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Synthesis and Biological Activity of Different Aldehydes Substituted Benzimidazole Derivatives

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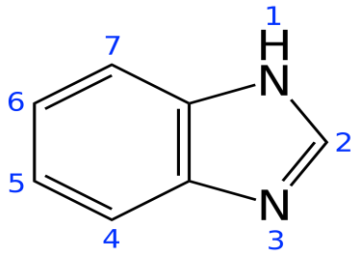
Abstract-
Benzimidazoles are showing different kinds of activities that are Antiviral, Antibacterial, Antiulcer etc and Benzimidazole formed of heterocyclic aromatic compound. Their therapeutic activity are depends on different substitution where all things are related to encourage the synthesis of the novel therapeutic agents. The main aim to review the work that was reported in few past years for the synthesis of new derivatives of Benzimidazole that are showing better activity and there are different Aldehydes substituted Benzimidazole derivatives are shown with their biological activity against E.coli and S.Aueus bacteria in different concentration that is 50 µ/ml and 100 µ/ml.

INTRODUCTION-

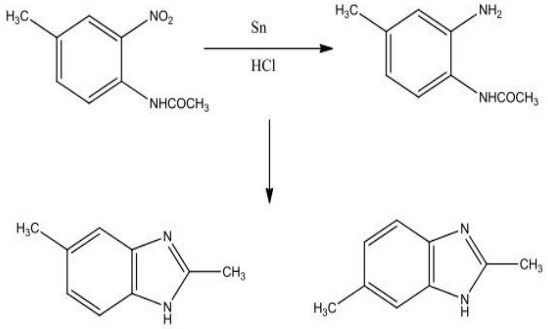
Benzimidazole is a heterocyclic aromatic organic compound this compound is bicyclic in nature which consist of the fusion of Benzene and Imidazole. The most prominent Benzimidazole in nature is N-ribosyl-dimethylbenzimidazole which serves as an axial ligand for cobalt in vitamins.



The important group of substances has found practical application in a number of fields Analgesic, Anti-inflammatory, Antibacterial, Antifungal, Antiviral, Antihelmentic, Anticonvulsant, Anticancer, Anti hypertensive.

History-

The first Benzimidazole was prepared in 1872 by Hoebrecker who obtained 2.5(or 2.6) di-methyl Benzimidazole by the reduction of 2-nitro-4 methyl acetanilide.



Spectral Properties-

Infra Red Spectroscopy-

The spectra of Benzimidazole near 2850 Å indicate the presence of Aryl ring absorption near 3107Å indicates the presence of N-H stretch 1690Å indicates presence of C-N stretch.

Mass Spectroscopy-

The fragmentation pathways of simple Benzimidazole are similar to those of imidazole. The spectrum of Benzimidazole indicates a sequential loss of two molecule of hydrogen cyanide from the molecular ion, the first of which is non specific as evidence by deuterium labelling procedure.

2-n-propylbenzimidazole is elimination of ethylene from molecular ion, 2- acylthiophene; 2-acyl & 2-benzoyl-benzimidazole are characterized by loss of carbon monoxide from the molecular ion.

Nuclear Magnetic Resonance-

Simple 5-6 membered heterocycles can be used to predict chemical shift changes resulting from nitrogen protonation and deprotonation in more complex molecules δ 7-9 values shows multiplet indicate the presence of Benzimidazole aryl ring.

Physical Properties-

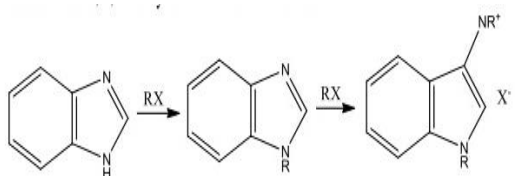
1. The melting point of number of Benzimidazole indicated that the introduction of a substituent into 1- position in general lower the melting point.
2. When other non polar substituent at difference is introduced than solubility places in non polar solvent is increased.
3. Polar grouping increases the solubility in polar solvents.
4. It distilled above 300°c.
5. These are weakly basic being somewhat less basic them imidazole and soluble in dilute acids.
6. The more acidic benzimidiazepine may be soluble in less basic solution such as potassium carbonate solution.

Chemical Properties-

The Benzimidazole ring possesses a high degree of stability. Benzimidazole is not affected by concentration of sulphuric acid, hot hydrochloric acid as well as alkalies.

Alkylation-

Benzimidazole undergoes alkylation with alkyl halides yielding 1- alkyl Benzimidazole and under more vigorous condition 1, 3- dialkyl benzimidazolium halides.

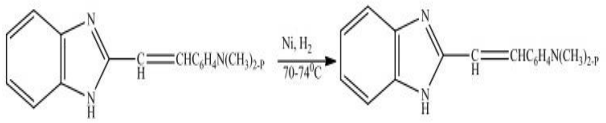


Hydrogenation and Dehydrogenation-

Catalytic reduction of Benzimidazole even under high pressure with nickel as the catalyst is reported to give negative results. Hydrogenation of 2-(p-dimethylaminostyryl) Benzimidazole with nickel at atmospheric pressure saturates only the olefin linkage in the 2- positions.

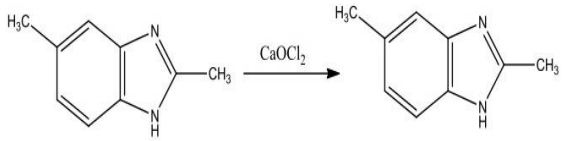
Cleavage of The Imidazole Ring-

The imidazole ring of Benzimidazole may be cleaved by reacting with pseudo bases, acid anhydride and halide.



Halogenation-

When 2.5 (2.6) di methylbenzimidazole is an aqueous solution on treatment with saturated solution of bleaching powder at 0-5°c 1- chloro-2, 5 (2, 6) – di-methyl Benzimidazole is obtained.

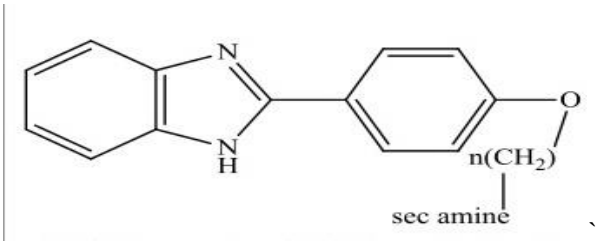


Nitration-

In most cases nitration appears to take place preferentially at the 5 or 6 positon.However the nitro group may also enter the 4 or 7 position especially if the 5 or 6 position is blocked.

Pharmacological Activity of Benzimidazole Derivatives-Analgesic and Anti Inflamentary Compound Structure-

A-

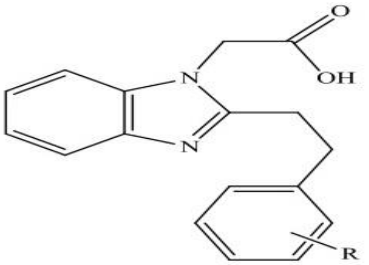


2, (4-Ethoxy-Phenyl)-1h-Benzimidazole Compound with Second Amine Derivative-

1. Piperidine
2. N-methyl cyclo-hexylamine
3. Dipropyl amine
4. 1 phenyl piperizine
5. N ethyl piperazine

Analgesic activity- 3, 4, 5 are showing significant analgesic activity, and other are not showing the analgesic effect.

B-



2-Substituted 3 Acetic Acid Derivatives (A-J)

R

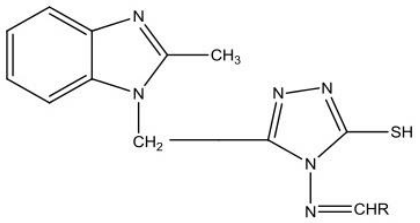
A. p-Cl
B. m-NO_2
C. p-OCH_3
D. $N(CH_3)_2$
E. 2-OH
F. (3,4,5)OCH_3
G. CH=CH-C_6H_5
H. P-NO_2
I. C_6H_5
J. M-Cl

Activity-

A, B, C, J is showing better analgesic activity.

A, B, C, H, J is showing anti-inflammatory activity.

C-



Schiff's Bases Of 2-Methyl Benzimidazole Derivative

A. --2-nitro benzaldehyde
B. --3-nitro benzaldehyde
C. --4-chloro benzaldehyde
D. --4-hydroxy benzaldehyde
E. --4-hydroxy3-methoxy benzaldehyde

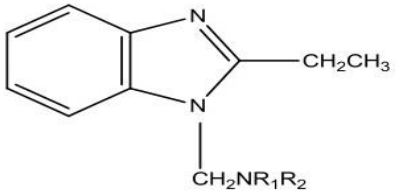
Activity-

A, B, C, D AND E is showing the analgesic activity. E responses the moderately analgesic activity.

A, D, E are anti-inflammatory activity.

B and C are showing non significant anti inflammatory activity.

D-



[1-(N-Substituted Amino) Methyl]-2-Ethyl Benzimidazole Derivative

NR_1R_2

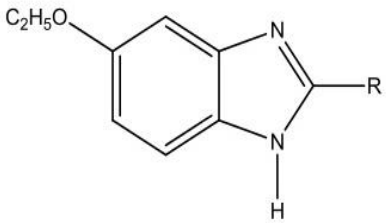
1. Diethyl amine
2. Piperidino

3. Morpholino
4. Diethanol
5. -2-chloroanilino
6. -3-cloroanilino
7. -2,3-dichloroanilino
8. -3,4-dichloroanilino
9. -4-fluroanilino
10. -4-bromoanilino

Activity-

1, 2, 8,9,10 are showing the anti-inflammatory activity.
2, 4, 6,8,10 are the potent analgesic activity.

E-



5-Ethoxy-2-Substituted Benzimidazole

R

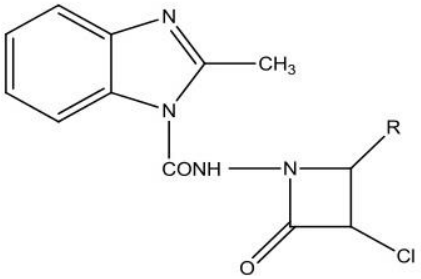
1. H
2. CH_3
3. CH_2CH_3
4. 2-substituted phenol
5. Phenyl
6. 2-substituted acetic acid
7. Phenyl ester
8. 2-substituted ethanol
9. substituted methanol

Activity-

1, 7, 8 are showing anti inflammatory activity.
2, 3,4,5,6 are showing the moderate activity according to the standard drug. Substitution at 2nd position is showing the anti inflammatory activity.

Anti Bacterial and Anti Fungal Activity-

A-



N-[3-CHLORO-2-(SUBSTITUTED) ARYL/ALKYL-4-OXAZETIDIN-1-YL]-1-CARBOXYAMIDE-2-METHYL-1H-BENZIMIDAZOLE

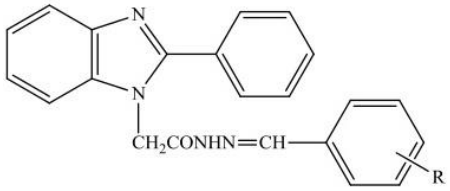
R

1) $-CH_3$
2) $-CH_2CH_3$
3) $-CH_2CH_2CH_3$
4) $-C_6H_5$
5) $2-CH_3C_6H_4$
6) $3-CH_3C_6H_4$
7) $2-ClC_6H_4$
8) $4-ClC_6H_5$
9) $2-OHC_6H_4$
10) $3-OHC_6H_4$
11) $4-OHC_6H_4$
12) $2-OCH_3C_6H_4$
13) $4-OCH_3C_6H_4$

Activity-

Compound with alkyl, phenyl and hydroxyphenyl at position 4 are increasing the anti bacterial activity.

B-



N-(Substituted Benzylidine)-2-[2-(Substituted Phenyl)-1H-Benzimidazole-1-Yl] Acetohydrazide

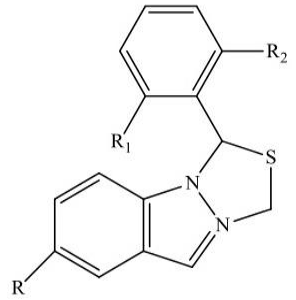
R

A. --H
B. $--2-NO_2$
C. $--3-NO_2$
D. --2-Cl
E. --4-Cl

Activity-

C is showing the minimum activity.
B and E are showing better activity of anti bacterial.

Anti Viral Activity-

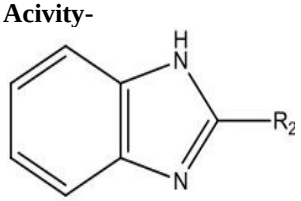


1 H, 3H-THIAZOLE [3, 4-A] BENZIMIDAZOLE DERIATIVE

	R	R2	R3
1.	-	F	F
2.	-	Cl	CL
3.	-	F	F
4.	-	Cl	F
5.	OCH3	F	F
6.	OCH3	Cl	F
7.	OCH3	Cl	F
8.	F	F	F
9.	F	Cl	F
10.	F	Cl	Cl
11.	CF3	F	F
12.	CF3	Cl	F
13.	CF3	Cl	Cl
14.	COPh	F	F
15.	COPh	Cl	F
16.	COPh	Cl	Cl

Activity-
Derivatives with 3,4,8,9 were found to inhibit HIV-1(III-B).

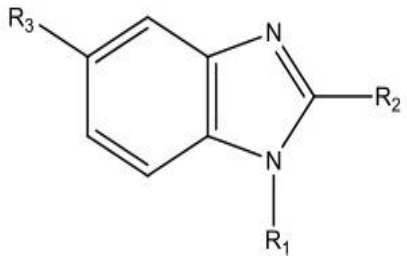
Antihelmentic Acivity-



R2
1. CH_3
2. C_6H_5
3. $CH_3C_6H_5$
4. $CH_3C_6H_5NH_2$

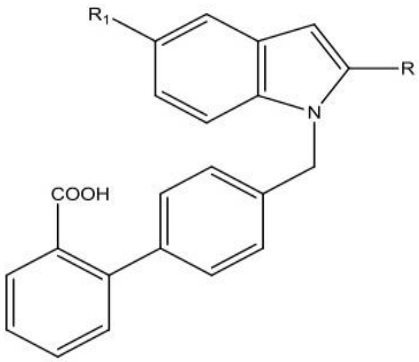
Activity-
2-phenyl Benzimidazole is showing the potential anthelmentic activity.

Anticonvulsant-



1,2,5-trisubstituted benzimidazole
R1= Picoline
R2= Varying alkyl chain
R3= NO3
Activity-
Optimum length at position two R2 is responsible for anti convulsant activity.
At position R3 with electron withdrawing group have been shown better anti convulsant activity.

Antihypertensive Activity-



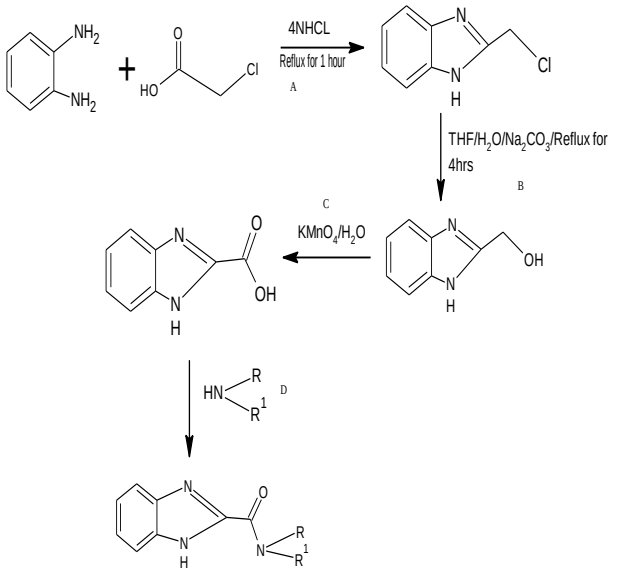
R1	R2
Phenyl	-NH2
Ethyl	-NO2

Activity-
At position 5 of Benzimidazole NH2 are showing the good activity.
2-phenyl are showing the better result and carboxylic group at ortho position at biphenyl ring are necessary for pharmacological activity.

Drugs Having Benzimidazole Nucleus-
Anthelmintics-
1- Albendazole
2- Piperazine
3- Mebendazole
4- Thiabendazole
5- Oxzmniquine
Anti Infective Agents-
1- Refamycin
2- Peginterferon alfa 2-a
3- Interferon alfa n-1
4- Daptomycin
Anti Parasitic Agents-
1- Ivermeetin
2- Dapsone
3- Doxycycline
4- Mefloquine
5- Sulfadiaine

MATERIAL AND METHODS-

General procedure of the preparation of different aldehyde Benzimidazole derivatives. Benzene1,2- Diamine of 125mg (1.155 milimole) and Chloracetic acid of 0.55gm (5.82 milimole) was taken into the round bottom flask in the presence of 4N HCL and refluxed for 1 hour. And then 2 chlormethyl Benzimidazole was weighed 0.25gm (1.500 milimole) was refluxed for 4 hrs in the presence of 0.19g (1.794 milimole) Sodium Carbonate and 2.5 ml DMSO then (1-H benzimidazole-2-yl) methanol of 125gm (843.96 milimole) was reacted with 159.7gm (1010.50 milimole) of Potassium Permanganate in the presence of water and formed 1 H Benzimidazole 2 Carboxylic acid and then reacted (D1 to D5 substitutes) for new derivatives.



Scheme 1-

Benzene1,2- Diamine of 125 mg (1.155 milimole) and Chloracetic acid of 0.55gm (5.82 milimole) was taken into the round bottom flask in the presence of 4N HCL and refluxed for 1 hour. And then 2 chlormethyl benzimidazole was weighed 0.25 gm (1.500 milimole) was refluxed for 4 hrs in the presence of 0.19g (1.794 milimole) Sodium Carbonate and 2.5 ml DMSO then (1-H benzimidazole-2-yl)methanol of 125 gm (843.96 milimole) was reacted with 159.7gm (1010.50 milimole) of Potassium Permanganate in the presence of water and formed 1 H Benzimidazole 2 Carboxylic acid and then reacted with 5 gm(49.43 milimole) of 4-(methyl amino) butanal.

Scheme 2-

Benzene1,2- Diamine of 125 mg (1.155 milimole) and Chloracetic acid of 0.55gm (5.82 milimole) was taken into the round bottom flask in the presence of 4N HCL and refluxed for 1 hour. And then 2 chlormethyl benzimidazole was weighed 0.25 gm (1.500 milimole) was refluxed for 4 hrs in the presence of 0.19g (1.794 milimole) Sodium Carbonate and 2.5 ml DMSO then (1-H benzimidazole-2-yl)methanol of 125 gm (843.96 milimole) was reacted with 159.7gm (1010.50 milimole) of Potassium Permanganate in the presence of water and formed 1 H Benzimidazole 2 Carboxylic acid and then reacted with 5 gm(42.68 milimole) of 3-hydroxy-4-(methyl amino) butanal.

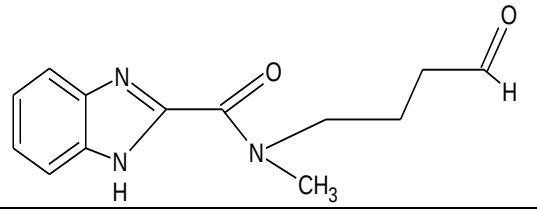
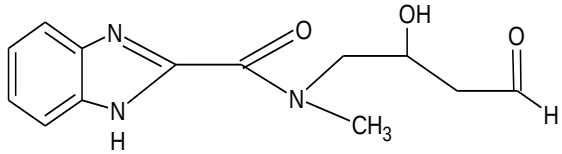
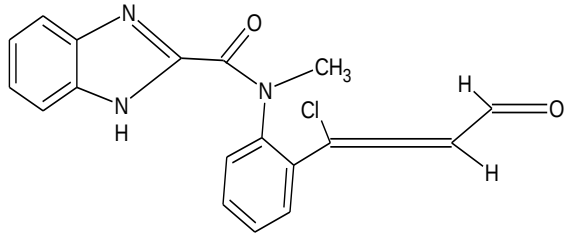
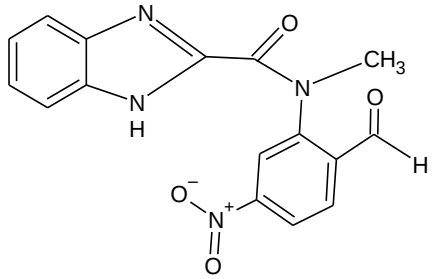
Scheme 3-

Benzene1,2- Diamine of 125 mg (1.155 milimole) and Chloracetic acid of 0.55gm (5.82 milimole) was taken into the round bottom flask in the presence of 4N HCL and refluxed for 1 hour. And then 2 chlormethyl benzimidazole was weighed 0.25 gm (1.500 milimole) was refluxed for 4 hrs in the presence of 0.19g (1.794 milimole) Sodium Carbonate and 2.5 ml DMSO then (1-H benzimidazole-2-yl)methanol of 125 gm (843.96 milimole) was reacted with 159.7gm (1010.50 milimole) of Potassium Permanganate in the presence of water and formed 1 H Benzimidazole 2 Carboxylic acid and then reacted with 5 gm(25.56 milimole) of 3-chloro-3[2-(methylamino)phenyl] propenal.

Scheme 4-

Benzene1,2- Diamine of 125 mg (1.155 milimole) and Chloracetic acid of 0.55gm (5.82 milimole) was taken into the round bottom flask in the presence of 4N HCL and refluxed for 1 hour. And then 2 chlormethyl benzimidazole was weighed 0.25 gm (1.500 milimole) was refluxed for 4 hrs in the presence of 0.19g (1.794 milimole) Sodium Carbonate and 2.5 ml DMSO then (1-H benzimidazole-2-yl)methanol of 125 gm (843.96 milimole) was reacted with 159.7gm (1010.50 milimole) of Potassium Permanganate in the presence of water and formed 1 H Benzimidazole 2 Carboxylic acid and then reacted with 5 gm(27.75 milimole) of 2-(methyl amino)-4-nitrobenzaldehyde.

Table-1 list of different aldehyde derivative with their % yield

S.no.	Compound code	Derivative name	Chemical structure	PracticalYield(%)
1	D1	N-methyl-N-(4-oxobutyl)-1H-benzimidazole-2-carboxamide		76.85%
2	D2	N-(2-hydroxy-4-oxobutyl)-N-methyl-1h-benzimidazole-2-carboxamide		74.27%
3	D3	N-{2-[(1Z)-1-chloro-3-oxoprop-1-en-1-yl]phenyl}-N-methyl-1H-benzimidazole-2-carboxamide		76.93%
4	D4	N-(2-formyl-5-nitrophenyl)-N-methyl-1-H-benzimidazole-2-carboxamide		81.66%

Spectral Data-

Table-2 list of spectral data of different benzimidazole derivatives with their melting point

S.No	Compound Code	^{1}HNMR spectral data(ppm)	Meltng point(^{0}C)
1	D1	19(9.67-9.65,T), 3(7.79-7.66,M), 4(7.66-7.64,M), 6,5(7.49-7.43,M), 14(3.46-3.44,T), 13(3.09,S), 16(2.50-2.46,M), 15(1.94-1.88,M)	215-217^{0}C
2	D2	20(9.52-9.48,M), 3(7.80-7.76,M), 4(7.68-7.66,T), 5,6(7.66-7.43,M), 15(4.29-4.25,M), 17(4.24-4.23,D), 14',14"(4.22-3.56,M), 13(3.56-2.51,M), 16'16"(2.51-2.46,M)	232-233^{0}C
3	D3	25(9.67-9.66,D), 3(7.79-7.76,T), 4,17(7.68-7.65), 5,6(7.65-7.62,M), 18(7.62-7.45,M), 16(7.45-7.35,M), 19(7.35-7.17,M), 23(7.17-6.72,M), 13(3.40,S)	179-181^{0}C
4	D4	16(8.89-8.89,T), 19,17(8.21-8.17,M), 3,4(7.60-7.56), 5,6(7.29-7.25), 8(5.00,S), 13(3.62,S)	245-248^{0}C

NOTE-S= Singlet, D= Duplet, T= Triplet, M= Multiplet

Table3: List of biological activity of different derivatives

S.No	Compound	Concentration (µ/ml)	E.coli	S.aureus
1	D1	50	8	7
	D1	100	9	8
2	D2	50	7	8
	D2	100	9	9
3	D3	50	6	4
	D3	100	8	6
4	D4	50	5	6
	D4	100	8	8

NOTE-

Zone of Inhibition against E. coli and S. aureus : Poor Activity 5-6 mm : Moderate Activity 7-9 mm;Good Activity 10-13 mm

Biological evaluation-

All the derivatives are evaluated against 2 different kinds of bacteria for anti bacterial activity and that bacteria are E.coli and S.Aureus by the preparation of different samples against the standard solution of ampiciline of different concentration that is 50µg/ml and 100µ/ml and for the preparation of test solution same concentration is used. Where we use different discs of sample and whattmann filter paper and then it will be sterilized in oven for 1 hrs at 140^0 c then add the standard and test solution to the disc for antibacterial activity.

RESULT AND DISCUSSION-

For the synthesis of different Benzimidazole derivatives there are different chemicals are used that are shown in schemes and different aldehydes are substituted for new Benzimidazole derivative that are showing different biological activity that shown in above table where different inhibition rate are showing the activity of substituted Benzimidazole derivative on E. coli and S. aureus and that are compared against Ampiciline for Antibacterial activity and that are differentiated in poor, moderate, good and also ^{1}H NMR is also done for spectral data and that are shown in above table no. 2.

And there we found **D3, D4** at 50µ/ml are showing poor activity and **D1, D2** at 50µ/ml and **D1, D2, D3, D4**at 100µ/ml are showing moderate activity against E.coli and **D3, D4** at 50µ/ml and **D3** at 100µ/ml are showing poor activity and **D1, D2** at 50µ/ml and **D1, D2, D4** at 100µ/ml are showing moderate activity against S. aureus.

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