Pi-Alkyl
A:LEU152	Pi-Orbitals	5.46632	Hydrophobic	Pi-Alkyl
A:ALA307	Pi-Orbitals	4.55727	Hydrophobic	Pi-Alkyl
12				
A:ALA306	H	2.48419	Hydrogen Bond	Conventional Hydrogen

				Bond
A:THR310	H	1.97834	Hydrogen Bond	Conventional Hydrogen Bond
A:THR310	C-H	3.85939	Hydrophobic	Pi-Sigma
A:MET374	Sulfur	5.6163	Other	Pi-Sulfur
A:ALA306	Pi-Orbitals	5.0647	Hydrophobic	Pi-Alkyl
13				
A:GLU129	H	3.03697	Hydrogen Bond	Conventional Hydrogen Bond
A:LYS376	O	2.24868	Hydrogen Bond	Conventional Hydrogen Bond
A:GLU92	Negative	3.36261	Electrostatic	Pi-Anion
A:LYS119	Pi-Orbitals	5.16566	Hydrophobic	Pi-Alkyl
14				
A:ALA306	H	2.34066	Hydrogen Bond	Conventional Hydrogen Bond
A:THR310	C-H	3.75713	Hydrophobic	Pi-Sigma
A:MET374	Sulfur	5.15477	Other	Pi-Sulfur
A:ALA306	Pi-Orbitals	5.2536	Hydrophobic	Pi-Alkyl
15				
A:TYR361	H	2.65387	Hydrogen Bond	Conventional Hydrogen Bond
A:MET444	Pi-Orbitals	5.0067	Hydrophobic	Pi-Alkyl
A:PRO429	Pi-Orbitals	5.00342	Hydrophobic	Pi-Alkyl
A:ILE347	Pi-Orbitals	5.37876	Hydrophobic	Pi-Alkyl
A:ILE350	Pi-Orbitals	5.04232	Hydrophobic	Pi-Alkyl
16				
A:MET303	H	2.09588	Hydrogen Bond	Conventional Hydrogen Bond
A:SER199	O	2.15246	Hydrogen Bond	Conventional Hydrogen Bond
A:LEU152	C-H	3.75542	Hydrophobic	Pi-Sigma
A:MET374	Sulfur	5.14397	Other	Pi-Sulfur
A:MET446	Sulfur	5.58993	Other	Pi-Sulfur
A:ILE133	Pi-Orbitals	4.80249	Hydrophobic	Pi-Alkyl
A:CYS437	Pi-Orbitals	5.08104	Hydrophobic	Pi-Alkyl
A:ALA306	Pi-Orbitals	4.38019	Hydrophobic	Pi-Alkyl
A:ALA307	Pi-Orbitals	4.55999	Hydrophobic	Pi-Alkyl
17				
A:LEU152	C-H	3.69749	Hydrophobic	Pi-Sigma
A:MET374	Sulfur	5.12605	Other	Pi-Sulfur
A:MET446	Sulfur	5.61916	Other	Pi-Sulfur
A:ILE133	Pi-Orbitals	4.78448	Hydrophobic	Pi-Alkyl
A:CYS437	Pi-Orbitals	5.0598	Hydrophobic	Pi-Alkyl

A:ALA306	Pi-Orbitals	4.42012	Hydrophobic	Pi-Alkyl
A:ALA307	Pi-Orbitals	4.64893	Hydrophobic	Pi-Alkyl
18				
A:LEU152	C-H	3.69301	Hydrophobic	Pi-Sigma
A:MET374	Sulfur	5.16266	Other	Pi-Sulfur
A:CYS437	Sulfur	4.72024	Other	Pi-Sulfur
A:ALA307	Alkyl	3.744	Hydrophobic	Alkyl
A:MET446	Alkyl	4.75034	Hydrophobic	Alkyl
A:ILE133	Pi-Orbitals	5.02984	Hydrophobic	Pi-Alkyl
A:ALA306	Pi-Orbitals	4.20068	Hydrophobic	Pi-Alkyl
A:ALA307	Pi-Orbitals	5.08251	Hydrophobic	Pi-Alkyl
A:PHE203	Pi-Orbitals	4.77675	Hydrophobic	Pi-Alkyl
19				
A:THR310	H	3.02233	Hydrogen Bond	Conventional Hydrogen Bond
A:ALA306	H	2.77767	Hydrogen Bond	Conventional Hydrogen Bond
A:THR310	H	1.94013	Hydrogen Bond	Conventional Hydrogen Bond
A:THR310	C-H	3.65298	Hydrophobic	Pi-Sigma
A:MET374	Sulfur	5.15383	Other	Pi-Sulfur
A:ALA443	Alkyl	3.38822	Hydrophobic	Alkyl
A:MET446	Alkyl	5.45268	Hydrophobic	Alkyl
A:VAL370	Pi-Orbitals	5.18741	Hydrophobic	Pi-Alkyl
A:LEU152	Pi-Orbitals	5.14384	Hydrophobic	Pi-Alkyl
A:ALA306	Pi-Orbitals	4.52294	Hydrophobic	Pi-Alkyl
A:ALA307	Pi-Orbitals	4.29137	Hydrophobic	Pi-Alkyl
20				
A:LEU152	C-H	3.87865	Hydrophobic	Pi-Sigma
A:MET446	Sulfur	5.88582	Other	Pi-Sulfur
A:PHE134	Pi-Orbitals	5.05611	Hydrophobic	Pi-Pi Stacked
A:ILE133	Pi-Orbitals	4.78005	Hydrophobic	Pi-Alkyl
A:CYS437	Pi-Orbitals	5.01985	Hydrophobic	Pi-Alkyl
A:ALA306	Pi-Orbitals	4.11183	Hydrophobic	Pi-Alkyl
A:ALA307	Pi-Orbitals	4.65537	Hydrophobic	Pi-Alkyl
A:MET374	Pi-Orbitals	5.12173	Hydrophobic	Pi-Alkyl

Table 3. The pharmacokinetics and drug-likeness properties of developed compounds

Compound codes	Pharmacokinetics									Drug-likeness			
	GI abs.	Y Y	P-gp sub.	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4	Log K_p (skin permeation, cm/s)	Ghose	Egan	Muegge	Bioavailability score
				inhibitors									
Ex	H	Y	N	N	Y	Y	N	N	-5.93	Y	Y	Y	0.55
23	H	Y	Y	Y	Y	N	Y	Y	-6.7	Y	Y	Y	0.55
25	H	Y	Y	Y	Y	N	Y	Y	-6.46	Y	Y	Y	0.55
27	H	Y	Y	Y	Y	N	Y	Y	-5.99	Y	Y	Y	0.55
29	H	Y	Y	Y	Y	N	Y	Y	-6.28	Y	Y	Y	0.55
30	H	N	Y	Y	Y	Y	Y	Y	-6.51	Y	Y	Y	0.55
31	H	N	N	Y	Y	Y	Y	Y	-6.6	Y	Y	Y	0.55
39	H	N	N	Y	Y	Y	Y	Y	-6.7	Y	Y	Y	0.55

Where: NL, Native ligand; GI abs., gastrointestinal absorption; BBB pen., blood brain barrier penetration; P-gp sub., p-glycoprotein substrate

Table 4. Lipinski rule of 5 and Veber's rule calculated for the designed N-(4-(1H-benzo[d]imidazol-2-yl)phenyl)arylamine derivatives

Compound codes	Lipinski rule of five					Veber's rule	
	Log P	Mol. Wt.	HBA	HBD	Violations	Total polar surface area (Å^2)	No. of rotatable bonds
Exemestane	3.51	296.40	2	0	0	34.14	0
23	3.41	332.36	3	3	0	83.12	3
25	3.47	338.38	3	3	0	111.36	3
27	4.07	337.4	2	3	0	98.47	3
29	3.89	371.39	3	4	0	98.91	3
30	3.89	371.39	3	4	0	98.91	3
31	2.31	269.3	2	3	0	70.23	4
39	3.41	332.36	3	3	0	83.12	4

Where: Mol. Wt., molecular weight; HBA, hydrogen bond acceptors; HBD, hydrogen bond donors

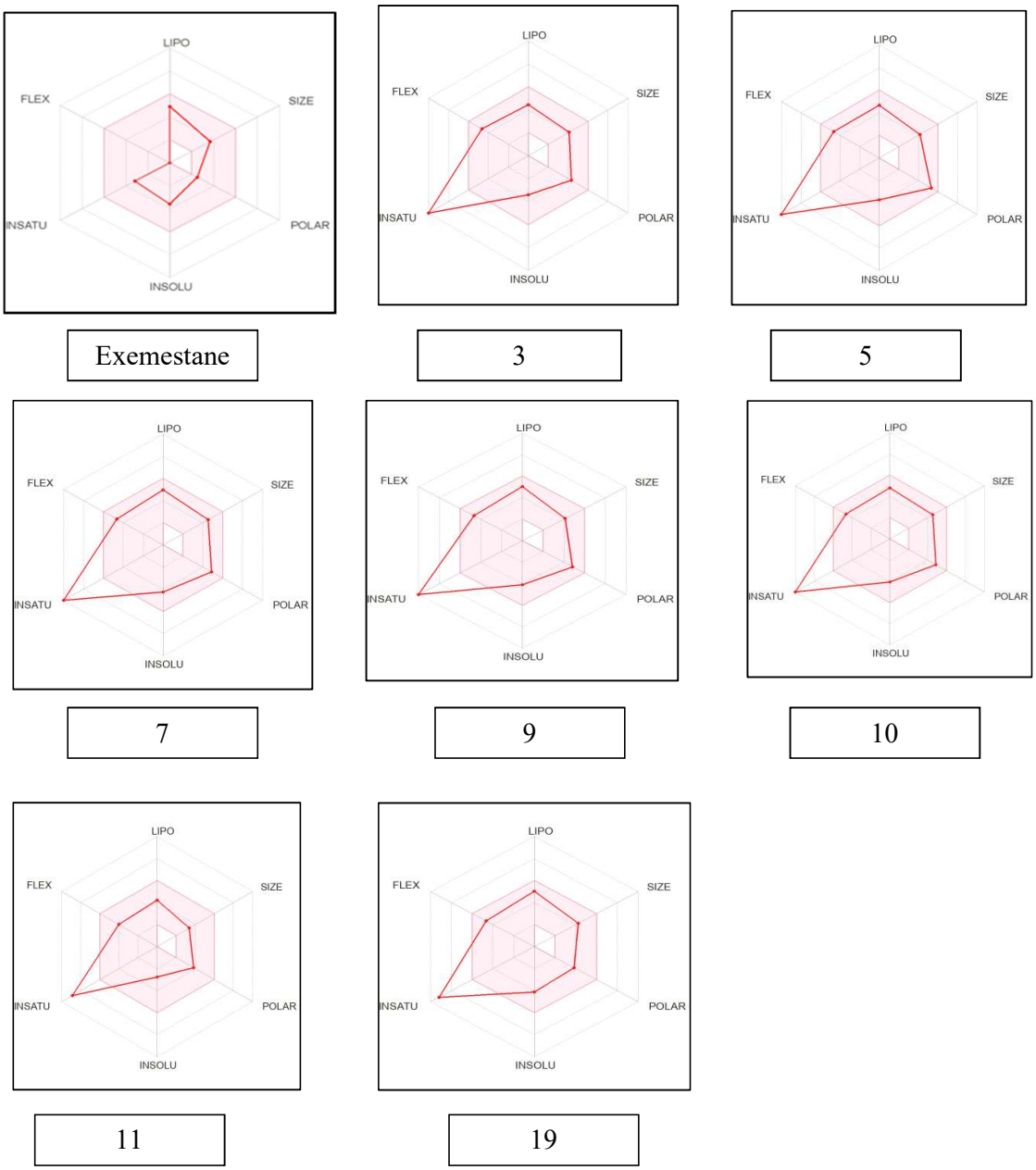
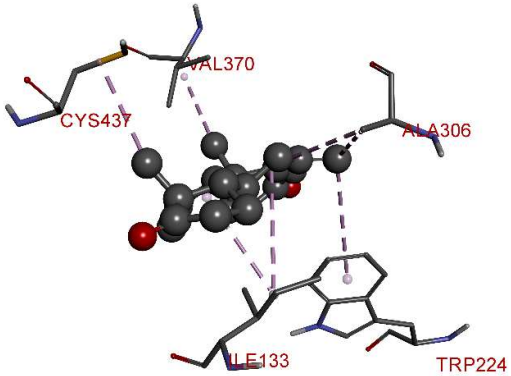
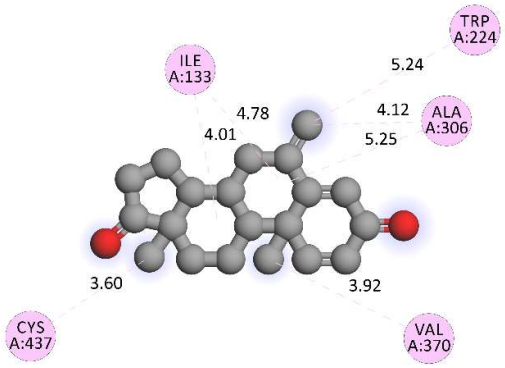
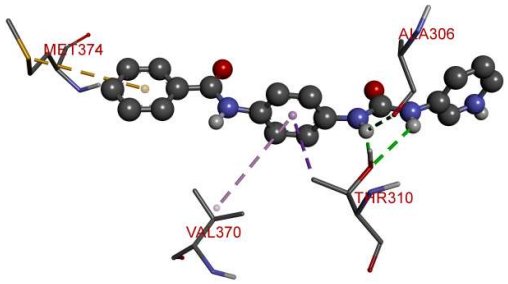
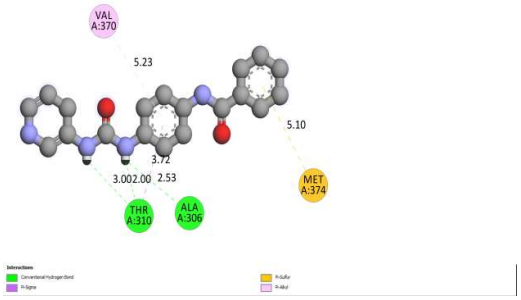
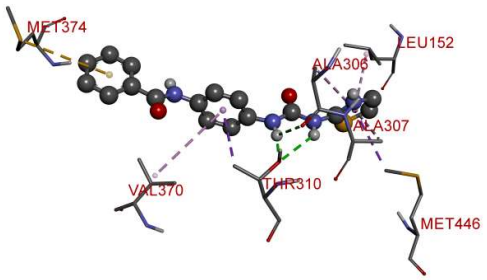
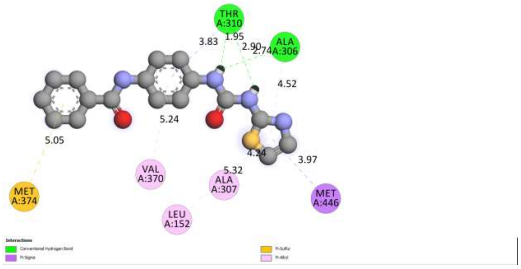
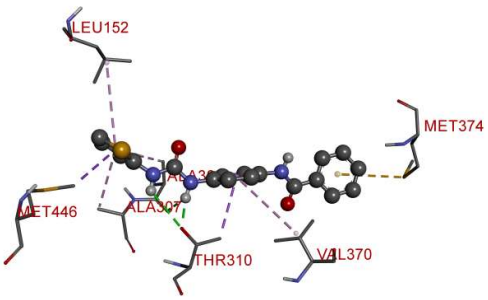
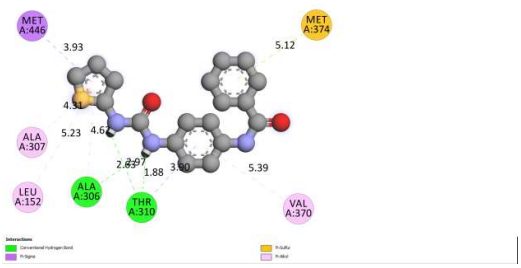
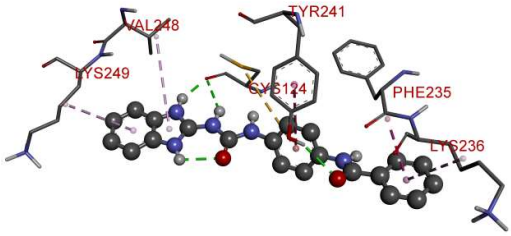
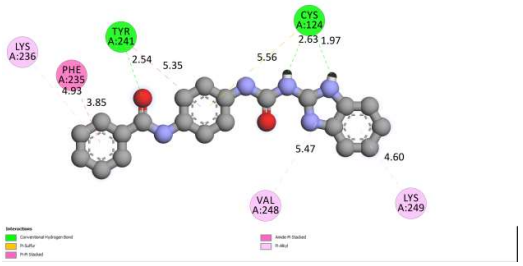
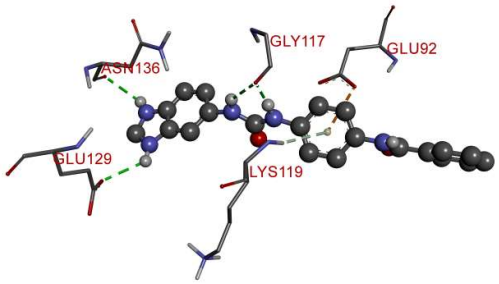
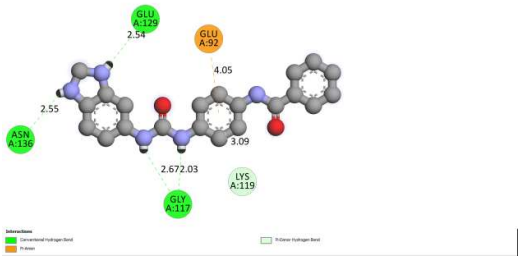
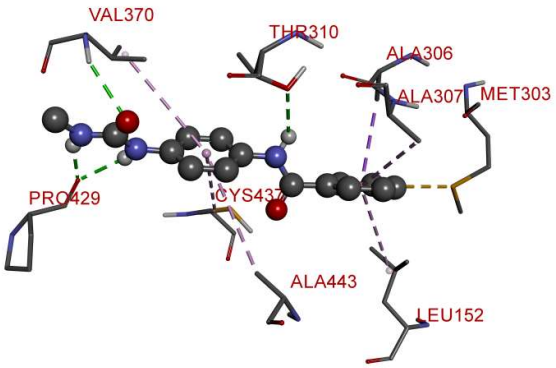
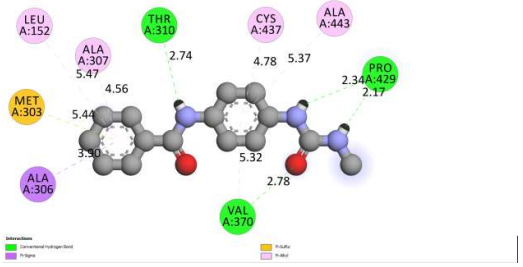
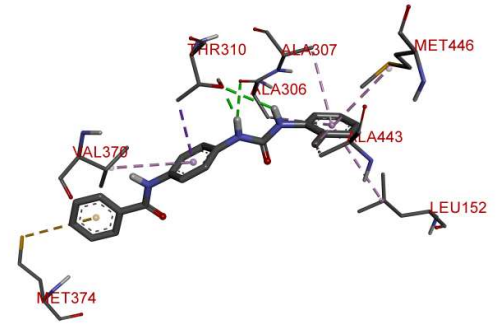
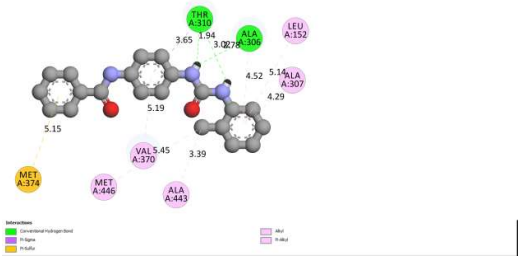


Fig. 2. The coloured zone is the acceptable physicochemical area for oral bioavailability, according to the physicochemical radar of the molecules. Where, LIPO (Lipophility): -0.7<XLOGP3<+5.0, SIZE: 150g/mol<MV<500g/mol, POLAR (Polarity): 20Å^2<TPSA<130Å^2, INSOLU (Insolubility): 0<LogS (ESOL)<6, INSATU (Instauration): 0.25<Fraction Csp3<1, FLEX (Flexibility): 0<Num. of rotatable bonds<9

Table 5. The most potent compounds' 2D and 3D binding poses

3D-binding pose	2D-binding pose
Exemestane	
	
3	
	
5	
	
7	
	

9	
 VAL248 TYR241 LYS249 CYS124 PHE235 LYS236	 LYS A:236 TYR A:241 CYS A:124 PHE A:235 2.54 5.35 5.56 2.63 1.97 4.93 3.85 5.47 4.60 VAL A:248 LYS A:249
10	
 GLY117 GLU92 ASN136 GLU129 LYS119	 GLU A:129 2.54 GLU A:92 4.05 2.55 ASN A:136 3.09 2.67 2.03 LYS A:119 GLY A:117
11	
 VAL370 THR310 ALA306 ALA307 MET303 PRO429 CYS437 ALA443 LEU152	 LEU A:152 THR A:310 CYS A:437 ALA A:443 ALA A:307 2.74 4.78 5.37 5.47 4.56 PRO A:429 2.34 2.17 MET A:303 5.44 3.30 5.32 ALA A:306 2.78 VAL A:370
19	
 THR310 ALA307 MET446 ALA306 ALA443 VAL370 LEU152 MET374	 THR A:310 3.65 1.94 ALA A:306 LEU A:152 4.52 5.14 ALA A:307 4.29 5.19 5.15 VAL A:370 5.45 3.39 MET A:374 MET A:446 ALA A:443

RESULT AND DISCUSSION

Drug development relies heavily on pharmacokinetic features because they allow scientists to examine the biological effects of potential pharmaceutical candidates[19]. This compound's oral bioavailability was evaluated using Lipinski's rule of five and Veber's rules (Table 4). To better understand the pharmacokinetics profiles and drug-likeness properties of the proposed compounds, the ADMET characteristics of all of them were examined (Table 3). Table 1 lists the ligand energies (kcal/mol), binding free energy (kcal/mol), root mean square deviation/upper bound (rmsd/ub), and root mean square deviation/lower bound (rmsd/lb) of all the docked molecules' conformers. Table 2 depicts the active amino acids, reactive atoms of ligands, bond length (Å), and kind of interactions of derivatives with the aromatase enzyme. Table 7 depicts the most potent compounds' 2D and 3D docking orientations.

The derivatives have been designed as per reaction schemes. The binding affinities of the derivatives have been compared with the binding mode of native ligand present in the crystal structure of aromatase enzyme (PDB ID: 3S7S). The native ligand exemestane exhibited -8.9 kcal/mol binding affinity with the enzyme. It has formed many hydrophobic interactions with ILE133 (4.78318A^0), CYS437 (3.59788A^0), VAL370 (3.9176A^0), ALA306 (4.12208A^0), ILE133 (4.00864A^0), ALA306 (5.2502A^0), and TRP224 (5.23612A^0). It did not form any kind of hydrogen bond with enzyme.

Many derivatives exhibited more than two hydrogen bonds with the target. The compounds which have formed three or more hydrogen bonds have been selected for the synthesis and biological activity. The formation of hydrogen bonds with target can effectively modulate the activity of enzyme and exhibit potent pharmacological response. There are many compounds which exhibited more binding affinity but did not formed more than three hydrogen bonds, in that case some more derivatives selected for the synthesis. The compound **3, 5, 7, 9, 10, 11,** and **19** have been selected as most potent molecules from virtual screening.

Compound **3** displayed -8.2 kcal/mol binding affinity and formed 3 conventional hydrogen bonds with THR310 (2.998A^0, 2.00243A^0), and ALA306 (2.52969A^0). It has developed 3 hydrophobic interactions with THR310 (3.71566A^0), MET374 (5.1018A^0), and VAL370 (5.23308A^0).Compound **5** exhibited -8 kcal/mol binding affinity and formed 3 conventional hydrogen bonds with THR310 (2.90166A^0, 1.95289A^0), and ALA306 (2.73553A^0). It has showed many hydrophobic interactions with THR310 (3.83414A^0), MET446 (3.96889A^0), MET374 (5.05165A^0), VAL370 (5.24051A^0), LEU152 (5.3237A^0),

ALA306 (4.51771A^0), and ALA307 (4.24055A^0). Compound **7** displayed -8.1 kcal/mol binding affinity and formed 3 conventional hydrogen bonds with THR310 (2.96757A^0, 1.87699A^0), and ALA306 (2.62519A^0). It has formed many hydrophobic interactions such as Pi-sigma, Pi-sulfur, and Pi-alkyl with same amino acids as formed by compound **5**. Compound **9** showed -7.9 kcal/mol binding affinity and formed 3 conventional hydrogen bonds with CYS124 (2.62578A0, 1.96848A^0), and TYR241 (2.54449A^0). It has developed Pi-sulfur, Pi-Pi stacked, amide-Pi stacked, and Pi-alkyl bonds with CYS124 (5.56438A^0), TYR241 (5.34825A^0), PHE235; LYS236 (3.85212A^0), VAL248 (5.46931A^0), LYS249 (4.6032A^0), and LYS236 (4.92931A^0).

Compound **10** exhibited -7.9 kcal/mol binding affinity and formed 4 conventional hydrogen bonds with GLY117 (2.0319A^0, 2.67471A^0), GLU129 (2.5366A^0), and ASN136 (2.55066A^0). It has also formed one Pi-anion and one Pi-donor hydrogen bond with GLU92 (4.05003A^0) and LYS119 (3.08756A^0), respectively. Compound **11** exhibited -7.8 kcal/mol binding affinity and formed 4 conventional hydrogen bonds with THR310 (2.73917A^0), PRO429 (2.16876A0, 2.33609A^0), and VAL370 (2.77996A^0). It has developed many Pi-sigma, Pi-sulfur, and Pi-alkyl interactions which contributed to his potency. Compound **19** showed -8.6 kcal/mol binding affinity. It has formed 3 conventional hydrogen bonds with THR310 (3.02233A^0, 1.94013A^0), and ALA306 (2.77767A^0). It has developed many hydrophobic interactions with THR310 (3.65298A^0), MET374 (5.15383A^0), ALA443 (3.38822A^0), MET446 (5.45268A^0), VAL370 (5.18741A^0), LEU152 (5.14384A^0), ALA306 (4.52294A^0), and ALA307 (4.29137A^0).

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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