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Green Synthetic Protocol for (*E*)-1-Aryl-3-(2-morpholinoquinolin-3-yl)prop-2-en-1-ones and Their Antimicrobial Activity

RELANGI SIVA SUBRAHMANYAM and VENKATESWARA RAO ANNA*

Department of Chemistry, Koneru Lakshmaiah Education Foundation, Vaddeswaram, Guntur-522502, India

*Corresponding author: E-mail: avrchemistry@gmail.com

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We report here an easy, efficient and green synthetic protocol for the (*E*)-1-aryl-3-(2-morpholinoquinolin-3-yl)prop-2-en-1-ones by the Claisen-Schmidt condensation of 2-morpholinoquinoline-3-carbaldehyde and different substituted acetophenones by using 1-butyl-3-methylimidazolium tetrafluoroborate (Bmim)BF_4. The compounds were characterized by using ^{1}H NMR, ^{13}C NMR and mass spectral data and screened there *in vitro* antimicrobial activity against different bacterial and fungal organisms.

Keywords: Claisen-Schmidt condensation, Ionic liquid, Chalcone, Quinoline, Antimicrobial activity.

INTRODUCTION

Nitrogen-heterocycles play a predominant role in medicinal chemistry due to their pharmacological activities. The quinoline derivatives play various biological activates such as anticancer [1], anti-HIV [2], antimicrobial [3], antituberculosis [4], antiviral [5], antimalarial [6], antioxidant [7], anti-inflammatory [8], antiprotozoal [9] and some of the quinoline derivatives found in marked drugs including as chloroquine, piperaquine, pyronaridine, ciprofloxacin, lenvatinib and tipifamib. In addition, morpholine core moiety is also important in pharmacological industry due to its antimicrobial [10] and anti-inflammatory [11] activities. Furthermore, chalcone derivatives are pharmacologically active with wide variety of activates as antimicrobial [12], anticancer [13], anti-inflammatory [14], antidiabetic [15] *etc*. Therefore, we wish to synthesize (*E*)-1-aryl-3-(2-morpholinoquinolin-3-yl)prop-2-en-1-ones derivatives. Generally, the synthetic approach of the chalcones involves methyl ketones and aromatic aldehydes, which is mainly catalyzed by a strong base or an acid. However, the use of strong base or acids condensation process suffers as low yields with higher reaction times and gives undesired products [16]. The chalcone also catalyzed by Lewis acids [17], Brønsted bases [18], heterogeneous catalysts [19] and metal complexes [20] but these were associated some disadvantages such as use of hazardous organic solvent system, which make the development of more greener and efficient protocol for the synthesis of these chalcones. In green chemistry concern, ionic liquids have become popular as novel and promising solvents for organic synthesis. Thus, we prompted us to synthesize (*E*)-1-aryl-3-(2-morpholinoquinolin-3-yl)prop-2-en-1-ones derivatives by using 1-butyl-3-methylimidazolium tetrafluoroborate (Bmim)BF_4. The method has proved to be an easy, efficient high yields with short routine and being more environmentally-friendly.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds was checked by TLC using precoated silica gel plates 60_{254} (Merck). The IR spectra were recorded on a Perkin-Elmer FT-IR-8400s, using samples in KBr disks. The purity of the compounds was checked by TLC using precoated silica gel plates 60_{254} (Merck). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance II 400 MHz spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a GCMS-QP 1000 EX mass spectrometer. Elemental analysis was performed on a Perkin Elmer CHN-2400 analyzer.

Synthetic procedure for (E)-1-aryl-3-(2-morpholinoquinolin-3-yl)prop-2-en-1-ones (Va-k): A mixture of 2-morpholinoquinoline-3-carbaldehyde (**1**) (1 mmol), aryl methyl keones (**IVa-c**) (1 mmol) and (Bmim)BF_4 was stirred at 80 °C for 40-50 min. Progress of the reaction was monitored by TLC, after

completion of the reaction. The reaction mixture poured into ice cold water, slowly the solid separates out, it filtered, washed with water, dried and purified by using column chromatography using *n*-hexane:ethyl acetate (9:1) to afford pure (*E*)-1-aryl-3-(2-morpholinoquinolin-3-yl)prop-2-en-1-ones **(Va-k) (Scheme-I)**.

(*E*)-3-(2-Morpholinoquinolin-3-yl)-1-phenylprop-2-en-1-one (Va): Colour: yellow; yield: 90 %; m.p.: 127-130 ºC. IR (KBr, ν_{max}, cm^{-1}): 1652 (C=O); 1586 (C=C); ^{1}H NMR ($CDCl_3$): 3.40-3.42 (t, 4H, N-CH_2), 3.90-3.93 (t, 4H, O-CH_2), 7.38-7.42 (t, 1H, ArH), 7.52-7.56 (m, 2H, ArH), 7.61-7.72 (m, 4H, ArH), 7.75-7.77 (d, 1H, ArH), 7.85-7.87 (d, 1H, ArH), 8.00-8.08 (m, 3H, ArH), 8.28 (s, 1H, ArH), ^{13}C NMR ($CDCl_3$): 51.0, 66.9, 122.7, 123.0, 124.8, 124.9, 127.6, 127.8, 128.5, 128.6, 128.7, 130.6, 133.0, 137.2, 137.9, 141.9, 147.7, 159.6, 190.2; MS: *m/z* = 345 $(M+H)^+$; Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.78; H, 5.78; N, 8.10.

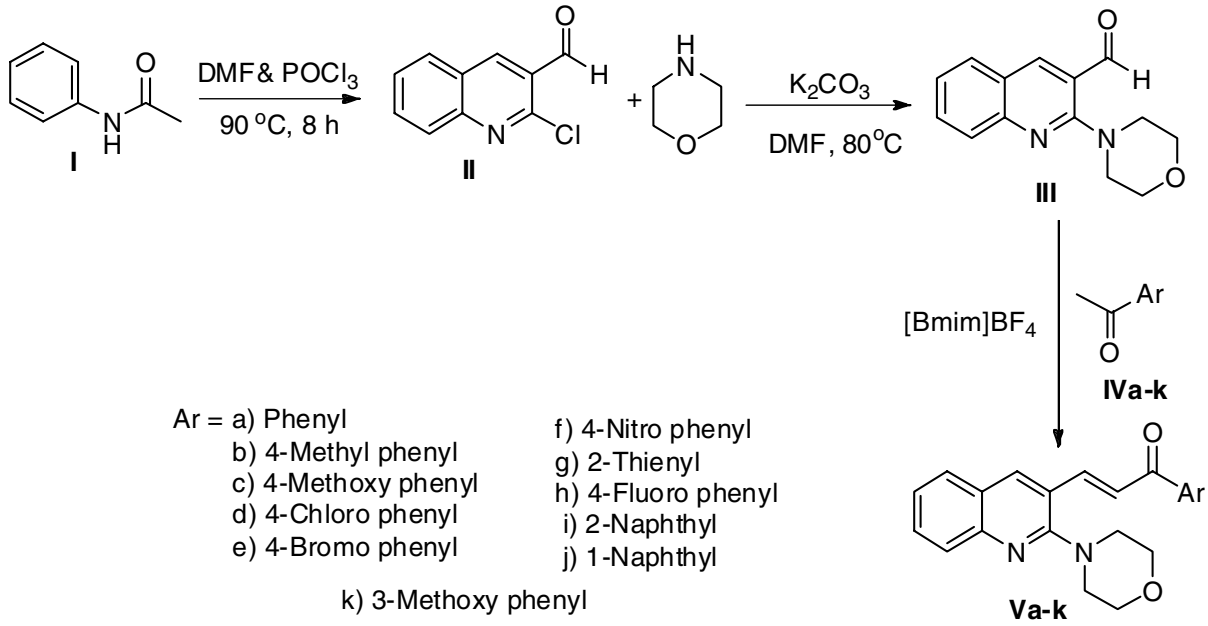
(*E*)-3-(2-Morpholinoquinolin-3-yl)-1-(*p*-tolyl)prop-2-en-1-one (Vb): Colour: yellow; yield: 92 %; m.p.: 130-133 ºC. IR (KBr, ν_{max}, cm^{-1}): 1651 (C=O); 1590 (C=C); ^{1}H NMR ($CDCl_3$): 2.46 (s, 3H, CH_3), 3.40-3.42 (t, 4H, N-CH_2), 3.90-3.93 (t, 4H, O-CH_2), 7.33-7.35 (d, 1H, ArH), 7.38-7.42 (t, 1H, ArH), 7.63-7.77 (m, 3H, ArH), 7.85-7.87 (d, 1H, ArH), 7.97-8.03 (m, 3H, ArH), 8.27 (s, 1H, ArH), ^{13}C NMR ($CDCl_3$): 21.4, 51.0, 66.9, 122.8, 123.0, 124.2, 124.7, 124.9, 125.9, 127.6, 127.8, 128.7, 129.4, 124.8, 130.5, 137.2, 138.4, 139.0, 141.4, 144.2, 147.6, 159.6, 189.6; MS: *m/z* = 359 $(M+H)^+$; Anal. Calcd. for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82. Found: C, 77.12; H, 6.14; N, 7.85.

(*E*)-1-(4-Methoxyphenyl)-3-(2-morpholinoquinolin-3-yl)prop-2-en-1-one (Vc): Colour: Pale yellow, Yield: 92 %, m.p.: 118-121 °C. IR (KBr, ν_{max}, cm^{-1}): 1655 (C=O); 1592 (C=C); ^{1}H NMR ($CDCl_3$): 3.40-3.42 (t, 4H, N-CH_2), 3.91-3.93 (m, 7H, O-CH_2), 7.00-7.02 (d, 2H, ArH), 7.37-7.41 (t, 1H, ArH), 7.62-7.76 (m, 3H, ArH), 7.74-7.76 (d, 1H, ArH), 7.85-7.87 (d, 1H, ArH), 7.99-8.03 (d, 1H, ArH), 8.08-8.10 (d, 2H, ArH), 8.26 (s, 1H, ArH), ^{13}C NMR ($CDCl_3$): 50.9, 55.5, 66.9, 113.9, 122.8, 122.9, 124.7, 124.9, 127.6, 127.7, 130.5, 130.7,130.8, 130.9, 137.1, 141.0, 147.6, 159.6, 163.6, 188.2; MS: *m/z* = 375 $(M+H)^+$; Anal. Calcd. for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.75; H, 5.99; N, 7.53.

(*E*)-1-(4-Chlorophenyl)-3-(2-morpholinoquinolin-3-yl)prop-2-en-1-one (Vd): Colour: Pale yellow, Yield: 89 %, m.p.: 136-139 °C. IR (KBr, ν_{max}, cm^{-1}): 1648 (C=O); 1588 (C=C); ^{1}H NMR ($CDCl_3$): 3.40 (s, 4H, N-CH_2), 3.91 (s, 4H, O-CH_2), 7.38-7.43 (t, 1H, ArH), 7.50-7.52 (d, 2H, ArH), 7.64-7.68 (m, 2H, ArH), 7.74-7.76 (d, 1H, ArH), 7.85-7.85 (m, 1H, ArH), 8.00-8.06 (m, 3H, ArH), 8.27 (s, 1H, ArH), ^{13}C NMR ($CDCl_3$): 51.0, 66.9, 122.3, 122.5, 123.0, 124.8, 124.9, 127.7, 127.8, 129.0, 129.9, 130.7, 136.1, 137.3, 139.5, 142.3, 147.7, 159.6, 188.6; MS: *m/z* = 379 $(M+H)^+$; Anal. Calcd. for $C_{22}H_{19}N_2O_2Cl$: C, 69.75; H, 5.05; N, 7.39. Found: C, 69.70; H, 5.01; N, 7.33.

(*E*)-1-(4-Bromophenyl)-3-(2-morpholinoquinolin-3-yl)prop-2-en-1-one (Ve): Colour: Pale yellow, Yield: 90 %, m.p.: 125-128 °C. IR (KBr, ν_{max}, cm^{-1}): 1647 (C=O); 1592 (C=C); ^{1}H NMR ($CDCl_3$): 3.41-3.43 (t, 4H, N-CH_2), 3.90-3.93 (t, 4H, O-CH_2), 3.91 (s, 3H, O-CH_3), 7.39-7.43 (m, 1H, ArH), 7.64-7.69 (m, 4H, ArH), 7.75-7.77 (m, 1H, ArH), 7.86-7.88 (d, 1H, ArH), 7.93-7.95 (d, 2H, ArH), 8.02-8.06 (d, 1H, ArH), 8.29 (s, 1H, ArH), ^{13}C NMR ($CDCl_3$): 51.0, 66.9, 122.3, 122.5, 124.8, 124.9, 127.6, 127.8, 128.2, 130.0, 130.8, 132.0, 136., 137.4, 142.4, 159.5, 189.8; MS: *m/z* = 423 $(M+H)^+$; Anal. Calcd. for $C_{22}H_{19}N_2O_2Br$: C, 62.42; H, 4.52; N, 6.62. Found: C, 62.47; H, 4.56; N, 6.60.

(*E*)-3-(2-Morpholinoquinolin-3-yl)-1-(4-nitrophenyl)-prop-2-en-1-one (Vf): Colour: Pale brown, Yield: 88 %, m.p.: 147-150 °C. IR (KBr, ν_{max}, cm^{-1}): 1655 (C=O), 1586 (C=C); ^{1}H NMR ($CDCl_3$): 3.40-3.42 (t, 4H, N-CH_2), 3.90-3.93 (t, 4H, O-CH_2), 7.40-7.44 (t, 1H, ArH), 7.66-7.70 (m, 2H, ArH), 7.76-7.78 (d, 1H, ArH), 7.86-7.88 (d, 2H, ArH), 8.08-8.12 (d, 1H, ArH), 8.20-8.22 (d, 2H, ArH), 8.31 (s, 1H, ArH), 8.38-8.40



Scheme-I: Synthesis of (*E*)-1-aryl-3-(2-morpholinoquinolin-3-yl)prop-2-en-1-ones

(d, 2H, ArH); ^{13}C NMR ($CDCl_3$): 51.0, 66.9, 123.7, 124.1, 124.7, 124.9, 127.5, 127.9, 128.5, 128.7, 129.3, 130.2, 133.2, 135.2, 136.2, 144.5, 149.6, 162.2, 190.2; MS: *m/z* = 390 $(M+H)^+$; Anal. Calcd. for $C_{22}H_{19}N_3O_4$: C, 67.86; H, 4.92; N, 10.79. Found: C, 67.82; H, 4.97; N, 10.82.

(*E*)-3-(2-Morpholinoquinolin-3-yl)-1-(thiophen-2-yl)-prop-2-en-1-one (Vg): Colour: Pale yellow, Yield: 92 %, m.p.: 137-140 °C. IR (KBr, ν_{max}, cm^{-1}): 1644 (C=O), 1582 (C=C); ^{1}H NMR ($CDCl_3$): 3.41 (s, 4H, N-CH_2), 3.93 (s, 4H, O-CH_2), 3.91 (s, 3H, O-CH_3), 7.23-7.26 (t, 1H, ArH), 7.38-7.42 (t, 1H, ArH), 7.59-7.77 (m, 4H, ArH), 7.85-7.87 (d, 2H, ArH), 7.92-7.93 (d, 2H, ArH), 8.04-8.08 (d, 1H, O=C-H_αC=C, *J*=16Hz), 8.26 (s, 1H, ArH), ^{13}C NMR ($CDCl_3$): 51.0, 66.9, 122.5, 122.6, 124.8, 124.9, 127.6, 127.8, 128.4, 130.6, 131.9, 134.2, 137.5, 141.2, 145.3, 147.6, 159.6, 181.7; MS: *m/z* = 351 $(M+H)^+$; Anal. Calcd. for $C_{20}H_{18}N_2O_2S$: C, 68.55; H, 5.18; N, 7.99. Found: C, 68.50; H, 5.22; N, 7.92.

(*E*)-1-(4-Fluorophenyl)-3-(2-morpholinoquinolin-3-yl)prop-2-en-1-one (Vh): Colour: Pale yellow, Yield: 89 %, m.p.: 151-154 °C. IR (KBr, ν_{max}, cm^{-1}): 1645 (C=O), 1587 (C=C); ^{1}H NMR ($CDCl_3$): 3.40-3.42 (t, 4H, N-CH_2), 3.91-3.93 (s, 4H, O-CH_2), 7.19-7.24 (m, 2H, ArH), 7.39-7.42 (t, 1H, ArH), 7.64-7.70 (m, 2H, ArH), 7.75-7.77 (d, 1H, ArH), 7.85-7.87 (d, 1H, ArH), 8.02-8.06 (d, 1H, ArH), 8.08-8.13 (m, 2H, ArH), 8.28 (s, 1H, ArH), ^{13}C NMR ($CDCl_3$): 51.8, 66.9, 121.9, 122.9, 124.3, 124.6, 127.5, 127.8, 129.0, 129.9, 130.5, 136.3, 137.0, 139.3, 143.1, 147.9, 160.7, 189.1; MS: *m/z* = 379 $(M+H)^+$; Anal. Calcd. for $C_{22}H_{19}N_2O_2F$: C, 72.91; H, 5.28; N, 7.73. Found: C, 72.94; H, 5.30; N, 7.77.

(*E*)-3-(2-Morpholinoquinolin-3-yl)-1-(naphthalen-2-yl)prop-2-en-1-one (Vi): Colour: Pale yellow, Yield: 89 %, m.p.: 141-144 °C. IR (KBr, ν_{max}, cm^{-1}): 1648 (C=O), 1590 (C=C); ^{1}H NMR ($CDCl_3$): 3.43 (t, 4H, N-CH_2), 3.93 (t, 4H, O-CH_2), 7.39-7.43 (t, 1H, ArH), 7.58-7.68 (m, 3H, ArH), 7.78-7.80 (d, 1H, ArH), 7.85-8.15 (m, 7H, ArH), 8.34 (s, 1H, ArH), 8.60 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$): 51.0, 66.9, 122.8, 122.9, 124.3, 124.8, 125.0, 126.9, 127.7, 127.8, 127.9, 128.6, 128.7, 129.5, 130.0, 130.6, 132.5, 135.2, 135.6, 137.2, 141.8, 147.7, 159.6, 189.8; MS: *m/z* = 395 $(M+H)^+$; Anal. Calcd. for $C_{26}H_{22}N_2O_2$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.11; H, 5.65; N, 7.16.

(*E*)-3-(2-Morpholinoquinolin-3-yl)-1-(naphthalen-1-yl)prop-2-en-1-one (Vj): Colour: Pale yellow, Yield: 90 %, m.p.: 137-140 °C. IR (KBr, ν_{max}, cm^{-1}): 1652 (C=O), 1582 (C=C); ^{1}H NMR ($CDCl_3$): 3.42 (s, 4H, N-CH_2), 3.90 (s, 4H, O-CH_2), 7.20-7.22 (d, 1H, ArH), 7.37-7.45 (m, 3H, ArH), 7.58-7.73 (m, 4H, ArH), 7.83-7.85 (m, 2H, ArH), 7.94-7.96 (d, 1H, ArH), 8.06-8.12 (m, 2H, ArH),8.23 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$): 51.0, 66.9, 120.8, 123.0, 123.8, 124.3, 124.5, 124.6, 125.5, 125.9, 127.4, 127.5, 127.8, 130.2, 130.5, 137.3, 137.4, 142.8, 147.9, 160.7, 193.1; MS: *m/z* = 395 $(M+H)^+$; Anal. Calcd. for $C_{26}H_{22}N_2O_2$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.21; H, 5.60; N, 7.17.

(*E*)-1-(3-Methoxyphenyl)-3-(2-morpholinoquinolin-3-yl)prop-2-en-1-one (Vk): Colour: Pale brown, Yield: 88 %, m.p.: 122-125 °C. IR (KBr, ν_{max}, cm^{-1}): 1645 (C=O), 1592 (C=C); ^{1}H NMR ($CDCl_3$): 3.40-3.42 (t, 4H, N-CH_2), 3.90-3.93 (m, 7H, O-CH_2), 7.16-7.18 (dd, 1H, ArH), 7.39-7.47 (m, 2H, ArH), 7.58-7.70 (m, 4H, ArH), 7.75-7.77 (d, 1H, ArH), 7.85-7.87 (d, 1H, ArH), 8.00-8.04 (d, 1H, ArH), 8.28 (s, 1H, ArH), ^{13}C NMR ($CDCl_3$): 51.7, 55.5, 66.9, 113.8, 113.9, 122.4, 123.3, 142.2, 124.7, 127.1, 127.4, 127.7, 130.2, 130.8, 130.9, 136.8, 141.7, 147.8, 160.7, 163.5, 188.6; MS: *m/z* = 375 $(M+H)^+$; Anal. Calcd. for $C_{23}H_{22}N_2O_2$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.80; H, 5.95; N, 7.45.

RESULTS AND DISCUSSION

The chalcones have successfully synthesized from 2-morpholinoquinoline-3-carbaldehyde (**1**) and aryl methyl ketones, the intermediate aldehyde was prepared by starting from acetanilide with the reaction of DMF and $POCl_3$ reagent followed by substitution of morppholine. The Claisen-Schimdt condensation was carried out by using 1-butyl-3-methylimidazolium tetrafluoroborate (Bmim)BF_4 in the place of hazardous strong bases and acids. The newly synthesized chalcone were characterized by ^{1}H NMR, ^{13}C NMR and Mass spectral data analysis. In the ^{1}H NMR spectrum the compounds (**Va-k**) showed characteristic newly generated two doublet in the range of δ 7.40 and 7.98 ppm integrating for each one proton was assigned for α,β-unsaturated carbonyl group protons. In the ^{13}C NMR spectrum, the compounds (**Va-k**) showed required number of carbon peaks. The LCMS spectra exhibited the $(M+H)^+$ peaks their *m/z* values.

Antibacterial activity: The synthesized compounds (**Va-k**) were evaluated for *in vitro* antibacterial activity against four

TABLE-1
ANTIMICROBIAL ACTIVITY OF (*E*)-1-ARYL-3-(2-MORPHOLINOQUINOLIN-3-YL)PROP-2-EN-1-ONES (**Va-k**)

Compound	Antibacterial				Antifungal	
	S. aureus	*B. subtilis*	*P. aeruginosa*	*E. coli*	*A. niger*	*Sclerotiumrol fsii*
Va	16.8	8.8	17.5	13.3	14.2	18.8
Vb	10.3	9.0	11.2	10.2	12.8	14.4
Vc	15.9	12.1	11.6	16.1	11.9	13.6
Vd	9.8	9.4	13.3	9.9	11.3	14.2
Ve	20.2	13.5	16.7	15.3	16.2	15.5
Vf	21.6	12.4	18.8	13.8	13.7	11.7
Vg	18.3	10.0	9.8	9.6	10.9	13.4
Vh	13.2	8.6	9.6	10.0	11.6	10.8
Vi	22.1	14.4	12.0	15.5	14.0	12.7
Vj	16.6	11.0	13.2	12.6	10.8	13.0
Vk	13.6	9.4	10.4	11.9	10.6	14.1
Norfloxacin	25.6	19.2	24.2	24.0	–	–
Ketoconazole	–	–	–	–	18.3	22.1

bacterial strains Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) and two Gram-negative (*Pseudomonas aeruginosa* and *Escherichia coli*) by paper disc method and norfloxacin used as the standard drug by measuring the zone of inhibition in mm. The compounds were screened at the concentrations of 100 µg/mL in DMSO. The compounds **Ve**, **Vf**, **Vg** and **Vi** were showed good antibacterial activity against all the bacterial stains and reaming compounds showed moderated to low activity (Table-1).

Antifungal and antibacterial activities: The synthesized compounds (**Va-k**) were evaluated for *in vitro* antifungal activity against two fungal strains (*Sclerotiumrolfsii* and *Aspergillus niger*) at a concentration of 500 mg/mL by disc diffusion method, zone of inhibition measured in mm and ketoconazole used as the standard. Careful observation of the results shows that compounds **Va**, **Ve**, **Vf** and **Vi** showed better antifungal activity and the remaining compounds were showed moderate activity against both the organisms (Table-1). The synthesized compounds were sreened their *in vitro* antimicrobial activity, the result suggeted that the compounds **Ve**, **Vf** and **Vi** showed good antimicrobial activity.

Conclusion

The use of ionic liquid ([Bmim]BF_4) synthetic protocal for the synthesis of chalcone deivatives offer many advantages simple reaction procedure, short rection times, high yields, exclusion of toxic solvents and easy work up.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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