IMPACT: International Journal of Research in Applied, Natural and Social Sciences (IMPACT: IJRANSS)
ISSN(P): 2347-4580; ISSN(E): 2321-8851
Vol. 4, Issue 10, Oct 2016, 33-38

SYNTHESIS, SPECTRAL STUDIES AND POTENT ANTIMICROBIAL ACTIVITY OF A SERIES OF SUBSTITUTED CHALCONES

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ABSTRACT

A series of several new chalcone analogues were synthesized and also evaluated for their *in vitro* antimicrobial activity against variety of bacterial and fungal strains. Among the synthesized chalcone derivatives **3a, 3b, 3c, 4a, 4b, 4c** showed excellent antibacterial and antifungal activities while substituted quinolinyl chalcones showed significant antifungal activities. The newly synthesized compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectroscopy and elemental analysis.

KEYWORDS: Chalcones, Quinoline, Synthesis, Antibacterial Activity, Antifungal Activity

INTRODUCTION

Chalcones either natural or synthetic are known to exhibit various biological activities. Chalcones are well known intermediates for synthesizing various heterocyclic compounds. The compounds with the backbone of chalcones have been reported to possess various biological activities such as antimicrobial[1], anti-inflammatory[2,] analgesic[3], antiplatelet[4], antiulcerative[5],antimalarial[6],anticancer[7],antiviral[8],antileishmanial[9],antioxidant[10],antitubercular[11],antihyperglycemic[12],immu nomodulatory[13], inhibition of chemical mediators release[14], inhibition of leukotriene B_4[15], inhibition of tyrosinase[16] and inhibition of aldose reductase[17] activities. The presence of a reactive □□β-unsaturated keto function in chalcones is found to be responsible for their antimicrobial activity as pharmacophores of a number of biologically active and medicinally useful molecules. Electron-rich nitrogen heterocycles play an important role in diverse biological activities. In the present communication we report the reaction of various acetophenone derivatives with appropriate aromatic aldehydes to form chalcones. These compounds were also screened for their antimicrobial activity.

EXPERIMENTAL SECTION

All chemicals were of analytical grade and used directly. Classical approaches were adopted to determine the melting points of synthesized compounds using open capillary method, and are reported uncorrected. Elemental analysis was carried out on Perkin-Elmer Series II CHN analyzer. NMR study was performed on Brucker AMX - 300 using $CDCl_3$ as solvent. Tetramethyl silane (TMS) was used as internal reference for ^{1}H-NMR (Chemical shifts in δ, ppm). ^{13}CNMR spectra were recorded on Brucker Top-Stin-300 MHz using $CDCl_3$ as solvent and TMS as an internal standard (chemical shifts in δ ppm). IR spectra were recorded on a Perkin Elmer Fourier-transform infrared (FT-IR) spectrometer (Spectrum 2000) in KBr pellets. Mass spectra were recorded on a Macromass G spectrophotometer.

PROCEDURE FOR THE SYNTHESIS OF VARIOUS SUBSTITUTED ACETOPHENONE

To a solution of 4-Chloroacetophenone (6.0 ml, 40mmol) in 20 ml anhydrous dimethyl formamide (DMF), imidazole (2.72g, 40 mmol) and K_2CO_3 (11.1g, 50 mmol) were added. The reaction mixture was refluxed for 18 hr at 110^{o}C. On completion, as checked by thin-layer chromatography (TLC), the DMF was evaporated in vacuo and redissolved into water (50ml). The aquous solution was extracted with chloroform (3×50ml) and the combined organic solution was dried over anhydrous Na_2SO_4 and evaporated in vacuo to yield crude 4-imidazole acetophenone. The intermediate was purified by flash column chromatography and characterized by mass (Macromass G spectrophotometer) and NMR prior to use in the next step. The remaining intermediates were prepared by the similar method.

GENERAL PROCEDURE FOR THE SYNTHESIS OF SUBSTITUTED 1, 3-DIARYLPROPENONE DERIVATIVES

A substituted methyl ketone (3 mmol) and a substituted aldehyde (3 mmol) were dissolved in a minimum amount of methanol (normally 5ml) with stirring. A cool solution of 10% NaOH was added into it at 0^{o}C. The reaction mixture was allowed to draw closer to room temperature and was stirred for 18-20 hrs. Appearance of off-white to yellow solids in solution within a few minutes to several hours indicated successful synthesis of chalcone. The product was filtered and washed with ice cold water. The product was recrystalized from appropriate solvents. Column chromatography was used to purify the products. The remaining substituted 1, 3-diarylpropenone was prepared by similar method.

1- (4-(1H-imidazol-1-yl) phenyl)-3-(2, 4- dichlorophenyl) prop-2-en-1-one (3a)

Yield 69%, yellow crystals, m.p 160-162^{o}C, MS m/z: 343 (M+1), IR (KBr)/cm^{-1} : 1659 (C=O), 1604 (C=C, Ar), 1524 (C=C, COC=C), 835, 806 cm^{-1} (C-C1), ^{1}HNMR ($CDC1_3$, 300 MHz): δ 7.90 (s, 1H, imidazolyl), 7.50 (d, 2H, imidazolyl), 7.31-8.09(m,9H,Ar).^{13}CNMR($CDC1_3$,300MHz):δ117.75,120.86,124.34,127.66,128.55,130.26,130.67,131.24,131.60,135.41,136.22,136.41,136.81,140.06,140.72,188.53.

1-(4-(1H-1, 2, 4 triazol-1-yl) Phenyl)-3-(2, 4 - dichlorophenyl) prop-2-en-1-one (3b)

yield 79%, yellow crystals, m.p 160-161^{o}C, MS m/z: 344 (M+1), IR (KBr)/cm^{-1}: 1670 (C=O), 1593 (C=C, Ar), 1464 (C=C, COC=C), 852cm^{-1} (C-Cl), ^{1}HNMR ($CDCl_3$, 300 MHZ) : δ 7.25 (s, 2H, triazolyl), 6.71-7.25 (m, 11H, Ar), ^{13}CNMR($CDC1_3$,300MHz):δ117.45,118.50,123.80,124.78,127.82,129.65,129.81,130.30,131.59,131.49,132.51,136.20,138.28,148.51,185.65.

1- (4- (1H - Pyrazol-1-yl) phenyl)-3-(2, 4-dichlorophenyl) prop-2-ene-1-one (3c)

yield 74%, yellow crystals, m.p 153-155^{o}C, MS m/z: 381 (M+K), IR (KBr)/cm^{-1}: 1660 (C=O), 1594 (C=C, Ar), 1389 (C=C, COC=C), 859 cm^{-1} (C-C1), ^{1}HNMR ($CDC1_3$, 300 MHz): δ 6.52 (t, 1H, Pyrazolyl- CH-), 7.25 (d, 2H, Pyrazolyl-CH-NNCH),6.917.61(m,9H,Ar),^{13}CNMR($CDC1_3$,300MHz):δ117.87,118.91,120.60,121.81,122.72,123.82,124.86,127.89,129.65,129.86,129.75,131.45,131.56,132.62,148.71,186.71.

1- (4- (1H-benzimidazol-l-yl) phenyl)-3-(2,4-dichlorophenyl) prop-2-en-1-one (3d)

Yield 62%, yellow crystals, m.p 158-159^{o}C, MS m/z:393 (M+), IR (KBr) /cm^{-1}: 1670 (C=O), 1604 (C=C, Ar), 1487 (C=C, COC=C),836cm^{1}(CCl),^{1}HNMR(CDCl$_3$,30MHz):δ7.38to8.27(m,14H,Ar),^{13}CNMR(CDC1$_3$,300MHz):δ110.43,120.87,122.92,123.31,123.39,124.18,124.23,127.60,128.49,130.19,130.63,131.48,132.97,136.16,136.73,136.77,140.08,140.12,141.78,144.20,188.56.

1- (4-(1H-benzo [d] [1, 2, 3] triazol-1-yl) phenyl)-3- (2, 4- dichlorophenyl) prop-2-en-1-one (3e)

Yield 60%, light yellow crystals, m.p 154-155^{o}C, MS m/z : 394 (M+1), IR (KBr)/cm^{-1}: 1660 (C=O), 1589 (C=C, Ar), 1383(C=C,COC=C),836cm^{1}(CC1),^{1}HNMR(CDC1$_3$,300MH$_z$):δ7.27to8.44(m,13H,Ar),^{13}CNMR(CDC1$_3$,300MHz):δ117.87,118.91,123.82,124.86,127.71,127.89,128.22,128.40,128.72,129.12,129.65,129.75,129.86,130.12,131.45,131.56,132.62,148.71,186.71.

1-(4-(1H-imidazol-1-yl) phenyl)-3-(2-chloro-quinolin-3-yl) prop-2-en-1-one (4a)

Yield 69%, yellow brown crystals, m.p 94-95^{o}C, MS m/z: 360 (M+1), IR (KBr) /cm^{-1}: 1686 (C=O), 1598 (C=C, Ar), 1475 (C=C, COC=C), 823 cm^{-1} (C-Cl), ^{1}HNMR (CDCl$_3$, 300 MH$_z$) : δ 7.76 (s,1H, imidazolyl), 7.32 (merged, 2H, - N-CH=CH-N),7.29to8.79(m,11H,Ar),^{13}CNMR(CDC1$_3$,300MHz):δ110.83,117.80,119.99,120.84,124.36,124.52,125.06,125.32,125.86,126.96,127.26,127.92,129.77,130.43,130.63,132.62,135.42,136.95,138.31,148.95,189.44.

1- (4-(1H-1, 2, 4- triazol-1-yl) phenyl) -3-(2-chloro-quinolin-3-yl) prop-2-en-1-one (4b)

Yield 85%, yellow crystals, m.p 150-152^{o}C, MS m/z: 383 (M+Na), IR (KBr)/cm^{-1}: 1650 (C=O), 1594 (C=C, Ar), 1398 (C=C, COC=C), 810 cm^{-1} (C-Cl), ^{1}HNMR (CDCl$_3$, 300 MH$_z$) : δ 7.90 (s, 2H, triazolyl), 7.19 - 8.00 (m, 11H, Ar), ^{13}CNMR(CDC1$_3$,300MHz):δ111.41,116.76,118.12,119.60,123.82,124.56,127.71,127.78,127.80,129.64,130.31,130.82,131.30,131.81,136.72,138.22,148.62,186.65.

1-(4- (1H-Pyrazol-1-yl) phenyl)-3- (2-Chloro-quinolin-3-yl) prop-2-en-1-one (4c)

Yield 45%, yellow crystals, m.p 90-92^{o}C, MS m/z : 360 (M+1), IR(KBr)/cm^{-1}: 1686 (C=O), 596 (C=C, Ar), 1497 (C=C, COC=C), 831 cm^{-1} (C-Cl), ^{1}HNMR (CDCl$_3$, 300 MHz): δ 8.09 (m, 3H, Pyrazolyl), 7.45-8.01 (m, 11H, Ar), ^{13}CNMR(CDC1$_3$,300MHz):δ119.98,123.71,124.22,124.35,125.05,126.89,127.26,127.42,128.16,128.57,128.95,129.20,129.77,130.93,132.61,133.66,135.50,148.94,189.42.

1- (4-(1H- benzimidazol-1-yl) phenyl)-3- (2-chloro-quinolin-3-yl) prop-2-en-1-one (4d)

Yield 54%, yellow crystals, m.p 160-162^{o}C,MS m/z: 410 (M+1), IR (KBr)/cm^{-1}: 1660 (C=O), 1597 (C=C, Ar), 1450 (C=C, COC=C), 848 cm^{-1} (C-Cl), ^{1}HNMR (CDCl$_3$, 300 MHz) : δ 7.82 (s, 1H, benzimidazolyl), 7.92 (m, 4H, benzimidazolyl), 7.40to8.50(m,11H,Ar),^{13}CNMR(CDC1$_3$,300MHz):δ,112.20,117.45,118.50,119.20,123.38,124.48,127.71,127.72,127.82,127.91,128.12,128.12,128.71,129.11,130.11,130.30,130.65,130.77,131.32,131.36,147.50,148.51,185.65.

1-(4-(1H-benzo [d] [1, 2, 3] triazol-1-yl) phenyl)-3- (2-chloro - quinolin-3-yl) prop-2-en-1-one (4e)

Yield 56%, yellowish white crystals, m.p 170-172^{o}C, MS m/z: 433 (M+Na), IR (KBr)/cm^{-1}: 1650 (C=O), 1590 (C=C, Ar), 1394 (C=C, COC=C), 809 cm^{-1} (C-Cl), ^{1}HNMR ($CDCl_3$, 300 MHz): δ 7.25-7.36 (m, 4H, benzotriazolyl), 7.30-7.87 (m, 11H,Ar),^{13}CNMR($CDC1_3$,300MHz):δ111.41,116.76,118.12,119.60,123.82,124.56,127.71,12.71,127.78,127.80,128.22,128.40,128.72,129.12,129.64,130.12,130.31,130.82,131.30,131.80,148.62,186.65.

RESULTS AND DISCUSSIONS

CHEMISTRY

Chalcone is an exceptional chemical template having multifarious biological activities. Chalcones **(3a-e)** and **(4a-e)** were prepared by standard Claisen- Schmidt condensation reaction of different acetophenone derivatives with appropriate aldehydes in 10% NaOH and MeOH. In chalcones **(3a-e)** in acetophenone moiety chloro group was replaced systematically with imidazole, pyrazol, triazol, benzimidazol and benzotriazol. Substituent chosen at aldehyde ring is 2, 4-dichloro and other aldehyde ring 2-chloro- quinolaldehyde. Two step synthesis protocol used to prepare chalcones. All the synthesized compounds were well characterized by spectroscopic methods such as IR, NMR, Mass and elemental analysis.

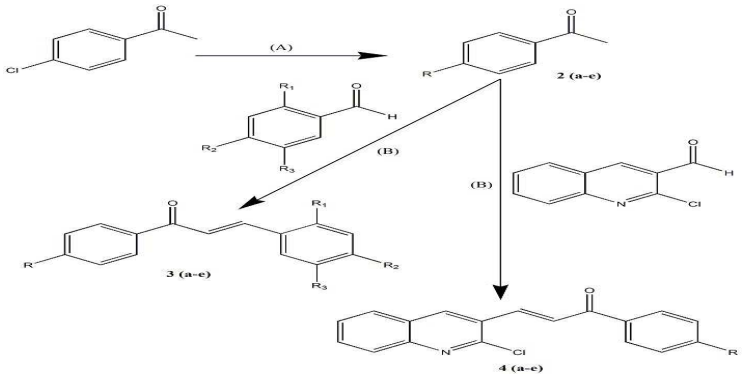

Figure 1

Here: (A) Cyclic amines, K_2CO_3, DMF, 18 hrs, 110^{o}C

(B) 10% NaOH, MeOH, 18-20 hrs, rt

R=Cyclic amines (Imidazole, Triazole, Pyrazole, Benzimidazole and Benzotriazole) and R_1 = Cl, R_2 = Cl, R_3 =H

BIOLOGICAL SCREENING

COMPOUNDS

Test compounds were dissolved in dimethyl sulphoxide (DMSO) to obtain desired concentrations and screene here: (A) Cyclic amines, K_2CO_3, DMF, 18 hrs, 110^{o}C

INOCULUM

The bacteria were inoculated into broth and were incubated at 37^{o}C for 4h and the suspension was checked to provide approximately 10^5 CFU/ml. The same procedure is applied for antifungal test.

MICROORGANISM USED

The newly synthesized compounds were screened for their antimicrobial activity against the bacterial strains such as *Escherichia coli* (ATCC 25922) *Staphylococcus aureus* (ATCC 25923), *Streptococcus pyrogens* (ATCC 6057), and fungi such as *Aspergillus niger, Candida albicans* and *Saccharomyces cerevisae*.

ANTIBACTERIAL ACTIVITY

The agar well diffusion method[18] is slightly modified. The nutrient Agar medium (NAM) was used for bacterial cultures. The culture medium is inoculated with the microorganisms suspended in Nutrient Broth. A total of 8 mm diameter wells were punched into the agar and is filled with 100 µl of the compound solvent.10% DMSO was used as the negative control and standard antibiotic Chloramphenicol, 100µg/ml was taken as positive control. The plates were then incubated at 37^{o}C for 18h. The antibacterial activity was evaluated by measuring the diameter of zone of inhibition.

ANTIFUNGAL ACTIVITY

For assaying the antifungal activity of compounds Potato Dextrose Agar (PDA) medium plates were used. The same procedure as that of assaying antibacterial activity was used and then the diameter of zone of inhibition was observed. Fluconazole, 100µg/ml was used as a positive control and 10% DMSO was used as negative control.

Table 1: Antimicrobial Activities of Chalcone Compounds

Zone of Inhibition in mm						
Compounds	**Antibacterial Activity**			**Antifungal Activity**		
	E.coli	**S.aureus**	**S.pyrogens**	**A.niger**	**C.albicans**	**S.cerevisae**
3a	10	22	20	50	50	50
3b	30	20	15	50	20	30
3c	40	40	30	50	30	50
3d	-	25	-	40	-	-
3e	15	20	-	20	20	-
4a	20	19	18	50	50	50
4b	10	24	-	30	30	30
4c	-	-	-	30	30	30
4d	-	-	-	20	20	20
4e	-	-	15	20	20	15
Chloramphenicol	13	12	11	-	-	-
Fluconazole	-	-	-	12	13	15

CONCLUSIONS

In conclusion, we have reported the *in vitro* screenings of these synthesized compounds against the bacterial strains such as *E.coli, Staphylococcus aureus, Streptococcus pyrogens*, and fungi such as *Aspergillus niger, Candida albicans, Saccharomyces cerevisae* have shown their promising biological activity. Out of the synthesized compounds, few of the chalcones showed appreciable antifungal activity.

The standard drugs used for comparision were Chloramphenicol and Fluconazole. The presence of more than one electron-withdrawing group on the aromatic ring B (aldehyde ring) in general increased the antimicrobial activity compared to compounds with electron donating groups. The information obtained in this study provides a tool for designing better compounds, and for guiding further structural modification and synthesizing potent new antimicrobial

agents.

ACKNOWLEDGEMENTS

The authors are thankful to the Head of the Chemistry Department, M.M.H. College, and Ghaziabad for providing research facilities and Sai Institute of paramedical and allied sciences Rajpur Road, Dehradun for screening the newly synthesized compounds for their Antimicrobial activities and IIT Delhi for providing spectral analysis.

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