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Synthesis And Antimicrobial Evaluation Of Benzimidazole Derivatives

Thandra Yakaiah[1], Upender Rao Eslawath[2], Sumanjari Thokala[3], Rajashekar Vadlakonda[4]

[1](*Department of Pharmaceutical Chemistry, Jangaon Institute of Pharmaceutical Sciences, Kakatiya University, India).*
[2](*Department of Pharmaceutical Analysis, Vikas College of Pharmacy, Kakatiya University, India).*
[3](*Department of Pharmacology, Jangaon Institute of Pharmaceutical Sciences, Kakatiya University, India).*
[4](*Department of Pharmaceutical Chemistry, Vikas College of Pharmacy, Kakatiya University, India).*

Abstract: *The present research work was oriented towards the finding newer benzimidazole derivatives with antimicrobial activity. The different substituted benzimidazole derivatives were synthesized by addition using different substituted aldehydes with o-phenylenediamine and followed by the condensation reaction. The structures of the different substituted benzimidazoles were confirmed by using different analylitical techniques. The synthesized compounds were screened for their antimicrobial activity against B.subtilis, S.aureus, E.coli, and P.aerugenosa. The results showed that the compounds 2a and 2c were having a very good anti bacterial activity and were having an appreciable antibacterial activity when compared to that of the Amoxicillin. The synthesized compounds were also screened for antifungal activity against A.niger, C.albicans and Showed that the compounds 2a and 2c were having significant antifungal activity when compared to standard Griseofulvin.*

Keywords*: Benzimidazole, antimicrobial, B.subtilis, S.aureus, E.coli, P.aerugenosa, antifungal.*

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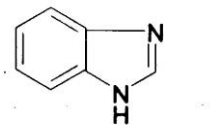
I. Introduction

An important feature of modern pharmaceutical chemistry is the introduction of more refined and sensitive methods of physicochemical analysis such as spectroscopy and chromatography that enable one to assay the quality and qual1tity of the drugs more accurately with the smallest consumption of the analyze, reagent and time. Pharmaceutical chemistry is a science that makes use of general laws of chemistry to study drugs, i.e. their preparation, chemical nature, composition, structure, influence on an organism and studies of the physical and chemical properties of drugs, the methods of quality control and the conditions of their storage. Pharmaceutical chemistry occupies the most important place among the related sciences e.g. drug technology, toxicological chemistry, pharmacognosy, and the organization of the pharmacy.

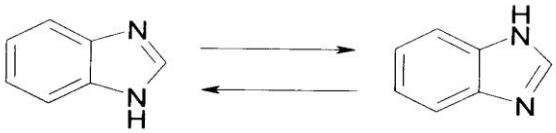
The benzimidazole contains a phenyl ring fused to an imidazole ring as indicated in the structure of benzimidazole (I)[1]. The important group of substances has found practical application in a number of fields. Recently benzimidazole chemistry has been revived somewhat by the discovery that the 5,6-dimethyl benzimidazole moiety is a part of the chemical structure of vitamin B_{12}.

Historically, the first benzimidazole was prepared in 1872 by Hoebrecker, who obtained 2,5 or 2,6-dimethyl benzimidazole by the reduction of 2-nitro-4-methyl acetanilide.

(I)



The benzimidazoles are also known as benziminazolones or benzoglyoxalines. They have been named also as derivatives of o-phenylenediamines. Benzimidazoles which contain a hydrogen atom attached to nitrogen in the 1-position readily tautomerise. This may be depicted as follows[2].



The benzimidazoles in fact, may be considered as a cyclic analogue of the amidines. Because of this tautomerism in benzimidazoles, certain derivatives which appear at first to be isomers are in reality tautomers; although two non equivalent structures can be written, only one compound is known. This may be illustrated with 5 or 6-methyl benzimidazole.

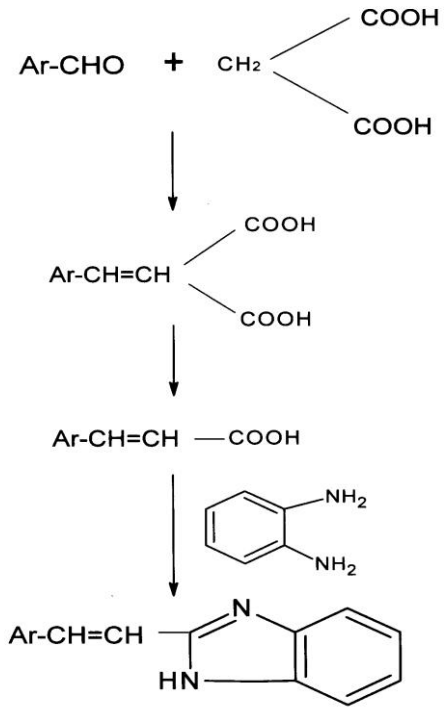
II. Experimental

Materials and Instruments used:

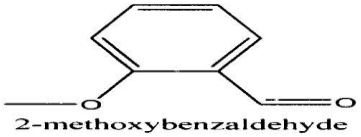
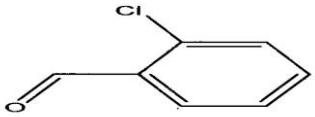
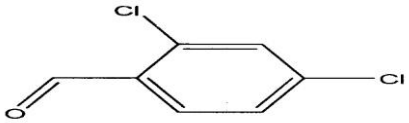
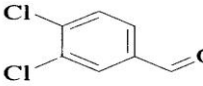
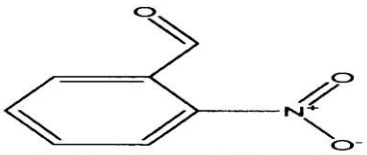
All the chemicals and solvents used were AnaLR quality and the drugs complies with the I.P standard.

Chemicals/Reagents	**Manufactures**
2,4-dichlorobenzaldehyde	CDH Kalvin scientific products
o-chlorobenzaldehyde	Hi-media laboratories
2-methoxybenzaldehyde	Hi-media laboratories
3,4-dimethoxybenzaldehyde	Hi-media laboratories
2-nitrobenzimidazole	Hi-media laboratories
Malonic acid	CDH Kavin scientific products
Pyridine	CDH Kavin scientific products
o-phenylenediamine	CDH Kavin scientific products
Ammonia	CDH Kavin scientific products
Methanol	Standard reagents Pvt. Ltd.
Piperidine hydrochloride	Hi-media laboratories
Hydrochloric acid	Standard reagents Pvt. Ltd.
Sodium bicarbonate	Standard reagents Pvt. Ltd.

SCHEME



Various substitution of the synthesized compounds:

Compound Code	R	Structure
2a	2-OCH_3	 2-methoxybenzaldehyde
2b	2-Cl	 o-chlorobenzaldehyde
2c	2,4-Dichloro	 2,4 dichlorbenzaldehyde
2d	3,4-Dichloro	 3,4 DICHLOROBENZALDEHYDE
2e	2-Nitro	 2-nitrobenzaldehyde

Procedure for the synthesis of table compounds:

Preparation of compound 2a:

2,4-dichlorobenzaldehyde and malonic acid were dissolved in a mixture of dry pyridine and piperidine and heated under reflux for 2 hrs. Then the reaction mixture is treated with *o*-phenyldiamine in 4N hydrochloric acid and stirred at room temperature for 1 hr and refluxed further for 4-6 hr, then the reaction mixture was neutralized with dilute ammonia and the formed precipitate was filtered. The residue was washed with water thoroughly and crystallized from alcohol to get solid crystals of pure.

Preparation of compound 2b:

2-chlorobenzaldehyde and malonic acid were dissolved in a mixture of dry pyridine and piperidine and heated under reflux for 2 hr. Then the reaction mixture is treated with *o*-phenyldiamine in 4N hydrochloric acid and stirred at room temperature for l hr, and refluxed further for 4-6 hr, then the reaction mixture was neutralized with dilute ammonia and the formed precipitate was filtered. The residue was washed with water thoroughly and crystallized from alcohol to get solid crystals of pure.

Preparation of compound 2c:

2-methoxy benzaldehyde and malonic acid were dissolved in a mixture of dry pyridine and piperidine and heated under reflux for 2 hr. Then the reaction mixture is treated with *o*-phenyldiamine in 4N hydrochloric acid and stirred at room temperature for l hr, and refluxed further for 4-6 hr, then the reaction mixture was neutralized with dilute ammonia and the formed precipitate was filtered. The residue was washed with water thoroughly and crystallized from alcohol to get solid crystals of pure.

Preparation of compound 2d:

3,4-dimethoxybenzaldehyde and malonic acid were dissolved in a mixture of dry pyridine and piperidine and heated under reflux for 2 hr. Then the reaction mixture is treated with *o*-phenyldiamine in 4N hydrochloric acid and stirred at room temperature for l hr, and refluxed further for 4-6 hr, then the reaction mixture was neutralized with dilute ammonia and the formed precipitate was filtered. The residue was washed with water thoroughly and crystallized from alcohol to get solid crystals of pure.

Preparation of compound 2e:

2-nitrobenzaldehyde and malonic acid were dissolved in a mixture of dry pyridine and piperidine and heated under reflux for 2 hr. Then the reaction mixture is treated with *o*-phenyldiamine in 4N hydrochloric acid and stirred at room temperature for l hr, and refluxed further for 4-6 hr, then the reaction mixture was neutralized with dilute ammonia and the formed precipitate was filtered. The residue was washed with water thoroughly and crystallized from alcohol to get solid crystals of pure.

Pharmacological Evaluation:

Antibacterial Evaluation:

The antibacterial activity of different compounds is done in disc diffusion method against the following organisms.

Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis and Staphylococcus aureus.

Media employed - M.H Agar
Solvent control used - Di Methyl Sulfoxide

Test samples:

2a - 2-[o-methoxy(2-phenyl ethenyl)]lh-benzimidazole
2b - 2-[o-chloro(2-phenyl ethenyl)]1h-benzimidazole
2c - 2-[2,4 dichloro(2-phenyl ethenyl)]1h-benzimidazole
2d - 2-[3,4 dichloro(2-phenyl ethenyl)]lh-benzimidazole
2e - 2-[2-nitro(2-phenyl ethenyl)]1h-benzimidazole
Standard used - Ciprofloxacin

The test samples used were used in concentration of l mg/ml using dimethylsulfoxide as solvent and Ciprofloxacin in concentration 1 mg/ml in suitable solvent was used as standard for Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis and Staphylococcus aureus.

Preparation of nutrient media:

Formula:

Peptone - 0.5%
Sodium chloride - 0.5%
Beef extract - 0.5%
Agar - 3.0%
Distilled water - q.s
ph adjusted to - 7.2-7.5

Then the medium is distributed into culture tubes and sterilized by autoclaving.

Disc diffusion method:

To the sterile nutrient agar, suspension of Escherichia coli was added at 45^{o}C and transferred to sterile petri dishes and allowed to solidify. Sterile discs (made from whatmann filter paper sterilized in isopropyl alcohol) were dipped in solution containing compound samples, standard and blank and placed on surface of agar plates. Leave the plates standing for one hour at room temperature as a period of pre incubation diffusion to minimize the effect of variation in time between the applications of different solutions. Then the plates were incubated at 37^{o}C for 18 hours and observed for antimicrobial activity. The diameters of zones of inhibition were measured for plates in which the zone of inhibition was observed and presented in table. The average area of zone of inhibition was calculated and compare with that of standard.

Antifungal evaluation:

The antifungal activity of different compounds is done by using disc diffusion method against the following organisms.

Aspergillus niger and Candida albicans.

Media employed - Sabouraud's dextrose agar media
Solvent control used - Dimethylsulfoxide

The sample was used in 1mg/ml concentration, using Dimethylsulfoxide as solvent and ketoconazole in concentration of l mg/ml was used as standard against Aspergillus niger and Candida albicans.

Test samples:

2a - 2-[o-methoxy(2-phenyl ethenyl)]1h-benzimidazole
2b - 2-[o-chloro(2-phenyl ethenyl)]1h-benzimidazol
2c - 2-[2,4 dichloro(2-phenyl ethenyl)]1h-benzimidazole
2d - 2-[3,4 dichloro(2-phenyl ethenyl)]1h-benzimidazole
2e - 2-[2-nitro(2-phenyl ethenyl)]1h-benzimidazole
Standard used - Ketoconazole

Preparation of medium used:

Mycological procedure	-	gm/lit.
Sabouraud's dextrose agar medium	-	10.0
Dextrose	-	40.0
Agar	-	15.0
Final pH	-	7.2-7.4

Disc diffusion method:

Suspensions of Aspergillus niger were added to sterile dextrose agar medium at 45°c, the mixture was transferred to sterile petri dishes and allow solidifying. Sterile disc 5 mm in diameters (made from whatmann filter paper previously sterilized in UV lamp) in solution of different samples, standards and a blank were placed on the surface of agar plates. Leave the plate standing for one hour at room temperature as a period of pre incubation diffusion to minimize the effect of variation in time between the applications of different solutions incubation time 48 h at 35°c. The average area of zone of inhibition was calculated and compared with that of standards.

III. Results And Discussions

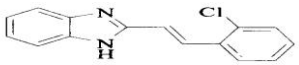
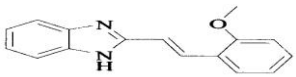
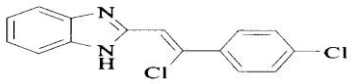
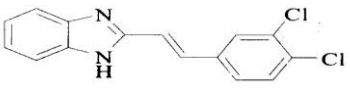
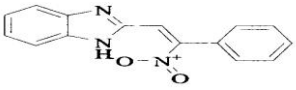
Synthesis of benzimidazole derivatives can be achieved through variety of methods. In the present investigation, the benzimidazole derivatives synthesised by condensation reaction between malonic acid and substituted aldehydes in the presence of pyridine and piperidine, then the reaction mixture was treated with o-phenylene diamine to obtained title compounds. All the procedures used along with step wise physical characterization data was presented in this section.

At present in the scheme the substituted benzimidazole derivatives were synthesized with 60-70% yield. It was further converted as substituted benzimidazole derivatives with yield between 70-80%.

The melting points of all synthesized compounds were found in open capillary tubes and readings were given in table. The synthesized compounds were screened for their antimicrobial activity against B.subtilis, S.aureus, E.coli, P.aerugenosa, which were presented in the table. The results showed that the compounds 2a and 2c were having a very good antibacterial activity and were having an appreciable antibacterial activity when compared to that of the Amoxycillin.

The synthesized compounds were also screened for antifungal activity against A.niger, C.albicans. The results tabulated here and it was observed that the compounds 2a and 2c were having significant antifungal activity when compared to standard Griseofulvin.

IUPAC name and structure of the synthesized compounds:

Compound	IUPAC Name	Structure
2a	2-[o-chloro(2-phenylethenyl)]lh-benzimidazole	
2b	2-[2-methoxy(2-phenylethenyl)]lh-benzimidazole	
2c	2-[2,4-dichloro(2-phenylethenyl)]lh-benzimidazole	
2d	2-[3,4-dichloro(2-phenylethenyl)lh-benzimidazole	
2e	2-[2-nitro(2-phenylethenyl)]1h-benzimidazole	

Physical Data of the Synthesized Compounds:

Compound	Molecular Formula	Molecular Weight	M.P (^{O}C)	Yield (%)	R_f Value
2a	$C_{15}H_{11}ClN_2$	254.37	144^{O}C	65	0.6
2b	$C_{16}H_{14}N_2O$	250.16	170^{O}C	70	0.25
2c	$C_{15}H_{10}Cl_2N_2$	289.15	181^{O}C	72	0.45
2d	$C_{15}H_{10}Cl_2N_2$	289.26	132^{O}C	65	0.2
2e	$C_{15}H_{11}N_3O_2$	265.27	150^{O}C	60	0.4

Antimicrobial activity of synthesized compounds:

S. No.	Compound		Zone of Inhibition in mcg/ml (in mm)					
			B.subtilis	S.aureus	E.coli	P.aerugenosa	A.niger	C.albicans
1	2a	50	16	13	13	18	15	16
		100	18	14	17	20	17	18
2	2b	50	13	15	12	14	14	17
		100	15	13	14	15	16	19
3	2c	50	14	12	14	13	18	13
		100	17	14	16	16	19	16
4	2d	50	12	16	15	18	16	14
		100	14	18	17	19	17	15
Amoxycillin		50	22	20	19	24	--	--
		100	27	25	23	28	--	--
Griseofulvin		50	--	--	--	--	21	20
		100	--	--	--	--	25	26

Control used: DMSO
Standard used: Amoxycillin, Griseofulvin
Method: Disc Diffusion Method

IV. Conclusion

The present research work was oriented towards the finding newer benzimidazole derivatives with anti microbial and anti inflammatory activity. The different substituted benzimidazole derivatives were synthesized by addition using different substituted aldehydes with o-phenylenediamine and followed by the condensation reaction. The structures of the different substituted benzimidazoles were confirmed by using different analytical techniques. The synthesized compounds were screened for their antimicrobial activity against B.subtilis, S.aureus, E.coli, and P.aerugenosa. The results showed that the compounds 2a and 2c were having a very good antibacterial activity and compounds so and so were having an appreciable anti bacterial activity when compared to that of the Amoxycillin. The synthesized compounds were also screened for antifungal activity against A.niger and C.albicans. The results showed that the compounds 2a and 2c were having significant antifungal activity when compared to standard Griseofulvin.

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