World Journal of Pharmaceutical ReseaRch
SJIF Impact Factor 5.045
Volume 3, Issue 8, 380-388. Research Article ISSN 2277 – 7105

A NOVEL ECOFRIENDLY SYNTHESIS OF CHALCONES AND COMPARATIVE CYTOTOXIC STUDY

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Article Received on
29 July 2014,

Revised on 20 August 2014,
Accepted on 21 Sept 2014

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ABSTRACT

Few chalcones are synthesized from substituted aceto phenones and substituted aryl aldehydes in presence of an efficient, ecofriendly and recyclable catalyst i.e.;- ***Aqs*** [Zn/L-Pipiridine -2-oic acid]‖ under reflux condition. Progress of the reaction was monitored by TLC. Obtained chalcones were characterized from I.R., HNMR and mass spectral data. Synthesized compounds were screened for comparative study of cytotoxic analysis.

Key Words: eco-friendly synthesis, Recyclable catalyst, Aqs [Zn/L-Pipiridine-2-oic acid], chalcones, cytotoxic analysis.

1. INTRODUCTION

Chalcones are belonging to flavonoid family; these are chemically 1, 3-diaryl-2-propen-1-one and its derivatives. These are remarkable organic compounds in the plant King Dom. Chalcones exhibit significant bio-logical activities [1] and are chief precursors to synthesize flavones [2]. Chalcones were synthesized from alkaline catalysts *viz;* aqs NaOH [3], hydrotalcites-zeolites [4], LiHDMS [5], BaOH [6], KOH [7], SiO2-NaOH [8], etc.; and acid catlysts *viz;* Con.HCl [9] , TiCl4 [10] , AlCl3 [11], RuCl3[12], etc. Chalcones exhibit anti-malarial [13], antibacterial [14], antifibrogenic [15], anticancer [16], anti trichomonal [17], anti-inflammatory [18], anti leismanial[19], anti trypanosomacruzi[20] activities. The activities of the derivatives of chalcones on enzyme cathepsin- B, were reported [21, 22].

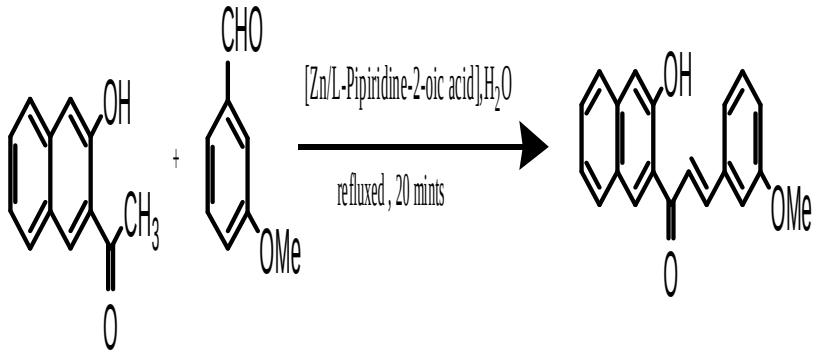
As these possess many biological activities and more convenient precursors to synthesize flavones; we focused on synthetic methods and developed an efficient method by using a

catalytic system i.e; "Aqs [Zn/L-Pipiridine-2-oic acid]" which is more convenient to handle, economical, recyclable and more eco-friendly.

2. MATERIALS AND METHODS

All chemicals used in our experimental work were obtained commercially from SVR chemical suppliers, Hyd. The progress of the reactions was monitored by TLC using silica gel-G (Merk grade) using U.V.light for detection of spots. The structures of compounds were elucidated by I.R., H NMR, and mass spectra. I.R. spectra were recorded in KBr on shimhadzu FTIR presige-21; HNMR spectra were recorded at 400 MHz on Bruker spectrometer using TMS as an internal reference.

3. Experimental



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3.1. General Procedure

3.1. A. Preparation of Complex for Catalytic System

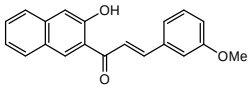
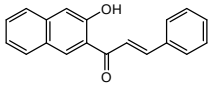
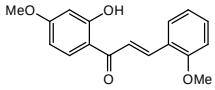
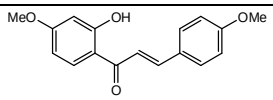
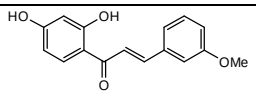
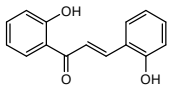
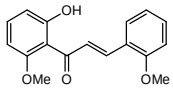
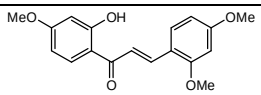
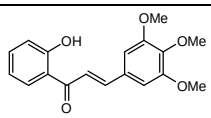
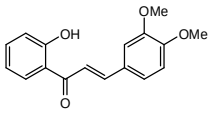
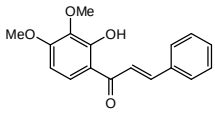
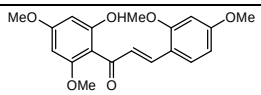
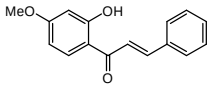
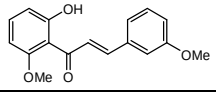
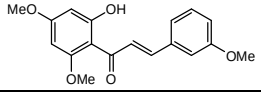
Alcoholic solution of L-Pipiridine-2-oic acid was prepared (20mmol of L-Pipiridine-2-oic acid in 50ml of ethyl alcohol containing 20mmol KOH) in a small beaker. Aqs. Solution of Zn (NO3)2. 6 H2O in a separate beaker (10mmol compound in distilled water) and was added to the solution of L-Pipiridine-2-oic acid drop wisely. Contents were stirred at room temperature for overnight. The formed white catalyst was filtered off and dried.

3.1. B. Preparation of Chalcone (S)

Equimolar ratio of compound 1 and 2 were charged in round bottom flask. The mixture of "5 m.mol of [Zn/L-Pipiridine-2-oic acid], 10ml of H_2O were added along with vigorous stirring. Reaction mixture was refluxed for 20 mints'. Almost no starting material was observed in the

TLC monitoring. The reaction mixture was allowed to cool, ice cold water was added. The precipitate is filtered, dried and recrystallized from ethanol.

Table: 1 Data of Physical Constants of Chalcones

Entry	Ar-CHO	Time (Mnts)	Yield (%)
3.1.1.		20	92
3.1.2.		25	90
3.1.3.		22	88
3.1.4.		25	92
3.1.5.		20	85
3.1.6.		25	92
3.1.7.		23	78
3.1.8.		28	80
3.1.9.		30	85
3.1.10.		25	82
3.1.11.		30	88
3.1.12.		30	92
3.1.13.		25	90
3.1.14.		20	86
3.1.15.		30	82

3.1.1. (E)-1-(3-Hydroxynaphthalen-2-Yl)-3-(3-Methoxy Phenyl) Prop-2-En-1-One

^{1}H NMR (CDCl3): 8.45(1H, d, J ¼ 15.863 Hz), 7.90 (2H,m),7.77 (2H, t), 7.63 (3H, t), 7.51 (3H, t), 7.30 (3H, m), 7.22 (1H, d, J ¼ 2,), 6.96 (1H, d, J ¼ 3.77 Hz),3.88 (3H,s).IR (KBr) mmax: 3427, 2921,1629, 1574 cm_1. EI-Ms:304(M+),115,134,170,69.

3.1.2. (E)-1-(3-Hydroxynapthalene-2-Yl)-3-Phenylprop-2-En-1-One

^{1}H NMR (300 MHz, $CDCl_3$) δ 14.78 (s, 1H), 8.49 (d, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 15.4 Hz, 1H), 7.82 (d, *J* = 9.0 Hz, 1H), 7.75 (s, 1H), 7.69 (dd, *J* = 10.5, 3.6 Hz, 3H), 7.61 (t, *J* = 6.8 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.42 (dd, *J* = 5.0, 1.9 Hz, 3H). IR (KBr) mmax: 3426, 2926, 2842, 1633, 1574 cm_1;

EI-Ms:274(M+),170,115,77.

3.1.3. (E)-1-(2-Hydroxy-4-Methoxyphenyl)-3-(2-Methoxy Phenyl) Prop-2-En-1-One

^{1}H NMR (CDCl3): 13.45 (1H, s), 8.13(1H, d, J ¼ 15.63 Hz), 7.77 (1H, m,),7.63 (2H, d, J ¼ 12.84 Hz), 7.34 (1H,

m), 6.94 (2H, dd, J ¼ 2, 8 Hz), 6.42 (2H, d, J ¼ 8 Hz), 3.95 (3H, s, J ¼ 2, 8 Hz), 3.85 (3H, d, J ¼ 2 Hz); IR (KBr) cm^{-1}: 3420, 3236, 2972, 1665, 1594;

EI-Ms:284(M+),253,177,151.

3.1.4. (E)-1-(2-Hydroxy-4-Methoxyphenyl)-3-(4-Methoxyphenyl)Prop-2-En-1-One

^{1}H NMR (CDCl3): 13.25 (1H, s), 8.12(1H, d, J ¼ 15.63 Hz), 7.76 (1H, m,),7.64 (2H, d, J ¼ 12.84 Hz), 7.33 (1H, m), 6.94 (2H, dd, J ¼ 2, 8 Hz), 6.42 (2H, d, J ¼ 8 Hz), 3.95 (3H, s, J ¼ 2, 8 Hz), 3.87 (3H, d, J ¼ 2 Hz); IR (KBr) cm^{-1}: 3420, 3236, 2972, 1665, 1594;

EI-Ms:284(M+),134,121,108,151.

3.1.5. (E)-1-(2,4-Dihydroxyphenyl)-3-(3-Methoxyphenyl)Prop-2-En-1-One

^{1}H NMR (CDCl3): 8.06(1H, d, J ¼ 15.48 Hz), 7.9 (1H, d, J ¼ 8.12 Hz),7.59 (2H, d, J ¼ 15.48 Hz), 7.16 (2H, s), 6.8(1H, t),6.4 (1H,m),6.3(1H,s),5.3(2H,s),3.8(3H,s); IR (KBr) cm^{-1}: 3285, 2925, 1628, 1581;. EI Ms:270(M+),150,137,121.

3.1.6. (E)-1, 3-Bis (2-Hydroxyphenyl) Prop-2-En-1-One

^{1}H NMR (CDCl3): 8.06(1H, d, J ¼ 15.48 Hz), 7.9 (1H, d, J ¼ 8.12 Hz),7.59 (2H, d, J ¼ 15.48 Hz), 7.16 (2H, s), 6.8(1H, t),6.4 (1H,m),6.3(1H,s),5.3(2H,s); IR (KBr) cm^{-1}: 3285, 2925, 1628, 1581; EI Ms:270(M+),150,137,121.

3.1.7. (E)-1-(2-Hydroxy-6-Methoxyphenyl)-3-(2-Methoxyphenyl)Prop-2-En-1-One

^{1}H NMR (CDCl3): 13.45 (1H, s), 8.13(1H, d, J ¼ 9 Hz), 7.77 (1H, m, J ¼ 16 Hz),7.63 (2H, d, J ¼ 16 Hz), 7.34 (1H, m, J ¼ 6 Hz), 6.94 (2H, dd, J ¼ 2, 8 Hz), 6.42 (2H, d, J ¼ 8 Hz), 3.95 (3H, s, J ¼ 2, 8 Hz), 3.85 (3H, d, J ¼ 2 Hz).EI Ms: IR (KBr) cm^{-1}: 3420, 3236, 2972, 1665, 1594; EIMs: 284(M+),108,177,151,77.

3.1.8. (E)-3-(2,4-Dimethoxyphenyl)-1-(2-Hydroxy-4-Methoxyphenyl)Prop-2-En-1-One

^{1}H NMR (CDCl3): 14.27 (1H, s), 7.71 (2H, s, J ¼ 15.863 Hz), 7.25 (1H, s, J ¼ 15.108 Hz),7.17 (1H, dd, J ¼ 1.5,8.3 Hz), 7.08 (1H, d, J ¼ 2.26 Hz), , 3.92 (9H, t, J ¼ 2.26 Hz); IR (KBr) mmax: 3420, 3236, 2972, 1665, 1594 cm_1; EI-Ms:314(M+),151,121,77.

3.1.9. (E)-1-(2-Hydroxyphenyl)-3-(3,4,5-Trimethoxy Phenyl) Prop-2-En-1-One

^{1}H NMR (CDCl3): 12.75 (1H, s), 7.89(1H, dd, J ¼ 1.5,7.5 Hz), 7.81 (1H, d, J ¼ 15.10 Hz),7.48 (2H, m, J ¼ 16 Hz), 7.00 (1H, d, J ¼ 7.5 Hz), 6.90 (1H, m, J ¼ 2, 8 Hz), 6.85 (2H, s, J ¼ 8 Hz), 3.93 (6H, d, J ¼ 3.7 Hz), 3.89 (3H, d, J ¼ 3.7 Hz); IR (KBr) cm^{-1}: 3420, 3236, 2972, 1665, 1594;

EI Ms: 314(M+), 181, 65, 121.

3.1.10. (E)-3-(3,4-Dimethoxyphenyl)-1-(2-Hydroxyphenyl) Prop-2-En-1-One

^{1}H NMR (CDCl3): 12.79 (1H, s), 7.89(1H, t, J ¼ 15.863 Hz), 7.47 (2H, m, J ¼ 15.108 Hz),7.23 (2H, m, J ¼ 8.30 Hz), 7.13 (1H, d, J ¼ 1.8 Hz), 6.99 (1H, d, J ¼ 0.9,8.3 Hz), 6.89 (1H, m, J ¼ 8 Hz), 3.96 (3H, s, J ¼ 2,), 3.93 (3H, s, J ¼ 3.77 Hz); IR (KBr) cm^{-1}: 3420, 3236, 2972, 1665, 1594;

EI Ms: 284(M+),152,137,103.

3.1.11. (E)-1-(2-Hydroxy-3,4-Dimethoxy)-3-Phenylprop-2-En-1-One

^{1}H NMR (CDCl3): 13.11 (1H, s), 7.88 (1H, d, J ¼ 15.63 Hz), 7.64 (3H, m),7.55 (1H, d, J ¼ 12.84 Hz), 7.40 (3H, m), 6.47 (1H, d, J ¼ 2, 8 Hz),3.96 (3H,s),3.90 (3H.s);IR (KBr) cm^{-1}: 3420, 3236, 2972, 1665, 1594; EI Ms:284(M+),152,137,103.

3.1.12. (E)-3-(2,4-Dimethoxyphenyl)-1-(2-Hydroxy-4,6-Di Methoxyphenyl) Prop-2-En-1-One.

^{1}H NMR (CDCl3): 14.43 (1H, s), 8.04(1H, d, J ¼ 15.863 Hz), 7.81 (1H, d, J ¼ 15.108 Hz),7.50 (1H, d, J ¼ 8.30 Hz), 6.48 (1H, dd, J ¼ 2.26,2.26 Hz), 6.04 (1H, d, J ¼ 2.26 Hz),

5.88 (1H, d, J ¼ 8 Hz), 3.91 (6H, s, J ¼ 2,), 3.84 (6H, d, J ¼ 3.77 Hz); IR (KBr) cm^{-1}: 3420, 3236, 2972, 1665, 1594., EI-Ms:344(M+),151,138,164,121.

3.1.13. (E)-1-(2-Hydroxy-4-Methoxyphenyl)-3-Phenylprop-2-En-1-One

^{1}H NMR (CDCl3): 13.45 (1H, s), 8.13(1H, d, J ¼ 15.63 Hz), 7.77 (1H, m,),7.63 (2H, d, J ¼ 12.84 Hz), 7.34 (1H, m), 6.94 (2H, dd, J ¼ 2, 8 Hz), 6.42 (2H, d, J ¼ 8 Hz), 3.95 (3H, s, J ¼ 2, 8 Hz), 3.85 (3H, d, J ¼ 2 Hz); IR (KBr) cm^{-1}: 3420, 3236, 2972, 1665, 1594; EI-Ms:254(M+),177,165,151,103.

3.1.14. (E)-1-(2-Hydroxy-6-Methoxyphenyl)-3-(3-Methoxy Phenyl) Prop-2-En-1-One.

^{1}H NMR (CDCl3): 13.45 (1H, s), 8.13(1H, d, J ¼ 15.63 Hz), 7.77 (1H, m,),7.63 (2H, d, J ¼ 12.84 Hz), 7.34 (1H, m), 6.94 (2H, dd, J ¼ 2, 8 Hz), 6.42 (2H, d, J ¼ 8 Hz), 3.95 (3H, s, J ¼ 2, 8 Hz), 3.85 (3H, d, J ¼ 2 Hz). IR (KBr) cm^{-1}: 3420, 3236, 2972, 1665, 1594; EI-Ms:283(M+),177,151,108,77.

3.1.15. (E)-1-(2-Hydroxy-4,6-Dimethoxyphenyl)-3-(3-Methoxy Phenyl)Prop-2-En-1-One

^{1}H NMR (CDCl3): 14.27 (1H, s), 7.71 (2H, s, J ¼ 15.863 Hz), 7.25 (1H, s, J ¼ 15.108 Hz),7.17 (1H, dd, J ¼ 1.5,8.3 Hz), 7.08 (1H, d, J ¼ 2.26 Hz), , 3.92 (9H, t, J ¼ 2.26 Hz); IR (KBr) cm^{-1}: 3420, 3236, 2972, 1665, 1594; EIMs:344(M+),151,164,207.

3.2. Cytotoxicity Analysis

Cellular viability in the presence of testcompounds was determined by MTT-micro cultured tetrazolium assay. The cells seeded to flat bottom 96(10000cells/100ul) well plates & cultured in the medium containing 10% serum and allowed to attach and recover for 24 hours in a humid chamber containing 5% CO_2.

MTT(3-(4, 5-dimethylthiazol-2yl)-2,5diphenyl tetrazolium bromide; sigma catalog noM2128) was dissolved in PBS at 5mg/ml and filtered to sterilize and remove a small amount of insoluble residue present in MTT.

Different concentrations of compounds were added to the cells. After 48 hours, stock MTT solution (10ul) was added to the culture plate .Cells were again kept in CO_2 incubator for 2 hours. After incubation 100ulof DMSO was added and mixed.

The absorbance was read at 562nm in a plate reader. The results were represented as percentage of cytotoxity/viability. All the experiments were carried out in triplicates. From the percentage of cytotoxicity the I C -50 value calculated.

Media used was MEM Catalog No M0643

DPBS Catalog No D5652

1X antibiotic solution of 100X Catalog No A5955

1% Sodium pyruvate Catalog No.S8636

1% Non-essential amino acids Catalog No M7145

10% Fetal bovine serum Catalog No F2442

DMSO Catalog No D5879

Trypsin-EDTA solution (0.25%, 2.5 g porcine trypsin and 0.2 g EDTA) Catalog NoT4049.

Trypsin-EDTA solution used for detaching cells during sub culturing process.

Cis-Platin was taken as reference.

Table 2 : Cytotoxic Analysis

Compound	IC50 Values in A-549 cell Line
3.1.1.	>100mM
3.1.2.	> 100 mM
3.1.3.	> 100 mM
3.1.4.	> 100 mM
3.1.5.	15.05 uM
3.1.6.	14.54uM
3.1.7.	19.55uM
3.1.8.	> 100mM
3.1.9.	11.21uM
3.1.10.	778.57uM
3.1.11.	103.58Um
3.1.12.	20.22uM
3.1.13.	> 100 mM
3.1.14.	>100mM
3.1.15.	20.06uM

3.3. RESULTS AND DISCUSSIONS

In order to overcome various demerits in previous methods like more expensive, un eco-friendly conditions, more time taking, etc; we aimed to develop an efficient catalytic system and was used to prepare chalcones and results have been reported. We achieved better yields within less time without formation of side products. The products were isolated and catalyst complex was recycled without any loss and struggle. Under chosen experimental conditions, reactions were completed within the time period of 20 to 30 mints' and 85% to 95% yield of products.

From the HNMR spectral data; characteristic doublet is conformed at 7.59-8.16 due to 1H of "=CH-Ar". The doublet appeared at 7.2 – 7.8 due to 1H of "-CO-CH=".

Molecular mass is confirmed by mass spectra; I.R. spectra gave the confirmation for the presence of " =C=O " by giving peak at 1650 cm-1 and peak at 1500 cm-1 for C=C quadrate of –Ar. In an attempt to generate novel anticancer structures with significant activities against human cancer cell line but more potent than those in use nowadays, a series of 15 chalcone derivatives were synthesized and evaluated for their cytotoxicity against A549, human tumor cell lines. Compounds 3.1.5, 3.1.6, 3.1.7, 3.1.9, 3.1.12 and 3.1.15 were identified as potent cytotoxic against A549 cell lines, respectively. Further, cell cycle perturbations induced by the chalcones synthesized were also studied on the A549 cell lines. The present study revealed that these chalcones were potent anti-proliferative agents against tumor cell lines without being more cytotoxic to normal cells. But when Naphthalene nucleus involved in the chalconic structure, activity was not observed.

3.4. CONCLUSION

The conclusion was made that; different Chalcones can be synthesized from aromatic Aldehyde (s) and acetophenone (s). For better yields, "[Zn/L-Pipiridine-2-oic acid], H2O" is an efficient catalytic system; Possessed - lesser times for completion of reactions, recyclability, eco-friendly and economic conditions.

Compounds 3.1.5, 3.1.6, 3.1.7, 3.1.9, 3.1.12 and 3.1.15 were identified as potent cytotoxic against A549 cell lines. The results of this study may find a lead toward the development of new therapeutic agents to fight cancer.

ACKNOWLEDGEMENT

We are thankful to the management of St. Mary's Pharmacy College, Deshmukhi, Hyderabad, India for their cooperation to finish our work.

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