*Bulgarian Chemical Communications, Volume 48, Number 2 (pp. 272 – 278) 2016*

# Anticancer evaluation of novel quinazolines carrying a biologically active pyrimidine, triazine, benzo[*d*][1,3]dioxol, morpholinophenyl, quinoline, sulfonamide moieties

M. M. Ghorab[1,2*], M. S. Alsaid[1]

[1] *Department of Pharmacognosy, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia*

[2]*Department of Drug Radiation Research, National Center for Radiation Research and Technology, Atomic Energy Authority, Nasr City, Cairo, Egypt*

Received April 25, 2015, Revised June 5, 2015

A novel series of quinazolines incorporating a biologically active 4, 6-dimethylpyrimidine, 1, 2, 4-triazine, benzo[*d*][1,3]dioxol, morpholinophenyl, quinoline, sulfonamide and thioureamoieties**9-14, 15,16,19, 20** and 2-hydrazinylquinazoline derivative **22**were designed and synthesized using methyl 2-isothiocyanato derivative**2** as strategic starting material. The structure of the newlysynthesized compounds was confirmed by elemental analyses and spectral data. All the prepared compounds were evaluated for their *invitro* anticancer activity against breast cancer cell lines. It was found that quinazoline carrying free amino group at 3-position with sulfa-phenazolegroup at 2-position**20** and thioureido derivative bearing sulfa-phenazole**16** with $IC_{50}$values (2.64 and 4.60 µg/mL) showed better activity thandoxorubicin as positive control. In addition compounds **14**, **12** and **15** are nearly as active as doxorubicin as reference drug, while compounds **9**, **13, 11** and **19** exhibited a moderate activity. On the other hand, compounds **10** and **22** showed no activity.

**Keywords**:Synthesis, DihydroquinazolineDerivatives,Anti-breast Cancer Activity.

## INTRODUCTION

Natural and synthetic quinazolinone derivatives constitute an important class of fused heterocycles, which influence numerous cellular processes. These scaffolds as a core unit have been extensively studied in a number of biologically active compounds because of their broad range of biological medicinal, physiological and pharmacological applications [1-8]. In recent years, quinazolines, as an important pharmacophore, have emerged as a versatile template for inhibition of a diverse range of receptor tyrosine kinases [9-13]. The most widely studied of these is the epidermal growth factor receptor (EGFR), with the small-molecule inhibitor gefitinib being the first agent from this class to be approved for the treatment of Non-Small Cell Lung Cancer [14-18]. Subsequent research aimed at further exploration of the SAR of this novel template has led to the discovery of highly selective compounds that target EGFR such as Erlotinib, Lapatinib and Vandetanib [19-21] (**Fig. 1**). These compounds act via competing with ATP for binding at the catalytic domain of tyrosine kinase. Later on, a great structural variety of compounds of structurally diverse classes have proved to be highly potent and selective ATP-competitive inhibitors [22-25].

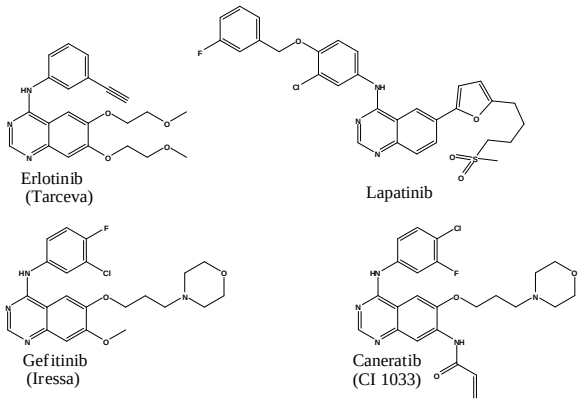



**Fig. 1.** EGFR-tyrosine kinase inhibitors.

Based on the good performance of quinazoline derivatives in anticancer application, the development of novel quinazoline derivatives as anticancer drugs is a promising field. Varied biological activities have been attributed to sulfonamide compounds, including carbonic anhydrase inhibition, antitumoral, antimalarial and antimicrobial activities [26-28]. In the design of new drugs, the development of hybrid molecules through the combination of different pharmacophores may lead to compounds with interesting biological profiles [29]. In view of the above mentioned knowledge based facts of different pharmacophores and in continuation of

our research programme [30-40], we have synthesized quinazoline carrying a biologically active 4, 6-dimethypyrimidine, 1, 2, 4-triazine, benzo[*d*][1,3]dioxol, morpholino-phenyl, quinoline, sulfonamide moieties to evaluate their anti-breast cancer activity.

## MATERIALS AND METHODS

Melting points (uncorrected) were determined in open capillary on a Gallen Kamp melting point apparatus (Sanyo Gallen Kamp, UK). Precoated silica gel plates *(Kieselgel* 0.25 mm, 60 F254, Merck, Germany) were used for thin layer chromatography. A developing solvent system of chloroform/methanol (8:2) was used and the spots were detected by ultraviolet light. IR spectra (KBr disc) were recorded using an FT-IR spectrophotometer (Perkin Elmer, USA). $^{1}$H-NMR spectra were scanned on a NMR spectrophotometer (Bruker AXS Inc., Switzerland), operating at 500 MHz for $^{1}$H- and 125.76 MHz for $^{13}$C. Chemical shifts are expressed in δ-values (ppm) relative to TMS as an internal standard, using DMSO-$d_6$ as a solvent. Elemental analyses were done on a model 2400 CHNSO analyser (Perkin Elmer, USA). All the values were within ± 0.4 % of the theoretical values. All reagents used were of AR grads.

## CHEMISTRY

### *Synthesis of quinazoline derivatives 9-14.*

### *General procedure*

A mixture of methyl-2-isothiocyanatobenzoate **2**(1.93g, 0.01mol) and aromatic amines (0.012mol) in dry dimethylformamide(10mL) containing 3 drops of triethylamine was refluxed for 12h., then left to cool. The solid product formed upon pouring onto ice/water was collected by filtration and recrystallized from dioxane to give **9-14,** respectively.

### *4-(2-Phenylquinazolin-4-ylamino)benzenesulfonamide (9)*

Yield, 84%; m.p. 172.5 $^{0}$C. IR: 3381 (NH), 3081 (arom.), 2971, 2828 (aliph.), 1691 (CO),1610 (CN), 1281 (CS).$^{1}$H-NMR: 2.2 [s, 6H, 2$CH_3$], 6.5 [s, 1H, CH pyrimidine], 7.0-8.2 [m, 4H, Ar-H], 8.6 [s,1H,NH]. $^{13}$C-NMR: 26.7 (2), 112.6, 114.6, 118.7, 122.8, 125.4, 130.6, 136.9, 161.2, 164.8 (2), 167.1, 173.6. Anal. Calcd. For $C_{14}H_{12}N_4OS$ (284.34): C, 59.14; H, 4.25; N, 19.70. Found: C, 59.46; H, 4.55; N, 19.39.

### *3-(5, 6-Dimethyl-1,2,4-triazin-3-yl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (10)*

Yield, 88%; m.p. 95.9$^{0}$C. IR: 3411 (NH), 3056 (arom.), 2917, 2837 (aliph.), 1686 (CO), 1621 (CN), 1272 (CS). $^{1}$H-NMR: 2.4, 2.8 [2s, 6H, 2$CH_3$], 6.9-8.2 [m, 4H, Ar-H], 8.5 [s,1H,NH]. $^{13}$C-NMR: 16.3, 18.7, 113.6, 118.0, 125.4, 126.1, 130.8, 140.3, 146.2, 161.3, 162.6, 168.5, 175.7. Anal.Calcd.For $C_{13}H_{11}N_5OS$ (285.32): C, 54.72; H, 3.89; N, 24.55. Found: C, 54.98; H, 4.13; N, 24.22.

### *3-(Benzo[d][1,3]dioxol-5-ylmethyl)-2-thioxo-2, 3-dihydroquinazolin-4(1H)-one(11)*

*Method A:*

A mixture of **2** (1.93g, 0.01 mole) and benzo[d][1,3]dioxol-5-ylmethanamine (1.51g, 0.01 mole) in dry dimethylformamide (15 mL ) containing 3 drops of triethylamine was refluxed for 3 h. The obtained solid while hot was separated and recrystllized from dioxane to give **11**.

*Method B:*

A mixture of **2** (1.93g, 0.01 mole) and benzo[*d*] [1,3]dioxol-5-ylmethanamine (1.51g, 0.01 mole) in dry dimethylformamide (15 mL) was stirred at room temperature for 2 h. The obtained material recrystllized from dioxane to give **11** (m.p and mixed m.p).

Yield, 79%; m.p. 281.5$^{0}$C. IR: 3261 (NH), 3100 (arom.), 2928, 2844 (aliph.), 1691 (CO), 1263 (CS). $^{1}$H-NMR: 5.5 [s, 2H, $CH_2$], 5.9 [s, 2H, $CH_2$ pipronyl], 6.8-7.9 [m, 7H, Ar-H], 12.9 [s, 1H, NH].$^{13}$C-NMR: 48.3, 100.8, 107.9, 108.2, 115.6, 120.9, 124.5 (2), 127.2, 130.3, 135.5, 139.0, 146.1, 146.9, 159.3, 175.7. Anal.Calcd.For $C_{16}H_{12}N_2O_3S$ (312.34): C, 61.53; H, 3.87; N, 8.97. Found: C, 61.81; H, 4.09; N, 8.62.

### *3-(4-Morpholinophenyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one(12)*

Yield, 93%; m.p. 392.4 $^{0}$C. IR: 3261 (NH), 3081 (arom.), 2966, 2881 (aliph.), 1679 (CO), 1260 (CS).$^{1}$H-NMR: 2.7- 3.3 [m, 8H, 4$CH_2$], 6.8-7.8 [m, 8H, Ar-H], 8.0 [s, 1H, NH]. $^{13}$C-NMR: 51.2 (2), 62.6 (2), 112.6 (2), 116.7, 120.1, 121.7, 123.8 (2), 125.1, 128.2, 133.0, 141.2, 144.3, 162.2, 173.6. Anal.Calcd. For $C_{18}H_{17}N_3O_2S$ (339.41): C, 63.70; H, 5.05; N, 12.38. Found: C, 63.40; H, 5.31; N, 12.05.

### *3-(Quinolin-3-yl) -2-thioxo-2,3-dihydroquinazolin-4(1H)-one(13)*

Yield, 72%; m.p. 341.8$^{0}$C. IR: 3167 (NH), 3062 (arom.), 1699 (CO), 1620 (CN), 1265 (CS).$^{1}$ H-NMR: 7.0- 8.1 [m, 10H, Ar-H], 8.3 [s, 1H,NH].$^{13}$C-NMR:114.6, 117.0, 126.7 (2), 127.3, 127.4, 127.8, 128.4, 128.7, 130.3, 135.5, 137.4, 139.0, 141.8,

163.6, 176.3. Anal.Calcd. For $C_{17}H_{11}N_3OS$ (305.35): C, 66.87; H, 3.63; N, 13.76. Found: C, 66.52; H, 3.95; N, 13.47.

*N-(5, 6-Dimethoxypyrimidin-4-yl)-4-(4-oxo-2-thioxo-1, 2-dihydroquinazolin-3(4H)-yl)benzenesulfonamide(14)*

Yield, 77%; m.p. 178.4$^0$C. IR: 3246 (NH), 3100 (arom.), 2943, 2861 (aliph.), 1670 (CO), 1618 (CN), 1338, 1199 ($SO_2$).$^1$H-NMR: 3.8, 3.9 [2s, 6H, $2OCH_3$], 7.0-8.3 [m, 9H, Ar-H], 8.7 [s,1H, NH],11.0 [s,1H, $SO_2NH$]. $^{13}$C-NMR: 54.1, 55.6, 113.2, 118.7, 119.6, 120.1, 121.3, 125.8, 127.3 (2), 129.1, 130.3, 133.4, 134.1, 140.8, 152.6, 153.1, 162.3, 164.6, 174.8. Anal.Calcd. For $C_{20}H_{17}N_5O_5S_2$ (471.51): C, 50.95; H, 3.63; N, 14.85. Found: C, 51.19; H, 3.37; N, 14.58.

*Methyl-2-(3-(4-morpholinophenyl)thioureido)benzoate (15) and methyl-2-(3-(4-(N-(1-phenyl-1H-pyrazol-5-yl)-sulfonyl)phenyl)thioureido)benzoate(16)*

A mixture of compound **2** (1.93g, 0.01 mole) and 4-morpholinoaniline and/ or sulfa-phenazole (0.01 mole) in dry dimethylformamide (15 mL) was stirred at room temperature for 2 h. The obtained solid upon pouring into ice water recrystallized from ethanol to give compounds **15** and **16**, respectively.

**15**: Yield, 69%; m.p. 381.3 $^0$C. IR: 3261, 3189 (NH), 3057 (arom.), 2981, 2861 (aliph.), 1678(CO), 1246 (CS). $^1$H-NMR: 2.7-3.7 [m, 8H, $4CH_2$], 4.1 [s, 3H, $OCH_3$], 6.8-8.0 [m, 8H, Ar-H],13.0 [s, 2H, 2NH]. $^{13}$C-NMR: 48.4 (2), 52.3, 66.0 (2), 114.9 (2), 121.2, 123.6, 125.5, 126.7 (2), 130.0, 132.6 (2), 141.0, 144.6, 162.2, 173.2. Anal.Calcd.For $C_{19}H_{21}N_3O_3S$ (371.45): C, 61.44; H, 5.70; N, 11.31. Found: C, 61.14; H, 5.44; N, 11.65.

**16**: Yield, 82%; m.p. 187.3$^0$C. IR: 3312, 3277 (NH), 3086 (arom.), 2976, 2831 (aliph.), 1682 (CO), 1618 (CN), 1371,1156 (CS).$^1$H-NMR: 3.7 [s, 3H**,**$OCH_3$], 6.6-8.2 [m, 15H, Ar-H], 11.0 [s,1H,$SO_2NH$], 11.9 [s, 2H, 2NH].$^{13}$C-NMR: 52.6, 103.7, 118.1, 120.7 (2), 122.0 (2), 124.4, 124.8, 125.1, 127.6 (2), 128.1 (2), 129.3, 130.8, 133.6, 134.7, 138.1, 139.5, 140.2, 142.9, 166.0, 176.3. Anal.Calcd. For $C_{24}H_{21}N_5O_4S_2$ (507.58): C, 56.79; H, 4.17; N, 13.80. Found: C, 56.48; H, 4.50; N, 14.07.

*3-Amino-2-(4-morpholinophenylamino) quinazolin-4(3H)-one(19) and 4-(3-amino-4-oxo-3, 4-dihydroquinazolin-2-ylamino)-N-(1-phenyl-1H-phenyl-1H-pyrazol-5-yl) benzenesulfonamide(20)*

A mixture of compounds **15** or **16** (0.01 mole) and hydrazine hydrate (0.012 mole) in absolute ethanol (20 mL) was refluxed for 15 h (after evolution of all $H_2S$). The reaction mixture was poured on to ice water and the obtained solid recrystallized from dioxane to give compounds **19** and **20**, respectively.

**19**: Yield, 86%;m.p. 184.6$^0$C. IR: 3408, 3366, 3219 (NH, $NH_2$), 3088 (arom.), 2937, 2843 (aliph.), 1688 (CO), 1622 (CN).$^1$H-NMR: 3.1- 3.7 [m, 8H, $4CH_2$], 5.6 [s, 2H, NH], 6.2-8.3 [m, 8H, Ar-H], 9.1[s,1H,NH].$^{13}$C-NMR: 48.8 (2), 66.2 (2), 116.4 (2), 117.5 (2), 121.5, 124.8, 126.8, 127.2, 130.6, 133.9, 134.0, 148.5, 160.9, 161.0. Anal.Calcd. For $C_{18}H_{19}N_5O_2$ (337.37): C, 64.08; H, 5.68;N, 20.76. Found: C, 64.33; H, 5.39; N, 20.48.

**20:** Yield, 85%; m.p. 331.3$^0$C. IR: 3448, 3275, 3205 (NH, $NH_2$), 3100 (arom.), 1666 (CO), 1620 (CN), 1346,1172 ($SO_2$).$^1$H-NMR: 5.8 [s, 2H, $NH_2$], 6.2-8.4 [m, 15H, Ar-H], 9.2 [s, 1H,NH], 11.2 [s,1H, $SO_2NH$]. $^{13}$C-NMR: 103.6, 112.0 (2), 117.6, 120.8 (2), 124.1, 124.8, 125.2, 126.3, 128.6 (2), 129.0, 129.6 (2), 131.4, 134.0, 137.1, 140.7, 145.9, 146.0, 161.2, 167.1. Anal.Calcd. For $C_{23}H_{19}N_7O_3S$ (473.51): C, 58.34; H, 4.04; N, 20.71. Found: C, 58.05; H, 4.30; N, 20.98.

*3-(Benzo[d][1,3]dioxol-5-ylmethyl)-2-hydrazinylquinazolin-4(3H)-one(22)*

A mixture of compound **11** (3.12g, 0.01 mole) and hydrazine hydrate (1g, 0.02 mole) was refluxed for 24 h (lead acetate paper). The obtained solid while hot was recrystallized from ethanol-dimethylformamide to give compound **22**.

Yield, 89%; m.p. 154.6$^0$C. IR: 3376, 3261 (NH, $NH_2$), 3059 (arom.), 2951,2873 (aliph.), 1688 (CO), 1617 (CN).$^1$H-NMR: 5.1 [s, 2H, N-$CH_2$], 5.9 [s, 2H, O-$CH_2$-O], 6.8-8.0 [m, 7H, Ar-H], 8.9 [s,1H,NH], 9.5 [s, 1H,$NH_2$]. $^{13}$C-NMR: 42.3, 101.0, 107.8, 108.5, 120.6, 121.7, 124.4, 127.0, 127.1, 133.6, 134.2, 147.7, 148.6, 151.7, 161.3, 162.0. Anal.Calcd.For $C_{16}H_{14}N_4O_3$ (310.30): C, 61.93; H, 4.55; N, 18.06. Found: C, 61.64; H, 4.23; N, 17.88.

## IN-VITRO ANTICANCER EVALUATION

The cytotoxic activity was measured *in vitro* for the newly synthesized compounds using the SulfoRhodamine-B stain (SRB) assay [41]. The in vitro anticancer screening was done at the Pharmacology Unit, the National Cancer Institute, Cairo University. Cells were plated in 96- multi-well plates ($10^4$ cells per well) for 24 h before treatment with the compound, to allow attachment of cells to the wall of the plate. Test compounds were dissolved in DMSO and diluted with saline to the appropriate concentration. Different concentrations of the compound under test (10, 25, 50 and 100 µg/ml) were added to the cell

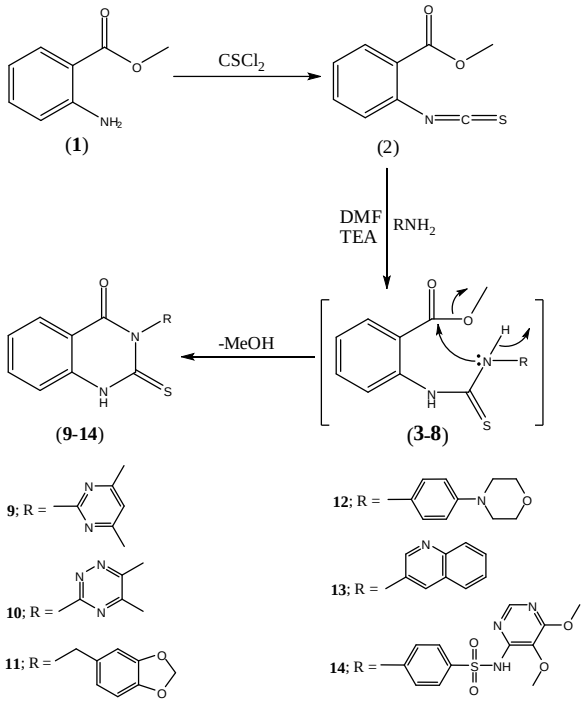
monolayer. Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compound(s) for 48 h at 37 ºC and in an atmosphere of 5% $CO_2$. After 48h cells were fixed, washed, and stained for 30 min with 0.4% (*m*/*V*) with SRB dissolved in 1 % acetic acid. Excess unbound dye was removed by four washes with 1 % of acetic acid and attached stain was recovered with a Tris-EDTA buffer. Color intensity was measured in an enzyme-linked immunosorbent assay ELISA reader. The relation between the surviving fraction and drug concentration is plotted to get the survival curve for the breast tumor cell line after the specified time. The molar concentration required for 50 % inhibition of cell viability ($IC_{50}$) was calculated and the results are given in (**Table 1**).

## RESULTS AND DISCUSSION

### *Chemistry*

The aim of this work was to design and synthesize novel quinazoline incorporating a biologically active 4, 6-dimethylpyrimidine **9**, 5,6-dimethyl-1,2,4-triazine **10**, benzo[*d*][1,3]dioxol-5-ylmethan **11**, 4-morpholinophenyl**12**, quinolone **13** and benzenesulfonamide**14**, thioureido derivatives **15** and **16**, 3-aminoquinazoline derivatives **19**, **20** and 2-hydrazinylquinazoline derivative **22** to evaluate their anti-breast cancer activity. Thus, interaction of methyl-2-isothiocyanatobenzoate **2** with 2-amino-4, 6-dimethylpyrimidine, 2-amino-5,6-dimethyl-1,2,4-triazine, benzo[*d*][1,3]dioxol-5-ylmethanamine, 4-morpholinoaniline, 3-aminoquinoline and sulfadoxinein dry *N*,*N*-dimethylformamide containing triethylamine as catalyst affordedthe corresponding quinazoline derivatives is presented in **9**-**14**(Scheme 1).

The IR of compound **15** showed the absence of a N=C=S group and the presence of the characteristic bands at 3261, 3189 $cm^{-1}$ (NH), 3057 $cm^{-1}$ (aromatic) 1678 $cm^{-1}$ (CO), 1246 $cm^{-1}$ (CS). The $^1$H-NMR of compound **15** exhibited signals at 4.1 ppm assigned to the $OCH_3$ group, 13.0 ppm due to 2NH groups. The IR of compound **16** revealed the absence of the N=C=S group and the presence of characteristic bands at 3312, 3277$cm^{-1}$ (NH), 1682 $cm^{-1}$ (CO), 1618$cm^{-1}$ (CN), 1371, 1156 $cm^{-1}$ ($SO_2$), 1256 $cm^{-1}$ (CS). The $^1$H-NMR of compound **16** revealed signals at 3.7 ppm attributed to the $OCH_3$ group, 11.0 ppm assigned to the $SO_2NH$ group, 11.9 ppm corresponding to 2NH groups. In addition the interaction of compound **15** and **16** with hydrazine hydrate in refluxing ethanol furnished the corresponding 3-aminoquinazoline derivatives **19** and **20**. Compounds **19** and **20** were obtained through the formation of the intermediated **17** and **18**.

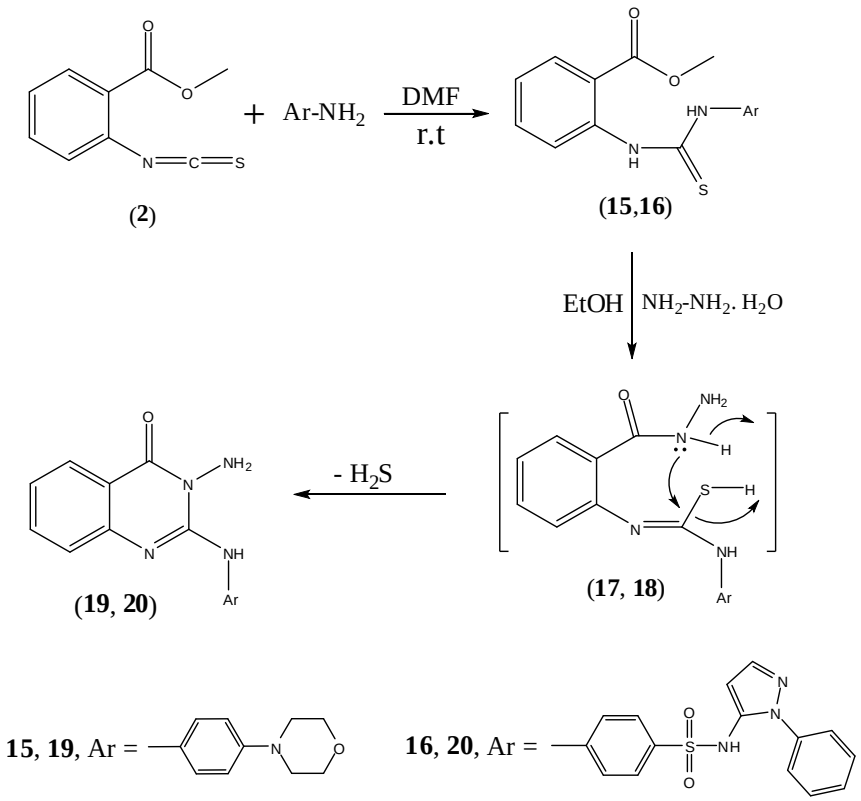



Scheme 1: Formation of quinazoline derivatives **9**-**14**

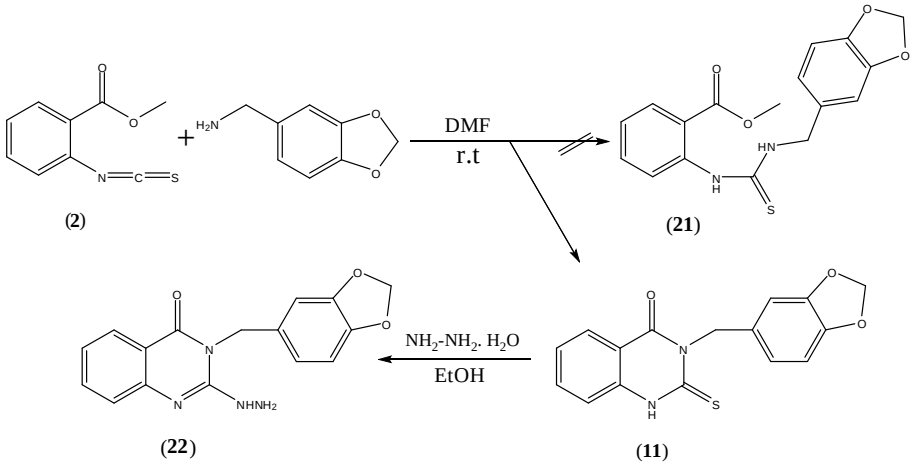
The structures of the obtained compounds were established on the basis of elemental analyses and spectral data. The IR spectra of compounds **9**-**14** showed the absence of N=C=S group and the presence of absorption bands for (NH), (aromatic), (aliphatic), (CO), (CN), (CS) and ($SO_2$) in compound **14**. $^1$H - NMR exhibited singlets assigned to the NH group which were exchanged upon deuteration. Also, the interaction of compound **2** with 4-morpholinoaniline and/or sulfa-phenazolein dimethylformamideat at room temperature furnished the corresponding thioureido derivatives **15** and **16**, respectively. The structure of compounds **15** and **16** was elucidated on the basis of microanalysis, IR, $^1$H-NMR and $^{13}$C-NMR (Scheme 2).

The reaction was proceeding via the elimination of 1 mole of $H_2S$. The structure of compound **19** and **20** was confirmed on the basis of elemental analyses, IR, $^1$H-NMR, and $^{13}$C-NMR. The IR of compound **19** revealed the absence of a $OCH_3$ group and the presence of the characteristic bands at 3408, 3366, 3219 $cm^{-1}$(NH, $NH_2$), 1688$cm^{-1}$ (CO), 1622 $cm^{-1}$ (CN). The $^1$H-NMR of compound **19** exhibited signals at 5.6 ppm assigned to the $NH_2$ group, 9.1 ppm attributed to the NH group. The IR of **20** showed characteristic bands at 3448, 3275, 3205 $cm^{-1}$ (NH, $NH_2$), 1666 $cm^{-1}$(CO), 1620$cm^{-1}$ (CN), 1346,1172$cm^{-1}$($SO_2$). $^1$H-NMR of **20**

revealed signals at 5.8 ppm due to the $NH_2$ group, 9.2 ppm corresponding to the NH group, 11.2 ppm attributed to the $SO_2NH$ group. When compound **2** reacted with benzo[d][1,3]dioxol-5-ylmethanamine in absolute ethanol at room temperature the unexpected cyclic 3-aminoquinazolie **11** was obtained instead of the expected thioureido derivative **21** (**Scheme 3**). The corresponding 2-hydrazinylquinazoline **22** was obtained in good yield via the reaction of compound **11** with hydrazine hydrate in refluxing ethanol. This reaction was proceeding through the elimination of one molecule of $H_2S$ (lead acetate paper). The structure of compound **22** was proved on the basis of elemental analysis, IR, $^1$H-NMR and $^{13}$C-NMR. The IR of **22** revealed the absence of the CS group and presence of characteristic bands at 3376, 3261cm$^{-1}$(NH, $NH_2$), 1688cm$^{-1}$(CO), 1617cm$^{-1}$(CN). $^1$H-NMR of **22** exhibited signals at 5.1 ppm attributed to the N-$CH_2$ group, 5.9 ppm assigned to the O-$CH_2$-O group, 8.8 ppm due to the NH group, 9.5 ppm corresponding to the $NH_2$ group.




Scheme 2: Formation of thiourea and quinazoline derivatives **15**, **16** and **19**, **20**




Scheme 3: Formation of 2-hydrazinylquinazoline derivative **22**

## IN-VITRO ANTICANCER EVALUATION

The newly synthesized compounds were evaluated for their *in vitro* anticancer activity versus the human breast cancer cell line (MCF7). Doxorubicin was used as the reference drug in this study. Table 1 shows the *in vitro* cytotoxic activity of the newly synthesized compounds. Some of the tested compounds exhibited significant activity compared to doxorubicin. It was found that quinazoline carrying the free amino group at the 3-position with a biologically active sulfa-phenazole at 2-position **20** and thioureido having a biologically sulfa-phenazole **16** (with $IC_{50}$ values of 2.64, 4.60 µg/ml) exhibited higher anti-breast cancer activity than the reference drug (with $IC_{50}$ value of 5.40 µg/ ml). Further, quinazoline bearing the biologically active sulfa-doxine at the 3-position with the thione group at 2-position **14**, quinazoline incorporating morpholinophenyl at 3-position with the thione group at 2-position **12** and thioureido carrying morpholinophenyl moiety **15** (with $IC_{50}$ values 5.68, 8.62, and 9.66 µg/ml) are nearly as active as doxorubicin. On the other hand, compounds **9**, **11**, **13** and **19** revealed slightly lower activity than that of doxorubicin. It is clear from the present data that the comparison of the cytotoxicity of the quinazoline derivatives against the breast cancer cell line (MCF7) (**Table 1**) has showed that the cell killing potency follows the order **20**>**16**>Doxorubicin >**14**>**12**>**15**>**9**>**13**>**1**>**19**with $IC_{50}$ values (2.64, 4.64, 5.40, 5.68, 8.62, 9.66, 16.63, 19.06, 24.20, 24.31 µg/ml). The biological screening of the tested compounds could offer an encouraging framework in this field which may lead to the discovery of potent anti-breast cancer agents.

**Table 1.** *In vitro* anti-breast cancer (MCF-7) activity of newly synthesized compounds

| Compound. No. | $IC_{50}$ (µg / mL)[a] MCF-7 |
|---|---|
| Doxorubicin | 5.40 |
| 9 | 16.63 |
| 10 | NA |
| 11 | 24.20 |
| 12 | 8.62 |
| 13 | 19.06 |
| 14 | 5.68 |
| 15 | 9.66 |
| 16 | 4.60 |
| 19 | 24.31 |
| 20 | 2.64 |
| 22 | NA |

[a]$IC_{50}$ value: Concentration causing 50% inhibition of cell viability.

NA: No activity.

## CONCLUSION

In this work, novel quinazolines having a biologically active 2,3-dihydroquinazoline, 1,2-dihydroquinazoline, quinazoline-4(3*H*)-one and 3,4-dihydroquinazoline derivatives were synthesized and their *in-vitro* anti-breast cancer activity was evaluated among the tested compounds, two candidates (**20** and **16**) showed effectiveness on the breast cancer cell line, the active compounds could be considered as useful templates for further development to obtain more potent anti-breast cancer agent(s). Also, compounds **14**, **12** and **15** are nearly as active as doxorubicin as a reference drug. In addition, compounds **9**, **11**, **13** and **19** exhibited a moderate activity. Compounds **10** and **22** showed no activity.

***Acknowledgment:*** *The authors would like to extend their sincere appreciation to the Deanship of Scientific Research at King Saud University for its funding of this research through the Research Group Project no.* ***RGP- 302****.*

## REFERENCES

1. G. Bonola, E. Sianesi, *J. Med. Chem.*,**13**, 329 (1970).
2. R. J. Alaimo, H. E. Russell, *J. Med. Chem.*,**15,** 335 (1972).
3. E. M. Bermanand, L. M. Werbel, *J. Med. Chem.*,**34,** 479 (1991).
4. O. I. El-Sabbagh, S.M. Ibrahim, M. M. Baraka, H. Kothayer, *Arch. Pharm.*,**343**, 274 (2010).
5. J. I. Levin, P. S. ChanBailey, A. S. Katocs, A. M. Venkatesan, *Bioorg. Med. Chem. Lett.*,**4**, 1141 (1994).
6. R. P. Maskey, M. Shaaban, I. Grun-Wollny, H. Laatsch, *J. Nat. Prod*., **67,** 1131 (2004).
7. D. J. Connolly, D. Cusack, T. P. O`Sullivan, P. J. Guiry, *Tetrahedron*.,**61,** 10153 (2005).
8. Y. S. Sadanandam, K. R. M. Reddy, A. BhaskarRao, *Eur. J. Med. Chem.*,**22**, 169 (1987).
9. S.K. Srivastava, V. Kumar, S.K. Agarwal, R. Mukherjee, A.C. Burman, *Anticancer Agents Med Chem.*, **9,** 246 (2009).
10. O. Cruz-López, A. Conejo-García, M.C. Núñez, M. Kimatrai, M.E. García-Rubiño, F. Morales, V. Gómez-Pérez, J.M. Campos, *Curr. Med. Chem*.,**18**, 943 (2011).
11. A. Garofalo, L. Goossens, P. Six, A. Lemoine, S. Ravez, A. Farce, P. Depreux, *Bioorg. Med. Chem. Lett*., **21,** 2106 (2011).
12. B.Lüth, W. Löwe, *Eur. J. Med. Chem.*, **43,** 1478 (2008).
13. Y.S. Lee, S.H. Seo, B.S. Yang, J.Y. Lee, *Arch. Pharm. (Weinheim*).,**338**, 502 (2005).
14. G. Cui, M. Cui, Y. Li, Y. Liang, W. Li, H. Guo, S. Zha, *Med. Oncol*., **32**, 570 (2015).
15. M.P. Mathew, E. Tan, C.T. Saeui, P. Bovonratwet, L. Liu, R. Bhattacharya, K.J. Yarema, *Bioorg. Med. Chem. Lett.,* **25**, 1223 (2015).

16. A. Bellizzi, M.R. Greco, R. Rubino, A. Paradiso, S. Forciniti, K. Zeeberg, R.A. Cardone, S.J. Reshkin, *Int. J. Oncol*., **46**, 1214 (2015).
17. D.M. Jackman, L.A. Cioffredi, L. Sharmeen, L.K. Morse, J. Lucca, S.R. Plotkin, P.J. Marcoux, M.S. Rabin, T.J. Lynch, B.E. Johnson, S. Kesari, *Oncotarget*., **6**, 4527 (2015).
18. M. Nakao, H. Muramatsu, K. Sone, S. Aoki, H. Akiko, Y. Kagawa, H. Sato, T. Kunieda, *Mol. Clin. Oncol*.,**3**,403 (2015).
19. T. Koizumi, S. Sasaki, A. Sakamoto, T. Kobayashi,*Ann.Palliat. Med*., **2**, 111 (2013).
20. M. Nolting, T. Schneider-Merck, M. Trepel, *Cancer Res*., **201,** 125 (2014).
21. M. Brassard, G.Rondeau, *Biologics*.,**6**,59(2012).
22. A. Levitzki, *Eur. J. Cancer*., **38**, 511 (2002).
23. S. Harakeh, M.D. Assef, M. El-Sabban, M. Haddadin, H.G. Muhatasib, *Chemico-Biol. Interactions.*, **148**, 101 (2004).
24. A. Levitzki, *Pharmacol.Ther.*, **82**, 231 (1999).
25. M.A. Bogoyevitch, D.P. Fairlie, *Drug. Discovery.Today.*,**12**, 622 (2007).
26. J. Drews, *Science.*, **287**, 1960 (2000).
27. C.T. Supuran , A. Casini , A. Mastrolorenzoand A. Scozzafava, *Mini-Rev. Med. Chem.*, **4**, 625 (2004).
28. F. Abbate, A. Casini, T. Owa, A. Scozzafava, C.T. Supuran, *Bioorg. Med. Chem. Lett.*, **14**, 217 (2004).
29. V.R. Solomon, C. Hu, H. Lee, *Bioorg. Med. Chem*., **17**, 7585 (2009).
30. M. M. Ghorab, F.A. Ragab, H.I. Heiba, M.G. El-Gazzar, S.S. Zahran,Synthesis, anticancer and radiosensitizing evaluation of some novel sulfonamide derivatives. *Eur. J. Med. Chem*., **92,** 682, (2015).
31. M.M. Ghorab, M.S. Alsaid, M. Ceruso, Y.M. Nissan, C.T. Supuran, *Bioorg. Med. Chem*., **14**, 3684 (2014).
32. M. M. Ghorab, M. Ceruso, M. S. Alsaid, Y. M. Nissan, R. K. Arafa, C. T. Supuran, *Eur. J. Med. Chem*., **87,** 186 (2014).
33. M.S. Al-Dosari, M.M. Ghorab, M.S. Alsaid, Y.M. Nissan, A.B. Ahmed, *Eur. J. Med. Chem*., **69**, 373 (2013).
34. M.M. Ghorab, F.A. Ragab, H.I.Heiba, R.M. El-Hazek, *Eur. J. Med. Chem.*, **46**, 5120 (2011).
35. M.S. Alsaid, M.M. Ghorab, M.S. Al-Dosari, M.M. Hamed, *Eur. J. Med. Chem.*, **46**, 201 (2011).
36. M.M. Ghorab, F.A. Ragab, H.I. Heiba, H.A. Youssef, M.G El-Gazzar, *Bioorg. Med. Chem. Lett.*, **20**, 6316 (2010).
37. M.S. Alsaid, M.M. Ghorab, S.I. Alqasoumi, E.M. El-Hossary, E. Noaman, *Eur. J. Med. Chem*., **45**, 3011 (2011).
38. S.I. Alqasoumi, A.M.Al-Taweel, A.M. Alafeefy, M.M. Ghorab, E.Noaman, *Eur. J. Med. Chem*., **45**, 1849 (2010).
39. S.I. Alqasoumi, A.M. Al-Taweel, A.M. Alafeefy, E. Noaman, M.M. Ghorab, *Eur. J. Med. Chem*., **45**, 738 (2010) .
40. M.M. Ghorab, F.A. Ragab, M.M. Hamed, *Eur. J. Med. Chem*., **44**, 4211 (2009).
41. P. Skehan, R. Storeng, D. Scudiero, A. Monks, J. McMahon, D. Vistica, J.T. Warren, H. Bokesch, S. Kenney, M.R. Boyd, *J. Nat. Cancer Inst*., **82**, 1107(1990).

# ОЦЕНКА НА ПРОТИВОТУМОРНАТА АКТИВНОСТ НА НОВИ ХИНАЗОЛИНИ, СЪДЪРЖАЩИ БИОЛОГИЧНО АКТИВНИ ПИРИМИДИН, ТРИАЗИН, БЕНЗО [*d*][1,3] ДИОКСОЛ, МОРФОЛИНОФЕНИЛ, ХИНОЛИН И СУЛФОНАМИДИ

М.М. Гораб[1,2*], М.С. Алсаид[1]

*[1] Департамент по фармакогнозия, Колеж по фармация, Университет „Крал Сауд“, Риад 11451, Саудитска Арабия*

*[2]Департамент по радиологични изследвания на лекарствата, Национален център за радиологичниизследвания и технологии, Служба по атомна енергетика, Наср Сити, Кайро, Египет*

Получена на 25 април, 2015 г., Коригирана на 5 юни, 2015 г.

(Резюме)

Нова серия хиназолини, включващи биологично активни 4,6-диметилпиридин, 1,2,4-триазин, бензо[*d*][1,3]диоксол, морфолинофенил, хинолин, сулфонамид и тиокарбамидни съставки **9-14, 15,16,19, 20 и** 2-хидразинил-хиназолиново производно **22** са конструирани с използването на метил 2-изоцианато- производно **2** като стратегически основно вещество. Структурата на ново-синтезираните съединения бе потвърдена с елементен анализ и спектрални данни. Всички приготвени съединения са оценени за тяхната *in vitro* противоракова активност срещу клетъчни линии за рак на гърдата. Намерено е, че хиназолинът със свободна аминогрупа на 3-то място с сулфа-феназолова група на 2-ро място (**20)** и тиокарбамидовите производни, носещи сулфа-феназол **16** с $IC_{50}$ - стойности (2.64 и 4.60 μg/mL) показват по-добра активност от доксорубицина като положителен контрол. Допълнително съединенията **14**, **12** и **15** са близки по активност до доксорубицина като сравнително лекарство, докато съединенията **9**, **13, 11** и **19** показват умерена активност. От друга страна съединенията **10** и **22** не показват активност.