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Synthesis and antimicrobial activity of some benzimidazole derivatives

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ABSTRACT

A series of substituted benzimidazole compounds were synthesized by phase transfer catalyst (PTC) method using quaternary ammonium salt. Reaction has been carried out by conventional method in inert gas. Synthesized compounds were confirmed by IR, NMR, mass spectral and elemental analysis. The synthesized compounds were screened for their antibacterial and antifungal activity using paper disc diffusion method against some microorganism such as *Escherichia coli, Bacillus pumilis, Staphylococcus aureus, Shigella sonnei, Proteus vulgaris, Pseudomonas aeruginosa, Aspergillus niger, Candida albicans.* Almost all compounds shows potent antibacterial and antifungal activity.

KEYWORDS

Benzimidazole derivatives;
Synthesis;
Antibacterial activity;
Antifungal activity.

INTRODUCTION

Synthesis of benzimidazole compound is emerged as essential need for development of new pharmaceutical entity. It may provide scaffolds on which pharmacophores can be arranged to yield potent and selective drug[1]. Every type of biological action detected, irrespective of the compounds involved in its induction, presents a potential lead[2]. The compounds responsible for the action have to be identified[3,4]. The range of the biological actions of potential interest is wide. Detection of biological action and identification of the chemical compounds involved to constitute the main and nearly unlimited source of leads for drug design[5,6]. The literature survey shows that in past recent years large number of compounds with different structures has been reported which exhibited antimicrobial activity[7,8]. However, their clinical usefulness is still restricted because of their side effects. The use of antimicrobial is limited mainly due to development of resistance power. The aim of our paper is to synthesize benzimidazole derivatives and evaluation of their antimicrobial activity which can be used for antimicrobial therapy.

MATERIALS AND METHODS

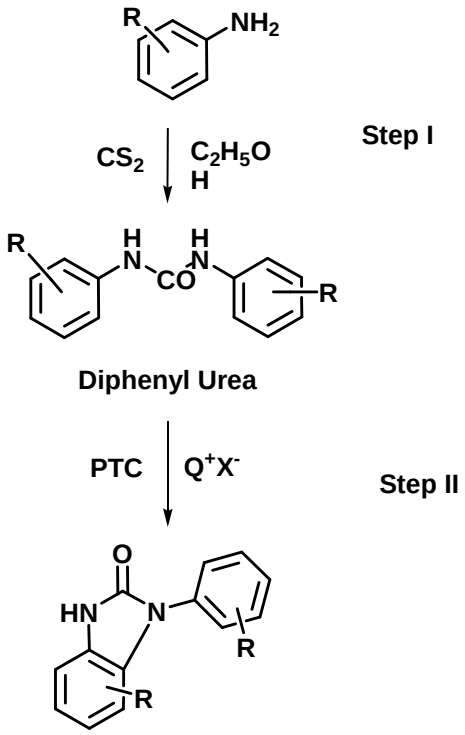
Synthesis of benzimidazole derivative[9-12]

All chemicals used in the synthesis were of synthetic grade.

STEP I: Synthesis Thiocarbanilide (Diphenyl Thiourea)

$$2\ C_6H_5NH_2 + CS_2 \xrightarrow{C_2H_5OH} S = C\ (NH.C_6H_5)_2 + H_2S$$

General chemical scheme



In a round bottom flask provided with efficient double surface condenser, 0.043 moles of aniline, 0.066 mol of carbon disulphide and 6.35 ml of ethanol were placed. The apparatus was set up in the fuming cupboard and heated on an electrically heated water bath for 8 hr or till content solidifies. Condenser was arranged for downward distillation, to remove the excess of carbon disulphide and alcohol. Residue in the flask was shaken with excess of dil. HCl (1:10) to remove any aniline present, It was filtered then washed with water and dried. The crude drug was recrystallized with rectified spirit.

STEP II: Synthesis of benzimidazole derivatives

Synthesis was carried out by phase transfer catalysis method by using quaternary ammonium salt. Six milliliter solution of potassium hydroxide (50% in water) and 0.25 mg of tetra butyl ammonium bromide (Q^+X^-) were added in necked round bottom flask filled with inert gas and fitted with septum. The solution was then continuously stirred for 30 min with magnetic stirrer. First step product was added drop wise in above solvent and stirred for 4 hr. It was then filtered and recrystallized with solvent and dried.

Synthesized benzimidazole derivatives with their respective yields are given in TABLE 1.

TABLE 1 : Synthesized benzimidazole derivatives.

Comp. Code	Substituent-R	M.P. (°C)	Yield (gm)
DP-1	H	258-260	2.3
DP-2	p-CH_3	257-259	1.8
DP-3	m-CH_3	281-283	1.5
DP-4	m-NO_2	296-297	2.5
DP-5	o-NO_2	284-286	2.1
DP-6	p-OCH_3	274-276	1.2
DP-7	o-Br	282-284	1.8
DP-8	p-Cl	285-287	2.3
DP-9	m-Cl	285-287	1.1
DP-10	COOH	291-293	1.4

Where DP-Benzimidazole Derivatives with substituent R

STEP III: Structure Confirmation

Synthesized compounds were confirmed by IR, NMR, mass spectra and elemental analysis.

STEP-IV: Antimicrobial screening

The standard pathogenic microorganism was procured from School of Life Sciences, Devi Ahilya Vishwavidyalaya, Indore, India and used in the study is given in TABLE 2. 0.1ml of broth was inoculated in 10ml sterile nutrient broth and incubated at 37°C for 3hr. Turbidity of culture was measured with the help of Nephelo-turbidimeter. Viable count (10^6) was measured by standard plate and used in the study.

TABLE 2 : Standard pathogenic microorganism with ATCC No. (American type culture collection)

Microorganism	ATCC No.
Escherichia coli	2109
Bacillus pumilis	2327
Staphylococcus aureus	2079
Shigella sonnei	--
Proteus vulgaris	2813
Pseudomonas aeruginosa	2036
Aspergillus niger	545
Candida albicans	--

Disc diffusion method as described by the National Committee of Clinical Laboratory Standards (2002)

was used to determine the antibacterial activity of the various synthesized compounds. For antibacterial properties, 0.1ml bacterial suspension of 10^5CFU/ml was uniformly spread on Muller Hinton agar and Potato Dextrose Agar plate to form lawn cultures. The solutions of synthesized compounds were prepared 100µg/ml in tetrahydrofuran (THF). The blotting paper discs (6 mm diameter) were soaked in prepared solutions, and tested for their antibacterial and antifungal activity by disc diffusion technique (NCCS 2000). After incubation of 24 hr at 37°C, zone of inhibition of growth was measured in mm. The antibacterial activity was classified as highly active (>21mm), mild active (15-21mm) and slightly active (12-15mm) and less than 12mm was taken as inactive. Gentamycin 10mcg/disc (Hi-Media disc) for antibacterial and Griseofulvin for antifungal was used as positive control, while discs soaked in THF were placed on lawns as negative control. Experiment was performed in triplet to obtain persistent result.

RESULTS AND DISCUSSION

In this work, series of compounds were synthesized and evaluated for biological activity against micro organism.

The anti-bacterial activity of the ten compounds was evaluated by paper disc diffusion method using Gentamycin as a standard. The minimum inhibitory concentration of the compound was determined. Compounds DP-1, DP-3 and DP-10 were good activity against *E. coli,* while DP-2 and DP-6 were moderately active. Compounds DP-1, DP-2, DP-4 and DP-10 have greatest activity against *B. pumilus,* while DP-3 and DP-5 were moderately active where as DP-6, DP-7 and DP-8 shows zero activity. All Compounds have moderate activity against *S. aureus,* except DP-6 and DP-7 which are poorly active and DP-8 with zero activity. DP-10 was active, while DP-5, DP-6 and DP-7 show zero activity and rest were poorly active against *S. sonnei.* Compounds DP-1, DP-2, DP-3, DP-7, DP-8 and DP-9 have moderate activity against *P. vulgaris,* while DP-4 and DP-6 were moderately active where as DP-5 and DP-10 shows zero activity. Compounds DP-3, DP-9, and DP-10 have moderate activity against *P. aeruginosa,* where DP-5 has zero activity and rest shows poor activity.

The anti-fungal activity of the ten compounds was evaluated by paper disc diffusion method using Griseofulvin as a standard. All compounds except DP-8, DP-9 and DP-10, which has zero activity shows moderate activity against *A. niger* as well as *C. albicans.* Detail results are depicted in TABLE 3.

Synthesized Compounds DP-1 to DP-10, were confirmed by IR, NMR, mass spectral and elemental analysis.

TABLE 3 : Antimicrobial activity of benzimidazole Derivatives against microorganism with zone of inhibition (mm)

Compounds code	*E. coli*	*B. pumilis*	*S. aureus*	*S. sonnei*	*P. vulgaris*	*P. aeruginosa*	*A. niger*	*C.albicans*
DP-1	18	17	16	15	14	11	18	17
DP-2	17	18	17	14	14	12	17	16
DP-3	18	15	14	16	15	14	16	14
DP-4	15	16	16	13	12	10	15	16
DP-5	-	14	15	-	-	-	15	14
DP-6	17	-	11	-	11	12	16	11
DP-7	14	-	09	-	14	09	16	13
DP-8	15	-	-	14	13	10	-	-
DP-9	14	13	14	15	14	13	-	-
DP-10	18	16	15	18	-	14	-	-
Gentamycin	19	16	18	19	15	16	-	-
Griseofulvin	-	-	-	-	-	-	22	21
Negative control	-	-	-	-	-	-	-	-

CONCLUSION

Our finding suggests that the compounds DP2 and DP8 with methyl and Cl substitute at para position are active molecule comparing to the previously synthesized derivatives. One can also synthesize the different substitute on methyl moiety to increase antimicrobial activity with minimal side effect. More potent benzimidazole derivative with substitute on methyl group at para position may find the active drug candidate in antimicrobial activity. The area of research on this molecule is still open to develop very potent agent in antimicrobial therapy.

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