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Synthesis and Biological Screening of Some Novel Hetero-Aryl Chalcone and their complexes

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ABSTRACT

A novel chalcones are synthesized using different substituted hydroxy acetophenone and quinoline carbaldehyde by claisen Schmidt condensation to give general 1-[substituted aryl] -3-[substituted hetero aryl]-2-propene-1-ones. In general the chalcones were obtained in good yield and high purity, we expect the chalcones derivatives with hydroxyl functionality on one of the aromatic rings and with some other appropriate substituent on other hetero aryl ring will be even more potent as antibacterial activity. The structure of synthesized compound is characterized by analytical and spectral technique. Review of literature shows that substituted chalcones are having wide range of bioactivity. Hence we have prepared some new chalcones and they were used for the synthesis of Cu(II), Ni(II), Co(II), Mn(II) and Zn(II) complexes expect improved bioactivity than respective chalcones.

Keywords: Hetero aryl aldehyde , Substituted hydroxyl acetophenone , Antibacterial activity, Metal complexes.

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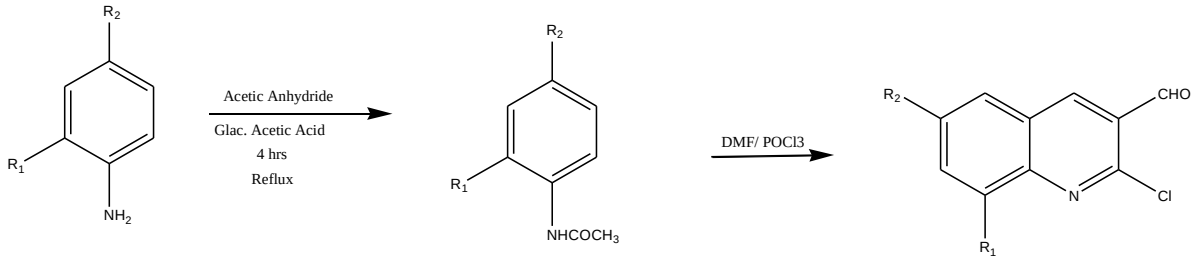
INTRODUCTION

Chalcones (α,β-unsaturated ketones) are promising candidates in the new era of medicines on account of their wide spectrum of antitumor, antibacterial and anti-inflammatory activities [1]. Chalcones from 2-hydroxy-5-bromo acetophenones exhibiting considerable antibacterial [2] antifungal and insecticidal activity [3]. It was shown that due to reactive keto vinyl moiety these compound may inter fare with normal function of the cell membrane of fungi and molds [13] and exhibit static properties against pathogens [4]. Chalcones also showed a potent inhibitory activity against Mycobacterium tuberculosis [5] malarial parasites [6]. Besides antimicrobial activities chalcones also showed to possess wide biological activity such as anticancer, antiviral, antiprotozal, enzyme inhibitory properties [7] and anti-inflammatory [8] and antiulcer agent [9,10].

The complexes of metallic salts are more potent and less toxic in many cases as compared to the parent drug [11]. These metal complexes are found to be interesting due to their biological applications like antifungal [12], antibacterial [13] and anti tumor [14] activity. Some chalcones derived from coumarin derivatives, possess significant antimicrobial activity [15]. Some 3-acetyl/acetoacetoacetyl-4-hydroxy benzopyran-2-ones have been reported as an anti-HIV agent [16]. Thus it was thought worthwhile to synthesize various novel metal complexes and to evaluate them for antimicrobial activity.

The present work has been undertaken to synthesize novel hetero aryl chalcone and their metal complexes.

Scheme I 1(a-c)



1a : R^1 = H , R^2 = OCH_3 ,1b : R^1 = H , R^2 = Br ,1c :R^1 = CH_3 , R^2 = CH_3

2(a-c)

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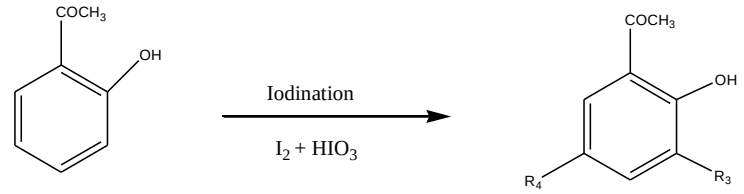
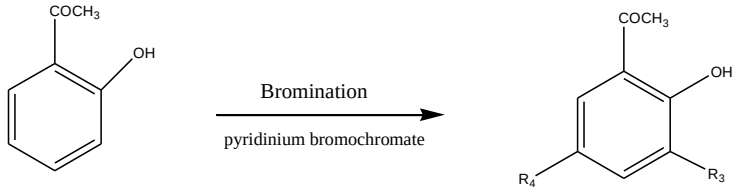
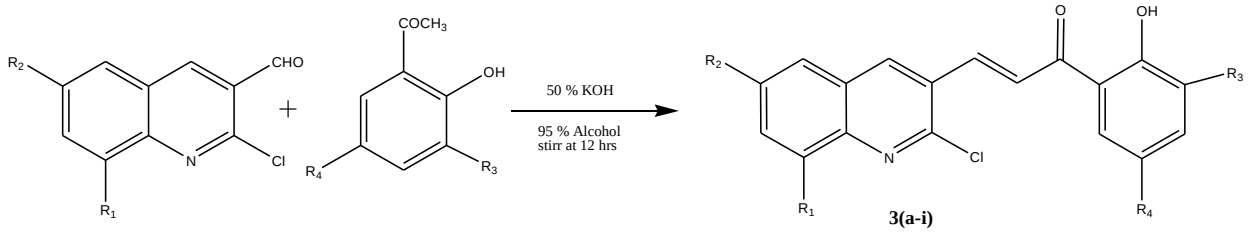




2a : R3 = I, R4 = I ,2b : R3 = Br, R4 = Br , 2c : R3 = H, R4 = Br

3(a-i)



1(a-c) **2(a-c)**

Experimental

Melting points were determined on a bio-technique point apparatus model no. BTI-38 in an open capillary tube the H NMR (400MHz) and C13 (75MHz) spectra were recorded. The chemical shift is reported in ppm. From internal TMSI standard **1(a-c) :** This preparation is carried out by using vilsmeiyer Hack reaction as 9.6ml (0.125 m) DMF cooled to 0^0C in flask equipped in drying tube and $POCl_3$ 32.65 ml (0.35 m) was added to it. Substituted acetanilide (0.05m) was added to it after 5 min. Solution reflux on water bath appropriate time after completion of reaction mixture was poured on ice cold water and solid product formed was recrystalized from ethanol-DMF [23].

2(a-c) : To a mixture of 2-hydroxyaryl ketone (50mmol), iodine (20mmol) dissolved in ethanol (30mL), iodic acid (10mmol) dissolved in water (1 mL) was added with stirring over 5 min and then the reaction mixture was stirred for 1.5 h at 35–40 ^{o}C. A solid separated out on dilution with water (15–20 mL). The solid product was filtered, washed with saturated sodium thiosulfate solution to remove excess iodine and then with cold water. The product was recrystallized from ethanol. [24]

Preparation of pyridinium bromochromate: This was synthesized by known procedure taking 20 g (0.2 mol) of chromium trioxide in water (25 ml) and cooled to 0°C. To this solution, 47% HBr (38 ml, 0.2mol) was added slowly with constant stirring. The contents were cooled to 0°C and then pyridine (16.3 ml, 0.2 mol) was added over 15–20 min, to give a brown solid. The reaction mixture was chilled for 4–5 h. The dark brown crystals were then filtered and dried. The product was recrystallized from aqueous acetic acid (40:60 v/v) and its purity was checked by TLC and confirmed by melting point and elemental analysis (108°C).

A typical procedure for bromination: By using known procedure mixture of hydroxyl acetophenone (1.36 g, 0.01 mol) and PBC (2.58 g, 0.01 mol) in glacial acetic acid (8–10 ml) was heated on a water bath for a 30 min [25]**.**

(a-i): A solution of 50% KOH is added to an equimolar solution of acetophenone (0.075 mol) and aldehyde (0.075 mol) in 95% ethanol; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum and recrystallized by ethanol.

1-(2'-hydroxy-3',5'-diiodophenyl)-3-(2-chloro-6-methoxy-quinolin-3-yl)-2-propen-1-one (3a) m.p. 148°C

IR (KBr) cm-1: 3100(-OH), 1630(C=O), 1570-1480, (ring C=C), 1040,(C-O). 1HNMR (400MHz, DMSO): δ, 6.2-6.5 (dd, 2H,), 7.00- 7.5 (s, 4H, Ar-H), 7.5-7.8 (dd, 2H,)11.5 (s, 1H, Ar-OH) 3.64 (s, 3H, OCH3). Mass M/Z (100%) M+1, 591 Anal. Calcd. For C19H12O3NI2Cl (591.5): C, 38.54; H, 2.02; N, 2.36.Found: C, 38.41; H, 1.91; N, 2.39.

(3b) 1-(2'-hydroxy-3',5'-dibromophenyl)-3-(2-chloro-6-methoxy-quinolin-3-yl)-2- propen- 1 - one m.p. 128°C

IR (KBr) cm-1: 3110 (-OH), 1635 (C=O), 1560-1450, (ring C=C), 1090,(C-O).
1HNMR (400MHz, DMSO): δ, 6.8-6.9 (dd, 2H,), 7.3- 7.5 (s, 4H, Ar-H), 7.8 (dd, 2H,),12.5 (s, 1H, Ar-OH) 3.94 (s, 3H, OCH3).

3c. 1-(2'-hydroxy-5'-bromophenyl)-3-(2-chloro-6-methoxy-quinolin-3-yl)-2- propen- 1-one m.p. 125°C

IR (KBr) cm-1: 3115 (-OH), 1626 (C=O), 1565-1470, (ring C=C), 1030, (C-O).
1HNMR (400MHz, DMSO): δ, 6.1-6.3 (dd, 2H,), 7.7- 7.8 (s, 3H, Ar-H), 6.9-7.2 (dd, 2H,), 7.8-7.9 (dd, 2H,),10.5 (s, 1H, Ar-OH) 3.50 (s, 3H, OCH3).

3d. 1-(2'-hydroxy-3', 5'-diiodophenyl)-3-(2-chloro-6-bromo-quinolin-3-yl)-2- propen- 1- one m.p. 140°C

IR (KBr) cm-1: 3125 (-OH), 1624 (C=O), 1561-1460, (ring C=C), 1030, (C-O).
1HNMR (400MHz, DMSO): δ, 6.4-6.8 (dd, 2H,), 7.4- 7.5(s, 4H, Ar-H), 7.6-7.8 (dd, 2H,), 11.9 (s, 1H, Ar-OH). Mass M/Z (100%) M+1, 640

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3e. 1-(2'-hydroxy-3', 5'-dibromophenyl)-3-(2-chloro-6-bromo-quinolin-3-yl)-2-propen-1-one m.p. 150°C

IR (KBr) cm-1: 3100 (-OH), 1650 (C=O), 1500-1460, (ring C=C), 1080,(C-O).
1HNMR (400MHz, DMSO): δ, 6.8-6.9 (dd, 2H,), 7.1- 7.3(s, 4H, Ar-H), 13.5 (s, 1H, Ar-OH).

3f . 1-(2'-hydroxy-5'-bromophenyl)-3-(2-chloro-6-bromo-quinolin-3-yl)-2- propen- 1- one m.p. 145°C

IR (KBr) cm-1: 3125(-OH), 1624(C=O),1561-1460, (ring C=C), 1030,(C-O).
1HNMR (400MHz, DMSO): δ, 6.4-6.8 (dd, 2H,), 7.4- 7.5(s, 4H, Ar-H), 7.3 (s, 1H, Ar-H) 11.9 (s, 1H, Ar-OH).

3g . 1-(2'-hydroxy-3',5'-diiodophenyl)-3-(2-chloro-6,8-dimethyl-quinolin-3-yl)-2-propen-1-one m.p. 147°C

IR (KBr) cm-1: 3090(-OH), 1660(C=O),1575-1430, (ring C=C), 1020,(C-O).
1HNMR (400MHz, DMSO): δ, 6.7-6.9 (dd, 2H,), 7.1- 7.4(s, 5H, Ar-H), 2.1(s,6H), 12.5 (s, 1H, Ar-OH). Mass M/Z (100%) M+, 590 Anal. Calcd. For $C_{20}H_{14}O_2NI_2Cl$ (590.5): C, 40.74; H, 2.39; N, 2.38.Found: C, 38.41; H, 1.91; N, 2.39.

3h. 1-(2'-hydroxy-3',5'-dibromophenyl)-3-(2-chloro-6,8-dimethyl-quinolin-3-yl)-2-propen-1-one m.p. 135°C

IR (KBr) cm-1: 3178(-OH), 1663 (C=O), 1561-1460, (ring C=C), 1030, (C-O). 1HNMR (400MHz, DMSO): δ, 6.4-6.8 (dd, 2H,), 7.4- 7.5(s, 4H, Ar-H),13.5, 2.3(s,6H), (s, 1H, Ar-OH).

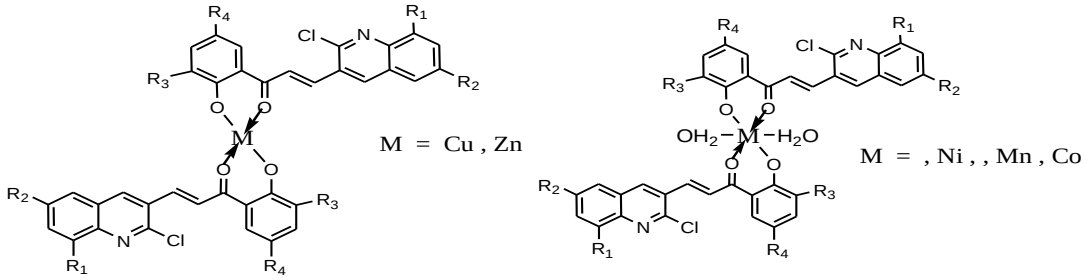
3i. 1-(2'-hydroxy-5'-bromophenyl)-3-(2-chloro-6,8-dimethyl-quinolin-3-yl)-2- propen- 1-One m.p. 122

IR (KBr) cm-1: 3125(-OH), 1624(C=O),1565-1480, (ring C=C), 1000,(C-O).
1HNMR (400MHz, DMSO): δ, 6.1-6.4 (dd, 2H,), 7.0- 7.1(s, 4H, Ar-H), 7.5 (s, 1H, Ar-H), 2.0(s,6H), 13.5 (s, 1H, Ar-OH).

Part II
Synthesis of Metal Complexes

The above prepared novel chalcones are used for the synthesis of Cu(II), Ni(II), Co(II), Mn(II), Zn(II) complexes expecting enhanced bioactivity than respective chalcones.

Scheme II



Metal complexes

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The complex is synthesized by refluxing methanolic solution of ligand and metal salt in 2:1 molar ratio for 2 hrs. and solid mass separated was filtrated through sintered glass crucible and the residue washed with hot methanol until washing ware free of excess of ligand.

Characterization of metal complexes table 1

Complex	IR cm^{-1}	NMR(400MHz)/ DMSO	µeff. B.M.	Geometry	Colour
4a $[Cu(L1)_2]H_2O$	3400,1620,1570-1480,1020, 425	d-3.65(S,3H),6.4-6.5(dd,2H),7-7.5-(S,4H) ,	1.6-1.8 Paramag.	Squre planar	Faint brown
4b $[Cu(L4)_2]H_2O$	3320,1620,1560-1460,1010,460	d-2.0(S,3H),6.4-6.8(dd,2H),7.4-7.5-(S,4H)	Paramag.	Squre planar	brown
4c $[Cu(L7)_2]H_2O$	3410,1620,1565-1470,1030,455	d-2.0-2.3(S,6H),6.2-6.5(dd,2H),7.1-7.3-(S,4H)	Paramag.	Squre planar	brown
4d $[Cu(L10)]H_2O$	3350,1615,1550-1460,1200,465		Paramag.	Squre planar	Faint yellow
4e $[Zn(L1)_2]H_2O$	3400,1625,1570-1480,1035,410	d-4.65(S,3H),6.42-6.55(dd,2H),7-7.5-(S,4H) ,	Dimagnetic	Squre planar	yellow
4f $[Zn(L4)_2]H_2O$	3250,1620,1561-1460,1020,425	d-2.4(S,3H),6.4-6.8(dd,2H),7.4-7.5-(S,4H)	Dimagnetic	Squre planar	Faint yellow
4g $[Zn(L7)_2]H_2O$	2990,1615,1570-1460,1042,455	d-2.0-2.1(S,6H),6.2-6.5(dd,2H),7.1-7.3-(S,4H)	Dimagnetic	Squre planar	Pale yellow
4h $[Zn(L10)]H_2O$	3400,1615,1555-1460,1300,412		Dimagnetic	Squre planar	brown
4i $[Ni(L1)_2(H_2O)_2]$	3350,1625,1540-1470,1030	d-3.75(S,3H),6.4-6.5(dd,2H),7-7.5-(S,4H) ,	2.7-3.2 Paramag.	Octahedral	Faint red
4j $[Ni(L4)_2(H_2O)_2]$	3450,1618,1550-1460,1350,470	d-2.6(S,3H),6.4-6.8(dd,2H),7.4-7.5-(S,4H)	Paramag.	Octahedral	red
4k $[Ni(L7)_2(H_2O)_2]$	3305,1615,1540-1470, 1205	d-2.0-2.3(S,6H),6.2-6.5(dd,2H),7.1-7.3-(S,4H)	Paramag.	Octahedral	red
4l $[Ni(L10)_2(H_2O)_2]$	3360,1615,1520-1470,1200,480		Paramag.	Octahedral	orange
4m	3400,1620,1570-	d-3.60(S,3H),6.4-	4.7-5.2	Octahedral	Black

$[Co(L1)_2(H_2O)_2]$	1480,1035,426	6.6(dd,2H),7-7.6-(S,4H) ,	Paramag.		brown
4n $[Co\ (L4)_2(H_2O)_2]$	3250,1618,1551-1450,1010,425	d-2.0(S,3H),6.4-6.8(dd,2H),7.4-7.5-(S,4H)	Paramag.	Octahedral	brown
4o $[Co\ (L7)_2(H_2O)_2]$	2890,1621,1575-1468,1032,439	d-2.2-2.5(S,6H),6.2-6.5(dd,2H),7.1-7.3-(S,4H)	Paramag.	Octahedral	Red brown
4p $[Co(L10)_2(H_2O)_2]$	3158,1615,1540-1430,1330		Paramag.	Octahedral	brown
4q $[Mn(L1)_2(H_2O)_2]$	3450,1621,1532-1439,1020	d-3.90(S,3H),6.5-6.9(dd,2H),7-7.5-(S,4H) ,	5.7-5.2 Paramag.	Octahedral	gray
4r $[Mn(L4)_2(H_2O)_2]$	3409,1618,1542-1435,1325	d-2.5(S,3H),6.4-6.8(dd,2H),7.4-7.5-(S,4H)	Paramag.	Octahedral	D. red
4s $[Mn(L7)_2(H_2O)_2]$	3305,1635,1540-1470, 1200	d-2.0-2.8(S,6H),6.2-6.5(dd,2H),7.1-7.5-(S,4H)	Paramag.	Octahedral	gray
4t $[Mn(L10)_2(H_2O)_2]$	2905,1625,1540-1470, 1100		Paramag.	Octahedral	brown

Evaluation of Antimicrobial Activity of newly synthesized compounds:

Agar diffusion method described by (Russell and Quesnel 1983) was used for assessment of antimicrobial activity of different honey concentrations. Lyophilized cultures of Bacillus subtilis, Pseudomonas aeruginosa, Staphylococcus aeruginosa, E. coli, Aspergillus niger and Aspergillus flavus. Zones of inhibition of microbial growth obtained after 24 h of incubation at $37^{o}C$ after treatment with 1 mM concentration of compounds were compared with the treatment of standard drug Ampicillin.

RESULTS AND DISCUSSION

Microorganism's viz., bacteria, fungi, viruses and protozoa which have the capacity to cause disease are referred to as pathogenic or infectious microorganisms. Pathogenic or infectious microorganisms can be killed or inhibited by agents of biological or non-biological origin commonly referred as antimicrobials. Antimicrobials are used therapeutically to treat infections. Microorganisms viz., bacteria, fungi, viruses and protozoa which have the capacity to cause disease are referred to as pathogenic or infectious microorganisms. Pathogenic or infectious microorganisms can be killed or inhibited by agents of biological or non-biological origin commonly referred as antimicrobials. Antimicrobials are used therapeutically to treat infections.

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Despite the existence of potent antibiotic and antifungal agents, resistant or multi-resistant strains are continuously appearing, imposing the need for a permanent search and development of new drugs (Silver, 1993). WHO (2002) in its annual report on infectious diseases, "Overcoming Antimicrobial Resistant", quotes that people throughout the world " may only have a decade or two to make use of many of the medicines presently available to stop infectious diseases". There is an urgent need to systematically evaluate the newly synthesized compounds. Chalcones complexes represent one of the important classes of compounds which show promising biological activities. To promote the proper use of new derivatives and to determine their potential as sources for new drugs, it is essential to study newly synthesized complexes of chalcone in a more intensified way. Taking into consideration the above fact, present work has been undertaken to evaluate the complexes of novel hetero-aryl chalcones for their antimicrobial activity.

The antimicrobial activity is presented in the Table. 2. Perusal of the Table 1.

Chalcone	Bacillus subtilis	Pseudomonas aeruginosa	Staphylococcus aureus	Escherichia coli	Aspergillus niger	Aspergillus flavus
$[Cu(L1)_2]H_2O$	+	NR	NR	NR	NR	NR
$[Zn(L1)_2]H_2O$	NR	NR	NR	13	NR	NR
$[Ni(L1)_2(H_2O)_2]$	+++	++	++	++	++	NR
$[Co(L1)_2(H_2O)_2]$	14	11	++	++	++	NR
$[Mn(L1)_2(H_2O)_2]$	+++	+++	+++	++	NR	NR
$[Cu(L10)_2]H_2O$	+	NR	NR	NR	NR	NR
$[Zn(L10)_2]H_2O$	NR	NR	NR	13	NR	NR
$[Ni(L10)_2(H_2O)_2]$	+++	++	++	++	++	NR
$[Co(L10)_2(H_2O)_2]$	14	11	++	++	++	NR
$[Mn(L10)_2(H_2O)_2]$	+++	+++	+++	++	NR	NR
	27			22		

CONCLUSION

We have synthesized some novel chalcones and their complexes by known reaction within few minutes at room temperature. The antimicrobial screening of the synthesized compounds showed moderate to good activity compared with the standard (Table 2).

Antimicrobial activity

Antimicrobial screening was conducted by using cup plate method at a concentration of 25µg/ml. All compounds were checked for their in vitro antimicrobial activity against different strains of bacteria mentioned in table 2. DMSO was used as solvent control .These compounds were compared with standard used, the data of activity of compounds as shown in table 2.

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