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Microwave assisted synthesis, physicochemical properties and antimicrobial activity of benzimidazole chalcones

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ABSTRACT

The objective of our research was to perform some benzimidazole chalcone moieties via an efficient method of microwave assisted and correlated their antimicrobial activity with CLogP value determined by ChemDraw Ultra 11.0 software. The structures of the final candidates were confirmed by spectral studies. All the synthetic derivatives were evaluated for their antimicrobial studies. Most of the derivatives were good activity towards Gram-positive bacteria and less activity towards Gram-negative bacteria. Some of the derivatives showed a moderate activity against tested fungi. SAR of the final candidates revealed a correlation between ClogP and antimicrobial studies. It has been concluded that higher logP value favours the activity ratio.

Key Words: Benzimidazole, ClogP, antimicrobial screening.

INTRODUCTION

Benzimidazole nucleus are widely accepted bioactive molecule having good against various strains of microorganisms, [1] Benzimidazoles are regarded as a promising class of biologically active agents. The benzimidazole nucleus exhibit a wide range of biological profile such as , antimicrobial,[3-5]anti-tubercular,[6,7]anticancer,[8-10]angiotensin II receptor antagonists,[11]. and antiHIV. [12,13]

The synthesis of (2E)-1-(1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-ones (**4a-g**) described in this study are outlined in Scheme 1 and physical data is presented in Table 1. O-phenylenediamine reacts with lactic acid gave 2(α -hydroxyethyl)benzimidazole (**2a**) which on subjected with oxidation in presence of potassium dichromate produced 2- acetyl

benzimidazole(**3a**).The chalcones (**4a–g**) were prepared by reacting 2-acetyl benzimidazole with appropriate aldehydes in the presence of a base by Claisen-Schmidt condensation.

MATERIALS AND METHODS

All the chemicals and reagents used were of AR grade. Melting points were determined by using melting point apparatus MP-DS TID 2000 V and the values were uncorrected. Reactions were monitored by thin layer chromatography (TLC) on pre coated silica gel G plates using iodine vapour as visualizing agent.IR spectra were recorded on JASCO FT/IR-140 spectrophotometer by using KBr pellets technique.PMR spectra were recorded using BRUCKER FT-NMR-500MHz spectrophotometer by using DMSO as solvent and TMS as internal standard. The chemical shift was expressed in δ ppm. The physicochemical chemical properties like ClogP of the derivatives were calculated by ChemDraw Ultra 11.0 software.

Micro wave assisted Synthesis of 2(α -hydroxyethyl) Benzimidazole. (**2a**)

O-Phenylenediamine (0.25 mol) was mixed with lactic acid (0.35 mol) in a beaker and subjected to microwave oven at 40% power over a period of 4 minutes. The reaction mixture was cooled added with 10% NaOH until basicity to litmus paper. The pink colored product obtained was thoroughly washed with water until it free from the added base in the product. The pale pink product obtained was dried over a hot air oven and recrystallized with hot water. The yield was found to be 88%^[14].

Synthesis of 2- acetyl benzimidazole. (**3a**)

To a solution of 2-(α -hydroxy) ethyl benzimidazole 2a (0.01 mol) in dil. H₂SO₄ (5%, 40 ml) was drop wise added the solution of K₂Cr₂O₇ (0.15 mol) and H₂SO₄ (25%, 80 ml) with constant stirring at room temperature over a period of 20 min. Further the reaction mixture was stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was neutralized with aqueous NH₃ solution (1:1) and resultant orange solid was filtered, washed with water and dried^[15].

Micro wave assisted Synthesis of (2E)-1-(1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-ones (**4a-h**)

2-Acetyl benzimidazole (0.01 mol) is taken in 10ml of ethanol in a beaker and stir well. To this add 4ml of 40% KOH with aldehydes (0.012).The whole mixture stirs vigorously for 20 minutes. Then it becomes viscous and that subjected to microwave oven at 60% power over a period of 2-3minutes.The resultant product cooled and diluted with cold water and neutralized with dil.HCl^[16]..

Characterization of the synthesized derivatives:

4a:IR(KBr):3230(N-H str),1693(C=O),1587(C=N).¹H NMR (DMSO-d₆ +CDCl₃) in δ ppm:8.9 (1H,s,NH benzimidazole), 7.2-7.9 (9H,m ArH),5.2-5.8(2H,d,=CH-).

4b:IR(KBr):3232(N-H str),1678(C=O),1581(C=N),771(Ar-Cl).¹H NMR (DMSO-d₆ +CDCl₃) in δ ppm:8.7 (1H,s,NH benzimidazole), 7.1-7.8(8H,m ArH),5.3-5.8(2H,d,=CH-).

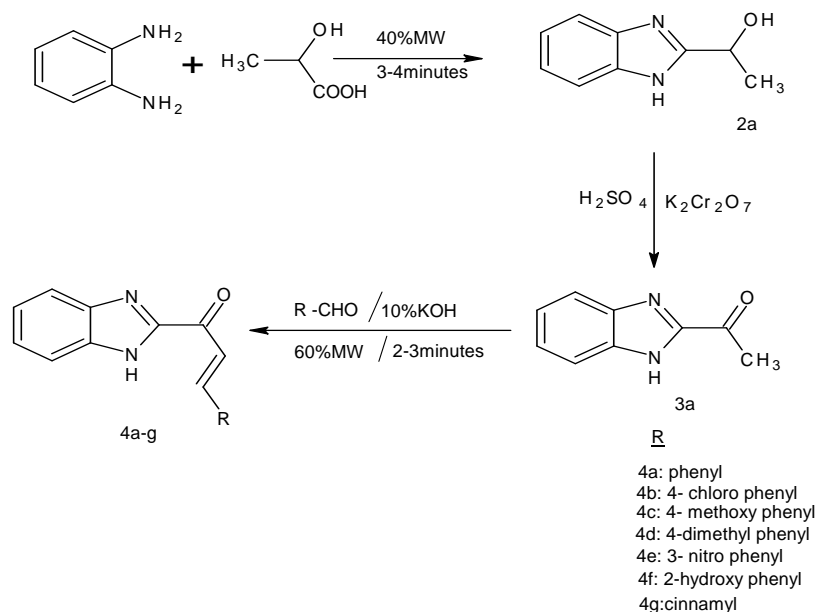
4c:IR(KBr):3238(N-H str),1673(C=O),1577(C=N).¹H NMR (DMSO-d₆ +CDCl₃) in δ ppm:8.9 (1H,s,NH benzimidazole), 7.3-7.8 (8H,m ArH),5.2-5.8(2H,d,=CH-),3.3(3H,s,OCH₃)

4d:IR(KBr):3252(N-H str),1680(C=O),1592(C=N).¹H NMR (DMSO-d₆ +CDCl₃) in δ ppm:8.8 (1H,s,NH benzimidazole), (8H,m ArH),5.2-5.8(2H,d,=CH-)3.1(6H,s N(CH₃)₂)

4e:IR(KBr):3244(N-H str),1678(C=O),1567(C=N).¹H NMR (DMSO-d₆ +CDCl₃) in δ ppm:8.9 (1H,s,NH benzimidazole), (8H,m ArH),5.4-6.1(2H,d,=CH-).

Table 1-Physical Data of the Synthesized Derivatives

Compound	Colour	MW	MP(°C)	% Yield	ClogP
4a	Brown	248	246	83	3.27
4b	Pale yellow	282	227	92	4.05
4c	Pale green	278	230	90	3.32
4d	Red	291	140	81	3.88
4e	Brown	293	262	79	2.85
4f	Pale yellow	264	271	69	3.01
4g	Brick red	274	138	82	3.82



Scheme1

Antimicrobial screening

The antimicrobial screening of the synthesized derivatives were evaluated against two Gram-positive bacteria viz., *Bacillus subtilis*, *Staphylococcus aureus*, two Gram-negative bacteria viz., *Escherichia coli*, *Klebsiella pneumoniae* and two fungi viz., *C. albicans*, *A.niger* using streptomycin, benzyl penicillin and amphotericin B respectively as standard drugs respectively by the Cup-plate method using DMSO as the solvent^[16,17]. The results were shown in table 2.

Table 2: Antimicrobial screening of (4a-g)
Zone of inhibition (mm)

	<i>B. subtilis</i>	<i>Staph. aureus</i>	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>C.albicans</i>	<i>A.niger</i>
4a	10	11	06	08	-	02
4b	11	12	10	09	03	-
4c	13	15	6	09	-	-
4d	15	17	10	11	04	01
4e	04	8	12	06	05	-
4f	05	04	11	12	-	02
4g	14					
Streptomycin	-	-	16	16	-	-
Benzyl Penicillin	18	17	-	-	-	-
Amphotericin B	-	-	-	-	22	24

RESULTS AND DISCUSSION

Our research attempted a environment hazard free technique synthesis of 2E)-1-(1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-ones (**4a-h**) via microwave assisted method. All the final structures were confirmed by spectral analysis. By comparing the antimicrobial activity of the synthesized compounds, it was found that the test compounds are more active against Gram-positive bacteria. It is believed that the strong lipophilic character of the molecule plays a crucial role in producing antimicrobial effect. The lipophilicity of the compounds expressed as logP, which explains the main predictor for the activity. Higher the value of calculated logP value favors for the activity.

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