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Synthesis, Anticancer and Antioxidant Evaluation of Some New 2-Aryl and 2-Pyrazole-2,3-dihydroquinazolin-4(1*H*)-ones

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A new and direct synthetic method was developed for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones by condensing 2-aminobenzamide and aldehydes in ethanol using thionyl chloride as a catalyst at room temperature. The simple reaction conditions, small timing, easy work up and very good yields are the greatest advantages of this methodology. By utilizing the approach six novel derivatives of 2-aryl-2,3-dihydroquinazolin-4(1*H*)-ones (**3a-3f**) were synthesized. All the compounds were tested for their anticancer activity on A549 cell line and antioxidant activity by using DPPH method. Compounds **3c** (74.22 %) and **3e** (73.45 %) showed better anticancer activity towards the A549 cell line.

Keywords: $SOCl_2$, Anthranilamide, Novel pyrazole derivatives, Anticancer; Antioxidant activity.

INTRODUCTION

Quinazoline skeletons showed potent biological activities such as anticancer, antitumor, antibiotic, antidefibrillator, antipyretic, analgesic, antihypertonic, antimalarial and diuretic activities depending up on the biological activities [1-9]. They were considered as important group in heterocyclic molecules. An accountable work was carried out to develop simple and direct approaches for the synthesis of dihydroquinazolin-4-ones skeleton for the past few years. These methods comprises of condensation of anthranilamide with substituted carbonyl compounds in the presence of various catalysts such as cyanuric trichloride [10], $Ce(NH_4)_2(NO_3)_6$ [11], citric acid-Al_2O_3 [12], H_3BO_3 [13], gallium(III) triflate [14], Sulfamic acid [15], $Bu_4N^+Br^{(-)}$ [16], zinc(II) chloride [17], toluene-4-sulfonic acid [18], ruthenium [19], 2,2,2-trifloroethanol [20], $TiCl_4$-Zn [21] and $ZrCl_4$ [22]. But many of the established methods are not feasible in all respects such as cost of the reagents, attaining good yields of the products, purification of the products and in some of the methods preparation of reagent is also complicate. So, in order to extend this study towards development of simple and viable method for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones an attempt was carried out with thionyl chloride as catalyst for ethanol mediated condensation of anthranilamide and aldehydes.

EXPERIMENTAL

All the chemicals used were of Merck. Reagent grade solvents (E. Merck) were used as such. All the melting points were obtained from Remi melting point apparatus. All reactions were monitored by TLC and all yields refer to isolated products. Proton NMR spectra were recorded in DMSO-d_6 on Bruker 400 MHz and ^{13}C NMR spectra were on Bruker 100 MHz, Mass studies were carried out on LC-MS system equipped with Agilent 1100 series, LC/MSD detector and 1100 series Agilent HPLC pump.

Preparation of 2,3-dihydroquinazolin-4(1*H*)-ones: To a mixture of anthranilamide (1 mmol) and aldehyde (1 mmol) in ethanol (10 mL), catalytic amount of thionyl chloride was added to reaction mixture at 0-5 °C, the mixture was stirred at room temperature for about 30-35 min. After completion of the reaction monitored by TLC, the ethanol was distilled off from the reaction mass, the solid mass was poured into cold water (25 mL) filtered off and the product then washed with cold ethanol for further purification. Finally, the dried compounds were characterized by their spectral data.

3-Methoxy-4-(4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)benzonitrile (3a): This compound was obtained as a white solid; m.p. 238-240 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 3.89 (s, 3H), 6.01 (s, 1H), 6.68 (t, *J* = 7.2 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.91 (s, 1H), 7.24 (t, *J* = 7.12 Hz, 1H), 7.43 (d,

J = 7.4 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.53 (s, 1H), 7.61 (d, *J* = 7.3 Hz, 1H), 8.10 (s, 1H): ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.60, 61.03, 112.33, 114.86, 117.65, 118.93, 124.83, 127.66, 127.97, 133.79, 135.0, 147.77, 156.87, 163.86, ESI-MS: *m/z* 280 (M+H). Calculated mass for the formula $C_{16}H_{13}N_3O_2$ -279. Calculated C, 68.81, H, 4.69, N, 15.05 %; Found: C, 68.79, H, 4.70, N, 15.08 %.

2,3-Dihydro-2-(3-ethoxy-4-methoxyphenyl)quinazolin-4(1*H*)-one (3b): This compound was obtained as a light yellow solid; m.p. 182-184 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.31 (t, *J* = 3.0 Hz, 3H), 3.73 (s, 3H), 2.03 (d, *J* = 6.12 Hz, 2H), 5.67 (s, 1H), 6.68 (t, *J* = 6.32 Hz, 1H), 6.75 (d, *J* = 7.42 Hz, 1H), 7.01 (m, 3H), 7.10 (s, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 6.68 Hz, 1H), 8.18 (s, 1H): ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.05, 55.87, 64.03, 66.76, 111.73, 112.05, 114.75, 115.39, 117.44, 119.50, 127.65, 133.55, 133.97, 148.06, 148.35, 149.46, 164.05 ESI-MS: *m/z* 299 (M+H). Calculated mass for the formula. $C_{17}H_{18}N_2O_3$ -298. Calculated C, 68.44, H, 6.08, N, 9.39 %; Found: C, 68.47, H, 6.11, N, 9.37 %.

2,3-Dihydro-2-(2,3,4-trimethoxy-6-methylphenyl)-quinazolin-4(1*H*)-one (3c): This compound was obtained as a light yellow solid; m.p. 170-172 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.51 (s, 3H), 3.71 (s, 6H), 3.80 (s, 3H), 6.26 (s, 1H), 6.72 (m, 4H), 7.23 (t, *J* = 7.10 Hz, 1H), 7.63 (d, *J* = 7.10 Hz, 1H), 7.91 (s, 1H): ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.74, 56.19, 60.64, 61.52, 61.89, 111.67, 114.48, 115.01, 117.09, 122.47, 127.78, 133.32, 134.78, 139.79, 149.47, 152.80, 153.25, 164.48; ESI-MS: *m/z* 329 (M+H). Calculated mass for the formula $C_{18}H_{20}N_2O_4$ -328. Calculated C, 65.84, H, 6.14, N, 8.53 %; Found: C, 65.85, H, 6.18, N, 8.56 %.

2,3-Dihydro-2-(1,3-diphenyl-1H-pyrazol-4-yl)quinazolin-4(1*H*)-one (3d): This compound was obtained as a white solid; m.p. 192-194 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.90 (s, 1H), 6.67 (s, 2H), 7.07 (s, 1H), 7.5 (m, 8H), 7.67 (s, 1H), 7.80 (s, 2H), 7.96 (s, 2H), 8.3 (s, 1H), 8.9 (s, 1H): ^{13}C NMR (100 MHz, DMSO-d_6): δ 60.57, 115.01, 115.95, 118.14, 118.64, 120.76, 126.91, 127.96, 128.57, 128.69, 128.80, 129.86, 130.0, 132.77, 133.54, 139.69, 148.99, 151.22, 164.45; ESI-MS: *m/z* 367 (M+H). Calculated mass for the formula $C_{23}H_{18}N_4O$ -366. Calculated C, 75.39, H, 4.95, N, 15.29 %; Found: C, 75.42, H, 4.92, N, 15.26 %.

2,3-Dihydro-2-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]quinazolin-4(1*H*)-one (3e): This compound was obtained as a white solid; m.p. 198-200 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.9 (s, 1H), 6.77 (d, *J* = 6.86 Hz, 2H), 7.04 (s, 1H), 7.29 (t, *J* = 6.75 Hz, 2H), 7.36 (t, *J* = 6.30 Hz, 1H), 7.50 (m, 2H), 7.67 (d, *J* = 6.82 Hz, 2H), 7.86 (d, *J* = 7.4 Hz, 2H), 7.96 (d, *J* = 7.09 Hz, 2H), 8.27 (s, 1H), 8.88 (s,1H): ^{13}C NMR (100 MHz, DMSO-d_6): δ 60.57, 115.06, 115.97, 118.18, 118.71, 120.81, 120.85, 127.04, 127.94, 128.80, 130.01, 130.40, 131.74, 133.32, 133.53, 139.59, 148.92, 148.99, 164.45; ESI-MS: *m/z* 401 (M+H). Calculated mass for the formula $C_{23}H_{17}ClN_4O$ -400. Calculated C, 68.91, H, 4.27, N, 13.98 %; Found: C, 68.94, H, 4.22, N, 14.01 %.

2,3-Dihydro-2-[3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]quinazolin-4(1*H*)-one (3f): This compound was obtained as a white solid; m.p. 180-182 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.77 (s, 3H), 5.86 (s, 1H), 6.77 (m, 2H), 7.04 (d, *J* = 8.31 Hz, 2H), 7.05 (s, 1H), 7.34 (m, 2H), 7.53 (t, *J* = 6.88 Hz, 1H), 7.67 (d, *J* = 7.18 Hz, 1H), 7.74 (d, *J* = 7.90 Hz, 2H), 7.95 (d, *J* = 7.42 Hz, 2H), 8.28 (s, 1H), 8.85 (s, 1H): ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.50, 60.67, 114.24, 115.02, 115.98, 118.12, 118.53, 120.30, 125.17, 126.75, 127.95, 129.70, 129.96, 133.57, 139.73, 149.04, 151.07, 159.65, 164.51. ESI-MS: *m/z* 397 (M+H). Calculated mass for the formula $C_{24}H_{20}N_4O_2$ -398 Calculated C, 72.71, H, 5.08, N, 14.13 %; Found: C, 72.68, H, 5.12, N, 14.09 %.

Anticancer activity: The compounds were tested on A549 (Human lung carcinoma cell line) cells using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT) cell proliferation assay [23]. A549 cell line was obtained from National Centre for Cell Science (NCCS), Pune (India) and cultivated in Dulbecco's modified Eagle's red medium (DMEM) (Sigma Life Science, USA) containing 10 % fetal bovine serum (FBS). The cells (2000 cells per well) were seeded in a 96-well micro plate containing 100 µL of Dulbecco's modified Eagle's red medium + 10 % fetal bovine serum medium per well and incubated at 37 °C with 5 % CO_2. The cells were treated with different concentration of compounds up to 72 h for every 24 h interval. Controls were maintained with 0.5 % DMSO. After 72 h treatment, 5 µL of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT) reagent (R&D Systems, USA) along with 45 µL of phenol red free Dulbecco's modified Eagle's red medium (Sigma Life Science, USA) without fetal bovine serum was added to each well and plates were incubated at 37 °C with 5 % CO_2 for 4 h. Thereafter, 50 µL of solubilization buffer (R&D Systems, USA) was added to each well to dissolve the coloured formazan crystals produced by the reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide. After 24 h, the optical density was measured at 550 nm using microplate reader (Bio-Rad, USA).

Antioxidant activity (DPPH) method: The DPPH free radical scavenging activity of the six novel analogs (**3a-3f**) was measured according to the method developed by Chew *et al.* [24]. The different concentrations of the titled compounds *i.e.* 100, 200, 300, 400 and 500 µg/mL were prepared in DMSO. 1 mL of each concentration was mixed with 4 mL of the 0.004 % (w/v) solution of DPPH prepared in methanol. The reaction mixture was kept for incubation in dark for 30 min. Methanol was used as control and Ascorbic acid was used as positive control. The absorbance was measured at 517 nm. The DPPH scavenging activity (%) was calculated by using the following formula:

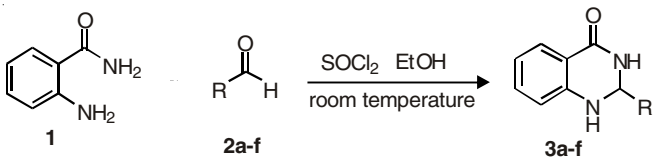
$$\text{DPPH scavenging activity (\%)} = \frac{(A_0 - A_s)}{A_0} \times 100$$

where, A_0 = absorbance of the control, A_s = absorbance of the sample.

RESULTS AND DISCUSSION

With the aim of developing a new method for the synthesis of 2-aryl-2,3-dihydroquinazolin-4(1*H*)-ones, we attempted to study for the formation of titled compounds by condensing 2-aminobenzamide with 2-cyano, 3-methoxy benzaldehyde in different catalysts such as $SnCl_2$, $NiSO_4$, celite, NaF, NaCl, ceric sulphate and various solvents like methanol, ethanol,

acetonitrile, dichloromethane, dichloroethane, tetrahydrofuran at room temperatutre and reflux there is no formation of product even maintained for long hours. But the progress of the reaction is observed with thionyl chloride catalyst in dichloroethane at room temperature for 1 h yielded 70 % product, so it clearly indicates that $SOCl_2$ catalyst promoted the reaction and new for the synthesis of 2-aryl-2,3-dihydroquinazolin-4(1*H*)-ones. There is no change in the product yield even maintained for long hours.



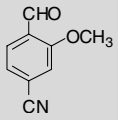
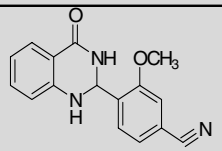
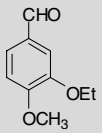
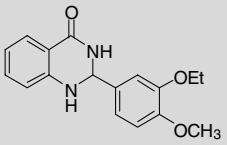
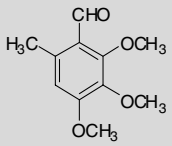
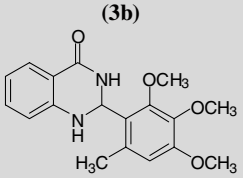
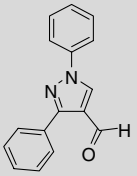
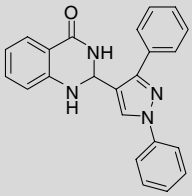
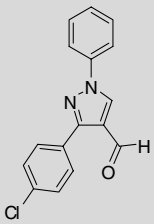
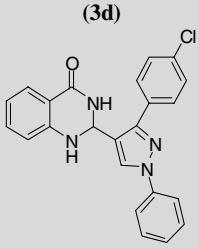
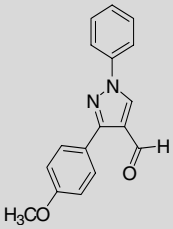
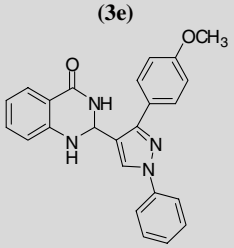
Scheme-I: Thionyl chloride catalyzed synthesis of 2-aryl and 2-pyrazol-2,3-dihydroquinazolin-4(1*H*)-ones

A study was also carried out in order to screening the solvent applicability with thionyl chloride methodology. We carried out the condensation of 2-amino benzamide and 2-cyano, 3-methoxy benzaldehyde with thionyl chloride catalyst in different solvents at room temperature, results are summarized in Table-1. Among the tested solvents it was found that ethanol-

TABLE-1
SELECTIVITY OF SOLVENT FOR THE SYNTHESIS OF 2-ARYL AND 2-PYRAZOL-2,3-DIHYDROQUINAZOLIN-4(1*H*)-ONES

S. No.	Solvent	Reaction time (min)	Yield (%)
1	Dichloromethane	100	50
2	Dichloroethane	110	45
3	Tetrahydrofuran	90	40
4	Methanol	70	60
5	Ethanol	30	95
6	Acetonitrile	120	40

TABLE-2
REACTION CONDITIONS OF SYNTHESIZED 2,3-DIHYDROQUINAZOLIN-4(1*H*)-ONES

Compound	Aldehyde	Product	Time (min)	Yield (%)	Reported m.p. (°C)
2a		 **(3a)**	30	95	238-240
2b		 **(3b)**	35	94	182-184
2c		 **(3c)**	30	95	170-172
2d		 **(3d)**	35	95	192-194
2e		 **(3e)**	32	94	198-200
2f		 **(3f)**	35	93	180-182

thionyl chloride be the best suitable system for the condensation. Yield of the product is 95 % in 30 min at room temperature. Finally, we got a conclusion that the ethanol-thionyl chloride system is better with good yield of the 2,3-dihydroquinazolin-4(1*H*)-ones in less reaction time.

The application of the optimized conditions to various aldehydes (**2a-2f**) resulted the formation of their corresponding 2-aryl-2,3-dihydroquinazolin-4(1*H*)-ones (**3a-3f**) in good yield and better purity without carrying any further purification (Table-2).

Anticancer activity: All the six compounds **(3a-3f)** were tested for their anticancer activity on A549 (human lung carcinoma) cell line and found that except the sample **3f** all the compounds were showed good percentage of inhibition (Table-3). Moreover, the compounds **3c** (74.22 %) and **3e** (73.45 %) had showed significant activity against the tested A549 cell line indicating the analogs of this kind may further increase the activity.

TABLE-3
ANTICANCER ACTIVITY RESULTS OF A549 CELL LINE

Compound	Concentration (µg/mL)	Inhibition (%)
3a	100	57.75
3b	100	56.98
3c	100	74.22
3d	100	54.07
3e	100	73.45
3f	100	33.14
Etoposide	100	100

Antioxidant activity: All the synthesized compounds (**3a-3f**) were also tested for their antioxidant activity by DPPH method at five different test concentrations *i.e.* 100, 200, 300, 400 and 500 µg/mL. From their related absorbance obtained the percentage of inhibition was calculated and found that no particular compound was showed better activity when compared with the reference sample ascorbic acid (Fig. 1).

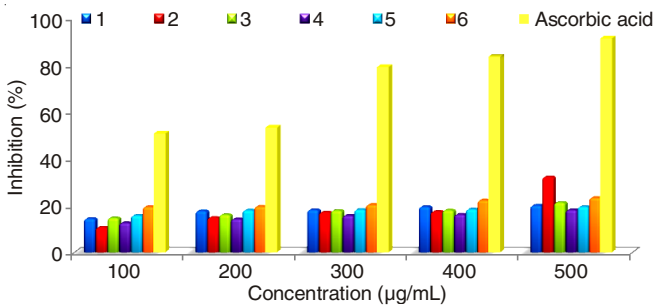


Fig. 1. Antioxidant activity comparison graph of synthesized new compound **3a**, **3b**, **3c**, **3d**, **3e** and **3f** with standard ascorbic acid

Conclusion

A simple and reliable method was developed for the synthesis of various bulky 2,3-dihydroquinazolin-4(1*H*)-ones, using thionyl chloride as catalyst in ethanol at room temperature. The simple reaction conditions, small timing, easy work up and very good yields are the greatest advantages of this methodology. Compounds **3c** (74.22 %) and **3e** (73.45 %) showed better anticancer activity against the tested A549 cell line and remaining have considerable activity except **3f**.

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