Rahul Srivastava et al /J. Pharm. Sci. & Res. Vol. 12(4), 2020, 507-515

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Synthesis and Biological Activity of Different Aromatic Compounds of Benzimidazole Derivatives

Rahul Srivastava [1], Meraj Ali [2], Urmila Nishad [3]

Aryakul College of Pharmacy and Research, Lucknow [1]
Gaya Prasad Institute Of Human Excellence For Pharmacy [2, 3]

Abstract-
Benzimidazole is a heterocyclic aromatic compound which are showing different kinds of activities such as Antimicrobial, Antiviral, Antiulcer etc. and substitution of different derivatives to the Benzimidazole nucleus is an important synthetic strategy in the drug discovery and therapeutic properties of the Benzimidazole related drugs have encourage the medicinal chemists to synthesize novel therapeutic agents. In the present review Benzimidazole nucleus with an aim to help medicinal chemists for developing an SAR on Benzimidazole for each activity. The article aims to review the work reported, chemistry and pharmacological activities of Benzimidazole derivatives during past years.

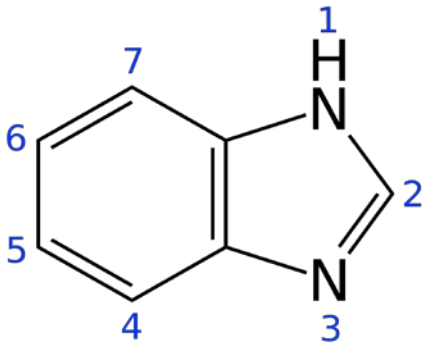
INTRODUCTION-

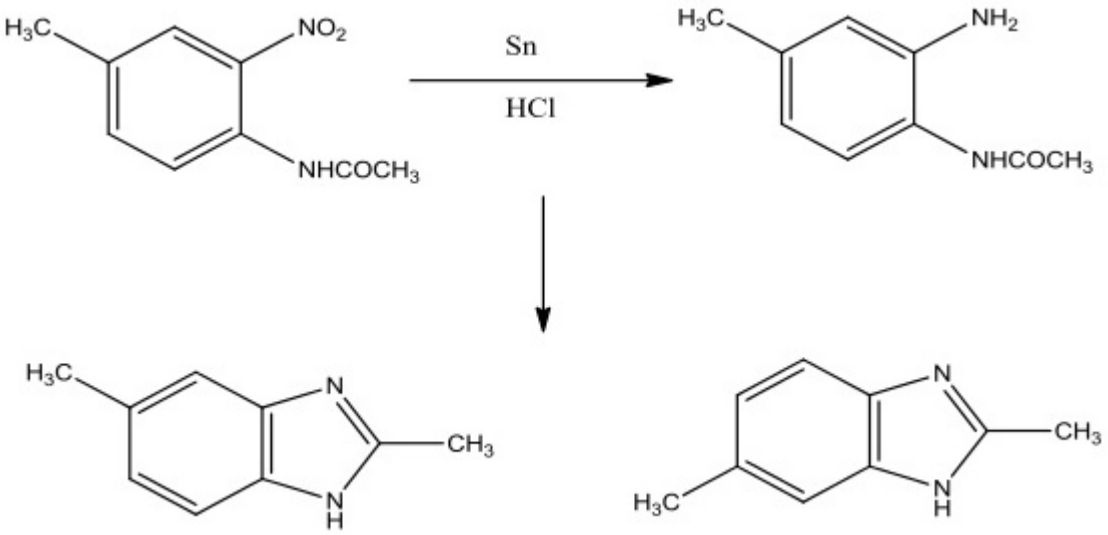
Benzimidazole is a heterocyclic aromatic organic compound this compound is bicyclic in nature which consist of the fusion of Benzene and Imidazole. The most prominent benzimidazole in nature is N-ribosyl-dimethylbenzimidazole which serves as an axial ligand for cobalt in vitamins.

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 methylacetanilide.





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 Benzimidazoles 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 labeling 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 imidazoles 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 sulfuric 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-

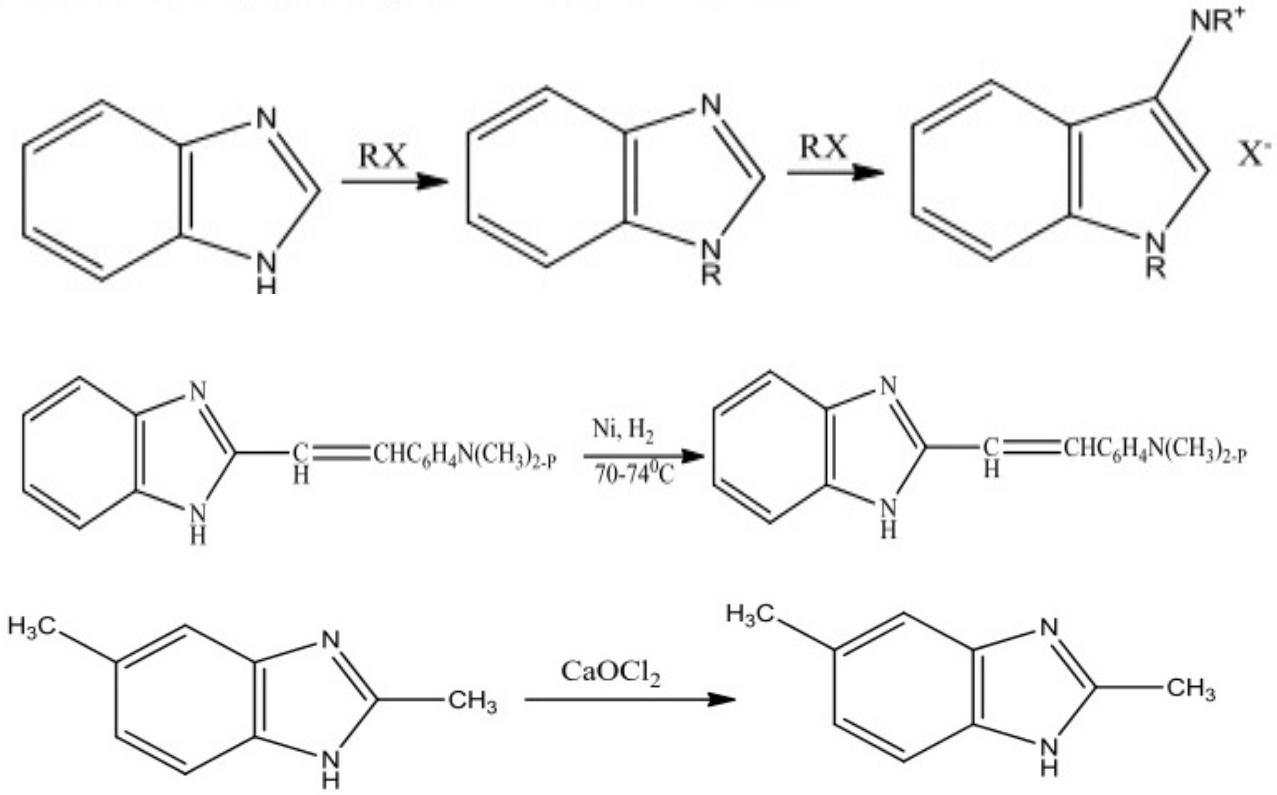
Catalytic reduction of benzimidazole even under high pressure with nickel as the catalyst is reported to give negative results. Hydrogenation of 2-(p-dimethylaminostyryl) benzimidazole with nickel at atmospheric pressure saturates only the olefin linkage in the 2- positions.

CLEAVAGE OF THE IMIDAZOLE RING-

The imidazole ring of benzimidazoles may be cleaved by reacting with pseudobases, acid anhydrideand halide.

HALOGENATION-

When 2.5 (2.6) di methylbenzimidazole is an aquous solution on treatment with saturated solution of bleachinfg powder at 0-5°c 1- chloro-2, 5 (2, 6) - dimethyl benzimidazole is obtained.



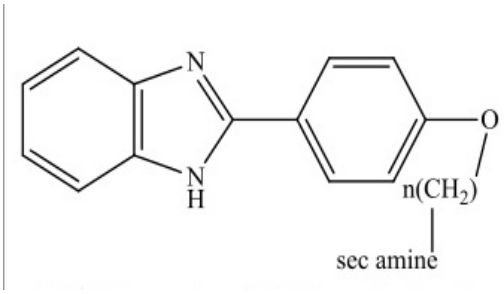
NITRATION-

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 especiaaly if the 5 or 6 position is blocked.

PHARMACOLOGICAL ACTIVITY OF BENZIMIDAZOLE DERIVATIVES-

ANALGESIC AND ANTI INFLAMENTARY COMPOUND STRUCTURE-

A-



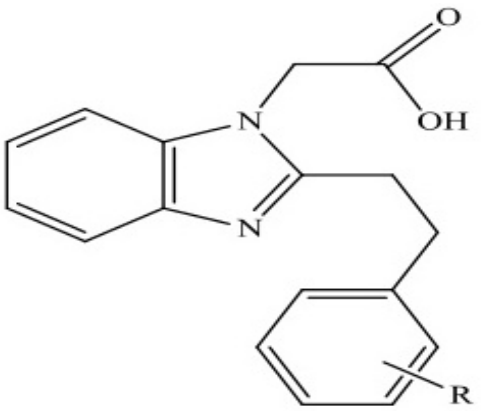
2, (4-ETHOXY-PHENYL)-1H-BENZIMIDAZOLE COMPOUND WITH SECOND AMINE

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 DERIVATIVE (A-J)

R

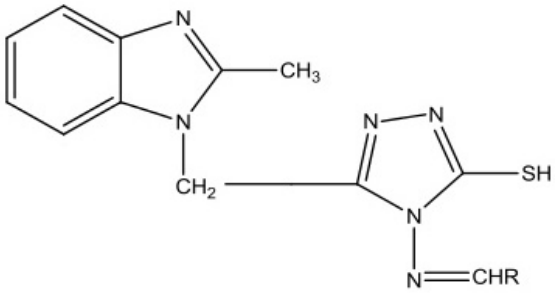
A. p-Cl
B. m-NO_2
C. p-OCH_3
D. $N(CH_3)_2$
E. 2-OH
F. (3,4,5)OCH_3
G. CH=CH-C_6H_5
H. P-NO_2
I. C_6H_5
J. M-Cl

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

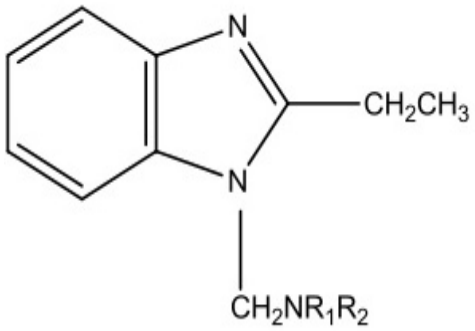
ACTIVITY-

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

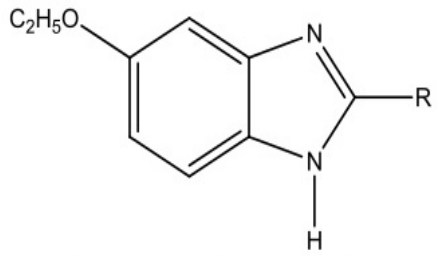
1. Diethylamine
2. Piperidino
3. Morpholino
4. Diethanol
5. -2-chloroanilino
6. -3-cloroanilino
7. -2,3-dichloroanilino
8. -3,4-dichloroanilino
9. -4-fluroanilino
10. -4-bromoanilino

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

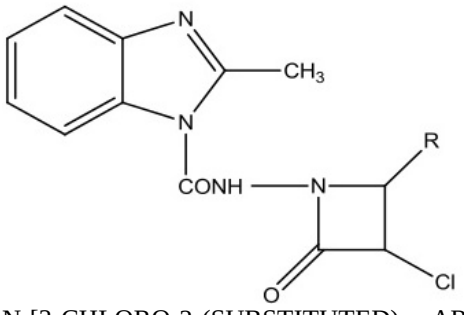
ACTIVITY-

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

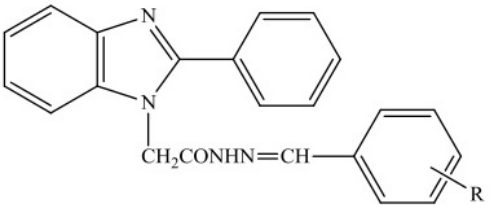
R

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

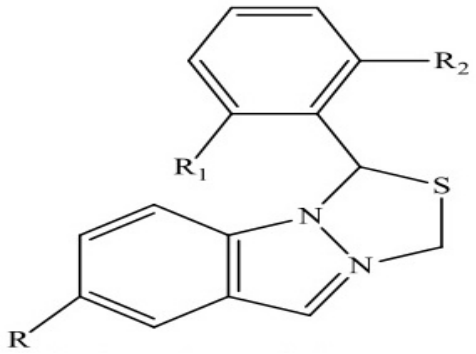
A. --H
B. $--2-NO_2$
C. $--3-NO_2$
D. --2-Cl
E. --4-Cl

ACTIVITY-

C is showing the minimum activity.

B and E are showing better activity of anti bacterial.

ANTI VIRAL ACTIVITY-



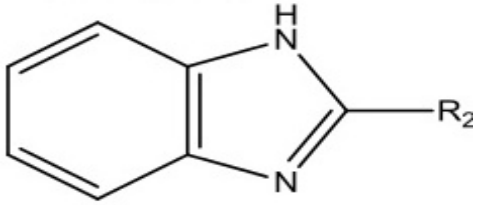
1 H, 3H-THIAZOLE [3, 4-A] BENZIMIDAZOLE DERIATIVE

	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-



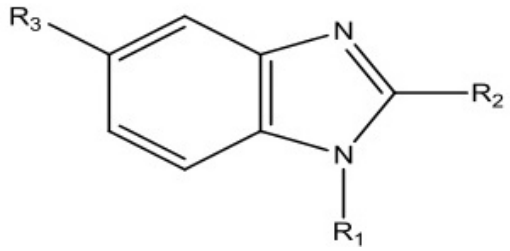
R2

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

ACTIVITY-

2-phenyl benzimidazole are showing the potential anthelmentic activity.

ANTICONVULSANT-

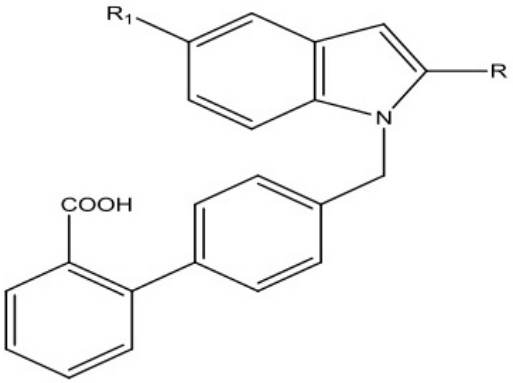


1,2,5-trisubstituted benzimidazole
R1= Picoline
R2= Varying alkyl chain
R3= NO3

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 pharmacologiocal 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 METHOD-

General procedure of the preparation of different aromatic benzimiadzole 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 with (D1 to D8 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(36.99milimol) of 2-(methylamino)benzaldehyde.

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(40.06milimole) of 2-(methylamino)phenol.

SCHEME-3

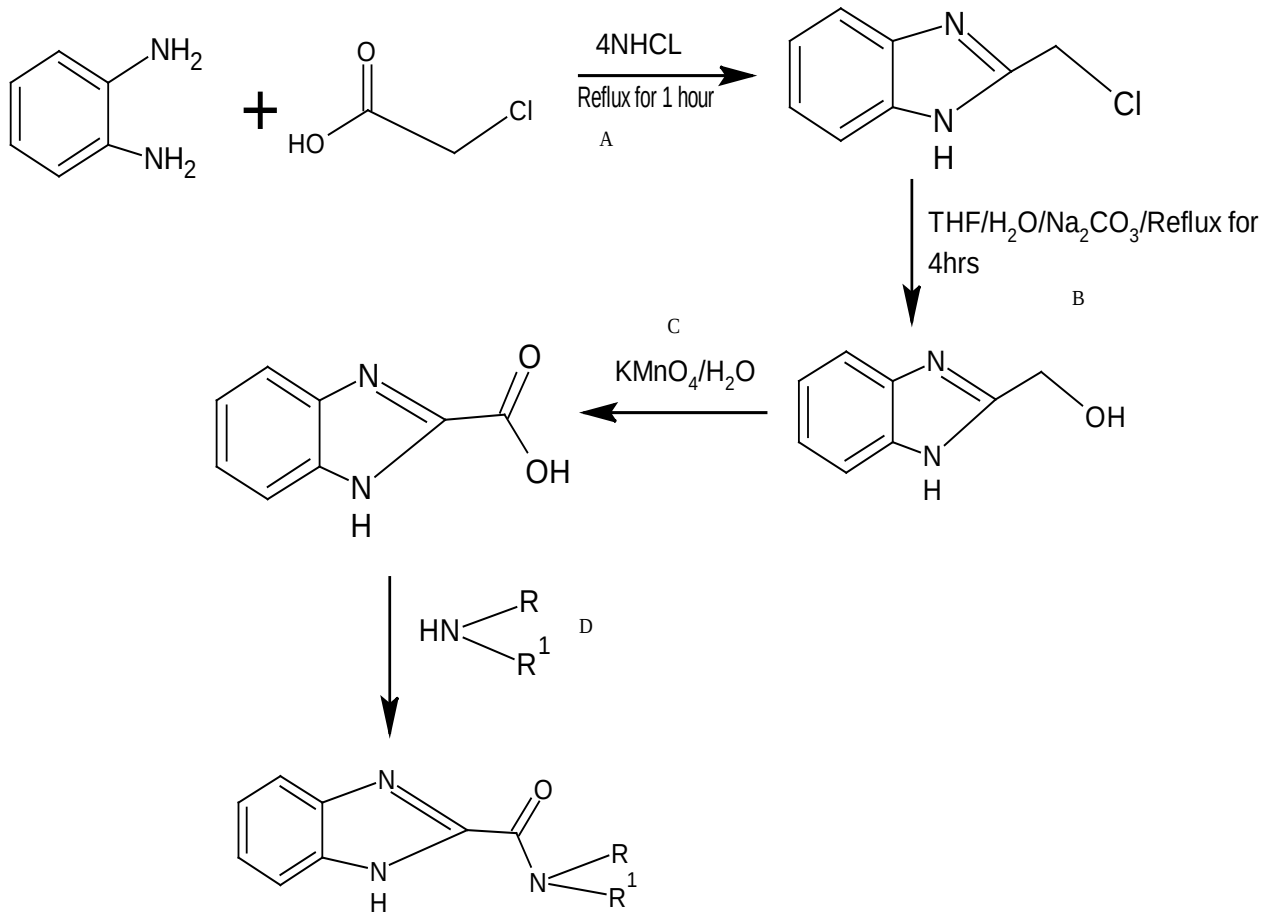
Benzene1,2- Diamine of 125 mg (1.155 milimole) and Chloracetic acid of 0.55gm (5.82 milimole) was taken into the round bottom flask in the presence of 4N HCL and refluxed for 1 hour. And then 2 chlormethyl benzimidazole was weighed 0.25 gm (1.500 milimole) was refluxed for 4 hrs in the presence of 0.19g (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(33.07milimole) of 2-(methyl amino) benzoicacid.

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(40.92milimole) of N^1-methylbenzene-1,2-diamine.

SCHEME-5

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(37.83milimole) of 2-(methyl amino)benzonitrile.



SCHEME-6

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(33.51milimole) of 1-[2-(methylamino)phenyl]ethane-1-one.

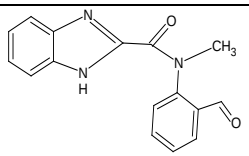
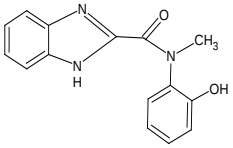
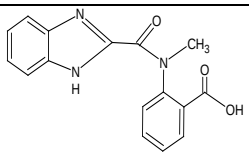
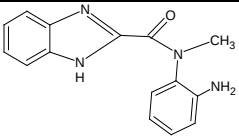
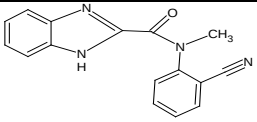
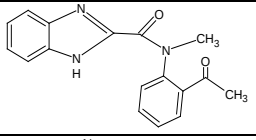
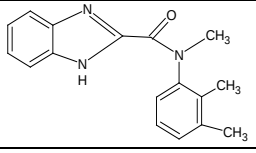
SCHEME-7

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(36.98milimole) of N,2,3-trimethylamine.

SCHEME-8

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(37.54milimole) of 2-ethyl-N-methylaniline.

Table 1: List of different substituted aromatic compounds and their % yield

S.No.	Compound code	Aromatic compound	Derivative name	Chemical structure	Yield(%)
1	D1	Benzaldehyde	N-[(2-formyl phenyl)N methyl]-1H-benzimidazole-2-carboxamide		71.83
2	D2	Phenol	N-(2-hydroxy phenyl)-N-methyl-benzimiadzole-2-carboxamide		81.86
3	D3	Benzoic acid	2[(1H Benzimidazole-2-carbonyl)(methyl)amino]benzoic acid		85.63
4	D4	Aniline	N-(2-aminophenyl)N-methyl-1H benzimiadzole-2-carboxamide		71.16
5	D5	Benzonitrile	N-(2-cynophenyl)-N-methy-1H-benzimidazole-2-carboxamide		81.83
6	D6	Acetophenone	N-(2-acetylphenyl)-N-methyl-1H benzimidazole-2-carboxamide		81.2
7	D7	Ortho-xylene	N-(2,3-dimethylphenyl)N-methyl-1H-benzimiadzole-2-carboxamide		79.6

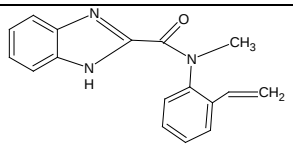
8	D8	Styrene	N-(2-ethenylphenyl)N-methyl-1H benzimiadzole-2-carboxamide		74.3

Table2: List of different substitution of ^{1}H NMR and their Melting point

S.no	Compound Code	^{1}HNMR spectral data(ppm)	Melting point(^{0}C)
1	D1	16(8.38-8.14,M), 17(8.14-8.12 M), 18,19(7.85-7.84, D), 3,4(7.83-7.25,M), 6,5(7.82-7.25,M), 8(5.00,S), 13(3.62,S)	245-247^{0}C
2	D2	3,4(7.60-7.27, M), 5,17,6,16 (7.27-7.25, T), 19(7.25, S) 18(7.25, S), 8(5.00,S) , 13(3.62,S)	185-187^{0}C
3	D3	16(8.37-8.39,D), 17(8.20-8.22,T), 18(7.91-7.87,M) , 4,3,19(7.60,S), 5,6(7.59-7.25,M), 8(5.00,S), 13(3.62,S)	205-207^{0}C
4	D4	3,4(7.60-7.37,M), 19(7.36-7.37,T), 5,6(7.29-7.26,M), 18(6.99-6.97,T), 17(6.96-6.91,T), 16(6.91-6.61,M), 8(5.00,S),13(3.62,S),20(3.51,S)	215-217^{0}C
5	D5	16(7.78-7.70,M), 17(7.70,S), 18(7.69,S), 4,3(7.68-7.67,D), 19(7.60,S), 5,6(7.69-7.25,M,7.29 Chloroform), 8(5.00,S), 13(3.62,S)	191-193^{0}C
6	D6	16(8.29-8.27,D), 17(7.96-7.94,D), 18(7.76-7.74,D), 3,4(7.73-7.58,M), 6,5(7.58-7.14,M), 19(7.13,S), 8(5.00,S), 13(3.62,S), 21(2.64,S)	170-172^{0}C
7	D7	16(8.25-8.23,D), 4,3(7.60-7.58,D), 18(7.57-7.56,D), 6,5(7.56-7.11,M), 19(7.11-7.09, T, 7.09 Chloroform), 8(5.00,S),13(3.62,S), 21(2.28,S),20(2.13, S, H_2O)	185-187^{0}C
8	D8	16(8.13-8.11, D), 17(8.11-7.80, M), 4,3,19(7.66-7.62, D), 18(7.60-7.59,D), 6,5(7.58-7.43, M), 20(7.43-7.16, M, 7.42 Chloroform), 21',21"(7.15-5.61, M), 8(5.00,S), 13(3.62,S)	206-209^{0}C

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

Biological evaluation-

All the derivatives are evaluated against 2 differenet 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.

Table3: List of biological activity of different derivatives

S.No	Compound	Concentration(µ/ml)	E.coli	S.aureus
1	D1	50	9	9
	D1	100	7	5
2	D2	50	8	6
	D2	100	6	3
3	D3	50	6	6
	D3	100	5	5
4	D4	50	10	8
	D4	100	6	6
5	D5	50	7	9
	D5	100	4	7
6	D6	50	8	7
	D6	100	6	6
7	D7	50	6	8
	D7	100	5	6
8	D8	50	7	8
	D8	100	5	5

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

RESULT AND DISCUSSION-

For the synthesis of different Benzimidazole there are different chemical are used that are shown in scheme 1 and different aromatic compounds 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 **D19,D20,D21,D22,D23,D24,D25** at 50µ/ml and **D20,D24** at 100µ/ml are showing poor activity and **D18** at 50µ/ml and **D18,D19,D22,D23,D25** at 100µ/ml are showing moderate activity and **D21** at 100µ/ml are showing good activity against E.coli and **D18,D19,D20,D21,D23,D24,D25** at 50µ/ml and **D19,D20** at 100µ/ml are showing poor activity and **D22** at 50µ/ml and **D18,D21,D22,D23,D24,D25** at 100µ/ml are showing moderate activity against S. aureus.

REFERENCES-

1- Srestha. N, Banerjee. J, Srivastava. S, (dec.2014) *j. pharm.*, vol.4 Issue 12, pp-28-41.
2- Petkar. K , Parekh. P, Mehta. P, Kumar. A, Baro. A, (2013) *Int. J Pharm. & Pharma. Sci.*{Bharti Vidyapeeth College Of Pharmacy India}, vol.5 Issue 02.
3- Soni. B, Ranawat. M. S, Bhandari. A , Verma. R, Sharma .R, Prajapati.R.P, (2012) 5(7) *J. Pharm*, pp-3523-3526.
4- Sanahanbi. N, Sivakumar. T, (2013) 4(4) *Int. J. Pharm.& Bio.Sur. Arch.*, pp-717-722.
5- Babu. S I, Selvakumar. S, Geeta. Manasa. M, Haritha. P, Neeraja. B, Rabia Basri. S, Sampath. B, (jan-mar 2012) *Int. J. Phar.& Ind. Res*., vol-2 Issue 1.
6- Walia. R, Hedaitallah.Md , Farha Naaz.S, Khalid Iqbal & H. S. Lamba, (2011) 1(3), *IJRPC*, ISSN 2231, pp-2781.
7- Marriapan. G , Hazarika. R , Alam. F, Karki. R, Patangia. U, Nath. S, (2015)8, *Arabian. J. Chem*., pp-715-719.
8- Ahamed A. Jafar,a Kaliapillai N. Vijayakumar,a Bathey R. Venkatramanb and Govindaraj Venkatesha, 2009(4), *Orbital Elec. J. Chem.*, pp-306-309.
9- K. F. Ansari, C. Lal and R. K. Khitoliya, 2011, 76(3) *j. serb. Chem.. soc*., pp-341-352.
10- Weijie Si, Tao Zhang, Yaofa Li, Dongmei She, Wenliang Pan, Zhanlin Gao, Jun Ning, Xiangdong Mei, (2015) vol.41, issue 1,*J. pestic. Sci.*, pp-15-19.
11- Fatmah A. S. Alasmary ,Anna M .Snelling, Mohammed E. Zain, Ahmed M. Alafeefy, Amani S. Awaad and Nazira Karodia, (2015), *MDPI*, pp-15206-15223.
12- Ekta Khare, G. Mariappan, (2018) 8(1), *IJRPC*, pp-61-68.
13- Anita Sharma, Chetna Rajyaguru, Jatin M. Upadhyay, and Manish K Shah, 2013, Int. J. Chem Sci, pp- 981-988.
14- Hamdan S.Al-Ebaisat, 2011, J. appl. Sci. environ. Manage, pp-451-454.