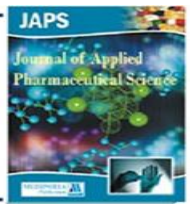
Journal of Applied Pharmaceutical Science
Available online at www.japsonline.com



ISSN: 2231-3354
Received on: 01-12-2011
Revised on: 08:12:2011
Accepted on: 13-12-2011

Synthesis and antimicrobial studies of substituted 2-phenylbenzimidazole derivatives

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ABSTRACT

The substituted 2-phenylbenzimidazole derivatives were synthesized by introducing different substituents at different positions. Six 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.

Keywords: Benzimidazole, antimicrobial activity, antifungal activity, antibacterial activity

INTRODUCTION

In recent decades, microbial diseases are more prevalent than they were during the first half of the last century and are still difficult to be diagnosed clinically. To combat them, various synthetic and semi-synthetic antimicrobial drugs have been used in clinical practice (park et al., 2007; Agh-Atabay et al., 2003). In the treatment of microbial infections only limited number of efficacious antimicrobial drugs are used even after availability of a number of antimicrobial agents. 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). 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 six substituted benzimidazole derivatives were synthesized by introducing different substituents at different positions.

MATERIAL AND METHODS

Experimental

The uncorrected melting point of all the six 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 **1-6** 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 2-phenylbenzimidazole

O-phenylenediamine 0.01 mole and 0.01 mole of benzoic acid were heated in a sealed tube with 10 mL of 20% hydrochloric acid for 4 hours at 145-150 ^{o}C. Neutralization of the reaction mixture gave a small amount of from which 6% crude product. Recrystallisation from aqueous ethanol gave colorless product (scheme shown in Fig. 1).

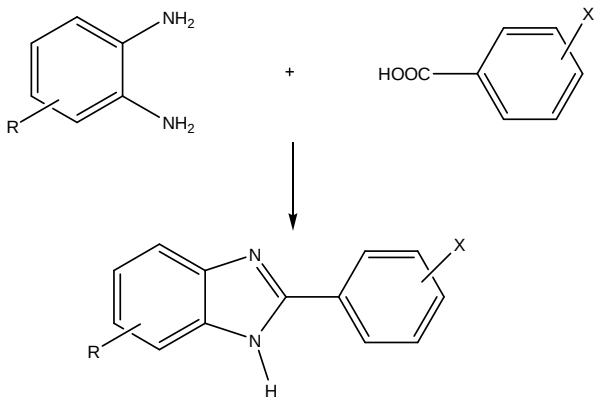

Fig. 1: Synthesis of 2-phenylbenzimidazole.

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. Shaken the reaction mixture 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. Extracted the solid with a little cold ether 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 synthesized compounds are given table 1.

Compound1 (B1.1.1)

Phenyl(2-phenyl-1*H*-benzo(*d*)imidazol-1-yl)methanone: - IR (KBr) (cm^{-1}): 1686.46 (C=O); ^{1}H NMR (δ, ppm) (DMSO): 7.0-7.9 (3m, 14H, ArH)

Compound2 (B1.1.2)

(4 - nitrophenyl) (2 - phenyl - 1 *H* - benzo (d) imidazol-1-yl) methanone: - IR (KBr) (cm^{-1}): 1724.05 (C=O), 1500.08 (-NO_2 str); ^{1}H NMR (δ, ppm) (DMSO): 7.0-8.5 (3m, 13H, ArH).

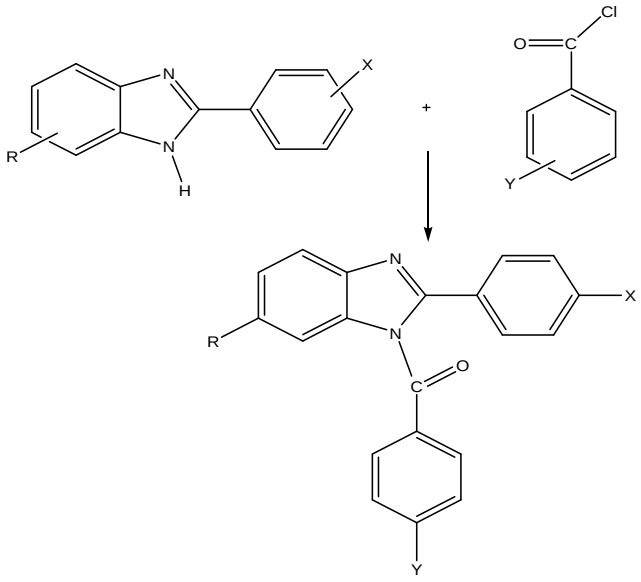

Fig. 2: Synthesis of 3-benzoylbenzimidazole derivatives.

Compound3 (B1.2.1)

(2- (4-nitrophenyl)-1*H*-benzo (*d*) imidazol-1-yl) (phenyl) methanone: - IR (KBr) (cm^{-1}): 1686.03 (C=O), 1498.12 (-NO_2 str); ^{1}H NMR (δ, ppm) (DMSO): 7.2-8.4 (3m, 13H, ArH)

Compound4 (B1.2.2)

(4-nitrophenyl)(2-(4-nitrophenyl)-1*H*-benzo(*d*)imidazol-1-yl)methanone: - IR (KBr) (cm^{-1}): 1696.30 (C=O), 1500.10 (-NO_2 str); ^{1}H NMR (δ, ppm) (DMSO): 7.2-8.3 (2m, 12H, ArH).

Compound5 (B1.3.1)

(2-(4-chlorophenyl)-1*H*-benzo(*d*)imidazol-1-yl) (phenyl) methanone: - IR (KBr) (cm^{-1}): 1685.17 (C=O), 1424.89 (-Cl str); ^{1}H NMR (δ, ppm) (DMSO): 7.1-7.9 (dm, 13H, ArH).

Compound6 (B1.3.2)

(2 - (4 - chlorophenyl) - 1*H* - benzo (*d*) imidazol - 1 - yl) (4-nitrophenyl) methanone: - IR (KBr) (cm^{-1}): 1692.25 (C=O); ^{1}H NMR (δ, ppm) (DMSO): 7.1-8.3 (3m, 12H, ArH)

Table 1: Physicochemical characteristics of synthesized compounds.

Compounds	R	X	Y	Melting point (°C)	Yield (%)
B1.1.1	-H	-H	-H	310-311	43.4
B1.1.2	-H	-H	-NO_2	318-319	96.2
B1.2.1	-H	-NO_2	-H	305-306	81.3
B1.2.2	-H	-NO_2	-NO_2	333-334	91.7
B1.3.1	-H	-Cl	-H	324-325	84.3
B1.3.2	-H	-Cl	-NO_2	346-347	96.4

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 2, the general structure of the synthesized compounds is shown in the Fig. 3 and MIC values of all the active compounds are given in table 3. 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.

Table 2: Response of synthesized compounds against fungal strains.

S. No.	Compounds	*C. albican*	*A. fumigatus*
1	B1.1.1	-	-
2	B1.1.2	+	+
3	B1.2.1	-	-
4	B1.2.2	+	+
5	B1.3.1	-	-
6	B1.3.2	+	+

+ indicates active, - indicates inactive.

Table 3: MIC values of active title compounds.

S. No.	R_1	R_2	R_3	*C. albican*	*A. fumigatus*
1	$-C_6H_5$	$-NO_2$	-H	110	64
2	$-C_6H_5NO_2$	$-NO_2$	-H	110	65
3	$-C_6H_5Cl$	$-NO_2$	-H	105	68
4	Standard Drug*	-	-	1	0.5

MIC value (µg/mL), * Amphotericin B

RESULT AND DISCUSSION

The synthetic work had been done on the benzimidazoles 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.

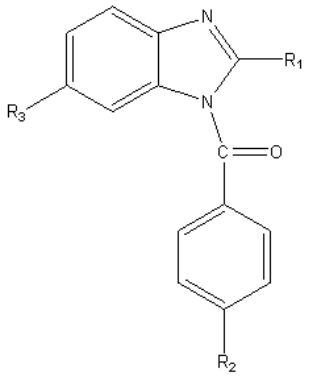

Fig. 3: General structure of synthesized compounds.

Antimicrobial screening of all the compounds was done by tube dilution method. Three compounds (B1.1.2, B1.2.2 and B1.3.2) 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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