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Synthesis and anti-bacterial activity of 1, 2 Di-substituted benzimidazole derivatives

***Ch.Madhava Reddy, Srivani Mallepalli, Santosh Kumar Bagh, Moktakin Jufikaralom, Dr.N.Sriram, Raju. Manda**

Department of Pharmaceutical Chemistry, Holy Mary Institute of Technology and Science (College of Pharmacy), Bogaram, Keesara, Ranga Reddy District, Hyderabad, Telangana 501301

Corresponding author: Ch.Madhava Reddy

ABSTRACT

Benzimidazole is the heterocyclic compound formed from benzene and imidazole ring containing nitrogen, oxygen sulphur and its derivatives are of wide interest because of their diverse biological activity and clinical applications, they are remarkably effective compounds both with respect to their inhibitory activity and their favorable selectivity ratio. Reported nucleus is a constituent of vitamin-B12. Benzimidazoles are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities like anti-microbial, anti-viral, anti-diabetic, anti-cancer activity, numerous anti-oxidant, anti-parasitic, anti-helmintics, anti-proliferative, anti-HIV, anti-convulsant, anti-inflammatory, anti-hypertensive, anti-neoplastic, proton pump inhibitor and anti-trichinellosis. Benzimidazoles exhibit significant activity as potential antitumor agents, smooth muscle cell proliferation inhibitors, a treatment for intestinal cystitis, and in diverse area of chemistry. Some of the important benzimidazole derivatives have been reported as thyroid receptor agonist gonadotropin releasing hormone receptor antagonists, non-nucleoside HIV-1 reverse transcriptase inhibitors and interestingly alkynylbenzimidazoles as modulators of metabotropic glutamate receptors. The imidazole core is a common moiety in a large number of natural products and pharmacologically active compounds. The synthesis of novel benzimidazole derivatives remains a main focus of medicinal research. This comprehensive overview summarizes the chemistry of different derivative of substituted benzimidazole along with their anti-microbial activity containing anti-malarial anti-fungal, anti-bacterial, anti-viral activities. In this study we had synthesized some Benzimidazole derivatives and screened for their antibacterial activity. o-Phenylenediamine was condensed with acids in presence of Polyphosphoric acid and solvents like water and dilute hydrochloric acid. All the synthesized compounds showed significant anthelmintic activity.

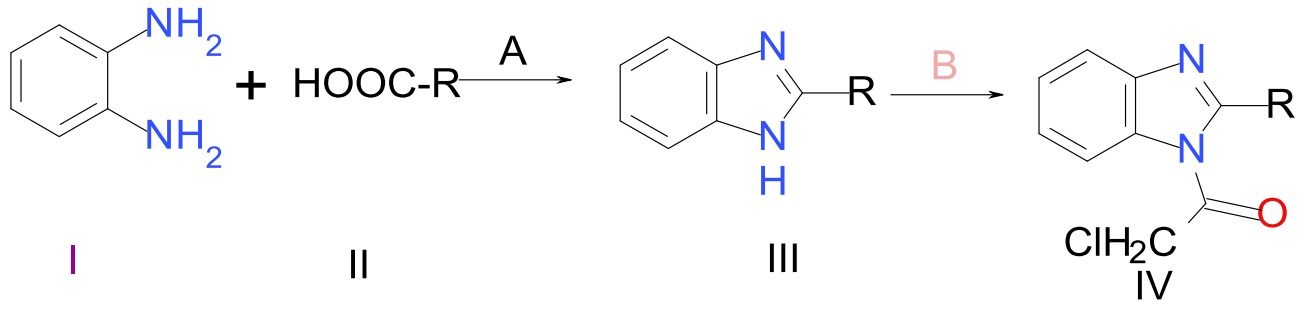
Keywords: Benzimidazole, Antibacterial, O-Phenylenediamine

INTRODUCTION

Benzimidazole is a heterocyclic aromatic organic compound. This bicyclic compound consists of the fusion of benzene and imidazole. The most prominent benzimidazole compound in nature is N-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B12. Benzimidazole, in an extension of the well-elaborated imidazole system, has been used as carbon skeletons for N-heterocyclic carbenes. The NHCs are usually used asligands for transition metal complexes. They are often prepared by deprotonating an N,N'-

disubstitutedbenzimidazolium salt at the 2-position with a base. Benzimidazole is a heterocyclic aromatic organic compound. It is an important pharmacophore and a privileged structure in medicinal chemistry. This compound is bicyclic in nature which consists of the fusion of benzene and imidazole. Nowadays is a moiety of choice which possesses many pharmacological properties. The most prominent benzimidazole compound in nature is N-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B12.

SCHEME



A-Hydrochloric acid

B - Chloro acetyl chloride + Dichloromethane (DCM) + Triethylamine (TEA)

I. O-Phenyl diamine

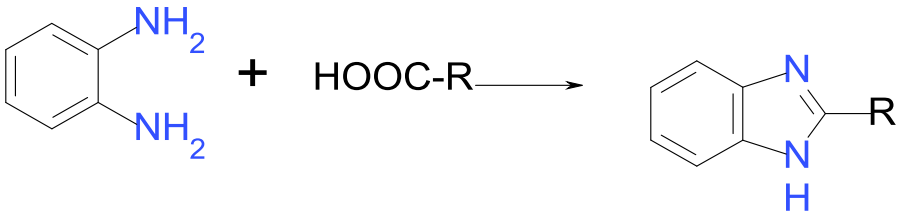
II. Substituted carboxylic acid, R= -H, -CH_3, C_6H_5 (Phenyl), -C_6H_4(P-NO_2)

III. 2-Substituted benzimidazoles

IV. 1,2-Disubstituted benzimidazoles

STEP-1: Preparation of 2-1subtituted bezimidazoles

Scheme



PROCEDURE

Preparation of Benzimidazole

Place 27gms (o.25 mol) of O-Phenylenediamine in a 250ml round bottom flask. Ass 17.5gms (16ml, 0.34 mol) of 9% ***Formic acid***. Heat the mixture on a water bath at 100^0C for 2hrs. Cool, Add 10% Sodium Hydroxide solution slowly with constant rotation of flask until the mixture is just alkaline to litmus. Filter off crude benzimidazole. Wash with ice-cold water. Drain well and wash again with 25ml of cold water. Dissolve the crude product in 400ml of boiling water, Add 2gms of Activated charcoal (Decolorizing carbon) and digest for 15min. Filter rapidly at pump through a pre heated Buchner funnel and flask. Cool the filtrate to about 10^0C, Filter off benzimidazole.

Wash with 25ml of cold water and dry at 100^0C. Yield: 40%, m.pt:150-170^0C, Rf value: 0.79

Preparation of 2-Methyl Benzimidazole

Heat together mixture of 5.43gms of O-Phenylenediaminedihyrochloride, 20 ml water and 5.4gms of ***acetic acid*** under reflux for 45min. Make the cold reaction mixture distinctly basic by gradual addition of concentrated ammonia solution. Collect the precipitated product. Recrystallise with 10% aqeous ethanol. The yield obtained is checked. Yield: 50%, m.pt: 177-180 C, Rfvalue: 0.469.

Preparation of 2-Benzyl Benzimidazole

Heat together mixture of 5.43gms of O-Phenylenediaminedihydrochloride, 20ml water, 12.3 gms ***Phenyl acetic acid*** under reflux for 45min. Make the cold reaction mixture distinctly basic by gradual addition of concentrated ammonia solution. Collect the precipitated product. Recrystallise with 40% aqueous ethanol. The yield of 3.4 grams is obtained. Yield: 48% m.pt: 235-236 C, Rf value: -10.315,

Preparation of 2-Phenyl Benzimidazole

Heat together mixture of 6gms of O-Phenylenediamine, 6 gms of ***Benzoic acid***, 25ml of 4N dil. Hydrochloric acid under reflux for 2hours at 180-185^0C temperature. The residue obtained is cooled and poured on to crushed ice. The product is filtered and washed with cold water. Product is recrystallised in boiling water using activated charcoal. yield: 33.58%, m.p.: 238-239 C, Rf value:0.34

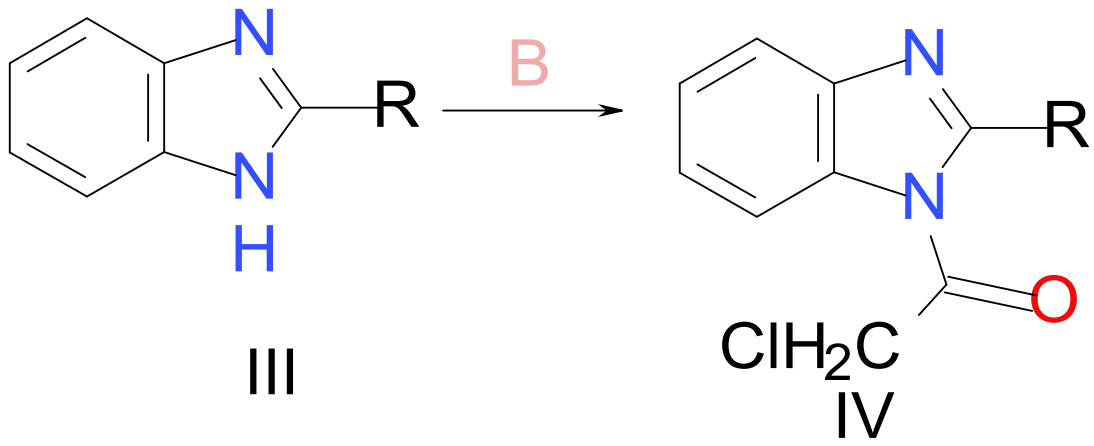
Synthesis of 2-(4-amino phenyl) benzimidazole

A mixture of **Para amino benzoic acid** (4.5g, 33 mM) and o-Phenylenediamine (3.8g, 34 mM) were stirred in a syrupy phosphoric acid (45ml) at 200 c for 2 hours. The reaction mixture was cooled and poured on to the crushed ice. The bulky white precipitate obtained was stirred in cold water (400 ml) and sodium hydroxide solution (5M) was added until the pH 7. The resulting solid was filtered and recrystallised from methanol, yield: 56.55%, yield: 56.55%, m. p: 248-1250 C, Rvalue: 0.250,
Benzimidazole Derivatives.

S.NO	COMPOUND NAME	R	Yield (%)	R_f	M.P(^{0}C)
IV_A	Benzimidazole	H	40	0.79	150-170
IV_B	2-Methyl Benzimidazole	$-CH_3$	50	0.469	177-180
IV_C	2-Phenyl benzimidazole	$-C_6H_5$	33.50	0.34	238-239
IV_D	2-(4-amino phenyl) benzimidazole	C_6H_4(P-	56.55	0.250	248-1250

STEP-2: Preparation of 1, 2 Di-Substituted benzene Derivatives

Scheme



PROCEDURE

To each of the above obtained benzimidazolederivatives 0.5 ml of Chloro acetyl chloride is added under cold conditions. To the mixture 1.2 ml of Dichloromethane and 0.5ml of triethylamine are added and is refluxed for 2hrs. The reaction mixture is collected, evaporated and crystals obtained are evaluated.

BIOLOGICAL EVALUATION

Agar Diffusion method

In our current study, antibacterial activity was carried out by the agar diffusion method. Here the responses of the organisms to the synthesized compounds were measured and compared with the responses of the standard drugs. The standard reference drug used in the antibacterial screening is streptomycin.

Micro-organisms

- Bacillus subtilis (gram positive bacteria)
- Escherichia coli (gram negative bacteria)

Sterilization of equipment's required

Petri dishes, Cork borer, Beakers, Glass syringes and test tubes were sterilizes by dry heat sterilization at 160^0 C for 1hr in a hot air oven.

Preparation of Sample solutions

All the synthesized compounds E_1-E_{10} were dissolved in DMSO to make the concentrations of 100, 300, 500 and 700µg/ml

Standard drugs

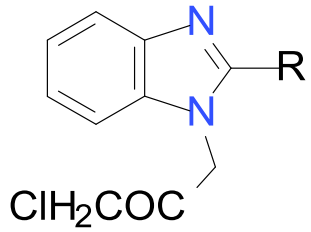
- Streptomycin- 100, 300 ,500, and 700µg/Ml

Preparation of Agar plates

The sterilized nutrient media was cooled to 45-46^0C and 200ml each of inoculated media was transferred into separate petridishes and allowed to cool at room temperature until the agar medium completely solidified. Then microorganism is inoculated in each petridish with inoculater and borer and 0.1ml solution of test drug of concentrations 100, 300, 500, 700µg/mL and standard solutions were separately added to each bores in separate petri plates. The sterile discs of standard reference drugs were placed on the surface. The petridishes were kept for 2hrs to allow the drug to diffuse into the agar media. A sterile atmosphere was maintained during the entire process by carrying out the work under Laminar Air Flow bench. All the plates were incubated for 24hrs at 37^0C. At the end of incubation period, diameters of the zone of inhibition were measured and recorded.

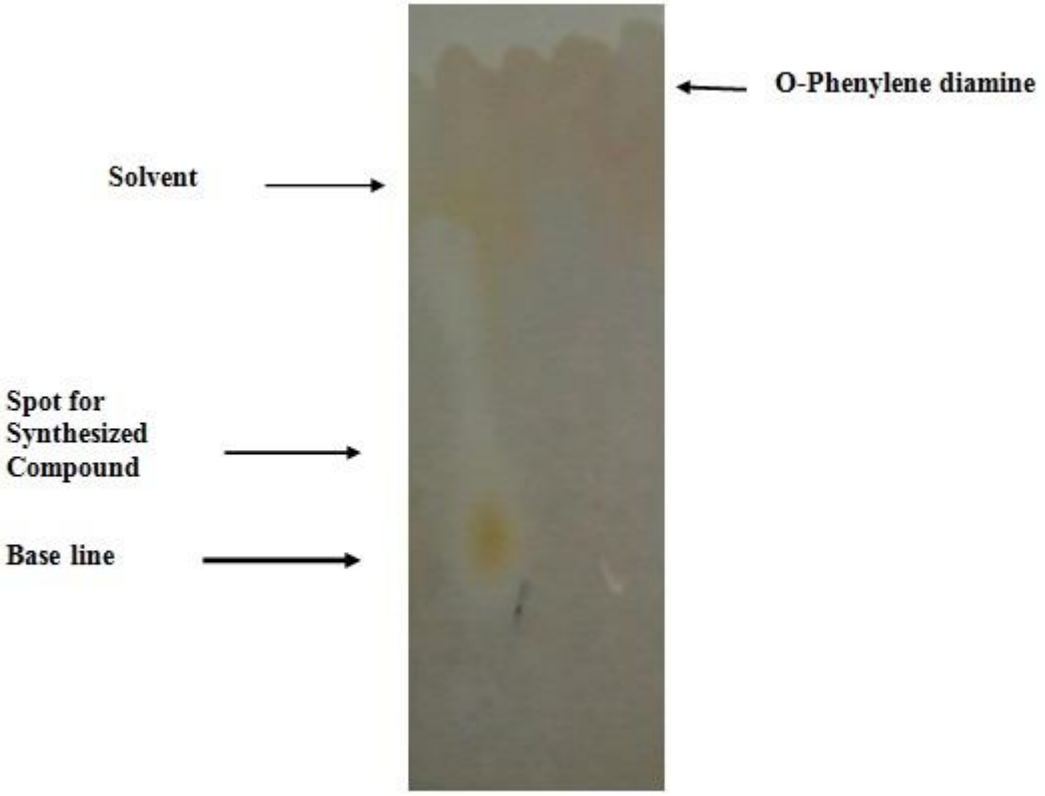
RESULTS AND DISCUSSION

Final derivative



S.NO	COMPOUND NAME	R	Yield (%)	R_f	M.P(^{0}C)
IV_A	Benzimidazole	H	40	0.79	150-170
IV_B	2-Methyl Benzimidazole	$-CH_3$	50	0.469	177-180
IV_C	2-Phenyl benzimidazole	$-C_6H_5$	33.50	0.34	238-239
IV_D	2-(4-amino phenyl) benzimidazole	C_6H_4(P-	56.55	0.250	248-1250

Thin layer chromatography



TLC FOR SYNTHESIZED COMPOUNDS

Anti-bacterial activity

Susceptibility of CBZ resistance induced Paecilomycesfarinosus LAR 10 to BMC

Strain	***Agar disk diffusion test***				
	Diameter of growth inhibition zone (mm) according to BMC concentration (%)				
	2	*1*	*0.5*	*0.1*	*0.05*
Bacillus	*48*	*48*	*48*	*46*	*31*
Escherichiacoli	*19*	*14*	*11*	*9*	*2*

MIC: Minimum inhibitory concentration.
BMC: methyl 2-benzimidazole carbamate

Physical data of the compounds

S.NO	Compound	Mol. Formula	Mol. Wt(gm/mol)	M.P(°C)	Yield (%)	R_f
IV_A	Benzimidazole	$C_7H_6N_2$	118.14	170-172 °C	40	0.76
IV_B	2-Methyl Benzimidazole	$C_8H_8N_2$	132.16	177-180	48	-10.3
IV_C	2-Phenyl benzimidazole	$C_{13}H_{10}N_2$	274	238-239	33.5	0.34
IV_D	2-(4-amino phenyl) benzimidazole	$C_{13}H_{12}N_4$	209.2	248-1250	56.55	0.25

Antibacterial activity of derivatives (E_1-E_{10})

Compound	Conc (µg/mL)	Zone of inhibition (mm)	
		Bacillus subtillus	Escherichia coli
IV_A	100	12	12
	300	14	14
	500	15	15
	700	17	16
IV_b	100	10	11
	300	11	12
	500	11	14
	700	13	16
IV_C	100	11	10
	300	12	10
	500	13	15

	700	16	17
	100	10	11
IV_d	300	11	14
	500	16	15
	700	18	16

Antibacterial activity of Streptomycin

Table-15

Compound	Conc (µg/mL)	Zone of inhibition (mm)	
		Bacillus subtilis	Escherichia coli
	100	10	9
Standard	300	12	11
Streptomycin	500	14	12
	700	15	13

CONCLUSION

The benzimidazole ring is an important pharmacophore in modern drug discovery. Benzimidazoles have been regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities like anti-microbial, anti-viral, anti-diabetic, anti-cancer activity, numerous anti-oxidant, anti-parasitic, anti-helmintics, anti-proliferative, anti-HIV, anti-convulsant, anti-inflammatory, anti-hypertensive, anti-neoplastic, proton pump inhibitor and anti-trichinellosis.

The objective of the present work was to synthesize, purify, characterize and evaluate the antibacterial activity of the newly synthesized 1,2 di-substituted benzimidazole derivatives

In this study we had synthesized some Benzimidazole derivatives and screened for their antibacterial activity. o-Phenylenediamine was condensed with acids in presence of Hydrochloricacid and solvents like water and ethanol. All the synthesized compounds showed significant antibacterial activity.

- The yield of the products ranged from 340-60%.
- The purity of the compounds was checked by TLC and standard biological methods

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