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SYNTHESIS OF BENZIMIDAZOLONE-BENZTHIAZOLE AND ITS PIPERAZINE DERIVATIVES WITH PHARMACOLOGICAL ACTIVITY

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Abstract:

Benzimidazole and Benzothiazole derivatives have its own biological activity such antimicrobial ,antiviral, anticancer antiulcer antifungal etc.Due to numerous significance value a novel series of Benzimidazolone –Benzothiazole derivatives were synthesized and checked its biological activities. It was observed that some of novel compounds show good antimicrobial activity. Investigation of antimicrobial activity of the compound was done by using Gram Positive and Gram negative bacteria and minimum inhibition concentration (MIC) values were determined.

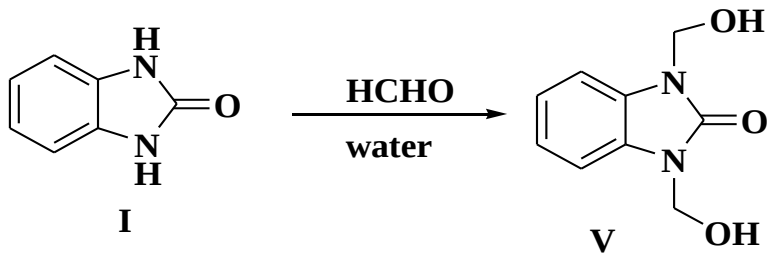
Keywords: Antimicrobial, Antifungal activity and Benzimdazolone –Benzothiazole

I.INTRODUCTION

Heterocycles are in the center of research due to their versatile application[1]. The benzimidazolone ring structure is of particular interest especially within the realm of medicinal chemistry because of their different biological activity and clinical applications[2-4]. They exhibit a wide variety of interesting biochemical and pharmacological Properties including antagonize neurotransmitters[5-7], inhibit aldose reductase show antiulcer and antisecretory properties enhance pulmonary surfactant secretion and modulate ion channels

Benzimidazolin-2-one **I** has been an important intermediate in the synthesis of a number of biologically active benzimidazole derivatives.

1,3-bishydroxymethyl benzimidazolone **V** has been obtained by the N-hydroxymethylation of **I**



I **V**

X.Diao,Y.Wang,Y.Jiang,D.Ma usedCuI/l-proline catalyzed coupling reaction for synthesis of benzimidazolone by aqueous ammonia with 2-iodoacetanilides and 2-iodophenylcarbamates affords aryl amination products at room temperature, which undergo in situ additive cyclization under acidic conditions or heating to give substituted 1H-benzimidazoles and 1,3-dihydrobenzimidazol-2-ones, respectively

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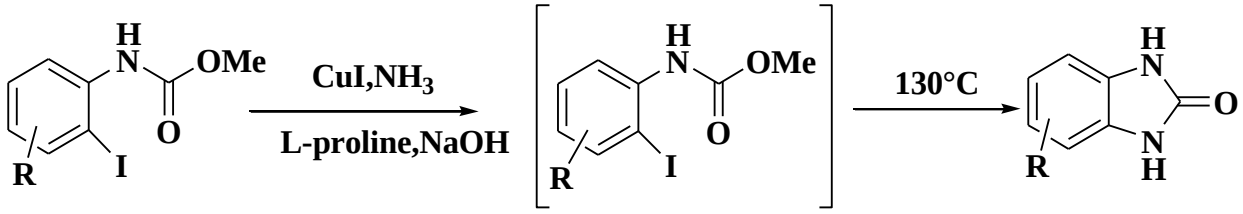
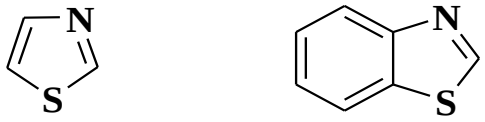


While heterocycles like benzothiazole A number of heterocyclic derivatives containing nitrogen and sulphur atom serve as a unique and versatile scaffolds for experimental drug design benzothiazoles are bicyclic ring system with multiple applications. In the 1950s, a number of 2- aminobenzothiazoles were intensively studied, as the 2-amino Benzothiazole scaffold is one of privileged structure in medicinal chemistry.

Thiazole is structurally related to thiophene and pyridine, but in most of its properties it resembles to the latter. Thiazole (A) was first described by Hantzsch and Waber in 1887



(A) **(B)**

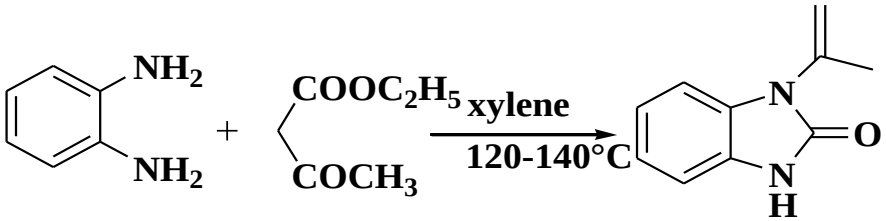
Popp confirmed its structure in1889. The numbering in thiazole starts from the sulphur atom. The basic structure of benzothiazole (B) consist of benzene ring fused with 4, 5 position of thiazole

II. EXPERIMENTAL DETAILS

2.1. Materials and Procedures

Melting points were determined in open capillaries with the help of VEGGO melting point apparatus and IR spectra (KBr) were recorded on SHIMADZU IR spectrophotometer. 1H NMR spectra were recorded by Bruker WM 400 FT instrument using D2O as solvent and tetramethylsilane (TMS) as internal reference standard. All chemical shifts (δ) are in ppm. The purities of the compounds were checked by thin layer chromatography (TLC) on silica gel-G plates. The major chemicals were purchased from Aldrich Chemical Corporation.

2.1.1 Preparation of 1-(prop-1-en-2-yl)-1H-benzo[d] imidazol-2(3H)-one (I)



OPDA **ethyl acetoacetate** **I**

To solution of OPDA (o- phenylene diamine) 10 g in 50 ml xylene in ethylacetoacetate 13.4 g(1.03 mole)in xylene 10 ml solution added at 140-150 °C in 3.0 hrs .Reaction monitored by TLC. Reaction filter out at cooled temperature and the cryatlised by Sodium hydroxide 20% solution .Solid separate out by filtration .It the purified by RO water at neutral pH by acetic acid to get pure Compound (I) and dry it 55-60°C yield 52.0%

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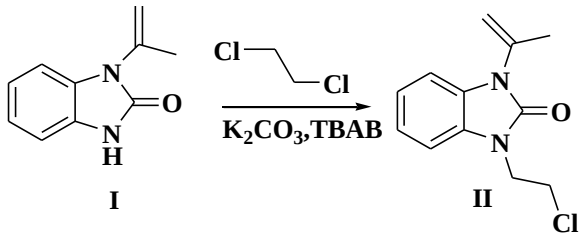
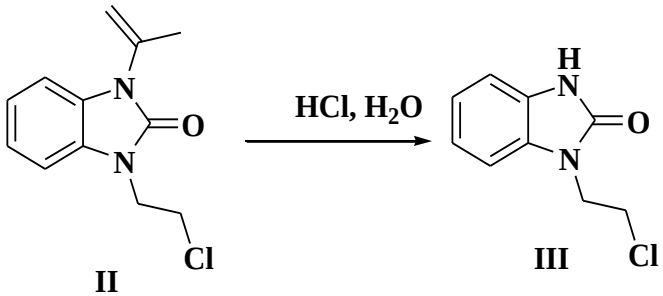
2.1.2 Preparation of 1-(2-chloroethyl)-3-(prop-1-en-2-yl)-1H-benzo[d]imidazol-2(3H)-one (II)



I II

To solution of Compound (I) 10 g in 1,2 dichloroethane 120 ml and anhydrous powder potassium hydroxide10.7 g(1.9 moles) and catalytic amount of tetra butyl ammonium bromide were heated to reflux for 2-3 hrs .Reaction monitored by TLC .wash the organic layer at cooled temperature Concentrate the organic layer by vaccum thick oil residue of compound (II) will obtained yield 92.0%

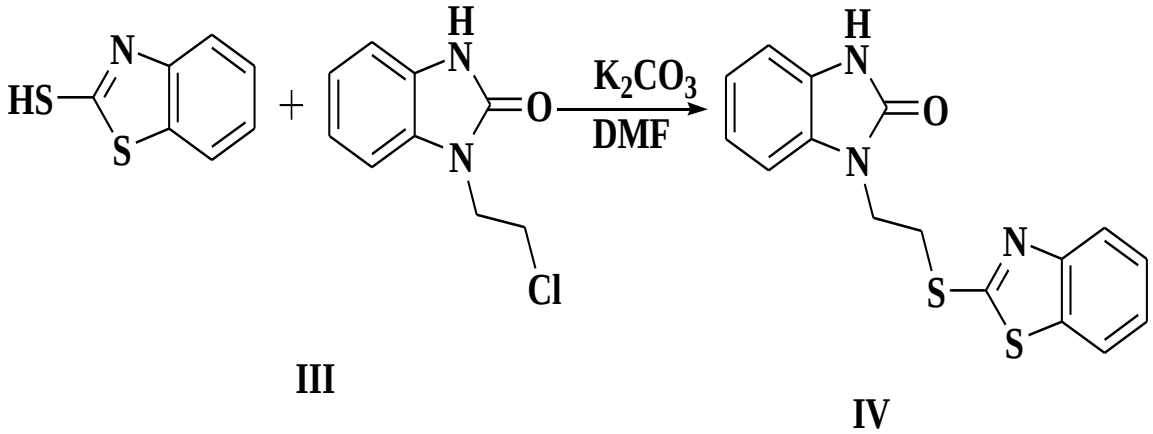
2.1.3 Preparation of 1-(2-chloroethyl)-3-(prop-1-en-2-yl)-1H-benzo[d]imidazol-2(3H)-one (III)



II III

To solution of Compound (II) in 100 ml water with hydrochloric acid 200 ml were heated to 55-60°C for 2-3 hrs . Reaction monitored by TLC. Cool the reaction mass and solid separate out by filteration.and wash with water till neutral pH to get compound(III) .Dry the product 60-70°C yield 84%

2.1.4 Preparation of 1-(2-(benzo[d]thiazol-2-ylthio)ethyl)-1H-benzo[d]imidazol-2(3H)-one (IV)

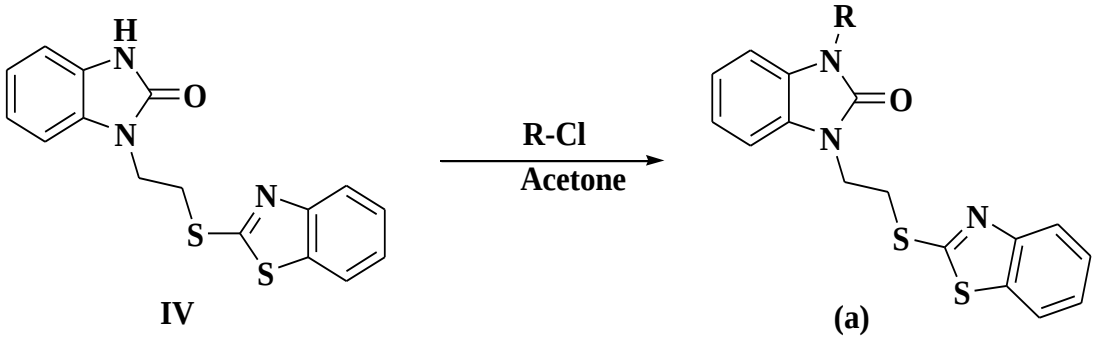


III IV

Condensation of compound -III 10 g with mercapto Benzothiazole 11.0 g(1.3 mol) in DMF by Porassium carbonate 5.0 gm heat to 80-85°Cfor 4.0 hrs .Reaction is monitored by TLC .Reaction mass concentrated by vaccum and extracted by Methylene dichloride 150 ml .wash the organic layer with RO water. Now concentrate the organic layer

by vaccum and isolate the product by acetone 50 ml .Separate out the product by filtration dry the product at 60-65°C .% yield 84%

2.1.5 Preparation of Ethyl 3-(2-(benzo[d]thiazol-2-ylthio) ethyl)-2,3-dihydro-2-oxobenzo[d]imidazole-1-carboxylate(a)

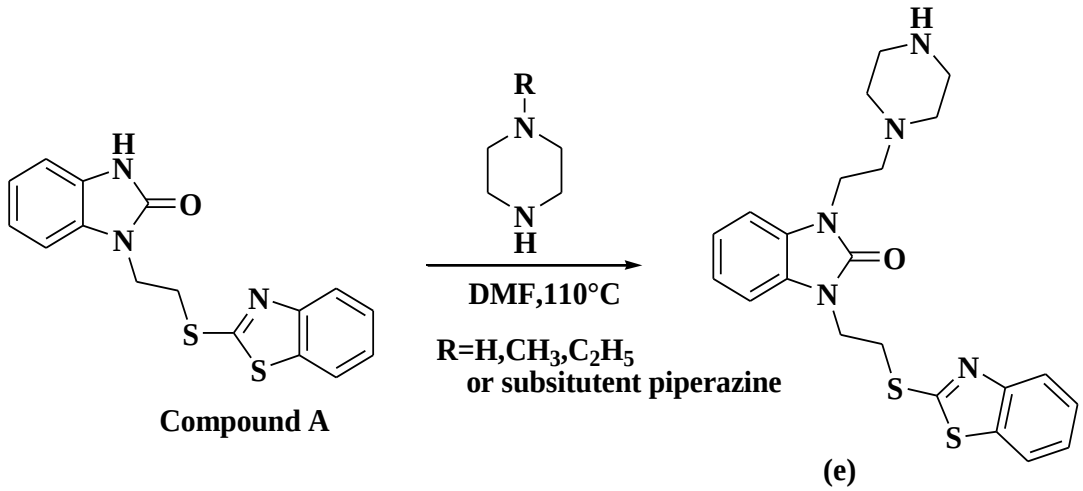


IV (a)

R= $ClCOOC_2H_5$,C_6H_5Br,CH_3COCl,$C_2H_4Cl_2$ or halogenated aromatic or non armoatic compound

To solution of Compound IV 10 gm in acetone 150 ml,Potassium carbonate 4.0 gm and ethyl chloroformate 5.0 ml (1.03 mol) or other halogenated aromatic or non aromatic compound were heated at reflux for 4.0 hrs and reaction monitored by TLC.Remove the salt by hot filteration.Reaction concentrated by vacuum, Isolated the product in isopropyl alcohol 150 ml at chilling condition .Separate out the product by filtration dry at 60-65°c Yield : 68.0 %

2.1.6 Preparation 1-(2-(benzo[d]thiazol-2-ylthio)ethyl)-3-(2-(piperazin-1-yl)ethyl)-1H-benzo[d]imidazol- 2(3H)-one(e)



Compound A (e)

To solution of compound A 5.0 g with powder potassium carbonate 3.5g (2.0 moles) ,piperazine 1.28 g (1.17 moles) or substituted piperazine and catalytic amount of potassium iodide in DMF 50 ml were heated at 105-110°C for 6.0 hours. Reaction monitored by TLC.Reaction mass concentrated by vacuum .Methyelne dichloride75 ml and water 75 ml were added to residue .Organic layer separate out and concentrate by vaccum .Thick residue was crystallized in acetone .Solid separate out by filtration and dry it 60-65°c Yield 76 %

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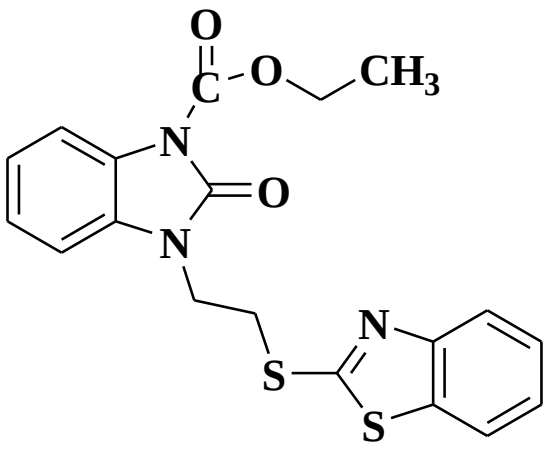
III.CHARACTERIZATION STUDIES

3.1Characterization of ethyl 3-(2-(benzo[d]thiazol-2-ylthio)ethyl)-2,3-dihydro-2-oxobenzo[d]imidazole-1-carboxylate



1HNMR:-

S.No	Chemical shift (δ ppm)	Multiplicity	Proton assignment	No. of protons
1	7.97-7.07	Multiplet	Aromatic – **H**	8
2	4.41-4.36	triplets	Ester –C**H**$_2$	2
2	4.28-4.22	Multiple	N-C**H**$_2$	2
3	3.73-3.70	triplets	S-C**H**$_2$	2
5	1.37-1.33	triplets	Ester-C**H**$_3$	3

CNMR:-

In CNMR Carbonyl carbon of shows the specific value appear at 165.61 δ ppm,Aromatic carbon appear at 152.51-108.44 δ ppm and the Aliphatic carbon appear at range 63.06 -13.98 δ ppm,

Mass:-

No	m/z (Theoritical)	m/z (Observed)	Relative intensity	Ion
1	399.49	399.0	42%	**(M^+)** $C_{19}H_{17}N_3O_3S_2$

Melting point:- 162-167°C

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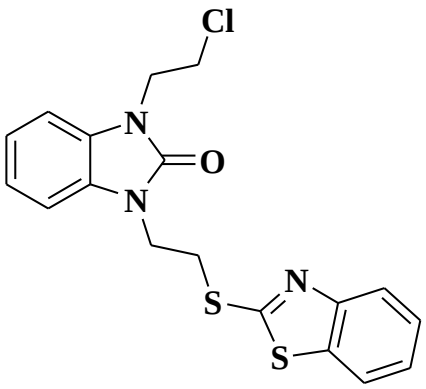
3.2 Characterization of 1-acetyl-3-(2-(benzo[d]thiazol-2-ylthio)ethyl)-1H-benzo[d]imidazol-2(3H)-one



1HNMR:-

S.No	Chemical shift (δ ppm)	Multiplicity	Proton assignment	No. of protons
1	8.01-7.05	Multiplet	Aromatic –**H**	8
2	4.32-4.28	triplets	N-C**H**$_2$	2
3	4.17-4.14	triplets	S-C**H**$_2$	2
4	3.89-3.86	triplets	Cl-C**H**$_2$	2
5	3.72-3.69	triplets	N-C**H**$_2$-CH_2-Cl	2

CNMR:-

In CNMR Carbonyl carbon of shows the specific value appear at 153.24 δ ppm,Aromatic carbon appear at 165.76,152.46-108.16 δ ppm and the Aliphatic carbon appear at range 42.21-30.89 δ ppm,

Mass:-

No	m/z (Theoritical)	m/z (Observed)	Relative intensity	Ion
1	389.92	389.0	42%	**(M^+)** $C_{19}H_{16}ClN_3OS_2$

3.3 Characterization of 1-(2-(benzo[d]thiazol-2-ylthio)ethyl)-3-(2-(4-methylpiperazin-1-yl)ethyl)-1H-benzo[d]imidazol-2(3H)-one

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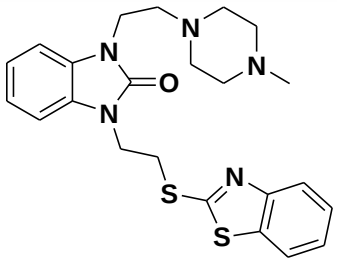

1HNMR:-

S.No	Chemical shift (δ ppm)	Multiplicity	Proton assignment	No. of protons
1	8.03-7.07	Multiplet	Aromatic –**H**	8
2	4.30-4.27	Multiplet	N-C**H**$_2$-C**H**$_2$-S	4
			N-C**H**$_2$-C**H**$_2$-N	4
3	3.83-3.44	Multiplet	Piperazine – (C**H**$_2$)$_4$	8
4	2.82	singlet	N-C**H**$_3$	3

CNMR:-

In CNMR Carbonyl carbon of shows the specific value appear at 153.24 δ ppm,Aromatic carbon appear at 165.76,152.46-108.16 δ ppm and the Aliphatic carbon appear at range 55.19-31.03 δ ppm,

Mass:-

No	m/z (Theoritical)	m/z (Observed)	Relative intensity	Ion
1	453.62	453	42%	**(M^+)** $C_{23}H_{27}N_5OS_2$

Melting point**:-** 182-188°C

IV. ANTIMICROBIAL ACTIVITY TEST

The synthesized novel compounds were tested by Broth Dilution Method (It is one of the non automated in vitro bacterial susceptibility tests). The bacterial strains used were Staphylococcus aureus MTCC 96(all Gram-positive) and Ecsherichia coli MTCC 442, S.Pyogenus MTCC 443and Pseudomonas aeruginosa MTCC 441 (all Gram-negative).

For testing the antifungal activity of the synthesized compounds the fungal strains Candida albicans MTCC 227 and Aspergillus niger The inhibition zones of synthesized compounds were determined using by Broth Dilution Method. In this method, Each synthesized drug was diluted obtaining 2000 microgram /ml concentration, as a stock solution.

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Primary screen; In primary screening 1000 micro/ml, 500 micro/ml, and 250 micro/ml concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms.

Secondary screen: The drugs found active in primary screening were similarly diluted to obtain 200 micro/ml 100 micro/ml, 50 micro/ml, 25 micro/ml, 12.5 micro/ml, 6.250 micro/ml, and concentrations.

Reading Result:- The highest dilution showing at least 99 % growth inhibition is taken as MIC.The result of this is much affected by the size of the inoculums. The test mixture should contain 108 organism/ml.

This is often used to determine the smallest amount of antibiotic necessary to inhibit a test organism. This amount is known as the minimum inhibitory concentration (MIC). A set of tubes with different concentrations of a particular antibiotic are prepared. The tubes are inoculated with the test organism, incubated, and examined for growth of bacteria.Growth is seen to diminish as the concentration of antibiotic increases, and eventually an antibiotic concentration may be observed at which growth fails to occur. This is the Minimum Inhibitory Concentration-MIC

Zone of inhibition

The principle used here is that antibiotic will diffuse from a paper disc or small cylinder into an agar medium that contains test organisms. Inhibition is observed as a failure of the organism to grow in the region of the antibiotic. A common application of this method is the Kirby Bauer test, developed in the 1960s.

The procedure is used to determine the sensitivity of an organism isolated from a patient to a series of antibiotics. The results serve a guide to physician to prescribe a drug. The results serve a guide to physician to prescribe a drug. An agar medium such as Mueller Hinton medium is inoculated with the organism and poured to the plate. Paper discs containing known concentrations of antibiotics are applied to the surface, and the plate is incubated. The appearance of a zone of inhibition surrounding the disc is indicative of sensitivity. By comparing the diameter of the zones to a standard table, one may determine if the test organism is susceptible, or resistant to the antibiotic. If the organism is susceptible, it is likely to be killed in the blood stream of the patient if that concentration of the drug is reached. Resistance indicates that the antibiotic will not be effective at that concentration in the blood stream.

The data on antimicrobial activity of compounds are shown in below table with standard

ANTIBACTERIAL ACTIVITY TABLE

MINIMAL INHIBITION CONCENTRATION				
Compound No	***E.COLI***	***P.AERUGINOSA***	***S.AUREUS***	***S.PYOGENUS***
R=	**MTCC 442**	**MTCC 441**	**MTCC 96**	**MTCC 443**
[MICROGRAMM/ML]				
$COOC_2H_5$	**200**	**250**	**100**	**125**
$CH_2COOC_2H_5$	**125**	**200**	**200**	**250**
CH_3CO	**50**	**200**	**62.5**	**100**
Piperazine	**62.5**	**125**	**250**	**200**
N-methyl piperazine	**50**	**25**	**50**	**50**

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Standards drugs table

MINIMAL INHIBITION CONCENTRATION				
DRUGS	***E.COLI***	***P.AERUGINOSA***	***S.AUREUS***	***S.PYOGENUS***
	MTCC 442	**MTCC 441**	**MTCC 96**	**MTCC 443**
[MICROGRAMM/ML]				
GENTAMYCIM	**0.05**	**1**	**0.25**	**0.5**
AMPICILLIN	**100**	**--**	**250**	**100**
CHLORAMPHENICOL	**50**	**50**	**50**	**50**
CIPROFLOXACIN	**25**	**25**	**50**	**50**
NORFLOXACIN	**10**	**10**	**10**	**10**

ANTIFUNGAL ACTIVITY TABLE			
MINIMAL FUNGICIDAL CONCENTRATION			
S.R.NO	**Compound No**	***C.ALBICANS***	***A.NIGER***
	R=	**MTCC 227**	**MTCC 282**
[MICROGRAMM/ML]			
1	**$COOC_2H_5$**	**1000**	**>1000**
2	**$CH_2COOC_2H_5$**	**500**	**500**
3	**CH_3CO**	**250**	**>1000**
4	**Piperazine**	**500**	**1000**
5	**N-methyl piperazine**	**500**	**500**

MINIMAL FUNGICIDAL CONCENTRATION			
S.R.NO	**DRUGS**	***C.ALBICANS***	***A.NIGER***
		MTCC 227	**MTCC 282**
[MICROGRAMM/ML]			
1	**NYSTATIN**	**100**	**100**
2	**GRESEOFULVIN**	**500**	**100**

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V. RESULTS AND DISCUSSION

With the purpose of finding new chemical entities when benzimidazolone condensed with benzothiazole will be show the enhanced antimicrobial activity as compared to standard drug. But the synthesized novel compound show negative results

VI. CONCLUSIONS

Benzimidazolone-Benzothiazole nucleus has been reported to possess several medicinal properties such as antibacterial, antiviral, anticancer, anticonvulsant,anthelminitic,antidepressant, antiasthamatic and antidiabetic activity etc. however; more experimental and clinical researchers should be conducted to support its therapeutic use. In conclusion, synthesis at different position of benzimidazole makes a wide variety of compounds. Given its broad spectrum of pharmacological activity benzimidazole presents itself as a novel nucleus

VII. ACKNOWLEDGMENTS

We are thankful to all analytical labs of Saurashtra University, Rajkot and Micro care laboratory, Surat for providing analysis support to analyzed newly synthesized compound

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