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"SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL ACTIVITY OF BENZIMIDAZOLE WITH ISOINDOLINE DERIVATIVES BY LEUCKART REACTION"

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ABSTRACT:
Some new benzimidazoles with iso indoline (JV1-JV5) have been synthesized by Leuckart reaction using microwave irradiation. Synthesis of1,4 aryl 1H benzimidazole-2yl alkyl-1H isoindol-1,3-dione compounds by using different aldehydes. The structures of newly synthesized compounds were characterized by elemental analysis, FT-IR, ^{1}H NMR, and MASS spectroscopy. Antibacterial activity of various synthesized compounds was studied by the presence of zone of inhibition using disc diffusion method. Amikacin was used as standard drug.

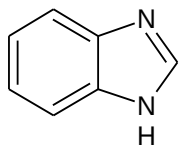
KEYWORDS:
Benzimidazole with isoindoline derivatives, leuckart reaction, microwave irradiation, Antibacterial activity

INTRODUCTION

Medicinal chemistry of drug synthesis involves, structure modification for optimization of their activity and other physical properties and total and semi synthesis for a thorough scrutiny of structure activity relationship. The techniques of molecular graphics and computational chemistry have provided novel chemical structure that have led to new drugs with potent medicinal activates.

BENZIMIDAZOLE

●The heterocyclic compound Benzimidazole derivatives are formed by the fusion of benzene and imidazole ring.



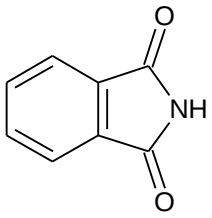
●The imidazole core is a common moiety in a large number of natural products and pharmacologically active compounds.

●On the basis of various literature surveys Benzimidazole derivatives shows various pharmacological activities like antifungal, antibacterial activity, anti-inflammatory activity, anti -tubercular activity, antidepressant activity, anticancer activity, antiviral activity.

●Benzimidazole derivatives are of wide interest because of their diverse biological activity and clinical applications, they are remarkably effective compounds with respect to their inhibitory activity as well as their selectivity.(13)

●Benzimidazole as ‘‘lead’’ molecule, binds with other heterocyclic act by intercalation or block cell growth by inhibit the enzymes directly responsible for the formation of nucleic acids. This inhibition is believed to prevent DNA transcription, which ultimately leads to

ISOINDOLINE

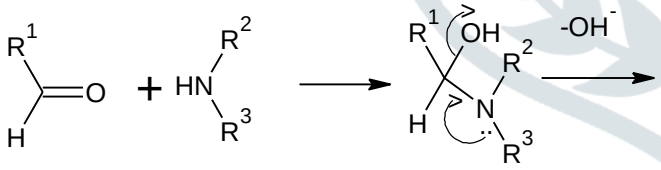


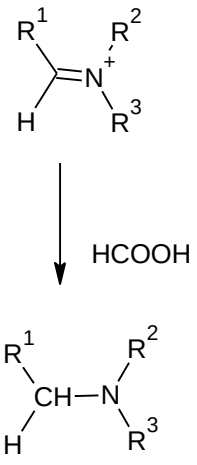
●The literature survey shows that indoline and isoindoline derivatives which have a wide range of biological activities such as antimicrobial, antibacterial, anti-inflammatory, antihistamine, antioxidant, antiproliferative, acetylcholinesterase inhibitors, inhibitor of human neuronal nitric oxide synthase.

●Out of the above mentioned heterocyclics, indole and benzimidazole derivatives comprise the ring system in a number of many drugs to name a few omeprazole, albendazole, indomethazine, indoprofen, etc(16)

MECHANISM:

- Amine reacts with aldehyde to give iminium ion.
- The iminium ion then react with formic acid to give methylated ammonium ion and release CO_2 gas, where formic acid act as a reducing agent or hydride transfer reagent.
- This CO_2 gas leads the synthesis process to the next level of synthesis.
- In this stage ammonium ion gets deprotonated to form final methylated amine product.
- If reaction occurs with primary amine same process follows twice to reach the tertiary amine as a final product(28)





METHODS AND METRIALS

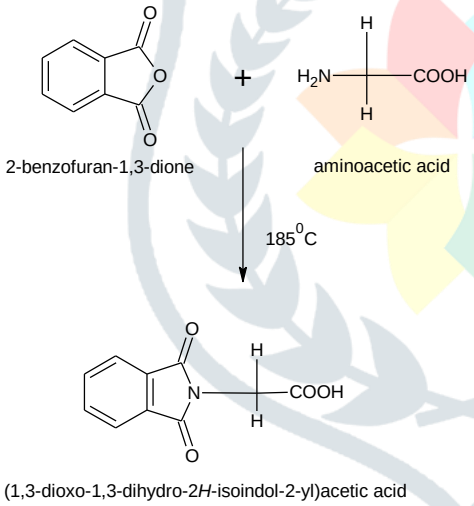
Instruments and materials

Microwave irradiation was carried out in a microwave oven (IFB-3way system, 23sc1, 2450 MHz) with power output of 800W. The reaction was monitored by TLC (Thin layer chromatography). The melting points of the synthesized compounds were estimated by open capillary tube method. IR spectra were recorded on Perkin-Elmer FT spectrophotometer used KBr disc the ranges of 4000-400 cm^{-1}. 1 H NMR spectra were recorded on Bruker 400 ultra-shield NMR spectrometer operating at 400MHz.For FT-NMR, DMSO is used as a solvent and chemical shift values were recorded in unit δ (ppm). Analytical grade chemicals were used for synthesis of compounds.

STEP :1

SYNTHESIS OF 2-GLYCYL ISOINDOLE-1,3 DIONE

Weighed equimolecular quantity of pthalic anhydride and glycine in a beaker were kept in a heated sand bath (180-185^{0}C). The melted mixture was stirred continually during the first five minutes and any solid Pthalic anhydride which sublimed into the melted reaction mixture till there was complete fusion occurs. The melted mixture was kept aside, undisturbed for 5 minutes observe the liquid mass solidified. The white solid obtained was then recrystallized from ethanol.(16)

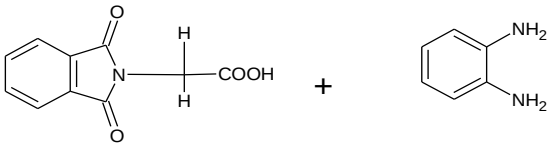


(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)acetic acid

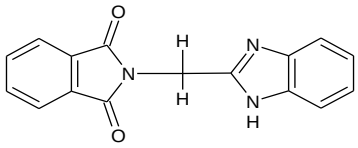
STEP:2

SYNTHESIS OF 2-METHYL BENZIMIDAZOLYL -ISOINDOLE-1, 3-DIONE

The 0.1 molar quantity of (1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)acetic acid and 0.1 molar of orthophenylene diamine were refluxed in 30 ml of 4N HCl for two hours. The solution was cooling gave a precipitate which was filtered with ice cold water, dried and then recrystallised from ethanol.(11)



(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)acetic acid benzene-1,2-diamine

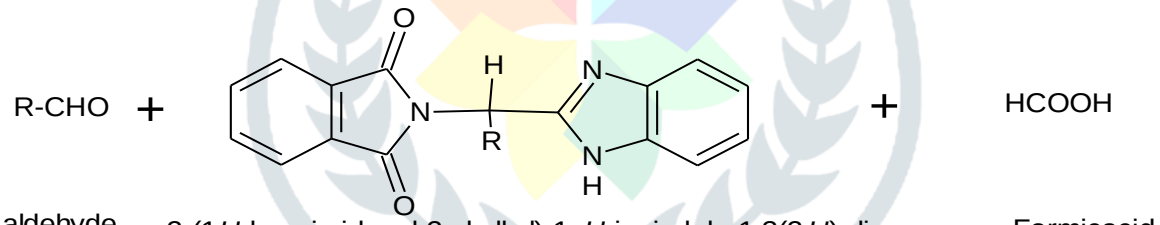


2-(1*H*-benzimidazol-2-ylmethyl)-1*H*-isoindole-1,3(2*H*)-dione

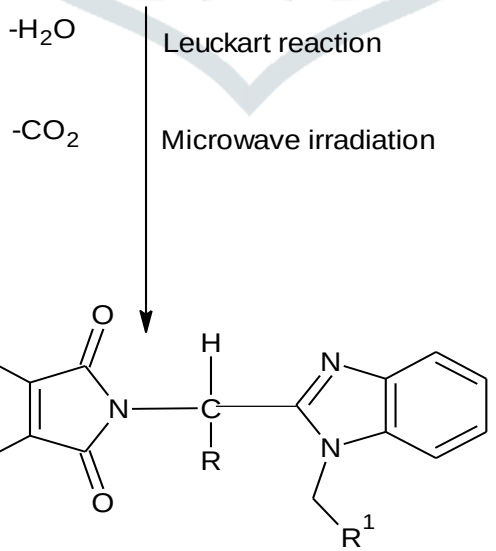
STEP:3

SYNTHESIS OF 2-{[1-(4-ARYL)-1*H*-BENZIMIDAZOL-2-YL] METHYL}-1*H*-ISOINDOLE-1,3(2*H*)-DIONE

Aldehyde (0.1M) and 2-(1*H*-benzimidazol-2-ylmethyl)-1*H*-isoindole-1,3(2*H*)-dione(0.1M) and formic acid(0.1M)) was irradiated in microwave at 80◦C for 5minutes in equimolar quantities. The solution was obtained and then cooled in ice bath until the crystals are formed. The crude product was obtained and washed with ice cold water and air dried.(19)



aldehyde 2-(1*H*-benzimidazol-2-yl alkyl)-1 *H*-isoindole-1,3(2*H*)-dione Formicacid



2-{[1-(4-aryl)-1 *H*-benzimidazol-2-yl]alkyl}-1 *H*-isoindole-1,3(2*H*)-dione

R_1
C6H5-Cl,
C6H5OCH3,
C6H5-OH,
C6H5-NCH3
C4H4O

SPECTRAL DATA OF SYNTHESIZED COMPOUNDS

JV1 Compound 2-{[1-(4-chlorobenzyl)-1*H*-benzimidazol-2-yl] methyl}-1*H*-isoindole-1,3(2*H*)-dione

IR: C-H str (Ar)3047 cm^{-1},C=C str (Ar)1547 cm^{-1}, N-C= O str 1717 cm^{-1},C=N str1603 cm^{-1},C- N str1217 cm^{-1},$^{1}CH_2$str2849 cm^{-1},C-H bend1458 cm^{-1}, Ar-Cl623 cm^{-1}
1HNMR(DMSO,80MHz,$^{\delta}$,ppm: m,8H ArH 7.6,d,4H2NCH_2 4.6, m,4H ArH 7.8
MASS (m/e):401.84
JV2 Compound 2-{[1-(4-methoxybenzyl)-1*H*-benzimidazol-2-yl] methyl}-1*H*-isoindole-1,3(2*H*)-dione

IR:C-H str (Ar)3049 cm^{-1},C=C str (Ar)1508 cm^{-1},^{N}-C= O str1763 cm^{-1},C=N str1609 cm^{-1},C- N str1248 cm^{-1},CH_2str2876 cm^{-1},C-H bend 1439 cm^{-1},$OCH_3$2837 cm^{-1}
1HNMR(DMSO,80MHz,$^{\delta}$,ppm: m,8H ArH 7.7,d,4H2NCH_2 4.9, m,4H ArH 7.8, s,3H OCH_3 6.6
MASS (m/e):397.42
JV3 Compound 2-{[1-(2-hydroxybenzyl)-1*H*-benzimidazol-2-yl] methyl}-1*H*-isoindole-1,3(2*H*)-dione

IR:C-H str (Ar)3032 cm^{-1},C=C str (Ar)1587 cm^{-1},N-C= O str1772 cm^{-1},C=N str1454 cm^{-1},C- N str1244 cm^{-1},CH_2str2939 cm^{-1},C-H bend 1436 cm^{-1},OH 3593 cm^{-1}
1HNMR(DMSO,80MHz,$^{\delta}$,ppm: m,8H ArH 7.7,d,4H2NCH_2 4.4, m,4H ArH 7.8, s 1H OH 4.9
MASS (m/e):383.39
JV4 Compound 2-{[1-(4-dimethylaminobenzyl)-1*H*-benzimidazol-2-yl] methyl}-1*H*-isoindole-1,3(2*H*)-dione

IR:C-H str (Ar)3030 cm^{-1},C=C str (Ar)1535 cm^{-1},^{N}-C= O str1711 cm^{-1},C=N str1604 cm^{-1},C- N str1271 cm^{-1},CH_2str2934 cm^{-1},C-H bend 1425 cm^{-1},$N(CH_3)_2$1385cm^{-1}
1HNMR(DMSO,80MHz,$^{\delta}$,ppm: m,8H ArH 7.6,d,4H2NCH_2 4.4, m,4H ArH 7.8,s6H $N(CH_3)_2$ 2.2
MASS (m/e):410.46
JV5 Compound 2-{[1-(furan-2-ylmethyl)-1*H*-benzimidazol-2-yl] methyl}-1*H*-isoindole-1,3(2*H*)-dione

IR:C-H str (Ar)3049 cm^{-1},C=C str (Ar)1510 cm^{-1},^{N}-C= O str1775 cm^{-1},C=N str1630 cm^{-1},C- N str1215 cm^{-1},CH_2str2853 cm^{-1},C-H bend 1425 cm^{-1},CO 1273 cm^{-1}
1HNMR (DMSO,80MHz,$^{\delta}$,ppm: m,8H ArH 7.5,d,4H2NCH_2 4.5, m,3H ArH 7.8
MASS (m/e):357.36

PHYSICAL DATA ANALYSIS
Table No: 1

COMPOUD CODE	SOLUBILIY	APPEARANCE/ COLOUR	PERCENGE YIELD
JV1	$CHCl_3$, DMSO	SOLID/PALE YELLOW	73.56%
JV2	$CHCl_3$, DMSO	SOLID/ ORANGE	67.50%
JV3	$CHCl_3$, DMSO	SOLID/PALE YELLOW	71.27%
JV4	$CHCl_3$, DMSO	SOLID/RED	75.60%
JV5	$CHCl_3$, DMSO	SOLID/BLACK	58.26%

THE MELTING POINT OF SYNTHESIZED COMPOUNDS

TABLE NO: 2

S.NO	COMPOUND	MELTING POINT ^{0}C
1	JV1	248
2	JV2	256
3	JV3	244
4	JV4	240
5	JV5	247

Rf VALUE OF SYNTHESISED COMPOUNDS

Table No:3

COMPOUND CODE	R_f VALUE
JV1	0.55
JV2	0.60
JV3	0.44
JV4	0.43
JV5	0.37

BIOLOGICAL EVALUATION

ANTIBACTERIAL ACTIVITY

The microbial assay is based upon a comparison of the inhibition of growth of microorganism. Antibacterial activity of various synthesized compounds was studied by the presence of zone of inhibition using disc diffusion method.All the compounds were used in the concentration of 50,100µg/ml using a solvent DMSO.

Details of micro organism

Table No: 4

S.NO	ORGANISM	Gram+Ve/ Gram –Ve
1	Klebsiella pneumonia	-Ve
2	Staphylococcus aureas	+Ve

SOLVENT USED

DMSO

STANDARD USED

Amikacin in the concentration of 50, 100µg/ml.

PREPARATION OF MULLER HINTON AGAR

Composition

Beef extract - 10 g
Casein acid hydrosylate - 17.5 g
Starch - 1.5 g
Agar - 20 g
Water - 1000 ml

Procedure

The constituents are dissolved in distilled water and the pH was adjusted to 7.2, then the medium was sterilized in an autoclave at 121°C for 15 minutes and it was used for the bacterial inoculation.

ANTIBACTERIAL ACTIVITY (By disc diffusion method)

Muller-Hinton agar medium was prepared and transferred into sterile petri plates aseptically with the thickness of 5 – 6mm.The plates were allowed to dry at room temperature and were inverted to prevent condensate falling on the agar surface. Uniform thickness of the medium was obtained by placing the plates on leveled surface.

Standardized bacterial inoculums were applied to the plates and spread uniformly over the surface of the medium by using a sterile non – absorbent cotton swap and finally the swap was passed around the edge of the medium. The inoculated plates were closed with the lid and allow drying at room temperature.

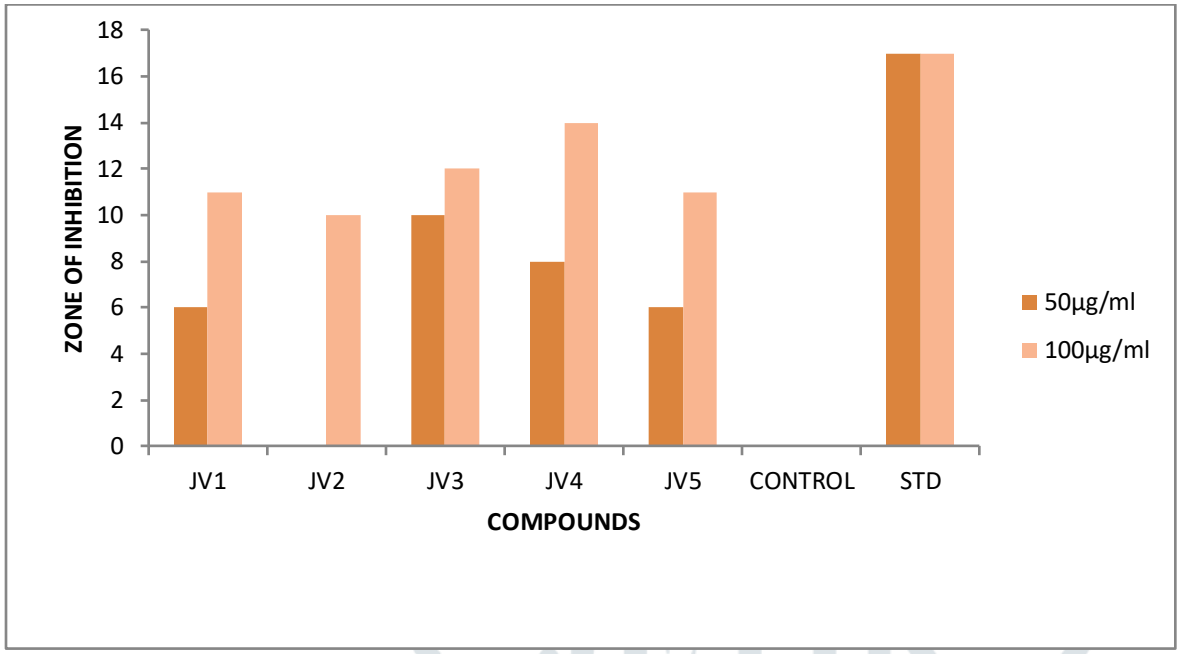
The sample impregnated discs were placed on the inoculated agar medium. All petriplates were incubated at 37°C for 24 hours. After incubation, diameter of zone of inhibition produced by the sample was measured and reading observed in millimeter.

ANTIBACTERIAL ACTIVITY AGAINST BACTERIA

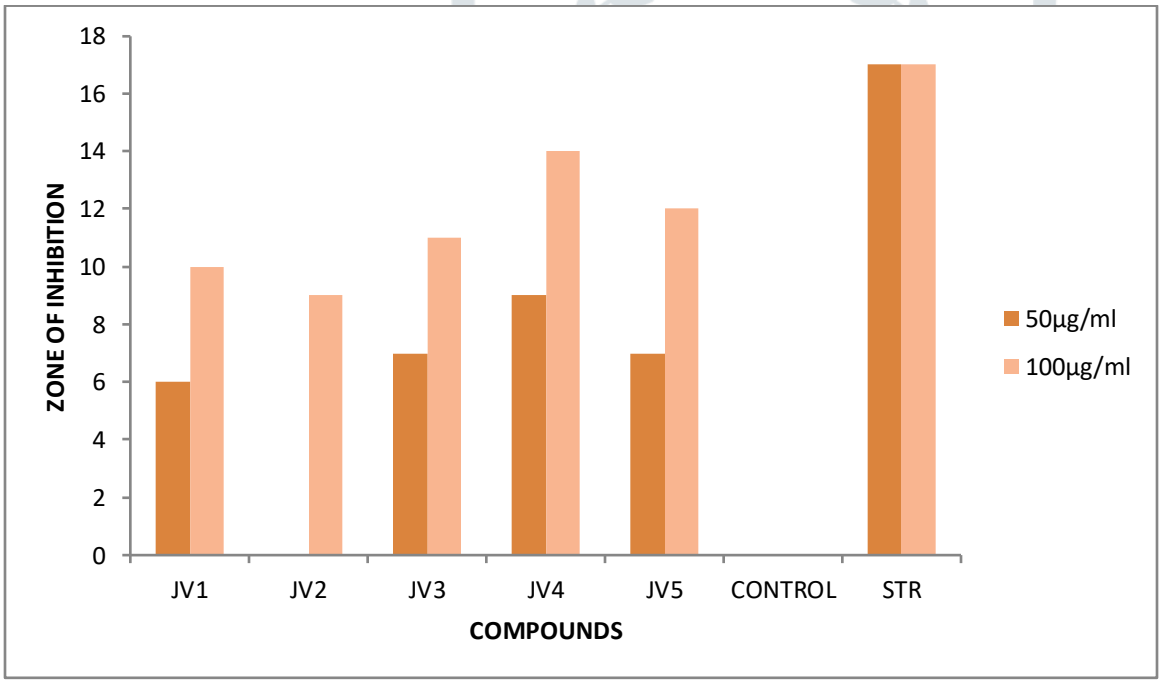
Table No: 5

COMPOUND CODE	**ZONE OF INHIBITION IN MM**			
	KLEBSIELLA PNEUMONIA		STAPHYLOCOCCUS AUREAS	
	150µg/ml	300µg/ml	150µg/ml	300µg/ml
JV1	6	11	6	10
JV2	R	10	R	9
JV3	10	12	7	11
JV4	8	14	9	14
JV5	6	11	7	12
CONTROL	R	R	R	R
STD	17		17	

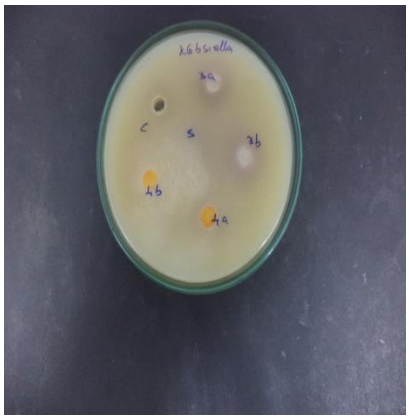
ANTIBACTERIAL ACTIVITY AGAINST KLEBSIELLA PNEUMONIA

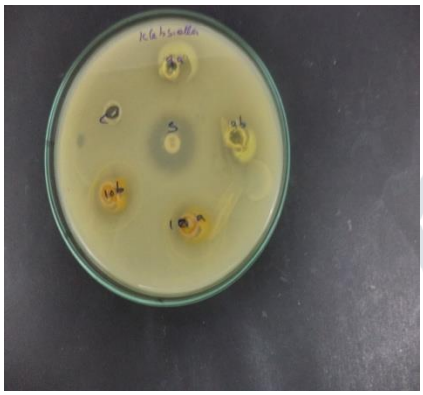
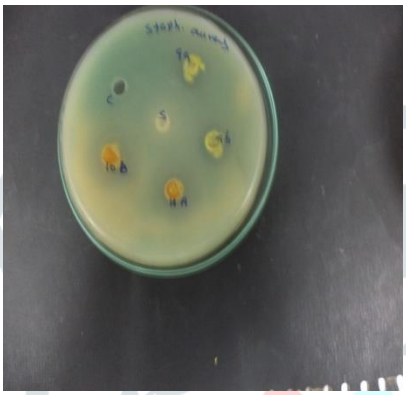


ANTIBACTERIAL ACTIVITY AGAINST STAPHYLOCOCCUS AUREAS



ANTIBACTERIAL ACTIVITY OF COMPOUNDS-JV4,J5



RESULT AND DISCUSSION

The structure, and properties of synthesized compounds were determined by using

various software such as chemdraw and chemsketch. The compounds JV1-JV5were synthesized by using microwave irradiation. The compounds were synthesized by "Leuckart reaction" which shows good percentage yield, melting point and solubility of the compounds are determined and shown in **Table no:1,&2**.The compounds are monitored by TLC and R_f value was calculated and shown in **Table no:3**.The compounds were confirmed by spectral analytical data. The Antibacterial activity of various synthesized compounds was studied by the presence of zone of inhibition using disc diffusion method.All the compounds were used in the concentration of 50,100µg/ml using a solvent DMSO.The results of antibacterial activity were shown in Table no:5. All the synthesized compounds showed comparable activity with standard amikacin drug.

CONCLUSION

Synthetic work: The present study describes the synthesis of benzimidazole with isoindoline derivatives by leuckart reaction using microwave irradiation. The reaction having lesser time reaction and yield higher percentage of products. All synthesized compounds were found to be good antibacterial activity. The furfuraldehyde, dimethyl amino benzaldehyde substituted synthesized compounds JV4, JV5 having good antibacterial activity as compared to standard drug Amikacin.

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