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Microwave-assisted preparation of azachalcones and their *N*-alkyl derivatives with antimicrobial activities

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Two new azachalcones were prepared by both Claisen–Schmidt condensation and a simple environmentally trendy microwave-assisted method. Ten new *N*-alkyl ($C_{6,8,10,12,14}$)-substituted azachalconium bromides **(3a–e**, **4a–e)** were prepared from compounds **1** and **2** with corresponding alkyl halides. The antimicrobial activities of all the compounds were tested against *Enterococcus faecalis*, *Yersinia pseudotuberculosis*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Staphylococcus aureus* micro-organisms.

Keywords: azachalcone; *N*-alkyl azachalconium bromide; microwave synthesis; antimicrobial activities

1. Introduction

Chalcones are medicinally important α,β-unsaturated ketones which constitute a class of naturally occurring substances. These compounds are potential bioactives (Ahmad et al. 2011; Joshi et al. 2012; Ngaini et al. 2012). They have found numerous applications as pesticides, photoprotectors in plastics, solar creams and food additives (Nowakowska 2007; Nowakowska et al. 2008). Azachalcones are derivatives of chalcones with an annular nitrogen atom in the phenyl ring. In the recent years, synthesis of azachalcones and their *N*-alkyl-substituted derivatives (Nowakowska et al. 2001, 2002; Usta et al. 2007, 2009; Yaylı et al. 2009) have been studied. Furthermore, the preparation of furan and thiophene analogues of azachalcones has been described, and some of them possess a wide variety of biological activities (Usta et al. 2007, 2009; Rateb & Zohdi 2009; Budhiraja et al. 2012; Raghav et al. 2012).

In the recent years, microwave irradiation has become a very powerful tool in organic synthesis and has been used by many organic chemists. Microwave-assisted reactions take place selectively in solvent and solid-phase condition in a very short time, with cleaner reaction, greater selectivity and improved yields (Gall et al. 1999; Azarifar & Ghasemnejad 2003; Ahmad et al. 2011).

2. Results and discussion

2.1. *Chemistry*

The aim of this investigation was to synthesise methyl-substituted (*E*)-1-alkyl-pyridinium bromide (**3a–e**, **4a–e**) from methyl-substituted (*E*)-3″-azachalcone and (*E*)-4″-azachalcone (**1**,

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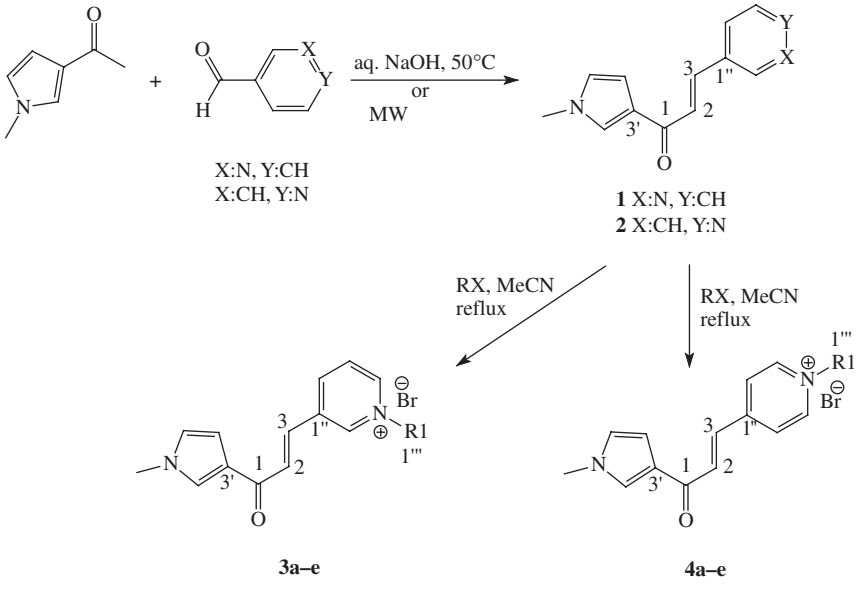

	R_1		R_1
3a :	C_6H_{13}	**4a** :	C_6H_{13}
3b :	C_8H_{17}	**4b** :	C_8H_{17}
3c :	$C_{10}H_{21}$	**4c** :	$C_{10}H_{21}$
3d :	$C_{12}H_{25}$	**4d** :	$C_{12}H_{25}$
3e :	$C_{14}H_{29}$	**4e** :	$C_{14}H_{29}$

Figure 1. Synthesis of azachalcones and their *N*-alkyl derivatives.

2), which might demonstrate biological activity. The synthesis of new azachalcones (**1** and **2**) and *N*-alkyl derivations (**3a**–**e**, **4a**–**e**) was performed according to the steps shown in Figure 1.

The most noticeable feature of structural characterisation of methyl-substituted (*E*)-3″-azachalcone and (*E*)-4″-azachalcone (**1**, **2**) is assignment of the ^{1}H resonances of H_α and H_β. The ^3J values of 15.8/15.6 Hz of H_α and H_β are consistent with a *trans* relationship at the C=C double bond of the α,β-unsaturated moiety of compounds **1** and **2**, respectively.

N-alkyl derivatives of new azachalcones were prepared from the corresponding azachalcone with *n*-bromoalkanes ($C_{6,8,10,12,14}$) in MeCN solution by reflux. The purity of all the newly synthesised compounds was checked on thin-layer chromatography (TLC). The spatial relation of the olefinic H-atoms of (*E*)-*N*-alkyl-3″- and 4″-azachalconium bromides (**3a**–**e**, **4a**–**e**) was also *E* based on their ^3J values ($^3J_{H\alpha-H\beta}$ = 15.2/15.6/15.6/15.2/15.2/16.4/15.4/15.6/15.6/15.2 Hz, respectively).

All the synthesised compounds (**1**, **2**, **3a**–**e**, **4a**–**e**) were characterised on the basis of spectral data studies (^{1}H, ^{13}C, APT, ^{1}H–^{1}H COSY NMR, ACD–NMR, FT–IR, LC–MS/MS and elemental analysis). All the newly synthesised compounds were in full agreement with the proposed structures.

2.2. *Antimicrobial activities*

The qualitative screening of the susceptibility spectra of different microbial strains to the complexes was performed by the quantitative assay of minimal inhibitory concentration (MIC, μg/mL) value based on liquid medium serial micro-dilutions (CLSI 2009; Kaspady et al. 2009). The MIC (CLSI 2009) was determined with two Gram-positive bacterial strains, that is *Enterococcus faecalis* ATCC 29212 and *Staphylococcus aureus* ATCC 25923, and three Gram-negative bacterial strains, that is *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, and *Yersinia pseudotuberculosis* ATCC 911, which were inoculated into the Luria broth (LB) at pH 7.2. The stock solutions of the compounds were prepared with dimethyl sulfoxide (DMSO). Dilution series of chemical compounds to be tested were prepared from 500 to 0.05 μg/mL concentrations in 100 μL medium. The microplates (Grainer, Frickenhausen, Germany) were incubated at 37.0 ± 1°C for 18–24 h. DMSO, LB medium with or without antibiotic, ampicillin, were used as solvent control, positive, and negative controls, respectively. The optical density of the bacteria from mid-log phase of growth was measured at 600 nm and diluted in fresh medium to obtain an optical density of 0.004 (corresponding to 5×10^5 colony forming units/mL). At the end of incubation, the effect of the compounds on the growth of micro-organisms was determined. The results of these compounds are shown in Table 1.

The results of anti-microbial activity of the compounds when compared revealed varied effects against the tested bacteria. The best result was of compound **4e** against *E. coli*. The second best effective concentration was of compounds **1** and **4e** with the MIC value of 0.97 μg/mL against *E. coli* and *E. faecalis*, respectively. The third effective concentration was of compound **3e** against *E. faecalis*. Other compounds were moderately effective against the bacteria. We also observed that the compounds **4b** and **3c** were more effective against Gram-positive bacteria tested in the study. The derivatives with 8–12 alkyl groups were active against the bacteria, and their activity was more pronounced against the Gram-positive bacteria compared with the Gram-negative bacteria. Nowakowska et al. have previously demonstrated a

Table 1. *In vitro* antibacterial activity data of compounds (**1**, **2**, **3a**–**e**, **4a**–**e**).

		Micro-organisms and MIC value				
		Gram-negative bacteria			Gram-positive bacteria	
Number of compound	Stock solution (μg/mL)	Ec	Pa	Yp	Ef	Sa
1	5000	0.97	250	250	125	500
2	5000	250	125	250	62.5	250
3a	5000	250	250	250	125	500
3b	5000	250	250	250	31.25	250
3c	5000	125	250	250	15.63	31.25
3d	5000	125	125	250	31.25	125
3e	5000	250	500	250	3.9	500
4a	5000	250	125	250	125	250
4b	5000	62.5	250	500	31.25	15.63
4c	5000	250	250	500	125	500
4d	5000	250	500	15.625	125	500
4e	5000	0.485	250	31.25	0.97	15.63kj
DMSO		NE	NE	NE	NE	NE
PC		+	+	+	+	+
PC + amp	100	−	−	−	−	−

Notes: Ec, *E. coli* ATCC 25922; Pa, *P. aeruginosa* ATCC 27853; Yp, *Y. pseudotuberculosis* ATCC 911; Ef, *E. faecalis* ATCC 29212; Sa, *S. aureus* ATCC 25923; PC, positive control as broth medium without chemical component and antibiotic; amp, ampicillin; NE, not effected for growing; '+', growth; '−', no growth.

similar trend in activity with respect to the bacterial type with 4-azachalcone derivatives (Nowakowska et al. 2002).

3. Experimental

3.1. *General*

3-acetyl-1-methylpyrrole, 3-pyridine carbaldehyde, 4-pyridine carbaldehyde, and *n*-bromoalkanes ($C_{6,8,10,12,14}$) were purchased from Fluka (Bushs SG, Switzerland) or Merck (Darmstadt, Germany), and used without further purification. All solvents used were of analytical grade or bulk solvents distilled before use. Melting points were determined by using a Thermo-var (Braunschweig, Germany) apparatus fitted with a microscope and uncorrected. Infrared spectra were obtained with Perkin-Elmer 100 FT-IR (4000–400 cm^{-1}) spectrometer (Waltham, MA, USA). NMR spectra were recorded on a Varian Mercury NMR (Darmstadt, Germany) at 200 MHz in $CDCl_3$. NMR data assignments were based on ^1H, ^{13}C, APT, $^1H-^1H$ COSY and ACD–NMR programme. The mass-spectral analyses were carried out on a Thermo Scientific TSQ Quantum Access Max LC–MS/MS (Braunschweig, Germany) spectrophotometer. The elemental analysis was performed on a Costech ECS 4010 (Valencia, CA, USA) instrument. A monomode CEM-Discover microwave (Matthews, NC, USA) was used in the standard configuration as delivered, including proprietary software. TLC was carried out on Merck precoated Kieselgel 60 F_{254} aluminium plates (Darmstadt, Germany).

3.2. *General procedure for synthesis of azachalcone derivatives*

Method A: Claisen–Schmidt condensation. A mixture of 3- or 4-pyridine carbaldehyde (1.23 g, 0.01 mol for each), 3-acetyl-1-methylpyrrole (1.21 g, 0.01 mol) in EtOH (3 mL) was added under stirring to a solution of NaOH (0.80 g, 0.02 mol) in 50 mL distilled water. The reaction mixture was stirred at 50°C (TLC control). The aqueous phase was extracted with $CHCl_3$ (3 × 30 mL). The residue was purified by column chromatography (column, 30 cm × 2 cm) on silica gel (35 g, Merck, 230–400 mesh).

Method B: Microwave-assisted method. Equimolar quantities (1.21 g, 0.01 mol) of 3-acetyl-1-methylpyrrole and respective pyridine carbaldehyde (1.23 g, 0.01 mol for each) were mixed and dissolved in minimum amount (3 mL) of EtOH. To this, NaOH solution (0.80 g, 0.02 mol) was added slowly and mixed. The entire reaction mixture was microwave irradiated for about 3 min at 300 W.

3.3. *General procedure for synthesis of* N*-alkyl derivatives of azachalcones*

Compounds **1** and **2** (~0.5 mol for each) and *n*-bromoalkanes in MeCN (30 mL) were refluxed separately for 18–22 h. On completion of the reactions, followed by TLC examination, the MeCN was removed using a rotary evaporator, The residues were purified by column chromatography on silica gel (25 g, Merck, 230-400 mesh).

4. Conclusion

The azachalcones are analogous to chalcone-type natural compounds. In consideration of the pharmacological activities of chalcones and their analogues, (*E*)-3″-azachalcone (**1**), (*E*)-4″-azachalcone (**2**), and their *N*-alkyl (**3a–e**, **4a–e**) derivatives were synthesised and tested against two Gram-positive and three Gram-negative bacteria. All synthesised compounds showed different effects against the bacteria. *N*-alkylated compounds (**3a–e**, **4a–e**) were better antimicrobials. The alkyl substitution apparently renders better permeability to these compounds

through bacterial cell walls. According to the results, the list of compounds which can be used against specific bacteria are compounds **4e** and **1** against *E. coli*, compounds **4e**, **3e**, **4b**, **3b**, **3d**, and **2** against *E. faecalis*, compound **4d** against *Y. pseudotuberculosis* or these compounds can be used selectively to these bacteria. Especially, the compounds which are effective against the bacteria can be used in environmental studies.

Supplementary material

Supplementary material relating to this article is available online, alongside Figures S1–S28.

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