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SYNTHESIS, CHEMICAL CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF SOME NEW BENZIMIDAZOLE DERIVATIVES

Sangram U. Deshmukh*, Dr. B. Rajeeva[1], Balaji N. Thakare[2], M. J. Birajdar[3], Nandkishor B. Bavage[4]

*Latur College of Pharmacy, Hasegaon, Tq. Ausa Dist. Latur (MH) India.

[1]V.L. College of Pharmacy, Raichur.

[2]MUPS College of Pharmacy, Degaon, Tq Risod.

[3]Channabasweshwar College of Pharmacy, Latur.

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***Corresponding Author**
Sangram U. Deshmukh
Latur College of Pharmacy,
Hasegaon, Tq. Ausa Dist.
Latur (MH) India.

ABSTRACT

Substituted benzimidazole have received considerable attention during last decades as they are endowed with variety of biological activities and have wide range of therapeutic properties. The Mannich base derivatives of (1H-Benzimidazol-2-ylsulfanyl) acetic acid & 5-Methyl(1H-Benzimidazol-2-ylsulfanyl) acetic acid were synthesized and the structure of synthesized compound confirmed by spectroscopic techniques like 1H NMR, IR and mass spectrometry. All the synthesized compounds were screened in vitro for antibacterial and antifungal activity by paper disc diffusion method using Nutrient agar media against *Bacillus subtilis*, *Bacillus pumilus*, *Escherichia coli* and *Pseudomonas aeruginosa*, bacterial strain & potato dextrose agar medium against *Aspergillus niger* and *Candida albicans*. Cefrofloxacin were used as standard for antibacterial and Clotrimazole used as standard for antifungal activity respectively. The antimicrobial activity screening reveled that, the $3a_1$, $3a_2$ and $3a_3$ compounds were found to possess a significant activity against bacteria and $3a_4$ against fungi and rest of compounds are mild to moderate active in the conc. 100 µg/ml.

KEYWORDS: Benzimidazole, Spectroscopy, Cefrofloxacin, bacillus subtilis, Clotrimazole, Disc diffusion.

INTRODUCTION

Many important biochemical compounds and drugs of natural origin contain heterocyclic ring structures. Among these eg: Carbohydrates, essential amino acids, vitamins, alkaloids, glycosides etc. the presence of heterocyclic structures in such diverse types of compounds is strongly indicative of the diverse types of the pharmacological activity and recognition of this is reflected in efforts to find useful synthetic drugs.

An important feature of modern pharmaceutical chemistry is the introduction of more refined and sensitive methods of physicochemical analysis such as photometry and chromatography that enable one to assay the quality and quantity of the drugs more accurately with the smallest consumption of the analyze, reagent and time.

Pharmaceutical chemistry is a science that makes use of general laws of chemistry to study drugs, i.e. their preparation, chemical nature, composition, structure, influence on an organism and studies of the physical and chemical properties of drugs, the methods of quality control and the conditions of their storage. Pharmaceutical chemistry occupies the most important place among the related sciences e.g. Drug technology, Toxicological chemistry, Pharmacognosy, and the organization of the pharmacy.

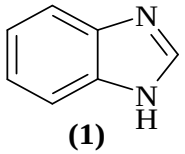
At the same time pharmaceutical chemistry being a specialized science depends on their chemical (inorganic, organic, analytical, physical and colloidal chemistry.) and also on medico biological (pharmacology, physiology, biological chemistry) disciplines.

Pharmaceutical chemistry began in 16th century and gave birth to Medicinal chemistry in the second half of the 17th century. Pharmacists played a major role in the birth and development of pharmaceutical chemistry. Medicinal chemistry, according to Berger, “tries to be based on the ever increasing hope that biochemical rationales for drug discovery may be found”. The first use of synthetic molecules for interference with the life process was probably, when chloroform and ether were introduced for anesthesia in the first half of 19th century.

BENZIMIDAZOLES

Benzimidazole[1]

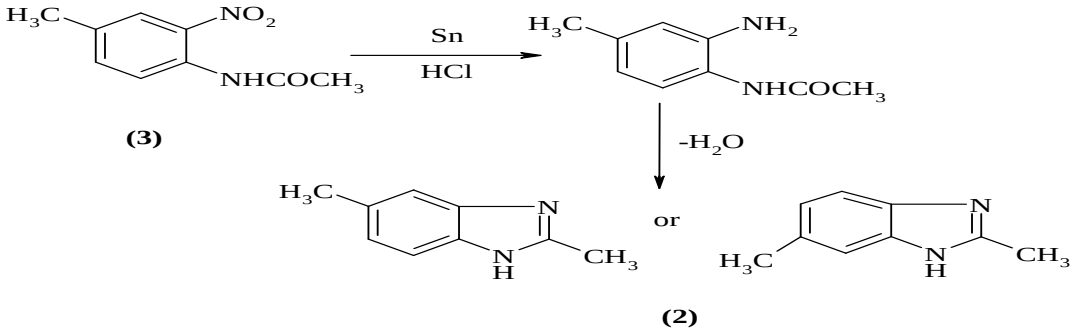
The benzimidazole contains a phenyl ring fused to an imidazole ring, as indicated in the structure of benzimidazole(1).



(1)

The important group of substances has found practical application in a number of fields. Recently in benzimidazole chemistry has been revived somewhat by the discovery that the 5, 6-dimethyl benzimidazole moiety is a part of the chemical structure of vitamin B_{12}.

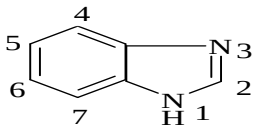
Historically, the first benzimidazole was prepared in 1872 by Hoebrecker, who obtained 2, 5 or 2, 6-dimethyl benzimidazole (2) by the reduction of 2-nitro-4-methyl acetanilide (3).



(3)

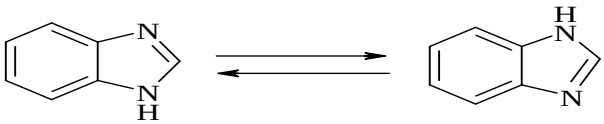
(2)

The numbering system for the benzimidazole is as follows: Occasionally 2-position is designated as the μ- position.



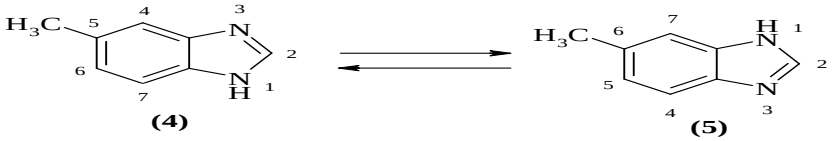
The benzimidazoles are also known as benziminazolones or benzoglyoxalines. They have been named also as derivatives of o-phenylene diamines.

Benzimidazole which contain a hydrogen atom attached to nitrogen in the 1-position readily tautamerise. This may be depicted as follows.[2]



The benzimidazoles in fact, may be considered as a cyclic analogue of the amidines. Because of this tautamerism in benzimidazoles certain derivatives which appear at first to be isomers

are in reality tautomers; although two non equivalent structures can be written, only one compound is known. This may be illustrated with 5 or 6-methyl benzimidazole.

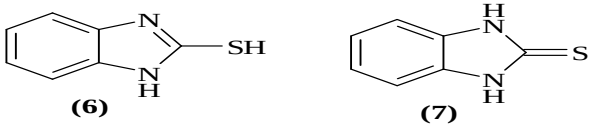


(4) (5)

Thus, 5-methyl benzimidazole (4) is a tautamer of 6-methyl benzimidazole (5) and both compounds represents the same compound.

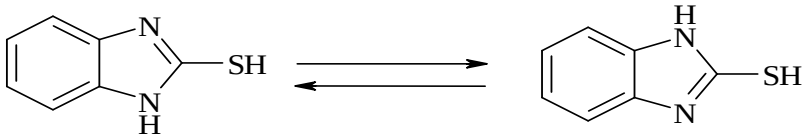
Benzimidazoline-2-thiones.[3]

A number of benzimidazoline 2-thiones have been synthesized by the general method described by Van allan and Deacon. The 2-mercapto benzimidazole (6) and benzimidazole -2- thione (7) are depicted as under.



(6) (7)

2-mercapto-benzimidazole which contain a hydrogen atom attached to nitrogen in the 1-position readily tautamerise. This may be depicted as follows.



EXPERIMENTAL WORK

Preparation of 2-mercapto benzimidazole(1a)

A mixture of o-phenylenediamine (0.1 mol), potassium hydroxide (0.1 mol) and carbon disulfide (0.1 mol), 100 ml of 95 % ethanol and 15 ml of water in a 500 ml round bottom flask were heated under reflux for 3 h. Then added 1-1.5 gm of charcoal cautiously and the mixture was further heated at the reflux temperature for 10 min, the charcoal was removed by filtration. The filtrate was heated to 60-70 ^{o}C, 100 ml of warm water was added and acidified with dilute acetic acid with good stirring. The product separated as glistering white crystals and the mixture is placed in a refrigerator for 3 h to complete the crystallization. The product was collected on a Buckner funnel and dried over night at 40 ^{o}C. The dried product is recrystalized by ethanol, the yield was (73%) and melting point was 300-302 ^{o}C. The

Compound (1b) can be prepared by using 4-methyl o-phenylenediamine by same procedure as mentioned above.The yield was (75%) and melting point was 290-292 ^{o}C.

SCHEME

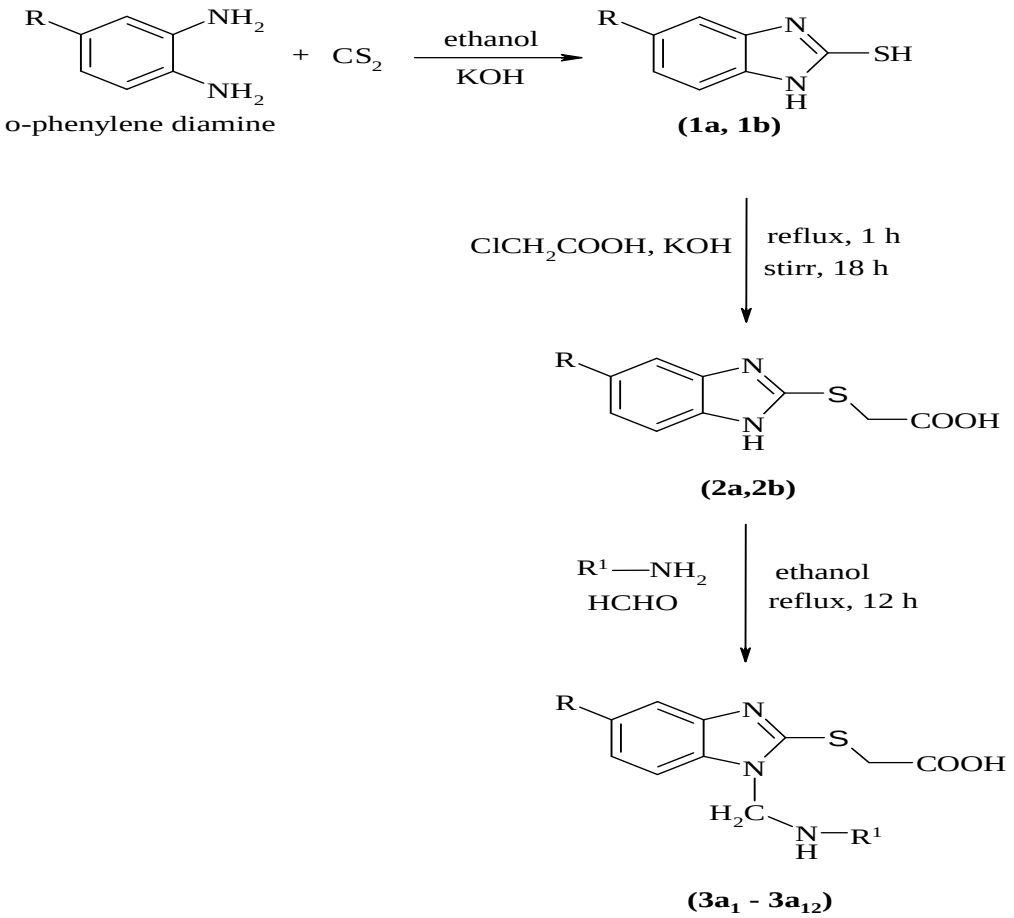


Fig-1: Scheme of Synthesis.

Preparation of (1H-benzimidazol-2-ylthio) acetic acid (2a)

Into a 250 ml round bottomed flask introduced a mixture containing 2-mercapto benzimidazole (0.013 mol), 20 ml of ethanol, potassium hydroxide (0.016 mol). The reaction mixture was refluxed at 78-80 ^{o}C for 1 h.

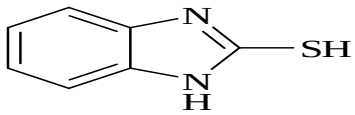
After cooling the resulting solution to 30 ^{o}C added chloro acetic acid (0.012 mol) in one portion, an exothermic reaction set in causing a temperature rise from 30-40 ^{o}C. After stirring at 25-30 ^{o}C for 18 h, the reaction mixture was added to 100 gm of ice-water and stirred for 30 min at 0-10 ^{0}C. The obtained precipitate was collected by filtration, washed with water until free of chloride, air dried at 50 ^{o}C and recrystalized from water. The yield was (79 %) and melting point was 206-208 ^{o}C. The Compound (2b) was prepared by using 5-methyl- 2-

mercapto benzimidazoleby same procedure as mentioned above. The yield was (74 %) and melting point was 214-216 ^{o}C.

Procedure for the preparation of Mannich Bases ($3a_1$-$3a_{12}$)

In to 100 ml clean and dry round bottom flask introduced benzimidazolyl thio acetic acid (**2a**) (0.002 mol) dissolved in sufficient quantity of ethanol and 3-4 drops of conc. HCl was added and reaction mixture was kept for stirring with help of magnetic stirrer. To the stirring reaction mixture formaldehyde (0.002 mol) was added drop wise and stirring was continued for 10 min. Meanwhile in another 100 ml beaker respective amine (i.e. R^1 see table 1 & 2) (0.002 mol) was dissolved in sufficient quantity of ethanol and was added into the above reaction mixture drop wise with continuous stirring, further stirring was continued for 15-20 min. After stirring the reaction mixture was refluxed for 12 h. The mixture was transferred into 100 ml beaker and allowed to cool at room temperature. The solid thus separated was filtered, dried and recrystallised from ethanol.

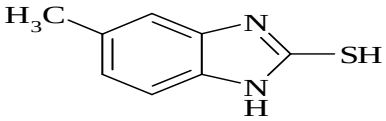
Compound (1a)



1H-Benzimidazole-2-thiol

Mol. Wt- 150, M.P.- 300-302°C, % Yield-73

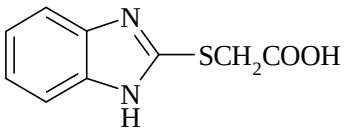
Compound (1b)



5-Methyl-1H-benzimidazole-2-thiol

Mol. Wt- 164, M.P.- 290-292°C, % Yield-75

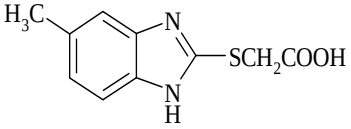
Compound (2a)



(1H-Benzimidazol-2-ylsulfanyl)acetic acid

Mol. Wt- 208, M.P.- 206-208°C, % Yield-79

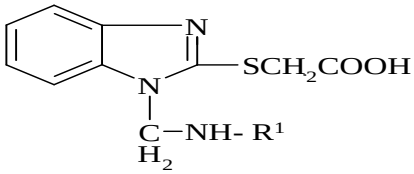
Compound (2b)



[(5-Methyl-1H-benzimidazol-2-yl)sulfanyl]acetic acid

Mol. Wt- 222, M.P.- 214-216°C, % Yield-74

Table-1.1: Physical characterization of the synthesized compounds ($3a_1$-$3a_6$).



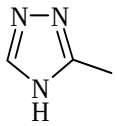
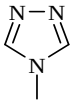
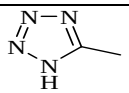
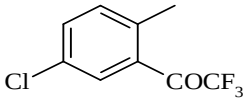
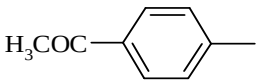
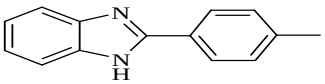
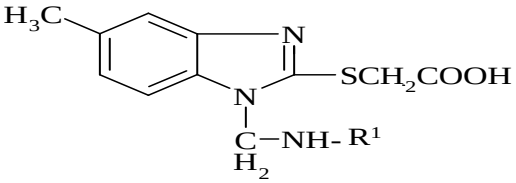
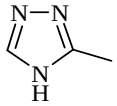
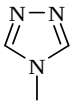
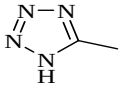
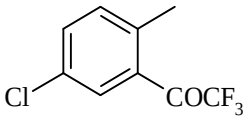
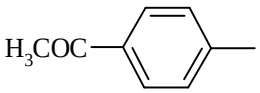
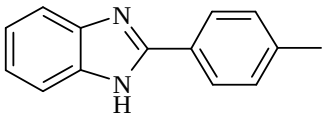
Compound Code	R^1	Molecular Formula	Molecular Weight	Melting Point (^oC)	Yield %
$3a_1$		$C_{12}H_{12}N_6O_2S$	304	256 - 258	56
$3a_2$		$C_{12}H_{12}N_6O_2S$	304	224 - 226	48
$3a_3$		$C_{11}H_{11}N_7O_2S$	305	234 -236	54
$3a_4$		$C_{18}H_{13}N_3O_3SClF_3$	444	276 -278	57
$3a_5$		$C_{18}H_{17}N_3O_3S$	355	203-205	49
$3a_6$		$C_{23}H_{19}N_5O_2S$	429	268-270	54

Table-1.2: Physical characterization of the synthesized compounds ($3a_7$-$3a_{12}$).



Compound Code	R^1	Molecular Formula	Molecular Weight	Melting Point (^oC)	Yield %
$3a_7$		$C_{13}H_{14}N_6O_2S$	318	182 - 184	52
$3a_8$		$C_{13}H_{14}N_6O_2S$	318	132 - 134	40
$3a_9$		$C_{12}H_{13}N_7O_2S$	319	174 -176	55
$3a_{10}$		$C_{19}H_{15}N_3O_3SClF_3$	458	252 -254	51
$3a_{11}$		$C_{19}H_{19}N_3O_3S$	369	183-185	50
$3a_{12}$		$C_{24}H_{21}N_5O_2S$	443	185-187	48

SPECTRAL DATA

Compound 2a

Table-2.1: ^{1}H NMR Spectra (δ ppm).

Value in δ ppm	Nature of segments	No of protons	Type of proton
12.7	Broad Singlet	1H	1H of NH
12.5	Singlet	1H	1H of OH of COOH
7.0-7.4	Multiplet	4H	4H of Ar-H
4.1	Singlet	2H	2H of CH_2 of CH_2COOH

MASS Spectra (m/z)

Molecular weight of the compound is 208; the molecular ion peak appeared at 209 as M+1.

Table-2.2: IR Spectra (cm^{-1}).

Type of Vibrations	Group frequency in Wave number (cm^{-1})
OH Band	3153
Benzimidazole NH stretching NH	3144
Ar-CH=CH Stretching	2980 and 2917
C=O Absorption band	1675

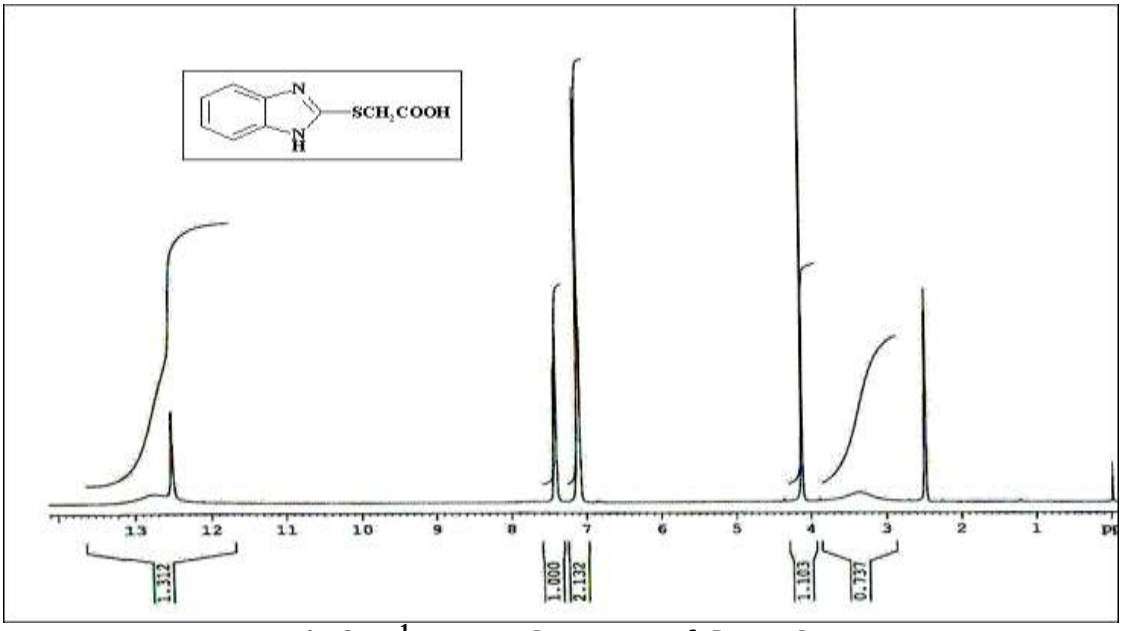


Fig-2.1: ^{1}H NMR Spectrum of Comp.2a.

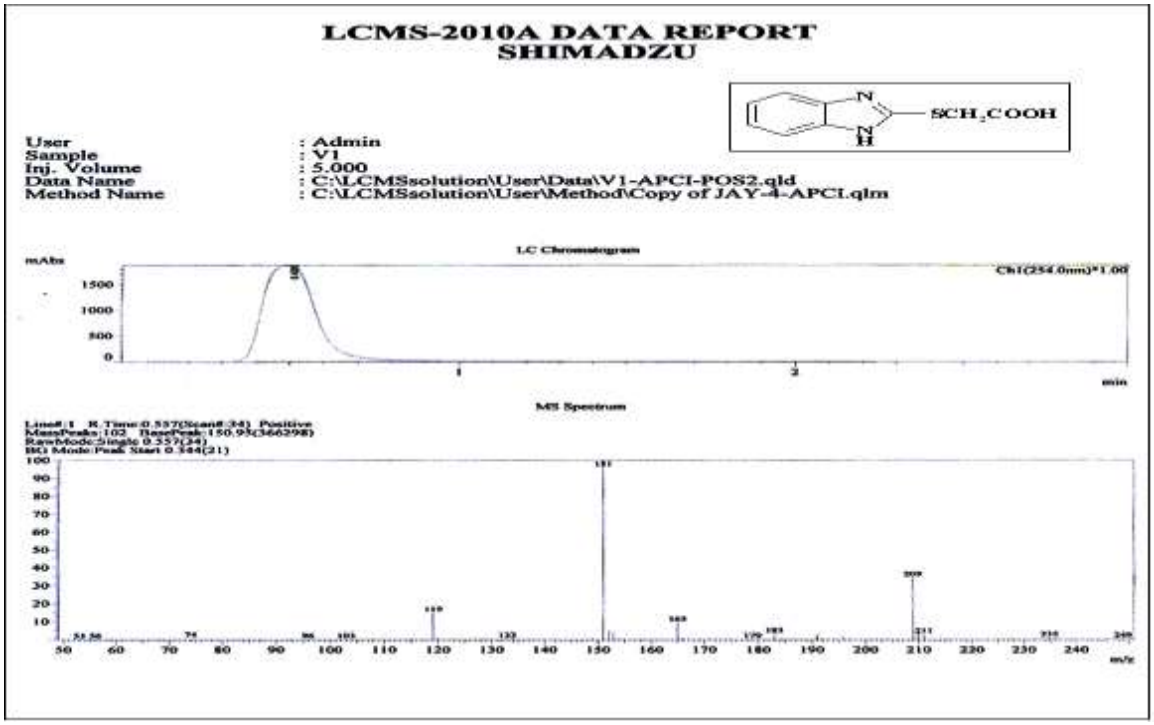


Fig-2.2: LCMS of Comp.2a.

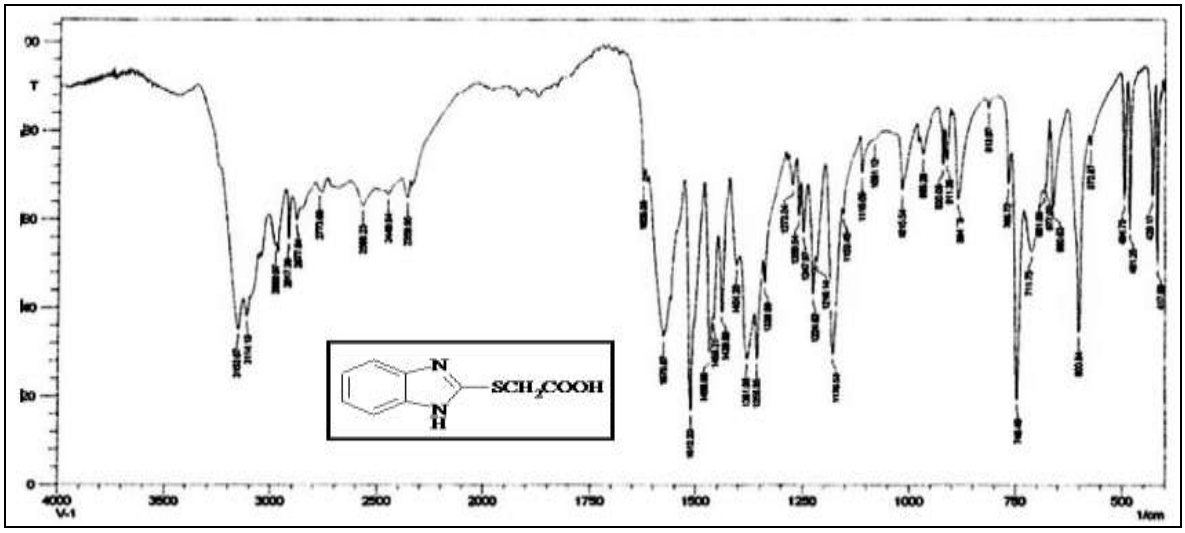
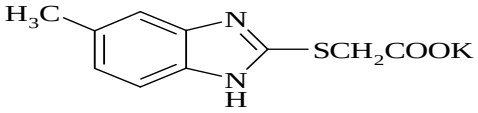


Fig-2.3: IR Spectrum of Comp.2a.

Compound 2b

Compound (2b)



Potassium salt of [(5-methyl-1H-benzimidazol-2-yl) sulfanyl]acetic acid

Table-2.3: ^{1}H NMR Spectra (δ ppm).

Value in δ ppm	Nature of segments	No of protons	Type of proton
12.4	Singlet	1H	1H of Benzimidazole NH
6.9-7.3	Multiplet	3H	3H of Ar-H
4.1	Singlet	2H	2H of -CH_2-COOK
2.3	Doublet	3H	3H of -CH_3

Table-2.4: IR Spectra (cm^{-1})

Type of Vibration	Group frequency in Wave number (cm^{-1})
NH Stretching	3114
Ar-CH Stretching	2980, 2917
C=O Absorption band	1680

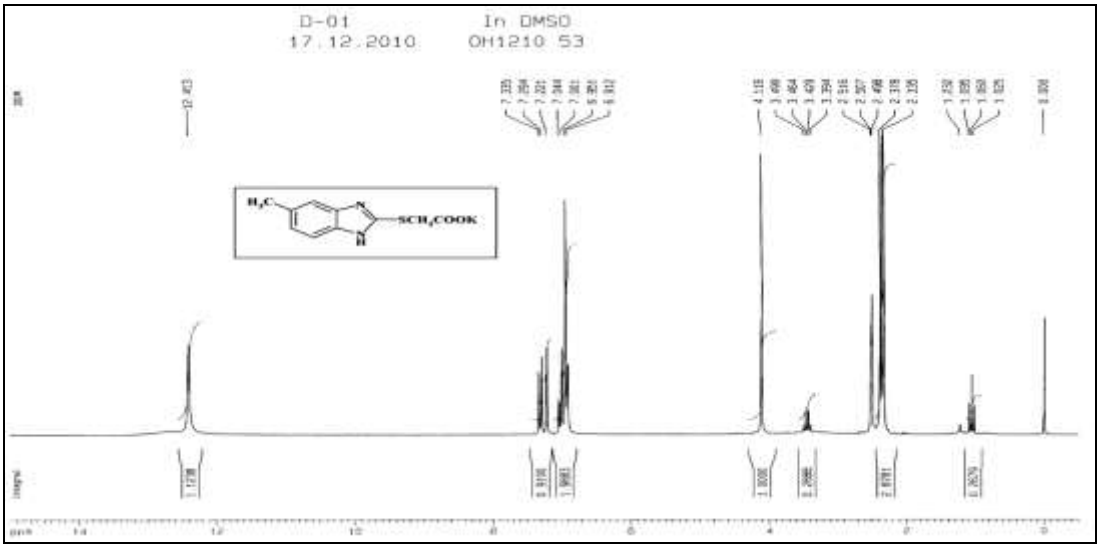


Fig-2.4: ^{1}H NMR Spectrum of Comp.2b.

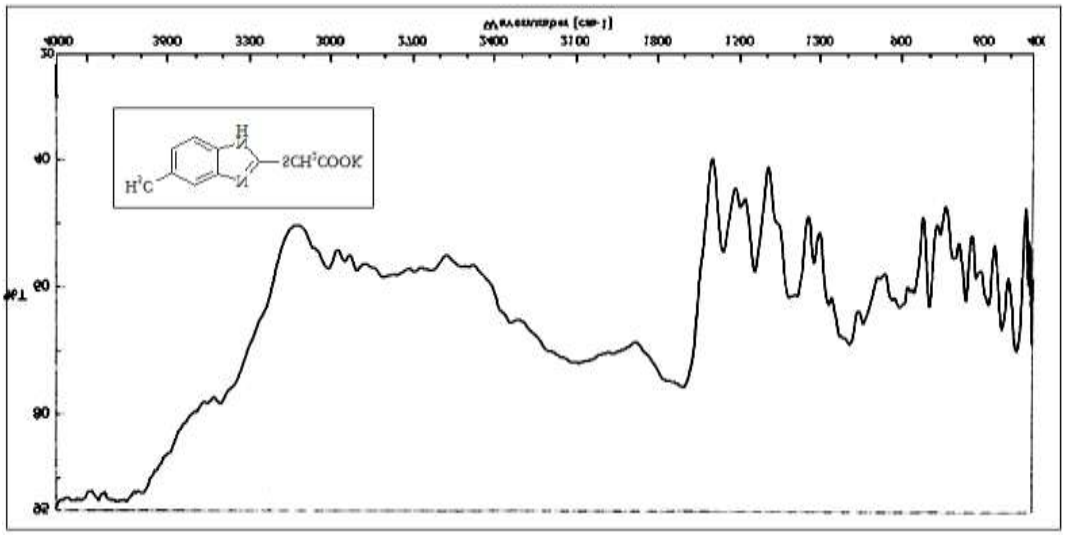
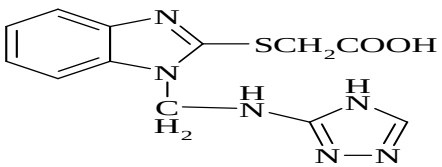


Fig-2.5: IR Spectrum of Comp.2b.

Compound 3a$_{1.}$

Compound ($3a_1$)



({1-[(4H-1,2,4-triazol-3-ylamino)methyl]-1H-benzimidazol-2-yl}sulfanyl)acetic acid

Table-2.5: ^{1}H NMR Spectra (δ ppm).

Value in δ ppm	Nature of segments	No of protons	Type of proton
9.6	Singlet	1H	1H of OH
7.6	Singlet	1H	1H of NH of (triazole)
6.4-7.3	Multiplet	6H	6H of (4H of Ar-H), (1H of CH triazole) and (1H of NH)
4.8	Doublet	2H	2H of N-CH_2-NH-
3.9-4.0	Doublet	2H	2H of CH_2 of CH_2COOH

Table-2.6: IR Spectra (cm^{-1}).

Type of Vibration	Group frequency in Wave number (cm^{-1})
NH Stretching	3180
Ar-CH=CH Stretching	2950 and 2870
C=O Absorption band	1678

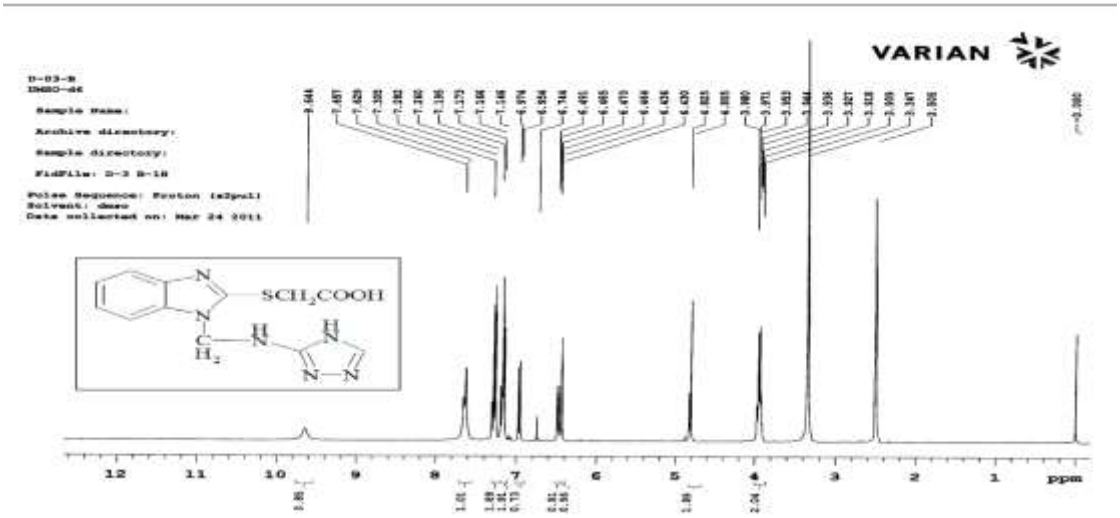


Fig-2.6: ^{1}H NMR Spectrum of Comp.3a$_1$.

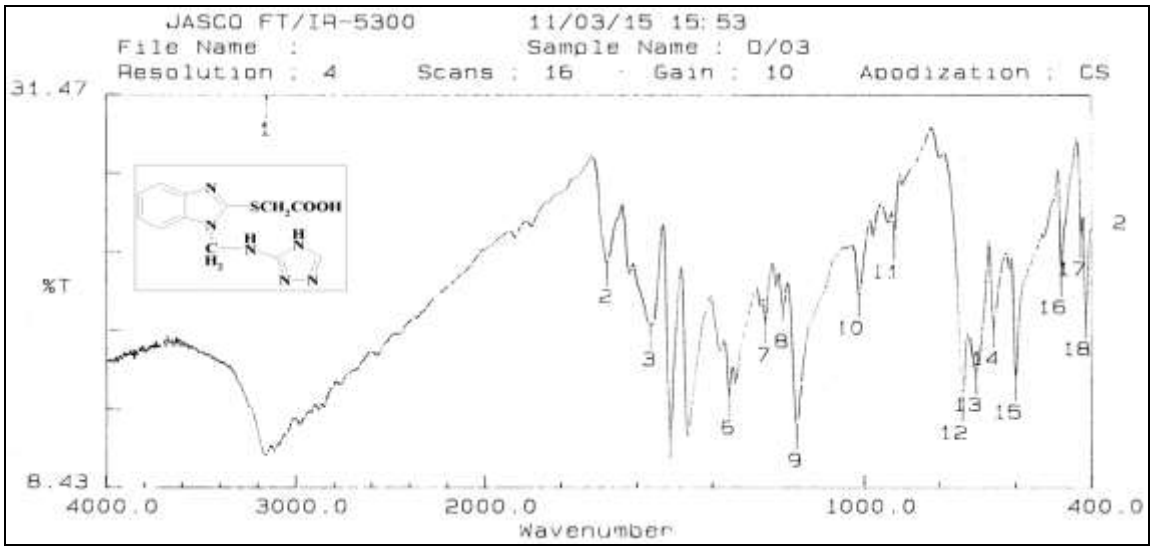
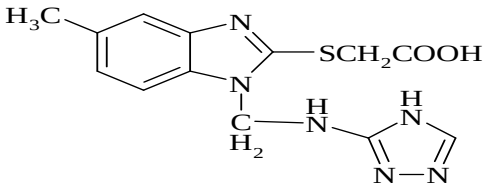


Fig-2.7: IR Spectrum of Comp.3a$_1$.

Compound 3a$_7$

Compound (3a$_7$)



({5-methyl-1-[(4H-1,2,4-triazol-3-ylamino)methyl] -1H-benzimidazol-2-yl}sulfanyl)acetic acid

Table-2.7: ^{1}H NMR Spectra (δ ppm).

Value in δ ppm	Nature of segments	No of protons	Type of proton
12.4	Singlet	1H	1H of OH
8.1-8.3	Broad Singlet	1H	1H of NH of (triazole)
6.9-7.4	Multiplet	5H	3H of (3H of Ar-H), (1H of CH triazole) and (1H of NH)
5.6	Multiplet	2H	2H of N-CH_2-NH-
4.2	Doublet	2H	2H of CH_2 of CH_2COOH
2.3-2.4	Doublet	3H	3H of CH_3

MASS Spectra (m/z)

Molecular weight of the compound is 318; the molecular ion peak appeared at 319 as M+1.

Table-2.8: IR Spectra (cm^{-1}).

Type of Vibration	Group frequency in Wave number (cm^{-1})
NH Stretching	3115
Ar-CH=CH Stretching	2950 and 2820
C=O Absorption band	1732
CH=N Stretching	1604

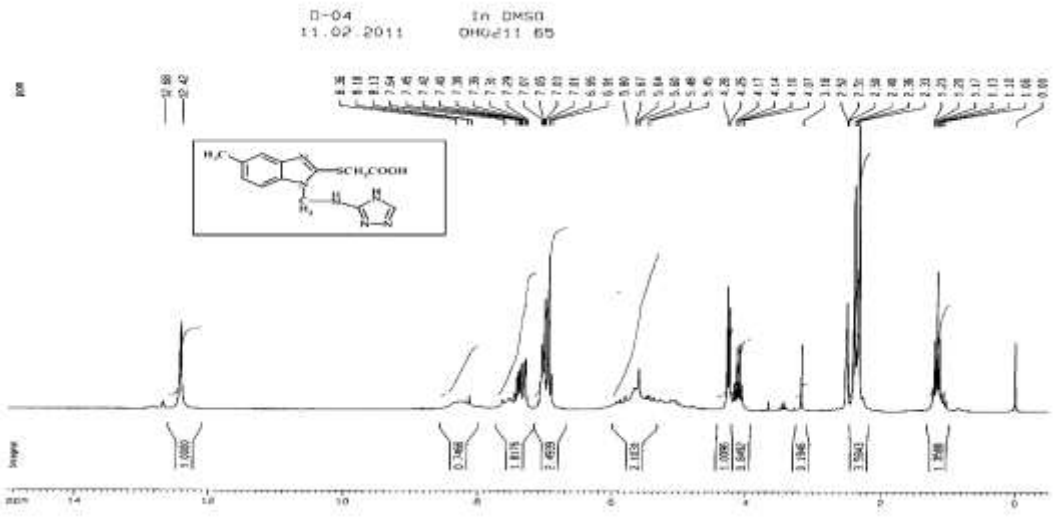


Fig-2.8: ^{1}H NMR Spectrum of comp.3a$_7$.

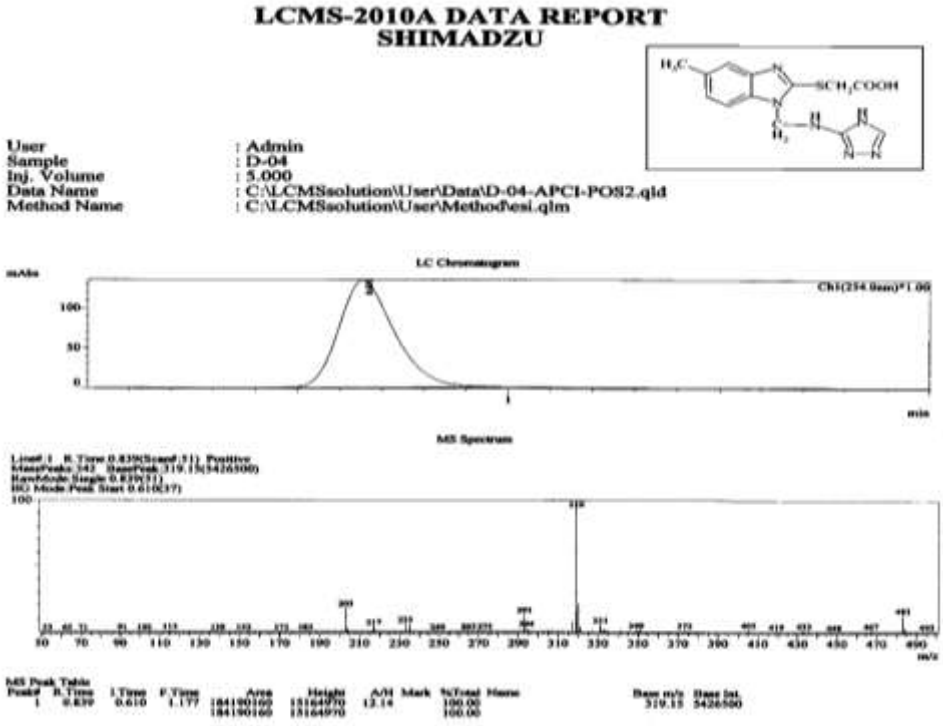


Fig-2.9: Mass Spectrum of Compound 3a$_7$.

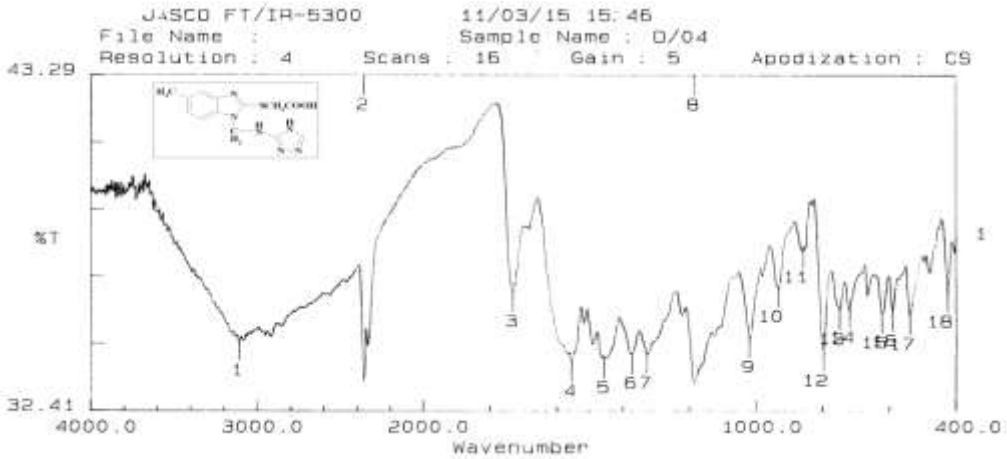


Fig-2.10: IR Spectrum of Compound3a$_7$.

BIOLOGICAL ACTIVITY

Antibacterial Activity

The compounds synthesized during the present investigation were screened for their antibacterial activity. The antibacterial tests were conducted on four common microorganisms such as *Bacillus subtilis*, *Bacillus pumilus*, *Escherichia coli* and *Pseudomonas aeruginosa*, which are the representative types of gram positive and gram-negative organisms respectively. The antibacterial activity of the compounds was assessed by disc diffusion method.

Table-3.1: Anti-bacterial activity of synthesized compounds ($3a_1$-$3a_{12}$).

Sample Code	*Inhibition of zone diameter in mm			
	B.subtilis	***B.pumilus***	***E.coli***	***P.aeruginosa***
	100µg/ml	**100µg/ml**	**100µg/ml**	**100µg/ml**
$3a_1$	17	12	8	16
$3a_2$	19	17	12	10
$3a_3$	18	19	11	14
$3a_4$	9	6	10	12
$3a_5$	8	7	9	10
$3a_6$	12	9	5	13
$3a_7$	5	10	8	12
$3a_8$	7	6	6	14
$3a_9$	10	6	13	9
$3a_{10}$	9	7	5	8
$3a_{11}$	6	8	8	8
$3a_{12}$	8	8	7	9
Standard Ciprofloxacin	28	30	32	30
DMF	-	-	-	-

*Each value is an average of three independent determination ± Standard deviation

Note: '-'denotes no activity, 8-12 mm poor activity, 13-17 mm moderate activity, 18-20 and above good activity.

Antifungal Activity.

Table-3.2: Antifungal activity of synthesized compounds ($3a_1$-$3a_{12}$).

Sample Code	Inhibition zone diameter in mm	
	A.niger	***C.albicans***
	100µg/ml	**100µg/ml**
$3a_1$	6	8
$3a_2$	13	12
$3a_3$	7	8
$3a_4$	10	14
$3a_5$	7	6
$3a_6$	8	7
$3a_7$	6	5
$3a_8$	7	6
$3a_9$	5	9
$3a_{10}$	6	8
$3a_{11}$	7	8
$3a_{12}$	13	8
Standard Clotrimazole	26	28
DMF	-	-

Note:- " NI" denote no activity, 06 – 08 mm poor activity, 08 – 12 mm moderate activity, 12-15 mm good activity.

RESULTS AND DISCUSSION

From the literature survey it reveals that novel benzimidazole have been reported for number of pharmacological and biological activities and some molecules have shown significant activities and some compounds shows moderate and good activities. Here we have synthesized some novel benzimidazole analogues and screened them for their anti-bacterial and anti-fungal activities and the results are as follows.

Antibacterial activity

All the synthesized compounds were screened for antibacterial activity studies at a concentration of 100µg/ml using DMF as a control against *B.subtilis, B.pumilus, E.coli* and *P.aeruginosa* by disc diffusion method on nutrient agar media, Ciprofloxacin 100µg /ml used as standard against Gram positive and Gram negative bacteria.

The data in the Table-3.1 indicate that$3a_{1,}$ $3a_2$ and $3a_3$ compounds were found to possess a significant activity against *Bacillus subtilis* and compound $3a_1$ shown significant activity against *Pseudomonas aeruginosa* and compounds $3a_2$and$3a_3$showed good activity against the organism*Bacillus pumilus* rest of the compounds were found to exhibit poor activity when compared to the standard Ciprofloxacin.

Antifungal activity

All the synthesized compounds were screened for antifungal activity studies at a concentration of 100 µg/ml using DMF as a control against *Aspergillus niger* and *Candida albicans* on potato dextrose agar media. Clotrimazole 100 µg/ml is used as standard. The data in Table-3.2 indicates that compound $3a_4$ show significant activity against *Candida albicans* rest of compound shown weak activity against *Candida albicans*. In addition $3a_2$and$3a_{12}$ showed significant activity against *Aspergillus niger* rest of compound show weak activity against *Aspergillus niger*.

CONCLUSION

From the data of the antibacterialand antifungal activity it is clearly concluded that the synthesized benzimidazole derivatives were found to be moderate to weak antibacterial agents. Here when the two moieties are fused and screened for antibacterial studies they showed moderate to weak antibacterial activity against Gram (+ve) and Gram (-ve) bacteria.

The substituted benzimidazole derivatives are already known for different biological activity. Here we have synthesized some novel benzimidazole analogues combining (1*H*-

benzimidazol-2-ylthio) acetic acid and 5-methyl (1*H*-benzimidazol-2-ylthio) acetic acidwith different amines in presence of formaldehyde with view to get good antibacterial agents with less toxic and side effects. Whereas the synthesised compounds shown moderate antibacterial activity.

Further the detail structure activity relationship studies are required along withthe molecular manipulation i.e. molecular modeling may give better drugs and furthertoxicological study is needed. Molecules prepared for the biological testing do notalwaysturn out as potential new molecules, but may be intended to serve as models forevaluation of the hypothesis.

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