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An Efficient Suitable Synthesis for Pyrazole, Pyrimidine Derivatives and Biological Evaluation

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Novel quinazoline derivatives were synthesized by reacting isatoic anhydride and 4-amino acetanilide to synthesize *N*-(4-(2,4-dioxo-1,2-dihydroquinazolin-3(4*H*)-yl)phenyl)acetamide which in turn reacted with substituted aromatic aldehydes to synthesize novel chalcones. The chalcones were allowed to react with hydrazine hydrochloride and guanidine to form pyrazoline and pyrimidine derivatives, respectively. The newly synthesized compounds were characterized by IR, NMR (^{1}H, ^{13}C), mass and elemental analysis. All the newly synthesized derivatives were screened for *in vitro* antimicrobial and antioxidant activities to evaluate their biological potency.

Keywords: Quinazoline, Chalcones, Pyrazoline, Pyrimidine, Antimicrobial, Antioxidant.

INTRODUCTION

Quinazoline derivatives belongs to N-containing heterocyclic compounds have a great interest in organic synthesis and medicinal chemistry as they possess a wide range of pharmacological activities. They exhibits antimicrobial [1-6], antioxidant [7], analgesic [8], anti-inflammatory [9], antidepressant [10], antitumor [11] and antimalarial [12-16]. The heterocyclic compounds usually possess a stable ring structure which does not readily hydrolyzed or depolymerized. Therefore, pyrazolines and pyrimidines play an important role in the biomedical fields [17].

Pyrazolines are electron rich nitrogen containing heterocycles which plays a vital role in diverse biological activities prompted by above mentioned observations attention has been focused on pyrazolines due to their interesting pharmacological activities like acetylcholinesterase inhibitors [18].

Pyrimidine plays an active role in many biological process since their ring system present in several vitamins and nuclic acids. The members of this group are important as antitubercular [19] and anticonvulsant [20]. The quinazolinone nucleus incorporated with substitution of different heterocyclic moieties at 2- or 3-position will modulate the biological activities. This prompted us to design and synthesize a new series of some novel 2,3-dihydroqunazolin-4(1*H*)-ones incorporated with chalcone, pyrazoline and pyrimidine moieties at position 3 of the quinazolinone nucleus and examined the potential role of these derivatives as antimicrobial and antioxidant agents.

EXPERIMENTAL

All the reagents and solvents were of AR grade and procured from Merck (Mumbai, India) and CDH (New Delhi, India), respectively. Distillation of strong ethyl alcohol containing more than 1 mol of calcium chloride (111 parts) for 1 mol of water (18 parts) yielded alcohol of 99.5% concentration or stronger. All the synthesized compounds were recrystallized in absolute ethanol. Melting points were recorded using open end capillaries and are uncorrected. Reaction improvement was monitored on thin-layer chromatography (TLC) using silica gel G (Merck) as stationary phase, iodine chamber and UV lamp were used for visualization of TLC spots.

The IR spectra were recorded in the solid state on JASCO spectrophotometer using KBr pellet. Bruker AVANCE-400 MHz was used to record ^{1}H NMR spectra of the synthesized compounds in $CDCl_3$/DMSO while ^{13}C NMR spectra were recorded using $CDCl_3$ or DMSO-d_6 at 100 MHz with TMS as internal reference. ESI-MS were recorded on WATER Q-TOF Premier-HAB213 and Perkin-Elmer 240 analyzer was used to perform elemental analysis.

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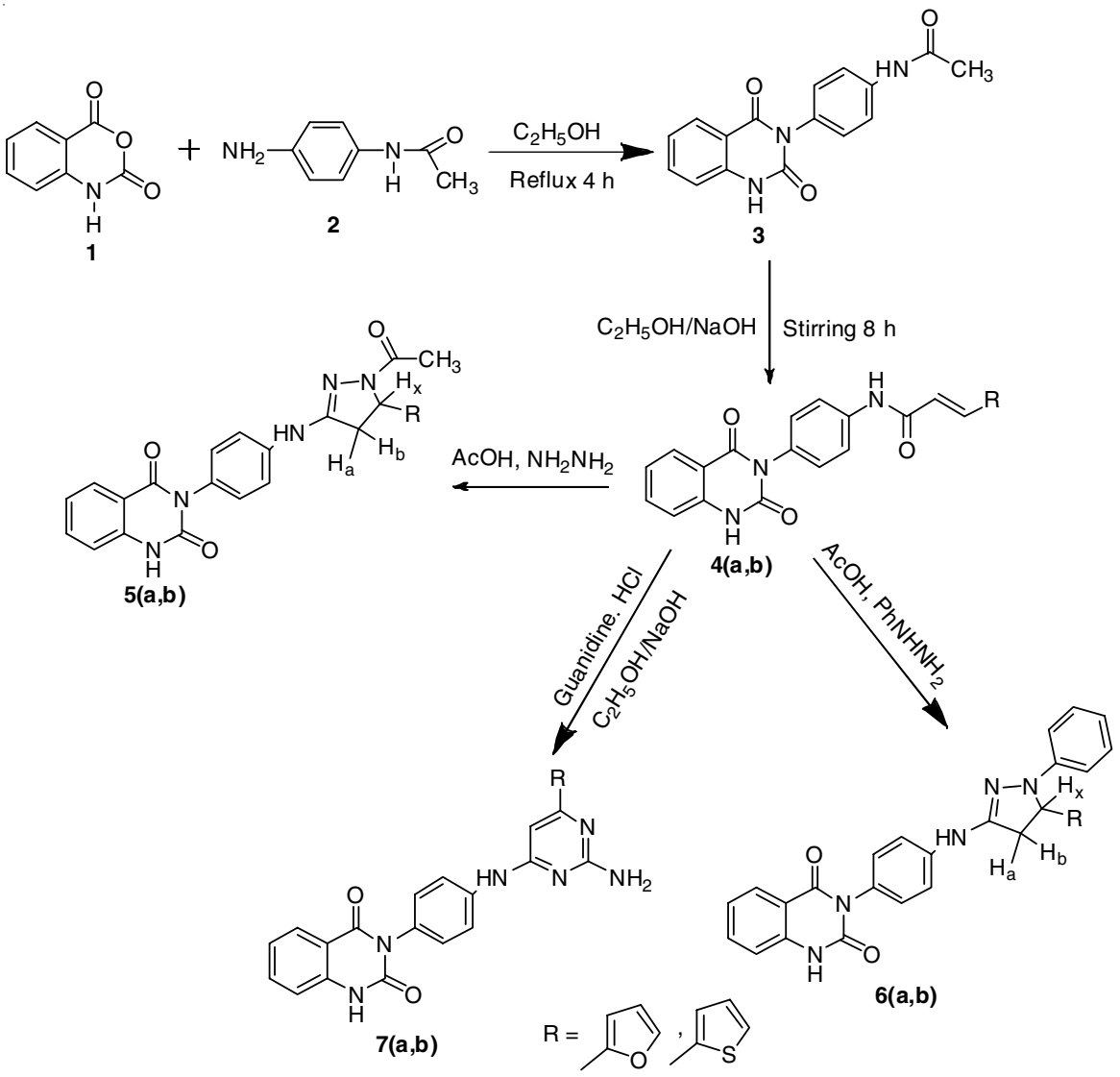
General procedure: As depicted in **Scheme-I**, a reaction between the commercially available isatoic anhydride (1 equiv., **1**) and 4-amino acetanilide (1 equiv., **2**) with pyridine in absolute ethanol is refluxed for 4 h. The reaction mixture is poured on crushed ice. The obtained intermediate **3** was filtered and recrystallized with absolute ethanol. Chalcone (**4a-b**) was synthesized by treating isolated compound **3** with different aldehydes with NaOH in ethanol and stirred for 8 h. Reaction was monitored by TLC. After the completion of reaction the reaction mixture was poured on ice cold water with constant stirring. The chalcones was washed with water, filtered and dried to give the crude product **4a-b** and finally recrystallized by absolute ethanol.

To chalcone **4a-b** (1 equiv.), hydrazine hydrate/phenylhydrazine (1 equiv.) was added in glacial acetic acid and refluxed in oil bath for 4 h. Reaction was monitored by TLC. After the completion of reaction, the reaction mixture was cooled to room temperature and concentrated. The solid obtained **5a-b/ 6a-b** was washed with water, filtered, dried and finally recrystallized from absolute ethanol.

To chalcone **4a-b** (1 equiv.), guanidine hydrochloride (1 equiv.) was added with NaOH in ethanol and refluxed for 6-8 h. Reaction was monitored by TLC. After the completion of reaction, the reaction mixture was cooled to room temperature and concentrated. The solid obtained **7a-b** was washed with water, filtered, dried and recrystallized from absolute ethanol.

***N*-(4-(2,4-Dioxo-1,2-dihydroquinazolin-3(4*H*)-yl)-phenyl)acetamide (3):** Dirty white powder, yield: 89%, m.p.: 144-146 ºC, R_f = 0.64, IR (KBr, ν_{max}, cm^{-1}): 754 (s), 837 (s), 1108 (s), 1112 (s), 1177 (m), 1249 (m), 1267 (s), 1396 (m) (C-N), 1512 (m), 1659 (m) (-NHC=O), 1745 (m) (C=O), 2835 (w), 2933 (w), 3073 (w), 3308 (s) (-NH *str*.). ^{1}H NMR (400 MHz, DMSO) δ ppm: 9.48 (s, 1H, -NH), 7.73 (d, *J* = 8 Hz, 2H, Ar-H), 7.91(d, 4 Hz, 2H, Ar-H), 6.10-7.14 (m, 4H, Ar-H), 4.24 (s, 1H, -NH), 2.05 (s, 3H, CH_3).

(*E*)-*N*-(4-(2,4-Dioxo-1,2-dihydroquinazolin-3(4*H*)-yl)-phenyl)-3-(furan-2-yl)acrylamide (4a): Yellow powder, yield: 82%, m.p.: 190-192 ºC, R_f = 0.66, IR (KBr, ν_{max}, cm^{-1}): 831 (m), 1012 (s), 109 (m), 1206 (m), 1280 (m), 1359 (m) (C-O-C-), 1391 (m), 1484 (m), 1581 (s) (C=C), 1650 (s) (NH-



Scheme-I:

C=O), 1696 (m) (N-C=O), 1719 (m) (C=O), 2912 (w), 3037 (w), 3405 (s) (-NH *str*.). ^{1}H NMR (400 MHz, DMSO) δ ppm: 10.50 (s, 1H, -NH), 8.16 (d, *J* = 8 Hz, 2H, Ar-H), 7.75-8.05 (m, 4H, Ar-H), 7.67 (d, *J* = 8 Hz, 1H, -CH=CH), 7.64 (d, *J* = 12 Hz, 2H, Ar-H), 7.26 (d, *J* = 8 Hz, 1H, -CH=CH), 6.78 (s, 1H, -NH).

(*E*)-*N*-(4-(2,4-Dioxo-1,2-dihydroquinazolin-3(4*H*)-yl)-phenyl)-3-(thiophen-2-yl)acrylamide (4b): Dark yellow powder, yield: 85%, m.p.: 202-204 ºC, R_f = 0.69, IR (KBr, ν_{max}, cm^{-1}): 458 (s), 537 (s), 687(m), 743 (m), 818 (m), 1019 (s), 1290 (s) (C-S-C), 1407 (m), 1505 (m) (C=C), 1630 (m) (-NH-C=O), 1680 (m) (N-C=O), 1714 (m) (-C=O), 2919 (s), 3342 (w) (-NH *str*.). ^{1}H NMR (400 MHz, SO) δ ppm: 10.47 (s, 1H, -NH), 8.18 (d, *J* = 4 Hz, 2H, Ar-H), 8.00 (d, *J* = 2 Hz, 2H, Ar-H) 7.68-7.80 (m, 4H, Ar-H), 7.33-7.67 (m, 3H, Ar-H), 7.27 (d, *J* = 8 Hz, 1H, -CH=CH), 7.23 (d, *J* = 8 Hz, 1H, -CH=CH), 6.93 (s, 1H, -NH).

3-(4-((1-Acetyl-5-(furan-2-yl)-4,5-dihydro-1*H*-pyrazol-3-yl)amino)phenyl)quinazoline-2,4(1*H*,3*H*)-dione (5a): Dark brown powder, yield: 81%, m.p.: 170-172 °C, R_f = 0.77, IR (KBr, ν_{max}, cm^{-1}): 526 (s), 595 (s), 749 (m), 824 (m), 1025 (s), 1118 (s) (N-N), 1168 (s), 1240 (m) (N-N=C), 1304 (s), 1407 (s) (C-N), 1519 (m), 1595 (m) (C=N), 1655 (m) (NHC=O), 1713 (m) (-C=O), 2829 (w), 2917 (w), 3307 (s) (-NH *str.*). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.06-7.39 (m, 4H, Ar-H), 6.91(d, *J* = 8 Hz, 2H, Ar-H), 6.76 (d, *J* = 8 Hz, 2H, Ar-H), 6.58 (s, 1H, -NH), 6.45 (dd, *J* = 8 Hz, 16 Hz, 1H, -CH), 4.10 (s, 1H, -NH), 3.94 (dd, *J* = 8 Hz, 12 Hz, 1H, -CH_2), 3.49 (dd, *J* = 2 Hz, 4 Hz, 1H, -CH_2), 2.49 (S, 3H, -$COCH_3$). ^{13}C NMR (100 MHz, DMSO): δ168.40, 168.16, 168.06, 167.14, 161.84, 158.54, 152.94, 146.61, 143.15, 137.60, 135.46, 131.76, 128.92, 128.34, 128.10, 127.98, 127.17, 126.98, 119.24, 116.98, 106.46, 69.73, 39.73, 24.04. MS (ESI) *m/z*: 430 [(M+1)]; Anal. calcd. (found) % for $C_{23}H_{19}N_5O_4$: C 64.33 (64.04); H 4.46 (4.09); N 16.31 (16.12).

3-(4-((1-Acetyl-5-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazol-3-yl)amino)phenyl)quinazoline-2,4(1*H*,3*H*)dione (5b): Brown powder, yield: 78%, m.p.: 188-190 ºC, R_f = 0.67, IR (KBr, ν_{max}, cm^{-1}): 692 (s), 747 (s), 838 (s), 955 (m), 1010 (w) (N-N), 1150 (s), 1232 (s) (N-N=C), 1301 (m), 1377 (s) (C-N), 1510 (s) (C=N), 1613 (w), 1640 (w) (NHC=O), 1696 (s) (-C=O), 2925 (w), 3055 (w), 3295 (s) (-NH *str*.). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.18-7.27 (m, 4H, Ar-H), 6.88-7.00 (m, 3H, Ar-H) 6.86 (d, *J* = 8 Hz, 2H, Ar-H), 6.80 (d, *J* = 8 Hz, 2H, Ar-H), 6.02 (s, 1H, -NH), 5.90 (dd, *J* = 4 Hz, 8 Hz, 1H, -CH), 4.08 (s, 1H, -NH), 3.49 (dd, *J* = 4 Hz, 8 Hz, 1H, -CH_2), 3.94 (dd, *J* = 8 Hz, 12 Hz, 1H, -CH_2), ^{13}C NMR (100 MHz, DMSO): δ 168.51, 168.21, 167.78, 161.75, 155.84, 149.76, 146.97, 146.47, 144.57, 137.58, 135.32, 135.10, 134.52, 133.90, 132.18, 131.10, 128.74, 128.04, 127.17, 126.54, 126.41, 121.12, 119.90, 119.24, 119.10, 116.47, 115.62, 115.42, 115.27, 114.87, 68.78, 39.52, 24.08, 24.00. MS (ESI) *m/z*: 447 [(M+2)]; Anal. calcd. (found) % for $C_{23}H_{19}N_5O_3S$: C 62.01 (62.00), H 4.30 (4.19), N 15.72 (15.45).

3-(4-((5-(Furan-2-yl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)amino)phenyl)quinazoline-2,4(1*H*,3*H*)dione (6a): Yellowish orange powder, yield: 86%, m.p.: 182-184 ºC, R_f = 0.69, IR (KBr, ν_{max}, cm^{-1}): 595 (m), 699 (m), 756 (s), 839 (m), 1019 (m) (N-N), 1128 (w), 1234 (m) N-N=C), 1308 (m), 1398 (m) (C-N), 1544 (m), 1630 (m) (C=N), 1675 (m) (NH-C=O), 1737 (m) (C=O), 2937 (w), 3055 (w), 3247 (s) (N-H). ^{1}H NMR (400 MHz, DMSO) δ ppm: 7.84-7.87 (m, 5H, Ar-H), 7.30 (d, *J* = 4 Hz, 2H, Ar-H), 6.85-7.28 (m, 4H, Ar-H), 6.55-6.83 (m, 3H, Ar-H), 6.43 (d, *J* = 8 Hz, 2H, Ar-H), 5.92 (dd, *J* = 8 Hz, 12 Hz, 1H, -CH), 5.91 (s, 1H, -NH), 3.94 (dd, *J* = 8 Hz, 12 Hz, 1H, -CH_2), 3.49 (dd, *J* = 2 Hz, 8 Hz, 1H, -CH_2), 2.49 (s, 1H, -NH), ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 167.49, 152.18, 148.51, 145.41, 142.02, 134.51, 133.95, 128.58, 128.00, 127.90, 126.25, 120.76, 119.74, 119.69, 118.40, 116.52, 115.71, 114.57, 112.02, 109.83, 108.19, 67.94, 40.15. MS (ESI) *m/z* 465 [(M+2)]; Anal. calcd. (found) % for $C_{23}H_{21}N_5O_3$: C 69.97 (69.24); H 4.57 (4.49); N 15.11 (15.02).

3-(4-((1-Phenyl-5-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazol-3-yl)amino)phenyl)quinazolie-2,4(1*H*,3*H*)dione (6b): Orange powder, yield: 89%, m.p.: 198-200 ºC, R_f = 0.71, IR (KBr, ν_{max}, cm^{-1}): 505 (s), 588 (m), 685 (m), 741 (s), 824 (m), 1010 (m), 1101 (m) (N-N), 1160 (s), 1240 (m) (N-N=C), 1310 (m)(C-N), 1380 (w), 1503 (s), 1606 (m) (C=N), 1660 (m) (NHC=O), 1723 (m) (C=O), 2832 (w), 2928 (w), 3289 (w) (-NH *str.*).^{1}H NMR (400 MHz, DMSO) δ ppm: 7.30-7.87 (m, 5H, Ar-H), 7.27 (d, *J* = 4 Hz, 2H, Ar-H), 6.83 (d, *J* = 8 Hz, 2H, Ar-H), 6.55-6.77 (m, 4H, Ar-H), 6.02-6.07 (m, 3H, Ar-H), 6.00 (s, 1H, -NH), 5.99 (dd, *J* = 4 Hz, 6 Hz, 1H, -CH), 3.94 (dd, *J* = 8 Hz, 12 Hz, 1H, -CH_2), 3.49 (dd, *J* = 2 Hz, 4 Hz, 1H, -CH_2), 2.14 (s, 1H, -NH), ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.96, 167.14, 161.94, 159.56, 149.76, 146.47, 144.57, 137.59, 135.92, 135.10, 132.20, 129.41, 127.32, 126.51, 126.01, 120.30, 112.89, 59.55, 39.58. MS (ESI) *m/z* [(M+2)]; Anal. calcd. (found) % for $C_{27}H_{21}N_5O_2S$: C 67.62 (67.56); H 4.41 (4.29); N 14.60 (14.25).

3-(4((2-Amino-6-(furan-2-yl)pyrimidin-4-yl)amino)-phenyl)quinazoline-2,4(1*H*,3*H*)-dione (7a): Dark brown powder, Yield: 82%, m.p.: 166-168 ºC, R_f = 0.71, IR (KBr, ν_{max}, cm^{-1}): 757 (m), 832 (m), 953 (s), 1155 (s), 1222 (s), 1316 (s) (C-N), 1396 (s), 1515 (s) (C=N), 1605 (m), 1640 (s) (-NHC=O), 1719 (s) (C=O), 3286 (m) (-NH *str.*), 3356 (s) 3444 (s) (-NH_2 *str*.). ^{1}H NMR (400 MHz, DMSO) δ ppm: 7.30 (s, 2H, -NH_2), 6.88 (d, *J* = 4 Hz, 2H, Ar-H), 6.70-6.87 (m, 4H, Ar-H), 6.69 (s, 1H, -CH), 6.52-6.56 (m, 3H, Ar-H), 6.50 (d, *J* = 4 Hz, 2H, Ar-H), 6.25 (s, 1H, -NH), 4.09 (s, 1H, -NH), ^{13}C NMR (100 MHz, DMSO) δ ppm: 168.51, 168.21, 167.79, 161.75, 155.94, 149.76, 146.47, 144.57, 137.59, 135.22, 135.10, 134.52, 133.90, 132.19, 131.10, 128.70, 128.04, 127.17, 126.54, 126.45, 126.01, 121.12, 119.30, 119.24, 118.18, 116.47, 115.82, 115.42, 115.27, 114.87. MS (ESI) *m/z*: 413 [(M+1)]; Anal. calcd. (found) % for $C_{22}H_{16}N_6O_3$: C 64.07 (64.01); H 3.91 (3.29); N 20.38 (20.14).

3-(4-((2-Amino-6-(thiophen-2-yl)pyrimidin-4-yl)-amino)phenyl)quinazoline-2,4(1*H*,3*H*)-dione (7b): Dark brown powder, yield: 86%, m.p.: 192-194 ºC, R_f = 0.70, IR KBr, ν_{max}, cm^{-1}): 512 (s), 746 (s), 824 (s), 944 (s), 1013 (m), 1100 (w), 1150 (s), 1222 (m), 1307 (s) (C-N), 1398 (s), 1512 (m) (C=N), 1630 (m) (-NHC=O), 1675 (m) (-C=O), 2929 (w), 3254 (m) (-NH *str.*), 3388 (s) 3459 (s) (-NH_2 *str*.). ^{1}H NMR (400 MHz, DMSO) δ ppm: 7.68 (s, 2H, -NH_2), 7.32-7.51 (m,

4H, Ar-H), 7.27-7.51 (m, 3H, Ar-H), 6.73 (d, *J* = 4 Hz, 2H, Ar-H), 6.56 (d, *J* = 4 Hz, 2H, Ar-H), 6.49 (s, 1H, -CH), 6.29 (s, 1H, -NH), 3.37 (s, 1H, -NH), ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 168.96, 168.06, 167.14, 161.84, 159.54, 152.18, 148.51, 145.41, 142.02, 134.51, 133.95, 128.50, 128.00, 127.90, 126.25, 120.76, 119.74, 119.69, 118.40, 116.51, 115.71, 114.57, 112.02, 109.82, 108.19. MS (ESI) *m/z*: 430 [(M+1)]; Anal. calcd. (found) % for $C_{22}H_{16}N_6O_2S$: C 61.67 (61.51); H 3.59 (3.76); N 19.61 (19.38).

Antimicrobial assay (antibacterial and antifungal): Antimicrobial analysis was followed using standard agar well diffusion method to study the antimicrobial activity of compounds. Each bacterial isolate was suspended in brain heart infusion (BHI) broth and diluted to approximately 10^5 colony forming unit (CFU) per mL. They were flood-inoculated onto the surface of Media (Mueller Hinton Agar for bacteria and Sabouraud's Dextrose agar for fungi) and then dried. 5 mm diameter wells were cut from the agar using a sterile cork-borer and 30 µL (5 µg compound in 500 µL DMSO) of the sample solution were poured into the wells. The plates were incubated for 18 h at 37 ºC for bacteria. Similarly, fungal plates were incubated at room temperature for 48 h. Antimicrobial activity was evaluated by measuring the diameter of the zone of inhibition in mm against the test microorganisms and the solvent. DMSO was used as solvent control. Ciprofloxacin was used as reference antibacterial agent. Amphotericin B was used as reference antifungal agent for fungi. The experiments were carried out in triplicates.

***in vitro* Antioxidant activity**

DPPH-free radical scavenging activity: The stable radical DPPH was used to measure the free radical scavenging activity of chalcone derivatives. DPPH (1×10^{-4} M) solution was prepared in DMSO and 1 mL of DPPH is added to different volume of chalcone derivatives (0.1, 0.2 and 0.3 mL) prepared in DMSO and the resulting mixture was allowed for vigorous stirring for complete dissolution. DPPH solution was used as a control. The sample test tubes were covered with aluminium foil before adding DPPH and then incubated at 37 ºC for about 30 min in dark condition. Later, inhibition of DPPH radical by the organic samples was measured by using a UV-visible spectrometer at λ 517 nm against the blank (DMSO). The DPPH scavenging activity of the synthesized chalcone derivatives was calculated by using the following formula:

$$\text{Inhibition (\%)} = \frac{A_{control} - A_{sample}}{A_{control}} \times 100$$

Ascorbic acid was used as a standard, the antioxidant activity exhibited by the standard and chalcone derivatives at various concentrations were observed.

Hydrogen peroxide scavenging method: The hydrogen peroxide scavenging potentiality of the synthesized compounds was carried out according to the method reported by Ruch *et al*. [21] with minor modifications. A solution of H_2O_2 was prepared in phosphate buffer (pH 7.4). Different concentration of sample was added to a hydrogen peroxide solution. Later, inhibition of H_2O_2 radical by the organic samples was measured by using a UV-visible at λ 230 nm was determined after 15 min against the blank solution (phosphate buffer). Ascorbic acid was used as standard. The free radical scavenging activity was determined by evaluating % inhibition as

$$\text{Inhibition (\%)} = \frac{A_{control} - A_{sample}}{A_{blank}} \times 100$$

where $A_{control}$ is the absorbance of the control reaction and A_{sample} is the absorbance of the chalcone derivatives. The experiments were carried in triplicate.

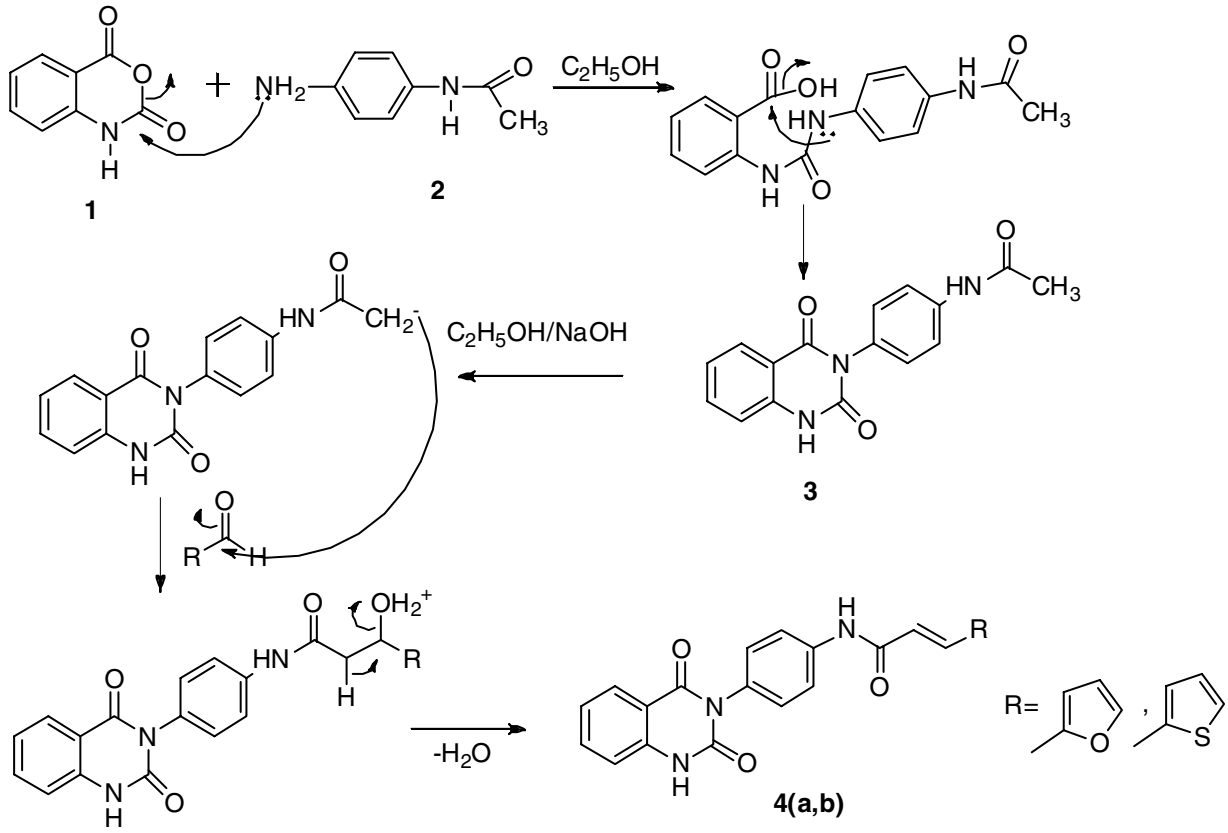
RESULTS AND DISCUSSION

In this work, we mainly focussed to synthesize a series of novel chalcones and their derivatives. In **Scheme-II**, required intermediate *N*-(4-(2,4-dioxo-1,2-dihydroquinazolin-3(4*H*)-yl)phenyl)acetamide (**3**) was synthesized by refluxing isatoic anhydride and amino acetanilide in the presence of ethanol and catalytic amount of pyridine.

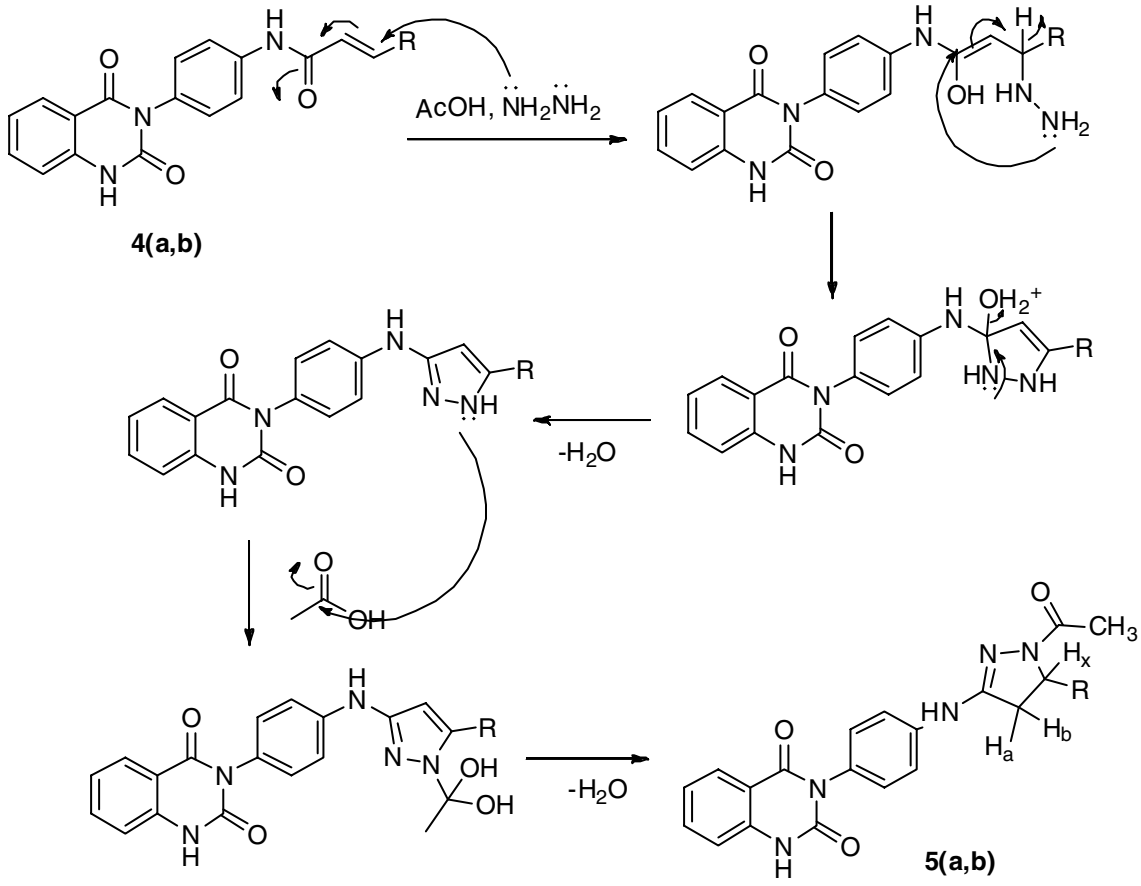
Mechanism: In the formation of compounds **5**, **6** and **7**, it follows 1,4-Michael addition, cyclization and dehydration. Particularly, for the formation of pyrazoline derivatives **5a-b** and **6a-b**, hydrazine and phenylhydrazine acted as a nucleophile. In this manner, the polar protic solvent (acetic acid) acted as a proton donor as well as dehydrating agent. In case of compound **5a-b**, acetylation takes place due to the presence of nucleophilic –NH group (**Scheme-III**) but in case of compound **6a-b** acetylation was not possible due to the absence of nucleophilic –NH group (**Scheme-IV**). In compound **7a-b**, guanidine hydrochloride act as a nucleophile and undergo nucleophilic substitution reaction followed by cyclization with the removal of water molecule (**Scheme-V**).

Characterization: Formation of compound **3** was confirmed by IR absorption spectra at 1396 cm^{-1} for C-N stretching. Compound **3** was then converted to chalcones (**4a-b**) by stirring with different substituted aldehydes. IR absorption band at 1719 cm^{-1} shows presence of carbonyl group and appearance of doublet at 7.67 and 7.26 δ ppm shows the presence of unsaturated alkenes.

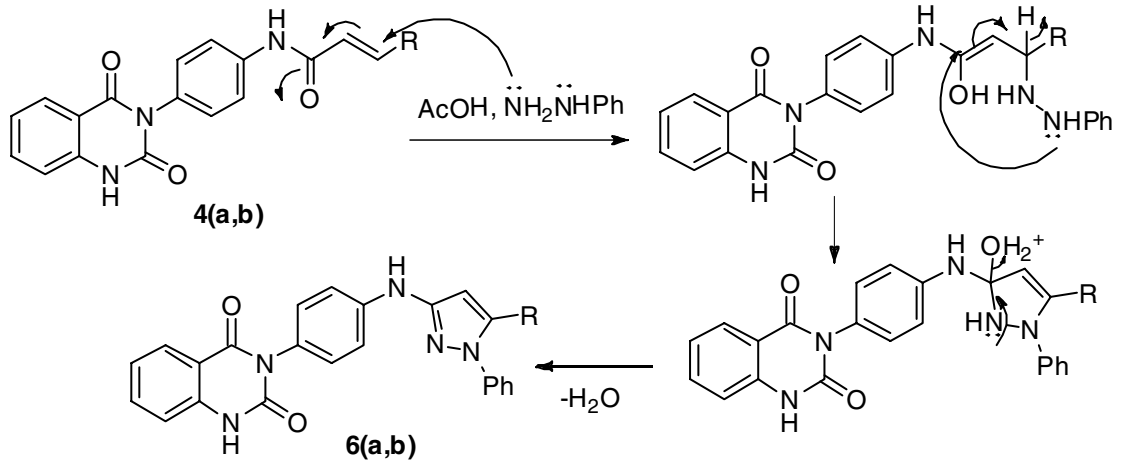
Compound **4a-b** when treated with hydrazine and acetic acid to obtain 3-(4-((1-acetyl-5-(furan-2-yl)-4,5-dihydro-1*H*-pyrazol-3-yl)amino)phenyl)quinazoline-2,4(1*H*,3*H*)-dione (**5a**) and 3-(4-((1-acetyl-5-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazol-3-yl)amino)phenyl)quinazoline-2,4(1*H*,3*H*)-dione (**5b**), respectively. Formation of these compounds has been confirmed by the formation of C=N at 1595 and 1510 cm^{-1}, respectively. From ^{1}H NMR, there is an existence of pyrazole ring by showing doublet of doublet for H_a, H_b and H_x at δ 3.94, 3.49 and 6.45, respectively. Compound **4a-b** when treated with phenyl hydrazine and acetic acid to obtain 3-(4-((5-(furan-2-yl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)amino)phenyl)-quinazoline-2,4(1*H*,3*H*)-dione (**6a**) and 3-(4-((1-phenyl-5-(thio-phen-2-yl)-4,5-dihydro-1*H*-pyrazol-3-yl)amino)phenyl)-quinazolie-2,4(1*H*,3*H*)-dione (**6b**), respectively. Formation of these compounds has been confirmed by the formation of C=N at 1606 and 1630 cm^{-1}, respectively. From ^{1}H NMR there is an existence of pyrazole ring by showing doublet of doublet for



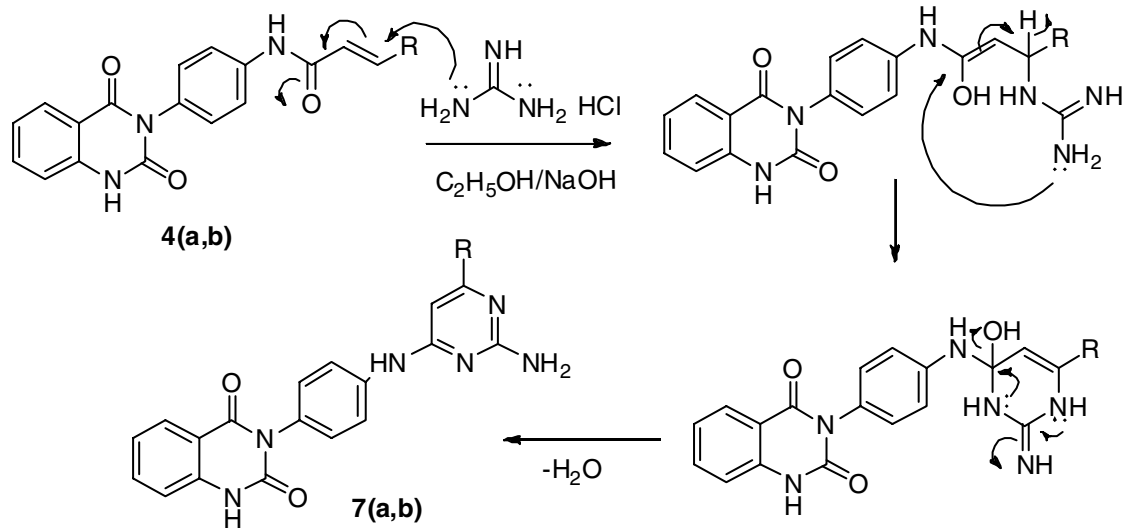
Scheme-II



Scheme-III



Scheme-IV



Scheme-V

H_a, H_b and H_x at δ 3.94, 3.49 and 5.99, respectively. Compound **4a-b** when treated with guanidine hydrochloride to form 3-(4((2-amino-6-(furan-2-yl)pyrimidin-4-yl)amino)phenyl)-quinazoline-2,4(1*H*,3*H*)-dione (**7a**) and 3-(4-((2-amino-6-(thiophen-2-yl)pyrimidin-4-yl)amino)phenyl)quinazoline-2,4-(1*H*,3*H*)-dione (**7b**), respectively. This structure has been confirmed by the presence of singlet with two spikes for NH_2 group, which appeared at 3356 and 3444 cm^{-1}.

Biological activities: The biological activity results showed that the compound **7a** exhibit good antibacterial and antioxidant (DPPH assay) activities compared to the standard drug (Table-1). Compound **6b** exhibit a notable antifungal activity and antioxidant activity (H_2O_2 assay) when compared to the standard drug (Table-2). Ultimately, it is concluded that in future to discover as a new class of drug by proceeding *in vivo* investigation for these synthesized derivatives.

TABLE-1
ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES OF PYAZOLE AND PYRIMIDINE DERIVATIVES
(ZONE OF INHIBITION IN mm, # MIC IN μg/mL GIVEN IN PARENTHESIS)

Compound	Antibacterial activity				Antifungal activity			
	Staphylococus aureus	*Enterococcus faecelis*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Aspergillus niger*	Amphotericin-B	*Aspergillus fumigatus*	Amphotericin-B
5a	10 (50)	9 (50)	8 (50)	-	-	5 (12.25)	-	10 (6.25)
5b	12 (12.5)	9 (50)	8 (50)	10 (50)	4 (12.25)	6 (8.22)	6 (9.75)	10 (6.25)
6a	15 (12.5)	6 (50)	-	-	15 (9.59)	5(12.25)	5 (12.25)	10 (6.25)
6b	8 (50)	9 (50)	6 (50)	9 (50)	11(7.24)	6 (8.22)	7 (9.25)	10 (6.25)
7a	10 (12.5)	11(12.5)	12 (12.5)	10 (50)	5 (12.25)	5 (12.25)	5 (12.25)	10 (6.25)
7b	12 (12.5)	10 (50)	10 (50)	9 (50)	5 (12.25)	6 (8.22)	8 (6.25)	10 (6.25)
Ciprofloxacin (mm)	20 (6.25)	22 (6.25)	22 (6.25)	30 (6.25)	–	–	–	–

TABLE-2
FREE RADICAL SCAVENGING ACTIVITY OF THE SYNTHESIZED PYRAZOLE AND PYRIMIDINE DERIVATIVES USING DPPH AND H_2O_2 ASSAY

Compound	DPPH				H_2O_2			
	Absorbance (%)			IC_{50}	Absorbance (%)			IC_{50}
	100 ppm	200 ppm	300 ppm		100 ppm	200 ppm	300 ppm	
5a	50.21 ± 0.13	70.72 ± 0.09	70.72 ± 0.04	0.64	35.31 ± 0.32	47.22 ± 0.26	72.72 ± 0.24	45.64
5b	48.72 ± 0.07	66.18 ± 0.05	69.88 ± 0.11	0.90	34.82 ± 0.18	46.18 ± 0.09	69.98 ± 0.41	44.46
6a	50.16 ± 0.11	67.90 ± 0.08	73.14 ± 0.21	0.81	24.26 ± 0.05	36.80 ± 0.28	73.14 ± 0.21	54.91
6b	49.43 ± 0.04	66.04 ± 0.02	68.69 ± 0.19	0.80	29.43 ± 0.34	43.64 ± 0.09	66.99 ± 0.14	42.80
7a	51.82 ± 0.15	70.99 ± 0.03	71.65 ± 0.08	0.50	35.42 ± 0.15	61.99 ± 0.23	71.65 ± 0.08	33.50
7b	46.07 ± 0.02	74.97 ± 0.12	76.48 ± 0.18	0.96	41.47 ± 0.12	66.97 ± 0.02	79.88 ± 0.18	31.96
Standard	52.66 ± 0.16	80.05 ± 0.09	81.05 ± 0.20	0.51	38.16 ± 0.06	50.05 ± 0.29	77.05 ± 0.07	39.32

Data represents mean ± SD of triplicates.

Conclusion

In summary, a new series of pyrazole and pyrimidine derivatives were synthesized and characterized. The newly synthesized compounds were also screened for their antimicrobial and antioxidant activities to know their biological potency.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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