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Synthesis and Biological Evaluation Of Some 2-Substituted Derivatives Of Benzimidazoles

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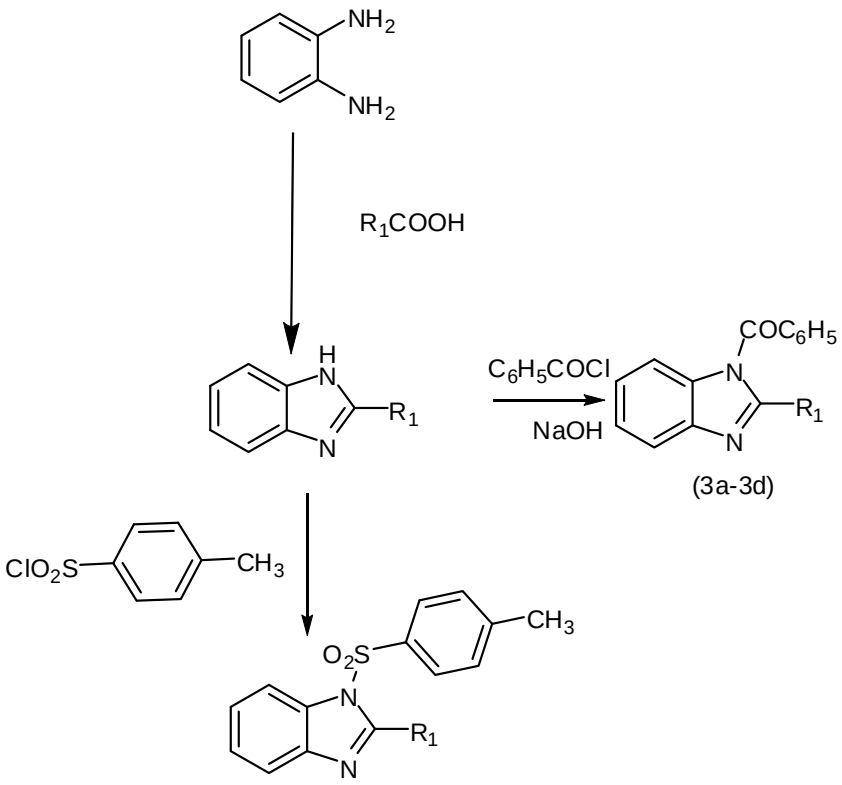
Abstract:
A large variety of 2-substituted benzimidazoles have been found to possess anti-inflammatory, antispasmodic, antihistaminic, antimicrobial, anticancer, cycloxygenase inhibitor, and HIV-1 reverse transcriptase inhibitor activities. 2-alkyl benzimidazole and 2-aryl benzimidazoles were synthesized with different acids namely acetic acid, o-chlorobenzoic acid, benzoic acid and cinnamic acid. These were further treated with tosyl chloride and benzoyl chloride to get N-substituted benzimidazole derivatives. These N-substituted benzimidazoles were tested for antimicrobial activity against *Escherichia coli, Pseudomonas aeruginosa and Staphylococcus aureus.* Some of the products exhibited interesting activity with known standard drug at same concentration. The study was aimed to develop some benzimidazoles with antimicrobial activity.
Keywords: *Antibacterial activity; Antifungal activity; Benzimidazoles; Ciprofloxacin*

Introduction:

Benzimidazoles are a group of molecules which have shown potential for application in a variety of pharmacological targets. They are of wide interest because of their diverse biological activity and clinical applications. A large variety of 2-substituted benzimidazoles have been found to possess anti-inflammatory[1], antispasmodic[2],antihistaminic[3], antimicrobial[4,5,6],antitumour[7],anticancer[8]and cycloxygenase inhibitors[9] activities. In addition benzimidazoles have also been investigated for their analgesic [10] and ant tubercular [11], activity. Although a variety of benzimidazole derivatives are known, the development of new and convenient strategies to synthesize new biologically active benzimidazoles is of considerable interest. **Antimicrobial activity:** The antibacterial activity was carried out by cup plate method. Standard cultures of E.coli, pseudomonas aeruginosa and staphylococcus aureus were used. Ciprofloxacin was taken on standard reference and the compounds were checked for their antibacterial activity. All compounds were also evaluated for their antifungal activity against Candida albicans using Fluconazole as a standard drug.

Materials and Methods:

Experimental:
The melting points of compounds were recorded using Thiel's melting point apparatus and are uncorrected. Purity of compounds was checked on silica get-G plates by TLC. IR spectra of compounds were recorded on Perkin-Elmer FIIR spectrophotometer in the range 4000-40000 in Nujol mull and KBr pellets.
HNMR spectra were recorded on Brucker Advance II 400 NMR spectrophotometer in $CDCl_3$ or DMSO using TMS as internal standard.
Synthesis of 2-substituted benzimidazoles (1a-1d): o-phenylene diamine (0.1mol) was refluxed with different aliphatic and aromatic carboxylic acids in equimolar quantity in presence of 4NHCl [12], After completion of reaction mixture was cooled, 10% NaOH solution was added slowly, crude product was washed with ice cold water and filtered and recrystallized with water ethanol mixture.
Synthesis of 1-(4-methyl benzene sulphonyl)-2-substituted benzimidazole (2a-2d): equimolar quantity of 1a -1d (0.01ml) and 4-methyl benzene sulphonyl chloride in aqueous NaOH solution (10%, 20ml) was stirred for 10-12 hrs. at room



Scheme: Synthesis of Compounds

Table 1: Physical and Analytical data of compounds

Com. No.	Mol. Formula	R	M.P. (^oC)	NMR (δppm)	IR(KBr)cm^{-1}
2a	$C_{15}H_{14}N_2O_2S$	methyl	117-120	2.9(3H,S,CH_3-C_2 benzimidazole) 2.4 (3H,S,aromatic, substituted CH_3)	1621.0 (C=N) 1357.6 (C-N) 1215.7 (SO2)
3a	$C_{14}H_{12}N_2O$	methyl	168-170	7.1-7.5 (9H,M,aromatic) 2.6 (3H,S,CH_3)	1621.5(C=N), 1358.1(C-N)
2b	$C_{20}H_{15}N_2O_2SCl$	o-chlorophenyl	134-138	7.2-8.0 (12H,M,aromatic), 2.9 (3H,S,CH_3 substituted benzimidazole)	1656.6 (C=O) 1590.2(C=N), 1314.8 (C-N), 1266.0 (SO_2), 709.6 (Cl)
3b	$C_{20}H_{13}N_2OCl$	o-chlorophenyl	122-127	7.1-7.2 (13H,M,aromatic)	1592.2 (C=N), 1312.9 (C-N), 1689.7 (C=O)
2c	$C_{20}H_{16}N_2O_2S$	phenyl	115-120	7.0-8.1 (13H,M,aromatic), 2.5 (3H,S,CH_3)	1598.6 (C=N), 1309.0 (C-N),

3c	$C_{20}H_{14}N_2O$	phenyl	175-180	7.3-7.5 (14H,M,aromatic)	1222 (SO_2) 1590.1 (C=N), 1314.9 (C-N), 1690.3 (C=O)
2d	$C_{22}H_{18}N_2O_2S$	2-phenyl-1-ethenyl	124-128	7.2-7.5 (13H,M,aromatic), 6.44-6.48 (2H,d,CH=CH), 2.3 (3H,S,CH_3)	1627.0 (C=N), 1310.9 (C-N), 1494.2(CH=CH) 1222.4 (SO_2)
3d	$C_{22}H_{16}N_2O$	2-phenyl-1-ethenyl	98-102	7.2-7.6 (14H,M,aromatic), 6.4-7.0 (2H,d,CH=CH)	1627.4 (C=N), 1494.1(CH=CH) 1324.0 (C-N), 1686.6 (C=O)

Table 2: Inhibition Zones (Antibacterial Activity)

Compound Esch	eria Coli (EC)	Pseudomonas aeruginosa (PA)	Staphylococus aureus (SA)
2a ++		+++	+
3a +		++	-
2b +		+	-
3b +		++	+
2c -		+	+
3c -		+	-
2d +		+++	+
3d -		++	-
Standard(Ciprofloxacin)	++++	++++	+++

Concentration = 100 μg/ml

Greatest inhibition zone ++++

Good inhibition zone ⟶ +++

Average inhibition zone ⟶ ++

Poor inhibition zone ⟶ +

No inhibition zone ⟶

temperature, excess of acid chlorides were removed by warming the solid separated was washed with dilute HCl, filtered dried and recrystallized from methanol to give 2a-2d.

Synthesis of 1-benzoyl-2-substituted benzimidazole (3a-3d): An equimolar mixture of 1a-1d (0.01mol) and benzoyl chloride in aqueous NaOH (10 %) solution was stirred for 10-12 hrs. at room temp. A solid ppt., that separated was filtered off and washed with dil HCl, recrystallized with THF.

Results and Discussion:

The 2-alkyl and aryl benzimidazoles were reacted with toluene sulphonyl chloride and benzoyl chloride to get N-substituted benzimidazole derivatives. These N-substituted benzimidazoles were selected for the study and tested for antimicrobial activity.

Table 3: Inhibition Zones (Antifungal Activity)

S. No.	Compound Code	Activity on Candida albicans
1. 2a		++
2. 3a		+
3. 2	b	-
4. 3	b	-
5. 2c		+
6. 3c		+
7. 2d		+++
8. 3	d	-
9. Standard	(Fluconazole)	++++

Concentration = 1000 µg/ml
Greatest inhibition zone ⟶ ++++
Good inhibition zone ⟶ +++
Average inhibition zone ⟶ ++
Poor inhibition zone ⟶ +
No inhibition zone ⟶ -

First the antibacterial activity was carried out against Escherichia coli, pseudomonas aeruginosa and staphylococcus aureus.Compound 2d had shown very good activity against pseudomonas aeruginosa, 2a also shown good activity against pseudomonas. While 3d and 3a exhibited average anti bacterial activity against same organism. The entire compounds exhibited very less or no activity against staphylococcus aureus. While 2a, 2d and 3d exhibited average or no activity against E. coli. Compound 2a and 2d showed very good antifungal activity against Candida albicans.

Conclusions:

We reported a convenient synthetic method for the synthesis of new compounds and the results of antibacterial and antifungal screening were encouraging. Further investigations with appropriate structural modifications of title compounds may result in therapeutically useful products.

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