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Sulfamic Acid as an Efficient, Cost-Effective, Eco-Friendly and Recyclable Solid Acid Catalyst for the Synthesis of a Novel Series of 2,3-Dihydroquinazolin-4(1*H*)-ones and Antitumor Evaluation.

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ABSTRACT

A new series of 4(1H)-quinazolinone derivatives was synthesized through one-pot reaction of isatoic anhydride, amines and aldehydes. Sulfamic acid efficiently catalyzes the three-component reaction to afford the corresponding 4(1H)-quinazolinones in high yields. The reaction occurred under stirring in deionized water at room temperature or in ethanol under reflux conditions. The synthesized compounds were tested against HepG2, MCF-7 and A549 tumor cell lines. The cytotoxic activity for the tested compounds showed that four compounds revealed good IC_{50} values compared with the values of standard drug doxorubicin.

Keywords: Quinazolinones; Isatoic anhydride; One-pot synthesis; Multicomponent; Sulfamic acid; Antitumor.

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INTRODUCTION

2,3-Dihydroquinazolin-4(1*H*)-ones are significant heterocyclic compounds and commonly used for their potential biological and pharmaceutical activities [1]. These heterocyclic compounds are valuable intermediates in the organic synthesis and revealed various medicinal properties such as anti-tumor, anti-cancer, herbicidal, diuretic, as well as plant growth regulation. Quinethazone, Proquazone, Afloqualone, Nolatrexed as representative examples of drug molecules having quinazolinone skeleton. Recently, 2,3-Dihydroquinazolin-4(1*H*)-ones observed as metabotropic glutamate receptor (mGluR) properties, antihyperlipidemic activities. Several synthetic protocols have been reported for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives by using different catalytic systems like Ethylene diamine diacetate, silica sulfuric acid, ionic liquid/water, *p*-TsOH, $KAl(SO_4)_2.12H_2O$, gallium triflate, $[bimm]BF_4$,[2-10] Montmorillonite K-10, $Al(H_2PO_4)_3$, condensation of 2-aminobenzamides with aldehyde in presence of *p*-TsOH/DDQ, $CuCl_2$, [14] chiral phosphoric acid, iodine, nano Fe_3O_4, use of *p*-toluenesulphonic acid-paraformaldehyde copolymer, silica bonded *N*-propyl sulfamic acid, tris(hydrogensulfato)boron $B(HSO_4)_3$, Bismuth (III) nitrate pentahydrate $Bi(NO_3)_3.5H_2O$, β-Cyclodextrin, silica-bonded S-sulfonic acid, silica supported with ferric chloride SiO_2-$FeCl_3$, mixture of choline chloride and malonic acid. The use of solid acids as heterogeneous catalysts has received tremendous interest in different areas of organic synthesis [11-27]. Heterogeneous solid acids are advantageous over conventional homogeneous acid catalysts as they can be easily recovered from the reaction mixture by simple filtration and can be re-used after activation or without activation, thereby making the process economically more viable. Sulfamic acid (NH_2SO_3H) (SA) has emerged as a substitute for conventional acidic catalysts. Sulfamic acid is a common inorganic acid with mild acidity, non-volatile & non-corrosive, insoluble in non polar organic solvents and easy soluble in polar solvents specially water.[28] SA is comprised not of an amino sulfonic acid, but rather of $H_3N^+SO_3^-$ zwitterionic units. In recent years, SA has been used as an efficient heterogeneous catalyst for many organic reactions [29].

Cancer is continuing to be a major health problem in developing as well as undeveloped countries. Although major advances have been made in the chemotherapeutic management of some patients, the continued commitment to the laborious task of discovering new anticancer agents remains critically important. Conventional chemotherapy, although directed toward certain macromolecules or enzymes, typically does not discriminate effectively between rapidly dividing normal cells (e.g., bone marrow and gastrointestinal tract) and tumor cells, thus leading to several toxic side effects [30]. Thus, targeted therapies represent a new and promising approach to cancer therapy and can lead to beneficial clinical effects. There are multiple types of targeted therapies monoclonal antibodies, inhibitors of tyrosine kinases and antisense inhibitors of growth factor receptors.[31] Poly(ADP-ribose)polymerase-1 (PARP-1) is a chromatin-bound nuclear enzyme involved in a variety of physiological functions related to genomic repair, including DNA replication and repair, cellular proliferation and differentiation, and apoptosis.[32]

BIOLOGICAL ACTIVITY: MATERIALS AND METHODS

Chemicals

Fetal bovine serum (FBS) and L-glutamine, were obtained from Gibco Invitrogen Company (Scotland, UK). Dulbecco's modified Eagle's (DMEM) medium was provided from Cambrex (New Jersey, USA). Dimethyl sulfoxide (DMSO), doxorubicin, penicillin, streptomycin and Sulfo-Rhodamine-B stain (SRB) (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) were obtained from Sigma Chemical Company (St. Louis, MO, USA). All other chemicals and reagents used in this study were of analytical grade and purchased from Sigma-Aldrich chemical Co. (St. Louis, MO, USA). Human Poly (ADP-ribose) Polymerase 1 (PARP-1) activity ELISA kit was purchase from Glory Science Co., Ltd (Del Rio, TX 78840, USA).

Cell lines and culturing

Anticancer activity screening for the tested compounds utilizing three different human cancer cell lines including, liver HepG2, breast MCF-7and lung A549 cell lines were obtained from the American Type Culture Collection (Rockville, MD, USA). The cancer cells were maintained in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% heat inactivated fetal calf serum (GIBCO), penicillin (100 U/ml) and streptomycin (100 µg/ml) at 37 ^oC in humidified atmosphere containing 5% CO_2. Cells at a concentration of 0.50×10^6 were grown in a 25 cm^2 flask in 5 ml of complete culture medium.

In Vitro cytotoxicity assay

The cytotoxicity activity was measured *in vitro* using the Sulfo-Rhodamine-B stain (SRB) assay according to the previous reported standard procedure.[33] Cells were inoculated in 96-well microtiter plate (10^4 cells/ well) for 24 h before treatment with the tested compounds to allow attachment of cell to the wall of the plate. Test compounds were dissolved in DMSO at 1 mg/ml immediately before use and diluted to the appropriate volume just before addition to the cell culture. Different concentration of the tested compounds and doxorubicin were added to the cells. Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compounds for 48 h at 37°C and in atmosphere of 5% CO_2. After 48 h cells were fixed, washed, and stained for 30 min with 0.4% (w/v) SRB dissolved in 1% acetic acid. Unbound dye was removed by four washes with 1% acetic acid, and attached stain was recovered with Tris-EDTA buffer. Color intensity was measured in an ELISA reader. The relation between surviving fraction and drug concentration is plotted to get the survival curve for each cell line after the specified time. The concentration required for 50% inhibition of cell viability (IC_{50}) was calculated and the results are given in Table 1.The results were compared to the antiproliferative effects of the reference control doxorubicin.[34]

Determination of Poly(ADP-ribose)polymerase-1 (PARP-1) activity

To elucidate the mechanism by which the prepared compounds exert their anticancer activity, we estimated the effect of treatment with the compounds on the activity of PARP-1in HepG2 and MCF-7 celllines activities. PARP-1inhibitors represent a promising new class of compounds for the treatment of cancer. The activity of PARP-1 in the lysate of hepatic HepG2 and breast MCF-7 cancer cells treated with the prepared compounds was measured using ELISA kit purchased from Glory Science Co., Ltd (Del Rio, TX 78840, USA).

EXPERIMENTAL

All melting points are uncorrected and measured using Electro-thermal IA 9100 apparatus, (Shimadzu, Tokyo, Japan). Microanalyses were carried out by the Micro analytical Laboratory, National Research Centre, Cairo, Egypt. Infrared spectra (KBr-disc) were recorded using a Jasco FT/IR-300E spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured in DMSO-d_6 using Varian Mercury 500 MHz and Varian Gemini 300 MHz with chemical shifts using TMS as standard solvent. Mass spectra were recorded on a GC/MS Finnigan SSQ 7000 spectrometer. Sulfamic acid was used as obtained from Aldrich. Reactions were monitored by TLC on 0.25 mm Merck Silica gel sheets (60 GF 354) (4 × 2 cm) and the spots were detected with UV light.

General procedure for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives

Method A*:* A mixture of isatoic anhydride (5 mmol), amine (5 mmol), aldehyde (5 mmol) and sulfamic acid (5 mole %) in EtOH was stirred under refluxing condition. On completion (the reaction progress was monitoring by TLC) the residue was filtered and washed with 20 ml water three times and the solvent was removed under vacuum and the residue was dried and recrystallized from EtOH to give pure products **3, 4, 5**.

Method B*:* A stirred mixture of isatoic anhydride (5 mmol), amine (5 mmol), aldehyde (5 mmol) and sulfamic acid (5 mole %) in deionized water was stirred at room temperature. On completion (the reaction progress was monitoring by TLC) the residue was filtered and washed with 20 ml water three times and the solvent was removed under vacuum and the residue was recrystallized from EtOH to give pure products **3, 4, 5**.

2-Phenyl-3-(3-(trifluoromethyl)phenyl)-2,3-dihydroquinazolin-4(1H)-one (3a) Mp = 175-176 °C; IR (KBr, cm^{-1}): 3304, 1637, 1615; ^{1}H NMR (DMSO-d_6, δ ppm): 6.43 (s, 1H, CH); 6.70 (t, 1H, J = 7.6 Hz, Ar-H), 6.76 (d, 1H, J = 7.6 Hz, Ar-H), 7.22 - 7.28 (m, 5H, Ar-H), 7.35 - 7.63 (m, 5H, Ar-H), 7.69 (s, 1H, Ar-H), 11.74 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, δ ppm): 72.9 (1C, CH in pyrimidine ring), 115.4, 115.5, 118.2, 123.6, 127.4, 128.9, 129.1, 130.7, 134.6, 140.5, 141.5, 147.1 (19C, aromatic carbons and CF_3), 163.2 (1C, C=O); MS, m/z (%): 368 (M^+); Anal. Calcd. for $C_{21}H_{15}F_3N_2O$ (368.35): C, 68.47; H, 4.10; N, 7.61; Found: C, 68.42; H, 4.06; N, 7.55%.

2-p-Tolyl-3-(3-(trifluoromethyl)phenyl)-2,3-dihydroquinazolin-4(1H)-one (3b) Mp = 221-223 °C; IR (KBr, cm^{-1}): 3296, 1634, 1614; ^{1}H NMR (DMSO-d_6, δ ppm): 2.34 (s, 3H, CH_3), 6.37 (s, 1H, CH), 6.67 - 7.31 (m, 5H,

Ar-H), 7.47 - 8.08 (m, 7H, Ar-H), 11.8 (br, 1H, NH, D_2O exchangeable); MS, m/z (%): 382 (M^+); Anal. Calcd. for $C_{22}H_{17}F_3N_2O$ (382.38): C, 69.10; H, 4.48; N: 7.33; Found: C, 69.07; H, 4.42; N, 7.28%.

2-(4-Methoxyphenyl)-3-(3-(trifluoromethyl)phenyl)-2,3-dihydroquinazolin-4(1H)-one (3c) Mp = 211-213 °C; IR (KBr, cm^{-1}): 3299, 1636, 1592. ^1H NMR (DMSO-d_6, δ ppm): 3.84 (s, 3H, OCH_3), 7.00 (s, 1H, CH), 7.06-7.44 (m, 5H, Ar-H), 7.65 - 8.10 (m, 7H, Ar-H), 11.7 (br, 1H, NH, D_2O exchangeable); MS, m/z (%): 398 (M^+); Anal. Calcd. for $C_{22}H_{17}F_3N_2O_2$ (398.38): C, 66.33; H, 4.30; N, 7.03; Found: C, 66.26; H, 4.24; N, 6.97%.

2-(4-Fluorophenyl)-3-(3-(trifluoromethyl)phenyl)-2,3-dihydro-1H-quinazolin-4-one (3d) Mp = 266-268 °C; IR (KBr, cm^{-1}): 3299, 1634, 1612; ^1H NMR (DMSO-d_6, δ ppm): 6.44 (s, 1H, CH), 6.70 - 7.38 (m, 5H, Ar-H), 7.47 - 8.23 (m, 7H, Ar-H), 11.53 (br, 1H, NH, D_2O exchangeable); MS, m/z (%): 386 (M^+); Anal. Calcd. for $C_{21}H_{14}F_4N_2O$ (386.34): C, 65.29; H, 3.65; N, 7.25; Found: C, 65.24; H, 3.61; N, 7.21%.

2-(4-Chlorophenyl)-3-(3-(trifluoromethyl)phenyl)-2,3-dihydro-1H-quinazolin-4-one (3e) Mp = 292-294 °C; IR (KBr, cm^{-1}): 3191, 1674, 1601; ^1H NMR (DMSO-d_6, δ ppm): 6.44 (s, 1H, CH), 6.70 - 7.38 (m, 5H, Ar-H), 7.47 - 8.23 (m, 7H, Ar-H), 11.53 (br, 1H, NH, D_2O exchangeable); MS, m/z (%): 402 (M^+); Anal. Calcd. for $C_{21}H_{14}ClF_3N_2O$ (402.80): C, 62.62; H, 3.50; N, 6.95; Found: C, 62.57; H, 3.46; N, 6.91%.

2-(3-Bromophenyl)-3-(3-(trifluoromethyl)phenyl)-2,3-dihydro-1H-quinazolin-4-one (3f) Mp = 236-238 °C. IR (KBr, cm^{-1}): 3240, 1678, 1608; ^1H NMR (DMSO-d_6, δ ppm): 6.83 (s, 1H, CH), 7.1 (d, 1H, J = 8.6 Hz, Ar-H), 7.32 (t, 1H, J = 7.2 Hz, Ar-H), 7.47 - 8.15 (m, 9H, Ar-H), 8.34 (s, 1H, Ar-H), 11.83 (br, 1H, NH, D_2O exchangeable); MS, m/z (%): 447 (M^+); Anal. Calcd. for $C_{21}H_{14}BrF_3N_2O$ (447.25): C, 56.39; H, 3.16; N, 6.26; Found: C, 56.33; H, 3.12; N, 6.22%.

2-(2-Thienyl)-3-(3-(trifluoromethyl)phenyl)-2,3-dihydro-1H-quinazolin-4-one (3g) Mp = 235-236 °C; IR (KBr, cm^{-1}): 3273, 1671, 1592; ^1H NMR (DMSO-d_6, δ ppm): 6.45 (s, 1H, CH), 7.23 (t, 1H, J = 8.1 Hz, Ar-H), 7.45 - 7.50 (m, 3H, Ar-H), 7.64 (d, 1H, J = 7.6 Hz, Ar-H), 7.77 - 7.86 (m, 5H, Ar-H), 8.12 (d, 1H, J = 8.1 Hz, Ar-H), 9.7 (br, 1H, NH, D_2O exchangeable); MS, m/z (%): 374 (M^+); Anal. Calcd. for $C_{19}H_{13}F_3N_2OS$ (374.38): C, 60.96; H, 3.50; N, 7.48; Found: C, 60.92; H, 3.47, N; 7.45%.

2-(2-Naphthyl)-3-(3-trifluoromethyl-phenyl)-2,3-dihydro-1H-quinazolin-4-one (3h) Mp = 179-180 °C; IR (KBr, cm^{-1}): 3305, 1631, 1609; ^1H NMR (DMSO-d_6, δ ppm): 6.60 (s, 1H, CH). 6.70 (t, 1H, J = 7.6 Hz, Ar-H), 6.77 (d, 1H, J = 7.6 Hz, Ar-H), 7.32 - 8.42 (m, 12H, Ar-H), 8.88 (s, 1H, Ar-H), 11.65 (br, 1H, NH, D_2O exchangeable); MS, m/z (%): 418 (M^+); Anal. Calcd. for $C_{25}H_{17}F_3N_2O$ (418.41): C, 71.76; H, 4.10; N, 6.70; Found: C,71.70; H, 4.07; N, 6.66%.

4-[4-Oxo-2-phenyl-1,4-dihydro-2H-quinazolin-3-yl]benzoic acid (4a) Mp = 219-220 °C; IR (KBr, cm^{-1}): 3448, 3316, 1680, 1646, 1506; ^1H NMR (DMSO-d_6, δ ppm): 6.41 (s, 1H, CH), 6.68 (t, 1H, J = 7.6 Hz, Ar-H), 6.76 (d, 1H, J = 7.6 Hz, Ar-H), 7.22 - 7.29 (m, 5H, Ar-H), 7.34 - 7.38 (m, 5H, Ar-H), 7.69 (d, 1H, J = 7.5 Hz, Ar-H), 7.78 (br, 1H, NH, D_2O exchangeable), 12.87 (br, 1H, OH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, δ ppm): 71.5(1C, CH in pyrimidine ring), 115.5, 115.8, 118.3, 125.8, 127.1, 128.3, 130.6, 134.6, 140.9, 145.2, 147.1(18C, aromatic carbons), 163.0(1C, C=O), 167.4(1C, COOH); MS, m/z (%): 344 (M^+); Anal. Calcd. for $C_{21}H_{16}N_2O_3$ (344.36): C, 73.24; H, 4.68; N, 8.13; Found: C, 73.20; H, 4.62; N, 8.08%.

4-[4-Oxo-2-p-tolyl-1,2-dihydroquinazolin-3(4H)-yl]benzoic acid (4b) Mp = 199-200 °C; IR (KBr, cm^{-1}): 3447, 3315, 1700, 1683, 1606; ^1H NMR (DMSO-d_6, δ ppm): 2.34 (s, 3H, CH_3), 6.32 (s, 1H, CH), 6.67 (t, 1H, J = 7.2 Hz, Ar-H), 6.76 (d, 1H, J = 8.0 Hz, Ar-H), 7.01 - 7.37 (m, 5H, Ar-H), 7.69 - 7.89 (m, 6H, Ar-H + NH), 12.70 (br, 1H, OH, D_2O exchangeable); MS, m/z (%): 358 (M^+); Anal. Calcd. for $C_{22}H_{18}N_2O_3$(358.39): C, 73.73; H, 5.06; N, 7.82; Found: C, 73.73; H, 5.06; N, 7.82%.

4-[2-(4-Methoxyphenyl)-4-oxo-1,2-dihydroquinazolin-3(4H)-yl]benzoic acid (4c) Mp = 221-222 °C; IR (KBr, cm^{-1}): 3480, 3307, 1695, 1630, 1610; ^1H NMR (DMSO-d_6, δ ppm): 3.83 (s, 3H, OCH_3), 6.30 (s, 1H, CH), 6.68 (t, 1H, J =7. 2 Hz, Ar-H), 6.73 (d, 1H, J = 8.1 Hz, Ar-H), 6.84 (d, 1H, J = 7.2 Hz, Ar-H), 7.43-7.00 (m, 6H, Ar-H), 7.80-7.56 (m, 4H, Ar-H + NH), 12,65 (br, 1H, OH, D_2O exchangeable); MS, m/z (%): 374 (M^+); Anal. Calcd. for: $C_{22}H_{18}N_2O_4$ (374.39): C, 70.58; H, 4.85; N, 7.48; Found: C, 70.52; H, 4.80; N, 7.43%.

4-[2-(4-Fluorophenyl)-4-oxo-1,2-dihydroquinazolin-3(4H)-yl]benzoic acid (4d) Mp = 236-238 °C; IR (KBr, cm^{-1}): 3434, 3307, 1698, 1629, 1605; ^{1}H NMR (DMSO-d_6, δ ppm): 6.39 (s, 1H, CH), 6.69 (t, 1H, *J* = 8.1 Hz, Ar-H), 6.75 (d, 1H, *J* = 7.1 Hz, Ar-H), 7.10 -7.36 (m, 8H, Ar-H), 7.69 (d, 1H, *J* = 6.7 Hz, Ar-H), 7.76 (br, 1H, NH, D_2O exchangeable), 7.86 (d, 1H, *J* = 8·1 Hz, Ar-H), 12.59 (br, 1H, OH, D_2O exchangeable); MS, m/z (%): 362 (M^+); Anal. Calcd. for $C_{21}H_{15}FN_2O_3$ (362.35): C, 69.61; H, 4.17; N, 7.73; Found: C, 69.57; H, 4.13; N, 7.67%.

4-[2-(4-Chlorophenyl)-4-oxo-1,2-dihydroquinazolin-3(4H)-yl]benzoic acid (4e) Mp = 278-280 °C; IR (KBr, cm^{-1}): 3450, 3300, 1698, 1645, 1509; ^{1}H NMR (DMSO-d_6, δ ppm): 6.40 (s, 1H, CH), 6.68 (t, 1H, *J* = 8.1 Hz, Ar-H), 6.80 (d, 1H, *J* = 7.1 Hz, Ar-H), 7.16 -7.45 (m, 6H, Ar-H), 7.70 (d, 1H, *J* = 6.7 Hz, Ar-H), 7.84 (br, 1H, NH, D_2O exchangeable), 7.87 (d, 1H, *J* = 8.1 Hz, Ar-H), 12.92 (br, 1H, OH, D_2O exchangeable); MS, m/z (%): 378 (M^+); Anal. Calcd. for $C_{21}H_{15}ClN_2O_3$ (378.81): C, 66.58; H, 3.99; N, 7.40; Found: C, 66.54; H, 3.95; N, 7.35%.

4-[2-(3-Bromophenyl)-4-oxo-1,2-dihydroquinazolin-3(4H)-yl]benzoic acid (4f) Mp = 231-232 °C; IR (KBr, cm^{-1}): 3444, 3318, 1680, 1651; ^{1}H NMR (DMSO-d_6, δ ppm): 6.42 (s, 1H, CH), 6.68 (t, 1H, *J* = 7. 6 Hz, Ar-H), 6.76 (d, 1H, *J* = 6.65 Hz, Ar-H), 7.23 - 7.31 (m, 5H, Ar-H), 7.32 - 7.40 (m, 3H, Ar-H), 7.70 (d, 1H, *J* = 6.65 Hz, Ar-H), 7.84 (br, 1H, NH, D_2O exchangeable), 7.87 (d, 1H, *J* = 8.6 Hz, Ar-H), 12.76 (br, 1H, OH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, δ ppm): 71.6 (1C, CH in pyrimidine ring), 115.7, 118.5, 122.5, 125.5, 126.0, 128.0, 131.7, 134.8, 143.7, 144.9, 146.8(18C, aromatic carbons), 162.8(1C, C=O), 167.4(1C, COOH). MS, m/z (%): 422 (M^+). Anal. Calcd. for $C_{21}H_{15}BrN_2O_3$(422.03): C, 59.59; H, 3.57; N, 6.62; Found: C, 59.53; H, 3.52; N, 6.57%.

4-[4-Oxo-2-(2-thienyl)-1,2-dihydroquinazolin-3(4H)-yl]benzoic acid (4g) Mp = 217-218 °C; IR (KBr, cm^{-1}): 3441, 3308, 1679, 1647, 1607; ^{1}H NMR (DMSO-d_6, δ ppm): 6.61 (s, 1H, CH). 6.75 (t, 1H, *J* = 7.6 Hz, Ar-H), 6.81 (d, 1H, *J*= 7.6 Hz, Ar-H), 6.85 (t, 1H, *J* =7. 6 Hz, Ar-H), 6.95 (d, 1H, *J*= 7.6 Hz, Ar-H), 7.31 (t, 1H, *J* =7.6 Hz, Ar-H), 7.33 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.43-7.45 (d, 2H, *J* =8. 6Hz, Ar-H), 7.72 (d, 1H, *J* = 8.6 Hz, Ar-H), 7.79 (br, 1H, NH, D_2O exchangeable), 7.89-7.91 (d, 2H, *J* = 8.6 Hz, Ar-H), 12.72 (b, 1H, OH, D_2O exchangeable); MS, m/z (%): 350 (M^+); Anal. Calcd. for $C_{19}H_{14}N_2O_3S$ (350.39): C, 65.13; H, 4.03; N, 7.99; Found: C, 65.08; H, 3.95; N, 7.96%.

4-[2-(2-Naphthyl)-4-oxo-1,2-dihydroquinazolin-3(4H)-yl]benzoic acid (4h) Mp = 244-254 °C; IR (KBr, cm^{-1}): 3426, 3315, 1683, 1645, 1604; ^{1}H NMR (DMSO-d_6, δ ppm): 6.59 (s, 1H, CH), 6.68 (t, 1H, *J* = 7.6 Hz, Ar-H), 6.76 (d, 1H, *J*= 7.6 Hz, Ar-H), 7.22 - 8.28 (m, 14H, 13 Ar-H + NH), 12.9 (br, 1H, OH, D_2O exchangeable); MS, m/z (%): 394 (M^+); Anal. Calcd. for $C_{25}H_{18}N_2O_3$ (394.42): C, 76.13; H, 4.60; N, 7.10; Found: C, 76.08; H, 4.55; N, 7.06%.

3-(2-Furfuryl)-2-phenyl-2,3-dihydroquinazolin-4(1H)-one (5a) Mp = 139-140 °C; IR (KBr, cm^{-1}): 3290, 3033, 1630, 1550; ^{1}H NMR (DMSO-d_6, δ ppm): 3.90 (d, 1H, *J* = 15.3 Hz,), 5.23 (d, 1H, *J* = 15.3 Hz,), 5.79 (d, 1H, *J* = 6.5 Hz, CH-furan), 6.30 (d, 1H, *J* = 8.6 Hz, Ar-H), 6.34 (s, 1H, CH), 6.65 (d, 1H, *J* = 8.6 Hz, Ar-H), 7.19-7.43 (m, 9H, Ar-H + NH + CH- furan), 7.53 (d, 1H, *J* = 8.2 Hz, Ar-H); ^{13}C NMR (DMSO-d_6, δ ppm): 39.9 (1C, CH_2), 70.3(1C, CH in pyrimidine ring), 109.26, 111.0, 114.8, 115.0, 117.8, 126.6, 128.12, 129.0, 129.1, 134.0, 140.9, 143.2, 146.8, 150.8 (16C, aromatic carbons), 162.7 (1C, C=O); MS, m/z (%): 304 (M^+); Anal. Calcd. for $C_{19}H_{16}N_2O_2$(304.34): C, 74.98; H, 5.30; N, 9.20; Found: C, 74.93; H, 5.25; N, 9.16%.

3-(2-Furfuryl)-2-(p-tolyl)-2,3-dihydroquinazolin-4(1H)-one (5b) Mp = 143-144 °C; IR (KBr, cm^{-1}): 3296, 1634, 1539; ^{1}H NMR (DMSO-d_6, δ ppm): 2.36 (s, 3H, CH_3), 3.82 (d, 1H, *J* = 15.2 Hz), 5.11 (d, 1H, *J* =15.2 Hz), 5.66 (d, 1H, *J* = 6.5 Hz, CH-furan), 6.25 (d, 1H, Ar-H), 6.34 (s, 1H, CH), 6.56 (d, 1H, *J* = 8.0 Hz, Ar-H), 6.63 (t, 1H, CH-furan), 6.84-6.86 (t, 2H, Ar-H), 7.00 -7.42 (m, 4H, Ar-H + NH), 7.58 (d, 1H, CH- furan), 7.65 (d, 1H, *J* = 8.2 Hz, Ar-H); MS, m/z (%): 318 (M^+); Anal. Calcd. for $C_{20}H_{18}N_2O_2$ (318.37): C, 75.45; H, 5.70; N, 8.80; Found: C, 75.38; H, 5.66; N, 8.74%.

3-(2-Furfuryl)-2-(4-methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (5c) Mp = 155-156 °C; IR (KBr, cm^{-1}): 3300, 1637, 1508; ^{1}H NMR (DMSO-d_6, δ ppm): 3.79 (s, 3H, OCH_3), 3.83 (d, 1H, *J* = 15.2 Hz), 5.13 (d, 1H, *J* =15.2 Hz), 5.67 (d, 1H, *J* = 6.5 Hz, CH-furan), 6.26 (d, 1H, Ar-H), 6.35 (s, 1H, CH), 6.57 (d, 1H, *J* = 8.0 Hz, Ar-H), 6.62 (t, 1H, CH-furan), 6.84-6.85 (t, 2H, Ar-H), 7.00 -7.44 (m, 4H, ArH + NH), 7.62 (d, 1H, CH-furan), 7·63 (d, 1H, *J* = 8.2 Hz); MS, m/z (%): 334 (M^+); Anal. Calcd. for $C_{20}H_{18}N_2O_3$ (334.37): C, 71.84; H, 5.43; N, 8.38; Found: C, 71.80; H, 5.38; N, 8.33%.

2-(4-Fluorophenyl)-3-(2-furfuryl)-2,3-dihydroquinazolin-4(1H)-one (5d) Mp = 145-146 °C. IR (KBr, cm^{-1}): 3304, 1635, 1507; ^{1}H NMR (DMSO-d_6, δ ppm): 3.94 (d, 1H, *J* = 15.2 Hz, CH_2), 5.10 (d, 1H, *J*=15.2 Hz), 5.76 (d,

1H, *J* = 6.6 Hz, CH-furan), 6.27 (d, 1H, *J* = 7.6 Hz, Ar-H), 6.33 (s, 1H, CH), 6.58 (d, 1H, *J* = 8.0 Hz, Ar-H), 6.64 (t, 1H, CH-furan), 7.12-7.18 (t, 2H, Ar-H), 7.19-7.34 (m, 4H, ArH + NH), 7.52 (d, 1H, CH- furan), 7.65 (d, 1H, *J* = 8.2 Hz); MS, m/z (%): 322 (M^+); Anal. Calcd. for $C_{19}H_{15}FN_2O_2$ (322.33): C, 70.80; H, 4.69; N, 8.69; Found: C, 70.76; H, 4.63; N, 8.62%.

2-(4-Chlorophenyl)-3-(2-furfuryl)-2,3-dihydroquinazolin-4(1H)-one (5e) Mp = 151-152 °C; IR (KBr, cm^{-1}): 3307, 2927, 1637, 1510; ^{1}H NMR (DMSO-d_6, δ ppm): 4.0 (d, 1H, *J* = 15.2 Hz, CH_2), 5.11 (d, 1H, *J* = 15.3 Hz), 5.76 (d, 1H, *J* = 6.5 Hz, CH-furan), 6.30 (d, 1H, Ar-H), 6.35 (s, 1H, CH), 6.58 (d, 1H, *J* = 8.6 Hz, Ar-H), 6.65 (t, 1H, *J* = 7.2 Hz, CH-furan), 7.18 - 7.20 (t, 1H, *J* = 8.6 Hz, Ar-H), 7.24 - 7.37 (m, 3H, Ar-H + NH), 7.44 (d, 1H, CH- furan), 7.52 (s, 1H, Ar-H), 7.65 (d, 1H, *J* = 7.60 Hz, Ar-H); MS, m/z (%): 336 (M^+); Anal. Calcd. for $C_{19}H_{15}ClN_2O_2$ (338.79): C, 67.36; H, 4.46; N, 8.27; Found: C, 67.31; H, 4.40; N, 8.22%.

2-(3-Bromophenyl)-3-(2-furfuryl)-2,3-dihydroquinazolin-4(1H)-one (5f) Mp = 101-102 °C; IR (KBr, cm^{-1}): 3305, 2925, 1633, 1506; ^{1}H NMR (DMSO-d_6, δ ppm): 4.1 (d, 1H, *J* = 14.8 Hz, CH_2), 5.09 (d, 1H, *J* = 15.3 Hz, CH_2), 5.83 (d, 1H, *J* = 6.5 Hz, CH-furan), 6.29 (d, 1H, Ar-H), 6.32 (s, 1H, CH), 6.6 (d, 1H, *J* = 8.6 Hz, Ar-H), 6.66 (t, 1H, *J* = 7.2 Hz, CH-furan), 7.21 - 7.54 (m, 7H, ArH + NH + CH-furan), 7.66 (d, 1H, *J* = 7.60 Hz, Ar-H); MS, m/z (%): 384 (M+1); Anal. Calcd. for $C_{19}H_{15}BrN_2O_2$ (383.24): C, 59.50; H, 3.88; N, 7.27; Found: C, 59.50; H, 3.88; N, 7.27%.

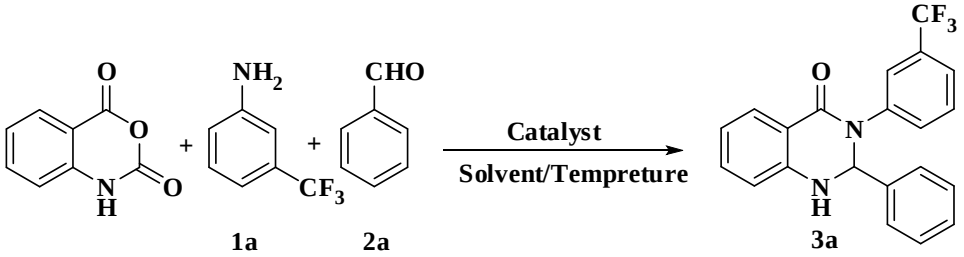
3-(2-Furfuryl)-2-(2-thienyl)-2,3-dihydroquinazolin-4(1H)-one (5g) Mp = 147-148 °C; IR (KBr, cm^{-1}): 3250, 3100, 1631, 1510; ^{1}H NMR (DMSO-d_6, δ ppm): 3.94 (d, 1H, *J* = 15.3 Hz), 5.14 (d, 1H, *J* = 15.3 Hz), 5.99 (d, 1H, *J* = 6.6 Hz, CH-furan), 6.35 (d, 1H, *J* = 8.6 Hz, Ar-H), 6.38 (s, 1H, CH), 7.54-5.65 (m, 8H, ArH + NH + CH-furan), 7.63 (d, 1H, *J* = 8.2 Hz, Ar-H); MS, m/z (%): 310 (M^+); Anal. Calcd. for $C_{17}H_{14}N_2O_2S$ (310.37): C, 65.79; H, 4.55; N, 9.03; Found: C, 65.79; H, 4.55; N, 9.03%.

3-(2-Furfuryl)-2-(naphthalen-2-yl)-2,3-dihydroquinazolin-4(1H)-one (5h) Mp = 157-158 °C; IR (KBr, cm^{-1}): 3300, 1638, 1614; ^{1}H NMR (DMSO-d_6, δ ppm): 4.0 (d, 1H, *J* = 15.2 Hz, CH_2), 5.24 (d, 1H, *J* = 15.3 Hz, CH_2), 5. 93 (d, 1H, *J* = 6.6 Hz, CH-furan), 6.34 (s, 1H, Ar-H), 6.35 (s, 1H, CH), 6.59 (d, 1H, *J* = 8.6 Hz, Ar-H), 6.64 (t, 1H, *J* = 7.2 Hz, CH-furan), 7.17 (t, 1H, *J* = 8.6 Hz, Ar-H), 7.48 - 7.93 (m, 10H, Ar-H +NH + CH furan); MS, m/z (%): 354 (M^+); Anal. Calcd. for $C_{23}H_{18}N_2O_2$ (354.40): C, 77.95; H, 5.12; N, 7.90; Found: C, 77.90; H, 5.07; N, 7.85%.

RESULTS AND DISSCUSION

Chemistry

In the initial study, when isatoic anhydride was reacted with 4-trifluoromethylaniline and benzaldehyde in deionized water without catalyst (entry 1), it was found that there is no reaction was occurred even at prolonged reaction time. Thus, the reaction requires a catalyst to obtain the aimed 2,3-dihydroquinazolin-4(1*H*)-one derivatives. In order to optimize the reaction conditions, isatoic anhydride, 3-trifluoromethylaniline and benzaldehyde were taken as model reactants.



Scheme 1: Optimization of the reaction conditions for the 2-Phenyl-3-(3-(trifluoromethyl)phenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3a)

The preliminary trial was investigated for the reaction conditions with regard to different catalysts and solvents. Also, the reaction was carried out using various catalysts (namely H_2NSO_3H, $FeCl_3$, $ZnCl_2$ and $SnCl_2$) in order to obtain the best catalyst (as shown in Table 1). The data revealed that, the reaction of isatoic anhydride, 4-trifluoromethylaniline and benzaldehyde as a model example (1 equiv-each), proceeded in the presence of sulfamic acid (H_2NSO_3H) as a catalyst with different molar ratios under stirring in various solvents. Non polar solvent such as cyclohexane and toluene were found to be less effective solvents than polar solvent

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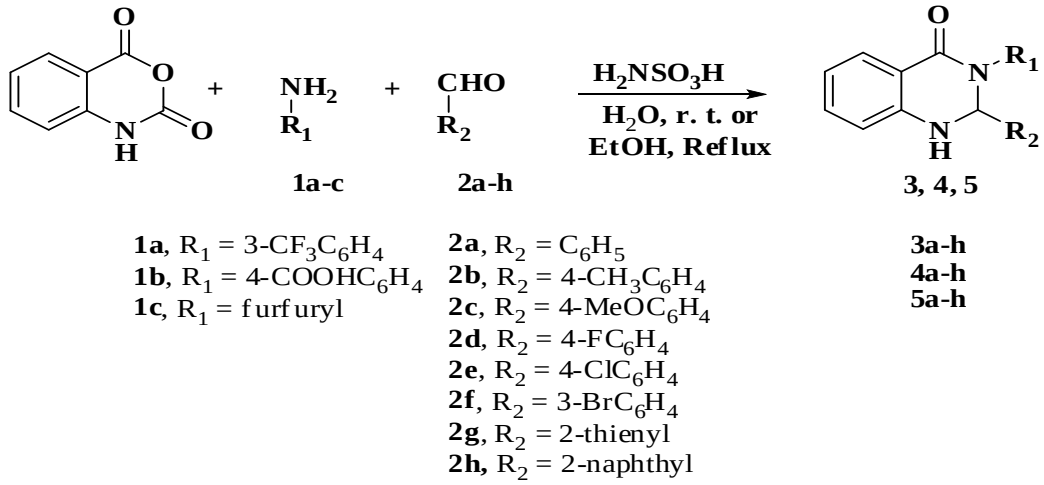
like ethanol and water, each one of them has the advantage than other; while ethanol gave more yield 82 % but needed thermal conditions and the water solvent needed no thermal conditions but gave slightly less yield 77 % and more reaction time. So, it was decided to do the reaction in two solvents ethanol in order to obtain high yield and deionized water towards eco-friendly conditions. Accordingly, the best results were obtained when H_2NSO_3H (5 mol %) was employed as a catalyst and (H_2O or ethanol) as a two comparative solvents (entry 7, 9 Table 1) afforded the desired product in high yield (82, 77 %) respectively.

Table 1: Effect of the catalyst type and ratio with different solvents on the yield and reaction time for the synthesis of 2-Phenyl-3-(3-(trifluoromethyl)phenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3a)

Entry	Catalyst	Solvent / T	Catalyst (mole %)	Time (h)	Yield (%)
1	None	Ethanol/ Δ	-	24	0
2	$FeCl_3$	Ethanol/ Δ	10	15	50
3	$ZnCl_2$	Ethanol/ Δ	10	8	80
4	$SnCl_2$	Ethanol/ Δ	10	15	60
5	H_2NSO_3H	Cyclohexane/ Δ	10	15	15
6	H_2NSO_3H	Toluene/ Δ	10	15	20
7	H_2NSO_3H	Ethanol/ Δ	5	6	82
8	H_2NSO_3H	Deionized water/r.t.	10	24	78
9	H_2NSO_3H	Deionized water/ r.t.	5	24	77
10	H_2NSO_3H	Deionized water/ r.t.	3	24	70
11	H_2NSO_3H	Deionized water/ r.t.	1	24	60

Δ reflux

Thus, it was prompted to explore the potential of using this protocol for the synthesis of various 2,3-dihydroquinazolin-4(1*H*)-ones. The reactions proceeded smoothly while stirring in deionized water or heated under reflux in ethanol as solvent and were completed within the required time. (Table 1) showed that the generality of the present protocol, which is equally effective for isatoic anhydride, various primary amines and various aldehydes. In all cases, the desired 2,3-dihydroquinazolin-4(1*H*)-ones were obtained as sole products and no by-products were observed. To expand the scope of this new methodology, several diversely substituted aldehydes having electron-donating as well as electron-withdrawing groups were reacted with 3-trifluoromethylaniline and isatoic anhydride in the presence of H_2NSO_3H. The reactions were finished at specified time and afford 2-substituted-3-(3-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-quinazolin-4-ones **3a-h** in good yields (72-84%) as shown in Scheme 2 and Table 2. From the obtained results it was found that aromatic aldehydes bearing electron-donating group (compounds **3b, 3c**) resulted the higher yield of the product (84%) with reducing the time of reaction compared to aldehydes with electron-withdrawing group.



1a-c **2a-h** **3, 4, 5**

1a, R_1 = 3-$CF_3C_6H_4$
1b, R_1 = 4-$COOHC_6H_4$
1c, R_1 = furfuryl

2a, R_2 = C_6H_5
2b, R_2 = 4-$CH_3C_6H_4$
2c, R_2 = 4-$MeOC_6H_4$
2d, R_2 = 4-FC_6H_4
2e, R_2 = 4-ClC_6H_4
2f, R_2 = 3-BrC_6H_4
2g, R_2 = 2-thienyl
2h, R_2 = 2-naphthyl

3a-h
4a-h
5a-h

Scheme 2: Synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives

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Table 2: Reaction of isatoic anhydride with a variety of primary amines and aromatic aldehydes

Entry	R_1	R_2	Product	Time EtOH/H_2O (h)	Yield[c] EtOH/H_2O (%)
1	3-CF_3Ph	Ph	**3a**	6/24	82/77
2	3-CF_3Ph	4-CH_3Ph	**3b**	4/21	84/79
3	3-CF_3Ph	4-OMePh	**3c**	4/20	84/78
4	3-CF_3Ph	4-F-ph	**3d**	4/21	82/76
5	3-CF_3Ph	4-ClPh	**3e**	5/22	80/75
6	3-CF_3Ph	3-BrPh	**3f**	6/24	78/72
7	3-CF_3Ph	2-thienyl	**3g**	4/20	82/78
8	3-CF_3Ph	2-naphthyl	**3h**	6/24	78/72
9	4-COOHPh	Ph	**4a**	4/18	88/83
10	4-COOHPh	4-CH_3Ph	**4b**	3/16	90/85
11	4-COOHPh	4-OMePh	**4c**	3/16	90/84
12	4-COOHPh	4-F-ph	**4d**	4/17	89/82
13	4-COOHPh	4-ClPh	**4e**	5/20	85/80
14	4-COOHPh	3-BrPh	**4f**	6/23	83/78
15	4-COOHPh	2-thienyl	**4g**	4/18	89/84
16	4-COOHPh	2-naphthyl	**4h**	6/24	83/78
17	2-furfuryl	Ph	**5a**	3/16	92/86
18	2-furfuryl	4-CH_3Ph	**5b**	2.5/14	96/91
19	2-furfuryl	4-OMePh	**5c**	2.5/14	95/90
20	2-furfuryl	4-F-ph	**5d**	3/15	92/87
21	2-furfuryl	4-ClPh	**5e**	4/18	93/89
22	2-furfuryl	3-BrPh	**5f**	5/21	91/86
23	2-furfuryl	2-thienyl	**5g**	3/16	92/88
24	2-furfuryl	2-naphthyl	**5h**	5/21	90/86

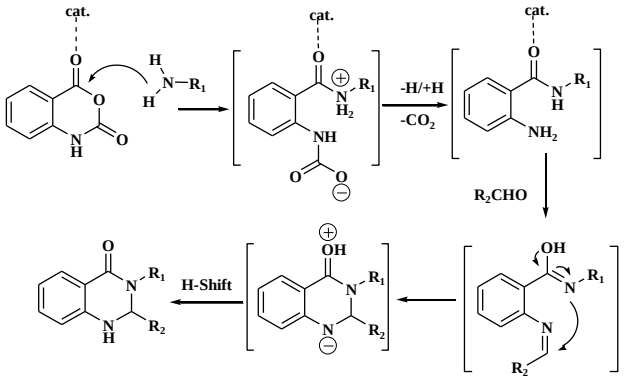
[c]Isolated yield

In order to generality of the above reaction, 3-trifluoromethylaniline was replaced by 4-carboxyaniline in the model of the one-pot reaction. When 4-carboxyaniline was left to react with various aldehyde and isatoic anhydride in the presence of H_2NSO_3H, the reaction was finished at specified time and afforded the 3-(4-(carboxy)phenyl)-2-substituted-2,3-dihydro-1*H*-quinazolin-4-one **4a-h** in good yields (78-90%). Also, it was observed that aromatic aldehyde bearing electron-donating group (compounds **4b, 4c**, 90%) resulted in higher yields of the products compared to amines with electron-withdrawing groups. Moreover, our investigation was extended to include the behavior of heterocyclic amine towards this reaction. Thus, when furfural amine (as heterocyclic amine) was reacted with various aldehyde and isatoic anhydride under similar conditions, the present reaction works well to afford 3-(2-furfuryl)-2-substituted-2,3-dihydroquinazolin-4(1*H*)-one **5a-h** in high yields (87-96%).

The results clearly indicated the generality and scope of the reaction with respect to various aromatic and hetero-aromatic aldehydes. From the data depicted in (Table 2) it was noticed that, aldehydes substituted with electron donating groups gave higher yields rather than those substituted by electron with drawing groups. Bulky aldehydes gave lower 2,3-dihydroquinazolin-4(1*H*)-ones yield due to their steric hindrance compared to homocyclic and hetero-aromatic aldehydes. Also, the amine type was found to affect the reaction time and yield and so the amine priority order towards faster and more yield reaction was furfurylamine, 4-carboxyaniline then 3-trifluoromethylaniline.

The structure of the obtained 2,3-dihydroquinazolin-4(1*H*)-ones was elucidated by spectroscopic methods. The IR spectra showed peaks at: ν = 3240-3318 and 1630-1651 cm^{-1} corresponding to (NH) and amidic carbonyl groups, respectively; ^{1}H-NMR spectra revealed singlet signals for (CH) in pyrimidine ring at: δ = 6.25-6.61. ^{13}C-NMR spectra showed characteristic signals at: 163.2 -162.7 for amidic C=O and 70.3-71.9 for CH

in pyrimidine ring. A plausible mechanism for the reaction leading to the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones was suggested as shown in (Scheme 3).



Scheme 3: Suggested mechanism

Biological Activity

The results are reported as Mean ± Standard error (S.E.) for at least three times experiments. Statistical differences were analyzed according to followed by one way ANOVA test followed by student's *t* test wherein the differences were considered to be significant at $p < 0.05$.

In vitro cytotoxicity activity

As shown in (Table 3), the cytotoxicity of the synthetic compounds was tested using SRB assay in HepG2, MCF-7 and A549 cell lines. For comparison, doxorubicin as standard drugs was also tested. The results revealed that all the compounds did not exert any activity against lung A549 cell line. Studying the anticancer activity of the compounds against MCF-7 and HepG2 cell lines, revealed that although compound **5b** showed no anticancer activity in HepG2 cell line and compound **5b** showed no anticancer activity in MCF-7 cell line, most of the compounds were found to be potent against the both cell lines with IC_{50} values ranging from 3.75±0.40 to 33.22±3.30 µg/ml for HepG2 and ranging from 4.30±0.47 to 34.30±4.20 µg/ml for MCF-7 while the IC_{50} values of standard drug doxorubicin was 2.90±0.27 and 3.70±0.35µg/ml for HepG2 and MCF-7 respectively. Moreover, the results showed that nearly four compounds **5e, 3f, 4b, 3d** were found to be potent and were nearly similar to doxorubicin against HepG2 and MCF-7 cell lines.

The poly (ADP-ribose)polymerase-1 (PARP-1) activity

To identify the mechanism of action responsible for the cytotoxicity of prepared compounds, the activity of PARP-1 expressed in the two cell lines (hepatic HepG2 and breast MCF-7 cancer cell line) were estimated quantitatively and the results were calculated as percentage of the control cancer cells as shown in (Table 3). The activity of PARP-1 in the lysate of hepatic HepG2 and breast MCF-7 cancer cells treated with the prepared compounds and doxorubicin, as a known inhibitor was measured and the data were calculated as percentage of inhibition as compared to the control untreated cancer cells. While, treatment of hepatic HepG2 and breast MCF-7cancer cells with doxorubicin resulted in 82% and 76% inhibition respectively as compared with control cancer cells, the treatment of both HepG2 and MCF-7 with compounds **5e, 3f, 4b, 3d** (which exerted good cytotoxicity effect) resulted in inhibitory potency of PARP-1 follows the order **3d**>**3f**>**5e**>**4b**, while the rest compounds showed weak to moderate inhibitory activity comparing to doxorubicin. The previous results were parallel with cell cytotoxicity activity of the tested compounds. Taken together, these findings suggested that there are correlation between the cytotoxicity of the tested compounds and inhibition of the PARP-1 activity. The tested compounds exert anti-carcinogenic activity in hepatic HepG2 and breast MCF-7 cancer cell lines through down regulation the activity of PARP-1 enzyme which may reduce the cell proliferation and resulted in significant growth inhibitory.

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Table 3: The IC_{50} values of the tested compounds in three human cancer cell lines and human Poly (ADP-ribose) Polymerase 1 (PARP-1) activities

Compound	IC_{50} (µg/ml)			% of PARP-1 inhibition		
	HepG2	MCF-7	A549	HepG2	MCF-7	A549
3b	28.30±3.90	29.80±3.35	N.A.	5±0.60	6±0.70	N.A.
3c	7.80±0.82	9.00±1.16	N.A.	40±4.70	31±4.00	N.A.
3d	3.75±0.40	4.30±0.47	N.A.	75±8.23	68±7.22	N.A.
3f	3.95±0.46	5.88±0.60	N.A.	64±0.70	61±6.70	N.A.
4a	23.20±2.50	24.73±2.50	N.A.	4±0.55	7±0.70	N.A.
4b	7.70±0.76	10.10±1.23	N.A.	50±5.85	39.75±5.00	N.A.
4d	15.60±1.60	19.00±2.20	N.A.	11±1.33	9.75±1.11	N.A.
4e	17.00±0.40	18.90±1.90	N.A.	9.50±1.00	8±0.86	N.A.
4f	13.10±1.40	14.95±1.50	N.A.	18±2.00	15±1.76	N.A.
5b	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
5c	25.20±2.60	26.80±2.76	N.A.	6.50±0.70	5±0.66	N.A.
5d	33.22±3.30	34.30±4.20	N.A.	5±0.65	4±0.47	N.A.
5e	4.00±0.50	4.90±0.44	N.A.	60±6.67	57±6.50	N.A.
DMSO	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Doxorubicin	2.90±0.27	3.70±0.35	4.30±0.40	83±9.10	76±8.33	75±7.67

Data were expressed as Mean ± Standard error (S.E.) of three independent experiments.
*The percentage changes as compared with control cancer cells (DMSO treated).
N.A. = no activity

CONCLUSION

An efficient procedure was investigated for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones through direct one-pot three-component cyclo-condensation of isatoic anhydride, aromatic primary amines and aldehydes in the presence of catalytic amount of sulfamic acid H_2NSO_3H in deionized at room temperature or in ethanol reflux. A simple reaction conditions, cost-effective, eco-friendly and recyclable solid acid catalyst are advantages of the present work. The cytotoxic activity of the synthesized compounds was evaluated against human hepatocellular carcinoma cell line (HEPG2), human breast cancer cell line (MCF-7) and human lung cancer cell line (A549). In general, tested compounds showed no activity against the growth of A549, but most of the tested compounds possessed significant cytotoxic activity against the growth of HEPG2 and MCF-7. Specially, four of the tested compounds introduced activity nearly equipotent to the reference drug.

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