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Synthesis and characterization of novel benzimidazole chalcones as antibacterial agents

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ABSTRACT

*Efficient synthesis of some new N-Benzyl substituted benzimidazole chalcone derivatives were performed by multistep reaction sequences. The synthesized compounds were characterized using IR, ^{1}H NMR, mass spectrometry and elemental analysis. The synthesized compounds were screened for their antibacterial activity against selective gram positive and gram negative bacteria. Compound **10** was found to be most active among the series.*

Keywords: Chlacone, N-benzylbenzimidazole, antibacterial activity.

INTRODUCTION

In present scenario bacterial infection became a serious threat to human lives due to their resistance to existing antibiotics. Thus, exploration of new types of antibacterial agents becomes very essential. Benzimidazole derivatives are very useful for the development of molecules of pharmaceutical interest due to their pharmacological activity including antimicrobial [1-3], anthelmintic [4,5], anticancer [6,7], antilukemic [8] and antidiabetic [9]. More over chalcones are associated with antibacterial activity [10-12]. Thus, a novel series of N-benzyl benzimidazole chalcones were synthesized and evaluated against different bacterial strain.

MATERIALS AND METHODS

Synthesis and characterization

The chemicals used were laboratory grade and procured from Merck (India) and Finar (India). IR spectra were obtained on a Bruker alpha-t FT-IR spectrometer (KBr Pellets). ^{1}H NMR spectra were recorded on a Bruker avance III 500 MHz spectrometer using TMS as internal standard in DMSO-d_6. The mass spectra were recorded on Agilent 6410 LC-MS Spectrometer. The elemental analysis was carried out by using Thermo finnigan element analyser. Melting points were determined by open tube capillary method and are uncorrected. Progress of the reaction and purity of the products was checked by thin layer chromatography (TLC). The spots were located under iodine vapors/UV light.

General procedure for synthesis of 1-(1-benzyl-1H-benzo[d]imidazol-2-yl)-3-aryl-2-propen-1-one (7-10)

Chalcones **3-7** (5 mmol) were dissolved in a 20 mL dry acetone and 5 mL of DMF under heating, then anhydrous K_2CO_3 (7.5 mmol) was added to the solution. Later benzyl chloride (15 mmole) was added to the mixture and the contents were heated under reflux. The progress of the reaction was monitorred by TLC (benzene-ethyl acetate, 4:1). After completion of reaction (20-24 h), the reaction mixture was cooled and poured into crushed ice. The solid obtained was filtered and recrystallized from mixture of acetone and DMF.

*(E)-1-(1-benzyl-1H-benzo[d]imidazol-2-yl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one (**7**).* Red colour solid; Yield: 76 %; Anal. Calcd. for $C_{25}H_{23}N_3O$: C, 78.71; H, 6.08; N, 11.02 %. Found: C, 78.80; H, 5.91; N, 10.92 %; IR (KBr, cm^{-1}): 1679 (C=O), 1611 (C=N); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 7.96 (1H, *d*, *J* = 15 Hz, H_α), 7.90 (1H, *d*, *J* = 8 Hz, Ar–H), 7.79 (1H, *d*, *J* = 15 Hz, H_β), 7.73-7.67 (3H, *m*, Ar-H), 7.44-7.18 (7H, *m*, Ar-H), 6.78 (2H, *d*, *J* = 8 Hz, Ar-H), 6.01 (2H, *s*, $–CH_2$), 3.03 [6H, *s*, $–N(CH_3)_2$]; ESI-MS m/z: 382.0 [M+H].

*(E)-1-(1-benzyl-1H-benzo[d]imidazol-2-yl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (**8**).* Fluorescent yellow solid; Yield: 78 %; Anal. Calcd. for $C_{25}H_{22}N_2O_3$: C, 75.36; H, 5.57; N, 7.03 %. Found: C, 75.26; H, 5.51; N, 6.90 %; IR (KBr, cm^{-1}): 1653(C=O), 1575 (C=N); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 8.11 (1H, *d*, *J* = 17.5 Hz, H_α), 7.93 (1H, *d*, *J* = 10 Hz, Ar–H), 7.83 (1H, *d*, *J* = 17.5 Hz, H_β), 7.75 (1H, *d*, *J* = 10 Hz, Ar-H), 7.47-7.38 (4H, *m*, Ar–H), 7.32-7.29 (2H, *m*, Ar-H), 7.26-7.23 (1H, *m*, Ar-H), 7.20-7.18 (2H, *m*, Ar-H), 7.07 (1H, *d*, *J* = 10 Hz, Ar-H), 6.01 (2H, *s*, $–CH_2$), 3.88 (3H, *s*, $–CH_3$), 3.84 (3H, *s*, $–CH_3$); ESI-MS m/z: 399.0 [M+H].

*(E)-1-(1-benzyl-1H-benzo[d]imidazol-2-yl)-3-(2-chlorophenyl)prop-2-en-1-one (**9**).* Off-white solid; Yield: 71 %; Anal. Calcd. for $C_{23}H_{17}ClN_2O$: C, 74.09; H, 4.60; N, 7.51 %. Found: C, 74.30; H, 4.51; N, 7.12 %; IR (KBr, cm^{-1}): 1659 (C=O), 1595 (C=N); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 8.30 (1H, *d*, *J* = 17.5 Hz, H_α), 8.13 (1H, *d*, H_β, *J* = 17.5 Hz), 8.11-8.09 (1H, *m*, Ar-H), 7.94 (1H, *d*, *J* = 10.0 Hz, Ar–H), 7.76 (1H, *d*, *J* = 10, Ar-H), 7.61-7.60 (1H, *m*, Ar-H), 7.54-7.46 (3H, *m*, Ar-H), 7.43-7.40 (1H, *m*, Ar-H), 7.33-7.30 (2H, *m*, Ar-H), 7.27-7.24 (1H, *m*, Ar-H), 7.21-7.20 (2H, *m*, Ar-H) 6.00 (2H, *s*, $–CH_2$).

*(E)-1-(1-benzyl-1H-benzo[d]imidazol-2-yl)-3-(3-methoxyphenyl)prop-2-en-1-one (**10**)*[1]. Fluorescent yellow solid; Yield: 75 %; Anal. Calcd. for $C_{24}H_{20}N_2O$: C, 78.24; H, 5.47; N, 7.60 %. Found: C, 78.10; H, 5.51; N, 7.55 %; IR (KBr, cm^{-1}): 1665 (C=O) 1600 (C=N); ESI-MS m/z: 369.0 [M+H].

Microbiology

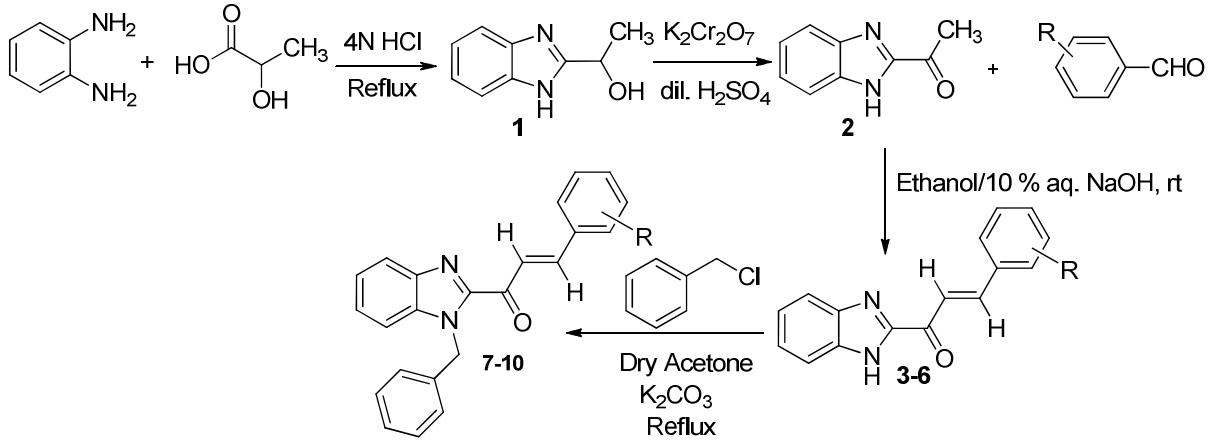
The compounds **7-10** were evaluated for their *in vitro* antimicrobial activity against bacterial strains *viz. Bacillus subtilis* MTCC 441, *Staphylococcus aureus* MTCC 3160, *Pseudomonas aeruginosa* MTCC 4673 and *Escherichia coli* MTCC 739. The reference cultures were purchased from Institute of Microbial Technology (IMTECH), Chandigarh, India. Minimum inhibitory concentrations (MIC) were determined using mueller hinton broth by two fold microdilution dilution method [13,14]. The cultures were incubated for 24 h at 35 ^{O}C and the growth was monitored. The lowest concentration required to arrest the growth of microorganism was regarded as minimum inhibitory concentration (MIC). Ciprofloxacin was used as positive control. The antimicrobial activity of the compounds was performed in duplicate.

RESULTS AND DISCUSSION

Chemistry

The desired compounds described in this study were prepared form from *o*-phenylenediamine in four steps as outlined in (Scheme **1**). 2-hydroxyethylbenzimidazole **1** was obtained by condensation of *o*-phenylenediamine with lactic acid using Phillips method [15]. Potassium dichromate promoted oxidation of 2-hydroxyethylbenzimidazole followed by neutralization with ammonia led to 2-acetylbenzimidazole **2** [16]. 1H-benzo[d]imidazol-2-yl)-3-aryl-2-propen-1-one **3-6** were obtained by claiesn-schmidt condensation of **2** with substituted aromatic aldehydes in presence of NaOH [17]. Condensation of 1-benzimidazolyl-3-aryl-2-propen-1-one derivatives **3-6** with benzyl chloride gave the novel 1-(1-benzyl-1H-benzo[d]imidazol-2-yl)-3-aryl-2-prpen-1-one derivatives **7-10**. Physical data of synthesized compounds are presented in Table No.1

In the IR spectra of compounds **7-10** (C=O) stretching was found in the expected region at 1652-1662 cm^{-1}. The ^{1}H NMR spectrum of compound **7** (Fig. **1**) displayed two doublets at δ 7.96 and δ 7.79 for two protons of α, β-unsaturated carbonyl system. The two doublets with J value 15 Hz confirmed olefinic protons of chalcone in E form. Two singlets were observed at δ 6.01 and 3.03 ppm corresponding to the methylene protons and dimethylamino group respectively. All the other additional peaks at δ 7.90 and δ 7.73-6.78 ppm observed are due to aromatic protons. The positive ion ESI mass spectrum of compound **7** (Fig. **2**) exhibited an [M+H] ion at m/z 382.



Scheme 1: Synthetic route to benzimidazole chalcone

Table 1. Physical data of synthesized compounds

Compound	R	Molecular formula	MP (°C)
7	4-$N(CH_3)_2$	$C_{25}H_{23}N_3O$	220-222
8	3,4-OCH_3	$C_{25}H_{22}N_2O_3$	188-190
9	2-Cl	$C_{23}H_{17}ClN_2O$	164-166
10	3-OCH_3	$C_{24}H_{20}N_2O$	132-134

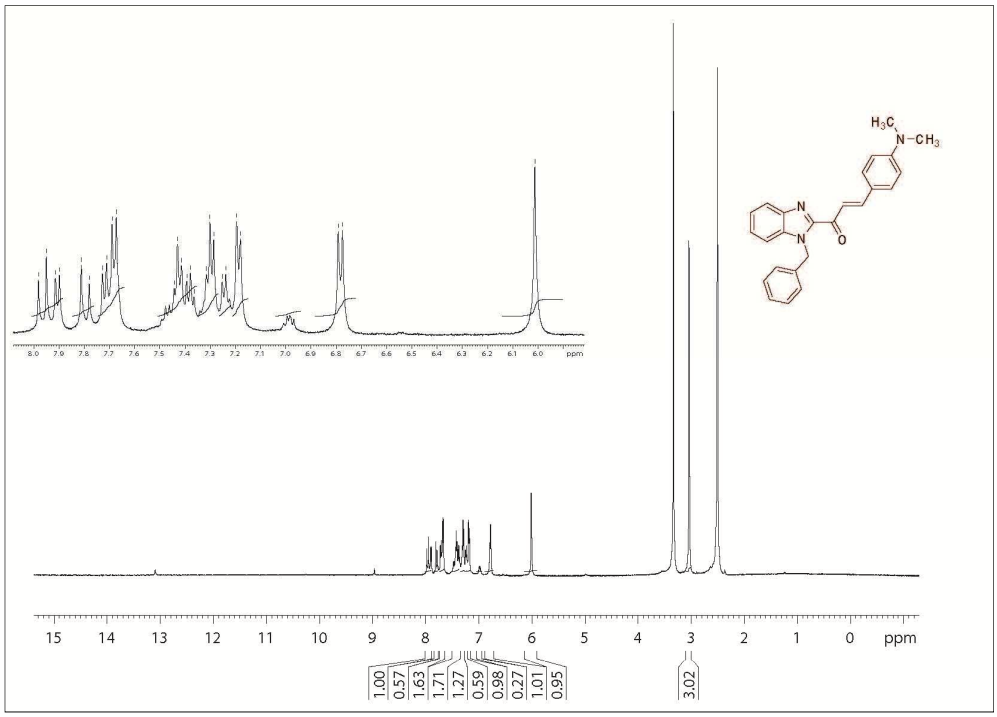


Fig. 1. ^{1}H NMR spectrum of compound 7

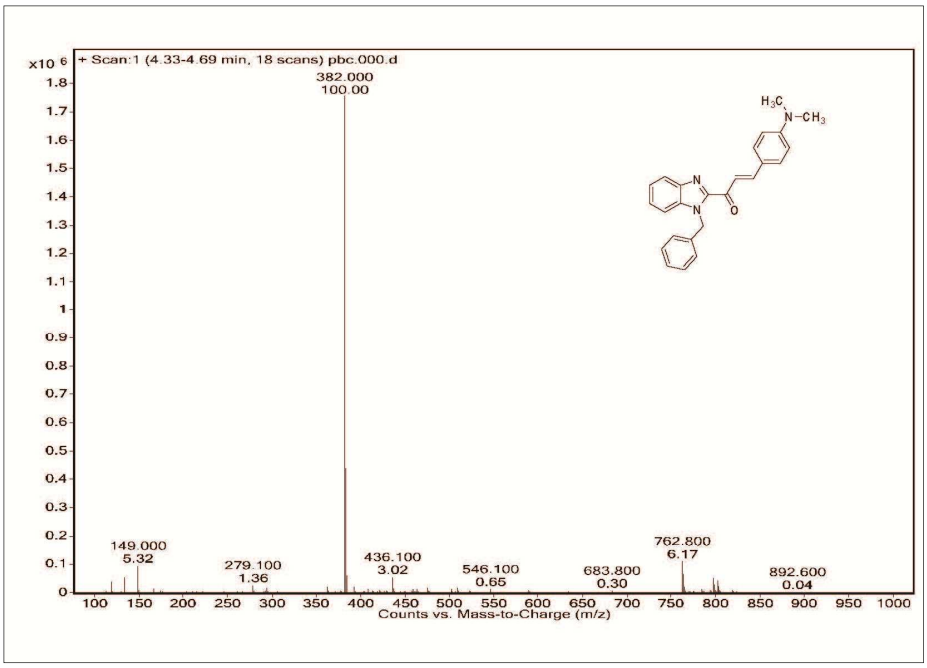


Fig. 2. Mass spectrum of compound 7

Two doublets at δ 8.11 and 7.83 ppm were observed in the ^{1}H NMR spectrum of compound **8** (Fig. **3**) for the two α, β-unsaturated protons. Three singlets were observed at δ 6.01, 3.88 and 3.84 ppm corresponding to the methylene protons and two dimethoxy groups respectively. All the other additional peaks observed were in agreement with the respective aromatic rings. The positive ion ESI mass spectrum of compound **8** (Fig. **4**) exhibited an [M+H] ion at m/z 399.

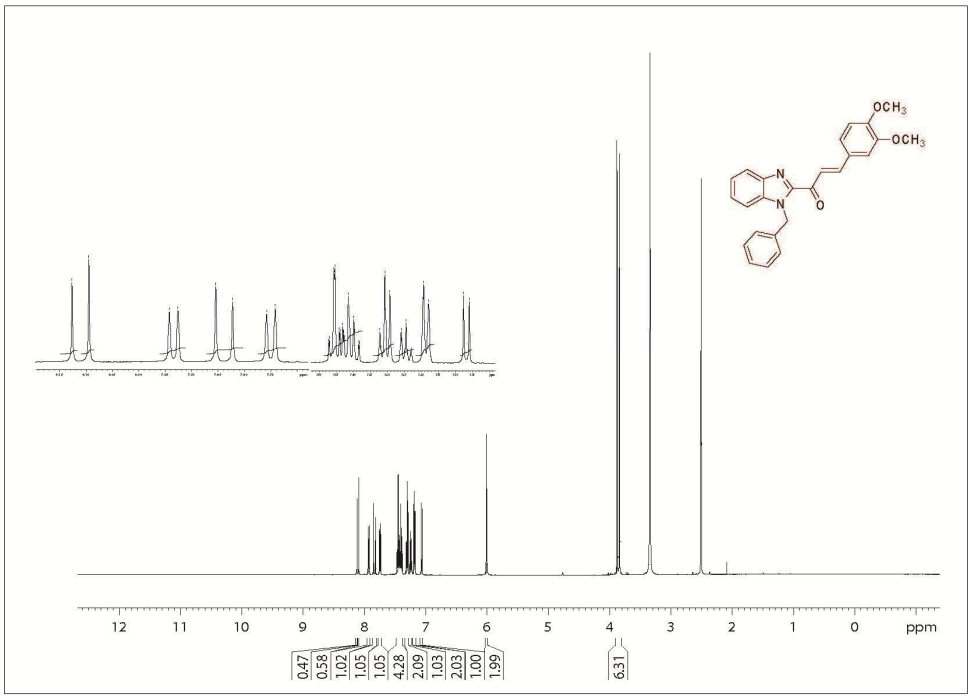


Fig. 3. ^{1}H NMR spectrum of compound 8

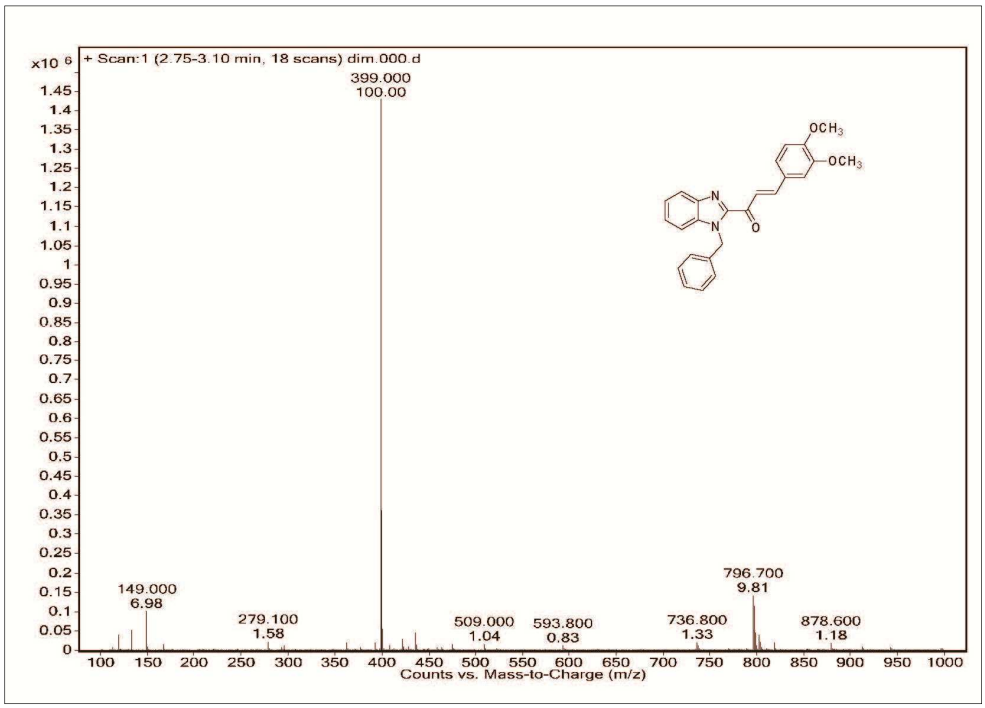


Fig. 4. Mass spectrum of compound 8

The positive ion ESI mass spectrum of compound **9** exhibited an [M+H] ion at m/z 399 (Fig. **5**).The ^{1}H NMR spectrum of compound **10** displayed two doublets at δ 8.30 and 8.13 ppm for two olefinic protons of α, β-unsaturated carbonyl system. The peak of methylene protons are observed at δ 6.0. Peaks at δ 8.11-7.20 ppm are due to aromatic protons (Fig. **6**).

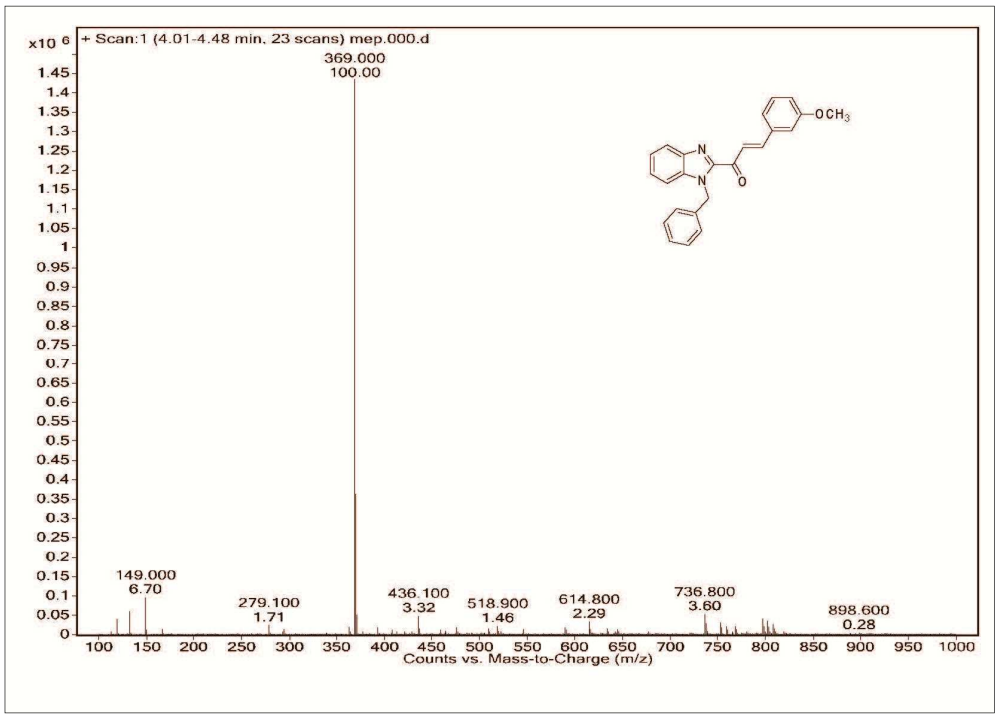


Fig. 5. Mass spectrum of compound 10

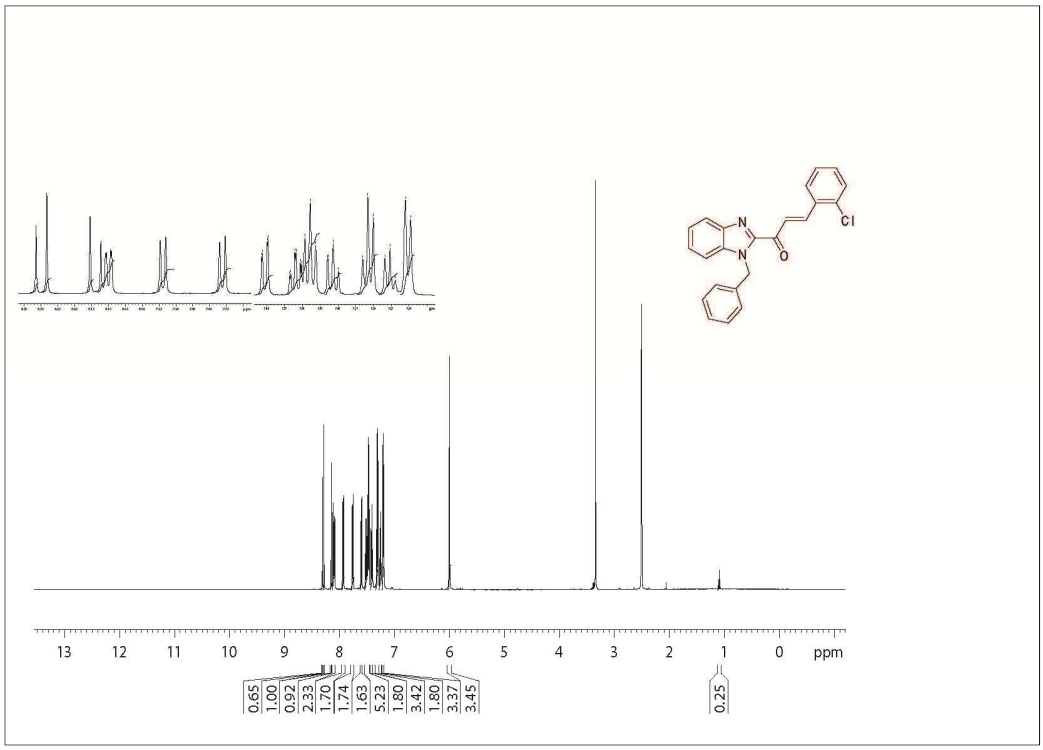


Fig. 6. ^{1}H NMR spectrum of compound 9

Antimicrobial activity

The synthesized compounds **7**–**10** were screened for their *in vitro* antimicrobial activity. The MIC values of the synthesized compounds ranged between 500–62.5 µg mL^{-1}. The results of antimicrobial activities of benzimidazole derivatives are presented in Table 2.

Table 2. *In vitro* antimicrobial activity of synthesized compounds 7-10 MIC µg mL^{-1}

	Gram-positive bacteria		Gram-negative bacteria	
Compound	*S. aureus*	*B. subtilis*	*E. coli*	*P. aeruginosa*
7	250	512	250	500
8	250	500	500	500
9	125	250	512	512
10	62.5	62.5	125	500
Ciprofloxacin	6.25	6.25	6.25	12.5

CONCLUSION

Four new chalcones containing the N-benzyl benzimidazole moiety were synthesized, characterized and investigated for their antimicrobial activity. The antimicrobial activity data indicated weak antibacterial activity, except for compound **10** which presented good activity against *S. aureus* and *B. subtilis*.

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