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Original Article

Synthesis and Pharmacological Evaluation of Novel Quinazoline Derivatives as Potential EGFR Inhibitors for Breast Cancer

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ABSTRACT

Background: Breast cancer is the highest mortality-causing disease among cancers in women and it can be cured by early diagnosis as well as treatment. Epidermal growth factor receptor-2 (HER2) is the prime factor that helps in the growth and development of breast cancer. There are several EGFR inhibitors approved for breast cancer treatment, but all are shown to cause resistance and severe toxicity. The present research work is based on the synthesis and pharmacological evaluation of novel derivatives against breast cancer cell lines. **Materials and Methods:** Ten novel Quinazoline derivatives (4a-j) were synthesized and characterized by IR, PMR, and CMR spectroscopic methods. Cell proliferation and cytotoxic effects of synthesized derivatives were determined by using MTT assay and hemolytic assay. **Results:** The growth inhibition potential of synthesized derivatives was evaluated against normal as well as mutated breast cancer cell lines i.e., MCF-7 and MDA-MB-231 using the MTT method. Nearly, five derivatives 4b, 4c, 4e, 4f, 4i for MCF-7 and 4b, 4c, 4d, 4e, 4f, 4i for MDA-MB231 were assessed for IC_{50} value. It was observed that these compounds of the series exhibited higher IC_{50} values (8.72 to 15.70, 12.66 to 21.21µM/mL) as compared to erlotinib with IC_{50} values (16.80, 22.80), respectively. Moreover, the hemolytic estimation of the derivatives (4e, 2-Br) and (4i 4-CN) displayed less toxicity with HD_{50} values 69.87±8.9, 58.40±3.2, respectively. **Conclusion:** The findings of the current study provide safe, less-toxic, cost-effective, and potent novel quinazoline derivatives for breast cancer.

Keywords: 5-nitroanthranilic acid, Anilines, Anti-cancer activity, Breast cancer, Hemolytic activity.

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INTRODUCTION

Breast cancer is the most common cancer in women, accounting for 51% of all new diagnoses.[1] Numerous nation have spent billions of dollars treating cancer, but it still poses a threat to human health.[2] Numerous chemotherapeutic approaches to the treatment of cancer have been put out, tested, and in some cases put into practice during the past few decades.[3] Despite enormous efforts to battle innovative chemotherapeutic approaches for the treatment of various cancers and accept to meet the challenge globally.[4] Therefore, there is an urgent need to develop novel derivatives that increase biological activity with potential novel mechanisms to combat this disease.

The members of the epidermal growth factor receptor (EGFR)/ ErbB family (also known as ErbB-1 and HER1), HER2 (also known as HER2/neu and ErbB-2), ErbB-3 (commonly known as HER3), and ErbB-4 (also known as HER4) are the most famous cancer molecular targets discovered to date.[5] The main established therapeutic target in breast cancer is HER2, which is overexpressed in 21–26% of cases. Large tumor size, poor differentiation, and poor clinical results are all linked to EGFR overexpression in breast cancer. EGFR overexpression is observed in all subtypes of breast cancer.[6]

The heterocyclic system becomes an important structural pharmacophore to develop potential chemotherapeutic agents.[7,8] Number of drugs based on the heterocyclic system have been discovered and used as potential chemotherapeutic agents. A literature survey revealed that Quinazoline analogs have been known as the fortunate prototypes in drug design and discovery. Quinazolines are widely recognized for having a wide range of biological and therapeutic effects, including anticonvulsant, antimicrobial, antidiabetic, antihypertensive, and anticancer activity.[9] Erlotinib and lapatinib are quinazoline-containing tyrosine kinase inhibitors approved for the treatment of breast cancer.[10] Unsuccessfully, in most of the cases, patients showed

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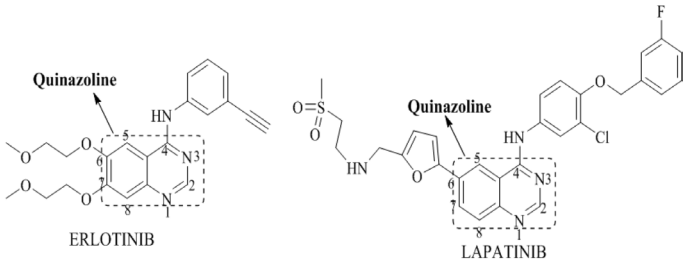


Figure 1: Quinazoline containing TK Inhibitors for breast cancer.

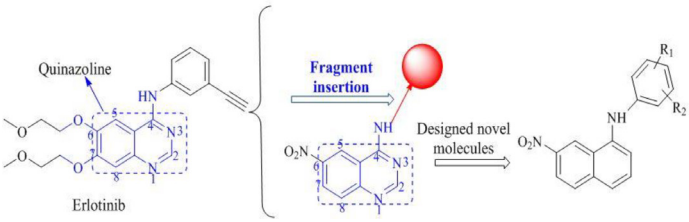


Figure 2: Molecular conception of Quinazoline derivatives (4a-j) designed as potential breast cancer agents.

frequent resistance to EGFR TKIs (tyrosine kinase inhibitors) within a few months of treatment (Figure 1).[11]

To overcome the resistance, there is a need to develop potential novel Quinazoline derivatives as EGFR inhibitors for breast cancer. We have introduced different anilines at the 4th position presented in (Figure 2) based on the structure of erlotinib which is broadly used in the treatment of breast cancer and help to design and synthesized novel quinazoline derivatives as improved efficacy agents for breast cancer.

MATERIALS AND METHODS

Experimental Section

Chemistry

Reagents and solvents were procured from Spectrochem and LOBA Chemie. Reaction progress was monitored by melting point (m.p.) and thin-layer chromatography (TLC) on silica gel precoated F_{254}. The spectra of compounds were recorded using FT-IR (Bruker, OPUS_7.8.44), ^{1}H NMR and ^{13}C NMR spectra and mass spectra (MS) were obtained from LC-MS.

Synthesis of 6-nitroquinazolin-4-(3H)-one (2)

Formamidine acetate (0.14 mol) in presence of ethanol was added to 5-nitroanthranilic acid (0.032 mol). The resulting mixture was refluxed for 11 hr at 150°C. Then the mixture was cooled and washed with 30 ml of ice water which resulted in the precipitation of a solid. Excess impurities are washed with water two to three times and removed from the reaction mixture. The residue was purified by ethanol to yield yellow crystals.[12]

Yield (71%); m. p.=205-210°C; IR (KBr) υ cm^{-1} (-NH) stretching 3331.07, (N-H) bending 1590.50, (Ar-C-H) stretching 3086.01, (C=O) stretching 1671.70, Ar-(C=C) Stretching 1620.71, (C=N) stretching 1590.57, (NO_2) 1495.74, 1320.13. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.44 (s, Ar-1H), 8.10 (d, *J*= 4Hz, Ar-1H), 7.97 (s, Ar-1H), 7.89 (s, Ar- NH), 7.21 (d, *J*= 8.0Hz, Ar-1H). ^{13}C NMR (500 MHz, DMSO-d_6) δ 161.26, 154.44, 150.27, 146.18, 138.63, 130.56, 124.27, 123.04.

Synthesis of 4-chloro-6-nitroquinazoline (3)

Phosphorous chloride (15 mL) was added to 6-nitroquinazolin-4(3H)-one (1.2 mmol) Then DMF was slowly added. The resulting mixture was refluxed for 9-10 hr at 110°C and excess Phosphorous chloride was removed under reduced pressure. After completion, crushed ice water was added neutralized with ammonium hydroxide, and filtered off. The residue was purified by ethanol to give a second intermediate.[13]

Yield (68%); m. p.=135-140°C; IR (KBr) υ cm^{-1} (Ar-C-H) Stretching 3090.59, (C=N) stretching 1555.86, (NO_2) 1510.02-1320.59, (C-Cl) stretching 741.12, ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.96 (s, Ar-1H), 8.62 (d, *J*=9.5Hz, Ar-1H), 8.17 (s, Ar-1H), 7.64 (d, *J*= 9.0 Hz, Ar-1H). ^{13}C NMR (500 MHz, DMSO-d_6) δ 160.69, 158.21, 151.18, 147.67, 129.23, 119.98, 117.69.

General procedure for the synthesis of substituted aniline with Quinazoline derivatives. (4a-j)

4-chloro-6-nitroquinazoline (2.0 mmol)] and Substituted aniline (2.0 mmol) were dissolved in methanol (20 ml). The resulting mixture was refluxed for 4-5 hr at 70°C. After completion, the crude product was filtered and washed with (15 ml) of water and extracted from ethyl acetate. The organic layer was collected and washed with brine solution and dried over anhydrous sodium sulfate to obtain targeted compounds.[14]

6-nitro-N-(4-phenoxyphenyl) quinazolin-4-amine (4a)

Yield (56.5%); m.p.=201-204°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.93 (s, 1H- Ar-H), 7.74 (d, *J*=9.5 Hz, Ar-1H), 7.44 (d, *J*=8.0 Hz, Ar-1H), 7.35(s, 1H, Ar-1H), 7.33 (d, *J*=8.0 Hz, Ar-1H), 7.23 (s, 1H, Ar-NH), 6.93 (m, 1H, Ar-H), 6.72 (d, *J*=9.5 Hz, Ar-1H),

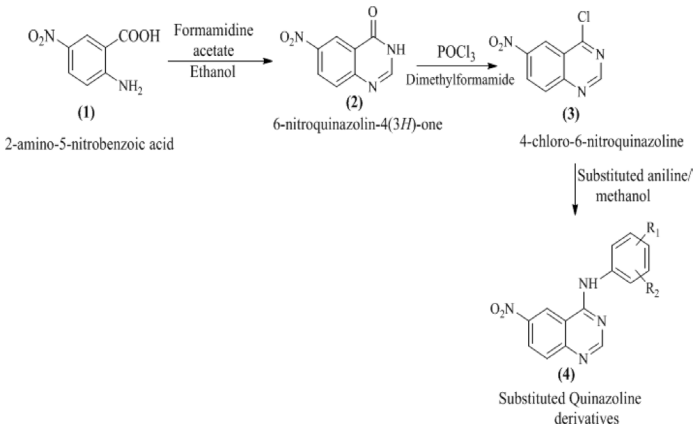


Figure 3: Scheme for Synthesis of Quinazoline derivatives (4a-j) for breast cancer.

6.59 (d, *J*=3.0Hz, 1H). ^{13}C NMR (500 MHz, DMSO-d_6) δ 171.21, 159.20, 157.32, 151.09, 147.89, 144.56, 133.79, 129.80, 127.56, 126.11, 119.90, 116.65, 114.78.

4-((6-nitroquinazolin-4-yl) amino) benzenethiol (4b)

Yield (65.5%); m.p.=196-200°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.95 (s, 1H- Ar-H), 7.71 (d, *J*=9.0 Hz, Ar-1H), 7.38 (d, *J*=8.0 Hz, Ar-1H), 7.10(s, 1H, Ar-NH), 7.04-7.01 (t, Ar-1H), 6.94 (d, *J*=8.0 Hz, Ar-1H), 3.75 (s, 1H, SH). ^{13}C NMR (500 MHz, DMSO-d_6) δ 169.01, 159.98, 152.34, 144.78, 137.89, 129.04, 127.87, 119.08, 115.67, 114.98.

2-((6-nitroquinazolin-4-yl) amino) benzonitrile (4c)

Yield (61.2%); m.p.=200-204°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.77 (s, 1H- Ar-H), 8.76 (d, *J*=8.0 Hz, Ar-1H), 8.39 (s, 1H- Ar-H),8.38 (d, *J*=9.0 Hz, Ar-1H), 8.20(s, 1H, Ar-NH), 7.10 (d, *J*=9.5 Hz, Ar-1H), 7.01-6.78 (t, Ar-1H), 6.28 (d, *J*=8.0 Hz, Ar-1H). ^{13}C NMR (500 MHz, DMSO-d_6) δ 171.76, 159.89, 151.23, 149.08, 146.78, 132.34, 130.05, 126.32, 118.07, 117.97, 116.41, 114.56, 97.87.

5-nitro-2-((6-nitroquinazolin-4-yl) amino) phenol (4d)

Yield (59.5%); m.p.=210-214°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.98 (s, 1H- OH), 8.68 (s, 1H- Ar-H), 8.51 (d, *J*=8.5 Hz, Ar-1H), 8.44 (s, 1H- Ar-H), 8.28 (d, *J*=8.0 Hz, Ar-1H), 8.01 (s, 1H, Ar-NH), 7,35 (d, *J*=9.0 Hz, Ar-1H), 7.09 (s, 1H, Ar-H), 6.86 (d, *J*=8.5 Hz, Ar-1H). ^{13}C NMR (500 MHz, DMSO-d_6) δ 170.01, 159.09, 152.89, 145.78, 144.23, 139.80, 138.21, 129.06, 126.12, 118.56, 117.09, 116.54, 108.89.

N-(2-bromophenyl)-6-nitroquinazolin-4-amine (4e)

Yield (59.5%); m.p.=210-214°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.90 (s, 1H- Ar-H), 8.85 (d, *J*=9.5 Hz, Ar-1H), 8.60 (s, 1H- Ar-H), 8.38 (d, *J*=8.5 Hz, Ar-1H), 8.10(s, 1H, Ar-NH), 7.74 (d, *J*=9.0 Hz, Ar-1H), 7.44-7.11 (m, Ar-1H), 7.08-6.81 (m, Ar-1H). ^{13}C NMR (500 MHz, DMSO-d_6) δ 173.09, 161.23, 153.78, 151.45, 148.09, 133.07, 132.11, 128.42, 127.23, 126.10, 118.23, 117.45, 116.43, 115.08.

N-(4-bromophenyl)-6-nitroquinazolin-4-amine (4f)

Yield (56.5%); m.p.=195-198°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.87 (s, 1H- Ar-H), 8.71 (d, *J*=9.5 Hz, Ar-1H), 8.67 (s, 1H- Ar-H), 8.38 (d, *J*=7.0 Hz, Ar-1H), 7.90(s, 1H, Ar-NH), 7.74 (d, *J*=8.5 Hz, Ar-1H), 7.34 (d, *J*=9.0 Hz, Ar-1H). ^{13}C NMR (500 MHz, DMSO-d_6) δ 171.09, 160.23, 152.78, 151.45, 147.09, 139.07, 132.11, 129.42, 118.23, 116.43, 114.98.

N-(2,6-dimethylphenyl)-6-nitroquinazolin-4-amine (4g)

Yield (63.5%); m.p.=198-203°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.57 (s, 1H- Ar-H), 8.46 (d, *J*=8.0 Hz, Ar-1H), 8.31 (s, 1H- Ar-H), 8.12 (d, *J*=9.0 Hz, Ar-1H), 7.93 (s, 1H, Ar-NH), 7.64-7.51 (m, Ar-1H), 7.40-7.23 (m, Ar-1H), 2.10 (s, 6H- 2×CH_3). ^{13}C NMR (500 MHz, DMSO-d_6) δ172.08, 160.53, 152.68, 151.45, 147.09, 137.87, 135.12, 135.12, 129.42, 127. 50, 120.34, 116.43, 114.98, 17.56.

6-nitro-N-(o-tolyl) quinazolin-4-amine (4h)

Yield (40.5%); m.p.=192-196°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.85 (s, 1H- Ar-H), 8.71 (d, *J*=8.0 Hz, Ar-1H), 8.51 (s, 1H- Ar-H), 8.38 (d, *J*=8.5 Hz, Ar-1H), 8.20 (s, 1H, Ar-NH), 7.30-7.21 (m, Ar-1H), 7.18-6.98 (m, Ar-1H), 6.79-6.67 (m, Ar-1H), 2.30 (s, 3H-CH_3). ^{13}C NMR (500 MHz, DMSO-d_6) δ171.38, 159.52, 152.23, 151.40, 147.09, 136.87, 135.10, 134.09, 129.42, 127. 50, 120.34, 116.43, 114.98, 18.06.

4-((6-nitroquinazolin-4-yl) amino) benzonitrile (4i)

Yield (45.5%); m.p.=198-205°C; ^{1}H NMR (500 MHz, DMSO-d_6 δ 8.95 (s, 1H- Ar-H), 8.81 (d, *J*=8.5 Hz, Ar-1H), 8.62 (s, 1H- Ar-H), 8.39 (d, *J*=8.0 Hz, Ar-1H), 7.90 (s, 1H, Ar-NH), 7.56 (d, *J*=9.0 Hz, Ar-1H), 7.34 (d, *J*=9.0 Hz, Ar-1H). ^{13}C NMR (500 MHz, DMSO-d_6) δ 169.19, 161.23, 153.78, 147.07, 144.89, 134.06, 132.51, 126.42, 118.03, 116.07, 102.98.

N-(2,4-dimethylphenyl)-6-nitroquinazolin-4-amine (4j)

Yield (44.5%); m.p.=210-214°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.01 (s, 1H- Ar-H), 8.91 (d, *J*=9.0 Hz, Ar-1H), 8.72 (s, 1H- Ar-H), 8.59 (d, *J*=9.0 Hz, Ar-1H), 8.20 (s, 1H, Ar-NH), 7.96 (d, *J*=8.0 Hz, Ar-1H), 7.74 (d, *J*=9.0 Hz, Ar-1H), 2.45 (s, 3H- CH_3), 2.20 (s, 3H- CH_3). ^{13}C NMR (500 MHz, DMSO-d_6) δ170.08, 161.53, 151.60, 150.45, 146.08, 138.57, 135.12, 129.42, 127. 50, 120.34, 116.43, 114.98, 22.01, 18.16.

In-vitro cell Proliferation analysis (MTT assay)

Cell proliferation activity was evaluated by using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. MCF-7 and MDA-MB231 cells were seeded 96-well tissue culture plate and incubating them at 37±0.5°C in a 5% CO_2 atmosphere. Prepared fresh media without using fetal bovine serum (FBS), containing the synthesized compounds, and erlotinib incubated for 72 hr at various concentrations (100 to 5 µg/mL). Then 25 µL of freshly prepared MTT solution was

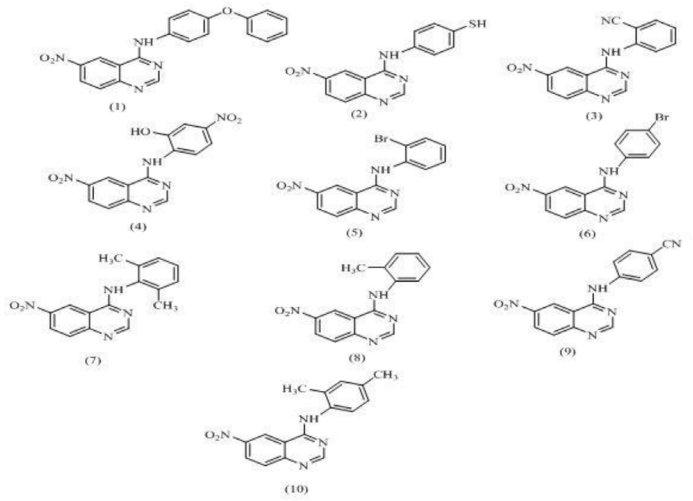


Figure 4: Synthesized Quinazoline derivatives (4a-j).

added in each cell and incubated for 4 hr. The formed formazan crystals were removed carefully and add 150 µL of DMSO was in each well. The 96-well plate was subjected to shaking for 15 sec, and UV absorption was determined at 540 nm.[15]

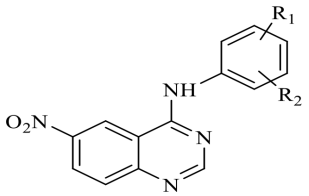
In-vitro Cytotoxic study (hemolytic study)

5 mL of whole human blood was centrifuged with (0.9%) NaCl solution for 10 min at 6000 rpm to create a red blood cell suspension. The erythrocyte cells were suspended in an equivalent volume of normal saline, removed from the supernatant, and centrifuged again. Until a clear supernatant was achieved, this procedure was repeated three times. After collecting erythrocytic suspension, 5% packed cell volume was prepared. 3 mL of isotonic solution of NaCl, 1 mL of PBS, and 1.5 ml of synthesized derivatives were added and allowed to stand for half an hour at 37°C. After incubation, absorbance was measured Spectrophotometrically at 540 nm. HD_{50} and Percentage hemolysis of the synthesized derivatives were calculated and presented in Table 1.[16]

RESULTS

The synthetic methodology of final derivatives as illustrated in (Figure 3) and the cell proliferation activity of final derivatives were evaluated against MCF-7 and MDA-MB-231 breast cancer cell lines. Erlotinib was selected as the reference standard drug. The IC_{50} value of all derivatives is presented in Table 1. The study revealed that most of the quinazoline derivatives (4b, 4c, 4e, 4f, 4i) exhibited stronger activity against cell lines, whereas derivative 4e (2-Br aniline) showed the most potent growth inhibitor with [IC_{50} values 8.97±1.5 (MCF-7) and 12.66±2.7µM (MDA-MB-231)] than that of erlotinib. Derivatives (4g, 4h, 4j) demonstrated mild to moderate activity. The hemolytic activity results state that the synthesized derivatives (4e, 2-Br) and (4i 4-CN) showed less toxicity as compared to another substituted group on aniline at the 4th position of quinazoline pharmacophore

Table 1: *In-vitro* cell proliferation and hemolytic activity of the final compounds (4a-j).



Comp. No.	R1	R2	IC_{50} (µM) MCF7	IC_{50} (µM) MDA-MB231	HD_{50} (µg)
4a	H	4-OC_6H_5	82.80±4.2	71.80±4.6	10.34±5.7
4b	H	4-SH	11.72±0.98	56.14±3.3	12.74±1.7
4c	2-CN	H	15.80±2.5	20.80±2.2	29.56±3.2
4d	2-OH	4-NO_2	78.80±4.2	21.80±2.6	20.98±4.6
4e	2-Br	H	08.97±1.5	12.66±2.7	69.87±8.9
4f	H	4-Br	19.70±2.2	18.21±1.7	46.60±5.2
4g	2-CH_3	6-CH_3	66.80±4.2	69.80±5.2	16.30±9.2
4h	2-CH_3	H	23.72±3.5	36.14±3.5	26.13±6.5
4i	H	4-CN	12.80±5.2	10.80±1.2	58.40±3.2
4j	2-CH_3	4-CH_3	75.80±1.2	71.80±1.7	11.70±4.7
Std. (Erlotinib)	-	-	16.80±2.2	22.80±4.2	18.52±7.6

DISCUSSION

The ten novel quinazoline derivatives (4a-j) shown in (Figure 4) were synthesized and characterized by different spectroscopic methods. The active molecules synthesized by three-step reactions starting from 5-nitroanthranilic acid (1) scaffold were treated with formamidine acetate in 2-methoxy ethanol to obtain intermediate [6-nitroquinazoline-4-(3H)-one] (2) with 71% yield. Then it was treated with dimethyl formamide and phosphorus Penta chloride, which yielded 4-chloro-6-nitroquinazoline with 68% yield. Finally, substituted anilines treated with 4-chloro-6-nitroquinazoline (3) in presence of methanol yielded final active molecules. The synthesized derivatives were verified by the results of different spectroscopical data.

IR spectra of intermediate (2), showed a characteristic band at υ (-NH) 3331.07, (N-H) 1590.50, (C=O) 1671.70, (C=N) 1590.57, (NO_2) 1495.74, 1320.13 whereas the intermediate (3) showed band at υ 3090.59, (C=N) 1555.86, (NO_2) 1510.02-1320.59, (C-Cl) 741.12. Target compounds showed ^{1}H NMR spectra of compound (4a-j) signals in the range of δ 8.908 - 6.683 due to aromatic protons. (C-NH), (C-OH), and (CH_3) showed singlets at 9.99, 8.21, and 2.12 respectively. ^{13}C NMR spectra of final compounds (4a-j) showed (C-O) and (CH_3) signals at around δ 173-169 and 17.73 respectively.

All the synthesized compounds have shown broad-range anti-cancer activity with (IC_{50} values of 08.97±1.5 to more than 82.80±4.2). *In-vitro* hemolytic studies showed that the two synthesized compounds (4e and 4i) lack the hemolysis of erythrocytes (RBCs) showing their suitability for further studies (Figure 5).

STRUCTURE ACTIVITY RELATIONSHIPS

In the SAR (Structure-activity relationship) study, we explored the effect of various substituted anilines at the 4th position on the quinazoline ring. According to pharmacological evaluation, quinazoline is necessary for anti-cancer activity. Initially, when the 4th position was substituted with a single halogen containing electron-withdrawing group (2 or 4-Br) enhance one to two times growth inhibition effect as compared to the different derivatives 4d (OH, NO_2), 4g (CH_3) substituted with another electron-withdrawing group. Further SAR study revealed that quinazoline ring substituted at 4th position with phenyl ring in place of halogen group growth inhibition activity reduced drastically. This

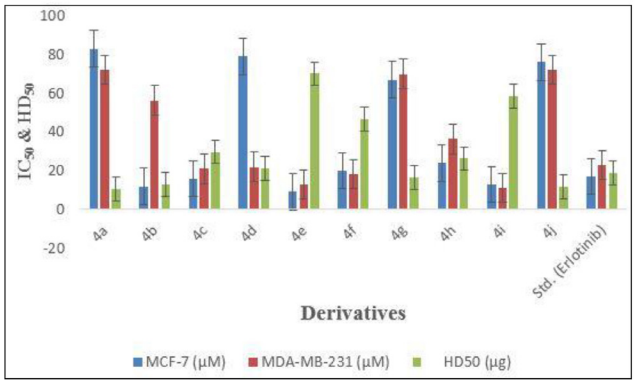


Figure 5: Cell proliferation and a hemolytic assay of synthesized derivatives.

study showed that halogen-containing anilines were preferred to enhance the anti-cancer potential of novel drugs.

CONCLUSION

The objective of the present study is to synthesize ten novel quinazoline derivatives with different substituted anilines concerning erlotinib. All the synthesized derivatives were evaluated against MCF-7 and MDB-MA-231 breast cancer cell lines. Compared with erlotinib, most of the derivatives showed significant growth inhibition effect, especially derivative (4e) which having (4-Br) exhibited the most potent activity with [IC_{50} values 8.97±1.5 (MCF-7) and 12.66±2.7µM (MDA-MB-231)], respectively. Furthermore, the SAR study and hemolytic study proved that the derivatives (4e and 4i) containing electron-withdrawing aniline at the 4th position in the quinazoline ring potentiate anti-cancer activity as well as reduced toxicity of the existing drugs. The results suggest a new path for the development of safe, effective as well as potential novel breast cancer agents.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

ABBREVIATIONS

EGFR: Epidermal growth factor receptor; **HER2:** Human epidermal growth factor receptor-2; **TKIs:** Tyrosine Kinase Inhibitors; **DMF:** Dimethylformamide; **UV:** Ultra Violet; **MTT:** 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; **IC_{50}:** Half-maximal inhibitory concentration; **HD_{50}:** Hemolytic Dose.

REFERENCES

1. Harbeck N, Penault-Llorca F, Cortes J, Gnant M, Houssami N, Poortmans P, *et al*. Breast cancer. Nat Rev Dis Primers. 2019;5(1):66. doi: 10.1038/s41572-019-0111-2, PMID 31548545.
2. Jönsson B, Ramsey S, Wilking N. Cost effectiveness in practice and its effect on clinical outcomes. J Cancer Policy. 2014;2(1):12-21. doi: 10.1016/j.jcpo.2014.02.001.
3. Press D. Nanotechnology-based approaches in anticancer research; 2012. p. 4391-408.
4. Sawyers C. Targeted cancer therapy. Nature. 2004;432(7015):294-7. doi: 10.1038/nature03095, PMID 15549090.
5. Masuda H, Zhang D, Bartholomeusz C, Doihara H, Hortobagyi GN, Ueno NT. Role of epidermal growth factor receptor in breast cancer. Breast Cancer Res Treat. 2012;136(2):331-45. doi: 10.1007/s10549-012-2289-9, PMID 23073759.
6. El-Azab AS, Al-Omar MA, Abdel-Aziz AAM, Abdel-Aziz NI, El-Sayed MAA, Aleisa AM, *et al*. Design, synthesis and biological evaluation of novel quinazoline derivatives as potential antitumor agents: Molecular docking study. Eur J Med Chem. 2010;45(9):4188-98. doi: 10.1016/j.ejmech.2010.06.013, PMID 20599299.
7. Yadagiri B, Gurrala S, Bantu R, Nagarapu L, Polepalli S, Srujana G, *et al*. Synthesis and evaluation of benzosuberone embedded with 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole moieties as new potential anti proliferative agents. Bioorg Med Chem Lett. 2015;25(10):2220-4. doi: 10.1016/j.bmcl.2015.03.032, PMID 25827522.
8. Lage H, Aki-sener E, Yalcin I. High antineoplastic activity of new heterocyclic compounds in cancer cells with resistance against classical DNA topoisomerase II-targeting drugs. Int J Cancer. 2006;220(1)(November 2005):213-20. doi: 10.1002/ijc.21792, PMID 16450374.
9. Karnakar K, Shankar J, Murthy SN, Ramesh K, Nageswar YVD. An efficient protocol for the synthesis of 2-phenylquinazolines catalyzed by ceric ammonium nitrate (CAN). Synlett. 2011;8:1089-96.
10. Alanazi AM, Abdel-aziz AA, Mohamed MA, El-azab ASAl-suwaidan IA. Bioorg Med Chem Lett Des Synth Biol Eval of. 2013;23(13):3935–41 2-mercapto-3-phen- ethylquinazoline bearing anilide fragments as potential antitumor agents : Molecular docking study Large fragment Fragment replacement. Bioorg Med Chem Lett [Internet]. doi: 10.1016/j.bmcl.2013.04.056.
11. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: Epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc. 2008;83(5):584-94. doi: 10.4065/83.5.584, PMID 18452692.
12. Wu X, Li M, Qu Y, Tang W, Zheng Y, Lian J, *et al*. Design and synthesis of novel gefitinib analogues with improved anti-tumor activity. Bioorg Med Chem. 2010;18(11):3812-22. doi: 10.1016/j.bmc.2010.04.046, PMID 20466555.
13. Alafeefy AM, Ahmad R, Abdulla M, Eldehna WM, Al-Tamimi AMS, Abdel-Aziz HA, *et al*. Development of certain new 2-substituted-quinazolin-4-ylaminobenzenesulfonamide as potential antitumor agents. Eur J Med Chem. 2016;109:247-53. doi: 10.1016/j.ejmech.2016.01.001, PMID 26774930.
14. Yu H, Li Y, Ge Y, Song Z, Wang C, Huang S, *et al*. Novel 4-anilinoquinazoline derivatives featuring an 1-adamantyl moiety as potent EGFR inhibitors with enhanced activity against NSCLC cell lines. Eur J Med Chem. 2016;110:195-203. doi: 10.1016/j.ejmech.2016.01.045, PMID 26829280.
15. Zou M, Jin B, Liu Y, Chen H, Zhang Z, Zhang C, *et al*. Synthesis and biological evaluation of some novel thiophene-bearing quinazoline derivatives as EGFR inhibitors. LDDD. 2019;16(2):102-10. doi: 10.2174/1570180815666180803125935.
16. Dwivedi DK, Sahu A, Dighade SJ, Agrawal RK. Design, synthesis, and antimicrobial evaluation of some nifuroxazide analogs against nosocomial infection. J Heterocycl Chem. 2020;57(4):1666-71. doi: 10.1002/jhet.3891.

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