Synthesis and Antimicrobial Activity of Some Novel Benzimidazolyl Chalcones

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Abstract: Some novel benzimidazolyl chalcones were synthesized by condensation of *N*-(4-(1*H*-benzo[d]imidazol-2-yl)phenyl)acetamide with aromatic aldehydes in presence of aqueous potassium hydroxide solution at room temperature. All the synthesized compounds were characterized on the basis of their IR, ¹H NMR spectroscopic data and elemental analysis. All the compounds have been screened for antimicrobial activity by the cup-plate method.

Key words: Benzimidazolyl, Chalcones, Aldehydes, Synthesis and Antimicrobial activity.

Introduction

Benzimidazole derivatives play a vital role in biological fields such as antimicrobial¹, antiviral², antidiabetic³, antispasmodic⁴, and anticancer⁵ activities. 2-Substituted benzimidazole derivatives have been found to be biologically most potent. Chalcones represent an essential group of natural as well as synthetic products and some of them possess wide range of pharmacological activity such as antibacterial⁶, antitumour⁷, anticancer⁸, antitubercular⁹, anti-inflammatory¹⁰, antioxidant¹¹, antimalarial¹², antileishmanial¹³ *etc.* The presence of reactive α , β -unsaturated keto group in chalcones is found to be responsible for their biological activity. In the present work chalcones have been prepared according to Claisen-Schmidt condensation by condensing ketone with different aromatic aldehydes. The structures of the synthesized compounds were elucidated on the basis of their elemental analysis, IR, ¹H NMR spectroscopic data. These compounds were also screened for their antimicrobial activity.

Experimental

The melting points were recorded on electrothermal apparatus and are uncorrected. IR spectra were recorded in KBr on a perkin-Elmer model-983. ¹HNMR spectrum recorded on Varian Mercury 300 MHz instrument using CDCl₃, DMSO-d₆ as solvent (chemical shift in δ ppm), using TMS as internal standard. Elemental analysis was performed on a Heracus CHN analyzer and was within the $\pm 0.5\%$ of the theoretical values.

General procedure for the preparation of benzimidazolyl-chalcones (**3a-h**) 4-(1H-benzo[d]imidazol-2-yl)benzenamine (**1**) have been prepared as per reported method¹⁴.

Synthesis of N1-[4-(1H-benzo[d]imidazol-2-yl)phenyl]acetamide(**2**)

Dissolve 4-(1H-benzo[d]imidazol-2-yl)benzenamine(**1**) (2.09 g, 0.01 mole) in chloroform (50 mL) and acetylchloride (0.78 g, 0.01 mole) was added drop wise with constant stirring at 0-5°C. The reaction mixture was stirred for 8 h. The excess solvent was distilled off and the solid product was filtered, dried and recrystallised from ethanol to give compound **2**, yield 75%, m.p.: 210-212°C. Anal. Calcd. for C₁₅H₁₃N₃O: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.62; H, 5.16; N, 16.64. IR (KBr, cm⁻¹): 3245 (NH), 1621 (C=N), 1678(-NHCOCH₃).

Synthesis of N1-[4-(1H-benzo[d]imidazol-2-yl)phenyl]-(E)-3-phenyl-2-propenamide(**3a**)

Dissolve N1-[4-(1H-benzo[d]imidazol-2-yl)phenyl]acetamide(**2**) (2.51 g, 0.01 mole) in ethanol (30 mL) and various aromatic aldehydes (1.06 g, 0.01 mole) were taken and then an aqueous solution of KOH (2%, 5 mL) added to it. The reaction mixture refluxed for 5 h and then the solvent was removed by vacuum distillation and then it was poured into crushed ice and acidified with HCl. The solid separated was filtered and recrystallised from ethanol (Scheme 1). Similarly remaining compounds **3a-h** was prepared by above method. The characterization data of these compounds is described in Table 1 and 2.

Scheme 1. Synthesis of benzimidazolyl chalcones.

Antimicrobial Activity

The synthesized compounds (**3a-3h**) were screened for their *in vitro* antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Salmonella typhosa* and antifungal activity against *Aspergillus niger*, *Candida albicans* by measuring the zone of inhibition in mm. The antimicrobial activity was performed by cup plate method¹⁵⁻¹⁶ at concentration 500 μ g/mL and reported in Table 3. Nutrient agar was employed as culture medium and DMSO was used as solvent control for antimicrobial activity. Streptomycin and griseofulvin were used as standard for antibacterial and antifungal activities respectively.

Table 1. Physical data of compounds **3a-h**.

Comp	R	M.F.	M.P. °C	Yield, %	Elemental analyses, %					
					C		H		N	
					Found	Calcd	Found	Calcd	Found	Calcd
3a	C ₆ H ₅	C ₂₂ H ₁₇ N ₃ O	155	75	77.86	77.76	5.05	5.10	12.38	12.31
3b	2-NO ₂ C ₆ H ₄	C ₂₂ H ₁₆ N ₄ O ₃	165	78	68.74	68.68	4.20	4.15	14.58	14.53
3c	4-N(CH ₃) ₂ C ₆ H ₄	C ₂₄ H ₂₂ N ₄ O	167	75	75.37	75.41	5.80	5.75	14.65	14.59
3d	4-OCH ₃ C ₆ H ₄	C ₂₃ H ₁₉ N ₃ O ₂	150	80	74.78	74.71	5.18	5.12	11.37	11.30
3e	3,4,5-(OCH ₃) ₂ C ₆ H ₄	C ₂₅ H ₂₃ N ₃ O ₄	160	78	69.92	69.81	5.40	5.34	9.78	9.71
3f	4-OHC ₆ H ₄	C ₂₂ H ₁₇ N ₃ O ₂	135	82	74.35	74.28	4.82	4.76	11.82	11.74
3g	3-BrC ₆ H ₄	C ₂₂ H ₁₆ BrN ₃ O	148	85	63.17	63.10	3.86	4.90	10.05	10.12
3h	3-FC ₆ H ₄	C ₂₂ H ₁₆ FN ₃ O	140	80	73.94	73.98	4.51	4.58	11.76	11.71

Table 2. Spectral data of the compounds **3a-3f**.

Compd.	IR, Cm ⁻¹ , (KBr)	¹ H NMR (CDCl ₃ /DMSO-d ₆ , ppm)
3a	3249(-NH-Benzimidazole), 1545(-NH), 1735(C=O), 1652(-CH=CH-)	12.8(1H, s, -NH- Benzimidazole), 6.68(1H, d, -CO-CH=), 7.65 (1H, d,=CH-Ar), 5.21 (1H, s,-NH), 7.21-7.59 (4H, m, Ar-Benzimidazole), 7.77-8.13 (4H, m, Ar-NH), 7.05-7.64 (5H, m, Ar-CH)
3b	3258(-NH-Benzimidazole), 1548(-NH),1732 (C=O), 1630(-CH=CH-),1578(-NO ₂)	12.7(1H, s, -NH- Benzimidazole), 6.41(1H, d, -CO-CH=), 7.09 (1H, d,=CH-Ar), 5.23 (1H, s,-NH), 7.20-7.60 (4H, m, Ar-Benzimidazole), 7.70-8.11 (4H, m, Ar-NH), 7.92-8.20 (4H, m, Ar-CH)
3c	3264(-NH-Benzimidazole), 1546(-NH),1725(C=O), 1648(-CH=CH-), 1321(-N(CH ₃) ₂)	13.05(1H,s,-NH-Benzimidazole), 6.83 (1H, d, -CO-CH=), 7.76(1H, d,=CH-Ar), 5.20 (1H, s,-NH), 2.87(6H, s, N-CH ₃), 7.22-7.65 (4H, m, Ar-Benzimidazole), 7.79-8.15 (4H, m, Ar-NH), 6.77- 7.12 (4H, m, Ar-CH)
3d	3254(-NH-Benzimidazole), 1543(-NH),1730(C=O), 1638(-CH=CH-), 2830(-OCH ₃)	12.5(1H, s,-NH-Benzimidazole), 6.87 (1H, d, -CO-CH=), 7.72 (1H, d,=CH-Ar), 5.21 (1H, s,-NH), 3.63(3H, s, -OCH ₃), 7.25-7.69 (4H, m, Ar-Benzimidazole), 7.78-8.13 (4H, m, Ar-NH), 7.09-7.19 (4H, m, Ar-CH)
3e	3276(-NH-Benzimidazole), 1550(-NH),1724(C=O), 1649(-CH=CH-), 2825(-OCH ₃)	13.06(1H, s,-NH-Benzimidazole),6.41(1H, d,-CO-CH=), 7.75(1H, d,=CH-Ar), 5.22 (1H, s,-NH), 3.89-3.93(9H, s,-OCH ₃), 7.25-7.68 (4H, m, Ar-Benzimidazole), 7.79-8.18 (4H, m, Ar-NH), 6.75(2H, s, Ar-CH)
3f	3260(-NH-Benzimidazole), 1547(-NH),1730(C=O), 1645(-CH=CH-), 3450(-OH)	12.9(1H, s, -NH- Benzimidazole), 6.68(1H, d, -CO-CH=), 7.09 (1H, d,=CH-Ar), 5.20 (1H, s,-NH), 9.83 (1H, s, -OH), 7.20-7.60 (4H, m, Ar-Benzimidazole), 7.70-8.11 (4H, m, Ar-NH), 6.75- 7.05 (4H, m, Ar-CH)

Table 3. Antimicrobial and antifungal data of compounds **3a-h**.

Compds.	R	Antibacterial ^a				Antifungal ^a	
		<i>S.a.</i>	<i>P.a.</i>	<i>E.c.</i>	<i>S.t.</i>	<i>A.n.</i>	<i>C.a.</i>
3a	C ₆ H ₅	12	13	11	10	08	06
3b	2-NO ₂ C ₆ H ₄	10	08	14	09	12	10
3c	4-N(CH ₃) ₂ C ₆ H ₄	08	12	10	10	13	11
3d	4-OCH ₃ C ₆ H ₄	13	10	15	10	10	12
3e	3,4,5-(OCH ₃) ₂ C ₆ H ₄	09	07	10	09	09	07
3f	4-OHC ₆ H ₄	08	11	09	11	11	09
3g	3-BrC ₆ H ₄	14	09	10	13	08	07
3h	3-FC ₆ H ₄	10	12	09	12	07	06
Streptomycin		17	18	22	20	--	--
Griesofulvin		--	--	--	--	18	20

^a zone of inhibition was measured in mm.

Staphylococcus aureus (*S.a.*), *Escherichia coli* (*E.c.*), *Pseudomonas aeruginosa* (*P.a.*), *Salmonella typhosa* (*S.t.*), *Aspergillus niger* (*A.n.*), *Candida albicans* (*C.a.*).

Conclusion

From the antimicrobial screening it was observed that all the compounds exhibited activity against all the organisms employed. Looking at the structure activity relation ship, marked inhibition in bacteria was observed in the compounds bearing Ar = C₆H₅, 4-OCH₃ C₆H₄, 4-OH C₆H₄, 3-FC₆H₄, 3-BrC₆H₄ (**3a,3d,3f,3g,3h**) substituents where as other compounds showed moderate to good activity. Fungicidal screening data also revealed that compounds bearing Ar = 2-NO₂C₆H₄, 4-N(CH₃)₂ C₆H₄, 4-OCH₃ C₆H₄ (**3b,3c,3d**) imparted maximum activity to the compounds, where as other compounds showed moderate to good activity. As we consider all results obtained from antibacterial and antifungal tests together we can say that entire compounds tested are active towards bacteria and fungi.

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