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Research Article

SYNTHESIS ANDANTIBACTERIAL ACTIVITY OF 3-PHENYL SUBSTITUTED QUINAZOLINONE DERIVATIVES VIA CHALCONES

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ABSTRACT

Synthesis of a new series of pyrazoline derivatives (Q_{1-4},P_{1-4},Ph_{1-4}& Py_{1-4}) have been obtained from the starting materials anthranilic acid (A) and benzoyl chloride (B) to 2[phenyl]-benzo(1,3)oxazine-4-one (C) in pyridine further reaction with *p*-amino acetophenonegives 3-(4-acetyl phenyl)-2-(phenyl)-3H quinazoline-4-one (D) derivatives.Then on condensation with different substituted aromatic aldehydes afforded four Q_{1-4} compounds. Then further incorporated into pyrazoline, N-phenyl pyrazoline and N-acetyl pyrazoline ring systems at position 3 of the quinazoline ring. The newly synthesized compounds have been supported by spectral data IR, H^1NMR and Mass spectra. The compounds Q_{1-4} and P_{1-4}were screened for antibacterial activity by using cup plate method.

INTRODUCTION

Quinazoline have been frequently used in medicine because of their wide range of biological activities[1-5]. Different quinazoline derivatives have been reported for their antibacterial, antifungal, anti HIV, anthelimentics, CNS depressants and ant tubercular activities. Besides these the quinazolinones kelton is frequently encountered as building block or hundreds of naturally occurring alkaloids and hence the exploration of this skelton as privileged new chemical entities in drug discovery research is beyond doubt of paramount importance for the synthetic chemist.

Experimental section

Melting points of the synthesized compounds were determined in open capillary tubes and were uncorrected.IR spectra were recorded on BRUKER FT-IR spectrometer using ATR.^{1}H-NMR spectra of the compounds in deutiriated dimethyl sulfoxide (DMSO) and $CDCl_3$was recorded on BRUKER Av 400 spectrometer. Mass spectra were recorded on LCMS QP 5000 Shimadzu.Thin layer chromatography was performed using pre-coated aluminiumplates, coated with silica gel GF_{254} [E.Merck]. Ethylacetate: Methanol in the ratio of 3 : 2 was used as the eluent. The spots were visualized in the UV/Iodine chamber.

METHOD OF SYNTHESIS

Synthesis of 3-(4-acetyl phenyl)-2-(phenyl)-3H quinazoline-4-one derivatives(D)

To 0.01moles of Anthralinic acid is added to 0.02moles of benzoyl chloride in pyridine (100ml). Kept for a reflux for 1hr 45 min. The mixture was shaken for 10 min and then set aside at room temp for further 1hr with occasional shaking. The reaction mixture was poured in to cold water with stirring then solid white color product was separated out, filtered and dried in a vacuum desiccator up to complete drying of compound. The compound was recrystallized from dioxane. Percentage yield 98%w/w was obtained and melting point was found to be 58-60^{0}C.To a mixture of compound (C) (0.01 moles) and p-amino acetophenone was heated at 150^{0}C on sand bath for 1hr. After cooling the crude mass was crystallised from ethanol twice to give reddish brown crystals.

Synthesis of 3(4(3(4-substituted phenyl) acrolyl) phenyl) 2-phenyl quinazoline (4*H*)-one (Q_{1-4})

Equimolar mixture of compound D (0.01mole) and the appropriate aromatic aldehydes (0.01mole) *p*-chlorobenzaldehyde, *p*-nitro benzaldehyde, *p*-methylbenzaldehyde and *p*-methoxybenzaldehyde were dissolved in ethanol and cold solution of 40% NaOH (15mL) was added in portion keeping the temperature below 10C with continuous stirring. The reaction mixture was kept overnight. Then it was acidified with dilute Hcl and poured ice cold water with stirring. The product obtained was filtered, washed with cold water dried and recrystallised from ethanol.

Synthesis of pyrazolines (P_{1-4})/ N-acetylpyrazolines (Py_{1-4}) / N-phenylpyrazolines (Ph_{1-4})

Mixture of compound Q_{1-4} (0.01mole) and phenyl hydrazine/hydrazine hydrate dissolved in 20 ml of 1, 4 dioxane/gla.aceticacid/ ethanol. To this reaction added 2-3 drops of sulphuric acid and the contents were refluxed for 4-8 hrs. After cooling the reaction mixture pour the contents in ice cold water. The obtained solid allow drying and recrystallized from ethanol (Scheme-I).

Q1: 3(4(3(4-chloro phenyl) acrolyl) phenyl) 2-phenyl quinazoline (4*H*)-onem. p. 140-142^{o}C; yield (%): 63; R_f:0.43; IR (ATR,Cm-^{1}): 1644 (C=O of chalcone, str), 1701 (C=O of quinazolinone, str), 1610 (C=N, str), 1567 (C=C, str), 2970 (C-H Ali, str), 3107 (C-H Aro, str), 819 (C-Cl, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) :7.10-9.12 (17H,m,Ar-H), 6.75 (2H,s,chalcone); Mass: m/z 142.

Q2: 3(4(3(4-nitro phenyl) acrolyl) phenyl) 2-phenyl quinazoline (4*H*)-onem. p. 168-170^{o}C; yield (%): 73; R_f:0.68; IR (ATR,Cm-^{1}):1647 (C=O of chalcone, str), 1707 (C=O of quinazolinone, str), 1608 (C=N, str), 1565 (C=C, str), 2979 (C-H Ali, str), 3117 (C-H Aro, str), 1463 (N=0, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) :7.3-9.9 (17H,m,Ar-H), 6.79 (2H,s,chalcone); Mass: m/z 170.

Q3: 3(4(3(4-methyl phenyl) acrolyl) phenyl) 2-phenyl quinazoline (4*H*)-onem. p. 210-212^{o}C; yield (%): 79; R_f:0.88; IR (ATR,Cm-^{1}):1651 (C=O of chalcone, str), 1707 (C=O of quinazolinone, str), 1596 (C=N, str), 1560 (C=C, str), 2935 (C-H Ali, str), 3113 (C-H Aro, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) :7.10-9.12 (17H,m,Ar-H), 6.75 (2H,s,chalcone); Mass: m/z 212.

Q4: 3(4(3(4-methoxy phenyl) acrolyl) phenyl) 2-phenyl quinazoline (4*H*)-onem. p. 178-180^{o}C; yield (%): 83; R_f:0.94; IR (ATR,Cm-^{1}):1668 (C=O of chalcone, str), 1701 (C=O of quinazolinone, str), 1608 (C=N, str), 1556 (C=C, str), 2955 (C-H Ali, str), 3104 (C-H Aro, str), 1117 (C-O-C, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) :7.2-9.0 (17H,m,Ar-H), 6.45 (2H,s,chalcone); Mass: m/z 180.

P_1: 3 (4-(5-(p-chlorophenyl) 4, 5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline 4(3H) one m. p. 190-192^{o}C; yield (%): 43; R_f:0.79; IR (ATR,Cm-^{1}): 1710 (C=O of quinazolinone, str), 3610 (N-H, str), 1555 (C=C, str), 1598 (C=N, str), 2930 (C-H Ali, str), 3097 (C-H Ar, str), 788 (C-Cl, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 5. 60 (1H,s,N_1-H), 8.05 (1H,s,N_3-H), 7.11-9.08 (17H,m,Ar-H),3.20 (2H,dd,C_4-pyrazole), 2.20 (1H,s,C_5-H-pyrazole); Mass: m/z 192.

P_2: 3 (4-(5-(p-nitrophenyl) 4, 5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline 4(3H) onem. p. 110-112^{o}C; yield (%): 85; R_f:0.76; IR (ATR,Cm-^{1}):1708 (C=O of quinazolinone, str), 3590 (N-H, str), 1562 (C=C, str), 1596 (C=N, str), 2976 (C-H Ali, str), 3111 (C-H Ar, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 5. 82 (1H,s,N_1-H), 7.21-8.98 (17H,m,Ar-H),3.20 (2H,dd,C_4-pyrazole), 2.20 (1H,s,C_5-H-pyrazole); Mass: m/z 112.

P_3: 3 (4-(5-(p-methylphenyl) 4, 5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline 4(3H) onem. p. 234-236^{o}C; yield (%): 56; R_f:0.82; IR (ATR,Cm-^{1}):1699 (C=O of quinazolinone, str), 3608 (N-H, str), 1560 (C=C, str), 1590 (C=N, str), 2970 (C-H Ali, str), 3127 (C-H Ar, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 5. 82 (1H,s,N_1-H), 7.32-9.01 (17H,m,Ar-H),3.10 (2H,dd,C_4-pyrazole), 2.36 (1H,s,C_5-H-pyrazole), 1.56 (3H,s,Ar-methyl); Mass: m/z 236.

P_4: 3 (4-(5-(p-methoxyphenyl) 4, 5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline 4(3H) one m. p. 161-163^{o}C; yield (%): 78; R_f: 0.68; IR (ATR,Cm-^{1}1699 (C=O of quinazolinone, str), 3627 (N-H, str), 1550 (C=C, str), 1593 (C=N, str), 2989 (C-H Ali, str), 3115 (C-H Ar, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 5. 82 (1H,s,N_1-H), 7.32-9.01 (17H,m,Ar-H),3.10 (2H,dd,C_4-pyrazole), 2.36 (1H,s,C_5-H-pyrazole), 2.06 (3H,s,Ar-methoxy); Mass: m/z 163.

P_{h1}: 3 (4-(1-phenyl- 5-(p-chlorophenyl) 4,5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline-4(3H) one m. p. 176-178^{o}C; yield (%): 59; R_f: 0.93; IR (ATR,Cm-^{1}): 1706 (C=O of quinazolinone, str), 1556 (C=C,str), 1598 (C=N, str), 2908 (C-H Ali, str), 3110 (C-H Aro, str), 820 (C-Cl, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) :7.32-9.01 (23H,m,Ar-H),3.10 (2H, d,CH_2 of pyrazole), 4.36 (1H,s,CH-pyrazole), 1.56 (3H,s,Ar-methyl); Mass: m/z 178.

P_{h2}: 3 (4-(1-phenyl- 5-(p-nitrophenyl) 4,5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline-4(3H) one m. p. 267-269^{o}C; yield (%): 81;

R_f:0.82; IR (ATR,Cm-^{1}):1710 (C=O of quinazolinone, str), 1522 (C=C, str), 1610 (C=N, str), 2918 (C-H Ali, str), 3120 (C-H Ar, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) :7.32-9.01 (23H,m,Ar-H), 2.96 (2H, d,CH_2 of pyrazole), 4.05 (1H,s,CH-pyrazole), 1.23 (3H,s,Ar-methyl); Mass: m/z 269.

P_{h3}: 3 (4-(1-phenyl- 5-(p-methylphenyl) 4,5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline-4(3H) one m. p. 155-157^{o}C; yield (%): 63; R_f: 0.43; IR (ATR,Cm-^{1}): 1712 (C=O of quinazolinone, str), 1530 (C=C, str), 1588 (C=N, str), 2899 (C-H Ali, str), 3100 (C-H Ar, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) :7.32-9.01 (23H,m,Ar-H), 3.12 (2H, d,CH_2 of pyrazole), 4.16 (1H,s,CH-pyrazole), 1.81 (3H,s,Ar-methyl); Mass: m/z 157.

P_{h4}: 3 (4-(1-phenyl- 5-(p-methoxyphenyl) 4, 5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline-4(3H) one m. p. 122-124^{o}C; yield (%): 72; R_f: 0.91; IR (ATR,Cm-^{1}): 1706 (C=O of quinazolinone, str), 1556 (C=C, str), 1598 (C=N, str), 2908 (C-H Ali, str), 3110 (C-H Aro, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) :7.32-9.01 (23H,m,Ar-H), 2.96 (2H, d,CH_2 of pyrazole), 4.21 (1H,s,CH-pyrazole), 1.28 (3H,s,Ar-methyl); Mass: m/z 124.

P_{y1}: 3 (4-(N-acetyl-5-(chlorophenyl)-4, 5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline-4(3H) one m. p. 190-192^{o}C; yield (%): 68; R_f:0.49; IR (ATR,Cm-^{1}): 1698 (C=O, str), 1706 (C=O of quinazolinone, str), 1592 (C=N, str), 1459 (C=C, str), 2930 (C-H Ali, str), 3097 (C-H Aro, str), 828 (C-Cl, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 2. 91 (2H,d,CH_2 of pyrazoline), 4.66 (1H,s,CH of pyrazoline), 7.2-7.4 (17H,m,Ar-H), 2.06 (3H,s,CH_3 of acetyl); Mass: m/z 192.

P_{y2}: 3 (4-(N-acetyl-5-(nitrophenyl)-4, 5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline-4(3H) one m. p. 217-219^{o}C; yield (%): 63; R_f:0.43; IR (ATR,Cm-^{1}):1698 (C=O, str), 1706 (C=O of quinazolinone, str), 1592 (C=N, str), 1459 (C=C, str), 2930 (C-H Ali, str), 3097 (C-H Aro, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 3.08 (2H, d, CH_2 of pyrazoline), 4.45 (1H,s, CH of pyrazoline), 7.2-7.4 (17H,m,Ar-H), 1.90 (3H,s,CH_3 of acetyl); Mass: m/z 219.

P_{y3}: 3-(4-(N-acetyl-5-(methylphenyl)-4,5 dihydro-1*H*-pyrazol-3-yl) phenyl quinazoline-4(3H) one m. p. 132-134^{o}C; yield (%): 78; R_f:0.84; IR (ATR,Cm-^{1}):1698 (C=O, str), 1706 (C=O of quinazolinone, str), 1592 (C=N, str), 1459 (C=C, str), 2930 (C-H Ali, str), 3097 (C-H Aro, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 2.81 (2H, d, CH_2 of pyrazoline), 4.72 (1H,s, CH of pyrazoline), 7.2-7.4 (17H,m,Ar-H),1.89 (3H,s,CH_3 of acetyl); Mass: m/z 134.

P_{y4}: 3 (4-(N-acetyl-5-(methoxyphenyl)-4, 5 dihydro-1H-pyrazol-3-yl) phenyl quinazoline-4(3H) one m. p. 97-99^{o}C; yield (%): 80; R_f:0.59; IR (ATR,Cm-^{1}):1698 (C=O, str), 1706 (C=O of quinazolinone, str), 1592 (C=N, str), 1459 (C=C, str), 2930 (C-H Ali, str), 3097 (C-H Aro, str); ^{1}H NMR (δppm; $CDCl_3$/DMSO-d_6) : 2. 80 (2H, d, CH_2 of pyrazoline), 4.69 (1H,s, CH of pyrazoline), 7.2-7.4 (17H,m,Ar-H),1.96 (3H,s,CH_3 of acetyl); Mass: m/z 99.

Antibacterial activity

The synthesised compounds (Q_{1-4}&P_{1-4})were screened for their in vitro antibacterial activity against *Escherichia coli, Pseudomonas aeruginosa and Staphylococcus aureus* by measuring the zone of inhibition in mm[6-8]. The antibacterial activity was performed by filter paper disc plate methodat concentration 100 µg/mL and reported in Table-1. Muller Hinton agar & Sabouroud Dextrose agar were employed as culture medium and DMSO was used as solvent control for antibacterial activity. Ciproflaxin was used as standard for antibacterial activity respectively.

RESULTS AND DISCUSSION

Synthesis of 16 novel compounds involve in three steps. The key intermediate compound D was preparedfromAnthralinic acid and benzoyl chloride in presence of pyridine to give 2[phenyl]-benzo(1,3)oxazine-4-one and further treated with*p*-amino acetophenone to give 3-(4-acetyl phenyl)-2-(phenyl)-3H quinazoline-4-one derivatives. The later refluxed with different substituted aromatic aldehydes in ethanol and cold solution of 40% alkali yielded the chalcone compounds Q_{1-4} and further treated with hydrazine hydrateand acetic acid yielded the desired compound $P_{1-4,}$ Ph_{1-4}& Py_{1-4}in good yield. For Q_{1-4} the IR spectra showed intense peaks at 1698 cm-1 for (C=O of chalcone, str), 1725 cm-1 for (C=O of quinazolinone, str), 1550-1585 cm-1 for (C=C, str) and 1590-1620 cm-1 for (C=N, str). The H^{1}NMR showed singlet at 6.50-6.65 (2H, s, CH=CH) indicating the presence of chalcone group. The targeted compounds P_{1-4},Ph_{1-4}& Py_{1-4} obtained from Q_{1-4}in presence of hydrazine hydrate and acetic acid in good yield. The IR showed intense peak at 3650-3590 cm-1 for (NH of pyrazoline, str) presence at P_{1-4}absence in Ph_{1-4} and Py_{1-4}.TheH^{1}NMR showed singlet at 5.6-6.4 (1H.s. NH for pyrazoline).The mass spectra of the all 16 compounds showed molecular ion peaks at corresponding to their molecular formula. The newly synthesized compounds were screened for antibacterial activity and it was found that the compounds Q_{1-4} showed no significant activityand the compounds P_{1-4} showed moderate activity when compared to standard.

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Scheme-I

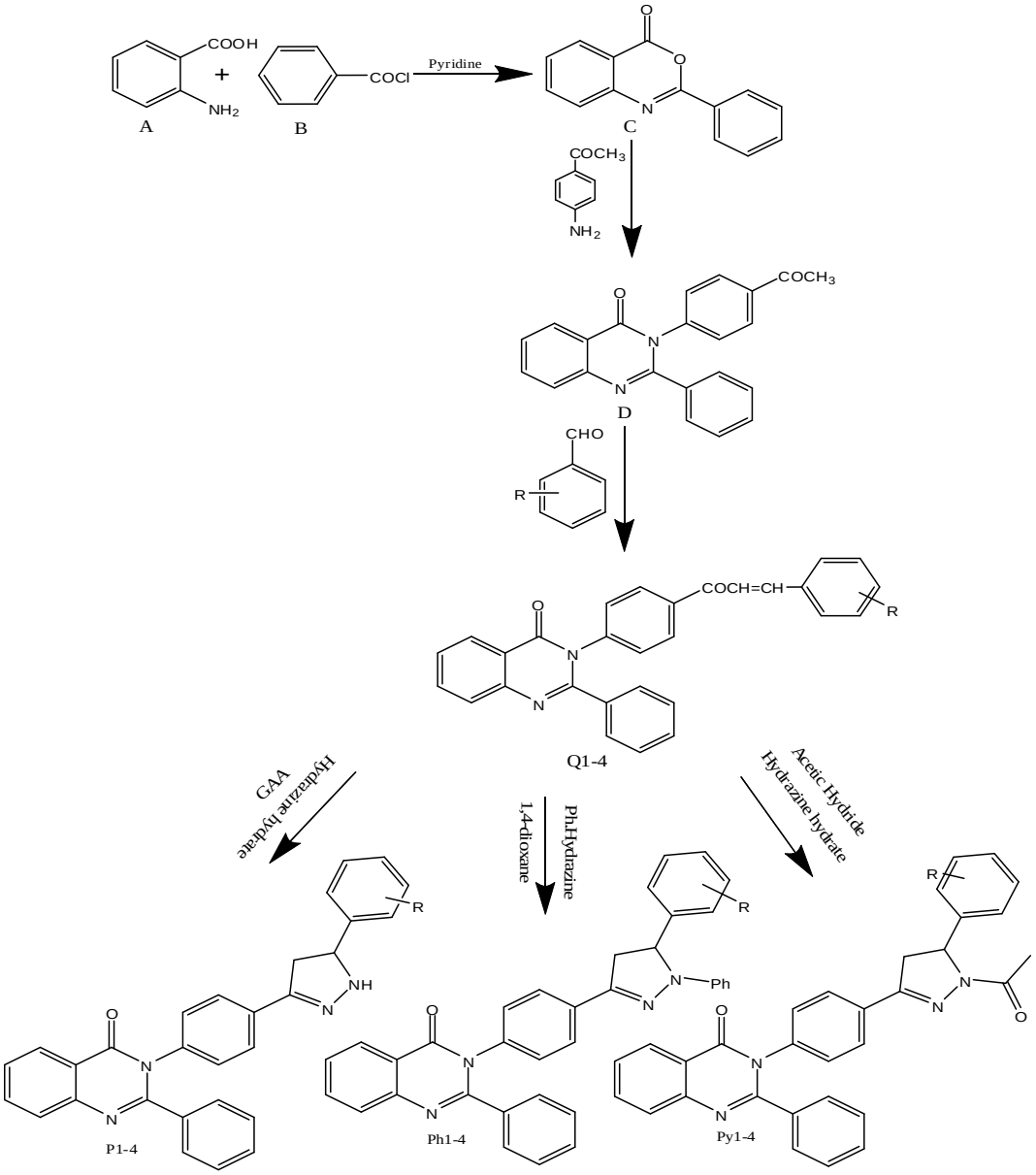

Table 1: Antibacterial activity of synthesized compounds (Q_{1-4}& P_{1-4})

S.No.	Compound	Zone of inhibition (mm)		
		E.Coli (443)	*P.Aeruginosa(424)*	*S.aureus(96)*
1	Q1	09	11	12
2	Q2	08	10	10
3	Q3	10	09	10
4	Q4	09	10	11
5	P1	26	25	24
6	P2	27	20	21
7	P3	24	24	23
8	P4	28	25	20
9	std	31	29	26

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