QUINAZOLINE DERIVATIVES AS ENOYL REDUCTASE INHIBITOR TARGETING TUBERCULOSIS AN IN-SILICO APPROACH

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Abstract

The quinazoline nucleus is an interesting molecule in the major class of two nitrogen atoms in the structure of aromatic cyclic compounds. Quinazolines and fused quinazolines have attracted the attention of medicinal chemists because of their potential biological activities. In this study, we address the design, synthesis, and evaluation of anti-breast cancer inhibitory activities of quinazoline derivatives. Breast cancer is the second leading cause of cancer-related deaths in women worldwide. Microbial infections: Emerging infectious diseases are diseases with an infectious cause. Their incidence has increased in the recent past and threatens to increase further in the near future. The potential activities of quinazoline derivatives against protein 3PP0 are analysed with different docking programmes such as Autodock vina and compared with the standard drug tamoxifen. The results of the in silico studies provide compelling evidence for the reflection of valuable ligands in quinazoline derivatives as potential HER2 inhibitors, and compounds A1b, A1c, A2c, A2d, B1c, B2db, B2c, B3a, B3c, and B3e with significant binding energy may generate significant antibreast activity for further development that may prove their therapeutic potential.

Keyword: Autodock Vina, Breast cancer, HER2, Quinazoline, Tamoxifen.

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INTRODUCTION

Breast cancer is considered the second cause of cancer-related deaths in women all over the world. Multiple drugs have been approved by the US-FDA for the treatment of breast-related malignancies. The frequent emergence of resistances leads to the urgent need for newer moieties to overcome such problems[1-3]. As one of the deadliest cancers, treating breast cancer requires the development of efficacious drugs and improved therapeutic strategies. Although, the expansion of new drugs is exceedingly long-term and costly. Thus, identifying new uses of existing non-oncology or oncology drugs in treating breast cancer is becoming an important step toward developing better treatment strategies and improving overall outcomes[4]. Breast cancer is considered to be one of the most widespread cancers that have an impact on women all over the world. It normally begins from milk ducts (ductal cancer) or the lobules that provide them with milk (lobular cancer) and then the tumor can extend to the entire body. It is worth mentioning that breast cancer represents 16% of all women's cancers and 18.2% of cancer deaths worldwide. In spite of all the vast efforts that are being done in this field, cancer is regarded as a leading reason for mortality in the world[5].

A new paradigm in research is being concerted towards discovery of novel, safe and therapeutically effective agents. Most innovation and development of new scientific insight consists of heterocyclic compounds[6]. Quinazoline and its derivatives belongs to fused heterocycles have been obtained from more than 200 natural products. The name quinazoline[7] was first proposed for its compound by scientist Weddige. It was isomeric with the compounds cinnoline and quinoxalin and large derivatives of quinazoline system alternatively known as keto-quinazolines. Other names have occasionally being used 5, 6-benzopyrimidine or benzo[a]pyrimidine and phenmiazine[8].

Quinazoline and/or quinazolinone constitute fused heterocycles of notably large interest. The stability of ring system has concentrated medicinal chemists to synthesize new potential medicinal agents by introducing more than one bioactive moieties in single scaffold. This framework has been attracted significant attentiveness due to their diverse pharmacological activities like antimicrobial, antimalarial, anti-inflammatory, antihypertensive, anticonvulsant, anti-diabetic, anticancer, anti-HIV, cholinesterase inhibition, dihydrofolate reductase inhibition and Tyrosine kinase inhibitory activity[9]. We developed quinazoline analogues for enoyl reductase inhibition by molecular docking studies using Autodcok Vina. The results showed that the newly developed heterocyclic substituted quinazoline analogues exhibited good inhibition of enoyl reductase. In general, the enoyl reductase inhibitors showed antitubercular and antimalarial activity[10].

MATERIALS AND METHODS

Ligands Preparation

The sixty structures of the novel quinazoline derivatives used in this work were analyzed (Tables 1and 2). The two-dimensional (2D) chemical structures of the ligands were sketched using ChemDraw Ultra 2008, and the energy minimizations of the primed ligands were performed using Chem3D Ultra and saved in pdb format [11].

Target Preparation and Validation of Docking Method

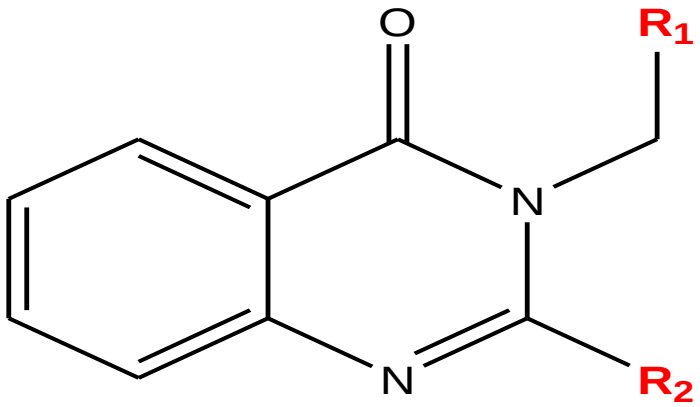
The 3D structure of human epidermal growth factor 2 (PDB ID: 3PP0) was obtained from the Protein Data Bank. The docking work began with the definition of a binding site, generally a restricted region of the protein. The size and location of this binding site was visualized in Discovery Studio. The target proteins were further authenticated using AutoDock Vina in PyRx by determining the RMSD value.

Molecular Docking Studies

Based on the literature, EGFR are selected as targets for breast cancer. The X-ray crystal structure of EGFR and co-crystallized ligand (PDB ID: 3PP0), are availed from Protein Data Bank. Te possible binding modes between the ligands and the target protein 3PP0 are loaded in the AutoDock Vina. AutoDock Vina is a computer program for predicting protein-ligand interactions. For a given protein and a ligand, AutoDock Vina software predicts the geometry of the complex as well as an estimate for the strength of binding. Preparation of the binding site was done using the Receptor Intelligence of the Receptor Preparation Wizard and this includes selection of chains, receptor protonation, and tautomers. Te active site of the target protein was defend around a radius of 6.50Å. AutoDock Vina software uses the constructive incremental build up algorithm. For validation of the sofware the co-crystalized ligands were extracted and redocked into the active sites. To evaluate the quality of co-crystallized ligands, their Root Mean Square Deviation (RMSD) values were obtained. An RMSD value cut-of lesser than 2Å is considered a good prediction for computed

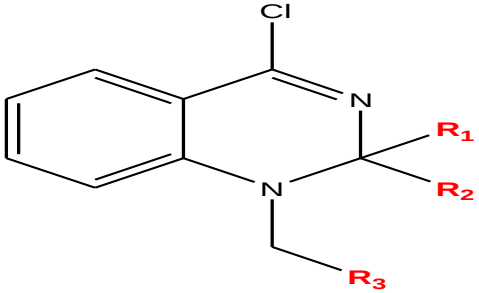
ligand-protein confirmation. Te results were compared with reference compounds obtained from the corresponding PDB IDs. Te docking scores and the 2D and 3D pose views were generated for further analysis of the interactions and binding afnities of the selected 60 quinazoline molecules [12-14].

Table 1. Quinazoline Substituted derivatives A series compound



S. No	Compound Code	R_1	R_2
1	A1a	Morpholine	Pyridine
2	A1b	N-ethyl benzenamine	Pyridine
3	A1c	Diphenylamine	Pyridine
4	A1d	Piperidine	Pyridine
5	A1e	Pyyrolidine	Pyridine
6	A1f	Piperazine	Pyridine
7	A1g	Diethylamine	Pyridine
8	A1h	N-methyl piperazine	Pyridine
9	A1i	1-(4-Chlorobenzhydryl)piperazine	Pyridine
10	A1j	Azetidine	Pyridine
11	A2a	Morpholine	Phenyl
12	A2b	N-ethyl benzenamine	Phenyl
13	A2c	Diphenylamine	Phenyl
14	A2d	Piperidine	Phenyl
15	A2e	Pyyrolidine	Phenyl
16	A2f	Piperazine	Phenyl
17	A2g	Diethylamine	Phenyl
18	A2h	N-methyl piperazine	Phenyl
19	A2i	1-(4-Chlorobenzhydryl)piperazine	Phenyl
20	A2j	Azetidine	Phenyl
21	A3a	Morpholine	Chloro
22	A3b	N-ethyl benzenamine	Chloro
23	A3c	Diphenylamine	Chloro
24	A3d	Piperidine	Chloro
25	A3e	Pyyrolidine	Chloro
26	A3f	Piperazine	Chloro
27	A3g	Diethylamine	Chloro
28	A3h	N-methyl piperazine	Chloro
29	A3i	1-(4-Chlorobenzhydryl)piperazine	Chloro
30	A3j	Azetidine	Chloro

Table 2. Quinazoline Substituted derivatives B series compound



S. No	Compound Code	R_1	R_2	R_2
31	B1a	methyl	methyl	Morpholine
32	B1b	methyl	methyl	N-ethyl benzenamine
33	B1c	methyl	methyl	Diphenylamine
34	B1d	methyl	methyl	Piperidine
35	B1e	methyl	methyl	Pyyrolidine
36	B1f	methyl	methyl	Piperazine
37	B1g	methyl	methyl	Diethylamine
38	B1h	methyl	methyl	N-methyl piperazine
39	B1i	methyl	methyl	1-(4-Chlorobenzhydryl)piperazine
40	B1j	methyl	methyl	Azetidine
41	B2a	hydroxyphenyl	methyl	Morpholine
42	B2b	hydroxyphenyl	methyl	N-ethyl benzenamine
43	B2c	hydroxyphenyl	methyl	Diphenylamine
44	B2d	hydroxyphenyl	methyl	Piperidine
45	B2e	hydroxyphenyl	methyl	Pyyrolidine
46	B2f	hydroxyphenyl	methyl	Piperazine
47	B2g	hydroxyphenyl	methyl	Diethylamine
48	B2h	hydroxyphenyl	methyl	N-methyl piperazine
49	B2i	hydroxyphenyl	methyl	1-(4-Chlorobenzhydryl)piperazine
50	B2j	hydroxyphenyl	methyl	Azetidine
51	B3a	Chlorophenyl	methyl	Morpholine
52	B3b	Chlorophenyl	methyl	N-ethyl benzenamine
53	B3c	Chlorophenyl	methyl	Diphenylamine
54	B3d	Chlorophenyl	methyl	Piperidine
55	B3e	Chlorophenyl	methyl	Pyyrolidine
56	B3f	Chlorophenyl	methyl	Piperazine
57	B3g	Chlorophenyl	methyl	Diethylamine
58	B3h	Chlorophenyl	methyl	N-methyl piperazine
59	B3i	Chlorophenyl	methyl	1-(4-Chlorobenzhydryl)piperazine
60	B3j	Chlorophenyl	methyl	Azetidine
61	Bedaquiline			

RESULTS AND DISCUSSION

Molecular docking studies of the Quinazolines at protein active sites were performed using the advanced molecular docking program Autodock Vina to determine binding affinities. The compounds were docked to human epidermal growth factor 2 (3PP0) to determine their EGFR activity. The binding energy of the compounds (A and B series) is shown in Table 3. The binding energy of compounds A1b, A1c, A2c, A2d, B1c, B2b, B2c, B3a, B3c and B3e is higher than that of the standard agent Tamoxifen, showed good affinity for the receptor The best affinity modes of the docked compounds (A1b, A1c, A2c, A2d, B1c, B2b, B2c, B3a, B3c and B3e) with human epidermal growth factor 2 receptor with good binding affinity are shown in Figure (1).

The quinazoline compounds (A&B series) had binding affinities ranging since -7.1 to -10.4 kcal/mol (Table 3), with the best result obtained with compounds A1b, A1c, A2c, A2d, B1c, B2b, B2c, B3a, B3c and B3e, (-8.7, -8.7, -9.2, -8.9, -8.4, -8.3, -8.6, -8.3, -8.9 and -8.3kcal/mol). The hydrogen bonds, residual interactions, of the best compounds were summarized in Table 4. [15-16].

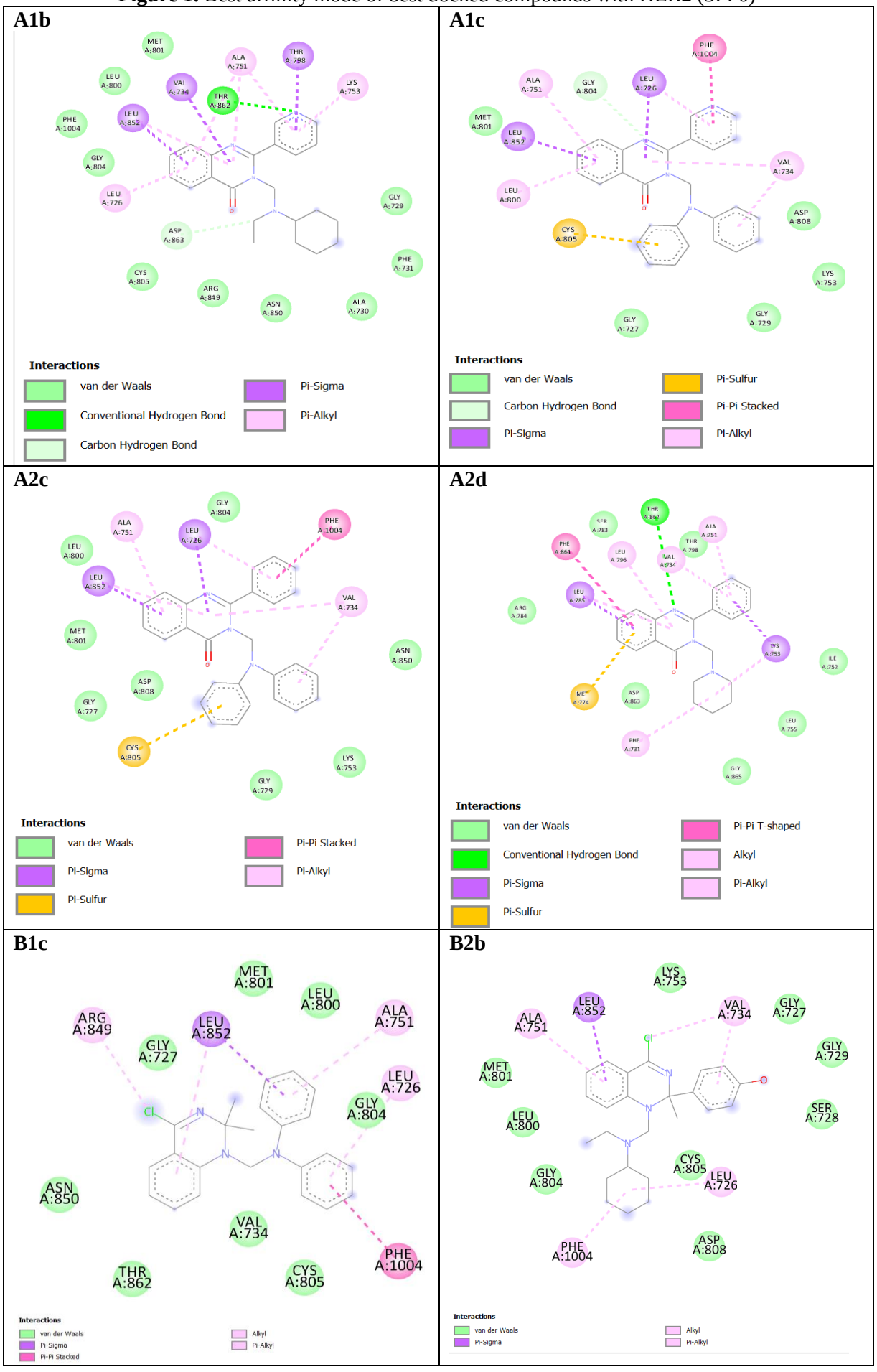
Table 3. Docking studies for A&B Series compounds with HER2 (3PP0)

S.No	Compound Code	Binding energy kcal/mol	S.No	Compound Code	Binding energy kcal/mol
1	A1a	-8.1	31	B1a	-7.5
2	**A1b**	**-8.7**	32	B1b	-8.0
3	**A1c**	**-8.7**	**33**	**B1c**	**-8.4**
4	A1d	-7.9	34	B1d	-7.9
5	A1e	-7.6	35	B1e	-7.7
6	A1f	-7.1	36	B1f	-7.5
7	A1g	-6.5	37	B1g	-7.3
8	A1h	-7.3	38	B1h	-8.0
9	A1i	-7.1	39	B1i	-6.9
10	A1j	-6.6	40	B1j	-7.5
11	A2a	-7.6	41	B2a	-7.8
12	A2b	-8.6	**42**	**B2b**	**-8.3**
13	**A2c**	**-9.2**	**43**	**B2c**	**-8.6**
14	**A2d**	**-8.9**	44	B2d	-7.6
15	A2e	-8.2	45	B2e	-7.7
16	A2f	-7.5	46	B2f	-7.5
17	A2g	-7.6	47	B2g	-7.1
18	A2h	-7.2	48	B2h	-7.3
19	A2i	-7.2	49	B2i	-7.2
20	A2j	-7.8	50	B2j	-7.9
21	A3a	-7.0	**51**	**B3a**	**-8.3**
22	A3b	-7.3	52	B3b	-7.8
23	A3c	-8.0	**53**	**B3c**	**-8.9**
24	A3d	-7.5	54	B3d	-8.1
25	A3e	-7.2	**55**	**B3e**	**-8.3**
26	A3f	-7.2	56	B3f	-7.4
27	A3g	-6.8	57	B3g	-7.1
28	A3h	-7.6	58	B3h	-6.9
29	A3i	-7.4	59	B3i	-7.3
30	A3j	-6.1	60	B3j	-7.2
61	S1	-8.5			

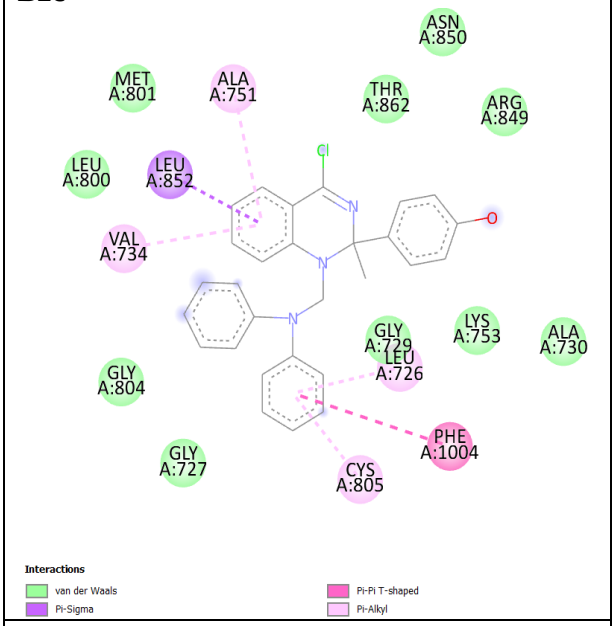
Table 4. Best Quinazoline derivative and receptor (human epidermal growth factor 2) interactions: binding affinity, conventional hydrogen bonds and interacting amino acid residues

Compound Code	Binding energy	H- Bond residues	Vander waals forces residues
A1b	-8.7	THR A:862, ASP A:863	CYS A:805, ARG A:849, ASN A:850, ALA A:730, PHE A:731, GLY A:729, GLY A:804, PHE A:1004, LEU A:800, MET A:801
A1c	-8.7	GLY A:804	MET A:801, GLY A:727, GLY A:729, LYS A:753, ASP A:808
A2c	-9.2		MET A:801, GLY A:727, ASP A:808, GLY A:727, LYS A:753, ASN A:850, GLY A:804
A2d	-8.9	THR A:862	ARG A:784, ASP A:863, GLY A:865, LEU A:755, ILE A:752, THR A:792, SER A:783
B1c	-8.4		ASN A:850, THR A:862, VAL A:734, CYS A:805, GLY A:804, LEU A:800, MET A:801
B2b	-8.3		MET A:801, LEU Al:800. GLY A:804, CYS A:805, LYS A:753, GLY A:727, GLY A:729
B2c	-8.6		MET A:801, LEU A:800, GLY A:804, GLY A:727, GLY A:729, LYS A:753, ALA A:730, ARG A:849, ASN A:850, THR A:862
B3a	-8.3	ASN A:850, ARG A:849	GLY A:729, GLY A:727, GLY A:704, THR A:798, LEU A:796, THR A:862
B3c	-8.9		GLY A:804, GLY A:727, ASNA:850, GLY A:729, ALA A:730, LYS A:753, THR A:862
B3e	-8.3	ASP A:863	ASN A:850, GLY A:727, ARG A:849, GLY A:729, THR A:862, LEU A:800, GLY A:804
Standard Tamoxifien	-8.5	GLN A:799, THR A:798, THR A:862	ASP A:863, ILE A:752, LEU A:726, GLY A:729, GLY A:727, GLY A:804, CYS A:805, PHE A:1004, MET A:774

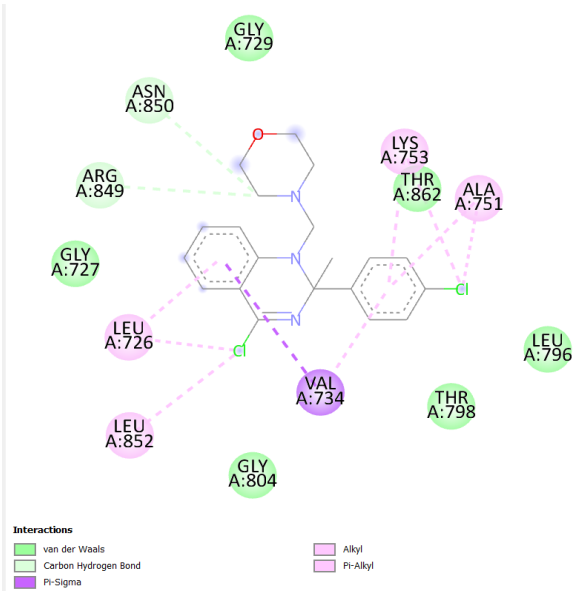
Figure 1. Best affinity mode of best docked compounds with HER2 (3PP0)



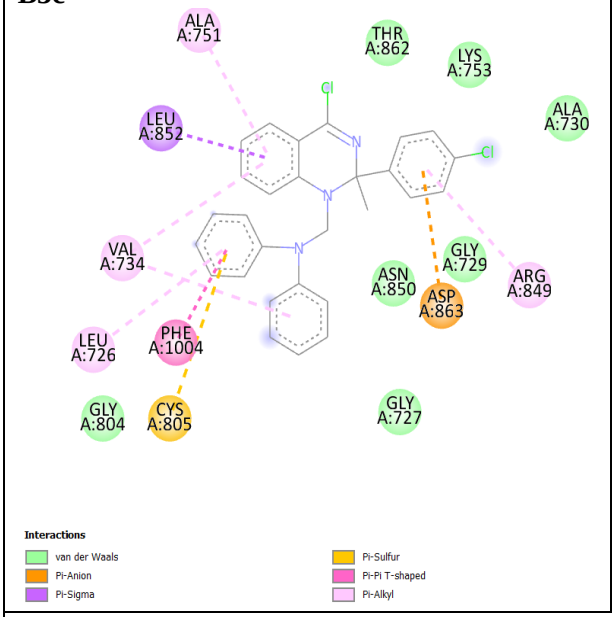
B2c



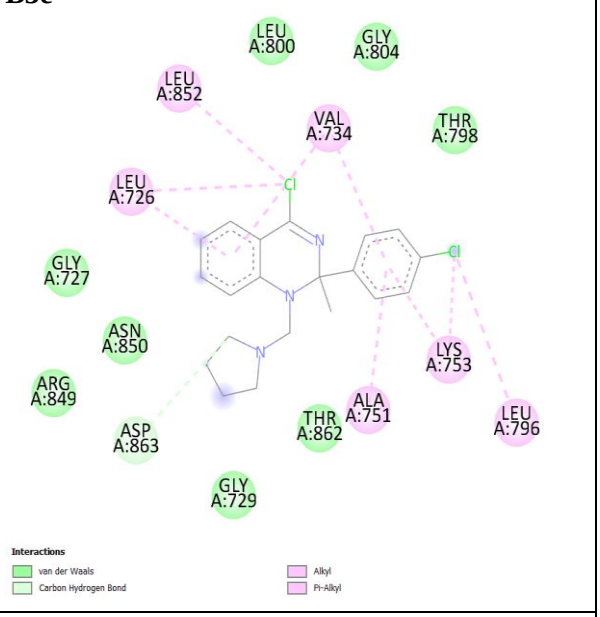
B3a



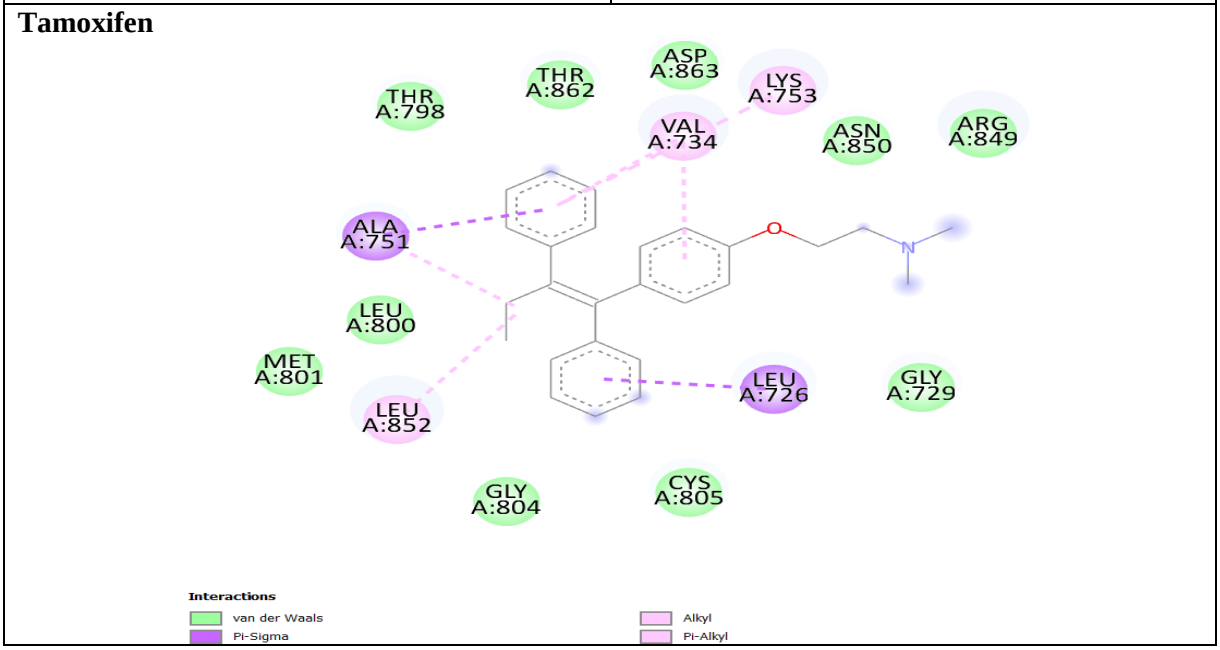
B3c



B3e



Tamoxifen



CONCLUSION

Various biological properties are attributed to quinazolines. A structure-based pharmacophore model was constructed and authenticated to obtain dynamic enoyl reductase inhibitors as of our self-generated folder of heterocyclic substituted quinazoline derivatives. Docking study exposed that quinazoline derivatives illustrated better alignment at the active site as they interacted with all major amino acid residues. Thus, the in silico method used in the present study helped in the identification of lead molecules and may also explain their beneficial effect for further studies to produce more important antimalarial and anticancer drugs. Significant results were achieved and some of these compounds, such as A1b, A1c, A2c, A2d, B1c, B2db, B2c, B3a, B3c and B3e, showed attractive binding energies and category of interactions compared to Tamoxifen, which was used as the reference drug.

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Conflicts of Interest: The authors declare no conflict of interest.

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