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"Synthesis, Characterization and Biological Evaluation of Some Benzimidazole Derivatives For Anti-Tubercular Activity."

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Abstract:

This research presents the synthesis, characterization, and biological evaluation of a series of novel benzimidazole derivatives designed as potential anti-tubercular agents. Tuberculosis (TB) remains a global health threat, necessitating the development of new and effective treatments. The study involved the design and synthesis of various benzimidazole derivatives, followed by their structural characterization using spectroscopic techniques such as NMR, IR, and mass spectrometry. Subsequently, the synthesized compounds were subjected to a comprehensive biological evaluation to assess their anti-tubercular activity using in vitro and in vivo models. The results indicate promising anti-tubercular potential for several of the synthesized benzimidazole derivatives, offering a foundation for further optimization and development of novel TB therapeutics.

Keywords: Benzimidazole derivatives, Biological evaluation, Anti-tubercular activity, Tuberculosis, NMR spectroscopy, Infrared spectroscopy, Mass spectrometry, Drug development

INTRODUCTION-

The study of carbon-containing molecules' structure, characteristics, content, reactions, and synthesis is known as organic chemistry. In addition to carbon andhydrogen, which make up the majority of organic molecules, other elements suchas nitrogen, oxygen,halogens, phosphorus, silicon, and sulphur may also be present[1].

What is the origin of organic chemistry? The term "organic chemistry" was first used in about 1807, when Swedish chemist Jöns Jacob Berzelius introduced it toexplain the study of compounds derived from the living resources available in nature[2].

Chemical engineers can design and investigate new molecules and compounds thanks to the very creative field of

organic chemistry. The majority of an organicchemist's time is spent creating new chemicals and improving the synthesis of already existing ones[3]. We are surrounded by organic substances. Many contemporary materials contain organic chemicals, at least in part. In addition to being fundamental to the fields of biochemistry, biotechnology, and medicine, they are essential to economic growth. Agrichemicals, coatings, cosmetics, detergent, dyestuff, food, gasoline, petrochemicals,medicines, plastics, and rubber are a few examples of products where you can find organic compounds.

Identification, synthesis, and development of novel chemical entities fit for therapeutic use are all part of medicinal chemistry. It also covers research on currently available medications, their biological characteristics, and quantitativestructure-activity correlations (QSAR)[4].

In order to find better and more effective medications, the field of medicinal chemistry integrates various chemical and biology subfields (Drug Discovery). Characterisation (analytical data) and synthesis (semi-synthesis/total synthesisemploying retro-analytical technique) of novel compounds (leads).

The creation of novel pharmacological drugs, from concept to clinic, is a component of medicinal chemistry. Design and synthesis of innovative drug candidates, as well as their biochemical effects, testing procedures, and regulatoryand ethical issues, are just a few of the many stages that are involved[5].

TUBERCULOSIS-

The illness known as tuberculosis (TB) is brought on by microbes that travel from person to person through the air. Although TB often affects the lungs, it can also harm other organs like the brain, kidneys, or spine. If a person with TB is not treated, they risk dying[6].

Mycobacterium tuberculosis is the bacteria that causes tuberculosis. People who have active TB disease in their voice box or lungs can transfer the infection. Theyexpel microscopic droplets into the air, which transmit the germs. This may take place as they speak, sing, laugh, cough, or sneeze.

Tuberculosis: Types

- Active TB Disease. Active TB is an illness in which the TB bacteria are rapidly multiplying and invading different organs of the body. ..
- Miliary TB. Miliary TB is a rare form of active disease that occurs when TBbacteria find their way into the bloodstream. ..
- Latent TB Infection.

Feelings of sickness or weakness, weight loss, a fever, and night sweats are all common signs of TB disease. Chest pain, bloody coughing, and coughing up debris are other signs of TB lung disease. The location of the infection determinesthe symptoms of TB disease in different body areas.

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Causes of tuberculosis (TB)

Tuberculosis (TB) is caused by bacteria. It can spread through close contact with people who have TB and have symptoms (active TB).

When someone with active TB coughs, they release small droplets containing the bacteria. You can catch TB if you regularly breathe in these droplets over a long period of time.

Some people have TB in their body but do not get ill or have any symptoms (latent TB). This type of TB cannot be spread to others, but it can turn into activeTB in the future.

Treatment for tuberculosis (TB)

Taking medicines for at least six months is the major treatment for tuberculosis.

You might also need to take steroid medication for a few weeks if TB has gone to your brain, spinal cord, or the region around your heart.

You often need to take antibiotics for 3 to 6 months if you have latent TB, which isTB in which there are no symptoms[7]

EXPERIMENTAL –

MATERIALS –

Chemicals -

- Ortho-phenylene diamine,
- 4-Bromobenzaldehyde,
- 2,3-Dihydroxybenzaldehyde,
- Ortho-chlorobenzaldehyde,
- Potassium-Ferrocyanide,

Apparatus -

- Mortar-pestle
- Beaker
- Stirrer
- Pipette

- Petri-plate
- TLC- plate

Instruments -

- Weighing balance
- Hot Air Oven

Characterization studies-

By using physical and chemical factors including melting point, solubility, chemical test, elemental analysis, etc., the newly synthesised substance was discovered. A brief summary of the additional analytical techniques used to characterise the newly

synthesised molecule is provided below, including TLC, IR, NMR, and massspectroscopy.

Thin layer chromatography-

Thin layer chromatography is an analytical technique in which the mobile phase, a liquid,is allowed to migrate across the plate's surface while the stationary phase, a finely split solid, is spread over a thin layer on a rigid plate.

The method is frequently used to identify chemical compounds having distinctive RF values. This approach is also used to monitor the reaction's development and check the final product's purity. The following solvents were used: acetone:chloroform(1:1), methanol:chloroform(1:9), prepared silica gel plates, etc. served as the mobile phase. Placing the plate in an iodine chamber allowed the spot to be found after the chromatogram had developed. Each compound's RF value was estimated using a formula.

RF=Distance traveled by the compound frontDistance traveled by the solvent front

Infrared spectral studies-

One of the most crucial methods for identifying different functional groups and potentialchemical structures is infrared spectroscopy. The main advantage of IR over other techniques is that it can quickly provide fingerprint (1300-650cm) information about the structure of molecules, including information about function groups and molecular interactions. There are no two compounds with the same fingerprint region. The method is based on the fact that every bond in a chemical vibrates at a particular frequency, andthatthis frequency corresponds to the IR frequency that the FTIR measures.

Mass spectral studies-

Mass spectroscopy is a crucial method for figuring out the molecular weight of unidentified molecules.

Nuclear magnetic resonance spectra-

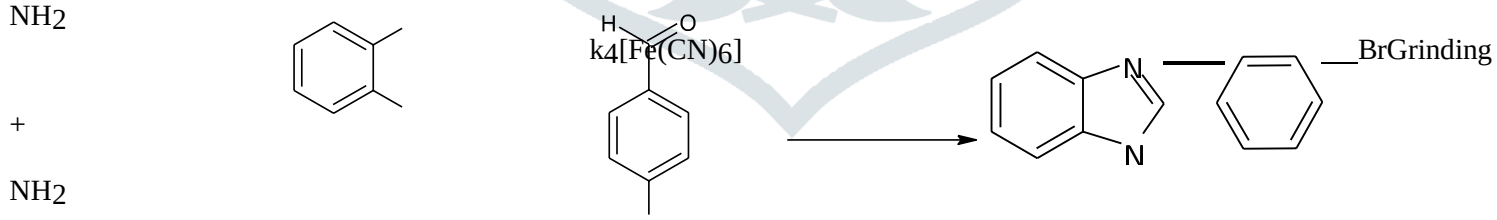
By concurrently exposing a substance to two magnetic fields, it is possible to examine how electromagnetic forces interact with matter. One is stable while the other changes ata ratio frequency. Energy is absorbed by the sample at a certain combination of field, and absorption can be seen as a change in single developed by a ratio frequency detector and amplifier. The spinning nuclei's magnetic dipolar character may be related to this energy absorption. The methods are helpful for studying the unspectral structure of compounds that have been synthesised.

METHODS-

SYNTHESIS-

Compound – 01

A mixture of substituted O-PD (1.08 gm), 4-Bromobenzaldehyde (1.85 gm), and Potassium-Ferrocyanide (0.42 gm) was crushed in a mortar with a pestle at room temperature for 1 hour, and was monitored by TLC.

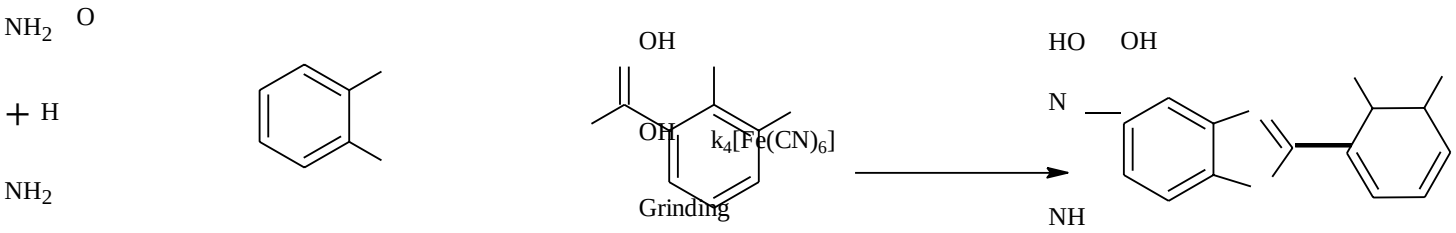


Br

Ortho-

Phenylenediamine 4-bromobenzaldehyde 2-(4-bromophenyl)-1*H*-1,3-benzimidazole

A mixture of substituted O-PD (1.08gm), 2,3-Dihydroxybenzaldehyde (1.38 gm) andPotassium-Ferrocyanide (0.42 gm) was crushed in a mortar with a pestle at roomtemperature for 1 hour, and was monitored by TLC.



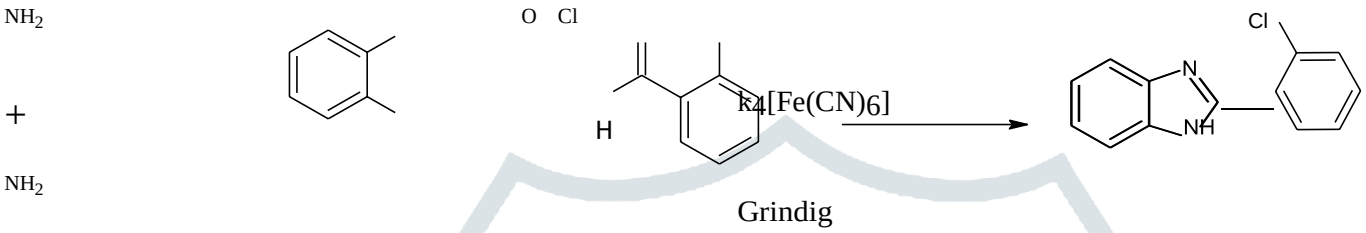
Ortho- Phenylenediamine

2,3-Dihydroxy-benzaldehyde

3-(1*H*-1,3-benzimidazol-2-yl) benzene-1,2-diol

Compound – 03

A mixture of substituted O-PD (1.08 gm), Ortho-chlorobenzaldehyde (1.40 gm), andPotassium-Ferrocyanide (0.42 gm) was crushed in a mortar with a pestle at roomtemperature for 1 hour, and was monitored by TLC.



Ortho-Phenylenediamine Ortho-Chlorobenzaldehyde 2-(2-chlorophenyl)-1*H*-1,3-benzimidazole

Table 01- Physicochemical data of synthesized benzimidazole derivatives-

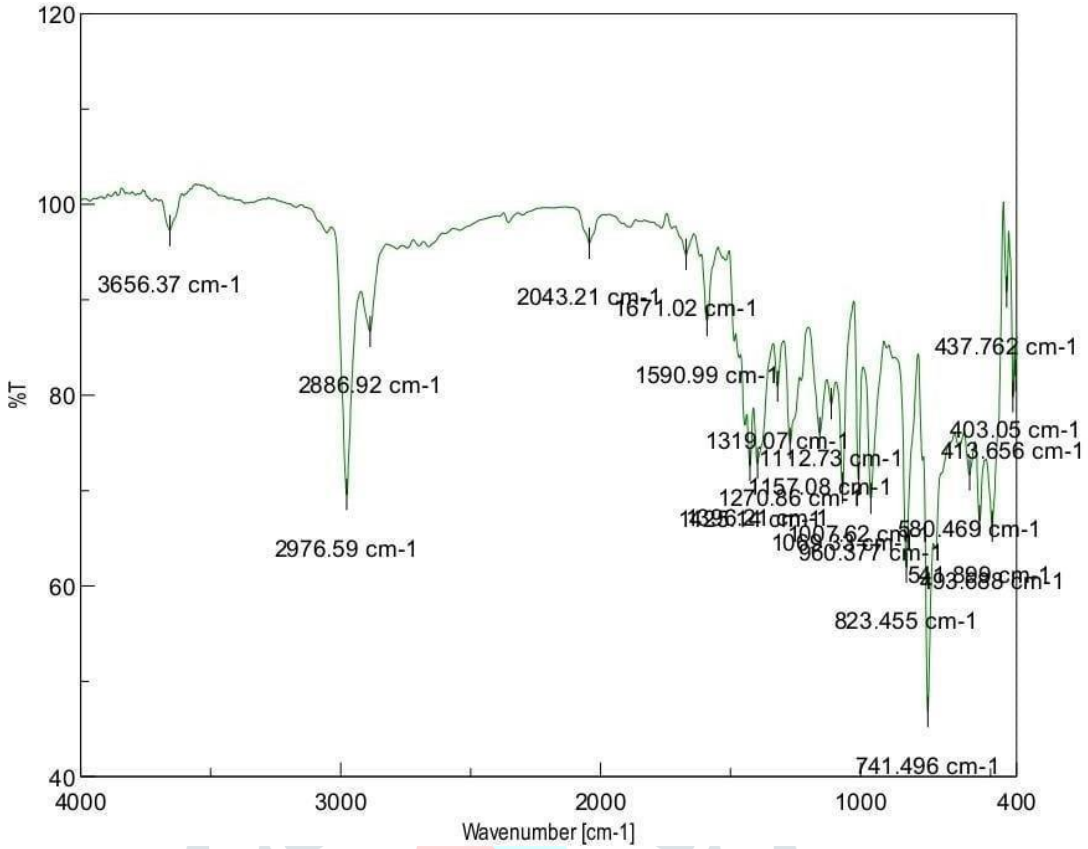
SR.NO.	Compound Code	Nature	Colour	Solubility	Molecular Formula	Molecular Weight
01.	C1	Solid	Off-White	Methanol, Acetone	$C_{13}H_9N_2Br$	272.9 g/mol
02.	C2	Solid	Brown	Methanol, Acetone	$C_{13}H_{10}N_2O_2$	226.23 g/mol
03.	C3	Solid	Yellow-White	Methanol, Acetone	$C_{13}H_9N_2Cl$	228.68 g/mol

Table 02- Physicochemical data of synthesized benzimidazole derivatives-

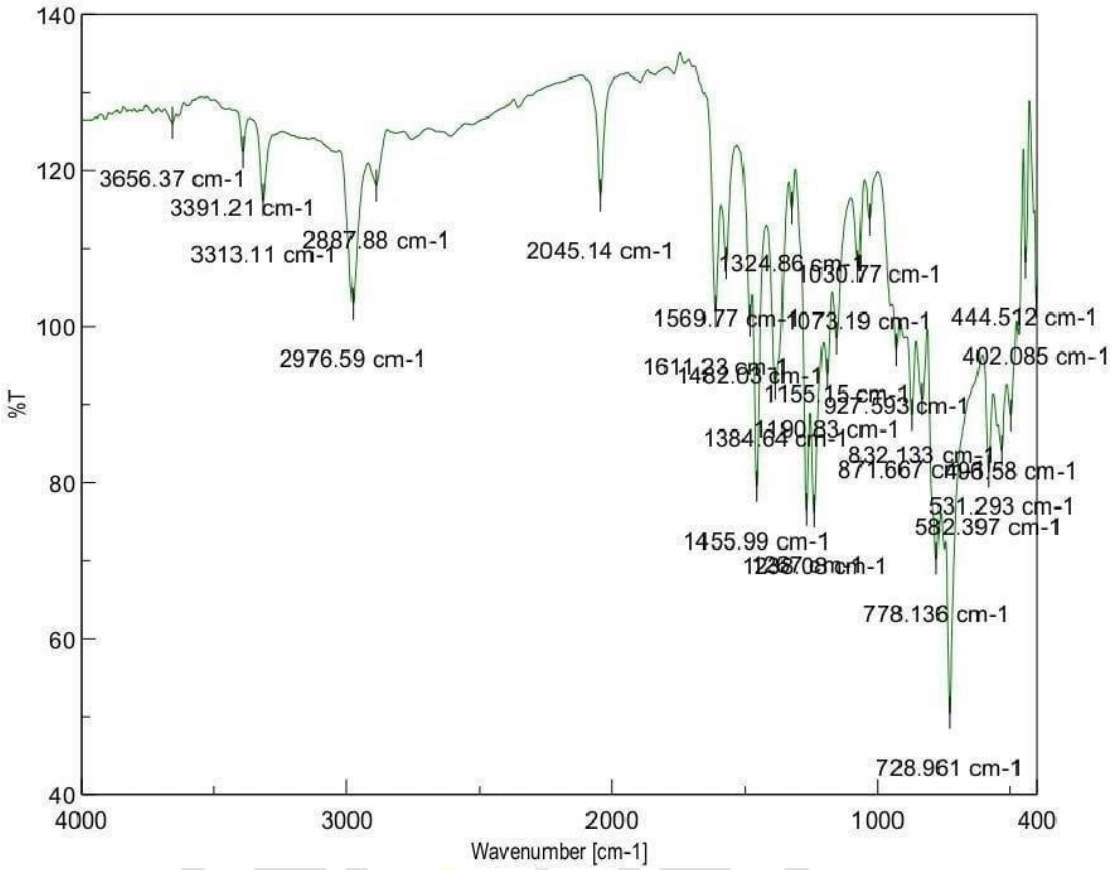
SR.NO.	Compound Code	RF- Value	M.P.(°C)	B.P.(°C)	Yeilds %
01.	C1	0.77	265°C	390.8±25.0°C	72%
02.	C2	0.706	247-250°C	418.1±28.0°C	89%
03.	C3	0.68	71-72°C	435.6±25.0°C	56%

SPECTRAL DATA- INFRARED SPECTROSCOPY-

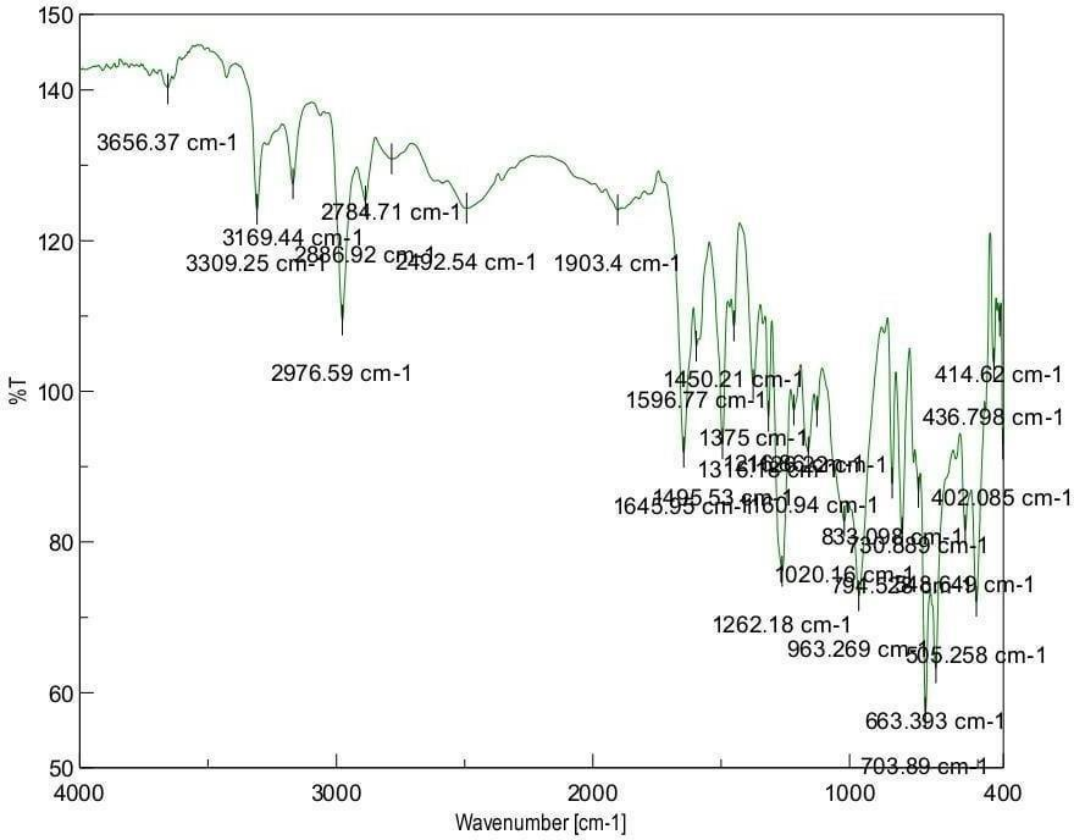
C1- 2-(4-bromophenyl)-1H-1,3-benzimidazole.


120
100
80
60
40
%T
4000
3000
2000
1000
400
Wavenumber [cm-1]
3656.37 cm-1
2886.92 cm-1
2976.59 cm-1
2043.21 cm-1
1671.02 cm-1
1590.99 cm-1
1319.07 cm-1
1112.73 cm-1
1157.08 cm-1
1270.86 cm-1
1007.62 cm-1
960.377 cm-1
823.455 cm-1
741.496 cm-1
580.469 cm-1
437.762 cm-1
403.05 cm-1
413.656 cm-1

C2- 3-(1H-1,3-benzimidazole-2-yl)benzene-1,2-diol .



C3- 2-(2-chlorophenyl)-1H-1,3-benzimidazole .



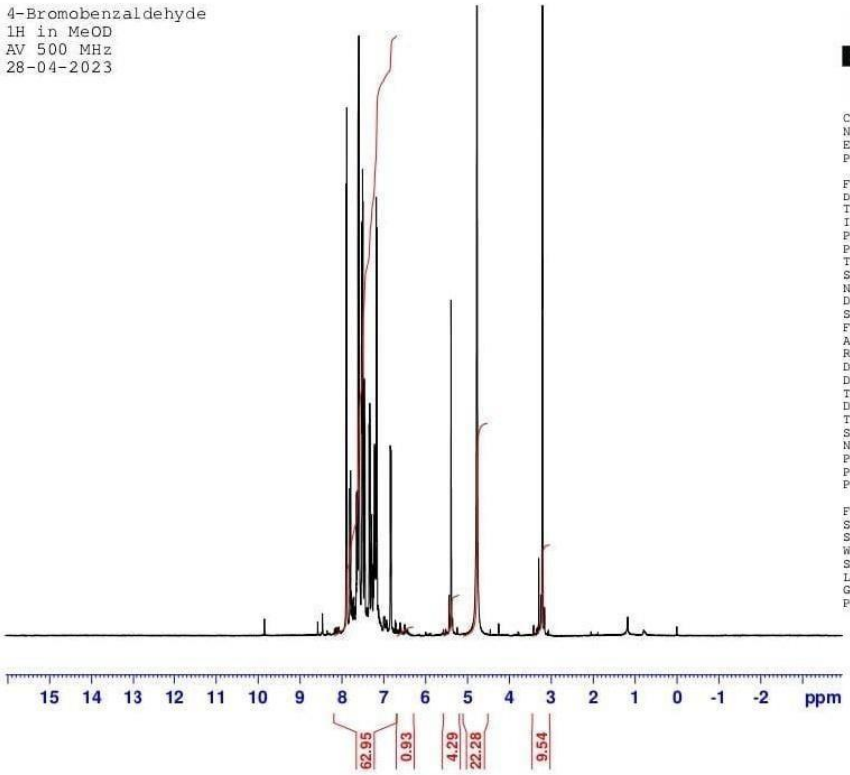
INFRARED SPECTROSCOPY DATA-

Table No. 03-

Code.	Type Of Vibration.	Observed Value(cm-1)
C1	C=C Stretch C-H Stretch NO_2 Stretch C-Br Stretch	1590.99 cm-1 2886.92 cm-1 1317.07 cm-1 <700
C2	C=C Stretch C-H Stretch N-H Stretch C-OH Stretch	1569.77 cm-1 2887.88 cm-1 3313.11 cm-1 3391.21 cm-1
C3	C=C Stretch C-H Stretch N-H Stretch C-Cl Stretch	1450.21 cm-1 2886.92 cm-1 3309.25 cm-1 703.89 cm-1

NMR SPECTROSCOPY –

C1- 2-(4-bromophenyl)-1H-1,3-benzimidazole.



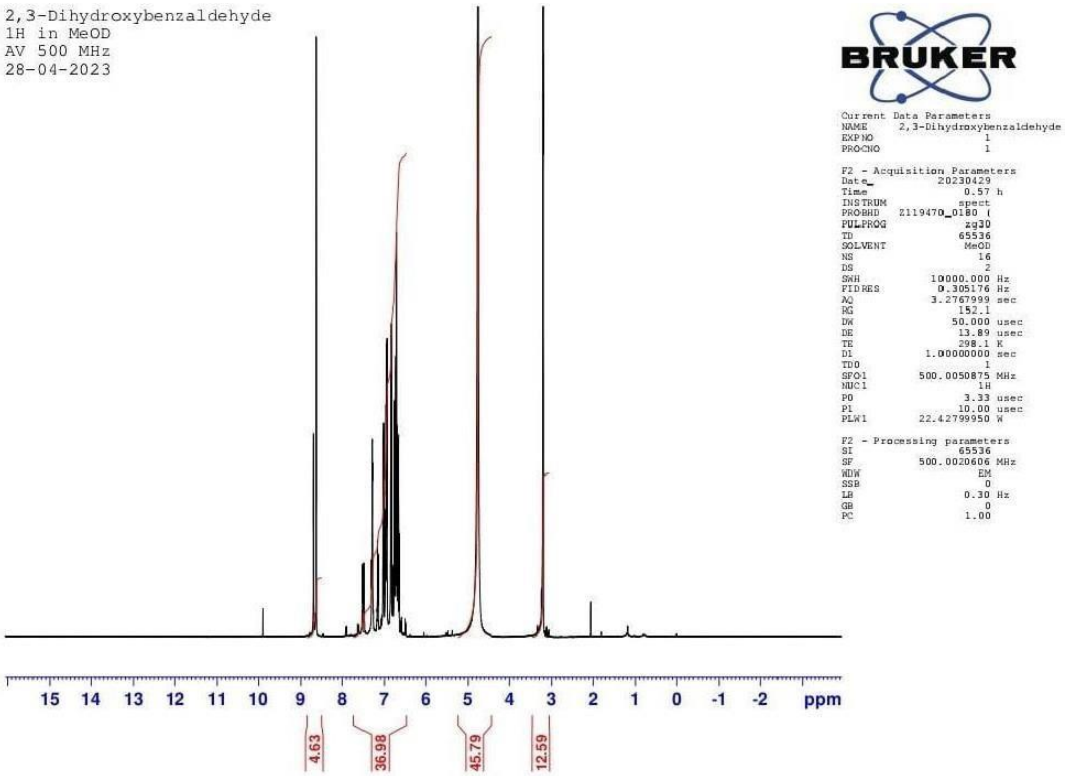
BRUKER

Current Data Parameters
NAME 4-Bromobenzaldehyde
EXPNO 1
PROCNO 1

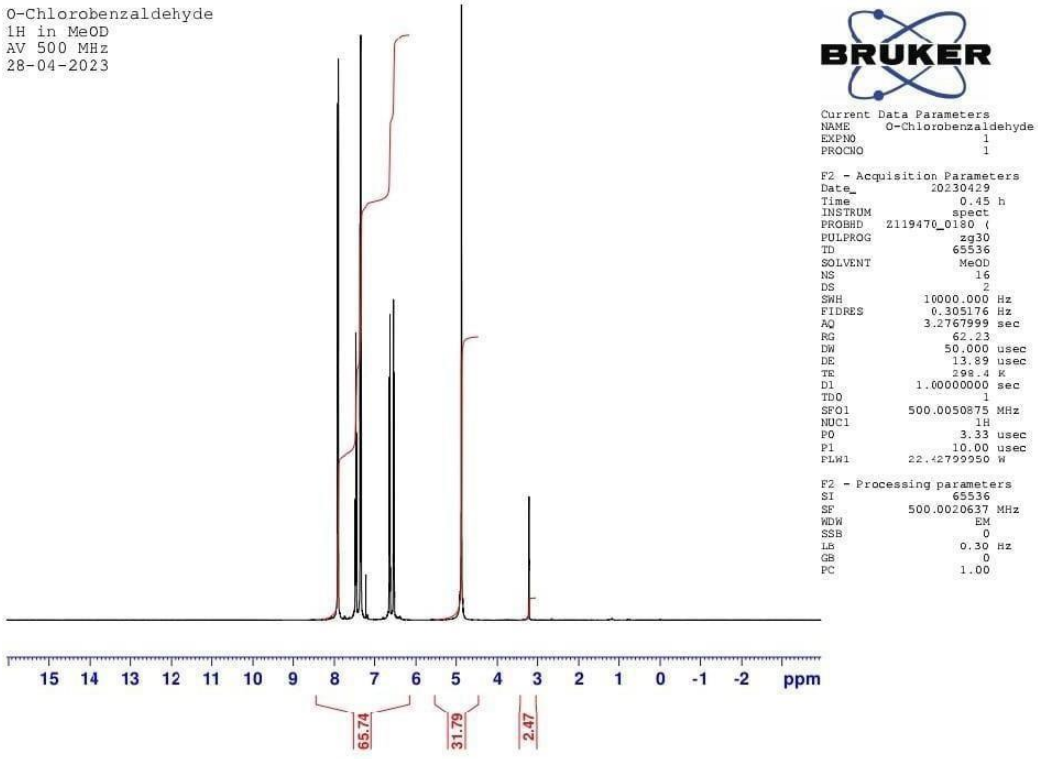
F2 - Acquisition Parameters
Date_ 20230429
Time 0.51 h
INSTRUM spect
PROBHD Z119470_0180 (
PULPROG zg30
TD 65536
SOLVENT MeOD
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767599 sec
RG 138.5
DW 50.000 usec
DE 13.89 usec
TE 298.2 K
D1 1.00000000 sec
TD0 1
SFO1 500.0050875 MHz
NUC1 1H
P0 3.33 usec
P1 10.00 usec
PLW1 22.42799550 W

F2 - Processing parameters
SI 65536
SF 500.0020605 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

C2- 3-(1H-1,3-benzimidazole-2-yl)benzene-1,2-diol.



C3- 2-(2-chlorophenyl)-1H-1,3-benzimidazole .



BRUKER

Current Data Parameters
NAME O-Chlorobenzaldehyde
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20230429
Time 0.45 h
INSTRUM spect
PROBHD 2119470_0180 (
PULPROG zg30
TD 65536
SOLVENT MeOD
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 62.23
DW 50.000 usec
DE 13.89 usec
TE 298.4 K
D1 1.00000000 sec
TD0 1
SFO1 500.0050875 MHz
NUC1 1H
P0 3.33 usec
P1 10.00 usec
PLW1 22.42799950 W

F2 - Processing parameters
SI 65536
SF 500.0020637 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

NMR SPECTROSCOPY DATA-

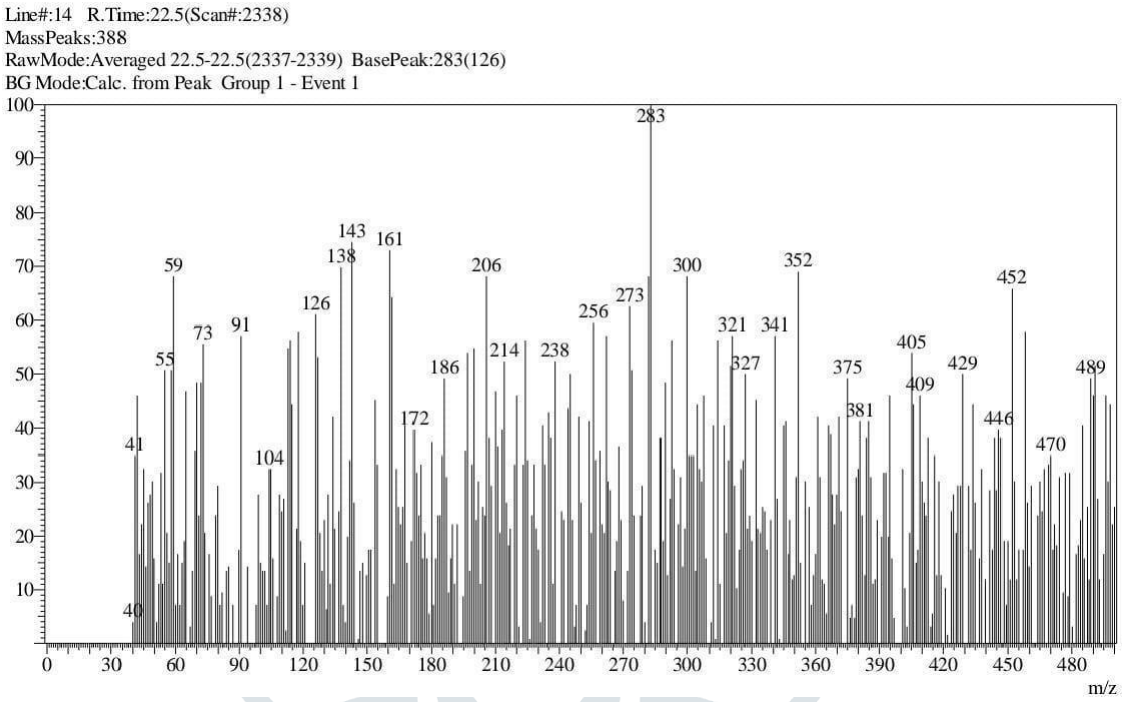
Table No. 04

Compound Code.	Observed Value In PPM.	Type Of Proton.
C1.	1-3 PPM 4-5 PPM 5-6 PPM 7-8 PPM	CH Br C=C AR-H
C2.	1.5-5.5 PPM 5-6 PPM 7-8.5 PPM	O C=C AR-H
C3.	3-4.5 PPM 1.5-5.5 PPM 7-8.5 PPM	Cl NH AR-H

MASS SPECTROSCOPY-

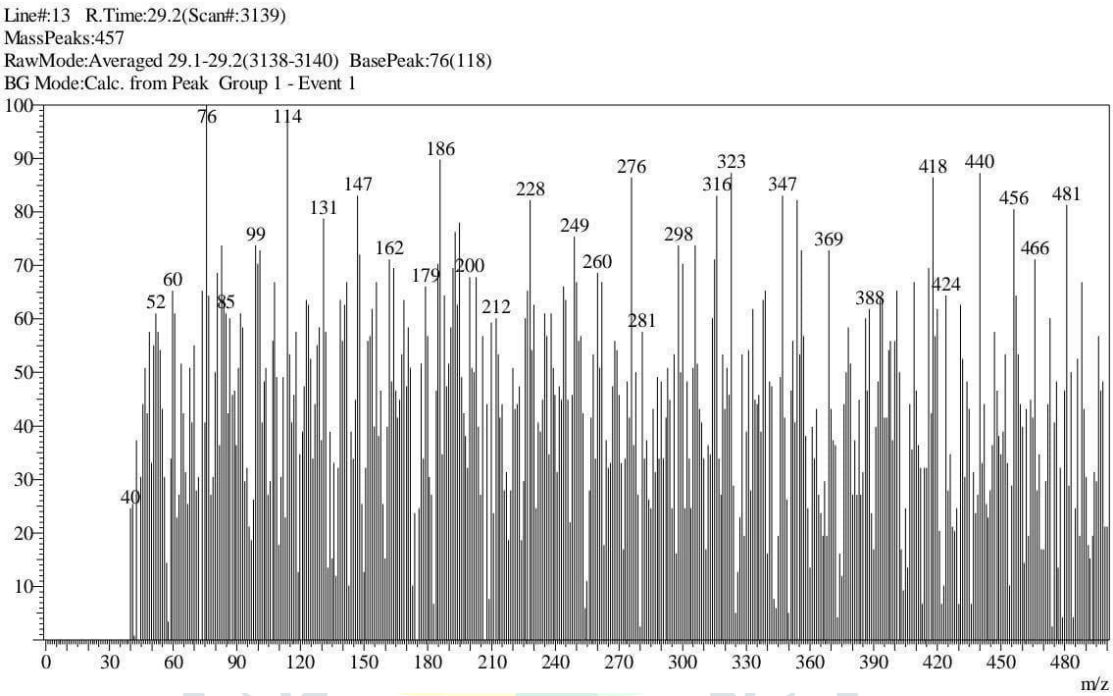
C1- 2-(4-bromophenyl)-1H-1,3-benzimidazole.

(Molecular weight-272.9 g/mol)



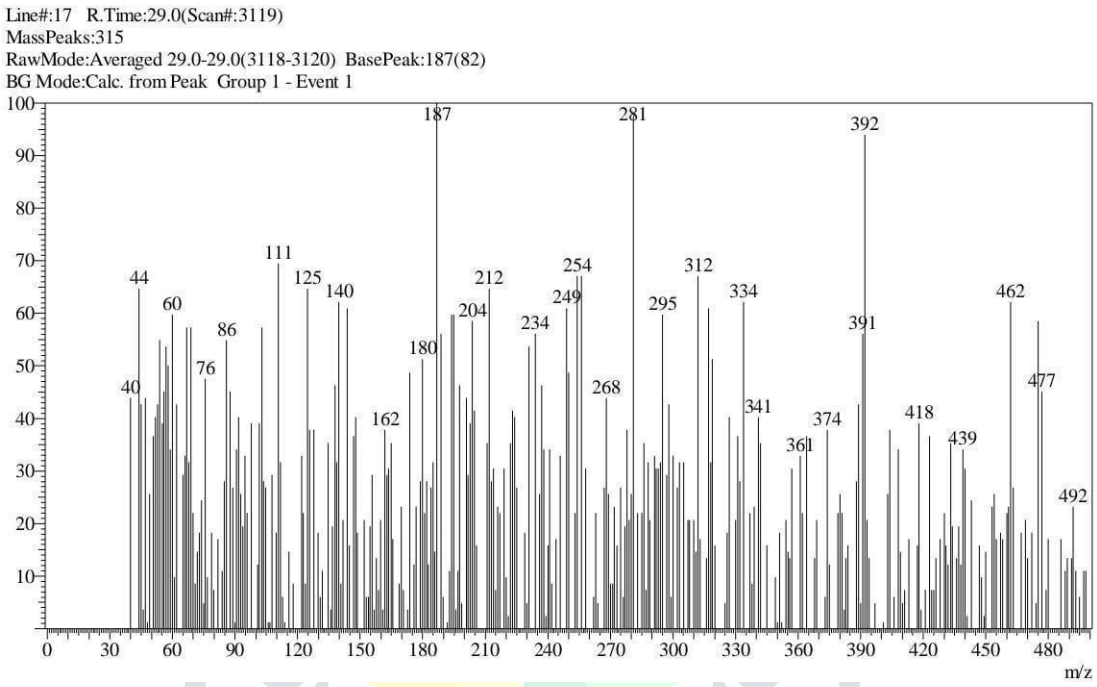
C2- 3-(1H-1,3-benzimidazole-2-yl)benzene-1,2-diol.

(Molecular weight – 226.23 g/mol)



C3- 2-(2-chlorophenyl)-1H-1,3-benzimidazole .

(Molecular weight – 228.68 g/mol)



MASS SPECTROSCOPY DATA-

Table no. – 05.

Compound	Observed Peak
C1.	273
C2.	228
C3.	234

BIOLOGICAL ACTIVITY-

Minimum Inhibitory Concentration Activity – *M. tuberculae*

Experimental Details-

Anti-Tubercular activity assay

0.5 Mcfarland Standard dilution of microbes to be used for the study. 500 µl diluted log cultures of bacteria (*M. tuberculae*, MTCC 300) was added to the micro centrifuge tube and added with 10 µl of prepared treatment dilutions of different concentrations (Mentioned in excel sheet) to the defined tubes and incubated for the 15 Days. After Incubation all content was transferred to the 96 well plate and added with MTT Solution (a final concentration of 250µg/ml) and incubated for 24 hours. After incubation, reading was taken by Elisa Plate Reader (iMarkBiorad) at 490nm and 595 nm. Ciprofloxacin (100µg) was used as Positive Control

Results-

Sample Code	**IC50(µg/ml)**
1) Compound 01	Approx 0.07 µg/ml
2) Compound 02	0.1 µg/ml
3) Compound 03	Approx 0.08 µg/ml

TestName MICAssay *M. tuberculae*
Sample ID Sample 1 Compound 01
GraphTitle MIC Assay-M. tuberculae-Sample 1
X Title Concentration (µg/ml)
Y Title Percentage Inhibition wrt Control

Sample Conc.	Test Replicates			
	1	2	3	4
0	1.584	1.691	1.684	1.621
0.1	0.952	0.921	0.938	0.921
1	0.87	0.815	0.787	0.881
10	0.657	0.734	0.839	0.741
100	0.538	0.526	0.542	0.513
1000	0.485	0.498	0.496	0.415
PC	0.168	0.211	0.202	0.193

Blank		
1	2	
0.035	0.037	
0.036	0.036	
0.053	0.053	
0.063	0.049	
0.021	0.018	
0.1	0.108	
0.062	0.06	

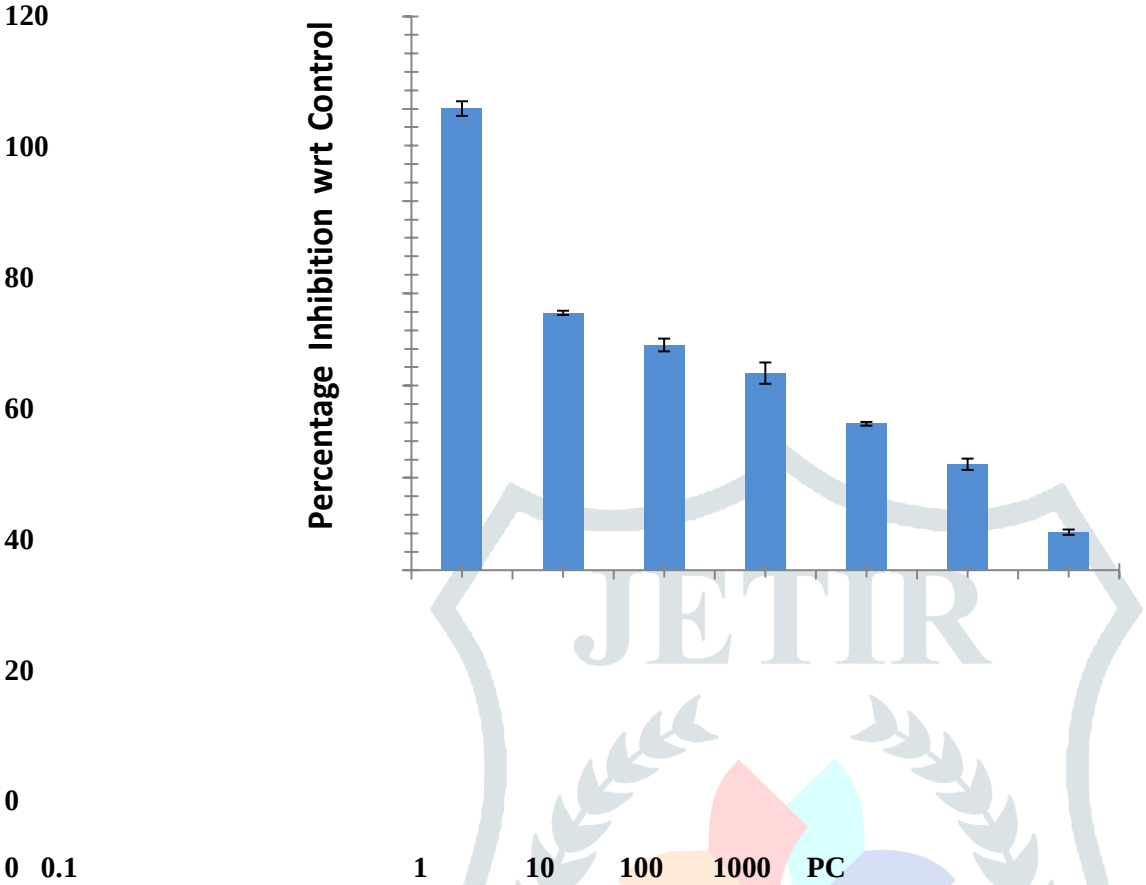
Corrected Values			
1	2	3	4
1.548	1.655	1.648	1.585
0.916	0.885	0.902	0.885
0.817	0.762	0.734	0.828
0.601	0.678	0.783	0.685
0.5185	0.5065	0.5225	0.4935
0.381	0.394	0.392	0.311
0.107	0.15	0.141	0.132

Average Values	
Blank	0
Control	1.609

	Final Replicate Values			
Sample Conc.	**1**	**2**	**3**	**4**
0	96.208825	102.8589	102.4239	98.50839
0.1	56.92977	55.00311	56.05966	55.00311
1	50.77688	47.35861	45.6184	51.46053
10	37.352393	42.13797	48.66377	42.57303
100	32.224984	31.47918	32.47359	30.67122
1000	23.679304	24.48726	24.36296	19.32878
PC	6.6500932	9.322561	8.763207	8.203853

	Status			
Sample Conc.	**Mean**	**SD**	**SEM**	**N**
0	100	3.196167	1.598083	4
0.1	55.74891	0.931565	0.465783	4
1	48.8036	2.780087	1.390044	4
10	42.68179	4.636596	2.318298	4
100	31.71224	0.812524	0.406262	4
1000	22.96457	2.449756	1.224878	4
PC	8.234929	1.151042	0.575521	4

MIC Assay-M. tuberculae-Sample 1



TestName MICAssay *M. tuberculae*
Sample ID Sample 2 Compound 02
GraphTitle MIC Assay-M. tuberculae-Sample 2
X Title Concentration (µg/ml)
Y Title Percentage Inhibition wrt Control

Sample Conc.	Test Replicates			
	1	2	3	4
0	1.349	1.4	1.419	1.473
0.1	1.194	1.187	1.152	1.186
1	0.866	0.858	0.845	0.851
10	0.831	0.798	0.797	0.837
100	0.743	0.754	0.724	0.737
1000	0.781	0.778	0.798	0.794
PC	0.206	0.219	0.209	0.208

Blank		
1	2	
0.032	0.041	
0.057	0.057	
0.04	0.04	
0.046	0.048	
0.066	0.069	
0.23	0.234	
0.059	0.07	

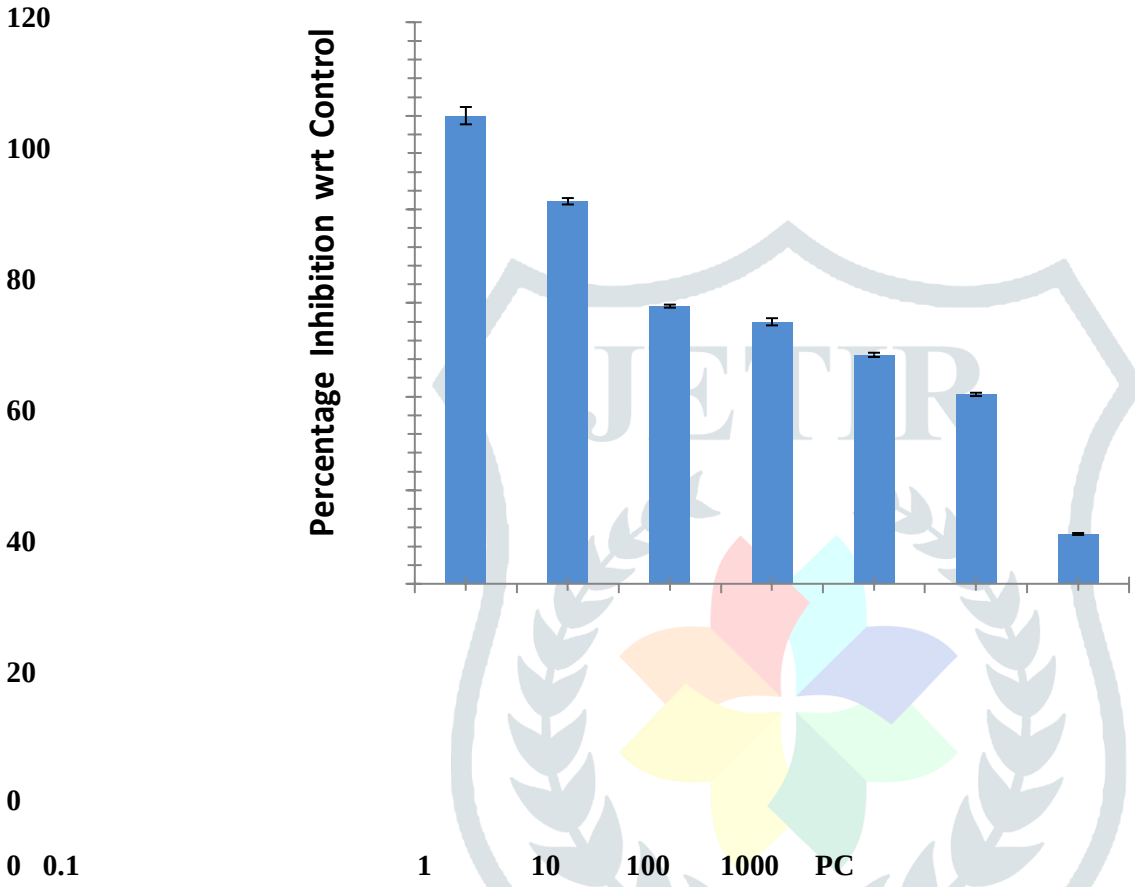
Corrected Values			
1	2	3	4
1.3125	1.3635	1.3825	1.4365
1.137	1.13	1.095	1.129
0.826	0.818	0.805	0.811
0.784	0.751	0.75	0.79
0.6755	0.6865	0.6565	0.6695
0.549	0.546	0.566	0.562
0.1415	0.1545	0.1445	0.1435

Average Values	
Blank	0
Control	1.37375

	Final Replicate Values			
Sample Conc.	**1**	**2**	**3**	**4**
0	95.541401	99.25387	100.6369	104.5678
0.1	82.766151	82.2566	79.70883	82.1838
1	60.127389	59.54504	58.59873	59.03549
10	57.070064	54.66788	54.59509	57.50682
100	49.171975	49.9727	47.7889	48.73521
1000	39.963603	39.74522	41.20109	40.90992
PC	10.300273	11.24659	10.51865	10.44586

	Status			
Sample Conc.	**Mean**	**SD**	**SEM**	**N**
0	100	3.728548	1.864274	4
0.1	81.72884	1.371373	0.685686	4
1	59.32666	0.659173	0.329586	4
10	55.95996	1.544611	0.772306	4
100	48.9172	0.910161	0.45508	4
1000	40.45496	0.709192	0.354596	4
PC	10.62784	0.422369	0.211185	4

MIC Assay-M. tuberculae-Sample 2



TestName	MICAssay	*M. tuberculae*
Sample ID	Sample 3	Compound 03
GraphTitle	MIC Assay-M. tuberculae-Sample 3	
X Title	Concentration (µg/ml)	
Y Title	Percentage Inhibition wrt Control	

Sample Conc.	Test Replicates			
	1	2	3	4
0	1.07	1.116	1.076	0.99
0.1	0.752	0.752	0.764	0.764
1	0.701	0.712	0.692	0.719

10	0.591	0.558	0.586	0.57
100	0.261	0.258	0.253	0.26
1000	0.266	0.278	0.264	0.268
PC	0.188	0.185	0.194	0.175

Blank	
1	**2**
0.034	0.035
0.032	0.038
0.04	0.039
0.065	0.053
0.055	0.054
0.151	0.135
0.066	0.079

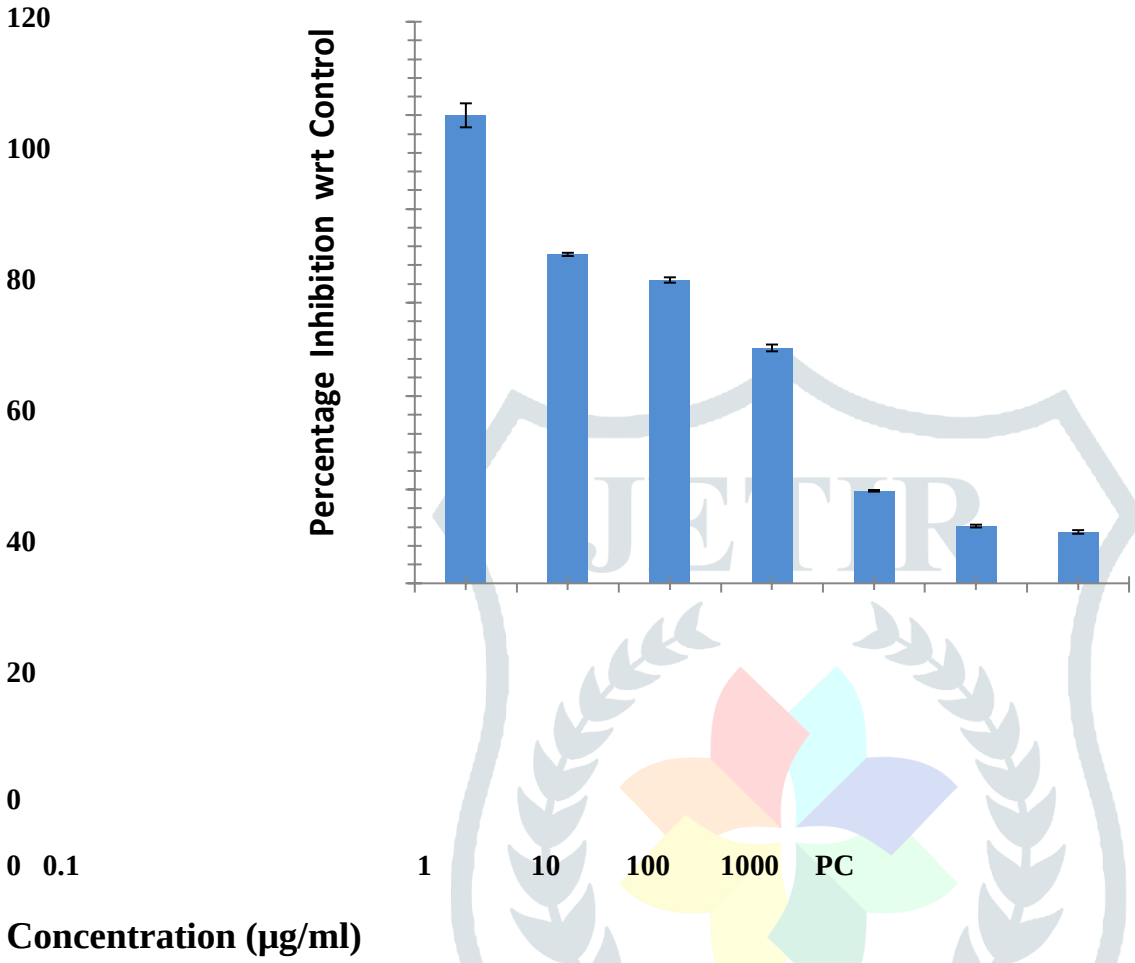
Corrected Values			
1	**2**	**3**	**4**
1.0355	1.0815	1.0415	0.9555
0.717	0.717	0.729	0.729
0.6615	0.6725	0.6525	0.6795
0.532	0.499	0.527	0.511
0.2065	0.2035	0.1985	0.2055
0.123	0.135	0.121	0.125
0.1155	0.1125	0.1215	0.1025

Average Values	
Blank	0
Control	1.0285

	Final Replicate Values			
Sample Conc.	**1**	**2**	**3**	**4**
0	100.6806	105.1531	101.264	92.90228
0.1	69.713175	69.71317	70.87992	70.87992
1	64.316966	65.38649	63.44191	66.06709
10	51.725814	48.51726	51.23967	49.68401
100	20.077783	19.7861	19.29995	19.98055
1000	11.959164	13.12591	11.76471	12.15362
PC	11.229947	10.93826	11.81332	9.96597

	Status			
Sample Conc.	**Mean**	**SD**	**SEM**	**N**
0	100	5.131381	2.565691	4
0.1	70.29655	0.673622	0.336811	4
1	64.80311	1.158617	0.579308	4
10	50.29169	1.46893	0.734465	4
100	19.7861	0.34604	0.17302	4
1000	12.25085	0.604594	0.302297	4
PC	10.98687	0.771731	0.385866	4

MIC Assay-M. tuberculae-Sample 3



RESULTS AND DISCUSSION –

The molecular designs of synthesized compound were done by using different software. Using the Chemsketch software, all synthesized compounds, their structures,andreactions are depicted.

Table No. 01 displays the colour, solubility, molecular formula, and molecular weight.The results of the TLC and RF Value calculations used to determine the melting point,boiling point, and purity of compounds are displayed in Table No. 02.

The IR, NMR, and mass spectra of synthesized compounds were used to confirm theirstructural details.

The values for interpreting IR spectra are displayed in table number 03.In table number 04, the NMR spectra interpret values are displayed.
The findings of the mass spectra interpret are displayed in table number 05.

The values and graphical representations of all the synthesized compounds' anti- tubercular activity screening results are provided above.

SUMMARY AND CONCLUSION-

Using the Chemsketch software, the C1, C2, and C3 benzimidazole derivatives underwent a preliminary screening. TLC was used to determine thechemicals that were synthesized.

The IR, NMR, and mass spectrum data were used to characterize and purify each of the synthesized compounds. The spectral data and the structure of the synthesized molecule were in agreement. In addition, all of the spectral data's pertinent peaks were recognised. The synthesized substances exhibited anti- tubercular action.

All of the synthetically produced compound's benzimidazole derivatives (C1, C2, and C3) were tested for anti-tubercular activity using the Minimum Inhibitory ConcentrationActivity (M. tuberculae, MTCC 300), with results expressed in units of (µg/ml).

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