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A Study of Antibacterial Activities of Indole Derivatives

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ABSTRACT

The following Indole derivatives were synthesized by Fischer Indole method.

Substituted-N_β-Carbethoxyindol-2-carboxyhydraszide (***1a-e***),
Substituted-2-(5'-oxo-1',3',4'-oxadiazol-2'-yl)indoles(***2a-f)***
Substituted-2-(5'-thioxo-1',3',4'-oxadiazol-2'-yl)indoles ***(3a &b***),
2-(5'-oxo-1'-3'-4'-oxadiazol-2'-yl amino) indoles (***4a&b***),
Substituted-indole-2-carboxyhydrazide(***5***), Indole-2- carboxyazides (***6a &b***),
Ethyl indole-2-carbamates (***7a & b***), Substituted-indole-2/3-semicarbazides (***8a-c***),

N_β-carbethoxyindole-2/3-semicarbazides (***9a&b***). The compounds were screened for their antibacterial activity. The compounds (1a), (1e), (2a), (2c),(2e), (2f), (3a), (3b), (4a), (4b), (6a), (6b), (8a), (9a), (9b), were found to be highly active and compounds (1b), (1c), (1d), (2b), (2d), (5), (7a), (8b), (8c) have shown highest activity against S.aureus, while the compounds (1a), (1b), (1d), (2a), (2b), (2e), (5), (6b), (8b), (8c), (9b),were found to be highly active against E-coli.

Keywords: Indoles, Antibacterial agents, Heterocyclic compounds, oxodiazoles, S.aureus, E.coli

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INTRODUCTION

Indole ring system itself is known for its diverse biological activities [1-3]. The development of resistance among the various pathogenic organisms towards the antibiotics has stimulated the invention of newer antimicrobial agents [4-6].

Syntheses of some of the indole-2-carboxyhydrazide derivatives and the study of antimicrobial property have been reported by Hiremath et al [7-11]. Sengupta and Avanti [12] have evaluated the antibacterial activity of several 1,3,4 oxidiazole derivatives against E-coli and S-aureus. Hiremath et al have reported that 1,3,4-oxadiazolylaminoindoles possess moderate activity against E-coli and S-aureus.

With this background of information, we have screened some indole derivatives for their microbial activities. The common microbes used are Staphylococcus aureus (S.aureus) is a gram positive organism (cocci) and Escherichia coli (E.coli) as gram negative bacteria (bacilli) and compared that with standard drug gentamycin.

MATERIALS AND METHODS

Cup-plate method: Antimicrobial activity of test compound was assessed against S.aureus and E.coli by cup-plate method. The following materials are used

i) Nutrient agar
ii) Sterilized Petridishes and pipettes of 0.1 to 0.2ml capacity
iii) Culture and nutrient broth and
iv) Sterilized test tubes containing solutions of the test compounds at known concentration.

Preparation of media

Nutrient agar was prepared by dissolving bacteriological peptone (0.1%), meat extract (0.5%), sodium chloride (0.5%) in distilled water and pH of the solution was adjusted to 7.4 by using sodium hydroxide solution (40%) (Approximately 0.125ml for 100ml of the solution). This solution was filtered and agar (2%) was added. Then it was sterilized for 30 min at 15 PSI pressure.

Preparation of sub-cultures

The organisms used in the present study for testing of antibacterial activity of the compounds were obtained from the laboratory stock. On the day of testing, the organisms were sub-cultured into sterilized nutrient broth. After incubating the same for 3hrs, the growth thus obtained was used as inoculum for the test.

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Sterilization of media and Glass wares

The media used in the present study, nutrient agar and nutrient broth, were sterilized in the conical flask of suitable capacity by autoclaving the same at 15 PSI pressure for 20 min. The cork borer, petridishes, test tube and pipettes, were sterilized by employing hot air oven at 160^{o}C for 1 hr.

Preparation of solutions of test compounds

1. Gentamycin :5mg of gentamycin was dissolved in 5ml of DMF to get a concentration of 1000µ/ml
2. Compounds: 5mg of each test compounds was dissolved in 5ml of DMF in serially and suitably labeled in sterile test tubes. Thus giving a final concentration of 1000µg/ml.

Method of testing

This method depends on the diffusion of a test drug from cavity through the solidified agar layer in petridish to an extent such that growth of added microorganism is prevented entirely in a circular area or zone around the cavity containing a solution of test drug.

About 15-20 ml of molten nutrient agar was poured into each of the sterile plates of 3.5" diameter. With the help of sterile cork borer, two cups of each with 6mm diameter were punched and scooped out the set agar (two cups were numbered for the particular test compounds). The agar plate so prepared are divided into two sets and each set of the plates were inoculated with the suspension of particular organism by spread plate technique.

The cups of inoculated plates were then filled with 0.1ml of the test solution, the plate were then incubated at 37^{o}C for 24 hours. The zones of inhibition developed, if any was then measured for the particular compound with each organism. The solvent DMF was used as control to know the activity of the solvent. The Indole derivatives were synthesized by Fischer Indole method[7] and results of antibacterial testing of all the compounds are summarized in the Tables-1-4.

1. Substituted -N$_{\beta}$-carbethoxyindole-2-carboxyhydrazides (1a-e)

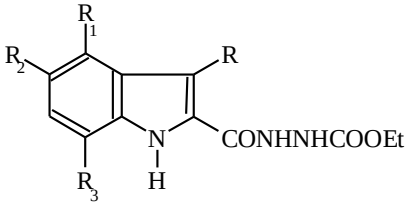

Fig.1(a-d)

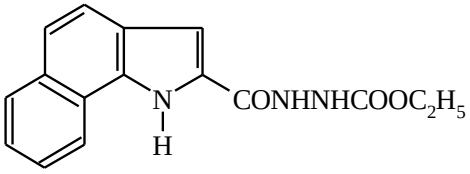

Fig.(1e)

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Table-1

Compound	Substituents				Zone of inhibition* in mm (Activity index**)	
	R	R_1	R_2	R_3	S.aureus 24 hrs	E.coli 24 hrs
1a	CH_3	H	Cl	CH_3	16 (0.72)	17 (0.85)
1b	CH_3	H	Cl	Cl	20 (0.90)	16 (0.80)
1c	H	H	H	H	20 (0.90)	12 (0.60)
1d	CH_3	CH_3	H	CH_3	20 (0.90)	16 (0.80)
1e	6,7 Benz.	-	-	-	17 (0.77)	08 (0.40)
Gentamycin	-	-	-	-	22	20
Control DMF	-	-	-	-	-	-

*Diameter of the well (bore size)- 6mm

** Activity index= Inhibition zone of the sample/inhibition zone of the standard given in the parenthesis

2. Substituted-2-(5'oxo-1',3',4'-oxadiazol-2'-yl) indoles (2a-f);
Substituted-2-(5' thioxo -1',3',4'-oxodiazol-2'-yl) indoles (3a & b)
Substituted- 2-(5'-oxo-1', 3', 4' oxodiazol-2'-yl amino) indole (4a) and
Substituted-3-(5'-oxo-1', 3', 4' oxodiazol-2'-yl amino) indole (4b)

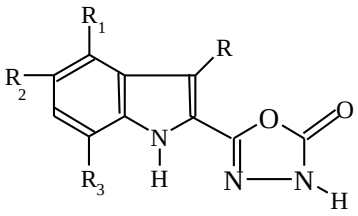

Fig.2(a-f)

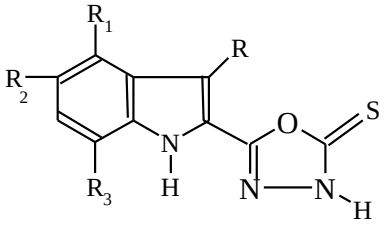

Fig.3(a &b)

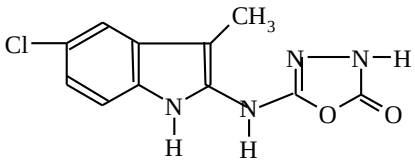

Fig.(4a)

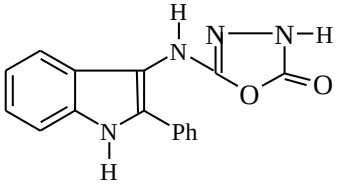

Fig.(4b)

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Table-2

Compound	Substituents				Zone of inhibition* in mm (Activity index**)	
	R	R_1	R_2	R_3	S.aureus 24 hrs	E.coli 24 hrs
2a	CH_3	H	Cl	CH_3	17 (0.77)	16 (0.80)
2b	CH_3	H	Cl	Cl	20 (0.90)	17 (0.85)
2c	H	H	H	H	16 (0.72)	09 (0.45)
2d	CH_3	CH_3	H	CH_3	21 (0.95)	12 (0.60)
2e	H	H	CH_3	H	17 (0.77)	17 (0.85)
2f	H	H	Cl	H	18 (0.81)	08 (0.40)
3a	H	H	H	H	17 (0.77)	12 (0.60)
3b	CH_3	CH_3	H	CH_3	16 (0.72)	14 (0.70)
4a	CH_3	Cl	-	-	17 (0.77)	07 (0.35)
4b	Ph	-	-	-	19 (0.86)	13 (0.65)
Gentamycin	-	-	-	-	22	20
Control DMF	-	-	-	-	-	-

*Diameter of the well (bore size)- 6mm
** Activity index= Inhibition zone of the sample/inhibition zone of the standard given in the parenthesis

3. Substituted-indole-2-carboxyhydrazide (5), indole-2-carboxyazides (6a&b) and ethyl indole-2-carbamates (7a & b)

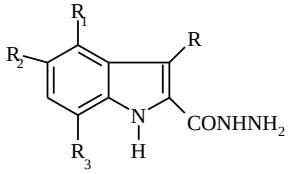

Fig.5

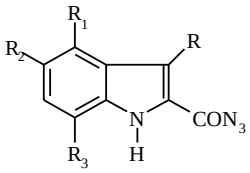

Fig.6 (a & b)

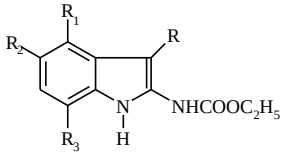

Fig. 7 (a & b)

Table-3

Compound	Substituents				Zone of inhibition* in mm (Activity index**)	
	R	R_1	R_2	R_3	S.aureus 24 hrs	E.coli 24 hrs
5	CH_3	CH_3	H	CH_3	21 (0.95)	16 (0.80)
6a	CH_3	CH_3	H	CH_3	17 (0.77)	14 (0.70)
6b	CH_3	H	CH_3	H	16 (0.72)	17 (0.85)
7a	CH_3	CH_3	H	CH_3	20 (0.90)	15 (0.95)
7b	CH_3	H	CH_3	H	14 (0.63)	12 (0.60)
Gentamycin	-	-	-	-	22	20
Control DMF	-	-	-	-	-	-

*Diameter of the well (bore size)- 6mm
** Activity index= Inhibition zone of the sample/inhibition zone of the standard given in the parenthesis

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4. Substituted indole-2-semicarbzides(8a&b); Substituted-indole-3-semicarbzide (8c); Substituted-N_β-carbethoxy indole-2-semicarbazide (9a) and Substituted-N_β-carbethoxy indole-3-semicarbazide (9b)

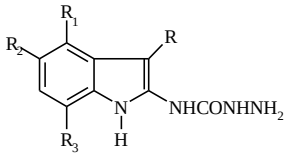

Fig.8 (a &b)

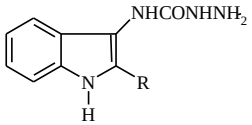

Fig.8c

3

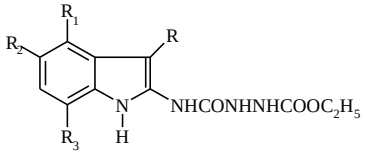

Fig.9 a

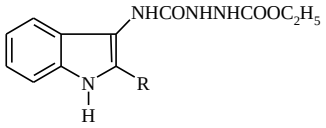

Fig.9b

Table-4

Compound	Substituents				Zone of inhibition* in mm (Activity index**)	
	R	R_1	R_2	R_3	S.aureus 24 hrs	E.coli 24 hrs
8a	H	H	Cl	H	18 (0.81)	08 (0.40)
8b	CH_3	H	CH_3	H	20 (0.90)	17 (0.85)
8c	Ph	-	-	-	21 (0.95)	18 (0.90)
9a	CH_3	H	Cl	H	17 (0.77)	15 (0.75)
9b	Ph	-	-	-	16 (0.72)	16 (0.80)
Gentamycin	-	-	-	-	22	20
Control DMF	-	-	-	-	-	-

*Diameter of the well (bore size)- 6mm

** Activity index= Inhibition zone of the sample/inhibition zone of the standard given in the parenthesis

Key for interpretation

Zone of inhibition in mm	interpretation
Less than 08	Inactive
09-11	weakly active
12-15	Moderately active
16-18	Highly active
More than 19	Highest active

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RESULTS AND DISCUSSION

Form the observations made during the screening of the compounds systematized in the Table-1-4 for the antibacterial activity, the following generalization can be made

- Of the substituted -N_{β}-carbethoxyindole-2-carboxyhydrazides (1a-e) listed in the Table-1 the compounds (1a) and (1e) are highly active against S.aureus where as the compounds, (1b-d) exhibit highest activity against the same organism. The compound (1a),(1b) and (1d) are highly active but, compound (1c) is moderately active and (1e) is weakly active against the E.coli organism.

- Amongst the derivatives of 2-(5'-oxo/thioxo 1',3',4'-oxodiazol-2'-yl)indoles (2a-f/3a,b) and 2/3–(5'-oxo-1',3',4',-oxadiazol-2'-yl aminoindoles (4a,b) listed in the Table-2, the compounds (2a), (2c), (2e), (2f), (3a), (3b), (4a) and (4b) are highly active to S.aureus, whereas (2b) and (2d) show highest inhibition of growth towards the same organism. The compounds (2a), (2b), and (2e) are highly active against E.coli, but the remaining compounds are either weakly or moderately active against the same organism.

- In hydrazides (5), azides (6a,b) and carbamates (7a,b) (Table-3), the compounds (5) and (7a) exhibit high inhibition of growth, whereas (6a), (6b) are highly active and (7b) is moderately active against S.aureus. The compound (5) and (6b) are highly active but (6a),(7a) and (7b) are moderately active against E.coli.

- In the case of semicarbazides (8a-c) and (9a,b) (Table-4), the compounds (8a), (9a) and (9b) are highly active where as the compounds (8b) and (8c) exhibit highest activity towards S.aureus. The compounds (8a) and (9a) are inactive and moderately active against the E.coli organism respectively, whereas the compounds (8b), (8c) and (9b) are highly active against the same organism.

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