**Synthesis, Biological Evaluation and Docking Analysis of Some Novel Quinazolin Derivatives as Antitumor Agents**

Walaa S. El-serwy*, Neama A. Mohamed, Emad M. M. Kassem, Khaled Mahmoud and M. M Mounier

---

**Abstract**

Different acid chlorides (2a-d) reacted with anthranilic acid to produce 2-substituted-3, 1-benzoxazin-4-one (3a-d) which was used as starting material to synthesize some condensed and non-condensed heterocyclic compounds by reaction with nitrogen nucleophiles e.g., hydrazine hydrate and formamide. Some of the newly synthesized analogues were chosen to evaluate their cytotoxic activity against human carcinoma cell lines (HePG2– MCF7– A549). The docking and the cytotoxic activity results revealed that nearly all of the compounds containing N-phenyl aniline showed significant inhibition for the three cell lines.

**Keywords:** Cytotoxic activity; Benzoxazin; Quinazolin; Antitumor; Docking analysis.

---

**Introduction**

The synthesis of quinazolinone heterocycles has become the cornerstone for synthetic chemists and gained extensive importance in medicinal chemistry because of their diverse pharmacological activities including anti-mycobacterial (1-3), anti-fungal (4), antimalarial (5), antihypertensive (6-8), anti-histaminic (9-13), cardiotonic (14), anticancer (15-17), antiviral (18) and thymidylate synthase inhibitory activities (19, 20).

Substituted quinazolin-3(4H)-ones are among the versatile heterocyclic compounds, as they have a broad spectrum of pharmacological activities like anti-inflammatory (21), anticonvulsant (22-24), analgesic (25), antitubercular (26, 27) and anticancer activities (28-32).

Benzoxazine heterocyclic compounds are potent non-steroidal progesterone receptor agonists (33) having many other activities such as anticancer, antiangiogenic (34), antidiabetic and hypolipidemic (35), antidepressant (36) and antiplatelet aggregation activities (37).

Epidermal growth factor receptor (EGFR), which is cellular trans-membrane tyrosine kinase, is over-expressed in a significant number of human tumors (e.g., breast, ovarian, colon and prostate). An EGFR expression level often correlates with vascularity and is associated with poor prognosis in patients. Inhibitors of the EGFR protein tyrosine kinase are therefore, expected to have great therapeutic potential in the treatment of malignant and nonmalignant epithelial diseases (38-43). These findings encourage us to synthesize novel 3, 1-benzoxazin-4-one derivatives.

**Experimental**

**Chemistry**

All melting points are uncorrected and were
180

2-[2-(Phenylamino) phenyl]-4H-3, 1-benzoxazin-4-one (3d)

Yield 85%. Yellow crystals. mp. 235-240 °C, IR (KBr, cm⁻¹): 1690 (C = O) and 3170 (NH). ¹H NMR (DMSO-d₆, δ ppm): 7.20-8.20 (m, 13H, aromatic), 11.72 (s, 1H, NH, exchangeable with D₂O). MS: (m/z) ≈ 314 (5%). Anal. Calcd for C₂₀H₁₄N₂O₂ (314.33): C, 76.42; H, 4.49; N, 8.91%. Found: C, 76.03; H, 4.20; N, 8.34%.

General procedure for the preparation of compounds (4a, b)

A mixture of (3a (44), 3b (45)) (0.01 mol) and formamide (0.015 mol) was refluxed for 3 h in boiling ethanol (30 mL), then poured into water. The precipitated solid after concentration and cooling was collected by filtration and crystallized from the proper solvent to give (4a, b). Spectroscopic data for all the compounds are given below.

2-(Pyridin-3-yl) quinazolin-4 (3H)-one (4a):

Yield 65%, White crystals. mp. >300 °C, IR (KBr, cm⁻¹): 1700 (C = O) and 3299 (NH). ¹H NMR (DMSO-d₆, δ ppm): 7.23-8.32 (m, 8H, aromatic), 12 (s, 1H, NH, exchangeable with D₂O). MS: (m/z) ≈ 223 (0.13%). Anal. Calcd for C₁₃H₉N₃O (223.23): C, 69.95; H, 4.06; N, 18.82%. Found: C, 69.62; H, 3.88; N, 18.60%.

General procedure for the preparation of compounds (5a, b)

A mixture of (4a, b) (0.01 mol) and chloroacetyl chloride (0.01 mol) was refluxed in boiling N, N-dimethylformamide (DMF) (30 mL) for 3 h. Then the mixture was poured into water. The precipitate was collected by filtration, dried and crystallized from the proper solvent to give (5a, b). Spectroscopic data for all the compounds are given below.

2-(Pyridin-3-yl) quinazolin-4 (3H)-one (4a):

Yield 65%, White crystals. mp. >300 °C, IR (KBr, cm⁻¹): 1700 (C = O) and 3299 (NH). ¹H NMR (DMSO-d₆, δ ppm): 7.23-8.32 (m, 8H, aromatic), 12 (s, 1H, NH, exchangeable with D₂O). MS: (m/z) ≈ 223 (0.13%). Anal. Calcd for C₁₃H₉N₃O (223.23): C, 69.95; H, 4.06; N, 18.82%. Found: C, 69.62; H, 3.88; N, 18.60%.

General procedure for the preparation of compounds (4a, b)

A mixture of (3a (44), 3b (45)) (0.01 mol) and formamide (0.015 mol) was refluxed for 3 h in boiling ethanol (30 mL), then poured into water. The precipitated solid after concentration and cooling was collected by filtration and crystallized from the proper solvent to give (4a, b). Spectroscopic data for all the compounds are given below.
3-(Chloroacetyl)-2-(pyridin-3-yl) quinazolin-4 (3H)-one (5a)

Yield 80%. Gray crystals. mp. >300 °C, IR (KBr, cm⁻¹): 1650 (C = O) and 1690 (C = O). 
¹H NMR (DMSO-d₆, δ ppm): 4.48 (s, 2H, CH₂), 7.63-9.07 (m, 8H, aromatic). MS: (m/z) ≈ 299 (6%), [M + 2]+ m/z ≈ 301 (3%). Anal. Calcd for C₁₅H₁₀ClN₃O₂ (299.71): C, 60.11; H, 3.36; N, 14.02%. Found: C, 59.90; H, 2.98; N, 13.90%.

3-(Chloroacetyl)-2-[(E)-2-(furan-2-yl) ethenyl] quinazolin-4 (3H)-one (5b)

Yield 90%. Black crystals. mp. 151-155 °C, IR (KBr, cm⁻¹): 1690 (C = O) and 1710 (C = O). 
¹H NMR (DMSO-d₆, δ ppm): 4.90 (s, 2H, CH₂), 6.23 (d, J = 8.1 Hz, 1H, CH), 6.70 (d, J = 5.4 Hz, 1H, CH), 6.95-8.21 (m, 7H, aromatic). MS: (m/z) ≈ 314 (1.8%), [M+2]+ m/z ≈ 316 (1%). Anal. Calcd for C₁₆H₁₁ClN₂O₃ (314.72): C, 61.06; H, 3.52; N, 8.90%. Found: C, 60.90; H, 3.30; N, 8.67%.

General procedure for the preparation of compounds (6a, b)

A mixture of (5a, b) (0.01 mol) and hydrazine hydrate (0.015 mol) was heated in boiling ethanol (30 mL) under reflux for 4 h. Then the mixture was poured into water. The precipitate was collected by filtration, dried and crystallized from the proper solvent to give (6a, b). Spectroscopic data for all the compounds are given below.

3-(Hydrazinylacetyl)-2-(pyridin-3-yl) quinazolin-4 (3H)-one (6a)

Yield 75%. Gray crystals. mp. 106-110 °C, IR (KBr, cm⁻¹): 1690, 1700 (2C = O), 3190 (NH) and 3300-3444 (NH₂). 
¹H NMR (DMSO-d₆, δ ppm): 3.55 (s, 2H, CH₂), 3.80 (s, 2H, NH₂, exchangeable with D₂O), 7.58-9.07 (m, 8H, aromatic), 10.49 (s, 1H, NH, exchangeable with D₂O). MS: (m/z) ≈ 295 (12%). Anal. Calcd for C₁₅H₁₃N₅O₂ (295.29): C, 61.01; H, 4.44; N, 23.72%. Found: C, 60.85; H, 4.20; N, 23.50%.

General procedure for the preparation of compounds (7c, d)

A solution of (3c, d) (44) (0.01 mol) in dry benzene (30 mL) and hydrazine hydrate (0.015 mol) was heated under reflux for 4 h. Then the mixture was poured into water. The precipitate was collected by filtration, dried and crystallized from the proper solvent to give (7c, d) (44). Spectroscopic data for all the compounds are given below.

3-Amino-2-(pyridin-4-yl) quinazolin-4 (3H)-one (7c)

Yield 75%, Black crystals. mp. 150-155 °C, IR (KBr, cm⁻¹): 1685 (C = O) and 3311-3420 (NH₂). 
¹H NMR (DMSO-d₆, δ ppm): 7.68-8.66 (m, 8H, aromatic), 10.08 (s, 2H, NH₂, exchangeable with D₂O). MS: (m/z) ≈ 238 (15%). Anal. Calcd for C₁₃H₁₀N₄O (238.24): C, 65.54; H, 4.23; N, 23.52%. Found: C, 65.32; H, 4.18; N, 23.40%.

3-Amino-2-[2-(phenylamino) phenyl] quinazolin-4 (3H)-one (7d)

Yield 85%. Yellow crystals. mp. 260-265 °C, IR (KBr, cm⁻¹): 1700 (C = O), 1311-3420 (NH₂). 
¹H NMR (DMSO-d₆, δ ppm): 3.60 (s, 2H, NH₂, exchangeable with D₂O), 6.68-8.54 (m, 13H, aromatic), 12.01 (s, 1H, NH, exchangeable with D₂O). MS: (m/z) ≈ 328 (20%). Anal. Calcd for C₂₀H₁₆N₄O (328.36): C, 73.15; H, 4.91; N, 17.06%. Found: C, 73.01; H, 4.75; N, 16.90%.

General procedure for the preparation of compounds (8c, d)

A solution of (7c, d) (44) (0.01 mol) was allowed to react with chloroacetyl chloride (0.01 mol) in refluxing pyridine about 2 h and then poured over ice/HCl. The precipitate was collected by filtration and crystallized from the proper solvent to give (8c, d). Spectroscopic data for all the compounds are given below.
2-Chloro-N-[4-oxo-2-(pyridin-4-yl) quinazolin-3 (4H)-yl] acetamide (8c)

Yield 70%. Yellow crystals. mp. > 300 °C, IR (KBr, cm⁻¹): 1698, 1715 (C = O) and 3175 (NH). ¹H NMR (DMSO-d₆, δ ppm): 4.78 (s, 2H, CH₂), 7.65-8.44 (m, 8H, aromatic), 11.87 (s, 1H, NH, exchangeable with D₂O). MS: (m/z) ≈ 314 (8%), [M + 2]+ m/z ≈ 316 (4%). Anal. Calcd for C₁₅H₁₁ClN₄O₂ (314.72): C, 57.24; H, 3.52; N, 17.80%. Found: C, 57.12; H, 3.40; N, 17.60%.

2-Chloro-N-{4-oxo-2-[2-(phenylamino) phenyl] quinazolin-3 (4H)-yl} acetamide (8d)

Yield 75%. Black crystals. mp. 190-195 °C, IR (KBr, cm⁻¹): 1677, 1690 (C = O) and 3230 (NH). ¹H NMR (DMSO-d₆, δ ppm): 4.90 (s, 2H, CH₂), 6.81-8.20 (m, 13H, aromatic), 11.90, 12 (2s, 2H, 2NH, exchangeable with D₂O). MS: (m/z) ≈ 404 (23%), [M + 2]+ m/z ≈ 406 (15%). Anal. Calcd for C₂₂H₁₇ClN₄O₂ (404.84): C, 65.27; H, 4.23; N, 13.84%. Found: C, 65.05; H, 4.18; N, 13.75%.

General procedure for the preparation of compounds (9c, d)

A solution of compounds (7c, d) (0.01 mol) and chloroacetamide (0.015 mol) was refluxed for 3 h in boiling N,N-dimethylformamide (DMF) (30 mL). Then the mixture was poured into water. The precipitate was collected by filtration, dried and crystallized from the proper solvent to give (9c, d). Spectroscopic data for all the compounds are given below.

6-(Pyridin-4-yl)-3,4-dihydro-2H-[1,2,4]triazino [2,3-c] quinazolin-2-one (9c)

Yield 65%. Black crystals. mp. > 300 °C, IR (KBr, cm⁻¹): 1710 (C = O) and 3189 (NH). ¹H NMR (DMSO-d₆, δ ppm): 3.76 (s, 2H, CH₂), 7.33-8.66 (m, 8H, aromatic), 10.70 (s, 1H, NH, exchangeable with D₂O). MS: (m/z) ≈ 277 (13%). Anal. Calcd for C₁₅H₁₁N₅O (277.28): C, 64.97; H, 4.00; N, 25.26%. Found: C, 64.70; H, 3.88; N, 25.07%.

6-[2-(Phenylamino) phenyl]-3,4-dihydro-2H-[1,2,4]triazino [2,3-c] quinazolin-2-one (9d)

Yield 85%. Yellow crystals. mp. 256-260 °C, IR (KBr, cm⁻¹): 1677 (C = O) and 3150 (NH). ¹H NMR (DMSO-d₆, δ ppm): 3.65 (s, 2H, CH₂), 6.87-7.96 (m, 13H, aromatic), 10.70, 11.30 (2s, 2H, 2NH, exchangeable with D₂O). MS: (m/z) ≈ 373 (5%). Anal. Calcd for C₂₀H₁₅N₅OS (373.43): C, 64.33; H, 4.05; N, 18.75%. Found: C, 64.12; H, 3.90; N, 18.50%.

General procedure for the preparation of compounds (10c, d)

A solution of compounds (7c, d) (44) (0.01 mol) and phenyl isothiocyanate (0.01 mol) was refluxed in boiling benzene (30 mL) for 3 h, then concentrated and crystallized from the proper solvent to give (10c, d). Spectroscopic data for all the compounds are given below.

1-[4-Oxo-2-(pyridin-4-yl) quinazolin-3 (4H)-yl]-3-phenylthiourea (10c)

Yield 90%. White crystals. mp. 195-200 °C, IR (KBr, cm⁻¹): 1685 (C = O) and 3190 (NH). ¹H NMR (DMSO-d₆, δ ppm): 7.33-8.96 (m, 13H, aromatic), 10.49, 11.01 (2s, 2H, 2NH, exchangeable with D₂O). MS: (m/z) ≈ 373 (5%). Anal. Calcd for C₂₀H₁₅N₅OS (373.43): C, 64.12; H, 3.90; N, 18.50%.

1-(4-Oxo-2-(2-(phenylamino) phenyl) quinazolin-3 (4H)-yl)-3-phenylthiourea (10d)

Yield 80%. Yellow crystals. mp. 200-205 °C, IR (KBr, cm⁻¹): 1700 (C = O) and 3200 (NH). ¹H NMR (DMSO-d₆, δ ppm): 7.09-8.24 (m, 18H, aromatic), 9.77, 9.86, 11.70 (3s, 3H, 3NH, exchangeable with D₂O). MS: (m/z) ≈ 463 (3%). Anal. Calcd for C₂₇H₂₁N₅OS (463.55): C, 69.96; H, 4.57; N, 15.11%. Found: C, 69.69; H, 4.48; N, 14.90%.

General procedure for the preparation of compounds (11c, d)

A solution of (7c, d) (0.01 mol) and benzoyl chloride (0.01 mol) in dry acetone (30 mL) was refluxed for 3 h. Excess solvent was removed and the precipitated solid obtained was crystallized from suitable solvent to obtain (11c, d). Spectroscopic data for all the compounds are given below.

N-[4-oxo-2-(pyridin-4-yl) quinazolin-3 (4H)-yl] benzamide (11c)

Yield 70%. Yellow crystals. mp. 180-185 °C, IR (KBr, cm⁻¹): 1677, 1690 (C = O)
mitochondrial dependent reduction of yellow MTT (3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) to purple formazan (46).

Procedure: All the following procedures were done in a sterile area using a Laminar flow cabinet biosafety class II level (Baker, SG403INT, Sanford, ME, USA). Cells were suspended in RPMI 1640 medium for HePG2- MCF7 and DMEM for A549. The media are supplemented with 1% antibiotic-antimycotic mixture (10,000 U/mL Potassium Penicillin, 10,000 µg/mL Streptomycin Sulfate and 25 µg/mL Amphotericin B), 1% L-glutamine and 10% fetal bovine serum and kept at 37 °C under 5% CO_{2}.

Cells were batch cultured for 10 days, then seeded at concentration of 10x10^{3} cells/well in fresh complete growth medium in 96-well Microtiter plastic plates at 37 °C for 24 h under 5% CO_{2} using a water jacketed Carbon dioxide incubator (Sheldon, TC2323, Cornelius, OR, USA). Media was aspirated, fresh medium (without serum) was added and cells were incubated either alone (negative control) or with different concentrations of sample to give a final concentration of (100-50-25-12.5-6.25-3.125-0.78 and 1.56 μg/mL). After 48 h of incubation, the medium was aspirated, 40 μL MTT salt (2.5 μg/mL) were added to each well and incubated for a further four hours at 37 °C under 5% CO_{2}.

To stop the reaction and dissolving the formed crystals, 200 μL of 10% Sodium dodecyl sulphate (SDS) in deionized water was added to each well and incubated overnight at 37 °C. A positive control which composed of 100 µg/mL was used as a known cytotoxic natural agent who gives 100% lethality under the same conditions (47, 48).

The absorbance was then measured using a microplate multi-well reader (Bio-Rad Laboratories Inc., model 3350, Hercules, California, USA) at 595 nm and a reference wavelength of 620 nm. A statistical significance was tested between samples and negative control (cells with vehicle) using independent t-test by SPSS 11 program. DMSO is the vehicle used for dissolution of plant extracts and its final concentration in the cells was less than 0.2%. The percentage of change in viability was calculated according to the formula:

1 H NMR (DMSO-d_{6}, δ ppm): 7.31-8.42 (m, 13H, aromatic), 12.01 (s, 1H, NH, exchangeable with D_{2}O). MS: (m/z) ≈ 342 (17%). Anal. Calcd for C_{20}H_{14}N_{4}O_{2} (342.35): C, 70.17; H, 4.12; N, 16.37%. Found: C, 70.02; H, 3.90; N, 16.17%.

N-(4-oxo-2-(2-phenylamino) phenyl) quinazolin-3 (4H)-yl benzamide (11d)

Yield 80%. Yellow crystals. mp. > 300 °C, IR (KBr, cm^{-1}): 1687, 1693 (2C = O) and 3177 (NH). 1 H NMR (DMSO-d_{6}, δ ppm): 7.16-8.45 (m, 18H, aromatic), 11.01, 12.01 (2s, 2H, 2NH, exchangeable with D_{2}O). MS: (m/z) ≈ 432 (10%). Anal. Calcd for C_{27}H_{20}N_{4}O_{2} (432.47): C, 74.98; H, 4.66; N, 12.95%. Found: C, 74.70; H, 4.50; N, 12.80%.

General procedure for the preparation of compounds (12c, d)

A solution of (11c, d) (0.01 mol) with ammonium acetate (0.01 mol) in acetic acid (30 mL) was heated under reflux for 3 h, then poured into water. The precipitated solid after concentration and cooling was collected by filtration and crystallized from suitable solvent to give (12c, d). Spectroscopic data for all the compounds are given below.

2-phenyl-5-(pyridin-4-yl) [1, 2, 4] triazolo [1, 5-c] quinazoline (12c)

Yield 65%. Gray crystals. mp. 215-220 °C, 1 H NMR (DMSO-d_{6}, δ ppm): 7.41-8.75 (m, 13H, aromatic). MS: (m/z) ≈ 323 (33%). Anal. Calcd for C_{20}H_{13}N_{5}O (323.35): C, 74.29; H, 4.05; N, 21.66%. Found: C, 74.11; H, 3.89; N, 21.56%.

N-phenyl-2-(2-phenyl-[1, 2, 4] triazolo [1, 5-c] quinazolin-5-yl) aniline (12d)

Yield 85%. Yellow crystals. mp. 240-245 °C, IR (KBr, cm^{-1}): 3177 (NH). 1 H NMR (DMSO-d_{6}, δ ppm): 6.69-8.28 (m, 18H, aromatic), 13 (s, 1H, NH, exchangeable with D_{2}O). MS: (m/z) ≈ 413 (11%). Anal. Calcd for C_{27}H_{19}N_{5} (413.47): C, 78.43; H, 4.63; N, 16.94%. Found: C, 78.22; H, 4.48; N, 16.80%.

Cytotoxic effect on human cell line (HePG2 – MCF 7 - A549)

Cell viability was assessed by the mitochondrial dependent reduction of yellow MTT (3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) to purple formazan (46).
(Reading of extract/Reading of negative control)-1) x 100. A probit analysis was carried for IC\textsubscript{50} and IC\textsubscript{90} determination using SPSS 11 program.

Molecular docking study

All docking studies were performed using "Internal Coordinate Mechanics" (Molsoft ICM 3.5-0a).

Preparation of small molecule

Compounds 2d, 3a, 3b, 3d, 4a, 4b, 5a, 5b, 6a, 6b, 7c, 7d, 8d, 9c, 9d, 10c, 10d, 11c, 11d, 12c, 12d were built in Chem Draw Ultra version 11.0 and their energy minimized through Chem3D Ultra version 11.0/MM2, Jop Type: minimum RMS Gradient of 0.100 and saved as MDL Mol File (*.Mol).

Generation of Ligand and Enzyme Structures

The crystal structures of EGFR (PDB code: 1M17) complex were retrieved from the RCSB Protein Data Bank (http://www.rcsb.org/pdb/home/home.do).

We inspect the quality of the PDB file that was used using the PROSESS (Protein Structure Evaluation Suite & Server) (http://www.prosess.com/index.php) (Figure 1, 2). In our investigation, the 3D-coordinates in X-ray crystal structure of EGFR in complex with the ligand, Erlotinib (PDB entry 1M17) was used as the receptor model in EGFR docking simulation (Figure 3). All bound waters ligands and cofactors were removed from the protein.

Docking using Molsoft ICM 3.5-0a program

The conversion of our PDB file into an ICM object involves the addition of hydrogen bonds, assignment of atom types and charges from the residue templates, then perform ICM small molecule docking through setup the receptor, review and adjust binding site makes receptor maps, then start docking simulation, followed by displaying the results. ICM stochastic global optimization algorithm attempts to find the global minimum of the energy function that include five grid potentials describing the interaction of the flexible ligand with the receptor and internal conformational energy of the ligand, during this process a stack of alternative low energy conformations is saved. All inhibitors were compared according to the best binding free energy (minimum) obtained among all the run.

Results and Discussion

Chemistry

Different acid chlorides namely, pyridine-3-carbonyl chloride, (2E)-3-(furan-2-yI) prop-2-enoyl chloride, pyridine-4-carbonyl chloride and 2-(phenylamino) benzoyl chloride 2a-d,
respectively reacted with anthranilic acid to produce 2-[substituted]-4H-3, 1-benzoxazin-4-one 3a-d (Scheme 1). Compounds 3a, b reacted with formamide to give 2-(substituted) quinazolin-4(3H)-one 4a, b which reacted with chloroacetyl chloride to give 3-(chloroacetyl)-2-[substituted] quinazolin-4(3H)-one 5a, b (Scheme 1). Compounds 5a, b reacted with hydrazine hydrate to give 3-(hydrazinylacetyl)-2-[substituted] quinazolin-4(3H)-one 6a, b (Scheme 1). The structures of all of the newly synthesized derivatives were established via the elemental analyses and IR, 1H NMR and mass spectral data. IR spectra of the compounds 6a,

**Overall Quality**

Overall Quality Index 6.5 was obtained using the following equation:

Unscaled overall score = 0.5*(Lowest quality index) + 0.5*(Average of the remaining quality indices).

**Contributing quality categories:**

- **Covalent Bond Quality = 6.5**
  - (Details)

- **Non-Covalent/Packing Quality = 6.5**
  - (Details)

*Figure 2.* Quality of the PDB file that was used using the Prosess.

*Figure 3.* Binding model of erlotinib in to active pocket of EGFR receptor.
b exhibited characteristic absorption bands in the range 3174-3444 cm\(^{-1}\) due to the respective NH and NH\(_2\). \(^1\)H NMR (DMSO-d\(_6\)) spectra of compounds 6a, b revealed signals at \(\delta\) 3.70-3.80 ppm and 10.49-11.21 ppm representing NH\(_2\) and NH groups, respectively.

Also, compounds 3c, d reacted with hydrazine hydrate to give 3-amino-2-(substituted) quinazolin-4(3H)-one 7c, d (Scheme 1) which reacted with chloroacetyl chloride to give 2-chloro-N-[4-oxo-2-(substituted) quinazolin-3(4H)-yl] acetamide 8c, d (Scheme 2). IR spectra of the derivatives 8c, d exhibited the disappearance of the characteristic band of NH\(_2\) group and showed the presence of bands at the range 1690-1715 cm\(^{-1}\) corresponding to CO groups.

Finally, compounds 7c, d reacted with chloroacetamide, phenyl isothiocyanate and benzoyl chloride to give compounds 9-11 (c, d), respectively (Scheme 2). Compounds 11c, d reacted with ammonium acetate to give N-phenyl-2-(substituted-[1, 2, 4] triazolo [1, 5-c] quinazolin 12c, d (Scheme 2).

\textit{In-vitro Antitumor Screening against A549, HePG2 and MCF7 cell lines}

The cytotoxic potencies of compounds 2d, 3a, 3b, 3d, 4a, 4b, 5a, 5b, 6a, 6b, 7c, 7d, 8d, 9c, 9d, 10c, 10d, 11c, 11d, 12c, 12d against a panel of three human tumor cell lines were investigated and compared with the reference drug doxorubicin (Table 1). The human tumor cell line panel consisted of breast carcinoma (MCF7), liver carcinoma (HePG2) and lung carcinoma (A549) using MTT assay. Tumor cells were incubated either alone (negative control) or with different concentrations of the test compounds (100–50–25–12.5–6.25–3.125–0.78 and 1.56 \(\mu\)M). With regard to sensitivity against individual cell lines, this class is more effective on hepatocellular carcinoma more than other two cell lines. Compound 10c showed selective potency.
against A549 cell line (IC\textsubscript{50} = 72.2) as shown in Table 2. However, compounds 11d and 9d showed selective potency against HePG2 cell line with IC\textsubscript{50} 53.4 and 66.7 µg/mL, respectively, as shown in Table 3 and compounds 4b and 8d for MCF7 cell line with IC\textsubscript{50} 81.9 and 90.5 µg/mL, respectively as shown in Table 4. However, compounds 7d, 3d and 2d showed effectiveness against all cell lines with IC\textsubscript{50} (62.6, 85.0 and 92.1 µg/mL), (65.1, 82.9 and 77.6 µg/mL) and (75.8, 81.9 and 86.1 µg/mL) for HePG2, MCF7 and A549 as shown in Table 3, 4, 2, respectively. In addition, compounds 10d and 6a displayed selective potency against A549 and HePG2 cell lines with IC\textsubscript{50} of 88.4, 92.1 and 45.6, 32.8 µg/mL concentrations, respectively as shown in Table 2, 3. While compound 12d displayed selective potency against HePG2 and MCF7 cell lines with IC\textsubscript{50} 33.3 and 87.4 µg/mL, respectively. Moreover, Compounds 6a and 12d considered the most potent compounds against the HePG2 cell line, while compounds 7d, 3d, 9d, 10d, 11d and 2d possessed moderate antitumor activity compared to positive control doxorubicin.

**Docking analysis**

Compounds 2d, 3a, 3b, 3d, 4a, 4b, 5a, 5b, 6a, 6b, 7c, 7d, 8d, 9c, 9d, 10c, 10d, 11c, 11d, 12c, 12d were used for docking study. All the calculations were performed using “Internal Coordinate Mechanics” (Molsoft ICM 3.5-0a). Molecular modeling docking studies is performed and ICM score values (49-51) combined with hydrogen bonds formed with the surrounding

Table 1. Positive control Adrinamycin (Doxorubicin) [Mw = 579.99].

|          | IC\textsubscript{50} (µg/mL) |
|----------|-----------------------------|
| HEPG2    | 21.6                        |
| A549     | 28.3                        |
| MCF7     | 26.1                        |
| PC3      | 23.8                        |
Table 2. Sample was tested against the human tumor cell line A549 [Lung carcinoma cell line].

| Sample Code | IC_{90} (µg/mL) | IC_{50} (µg/mL) | Remarks |
|-------------|-----------------|-----------------|---------|
| 2d          | 86.1            | 137             | 57.8% at 100ppm |
| 3a          | 20.6% at 100ppm | 32.8% at 100ppm |         |
| 3b          | 65.1% at 100ppm | 22.3% at 100ppm |         |
| 3d          | 20.7% at 100ppm |                 |         |
| 4a          | 28.2% at 100ppm |                 |         |
| 4b          | 0% at 100ppm    |                 |         |
| 5a          | 92.1            | 145.4           | 51.7% at 100ppm |
| 5b          | 1.4% at 100ppm  |                 |         |
| 6a          | 44.9% at 100ppm |                 |         |
| 6b          | 0% at 100ppm    |                 |         |
| 7c          | 78.6% at 100ppm |                 |         |
| 7d          | 69.6% at 100ppm |                 |         |
| 8d          | 54.5% at 100ppm |                 |         |
| 9c          | 45.6% at 100ppm |                 |         |
| 9d          | 13.9% at 100ppm |                 |         |
| 10c         | 69.6% at 100ppm |                 |         |
| 10d         | 4.3% at 100ppm  |                 |         |
| 11c         | 0% at 100ppm    |                 |         |
| 11d         | 0% at 100ppm    |                 |         |
| 12c         | 40.8% at 100ppm |                 |         |
| 12d         | 19.8% at 100ppm |                 |         |
| DMSO        | 5% at 100ppm    |                 |         |
| Negative control | 0%         |                 |         |

IC_{90}: Lethal concentration of the sample which causes the death of 90% of cells in 48 h.
IC_{50}: Lethal concentration of the sample which causes the death of 50% of cells in 48 h.

Table 3. Sample was tested against the human tumor cell line HePG2 [Human hepatocellular carcinoma cell line].

| Sample Code | IC_{90} (µg/mL) | IC_{50} (µg/mL) | Remarks |
|-------------|-----------------|-----------------|---------|
| 2d          | 75.8            | 120.9           | 70.5% at 100ppm |
| 3a          | -47% at 100ppm  |                 |         |
| 3b          | 35.3% at 100ppm |                 |         |
| 3d          | 78.6% at 100ppm |                 |         |
| 4a          | 21.3% at 100ppm |                 |         |
| 4b          | 2.3% at 100ppm  |                 |         |
| 5a          | 0% at 100ppm    |                 |         |
| 5b          | 0% at 100ppm    |                 |         |
| 6a          | 100% at 100ppm  |                 |         |
| 6b          | 5.7% at 100ppm  |                 |         |
| 7c          | 94.2% at 100ppm |                 |         |
| 7d          | 84.5% at 100ppm |                 |         |
| 8d          | 40.6% at 100ppm |                 |         |
| 9c          | 4.3% at 100ppm  |                 |         |
| 9d          | 84.2% at 100ppm |                 |         |
| 10c         | 0% at 100ppm    |                 |         |
| 10d         | 94.2% at 100ppm |                 |         |
| 11c         | 0% at 100ppm    |                 |         |
| 11d         | 0% at 100ppm    |                 |         |
| 12c         | 85.4% at 100ppm |                 |         |
| 12d         | 22.5% at 100ppm |                 |         |
| DMSO        | 1% at 100ppm    |                 |         |
| Negative control | 0%         |                 |         |

IC_{90}: Lethal concentration of the sample which causes the death of 90% of cells in 48 h.
IC_{50}: Lethal concentration of the sample which causes the death of 50% of cells in 48 h.
Table 4. Sample was tested against the human tumor cell line MCF7 [Human Caucasian breast adenocarcinoma].

| Sample Code | IC$_{50}$ (µg/mL) | IC$_{90}$ (µg/mL) | Remarks |
|-------------|------------------|------------------|---------|
| 2d          | 81.9             | 131.7            | 61.9% at 100ppm |
| 3a          | 82.9             | 131.8            | 50.2% at 100ppm |
| 3b          | 81.9             | 132.1            | 33.7% at 100ppm |
| 3d          | 85.0             | 132.2            | 10.7% at 100ppm |
| 3a          | 90.5             | 143.1            | 42.9% at 100ppm |
| 3b          | 9.8% at 100ppm   | 4.4% at 100ppm   |
| 3d          | 60.7% at 100ppm  | 9.8% at 100ppm   |
| 4a          | 55.4% at 100ppm  | 56.5% at 100ppm  |
| 4b          | 44.7% at 100ppm  | 52.9% at 100ppm  |
| 5a          | 58.6% at 100ppm  | 60.7% at 100ppm  |
| 5b          | 10.7% at 100ppm  | 55.4% at 100ppm  |
| 6a          | 55.4% at 100ppm  | 60.7% at 100ppm  |
| 6b          | 10.7% at 100ppm  | 52.9% at 100ppm  |
| 7c          | 50.2% at 100ppm  | 44.7% at 100ppm  |
| 7d          | 61.7% at 100ppm  | 52.9% at 100ppm  |
| 8d          | 44.7% at 100ppm  | 52.9% at 100ppm  |
| 9c          | 55.4% at 100ppm  | 52.9% at 100ppm  |
| 9d          | 44.7% at 100ppm  | 52.9% at 100ppm  |
| 10c         | 44.5% at 100ppm  | 52.9% at 100ppm  |
| 10d         | 2.9% at 100ppm   | 52.9% at 100ppm  |
| 11c         | 44.5% at 100ppm  | 52.9% at 100ppm  |
| 11d         | 52.9% at 100ppm  | 52.9% at 100ppm  |
| 12c         | 52.9% at 100ppm  | 52.9% at 100ppm  |
| 12d         | 52.9% at 100ppm  | 52.9% at 100ppm  |
| DMSO        | 57.5% at 100ppm  | 52.9% at 100ppm  |
| Negative control | 3% at 100ppm   | 0%                   |

IC$_{50}$: Lethal concentration of the sample which causes the death of 50% of cells in 48 h.
IC$_{90}$: Lethal concentration of the sample which causes the death of 90% of cells in 48 h.

amino acid residues help to predict the correct binding geometry for each binder at the active site. The molecular docking was performed into the hydrophobic site of EGFR with the aim to predict antitumor activity of compounds of the study (2d, 3a, 3b, 3d, 4a, 4b, 5a, 5b, 6a, 6b, 7c, 7d, 8d, 9c, 9d, 10c, 10d, 11c, 11d, 12c, 12d) against A549, HePG2 and MCF7 cell lines.

As shown in Table 5, Erlotinib (ligand) reveals ICM score of -90.54 and forms 3 H bonds with Met769, Cys773 and Gln767 (Figure 3), the target compounds elicited binding affinities (ICM scores range from -40.86 to -73.01). Compounds 10d, 12d, 8d, 11d, 9d showed activity probably due to their high ICM scores which ranged from -62.33 to -73.01 however compounds 4a, 6b, 7c, 5a are biologically inactive; they have low ICM scores of ranges from -40.86 to -50.44.

Conclusion
A novel series of some new quinazolin derivatives were synthesized and evaluated as antitumor agents against human carcinoma cell lines (HePG2– MCF7– A549). The antitumor activity results exhibited that, compounds 2d, 3d, 6a, 7d, 10c, 10d showed significant and selective inhibition for A549 (Table 2) (Figure 4). On the other hand, compounds 2d, 3d, 4a, 6b, 7d, 10d, 11d, 12d showed significant and selective inhibition for HePG2 (Table 3) (Figure 5). Compounds 2d, 3d, 4b, 7d, 8d, 12d showed significant inhibition for MCF7 (Table 4) (Figure 6) comparing to the used reference drug Doxorubicin. Docking result shows that compound 10d have high ICM score -73.01 forms 3 H bonds with Lys721 and Asp831 (Figure 7). However, compound 5a has low ICM scores -40.86 forms 3 H bonds with Asn784, Ile 785 and Gly 959 (Figure 8).
### Table 5. Docking of compounds on EGFR.

| Cpd No | ICM score (ΔG) | No. of H-bonds | Atom of ligand involved | Amino acid residues forming the hydrogen bonds | Length of H-bond Å |
|--------|----------------|----------------|------------------------|---------------------------------------------|-------------------|
| 2d     | -50.98         | 1              | m of M o1              | Lys721                                      | 1.66              |
| 3a     | -54.01         | 2              | m of M n1 m of M n2    | Thr766 Met769                               | 2.65  1.97        |
| 3b     | -54.34         | 1              | m of M o3              | Ile758                                      | 2.73              |
| 3d     | -56.61         | 1              | m of M o2              | Glu958                                      | 1.64              |
| 4a     | -50.44         | 3              | m of M n3 m of M o1 m of M h5 | Lys721 Met769 Thr766 | 2.62  2.11  2.67 |
| 4b     | -58.07         | 2              | m of M o2 m of M o1    | Thr766 Met769                               | 2.65  1.35        |
| 5a     | -40.86         | 3              | m of M o2 m of M n2    | Asn784 Ile 785 Gly 959                      | 2.08  1.82  2.37  |
| 5b     | -53.34         | 2              | m of M n2 m of M o2    | Gly 786 Gln 788                             | 2.27  1.96        |
| 6a     | -50.45         | 6              | m of M n4 m of M n5 m of M h13 m of M h11 m of M h12 | Lys721 Lys721 Glu738 Asp831 Asp831 Asp831 | 2.72  1.59  2.31  2.40  2.29  2.61 |
| 6b     | -49.58         | 6              | m of M n3 m of M n2 m of M h12 m of M h13 m of M h14 m of M h12 | Asp 783 Gln 958 Lys 782 Lys 782 Lys 782 Asp 783 | 2.33  2.32  1.07  1.22  2.28  |
| 7c     | -42.33         | 4              | m of M o1 m of M n3 m of M n2 m of M n2 | Gln 677 Arg 752 Arg 807 Arg 807 | 2.32  1.94  2.62  2.50 |
| 7d     | -56.93         | 3              | m of M h16             | Lys 782                                     | 2.39  1.46  2.19  |
| 8d     | -66.51         | 2              | m of M o2 m of M o1    | Thr766 Met769                               | 2.78  2.05        |
| 9c     | -59.05         | 1              | m of M o1              | Met769                                      | 1.98              |
| 9d     | -62.33         | 1              | m of M h15             | Asp 783                                     | 1.55              |
| 10c    | -54.63         | 1              | m of M h10             | Asp 783                                     | 1.81              |
| 10d    | -73.01         | 3              | m of M o1 m of M h15 m of M h16 | Lys721 Asp831 Asp831 | 2.18  2.89  2.38 |
| 11c    | -50.55         | 1              | m of M o1              | Gln958                                      | 1.53              |
| 11d    | -66.26         | 2              | m of M o2 m of M h15   | Gly 786 Gln 961                             | 1.34  1.39        |
| 12c    | -56.70         | 1              | m of M n5              | Gln958                                      | 2.46              |
| 12d    | -68.71         | 2              | m of M n3 m of M h9    | Gly786 Gln961                               | 2.13  1.35        |
| Erlotinib | -90.54       | 3              | m of M n4 m of M h7    | Met769 Cys773 Gln767                        | 1.90  1.75  2.01  |
**Structure-activity relationship**

The activity of the tested compounds could be correlated to structure variation and modifications. By investigating the variation in the selectivity of the tested compounds over the three cell lines, it was revealed that: (1) the activity of the designed compounds is dependent upon the substituent at the R positions. The obtained screening results showed that, nearly all of the compounds containing \(N\)-phenyl aniline showed significant inhibition for the tested three cell lines (2). Cyclization of
Figure 5. Probit Transformed Responses of some compounds against the human tumor cell line HePG2 [Human hepatocellular carcinoma cell line].
compound 2d afforded compound 3d (44) with the increase in activity against A549 with IC\textsubscript{50} values 86.1 and 77.6 µg/mL, respectively and for HePG2 with IC\textsubscript{50} values 75.8 and 65.1 µg /mL, respectively, while result in a little decrease in activity against MCF7 with IC\textsubscript{50} values 81.9 and 82.9 µg/mL, respectively (Table 2, 3, 4) (3). Compounds which have-CSNHPPh group were found to be more active in the biological activities discussed in this paper than compounds which have –H. These results suggest that electron withdrawing hydrophilic
substitutes (e.g., -CSNHPh) are more desirable for achieving the desired activity. Also, certain isothiocyanates have also been shown to bind to the mutated p53 proteins found in many types of tumors, causing an increase in the rate of cell death (4). Compounds which have CO₂CH₂Cl yielded the least active series of compounds in this study. Which suggests that electron withdrawing groups with lipophilic characteristics like –Cl may not be an ideal substitution to get the good activity of the designed compounds.

References

(1) Ammar YA, Mohamed Y, El-Sharief A, El-Gaby M and Abbas S. Synthesis of some biologically active 4 (3H)-quinazolinones derived from 2, 3-pyridine dicarboxylic anhydride. *Chem. Sci. J.* (2011) 2:15.

(2) Grover G and Kini SG. Synthesis and evaluation of new quinazolone derivatives of nalidixic acid as potential antibacterial and antifungal agents. *Eur. J. Med. Chem.* (2006) 41: 256-262.

(3) Waisser K, Gregor J, Dostál H, Kuneš J, Kubícová L, Klimešová V and Kaustová J. Influence of the replacement of the oxo function with the thioxo group on the antimycobacterial activity of 3-aryl-6,
8-dichloro-2H-1, 3-benzoazine-2, 4 (3H)-diones and 3-aryl quinazoline-2, 4 (1H, 3H)-diones. *Farmaco.* (2001) 56: 803-807.

(4) Tiwari AK, Singh VK, Bajpai A, Shukla G, Singh S and Mishra AK. Synthesis and biological properties of 4-(3H)quinazolone derivatives. *Eur. J. Med. Chem.* (2007) 42: 1234-1238.

(5) Martin TA, Wheeler AG, Majewski RF and Corrigan JR. Sulfinilamidoquinazolines. *J. Med. Chem.* (1964) 7: 812-814.

(6) Alagarsamy V and Pathak US. Synthesis and antihypertensive activity of novel 3-benzyl-2-substituted-3H-[1, 2, 4] triazolo [5, 1-b] quinazolin-9-ones. *Bioorg. Med. Chem.* (2007) 15: 3457-3462.

(7) Garcia J, Somanathan R, Rivero I, Aguirre G and Hellberg L. Synthesis of deuterium-labeled antihypertensive 3-(4-phenyl-1-piperazinyl)-propyl-2, 4-quinazolinedione. *Synthetic Commun.* (2000) 30: 2707-2711.

(8) Jen T, Dielen B, Dowalo F, Van Hoeven H, Bender P and Loew B. Synthesis of pyrrolo[2, 3-b] quinazolin-5(4H)-ones as a new class of h1-antihistamine agents. *J. Med. Chem.* (1973) 16: 633-637.

(9) Alagarsamy V, Giridhar R and Yadav M. Synthesis and pharmacological investigation of novel 1-substituted-4-(4-substituted phenyl)-4H-[1, 2, 4] triazolo [5, 1-b] quinazoline and related compounds: Their synthesis, cytotoxicity and inhibition of tubulin polymerization. *J. Med. Chem.* (2000) 43: 4479-4487.

(10) Alagarsamy V, Giridhar R and Yadav MR. Synthesis and h1-antihistaminic activity of some novel 1-substituted-4-(3-methylphenyl)-1, 2, 4-triazolo [4, 3-a] quinazolin-5(4H)-ones *Indian J. Pharm. Sci.* (2009) 44: 2184-2189.

(11) Alagarsamy V, Giridhar R and Yadav MR. Corrigendum to synthesis and pharmacological investigation of novel 1-substituted-4-phenyl-1, 2, 4-triazolo [4, 3-a] quinazolin-5(4H)-ones as a new class of h1-antihistaminic agents. *Bioorg. Med. Chem. Lett.* (2005) 15: 3316.

(12) Alagarsamy V, Giridhar R and Yadav MR. Synthesis and pharmacological investigation of novel 1-substituted-4-phenyl-1, 2, 4-triazolo[4, 3-a] quinazolin-5(4H)-ones as a new class of h1-antihistaminic agents. *Acta Pharm.* (2003) 53: 127-138.

(13) Alagarsamy V, Yadav MR and Giridhar R. Synthesis and pharmacological investigation of novel 1-alkyl-4-(4-substituted alkylheteroaryl)-1, 2, 4-triazolo [4, 3-a] quinazolin-5(4H)-ones as a new class of h1-antihistaminic agents. *Arzneimittelforschung* (2006) 56: 834-841.

(14) Dempcy RO and Skibo EB. Kinetic studies of 2-(2′-haloethyl) and 2-ethyl substituted quinazolinoine alkylating agents. Acid-catalyzed dehydralogenation and alklylation involving a quinazolinoine prototropic tautomer. *Bioorg. Med. Chem. Lett.* (1993) 1: 39-43.

(15) Abdel-Rahman T. Synthesis of some new biologically active 2, 3-disubstituted quinazolin-4-ones. *Boll. Chim. Farm.* (1998) 137: 43-47.

(16) El-Bayouki KA, Aly MM, Mohamed YA, Basyouni W and Abbas SY. Novel 4 (3H)-quinazolinone containing biologically active thiazole, pyrazole, 1, 3-dihzole, pyridine, chromone, pyrazolopyrimidine and pyranochromene of expected biological activity. *World J. Chem.* (2009) 4: 161-170.

(17) Hour M-J, Huang L-J, Kuo S-C, Xia Y, Bastow K, Nakanishi Y, Hamel E and Lee K-H. 6-alkylamino- and 2, 3-dihydro-3′-methoxy-2-phenyl-4-quinazolinones and related compounds: Their synthesis, cytotoxicity and inhibition of tubulin polymerization. *J. Med. Chem.* (2000) 43: 459-462.

(18) Alagarsamy V, Revathi R, Meena S, Ramesh K, Rajasekaran S and De Clercq E. Anti-HIV, antibacterial and antifungal activities of some 2, 3-disubstituted quinazolin-4(3H)-ones. *Indian J. Pharm. Sci.* (2004) 66: 459-462.

(19) Bennet CJ. Synthesis and biological investigation of antihypertensive 3-benzyl-2, 3-dihydro-3′-methoxy-2-phenyl-4-quinazolinones. *Synthetic Commun.* (2006) 36: 785-789.
evaluation of some new quinazoline derivatives. *Eur. J. Med. Chem.* (2010) 45: 4947-4952.

(27) Mosaad S, Mohammed K, Ahmed M and Abdel-Hamid S. Synthesis of certain new 6-iodoquinazolines as potential antitubercular agents. *J. Appl. Sci.* (2004) 4: 302-307.

(28) Cao S-L, Feng Y-P, Jiang Y-Y, Liu S-Y, Ding G-Y and Li R-T. Synthesis and in-vitro antitumor activity of 4(3h)-quinazolinone derivatives with diithiocarbamate side chains. *Bioorg. Med. Chem. Lett.* (2005) 15: 1915-1917.

(29) Joseph A, Pai A, Kedar T, Thomas AT and Singla R. Synthesis and antitumor activity of some novel 3-(1,3,4-thiadiazol-2-yl)-quinazolin-4(3h)-ones. *Orbital: Electron. J. Chem.* (2010) 2: 158-167.

(30) Raghavendra NM, Thampi P, Gurubasavarajswamy PM and Sriman D. Synthesis, antitubercular and anticancer activities of substituted furyl-quinazolin-3(4h)-ones. *Arch. Pharm.* (2007) 340: 635-641.

(31) Skelton L, Ormerod M, Titley J, Kimbell R, Brunton L and Jackman A. A novel class of lipophilic quinazoline-based folic acid analogues: Cytotoxic agents with a folate-independent locus. *Br. J. Cancer.* (1999) 79: 1692.

(32) Xia Y, Yang Z-Y, Hower M-J, Kuo S-C, Xia P, Bastow KF, Nakanishi Y, Nampoothiri P, Hackl T and Hamel E. Synthesis and biological evaluation of substituted 2-aryl quinazolinones. *Bioorg. Med. Chem. Lett.* (2001) 11: 1193-1196.

(33) Zhang P, Terefenko EA, Fensome A, Zhang Z, Zhu Y, Cohen J, Winneker R, Wrobel J and Yareldy J. Potent nonsteroidal progesterone receptor agonists: Synthesis and sar study of 6-aryl benzoxazines. *Bioorg. Med. Chem. Lett.* (2002) 12: 790-791.

(34) Lu DS, Belzile J, Bready JV, Coxon A, DeMelfi T, Doerr N, Estrada J, Flynn JC, Flynn SR and Graceffia RF. Novel 2, 3-dihydro-1,4-benzoxazines as potent and orally bioavailable inhibitors of tumor-driven angiogenesis. *J. Med. Chem.* (2008) 51: 1695-1705.

(35) Madhavan GR, Chakrabarti R, Anantha Reddy K, Rajesh B, Balraj V, Bheema Rao P, Rajagopalan R and Iqbal J. Dual ppar-α and -γ activators derived from novel benzoxazine containing thiazolidinediones having anti-diabetic and hypolipidemic potential. *Bioorg. Med. Chem.* (2006) 14: 584-591.

(36) Zhou D, Harrison BL, Shah U andree TH, Hornby GA, Scerni R, Schechter LE, Smith DL, Sullivan KM and Mewshaw RE. Studies toward the discovery of the next generation of antidepressants. Part 5: 3,4-dihydro-2H-benzo [1, 4] oxazine derivatives with dual 5-htg receptor and serotonin transporter affinity. *Bioorg. Med. Chem. Lett.* (2006) 16: 1338-1341.

(37) Pritchard KM, Al-Rawi J and Bradley C. Synthesis, identification and antiplatelet evaluation of 2-morpholino substituted benzoxazines. *Eur. J. Med. Chem.* (2007) 42: 1200-1210.

(38) Arteaga CL and Johnson DH. Tyrosine kinase inhibitors-zd1839 (irressa). *Curr. Opin. Oncol.* (2001) 13: 491-498.

(39) Barlesi F, Tchouhadjian C, Doodoli C, Villani P, Greilrier L, Kleibauer JP, Thomas P and Astoul P. Gefitinib (zd1839, irressa) in non-small-cell lung cancer: A review of clinical trials from a daily practice perspective. *Fundam. Clin. Pharmacol.* (2005) 19: 385-393.

(40) Dhillon S and Wagstaff AJ. Lapatinib. *Drugs* (2007) 67: 2101-2110.

(41) El-Azab AS, Al-Omar MA, Abdel-Aziz AA-M, Abdel-Aziz NI, El-Sayed MA-A, Aleisa AM, Sayed-Ahmed MM and Abdel-Hamide SG. Design, synthesis and biological evaluation of novel quinazoline derivatives as potential antitumor agents: Molecular docking study. *Eur. J. Med. Chem.* (2010) 45: 4188-4198.

(42) Ganjoo KN and Wakelee H. Review of erlotinib in the treatment of advanced non-small cell lung cancer. *Biol. Targets Ther.* (2007) 1: 335.

(43) Kopper L. Lapatinib: A sword with two edges. *Pathol. Oncol. Res.* (2008) 14: 1-8.

(44) Walaas SE, Neama AM, Weam SE, Emad MMK and Khaled M. Synthesis and evaluation of cytotoxic activities of novel quinazoline derivatives. *Int. J. Res. Pharm. Sci.* (2015) 6 (1): 62-74.

(45) Fatihalla OAE-FM, Kassem EM, Ibrahim NM and Kamel MM. Synthesis of some new quinazolin-4-one derivatives and evaluation of their antimicrobial and anti-inflammatory effects. *Acta Pol. Pharm.* (2008) 65: 11-20.

(46) Mosmann T. Rapid colorimetric assays for cellular growth and survival: Application to proliferation and cytotoxicity assays. *J. Immunol. Methods.* (1983) 65: 55-63.

(47) El-Meneshawi BS, Fayad W, Mahmoud K, El-Hallouy SM, El-Manawy M, Olofsson MH and Linder S. Screening of natural products for therapeutic activity against solid tumors. *Indian J. Exp. Biol.* (2010) 48.

(48) Thabrew M, Hughes RD and Mcfarlane IG. Screening of hepatoprotective plant components using a hepg2 cell cytotoxicity assay. *J. Pharm. Pharmacol.* (1997) 49: 1132-1135.

(49) Anderson A and Weng Z. Vrdv: Applying virtual reality visualization to protein docking and design. *J. Mol. Graph. Model.* (1999) 17: 180-186.

(50) Cavasotto CN and Abagyan RA. Protein flexibility in ligand docking and virtual screening to protein kinases. *J. Mol. Biol.* (2004) 337: 209-225.

(51) Halperin I, Ma B, Wolfson H and Nussinov R. Principles of docking: An overview of search algorithms and a guide to scoring functions. *Proteins* (2002) 47: 409-443.

This article is available online at http://www.ijpr.ir