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A Convenient Synthesis of Quinazoline Acetamide Incorporated Pyrazole And Pyrimidine Derivatives And Their Antibacterial Activity

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Abstract: *A facile synthesis of novel chalcones (E)-3-(4-chlorophenyl)-N-(4-(2,4-dioxo-dihydroquinazolin-3(4H)-yl)phenyl)acrylamide (2a,b) has been achieved by the condensation of isatoic anhydride, aromatic ketones with different aldehydes. These chalcones on cyclization with hydrazine hydrate, phenyl hydrazine in the presence of glacial acetic acid and guanidine hydrochloride in the presence of alkali to afford corresponding acetyl pyrazoline (3a,b) phenyl pyrazoline (4a,b) and amino pyrimidines (5a,b) respectively. All synthesised compounds were fully characterized by spectral studies and elemental analysis. Antibacterial activities of the final compounds have been Sent for bacterial growth.*

Keywords *: Chalcones, pyrazoline, aminopyrimidine, antibacterial activity.*

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I. Introduction

Chalcones are biosynthetic precursors of flavanoids including flavanones which also possess various enthusiastic pharmacological activities continue to focus due to their effective range of biological activities . Both chalcones and flavanones show similar biological activities. The compounds of chalcone have been reported to possess diverse pharmacological effects including antimalarial [1], anticancer [2-5],anti inflammator [6,7],antibacterial [8], antimicrobial [9,10], anti fungal [11,12], antioxidant[13],anti leishmanial[14-17,] anti tumor [18] activities. A unique synthesis of these compounds involves the base catalysed Aldol condensation of aromatic ketones (chalcones),which undergo a cyclization reaction with hydrazine, phenyl hydrazine and guanidine hydrochloride affording pyrazolines and pyrimidines respectively.

II. Materials And Methods

All the reagents and solvents were of LR grade and were purchased locally from S.D. Fine (Mumbai, India), Merck (Mumbai, India) and CDH (New Delhi, India). Melting points were recorded using open end capillaries and are uncorrected. The IR spectra were recorded on a 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; TMS was used as an internal standard and chemical shift values (δ) are expressed as parts per million (ppm). Perkin-Elmer 240 analyzer was used to perform elemental analysis (C, H, N) and were found in the range of ±0.4%for each analyzed element. 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.

Synthesis of N-(4-(2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl)phenyl)acetamide (1)

A mixture of p-aminoacetanilide (0.02 mol) and isatoic anhydride (0.02 mol) in ethanol was added to it with a catalytic amount of pyridine. Reaction mixture was refluxed for 4 hrs and poured on crushed ice. The solid obtained was filtered, and recrystallized from ethanol.

IR (KBr)cm^{-1}: 3312 (N-H,str.),3089 (C-H str.Ar-H), 1654 (C=O str.).^{1}H- NMR (DMSO , δ ppm), 6.57-7.75 (m,8H, Ar-H) , 2.05 (s, 3H, -CO-CH3), 6.1 (s, 1H, NH), 7.1 (s, 1H, NH-CO).

Synthesis of (E)-3-(4-chlorophenyl)-N-(4-(2,4-dioxo-dihydroquinazolin-3(4H)-yl)phenyl)acrylamide (2a)

To a compound I (0.01 mol) , chlorobenzaldehyde (0.01 mol) in ethanol (30 ml), 40% NaOH was added. The reaction mixture is stirred for 8hrs. The contents were poured onto crushed ice with stirring , the product is kept in refrigerator for overnight. The product is filtered and recrystallized from ethanol.

IR (KBr)cm^{-1}: 3440 (N-H str.),1637 (N-H-C=O str.), 1511 (C=C str.),754 (C-Cl), ^{1}H NMR (DMSO, δ ppm), 7.20 – 7.98 (m, 12H, Ar-H), 7.16 (d, 1H, CO-CH), 7.31 (d, 1H , CH),6.74 (s, 1H, NH), 10.47 (s, 1H, NH-CO).

Synthesis of (E)-3-(benzo[d][1,3]dioxol-5-yl)-N-(4-(2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl)phenyl)acrylamide (2b)

To a compound I (0.01 mol) , piperonaldehyde (0.01 mol) in ethanol (30 ml), 40% NaOH was added. The reaction mixture is stirred for 8hrs. The contents were poured onto crushed ice with stirring , the product is kept in refrigerator for overnight. The product is filtered and recrystallized from ethanol.

IR (KBR)Cm^{-1} : 3271 (N-H str.),3051 (C-H str.Ar-H),1657 (N-H-C=O str.),1533 (C=C str.), 1HNMR (DMSO, δ ppm), 6.97-8.03 (m, 11H, Ar-H), 6.97 (d, 1H, COCH), 7.30 (d, 1H , CH),6.31 (s, 1H, NH), 10.12 (s, 1H, NH-CO), 6.45 (s, 2H,CH_2).

Synthesis of 3-(4-(1-acetyl-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)amino)phenyl)quinazoline-2,4(1H,3H)-dione (3a)

The (E)-3-(4-chlorophenyl)-N-(4-(2,4-dioxo-dihydroquinazolin-3(4H)-yl)phenyl)acrylamide 2a (0.01 mol) and hydrazine hydrate (70%) is taken in 20ml of acetic acid. Reaction mixture is refluxed and stirred for 4 hrs. Cool the contents to room temperature and add to crushed ice with vigorous stirring. Filtered the solid separated, dried and recrystallized from hot ethanol.

IR (KBr)cm^{-1}: 3297 (N-H str.),3058 (Ar C-H str.),1640 (C=O str.),2922 (Ali C-H str.),1387 (C-N str.),751 (C-Cl str.), ^{1}HNMR (DMSO, δ ppm), 7.02 – 7.96 (m,12H,Ar-H), 3.28 (d,2H,CH_2 pyrazoline),6.99 (s,1H,NH),2.33 (s,3H,CO-CH_3) ; ^{13} C NMR (DMSO), 23.4 (1C,CH_3 in $COCH_3$), 39.4 (1C,pyrazoline-CH_2), 76.2 (1C,pyrazoline-CH),166.3 (1C,C=0 in $NHCOCH_3$), 162.7(1C,C=O in -N-C=O).

Synthesis of 3-(4-((1-acetyl-5-(benzo[d][1,3]dioxol-5-yl)-4,5-dihydro-1H-pyrazol-3-yl)amino)phenyl)quinazoline-2,4(1H,3H)-dione (3b)

The(E)-3-(benzo[d][1,3]dioxol-5-yl)-N-(4-(2,4-dioxo-1,2-dihydroquinazolin-3(4H)- phenyl)acrylamide (2b**)** (0.01 mol) and hydrazine hydrate (70%) is taken in 20ml of acetic acid. Reaction mixture is refluxed and stirred for 4 hrs. Cool the contents to room temperature and add to crushed ice with vigorous stirring. Filtered the solid separated, dried and recrystallized from hot ethanol.

IR (KBr)cm^{-1}: 3277 (N-H str.),3058 (Ar C-H str.),1678 (C=O str.),2967 (Ali C-H str.),1402 (C-N str.), ^{1}HNMR ($CDCl_3$, δ ppm), 6.80 – 7.67 (m,11H,Ar-H), 2.35 (d,2H,CH_2pyrazoline),6.00 (s,1H,NH),2.07 (s,3H,CO-CH_3), 6.07 (s,2H,- OCH_2) ; ^{13} C NMR ($CDCl_3$), 20.4 (1C,CH3 in COCH3), 39.4 (1C,pyrazoline-CH2), 68.1 (1C,pyrazoline-CH),174.3 (1C,C=0 in NHCOCH3), 150.2(1C,C=O in -N-C=O) .

Synthesis of 3-(4-((5-(4-chlorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)amino)phenyl)quinazoline-2,4(1H,3H)-dione (4a)

The (E)-3-(4-chlorophenyl)-N-(4-(2,4-dioxo-dihydroquinazolin-3(4H)-yl)phenyl)acrylamide 2a (0.01 mol) and phenyl hydrazine hydrate (70%) is taken in 20ml of acetic acid. Reaction mixture is refluxed and stirred for 4 hrs. Cool the contents to room temperature and add to crushed ice with vigorous stirring. Filtered the solid separated, dried and recrystallized the compound from hot ethanol.

IR (KBr)cm^{-1}: 3298 (N-H str.),3110 (Ar C-H str.),1698 (C=O str.),2927 (Ali C-H str.),1387 (C-N str.),753 (C-Cl str.), ^{1}HNMR ($CDCl_3$, δ ppm), 7.05 – 8.27 (m,17H,Ar-H), 3.39 (d,2H,CH_2 pyrazoline),6.96 (s,1H,NH), 6.45 (t,1H,CH pyrazoline) ; ^{13} C NMR (DMSO), 20.6 (1C,CH_3 in $COCH_3$), 39.1 (1C,pyrazoline-CH_2), 76.8 (1C,pyrazoline-CH),145.6 (1C,C=0 in NHCOCH3), 138.7(1C,C=O in -N-C=O) .

Synthesis of 3-(4-((5-(benzo[d][1,3]dioxol-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)amino)phenyl)quinazoline-2,4(1H,3H)-dione (4b)

The(E)-3-(benzo[d][1,3]dioxol-5-yl)-N-(4-(2,4-dioxo-1,2-dihydroquinazolin-3(4H)- phenyl)acrylamide (2b**)** (0.01 mol) and phenyl hydrazine hydrate (70%) is taken in 20ml of acetic acid. Reaction mixture is refluxed and stirred for 4 hrs. Cool the contents to room temperature and add to crushed ice with vigorous stirring. Filtered the solid separated, dried and recrystallized the compound from hot ethanol.

IR (KBr)cm^{-1}: 3308 (N-H str.),2922 (Ar C-H str.),1745 (C=O str.),2853 (Ali C-H str.),1382 (C-N str.), ^{1}HNMR ($CDCl_3$, δ ppm), 6.44 – 8.06 (m,16H,Ar-H), 3.23 (d,2H,CH_2 pyrazoline),6.39 (s,1H,NH),6.33 (

t,1H,CH pyrazoline), 6.34 (s, 2H,CH_2) ; ^{13} C NMR (DMSO), 39.2(1C,pyrazoline-CH2), 76.8 (1C,pyrazoline-CH),145.1 (1C,C=0 in $NHCOCH_3$), 130.2(1C,C=O in -N-C=O) .

Synthesis of 3-(4-((2-amino-6-(4-chlorophenyl)pyrimidin-4-yl)amino)phenyl)quinazoline-2,4(1H,3H)-dione (5a)

The(E)-3-(4-chlorophenyl)-N-(4-(2,4-dioxo-dihydroquinazolin-3(4H)-yl)phenyl)acrylamide 2a (0.01 mol) and guanidine hydrochloride (0.01 mol) were dissolved in ethanol and refluxed for 45 min.20% NaOH solution is added dropwise to the contents and refluxing followed for 10 hrs. The Reaction mixture is cooled and poured in crushed ice slowly. The solid seperates out is filtered, dried and recrystallized from ethanol

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IR (KBr)cm-1: 3461 (N-H str.),2929 (Ar C-H str.),1629 (C=O str.),2857 (Ali C-H str.),1390 (C-N str.), ^{1}HNMR (DMSO, δ ppm), 6.75 – 8.02 (m,13H,Ar-H), 6.85 (d,2H,pyrimidine),6.552 (s,1H,CH pyrimid ine), 4.08 (s,1H,NH) ,6.43 (s, 1H,NH-CO) ; ^{13} C NMR (DMSO) 94.9 (1C,C=C in pyrimidine), 150.4 (1C,C=O in NH-C=O), 126.1 (1C,C-Cl), 162.5 (1C,C-NH_2 in pyrimidine), 163.3(1C,C=O in N-C=O), 172.2 (1C,C=N in pyrimidine).

Synthesis of 3-(4-((2-amino-6-(benzo[d][1,3]dioxpl-4-yl)pyrimidin-4-yl)amino)phenyl)quinazoline-2,4(1H,3H)-dione (5b)

The(E)-3-(benzo[d][1,3]dioxol-5-yl)-N-(4-(2,4-dioxo-1,2-dihydroquinazolin-3(4H)- phenyl)acrylamide (2b**)** (0.01 mol) and guanidine hydrochloride (0.01 mol) were dissolved in ethanol and refluxed for 45 min.20% NaOH solution is added dropwise to the contents and refluxing followed for 10 hrs. The Reaction mixture is cooled and poured in crushed ice slowly. The solid seperates out is filtered, dried and recrystallized from ethanol.

IR (KBr)cm^{-1}: 3342 (N-H str.),3034 (Ar C-H str.),1611 (C=O str.),2891 (Ali C-H str.),1507 (C=C str.), ^{1}HNMR ($CDCl_3$, δ ppm), 6.04 – 7.31 (m,11H,Ar-H), 6.90(d,2H,pyrimidine),6.53 (s,1H,CH, pyrimidine), 3.77 (s,1H,NH) ,6.01 (s, 1H,NH-CO) ; ^{13} C NMR ($CDCl_3$), 98.6 (1C,C=C in pyrimidine), 150.4 (1C,C=O in NH-C=O), 162.7 (1C,C-NH_2 in pyrimidine), 162.3(1C,C=O in N-C=O), 173.2 (1C,C=N in pyrimidine);

III. Result And Discussion

A simplified procedure based on a Claisen-Schmidt condensation was used for synthesis of chalcones and their derivatives. The route for obtaining the final product is presented in scheme 1. The intermediate N-(4-(2,4-d ioxo-1,2-dihydroquinazolin-3(4H)-yl)phenyl)acetamide (1) was prepared by reaction with isatoic anhydride with p-aminoacetanilide by refluxing with ethanol. Formation of (1) is confirmed by IR spectra at 1654 cm^{-1} due to carbonyl group. Further, this is supported by ^{1}HNMR signal at 6.1 δ ppm for NH proton. Compound (1) was converted to chalcone by treating with aromatic aldehyde in alkali/ethanol by stirring. Formation of compound (2) is confirmed by IR spectra at 1637 cm-1 due to α ,β- unsaturated carbonyl group. Compounds (2a,b) when treated with hydrazine hydrate , phenyl hydrazine in the presence of acetic acid and guanidine hydrochloride in the presence alkali, afforded 3-(4-(1-acetyl-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)amino)phenyl)quinazoline-2,4(1H,3H)-dione (3a,b), 3-(4-((5-(4-chlorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)amino)phenyl)quinazoline-2,4(1H,3H)-dione (4a,b) and 3-(4-((2-amino-6-(4-chlorophenyl)pyrimidin-4-yl)amino)phenyl)quinazoline-2,4(1H,3H)-dione (5a,b) respectively. Formation of these compounds were confirmed by disappearance of C=0 stretching band at 1637 cm^{-1} for all the derivatives. From^{1}H NMR,^{13}C NMR and mass spectral studies we were elucidated the structure of our novel compounds. Spectral data of all the compounds and C, H, N analysis are depicted.

Table 1: The physiochemical data of compounds 3a,b; 4a,b and 5a,b.

Compd no.	R	M.P. ^{0}C	Yield %	Molecular formula	Elemental analysis (calcd/found)%		
					C	H	N
3a	4-chloro	198-202	73	$C_{25}H_{20}ClN_5O_3$	(63.36 63.37)	(4.25 4.26)	(14.78 14.79)
3b	4-piperonyl	160-162	68	$C_{26}H_{21}N_5O_5$	(64.59 64.50)	(4.38 4.38)	(14.49 14.49)
4a	4-chloro	232-234	77	$C_{29}H_{22}ClN_5O_2$	(68.57 68.58)	(4.37 4.38)	(13.79 13.79)
4b	4-piperonyl	106-110	75	$C_{30}H_{23}N_5O_4$	(69.62 69.62)	(4.48 4.49)	(13.53 13.54)
5a	4-chloro	240-242	66	$C_{24}H_{17}ClN_6O_2$	(63.09 63.10)	(3.75 3.76)	(18.39 18.39)
5b	4-piperonyl	158-160	79	$C_{25}H_{18}N_6O_4$	(64.37 64.37)	(3.89 3.90)	(18.02 18.03)

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Figure 1. Scheme for synthesis of chalcones and its derivatives

IV. Antibacterial Activity

The synthesized compounds were tested for antibacterial activity. Gram positive bacteria (S.aureus) and Gram negative bacteria (E.coli) were screened for their antibacterial activity by using agar diffusion method. Ciprofloxacin used as standard for the study of antibacterial activity . Anti bacterial data of compounds 3a, 3b, 4a, 4b, 5a and 5b were found to be active or inactive against bacterial strain.(Table 2)

Table 2. Antibacterial activity data of compounds 3a,b; 4a,b and 5a,b.

S.No.	Microorganism	Control	3a	3b	4a	4b	5a	5b	Ciprofloxacin
1.	Staphylococcus aureus	DMSO	9	5	7	6	8	5	13
2.	Escherichia coli	DMSO	5	13	11	10	6	11	10

V. Conclusion

A group of chalcones and their derivatives were synthesised and characterised by spectral and analytical studies. The novel synthesised compounds are evaluated for antibacterial activity. The study showed that the activity is from moderate to good.

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