Journal of Applied Pharmaceutical Science

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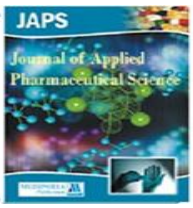

ISSN: 2231-3354
Received: 08-06-2011
Accepted: 11-06-2011

Synthesis and Antimicrobial studies of novel Benzimidazole derivatives

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ABSTRACT

Two series of novel benzimidazole derivatives were synthesized. The first one comprise of 2-methyl, the second one comprise of 2-phenyl substitution on benzimidazole moiety. Seven novel benzimidazole derivatives were synthesized successfully in appreciable yields and characterized physicochemically. The structures of all the synthesized derivatives were confirmed by IR and ^{1}HNMR. Furthermore, the synthesized compounds were screened for antimicrobial activity (antibacterial activity and antifungal activity) by tube dilution method. Some of the synthesized compounds showed appreciable antifungal activity.

Key words: Substituted benzimidazoles, antimicrobial activity, antifungal activity, antibacterial activity

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INTRODUCTION

Despite of the availability of a number of antimicrobial agents the main matter of concern in the treatment of microbial infections is the limited number of efficacious antimicrobial drugs. Many of the currently available drugs are toxic, enable recurrence because they are bacteriostatic/fungistatic and not bactericidal/fungicidal or lead to the development of resistance due in part to the prolonged periods of administration. The impact is more acute in developing countries due to nonavailability of desired medicines (Tomar et al., 2007; Sharma et al., 2009). There is a real perceived need for the discovery of new compounds that are endowed with antibacterial and antifungal activities, possibly acting through mechanism of actions, which are distinct from those of well known classes of antimicrobial agents to which many clinically relevant pathogens are now resistant (Sharma et al., 2009; Tuncbilek et al., 2009; Sharma et al., 2009). Benzimidazoles exhibit significant activity as potential antitumor agents, antimicrobial agents, smooth muscle cell proliferation inhibitors, a treatment for intestinal cystitis, and in diverse area of chemistry (Ansari et al., 2009; Kumar et al. 2008). The outcome of numerous attempts to develop new structural prototype in the search for effective antimicrobials indicates that the benzimidazoles still remain as one of the most versatile class of compounds against microbes (Kumar et al., 2006; Goker et al., 2005). The benzimidazole has been an important pharmacophore and privileged structure in medicinal chemistry, encompassing a diverse range of microbial activities (Goker et al., 2005). A total of seven benzimidazole derivatives were synthesized in two series by introducing different substituents at different positions.

MATERIAL AND METHODS

EXPERIMENTAL: The uncorrected melting point of all the seven title compounds was determined in open capillary tube. The purity of the compound was checked by TLC. The various

spectroscopic techniques can be used to define the structure of an unknown compound. The combination of IR and NMR data is often sufficient to determine completely the structure of an unknown molecule. The structure of the compounds **1-7** were assigned by IR and ^{1}H NMR spectroscopic data (Pavia et al., 2007; Silverstein et al., 1998), which are consistent with the proposed molecular structures.

GENERAL PROCEDURE (Wright, 1951; Preston, 1974; Furniss et al., 1996):

Synthesis of Series 1 Compounds

Synthesis of 2-methylbenzimidazole: Heated together mixture of *o*-phenylenediamine dihydrochloride (0.03 mole), 20 mL of water, acetic acid (0.09 mole) under reflux for 45 minutes. Made the cooled reaction mixture distinctly basic by the gradual addition of the concentrated ammonia solution, the precipitated product was collected and recrystallised from 10% ethanol (scheme is shown in Fig. 1).

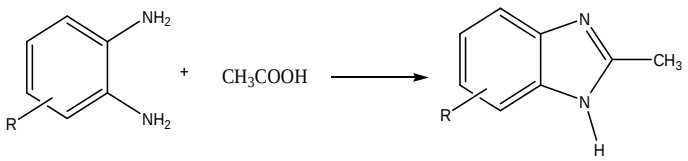

Fig. 1: *Synthesis of 2-methylbenzimidazole*

Synthesis of 3-benzoylbenzimidazole derivative: Dissolved 0.5 g (gram) of the above product (2) in 10 mL (mili litre) of 10% sodium hydrogen carbonate solution and added 1 gram of benzoyl chloride. The reaction mixture was shaken vigorously in a stoppered test tube. The stopper was removed from time to time since carbon dioxide was evolved. When the odour of benzoyl chloride had disappeared, acidified with dilute hydrochloric acid to Congo red and filtered. The solid with a little cold ether was extracted to remove any benzoic acid which may be present. The benzoyl derivative was recrystallised from dilute ethanol (scheme is shown in Fig. 2). The physicochemical characteristics of series 2 compounds are given table 2.

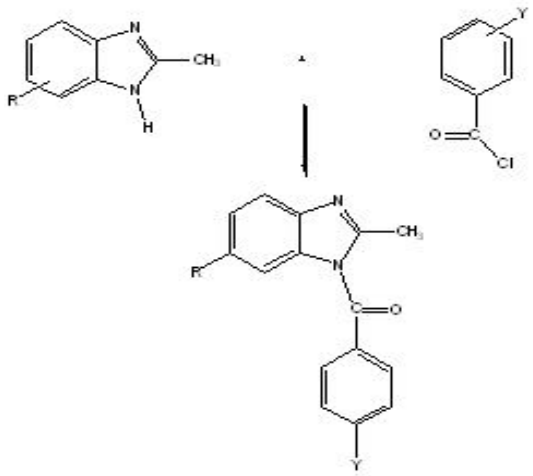

Fig. 2: Synthesis of 3-benzoylbenzimidazole derivatives series 1

Table 1: Physicochemical characteristics of Series 1 compounds

Compounds	R	Y	Melting point (°C)	Yield (%)
A1.1	-H	-H	230-231	87.06
A1.2	-H	$-NO_2$	251-252	87.8
A2.1	-OH	-H	301-302	75.0

Table 2: Physicochemical characteristics of Series 2 compounds

Compounds	R	X	Y	Melting point(°C)	Yield (%)
P1.1.1	-H	-H	-H	315-316	92.6
P1.2.1	-H	$-NO_2$	-H	323-324	81.6
P1.2.2	-H	$-NO_2$	$-NO_2$	342-343	94.4
P2.1.1	-OH	-H	-H	334-335	59.2

Compound1 (A1.1)

(2-methyl-1*H*-benzo(*d*)imidazol-1-yl)(phenyl)methanone: - IR (KBr) (cm^{-1}): 1692.37 (C=O); ^{1}H NMR (δ, ppm) (DMSO): 7.1-7.9 (2m, 9H), 2.48 (s, 3H)

Compound2 (A1.2)

(2-methyl-1*H*-benzo(*d*)imidazol-1-yl)(4-nitrophenyl) methanone: - IR (KBr) (cm^{-1}): 1692.37 (C=O), 1453.92 ($-NO_2$ str); ^{1}H NMR (δ, ppm) (DMSO): 6.9-7.8 (2m, 8H), 2.48 (d, 3H)

Compound3 (A2.1)

(6-hydroxy-2-methyl-1*H*-benzo(*d*)imidazol-1-yl)(phenyl)methanone: - IR (KBr) (cm^{-1}): 3415.60 (OH), 1640.72 (C=O); ^{1}H NMR (δ, ppm) (DMSO): 7.1-7.9 (2m, 8H), 9.7 (suppressed OH peak, 1H), 2.48 (s, 3H)

Synthesis of Series 2 Compounds

Synthesis of 2-benzylbenzimidazole: Heated together mixture of *o*-phenylenediamine dihydrochloride (0.03 mole), 20 mL of water, phenylacetic acid (0.09 mole) under reflux for 45 minutes. Made the cooled reaction mixture distinctly basic by the gradual addition of the concentrated ammonia solution, the precipitated product was collected and recrystallised from 40% ethanol (scheme is shown in Fig. 3).

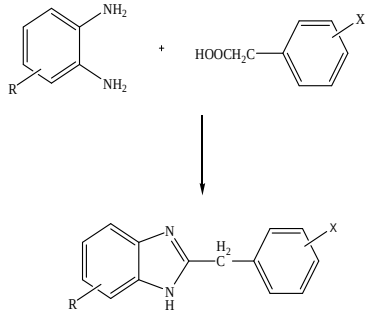

Fig. 3: Synthesis of 2-benzylbenzimidazole

Synthesis of 3-benzoylbenzimidazole derivative: Dissolved 0.5 gram of the above product in 10 mL of 10% sodium hydrogen carbonate solution and added 1 gram of benzoyl chloride. The reaction mixture was shaken vigorously in a stoppered test tube. The stopper was removed from time to time since carbon dioxide

was evolved. When the odour of benzoyl chloride had disappeared, acidified with dilute hydrochloric acid to Congo red and filtered. The solid with a little cold ether was extracted to remove any benzoic acid which may be present. The benzoyl derivative was recrystallised from dilute ethanol (scheme is shown in Fig. 4). The Physicochemical characteristics of Series 2 compounds are given table 2.

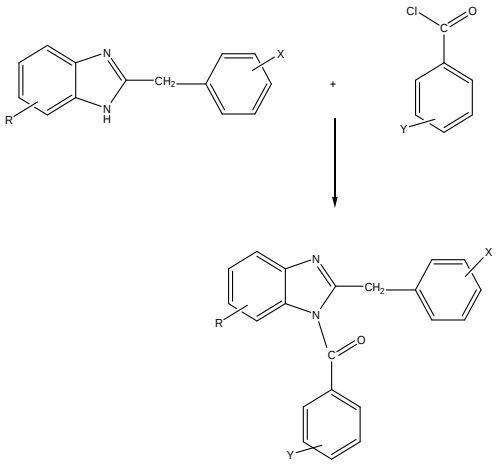

Fig. 4: Synthesis of 3-benzoylbenzimidazole derivatives series 2

Compound4 (P1.1.1)

(2-benzyl-1*H*-benzo(*d*)imidazol-1-yl)(phenyl)methanone: - IR (KBr) (cm^{-1}): 1686.74 (C=O); ^{1}H NMR (δ, ppm) (DMSO): 7.0-7.9 (3m, 14H), 3.3 (s, 2H)

Compound5 (P1.2.1)

(2-(4-nitrobenzyl)-1*H*-benzo(*d*)imidazol-1-yl)(phenyl) methanone: - IR (KBr) (cm^{-1}): 1686.50 (C=O), 1421.96 (NO_2 str); ^{1}H NMR (δ, ppm) (DMSO): 7.2-8.2 (3m, 13H), 3.4 (s, 2H)

Compound6 (P1.2.2)

(2-(4-nitrobenzyl)-1*H*-benzo(*d*)imidazol-1-yl)(4-nitrophenyl) methanone: - IR (KBr) (cm^{-1}): 1695.63 (C=O), 1422.22 (NO_2 str); ^{1}H NMR (δ, ppm) (DMSO): 7.2-8.3 (3m, 12H), 3.3 (s, 2H)

Compound7 (P2.1.1)

(2-benzyl-6-hydroxy-1*H*-benzo(*d*)imidazol-1-yl)(phenyl) methanone: - IR (KBr) (cm^{-1}): 3423.05 (OH), 1686.47 (C=O); ^{1}H NMR (δ, ppm) (DMSO): 7.1-8.1 (3m, 13H), 4.1 (s, 1H), 3.3 (s, 2H)

ANTIMICROBIAL ACTIVITY

The synthesized compounds were screened for their in vitro antimicrobial activities by using tube dilution method. The antimicrobial activity includes antifungal activity and antibacterial activity (Pelczar et al., 2005; Black et al., 1993; IP 1996). The response of synthesized compounds against fungal strains given in the table 3, the general structure of the synthesized compounds is shown in the Fig. 5 and MIC values of all the active compounds are given in table 4. All the synthesized title compounds were not able to inhibit the bacterial strains even at the highest concentration of the study. So, further evaluation of these compounds was not done.

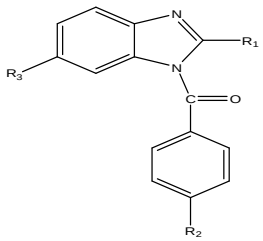

Fig. 5: General structure of synthesized compounds

Table 3: Response of synthesized compounds against fungal strains

S. No.	Compounds	*C. albican*	*A. fumigatus*
1	A1.1	-	-
2	A1.2	+	+
3	A2.1	+	+
4	P1.1.1	-	-
5	P1.2.1	-	-
6	P1.2.2	+	+
7	P2.1.1	+	+

+ indicates active, - indicates inactive

Table 4: MIC values of active title compounds

S. No.	R_1	R_2	R_3	*C. albican*	*A. fumigatus*
1	$-CH_3$	$-NO_2$	-H	115	65
2	$-CH_3$	-H	-OH	105	63
3	$-CH_2C_6H_5NO_2$	$-NO_2$	-H	120	64
4	$-CH_2C_6H_5$	-H	-OH	120	66
5	Standard Drug*	-	-	1	0.5

MIC value (µg/mL), * Amphotericin B

RESULT AND DISCUSSION

The synthetic work had been done on the two series of the benzimidazole by following the general scheme. The synthesis of the title compounds involves simple cyclization reaction between substituted o-phenylene diamine and corresponding carboxylic acid derivatives and was reacted with the substituted benzoyl chloride derivatives to form the corresponding benzoyl substituted benzimidazoles. The structures of all the synthesized derivatives were confirmed by IR and ^{1}H NMR. Antimicrobial screening of all the compounds was done by tube dilution method. Four compounds (A1.2, A2.1, P1.2.2 and P2.1.1) showed appreciable antifungal activity indicating that hydroxyl group at position 5 of benzimidazole may be required for activity, the electron withdrawing groups at *para* position of benzoyl group may have the positive effect on the antifungal activity and the *p*-substitutions at 2-phenyl benzimidazoles may have no effect on the activity.

CONCLUSION

The antifungal activities by incorporating the other electron withdrawing substituents on the benzoyl group at *para* position can be further explored.

ACKNOWLEDGEMENT

The author is gratefully thankful to Mr. Rakesh Kumar and Dr. Harish Dureja for giving a lot of unforgettable support in the research work.

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