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Synthesis and antimicrobial screening of some acid chloride derivatives of 2-substituted 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.

Key words: Benzimidazoles, antibacterial activity, acid chloride.

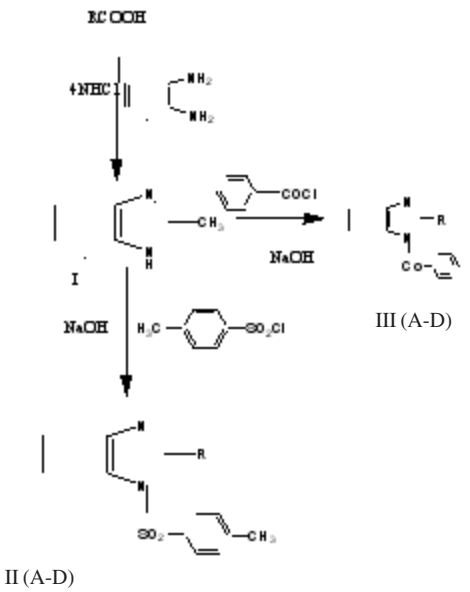
INTRODUCTION

The Benzimidazole ring is an important pharmacophore in modern drug discovery. 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 antitubercular activity[11]. In the interest of above, synthesis of some novel benzimidazole derivatives and investigation of their possible activity were aimed in this study.

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.

MATERIAL AND METHODS



Scheme 1

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 (IA-ID)

o-phenylene diamine (0.1mol) was refluxed with different aliphatic and aromatic carboxylic acids in equimolar quantity in presence of 4NHCl[12] for 20 hrs. 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 (IIA-IID)

equimolar quantity of IA-ID (0.01ml) and

Table 1: Physical and Analytical data of compounds.

Com. No.	Mol. Formula	R	M.P. (°C)	NMR (δppm)	IR(KBr)cm^{-1}
IIA	$C_{15}H_{14}N_2O_2S$	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)
IIIA	$C_{14}H_{12}N_2O$	methyl	168-170	7.1-7.5 (9H,M,aromatic) 2.6 (3H,S,CH_3)	1621.5(C=N), 1358.1(C-N)
IIB	$C_{20}H_{15}N_2O_2SCl$	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)
IIIB	$C_{20}H_{13}N_2OCl$	o-chlorophenyl	122-127	7.1-7.2 (13H,M,aromatic)	1592.2 (C=N), 1312.9 (C-N), 1689.7 (C=O)
IIC	$C_{20}H_{16}N_2O_2S$	phenyl	115-120	7.0-8.1 (13H,M,aromatic), 2.5 (3H,S,CH_3)	1598.6 (C=N), 1309.0 (C-N), 1222 (SO_2)
IIIC	$C_{20}H_{14}N_2O$	phenyl	175-180	7.3-7.5 (14H,M,aromatic)	1590.1 (C=N), 1314.9 (C-N), 1690.3 (C=O)
IID	$C_{22}H_{18}N_2O_2S$	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)
IIID	$C_{22}H_{16}N_2O$	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)

4-methyl benzene sulphonyl chloride in aqueous NaOH solution (10%, 20ml) was stirred for 10-12 hrs. at room 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 IIA-IID.

Synthesis of 1-benzoyl-2-substituted benzimidazole (IIIA-IIID)

An equimolar mixture of IA-ID (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.

RESULT AND DISCUSSION

2-Alkyl benzimidazole and 2- aryl benzimidazoles were synthesized with different acids namely acetic acid, o-chlorobenzoic acid, benzoic acid and cinnamic acid. These 2- alkyl benzimidazoles or 2- 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. First the antibacterial activity was carried out against *Escherichia coli, pseudomonas aeruginos*a and *staphylococcus aureus*. Compound IID had shown very good activity against pseudomonas aeruginosa, IIA also shown good activity against pseudomonas. While IIID and IIIA exhibited average antibacterial activity against same organism. The entire compounds exhibited very less or no activity against staphylococcus aureus. While IIA, IID and IIID exhibited average or no activity against *E. coli* .We provided a convenient synthetic method for the synthesis of new compounds and the results of antibacterial screening are encouraging. Further investigations with appropriate structural modifications of title compounds may result in therapeutically useful products.

Table 2: Antibacterial activity data

Compound No	Antibacterial activity: zone of inhibition in mm		
	***Escheria Coli* (EC)**	***Pseudomonas aeruginosa*(PA)**	***Staphylococcus aureus* (SA)**
IIA	2	3	1
IIIA	1	2	NA
IIB	1	1	NA
IIIB	1	2	1
IIC	NA	1	1
IIIC	NA	1	NA
IID	1	4	1
IIID	NA	2	1
Standard(ciprofloxacin)	18	20	13

Dose Concentration = 100 µg/ml

NA = No Activity

REFRENCES

1. S. N. Sawhney, S. Bhutani and Dharam Vir, *Indian J. Chem.,* **26**B: 348 (1987).
2. L. Isikdag and Y. Ozturk. Doga Turk Saglik Bilimleri Derg. **14**: 169. (*Chem. Abstr*., **113**: 231269 (1990)).
3. A. Orjales.,V. Rubio and M. Bordell, Eur. Pat. EP., **818**: 4545. (*Chem. Abstr*., **128**: 140702 (1998)).

4. E. Cetinkaya, B. Alici, Y. Gok, R. Durmaz and S. guanl, *J. Chemother,* **11**: 83 (1999).
5. I. Oren, O. Temiz, I.Yalcin, E. Sener and N. Altanlar, *Eur. J. Pharm. Sci.,* **7**: 153 (1999).
6. A. H. Leeman, M. L. Hammond, M. Maletic, G. M. Bantorelli., S. F. Waddell., J. Finn, M. Marytko, S. Ram and d. Keith. PCT INT. 0066. 119 (2000) (*Chem. Abstr*. **133**: 350507 (2000).
7. I. H. Hall, N. J. Peaty, J. R. Henry, J. Easmon, G. Heinisch and G. purstinger, *Arch. Pharm.* (Weinheim), **332**: 115 (1999).
8. D. Kumar , M. R. Jacob, M.B. Reynolds and S. M. Kerwin, *Bioorg. Med. Chem.* **10**: 3997 (2002).
9. R. Paramashivappa, P.Phanikumar, P. Phanikumar, P.V. Subba Rao and A. Srinivasa Rao., *Bioorg. Med. Chem. Lett.,* **13**: 657 (2003).
10. A. Orjales, V. Rubio and M. Bordell, *Eur. Pat. EP*, **818**: 4545. (*Chem. Abstr*. **128**: 140702: (1998).
11. Vera Klimesova, Jan Koci, Milan pour and jiri Stachel, *Eur. J. Med. Chem.* , **37**: 409 (2002).
12. M. A. Phillips, *J. Chem. Soc.*, 1143 (1931).