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Synthesis and Characterization of Indole Derivatives as Potent Antibacterial Agents

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ABSTRACT

To curtail the development and spread of antimicrobial resistance, the current antimicrobials should be preserved through their appropriate use, as well as the discovery and development of new agents. Indole is a versatile pharmacophore, a privileged scaffold with extensive pharmacological properties. This research work explored the antibacterial property of indole derivatives through the molecular modifications in the nucleus. A series of novel indole subordinates were synthesized and characterized by physical as well as spectral methods. Selected compounds were exposed to antibacterial assays and the results indicated that the compounds exhibited promising bacterial inhibition.

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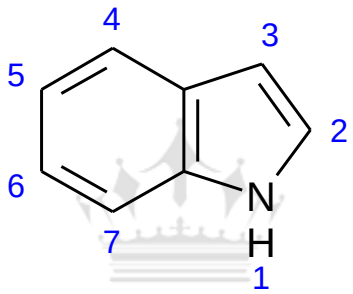
1. INTRODUCTION

Bicyclic heterocyclic structures occur widely in many biologically important molecules, one of them is Indole. Indole or benzopyrrole is an organic compound containing six-membered benzene fused to the five-membered nitrogen-containing pyrrrole which plays key role in the field of drug discovery and development.[1] Among the privileged indole nucleus with substituents at various positions, 2- and 3- functionalized indoles appear to be most promising ith diverse biological properties.[2] To combat the bacterial resistance against existing antibiotics, there is a need to develop new modified therapeutics or to restrict the drug resistant enzymes. So in this study, we report a series of novel compounds bearing an indole scaffold with modifications in C-3 position as potent antimicrobial agents.

SAR studies of indole[3,4]

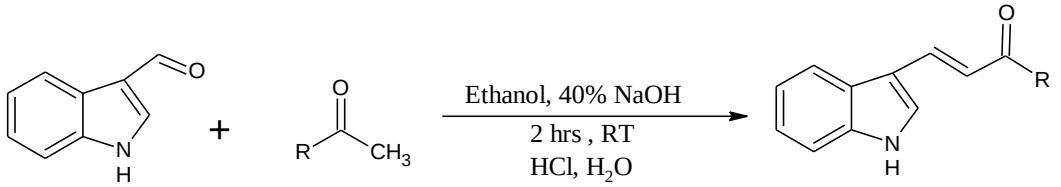


1*H*-Indole[5]

- The presence of thiophene and imidazole ring increases the antimicrobial activity.
- Polar substituents such as the ester group in the C3 position might be important for the inhibitory effect.
- Electron withdrawing group like NO_2, CN at C5 position increases the antimicrobial activity. It improves the metabolic stability of the drug candidate.
- Presence of electron donor group induces a slight metabolic stability drop due to the further metabolic reactions by direct involvement of the electron donating group.

2. MATERIALS AND METHODS

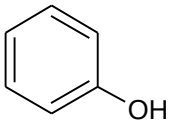
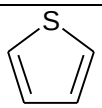
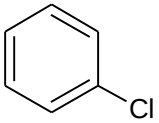
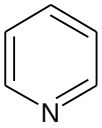
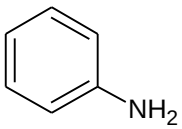
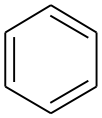
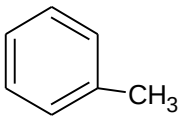
2.1. SYNTHETIC METHODOLOGY[6]



1*H*-indole-3-carbaldehyde Acetyl analogues Substituted indole derivatives

Scheme-1

Table No. 1: List of synthesized compounds

Compound	R
IN-1	
IN-2	
IN-3	
IN-4	
IN-5	
IN-6	
IN-7	

General procedure for the synthesis of substituted indole derivatives

To a stirred mixture of into aldehyde (14.5g, 100 mmol) and an acetyl derivative (15.0g, 100 mmol) in 200ml ethanol at room temperature, 40% NaOH aqueous solution was added portion-wise after which stirring was continued for further 2 hrs. The colored precipitate formed was filtered and washed with 3% aqueous HCl, and crystallized from ethanol to obtain the final product.

TLC was performed using ethyl acetate and hexane (8:2).

2.2. CHARACTERIZATION

Compounds were characterized by both physical and spectral methods. Melting points were recorded by capillary tube method. Reaction progress was monitored by TLC. IR spectra were obtained using the FTIR Jasco spectrometer. Mass spectra were recorded using Thermoscientific executive.

2.3. ANTIBACTERIAL SCREENING

The compounds (IN1-IN3) were evaluated for their antibacterial property against *Staphylococcus aureus*, *Escherichia coli* by agar well diffusion assay using Mueller-Hinton agar medium at a concentration of 50 µg/ml. Zone of inhibition of the microbial growth was measured in mm.[7,8,9]

3. RESULTS AND DISCUSSION

3.1. CHARACTERIZATION OF SYNTHESISED COMPOUNDS

Physical characterization

Table No. 2: Physical Characterization of synthesized compounds

Compound	Molecular formula	Molecular weight	Color	Melting point (°C)	R_f value	Percentage Yield (%)
IN-1	$C_{16}H_{12}N_2O$	248.27	Yellow	191	0.94	67
IN-2	$C_{15}H_{11}NOS$	253.31	Purple	192	0.91	78
IN-3	$C_{17}H_{12}NOCl$	281.73	Pale brown	187	0.99	73
IN-4	$C_{17}H_{13}NO_2$	263.29	Dark brown	190	0.91	68
IN-5	$C_{17}H_{14}N_2O$	262.30	Purple	185	0.93	59
IN-6	$C_{17}H_{13}NO$	247.29	brown	188	0.96	78
IN-7	$C_{18}H_{15}NO$	261.31	Yellowish orange	189	0.97	65

Spectral characterization

1-(4-hydroxyphenyl)-3-(1*H*-indol-3-yl)prop-2-en-1-one

IR (KBr): 3415.93 cm^{-1} (N-H), 3041.74 cm^{-1} (C=O)**,** 3197.98 cm^{-1} (O-H), 1446.61 cm^{-1} (Ar C=C)

Mass: *m/z* 264.1016 $[M+H]^+$

3-(1*H*-indol-3-yl)-1-(thiophen-2-yl)prop-2-en-1-one

IR (KBr): 3199.91 cm^{-1} (N-H), 3041.74 cm^{-1} (C=O), 1446.61 cm^{-1} (Ar C=C), 1244.09 cm^{-1} (C-S)

Mass: *m/z* 254.1534 $[M+H]^+$

1-(4-chlorophenyl)-3-(1*H*-indol-3-yl)prop-2-en-1-one

IR (KBr): 3421.72 cm^{-1} (N-H), 3092.72 cm^{-1} (C=O), 1446.61 cm^{-1} (Ar C=C), 885.33 cm^{-1} (C-Cl)

3-(1*H*-indol-3-yl)-1-(pyridin-3-yl)prop-2-en-1-one

IR (KBr): 3201.83 cm^{-1} (N-H), 3113.11 cm^{-1} (C=0), 1446.61 cm^{-1} (Ar C=C)

1-(4-aminophenyl)-3-(1*H*-indol-3-yl)prop-2-en-1-one

IR (KBr): 3456.44 cm^{-1} (N-H), 3051.39 cm^{-1} (C=O), 1446.61 cm^{-1} (Ar C=C)

3-(1*H*-indol-3-yl)-1-phenylprop-2-en-1-one

IR (KBr): 3199.92 cm^{-1} (N-H), 3041.74 cm^{-1} (C=O), 1446.61 cm^{-1} (Ar C=C)

3.2. ANTIBACTERIAL ACTIVITY

The three compounds (IN-1 to 1N-3) showed a satisfactory zone of inhibition against *E.coli* of which IN-2 showed superior inhibitory effect than standard. Among the other compounds, IN-2 displayed better antibacterial activity against both organisms.

Table No. 3: Antibacterial activity of selected compounds

Compound No:	Concentration (µg)	Zone of inhibition (mm)	
		E.coli	*S.aureus*
IN-01	50	6	4
IN -02	50	7	5
IN -03	50	6	4
Gentamycin (std)	50	7	6

4. CONCLUSION

Indole was chosen as a pharmacophore and was subjected to various molecular modifications for developing agents against bacterial infections. Among the seven synthesized compounds, three of them were exposed to Antibacterial assay, of which IN-2 experienced better inhibitory action against both *E.coli* and *S.aureus.*

5. ACKNOWLEDGEMENT

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