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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF CHALCONES AND ITS HETEROCYCLIC DERIVATIVES

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ABSTRACT

In this work, an attempt was made to synthesize chalcone (E)-N-(4-(2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl) phenyl)-3-(4-fluorophenyl) acrylamide by condensation of substituted aldehydes with N-(4-(2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl) phenyl) acetamide under basic conditions. The synthesized chalcone is reacted with hydrazine, phenyl hydrazine and guanidine afford pyrazole, phenyl pyrazole and pyrimidine derivatives respectively. The synthesized compounds were characterized by IR, ^{1}H-NMR & ^{13} C-NMR and studied for their antibacterial, antifungal activity and compared with the standard drugs. Some compounds possess moderate to good activity.

KEY WORDS

Chalcone, aldehyde, pyrazole, pyrimidine, antibacterial activity, antifungal activity.

INTRODUCTION

Chalcones are synthetic or naturally occurring α, β-unsaturated diaryl ketones. It represents an important class of compounds due to their chemical flexibility. Chalcones are synthesized by claisen-schmidt condensation of aldehyde and ketone by base catalyzed or acid catalyzed followed by dehydration to yield the product. They shows a wide range of biological properties and activities such as anti-microbial[1], anti-viral [2,] anti-fungal [3-6], anti-malarial [7-11], cytotoxicity [12], anti-oxidant [13-15], anti-tumor [16] and anti-inflammatory [17,18]. It has been found that their pharmacological activities have been magnified by the addition of heterocyclic rings in their structures and it has been fulfilled by proceeding the reactions with hydrazine, guanidine and phenyl hydrazine etc.,

MATERIALS AND METHODS

All the reagents and solvents were of LR grade and were purchased locally from S.D. Fine (Mumbai, 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, O) and were found in the range of ±0.2%for each analyzed element. Reaction progress was monitored on thin-layer chromatography (TLC) using silica gel G as stationary phase 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 (0.01 mol) and isatoic anhydride (0.01mol) in ethanol was added. Reaction mixture is heated for 10 min and now 2 ml of pyridine is added in drop-wise. The reaction mixture was refluxed

for 4 hrs and poured on crushed ice. The solid obtained was filtered, dried and recrystallised from hot 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)-N-(4-(2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl) phenyl)-3-(4-fluorophenyl) acrylamide (2a)

To a compound I (0.005 mol), fluoro benzaldehyde (0.005 mol) in ethanol (30 ml), 40% NaOH was added. The reaction mixture is stirred for 10hrs. The contents were poured onto crushed ice with effective stirring, the product is kept in refrigerator for overnight. The product obtained is filtered and recrystallised from ethanol.
IR (KBr)cm^{-1}: 3437 (N-H str.),1633 (N-H-C=O str.), 1512 (C=C str.), 754 (C-F), ^{1}H NMR (DMSO, δ ppm), 7.10 – 7.72 (m, 12H, Ar-H), 7.15 (d, 1H, CO-CH), 7.35 (d, 1H , CH),6.74 (s, 1H, NH), 10.05 (s, 1H, NH-CO).

Synthesis of (E)-N-(4-(2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl) phenyl)-3-(4-methoxyphenyl) acrylamide (2b)

To a compound I (0.005 mol), methoxy benzaldehyde (0.005 mol) in ethanol (30 ml), 45% alkali was added. The reaction mixture is stirred for 8hrs. The contents were poured onto crushed ice with stirring, the product is kept in cold condition for overnight. The product obtained is filtered and recrystallised from ethanol.
IR (KBR)Cm^{-1} : 3464 (N-H str.),3061 (C-H str.Ar-H),1609 (N-H-C=O str.),1513 (C=C str.), 1HNMR (DMSO, δ ppm), 7.15-8.08 (m, 12H, Ar-H), 7.12 (d, 1H, COCH), 7.37 (d, 1H , CH),6.45 (s, 1H, NH), 10.01 (s, 1H, NH-CO), 3.63 (s, 3H, OCH_3).

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

The **(**E)-N-(4-(2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl) phenyl)-3-(4-fluorophenyl) acrylamide (2a) (0.005 mol) and hydrazine hydrate (80%) is taken in 30ml of acetic acid. Reaction mixture is refluxed and stirred for 6 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}: 3289 (N-H str.),3063 (Ar C-H str.),1637 (C=O str.),2926 (Ali C-H str.),1399 (C-N str.),752 (C-F str.), ^{1}HNMR (CDCl3, δ ppm), 6.57 – 7.68 (m,12H,Ar-H), 2.49 (d,2H,CH_2 pyrazoline),5.78 (s,1H,NH),2.13 (s,3H,CO-CH_3) ; ^{13} C NMR ($CDCl_3$), 23.7 (1C,CH_3 in $COCH_3$), 39.3 (1C,pyrazoline-CH_2), 76.4 (1C,pyrazoline-CH),160.3 (1C,C=0 in $NHCOCH_3$), 168.4(1C,C=O in -N-C=O).

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

The **(**E)-N-(4-(2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl) phenyl)-3-(4-methoxyphenyl) acrylamide (2b) (0.005 mol) and hydrazine hydrate (80%) is taken in 30ml of acetic acid. Reaction mixture is refluxed and stirred for 6 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}: 3305 (N-H str.),3061 (Ar C-H str.),1670 (C=O str.), 2926 (Ali C-H str.),1401 (C-N str.), ^{1}HNMR ($CDCl_3$, δ ppm), 6.80 – 7.99(m,12H,Ar-H), 2.52 (d,2H,CH_2pyrazoline),6.43 (s,1H,NH),2.5 (s,3H,CO-CH_3), 6.07 (s,2H,- OCH_2), 3.38 (s,3H,-OCH3) ; ^{13} C NMR ($CDCl_3$), 23.7 (1C,CH3 in COCH3), 39.3 (1C,pyrazoline-CH2), 76.8 (1C,pyrazoline-CH),162.8 (1C,C=0 in NHCOCH3), 159.2(1C,C=O in -N-C=O).

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

The **(**E)-N-(4-(2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl) phenyl)-3-(4-fluorophenyl) acrylamide (2a) (0.005 mol) and phenyl hydrazine hydrate (80%) is taken in 30ml of acetic acid. Reaction mixture is refluxed and stirred for 6 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}: 3318 (N-H str.),2964 (Ar C-H str.),1627 (C=O str.),2853 (Ali C-H str.),1386 (C-N str.),751 (C-F str.), ^{1}HNMR ($CDCl_3$, δ ppm), 7.04 –7.66 (m,17H,Ar-H), 2.35 (d,2H,CH_2 pyrazoline),6.86 (s,1H,NH), 6.87 (t,1H,CH pyrazoline) ; ^{13} C NMR (DMSO), 39.3 (1C,pyrazoline-CH_2), 76.8 (1C,pyrazoline-CH),144.6 (1C,C=0 in $NHCOCH_3$), 129.4(1C,C=O in -N-C=O)

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

The **(**E)-N-(4-(2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl) phenyl)-3-(4-methoxyphenyl) acrylamide (2b) (0.005 mol) and phenyl hydrazine hydrate (80%) is taken in 40ml of acetic acid. Reaction mixture is refluxed and stirred for 8 hrs. Cool the contents to room temperature and add to crushed ice with effective stirring. Filtered

the solid separated, dried and recrystallzied the compound from hot ethanol.

IR (KBr)cm^{-1}: 3316 (N-H str.),2925 (Ar C-H str.),1628 (C=O str.),2856 (Ali C-H str.),1383 (C-N str.), ^{1}HNMR ($CDCl_3$, δ ppm), 6.45 – 8.22 (m,17H,Ar-H), 2.49 (d,2H,CH_2 pyrazoline),6.47 (s,1H,NH),6.45 (t,1H,CH pyrazoline), 3.5 (s,3H,-OCH_3) ; ^{13} C NMR ($CDCl_3$), 39.3(1C,pyrazoline-CH_2), 76.8 (1C,pyrazoline-CH),145.1 (1C,C=0 in NHCOCH).

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

The (E)-N-(4-(2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl) phenyl)-3-(4-fluorophenyl) acrylamide (2a) (0.005 mol) and guanidine hydrochloride (0.005 mol) were dissolved in ethanol and refluxed for 30 min.25% NaOH solution is added dropwise to the contents and refluxing followed for 12 hrs. The Reaction mixture is cooled and poured in crushed ice slowly.The solid seperates out is filtered, dried and recrystallised from ethanol.

IR (KBr)cm-1: 3462 (N-H str.),2929 (Ar C-H str.),1629 (C=O str.),2857 (Ali C-H str.),1386 (C-N str.), ^{1}HNMR ($CDCl_3$, δ ppm), 6.67 – 7.86 (m,13H,Ar-H), 6.99 (d,2H,pyrimidine),6.51 (s,1H,CH pyrimidine), 4.43 (s,1H,NH) ,6.49 (s, 1H,NH-CO) ; ^{13} C NMR ($CDCl_3$) 94.8 (1C,C=C in pyrimidine), 150.5 (1C,C=O in NH-C=O), 162.6 (1C,C-NH_2 in pyrimidine), 164.3(1C,C=O in N-C=O), 172.2 (1C,C=N in pyrimidine).

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

The **(E)-N-(4-(2, 4-dioxo-1, 2-dihydroquinazolin-3 (4H)-yl) phenyl)-3-(4-methoxyphenyl) acrylamide (2b)** (0.005 mol) and guanidine hydrochloride (0.005 mol) were dissolved in ethanol and refluxed for 20 min.25% 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 recrystallised from ethanol.

IR (KBr)cm^{-1}: 3440 (N-H str.),3002 (Ar C-H str.),1609 (C=O str.),2926 (Ali C-H str.),1508 (C=C str.), ^{1}HNMR ($CDCl_3$, δ ppm), 5.94 – 8.31 (m,H,Ar-H), 6.86(d,2H,pyrimidine),5.94 (s,1H,CH, pyrimidine), 3.85 (s,1H,NH) ,6.55 (s, 1H,NH-CO) ; ^{13} C NMR ($CDCl_3$), 113.4 (1C,C=C in pyrimidine), 148.4 (1C,C=O in NH-C=O), 127.7 (1C,C-NH_2 in pyrimidine), 172.2 (1C,C=N in pyrimidine).

RESULT AND DISCUSSION:

In this article the focus was on synthesis of some novel chalcones and their derivatives. The novel heterocyclic chalcone and their derivatives were prepared, and all are subjected for characterisation by IR, ^{1}H NMR, ^{13}C NMR, elemental analysis and anti-microbial activity. Thus, the synthesis of chalcones and their derivatives has produced a wide knowledge to organic as well as for medicinal chemists.

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	O
3a	4-fluoro	182-184	77	$C_{25}H_{20}FN_5O_3$	66.66/66.64	4.41/4.41	10.51/10.49
3b	4-methoxy	148-150	63	$C_{26}H_{23}N_5O_4$	66.52/66.51	4.96/4.94	13.64/13.63
4a	4-fluoro	202-204	67	$C_{29}H_{22}FN_5O_2$	70.87/70.86	4.53/4.51	6.52/6.51
4b	4-methoxy	102-104	80	$C_{30}H_{25}N_5O_3$	71.56/71/56	5.02/5.00	9.54/9.53
5a	4-fluoro	250-252	71	$C_{24}H_{17}FN_6O2$	65.47/65.45	3.90/3.89	7.28/7.27
5b	4-methoxy	188-190	69	$C_{25}H_{20}N_6O_3$	66.35/66.36	4.46/4.47	10.62/10.61

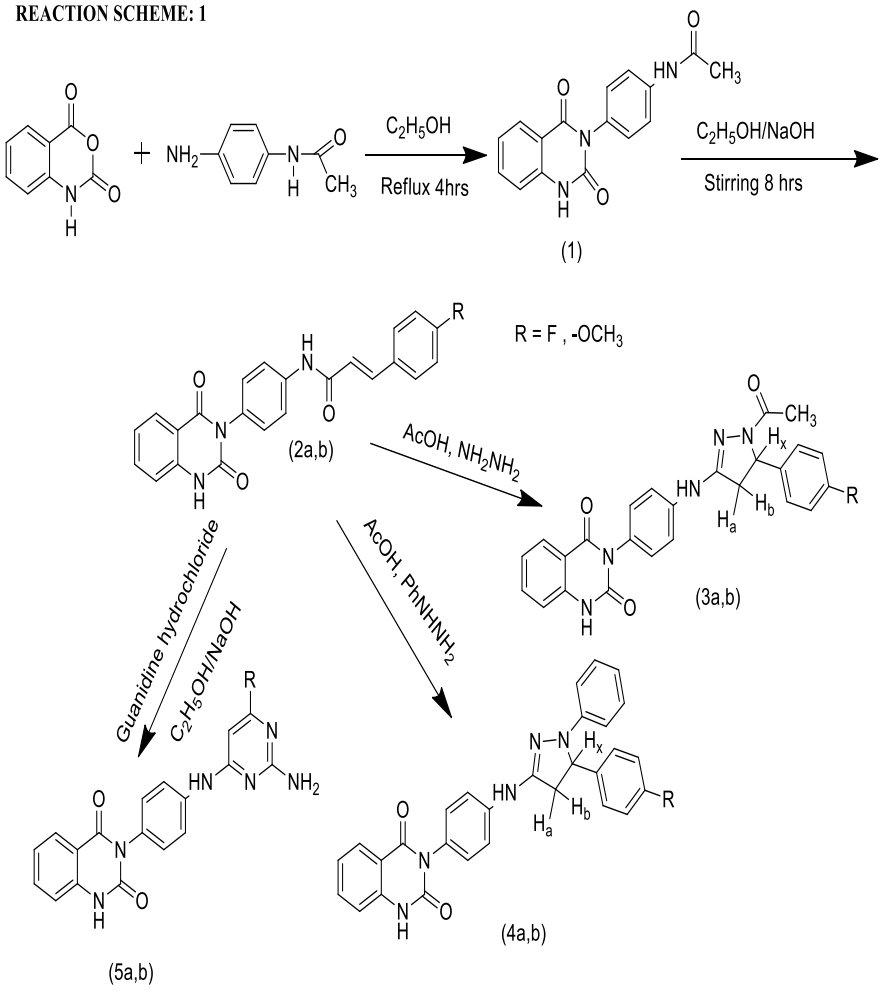


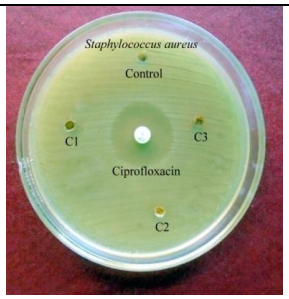
Figure 1: Scheme for synthesis of chalcones and its derivatives

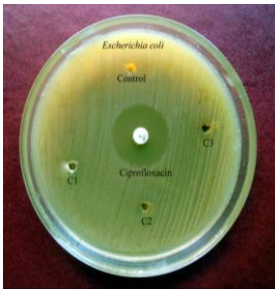
CONCLUSION:

In summary, we have successfully synthesized some chalcones, their derivatives and identified them from their spectral data. From the anti –bacterial and anti-fungal activity it was observed that the compounds exhibit moderate to good activity against the tested organism.

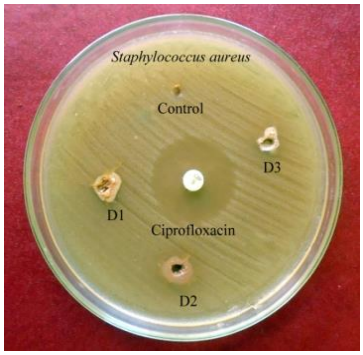
ANTI – BACTERIAL ACTIVITY:

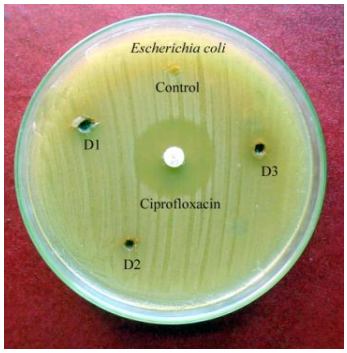
S.NO	Microorganisms	Control	C1	C2	C3	Ciprofloxacin
		Zone of inhibition in mm				
1.	Staphylococcus aurteus	-	7	-	5	20
2.	Escherichia coli	-	8	7	8	22





S.NO	Microorganisms	Control	D1	D2	D3	Ciprofloxacin
		Zone of inhibition in mm				
1.	Staphylococcus aurteus	-	10	15	10	20
2.	Escherichia coli	-	8	-	12	22

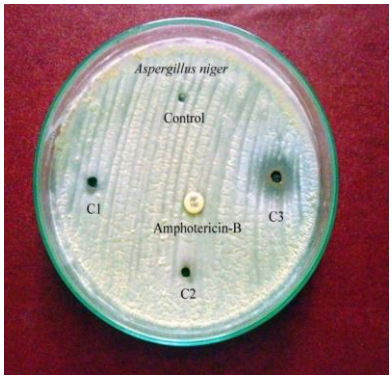




ANTI-FUNGAL ACTIVITY:

S.No.	Microorganisms	Control	D1	D2	D3	Amphotericin-B
		Zone of inhibition in mm				
1.	Aspergillus niger	-	5	25	5	9

S.No.	Microorganisms	Control	C1	C2	C3	Amphotericin-B
		Zone of inhibition in mm				
1.	Aspergillus niger	-	5	5	12	9



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