# QUINAZOLINE DERIVATIVES AS ANALOGUES WITH POTENT ACTIVITY AGAINST BREAST CANCER: 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 3RCD are analysed with Glide software (Schrödinger Suite 2018–1) docking programmes 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**: HER2, Glide software (Schrödinger Suite 2018–1), 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 moiety 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 Glide software (Schrödinger Suite 2018–1). The results showed that the newly developed heterocyclic substituted quinazoline analogues exhibited good inhibition of human epidermal growth factor receptor 2 [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].

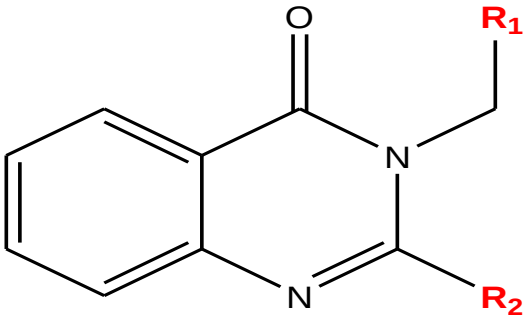
### Target Preparation and Validation of Docking Method

The 3D structure of human epidermal growth factor 2 (PDB ID: 3RCD) 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 Glide software (Schrödinger Suite 2018–1) by determining the RMSD value.

### Molecular Docking Studies

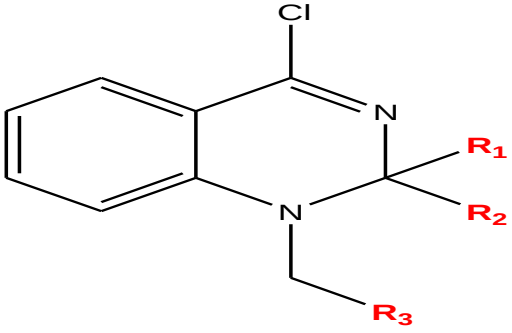
Based on the literature, EGFR are selected as targets for breast cancer. The X-ray crystal structure of EGFR and co-crystallized ligand (PDB ID: 3RCD), are availed from Protein Data Bank. All the ligands (A&B series) were docked into the synergist pocket of HER2 protein (PDB ID: 3RCD). The best-docked ligands were chosen based on the total glide score. The best gathering among the ligands and the receptor were scored using the ligand docking module. Extra precision XP visualizer of flow module was utilized to analyze the results. The upgrading parameters and the diminishing motion were cited concurrently to achieve better outcome in the glide-ligand docking. [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 Glide software (Schrödinger Suite 2018–1)to determine binding affinities. The compounds were docked to human epidermal growth factor 2 (3RCD) 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&2). The quinazoline compounds (A&B series) had binding affinities ranging since -3.12547 to -5.79437 kcal/mol (Table 3), with the best result obtained with compounds A1b, A1c, A2c, A2d, B1c, B2b, B2c, B3a, B3c and B3e (Table 3). [15-16].

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

| S.No | Compound Code | Binding energy kcal/mol | S.No | Compound Code | Binding energy kcal/mol |
|---|---|---|---|---|---|
| 1 | A1a | -3.74217 | 31 | B1a | -3.15244 |
| **2** | **A1b** | **-4.87532** | 32 | B1b | -3.14368 |
| **3** | **A1c** | **-4.62908** | **33** | **B1c** | **-5.41882** |
| 4 | A1d | -3.44264 | 34 | B1d | -3.94211 |
| 5 | A1e | -3.14237 | 35 | B1e | -3.63571 |
| 6 | A1f | -4.34346 | 36 | B1f | -4.02758 |
| 7 | A1g | -3.52478 | 37 | B1g | -3.45217 |
| 8 | A1h | -4.46013 | 38 | B1h | -3.42587 |
| 9 | A1i | -4.35112 | 39 | B1i | -3.12547 |
| 10 | A1j | -3.56987 | 40 | B1j | -3.44264 |
| 11 | A2a | -4.19125 | 41 | B2a | -3.12547 |

| | | | | | |
|---|---|---|---|---|---|
| 12 | A2b | -4.44212 | **42** | **B2b** | **-5.79437** |
| **13** | **A2c** | **-5.31621** | **43** | **B2c** | **-5.15329** |
| **14** | **A2d** | **-4.70326** | 44 | B2d | -3.68741 |
| 15 | A2e | -3.99850 | 45 | B2e | -3.68724 |
| 16 | A2f | -3.76761 | 46 | B2f | -4.25185 |
| 17 | A2g | -4.16479 | 47 | B2g | -4.14125 |
| 18 | A2h | -3.68740 | 48 | B2h | -3.31254 |
| 19 | A2i | -4.29391 | 49 | B2i | -4.01254 |
| 20 | A2j | -4.21229 | 50 | B2j | -4.12540 |
| 21 | A3a | -4.37041 | **51** | **B3a** | **-5.03166** |
| 22 | A3b | -4.12563 | 52 | B3b | -4.26587 |
| 23 | A3c | -3.67142 | **53** | **B3c** | **-5.26876** |
| 24 | A3d | -4.16111 | 54 | B3d | -4.25871 |
| 25 | A3e | -3.82701 | **55** | **B3e** | **-5.33112** |
| 26 | A3f | -4.41980 | 56 | B3f | -4.65421 |
| 27 | A3g | -4.18157 | 57 | B3g | -3.25478 |
| 28 | A3h | -4.03600 | 58 | B3h | -3.25471 |
| 29 | A3i | -3.36379 | 59 | B3i | -4.05784 |
| 30 | A3j | -3.38676 | 60 | B3j | -3.69871 |
| 61 | S1 | **-4.57942** | | | |

**Table 4.** Best Quinazoline derivative against receptor (human epidermal growth factor 2

| **Compound Code** | **Binding energy** |
|---|---|
| A1b | -4.87532 |
| A1c | -4.62908 |
| A2c | -5.31621 |
| A2d | -4.70326 |
| B1c | -5.41882 |
| B2b | -5.79437 |
| B2c | -5.15329 |
| B3a | -5.03166 |
| B3c | -5.26876 |
| B3e | -5.33112 |
| Standard Tamoxifien | -4.57942 |

**Figure 1.** Best affinity mode of best docked compounds(B2c) with HER2 (3RCD)

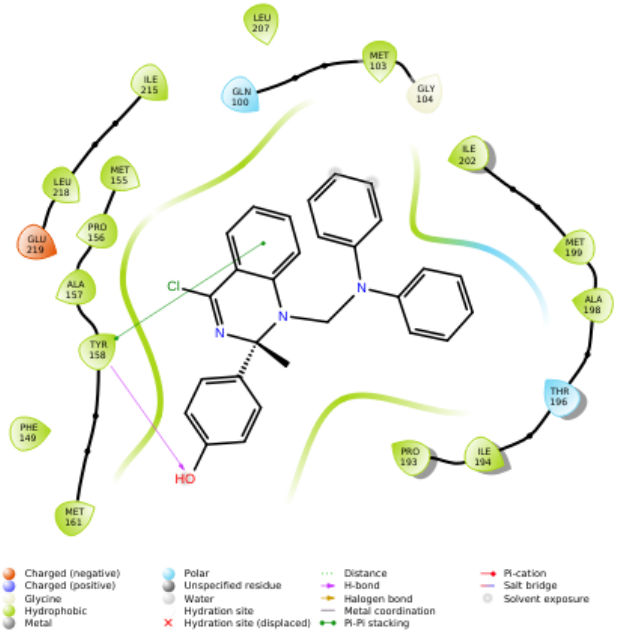
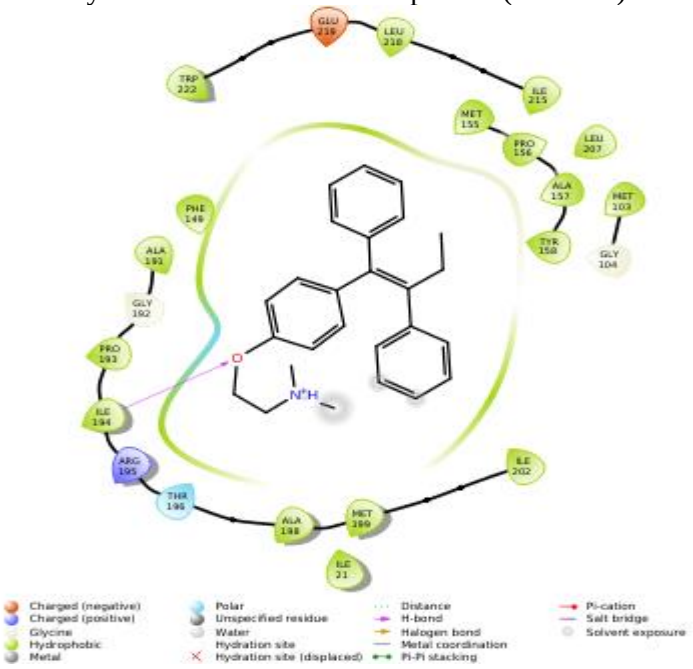


**Figure 2.** Best affinity mode of best docked compounds (Standard) with HER2 (3RCD)




## 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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