CHAPTER II

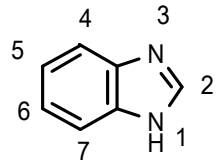
Synthesis of 2-propyl substituted

Benzimidiazole

INTRODUCTION AND LITERATURE SURVEY:

Benzimidazole is a heterocyclic aromatic organic compound. This bicyclic compound consists of the fusion of benzene and imidiazole. The most prominent benzimidazole compound in nature is *N*-ribosyl-dimethyl benzimidazole, which serves as an axial ligand for cobalt in vitamin B_{12} [1].

Benzimidazole, in an extension of the well-elaborated imidiazole system, has been used as carbon skeletons for *N*-heterocyclic carbenes. The NHCs are usually used as ligands for transition metal complexes. They are often prepared by deprotonating an *N, N'*-disubstituted benzimidazolium salt at the 2-position with a base [2, 3].

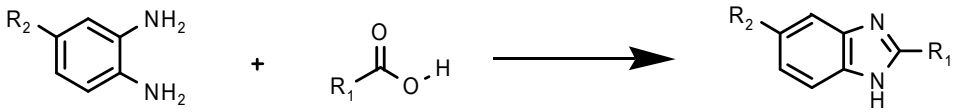


Benzimidiazole

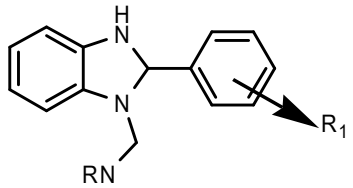
O-Phenylenediamine reacts with formic acid at 100°C to give benzimidazole in a yield of over 80%. *N*-mono substituted o-phenylenediamines react with other carboxylic acids more slowly, necessitating the addition of hydrochloric or phosphoric acid.

A mixture of tri fluoro methane sulfonic acid anhydride and trioxide in dichloromethane is a very efficient dehydrating agent. In light of the affinity they display towards a variety of enzymes and protein receptors,

medicinal chemists would certainly classify them as privileged 'sub-structures' for drug dosing. The incorporation of the nucleus is an important synthetic strategy in studies of antimicrobial drug discovery. In the past few decades, benzimidazole and its derivatives have received much attention due to their chemotherapeutic values.

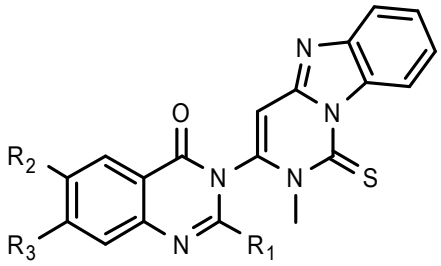


The compound which shows anti-inflammatory activity[4]. The compound showed maximum (54.6%) inhibition of edema at doses of 50 mg/kg.



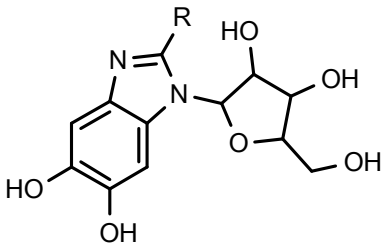
R= morpholine, diphenylamine, dimethyl amine, imidazoe
R_1= Cl

The compound 3-(2-methyl-1,2-dihydropyrimido (1,2-c)benzimidazole-1-thionyl)-6,8- dibromo-2-substituted-3*H*-quinazolin-4-one[5]. Synthesized compound showed moderate diuretic activity.



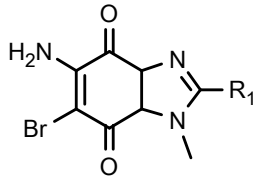
R_1=CH_3, Br, R_2= C_6H_5, R_3= H, Br,

The compound 2-(benzylthio)-5, 6-dichloro-1-(*β-D*-ribofuranosyl) benzimidazoles[6]. Compounds performed antiviral activity against HSV-1 and HCMV.



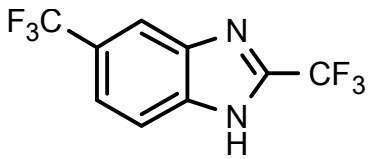
R= SCH_3, SO_2CH_3, $SO_2C_6H_5$

Some new benzimidazole-4,7-diones substituted at 2-position [7]. The compounds (10μM, 8μM and 3μM), performed excellent cytotoxic activity against colon (HT29), breast (T47D) and lung (A549) cancer cell lines and shown lowest IC50 values in (3μM).



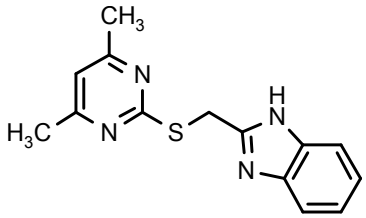
R_1= -$CHMe_2$, -CH_2-$CHMe_2NO_2$

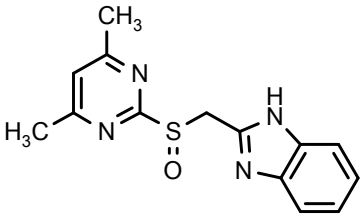
The compound anti-protozoal activity of 2-(trifluoromethyl)-1*H*-benzimidazole[8]. A series of 2-(triflouromethyl)-1*H*-benzimidazole derivatives with 5 and 6 position bio iso steric substituent (-Cl, -F, -CF3, -CN) were prepared by using short synthetic route. Analogues were tested *in vitro* against the protozoa *Giardia intestinals* and *Trichomonas vaginalis* compared with Albendazole and Metronidazole, have IC50 < 1 μM and compound was more active than Albendazole against *T. vulgaris* and also showed moderate antimalarial activity against W2 and D6 strains of *Plasmodium* falciparum.



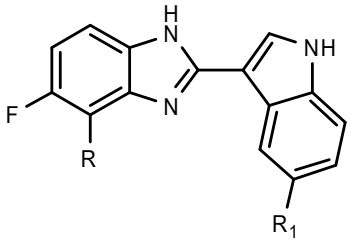
2,5-Bis-trifluoromethyl-1H-benzoimidazole

A series of novel pyrimidyl-thio-methyl- benzimidazole pyrimidyl-sulfinyl-methyl benzimidazole were synthesized[9] and Compounds evaluated for the antiulcer activity, the synthesized compound 30 mg/kg doses reduced the ulcer formation significantly comparable to standard (Omeprazole) and (sulfinyl derivative) compounds were more effective.

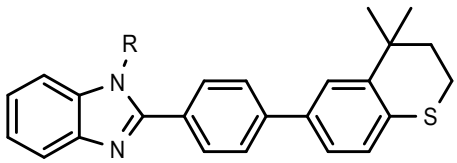




Some of 6-flouro-5-substituted *benzimidazole* in which indole and 1,4,4,4-tetramethyl-1,2,3,4-tetrahydro naphthalene groups were attached to the 2-position ring and tested for antioxidant activity were synthesized[10] .



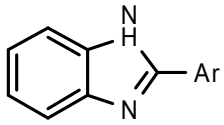
A series of novel and functionalized benzimidazole derivatives were synthesized[11] and the compounds have shown anti-diabetic activity against DPP-IV and PTP-IB and the compounds which shown inhibitory activity against PTP-IB (1.64 %, 2.42 %) at 30μM doses and 14c has shown inhibitory activity against DPP-IV (3%) at 0.3 μM doses.



R= H, Butyl

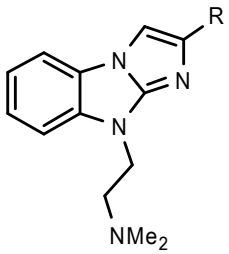
The compound 2-(aryloxyaryl)-1*H*-benzimidazole derivatives were synthesized [12] and compounds showed significant antispasmodic effect

in a concentration dependent manner, IC50 1.94 μM, 1.19 μM and 1.8 μM, compounds have shown potent relaxant smooth muscle activity.



Ar= $C_6H_5COC_2H_5$, 4-OH-3$OCH_3C_6H_5$,
2,3,4-$OCH_3C_6H_5$.

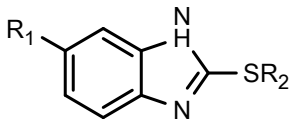
9-dialkylaminomethyl-2-oxy(dioxy)phenylimidazo[1,2-*a*]were synthesized benzimidazole and compounds possessed hypotensive activity (ED50: 2.8 mg/kg, 0.8 mg/kg, 0.13 mg/kg) ,(LD50: 121.0 mg/kg, 182 mg/kg, 143 mg/kg) and (LD50/ED50: 43.2, 227.5, 1100), the most active compound out of these was exceeded the reference drugs (Dibazole and Apressin) (ED50: 22.1, 4.0) with respect to both the degree of the hypertensive action (ED50) and the conditional therapeutic index (LD50/ED50).



R= 1-4 dihydroxy methyl benzene
1,3-dihydroxymethyl benzene

Substituted 2-polyfluroalkyl and 2-nitrobenzyl sufanyl benzimidazole[13] Were synthesized and Compounds were evaluated for

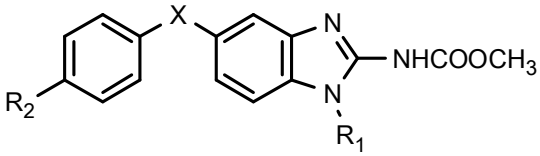
their activity against mycobacterium strains and compounds which showed appreciable anti-mycobacterial activity compound 20a, 20b and 20c have shown their MIC values 2 μmol L-1, 2 μmol L-1 and 4 μmol L-1.



$R_{1=}$ Cl, Br

R_2= Methyl Nitro Benzene, C_4H_9

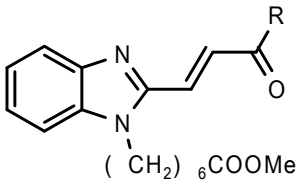
2-benzimidazole carbamic acid methyl ester derivatives [14] were synthesized and the Compounds have shown anthelmintic activity against *Nippostrongilus*, *Ankilostoma* and *Haemonhus* larvae that exceeded 65% upon per oral administration in animals (rats, sheep, dogs) at a dose of 2.5-50 mg/kg. In another group of animal inhibition action is below 40% upon per oral administration in a dose of 50-100 mg/kg.



R_1= $COOCH_2CH_2OCH_3$,$CONHCH_2CH_2COOCH_3$

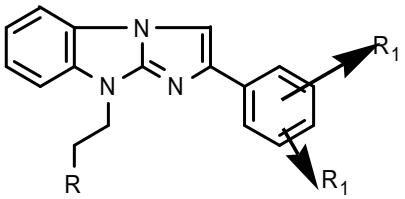
R2 = H, X = S

2-(1-2-methylene-3-methylene-3-hydroxyoctyl)-*N*-(6-methoxy carbonyl hexyl) benzimidazole derivatives were synthesized[15] compounds shown comparable results with F2α prostaglandin preparation Enzaprost and spasmogenic action of these compounds significantly lower (4-6 times) than Enzaprost.



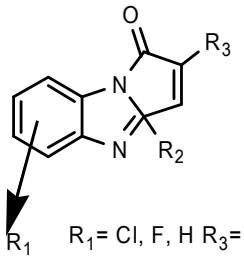
R= Cyclopropylheptan-1-ol,
cyclopropylheptan-1-one

The compound 9-dialkylaminoethyl-2-oxy(dioxy)phenylimidazo [1,2-a]benzimidazole derivatives[16] were synthesized the compounds exhibited the anti-arrhythmic activity.



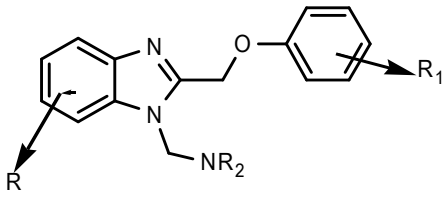
R=Diethylamine, Ethoxyethylethanamine.
R_1= OH, R_2= H

A novel 1*H*-pyrrolo (1,2-a)benzimidazole-1-one derivative synthesized and Compounds showed (84 %, 67% and 69 %) by maximal electroshock method, at dose level 25 mg/kg orally. The compound showed maximum anticonvulsant activity.



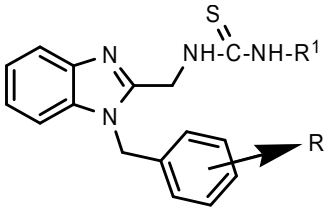
R_1= Cl, F, H R_3= H
R_2= C_6H_5

A series of 1-heterocyclic amino/iminomethyl-2- substituted benzimidazoles were synthesized [17] and were screened for their neuro pharmacological and monoamine-oxidase inhibitory properties. A number of such compounds showed CNS stimulant, anticonvulsant and mono amine oxidase inhibitory activities.



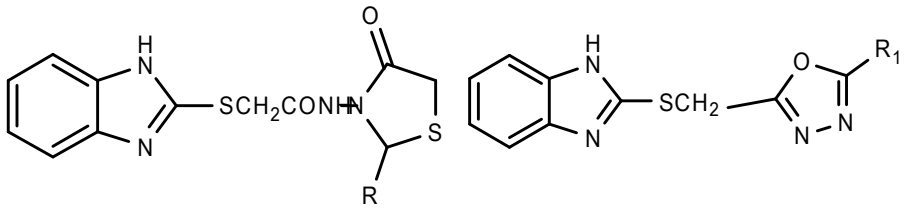
R= H,Cl, R_2= H,CH_3,C_2H_5
R_2= H.C_6H_5.

A number of new 1-[(1-(2-substituted benzyl)-1*H*-benzo[*d*]imidazol-2-yl) methyl]-3-arylthioureas compounds were synthesized [18]. All the newly synthesized compounds were screened for their anticonvulsant activity in ip MES and sc PTZ model and were compared with the standard drug phenytoin. Majority of the compounds exhibited significant activity against both the animal models however compounds displayed promising activity.



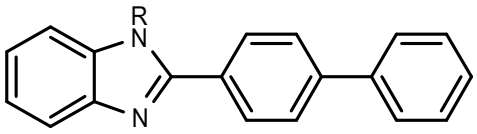
R= H,Cl. R^1= Ph. 2-$CH_3C_5H_5$, 3-$CH_3C_5H_5$ 4-$CH_3C_5H_5$,
2-$OCH_3C_5H_5$, 3-$OCH_3C_5H_5$, 4-$OCH_3C_5H_5$

A benzimidazole derivatives, a group of 4-thiazolidinones and 1,3,4-oxadiazoles containing 2-mercapto benzimidazole were synthesized[19] and the compound screened for *in vivo* anticonvulsant activity by Maximal Electroshock (MES) model and antidiabetic activity using Oral Glucose Tolerance Test (OGTT). Compounds exhibited potent anticonvulsant results and showed excellent antidiabetic activities and also pharmacophore derived from active molecules suggested that presence of –OH group was a common feature in all active compounds.



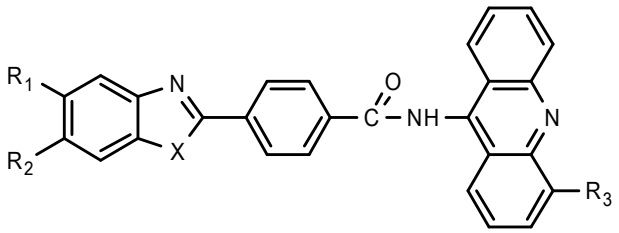
R= Ph, 4-Cl Ph, 2-PhOl,4-PhOl,4-$PhOCH_3$,4-$PhCH_3$
R^1= Ph, 4-Cl Ph, 2-PhOl,4-PhOl,4-$PhOCH_3$, 4-$PhCH_3$

A novel and functionalized benzimidazole derivatives were synthesized [20] and the compounds were tested against PDE-1V for potential anti-asthmatic effect, compound shown inhibitory activity (3.40%, 13.52% and 8.91%) at 1μm dose.



R= H, C_2H_5, $CH_2CH_2CH_3$

A series of *N*-(acridin-9-yl)-4-(benzo[*d*]imidazol/oxazol-2-yl) benzamide were synthesized[21] and the compound containing R1 = NO2, R2 = H, R3 = H, X = NH showed significant *in vitro* activity against CDK-5 (IC50 = 4.6 lM) and CDK-1(IC50 = 7.4 lM) and compound having R1 = Cl, R2 = H, R3 = H, X = NH showed moderate CDK-5 inhibitory activity (IC50 = 7.5 lM). The other compounds showed moderate anti-inflammatory and analgesic activities.

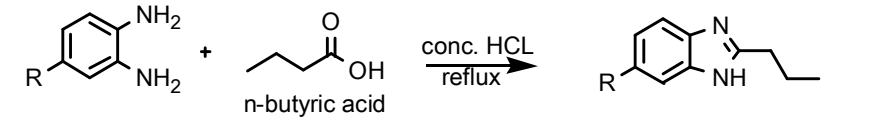


R_1= Cl, NO_2, CH_3,H R_2= H, CH_3.
R_3= H, OCH_3, X= NH, O

Experimental and spectral studies:

Synthesis of substituted 2-propyl Benzimidiazole.

Scheme I



0-phenelenediamine

2-Propyl-1H-benzoimidazole

1a-d

Experimental:

A mixture of substituted o-phenylenediamine (0.092mole) and aliphatic acid n-butyric acid (0.11mole) was refluxed in presence of Conc. HCl for four hours. A mixture of substituted o-phenylenediamines (0.92moles) and n-butyric acid (0.11moles) was dissolved in conc. HCl (10ml) and refluxed at 150C for four hours. Completion of reaction mixture was monitored by TLC. The content was cooled to room temp. and neutralized by saturated solution of NaHCO3, the solid separated was filtered, dried and taken as such for the synthesis of ethyl-(2-subsitituted -1-4-benzimidiazol-1-yl) acetate.

Physical properties:

Table No.2.1 Synthesis of substituted 2-propyl Benzimidiazole

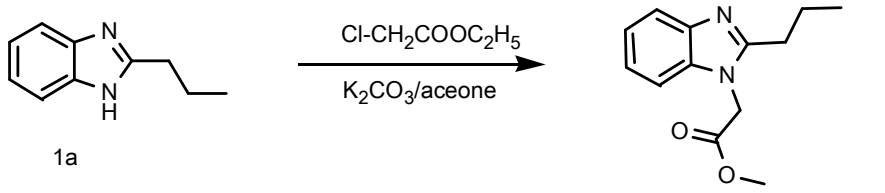
	R	Mol Wt	Mol. formula	% C	%H	N	Br	O
1a	H	160	$C_{10}H_{12}N_2$	75	7.5	17.5	---	-----
1b	Br	239	$C_{10}H_{11}N_2Br$	50.23	4.64	11.72	33.42	-----
1c	NO_2	205	$C_{10}H_{11}N_3O_2$	58.53	5.4	20.48	------	15.59
1d	OCH_3	190	$C_{11}H_{14}N_2O$	69.45	7.42	14.73	--------	8.41

Table No.2.2 Spectral data for synthesis of substituted 2-propyl Benzimidiazole

Comps.	R	Spectral data
1a	H	NMR - δ_{ppm}= 4H(s) 7.1, δ 2H(t) 2.60, 2H(m) 2.1, 3H(t) 1.3 IR -Ar H 3050 cm^{-1} γ C-H 2970 cm^{-1} γ C= H 1940 cm^{-1}
1b	Br	IR -Ar H 3050 cm^{-1} , γ C-H 2970 cm^{-1} , γ C= H 1940 cm^{-1}, γ C=C 1645 cm^{-1}, C-Br 800 cm^{-1} , NMR - δ_{ppm}= 4H(s) 7.0, δ 2H(t) 2.60, 2H(m) 2.1, 1H(t) 5.2 cm^{-1}
1c	NO_2	NMR - δ_{ppm}= 4H(s) 7.8, δ 2H(t) 2.60, 2H(m) 2.1, 3H(t) 1.3 1H(s) 5.6 γN-H 3500 $cm^{-1,}$ γ C=C 1640 $cm^{-1,}$ γ C-H 2975 cm^{-1}
1d	OCH_3	NMR - δ_{ppm}= 4H(s) 7.8, δ 2H(t) 2.60, 2H(m) 2.1, 3H(t) 1.3 1H(s) 5.7 IR -Ar H 3050 cm^{-1} ,γ C-H 2965 cm^{-1} , γ C= H 1940 cm^{-1} γ N-H 3500 $cm^{-1,}$ γ C=C 1640 $cm^{-1,}$

Scheme II

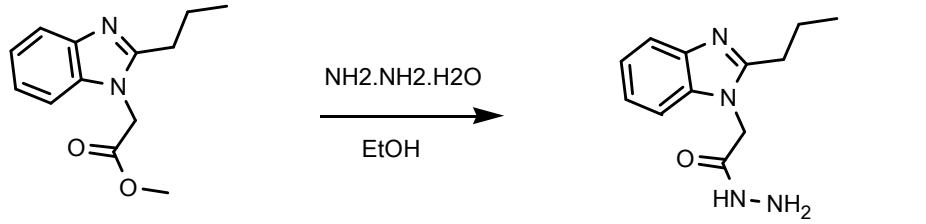
1]



1a

(2-Propyl-benzoimidazol-1-yl)
-acetic acid methyl ester

2]



(2-Propyl-benzoimidazol-1-yl)
-acetic acid methyl ester

(2-Propyl-benzoimidazol-1-yl)
-acetic acid hydrazide

comp I

Results and discussion:

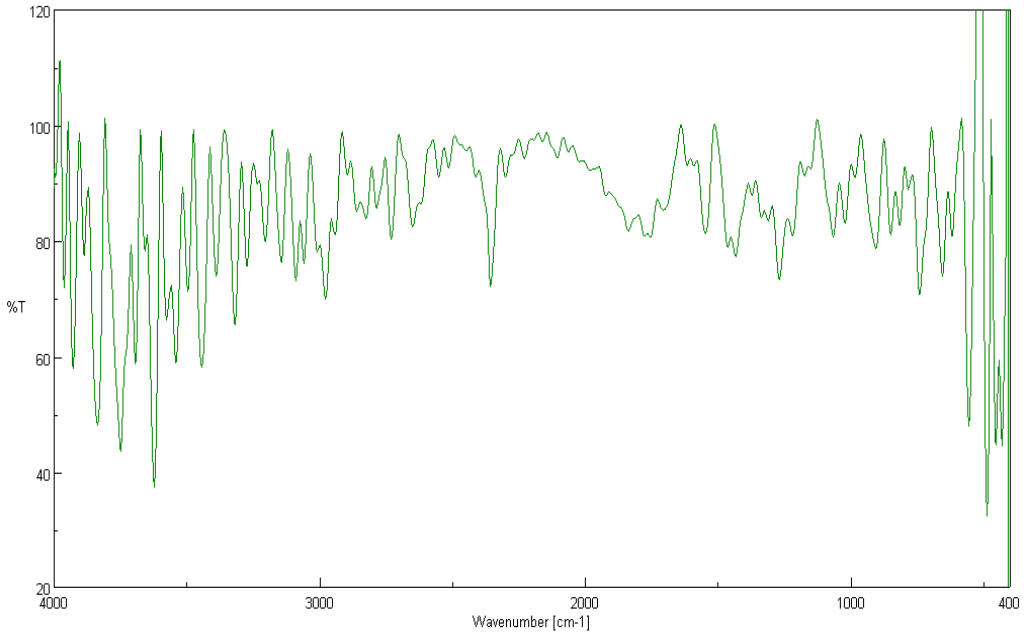
Here in the view of synthesis of some new benzimidazole analogue we have chosen multistep sequential routes. First we have synthesized different substituted benzimidiazole by the reaction of substituted o-Phenylenediamine and aliphatic n-butyric acid. Here we have performed the reaction by taking conc. HCl as a catalyst, after completion of the reaction for four hours, the reaction mixture was transferred to ice cold water containing $NaHCO_3$, and the precipitated solid was filtered and re-crystallized from alcohol.

The 2-substituted benzimidiazole on reaction with ethyl chloro acetate in presence of K_2CO_3 in dry acetone gave ethyl (2-substituted1H-benzimidiazole-1-yl) acetate, which on reaction with hydrazine hydrate gave 2-(2-propyl-1H-benzimidiazol-1-yl) acetohydrazide (comp I).

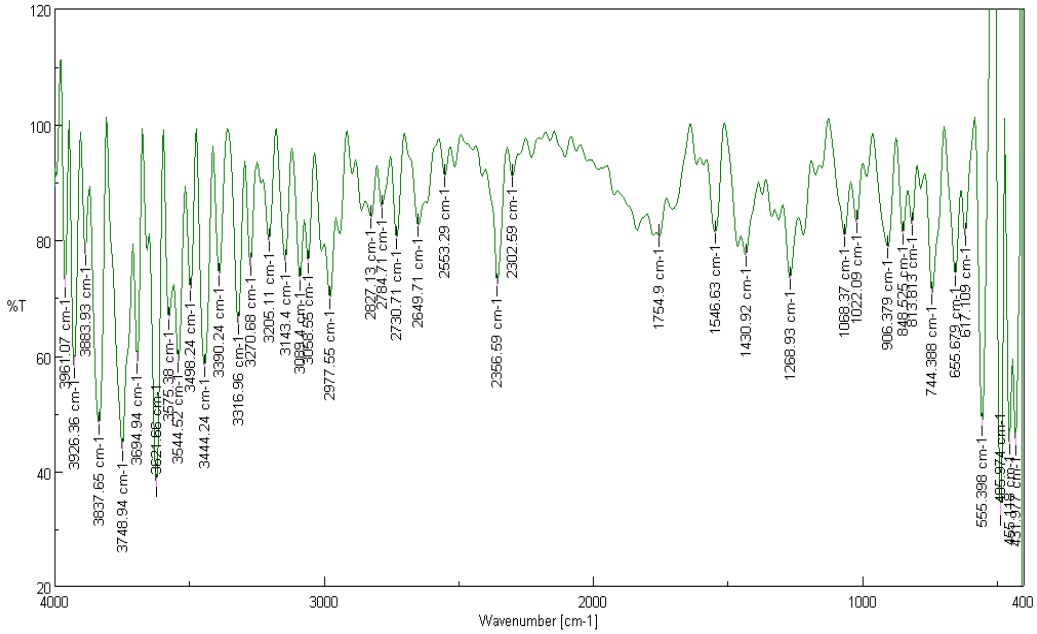
In the present work 2-propyl-1H-benzimidiazol-1-yl) acetohydrazide (comp I), which was previously prepared, was used as the key intermediate for further synthesis. Thus when compound 2-propyl-1H-benzimidiazol-1-yl) acetohydrazide was treated with carbon disulphide and potassium hydroxide 5-[2-(2-propyl benzimidiazole-yl) methyl][1,3,4]-oxadiazole -2(3H) thione was obtained.

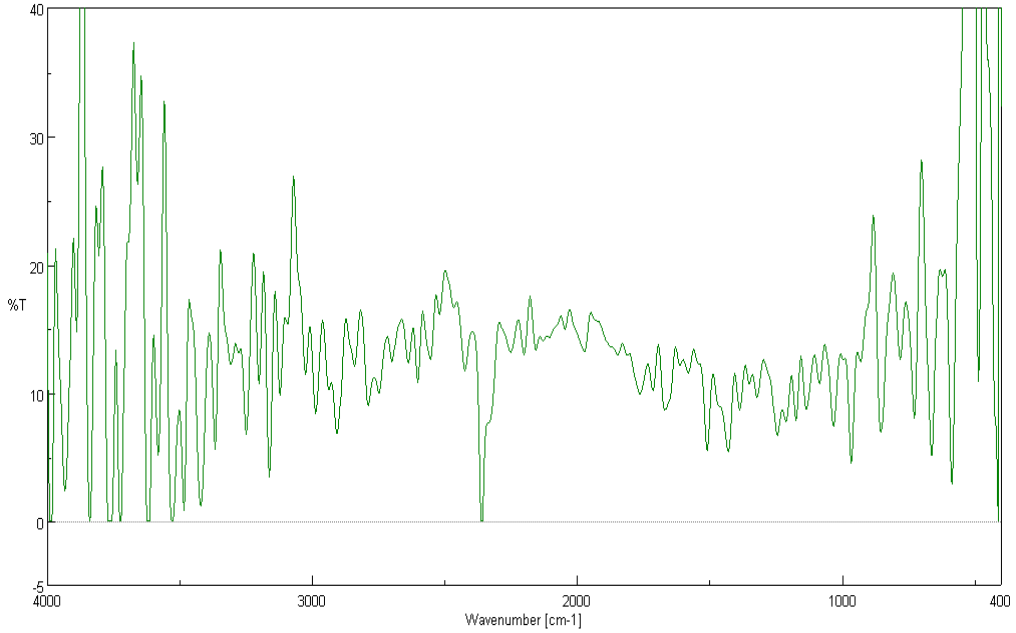
A 2-propyl benzimidiazole moiety incorporated into a triazole moiety was synthesized by the reaction of hydrazine hydrates (80%) in absolute alcohol which afforded 4-amino-5-(2-propylbenzimidiazole-1-ylmethyl)-4H-triazole-3-thiol. A number of arylidine hydrazone were synthesized from the parent benzimidiazole. Thus condensation of (2-propylbenzimidiazole) acetic acid hydrazide with aromatic aldehyde namely p-methoxybenzaldehyd, o-chlorobenzaldehyde etc. in absolute ethanol obtained hydrazone (Schiff's bases).

(CompI) 2-(2-propyl-1H-benzimidiazol-1-yl) acetohydrazide further reacts with substituted benzaldehyde in presence of catalyst iodine form corresponding hydrazones , after completion of the reaction monitored by TLC and re-crystallized by alcohol. The excess of iodine was removed by treating with sodium thio Sulphite solution, which removes excess of Iodine.

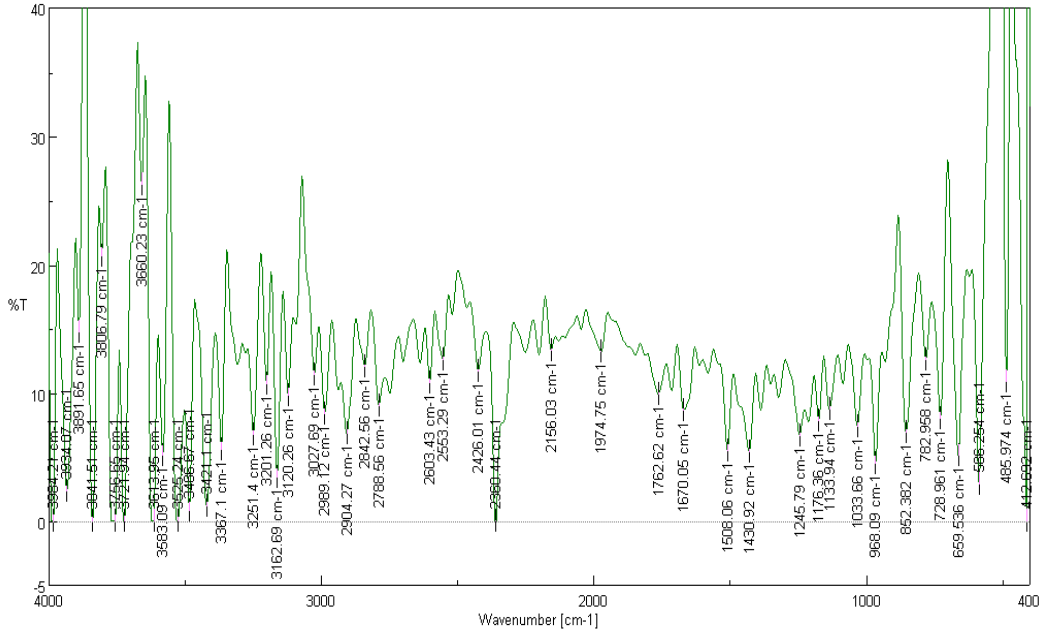


IR of 2-propyl benzimidizole





2- propyl-benzimidiazole-1-yl-acetic acid methyl ester



2- propyl-benzimidiazole-1-yl-acetic acid methyl ester.

Biological Screening Antimicrobial Activity:

The newly synthesized compounds were screened for their antimicrobial activity in vitro against gram positive (Bacillus cereus) and gram negative bacteria (E.coli) yeast (Saccharomyces cerevisae) and Fungi (Aspergillus Niger). The test was performed by disc diffusion method adopted with some modification for the prepared compound using Gentamycin and Ampicillin as reference. Whatmann filter paper No.1 disk of 5 of diameter were sterilized by autoclaving for 10 minutes at 120℃. The sterile discs were impregnated with different (600µg/disc).

Agar plates were surface inoculated uniformly from the broth culture of the tested microorganism. The impregnated disks were placed on the medium suitably spaced apart and the plates were incubated at 5℃ for 45 minutes to permit good diffusion and then transferred to an incubator at 37℃ for 24 hours. For bacteria incubator 27 ℃ for 48 hours. The inhibition caused by the various compounds on the microorganism was examined. The results of the preliminary screening test in table.

The antibacterial and antifungal activity compounds [1a- 1d] were tested and found that compound [1a-1d] was highly active against Bacillus cereus but slightly active against Escherichia Coli while compound 1b found slightly active and compound 1c and 1d were found moderately

active against B.Cereus . All compounds were inactive against Saccharomyces cerevisae and Aspergillus Niger.

Result of anti-microbial activites of the tested compounds.

Table No.2.3 Antimicrobial activities for synthesis of substituted 2-propyl Benzimidiazole

Compound No.	B. cereus	E.Coli	S.cerevisae	A.niger
Gentamycin	+++	+++	–	–
Ampicillin	+++	+++	–	–
1 a	+++	++	–	–
1b	+++	++	–	–
1c	+++	++	–	–
1d	+++	++	–	–

Key to symbols

Highly active = +++ (inhibition zone>12mm)

Moderately active = ++ (inhibition zone 9-12mm)

Slightly active = + (inhibition zone 6-9mm)

Conclusion:

2-propyl-1H-benzimidiazole,5-bromo-2-propyl-1H-benzimidiazole,5-nitro-2-propyl-1H-benzimidiazole and 5-methoxy-2-propyl-1H-benzimidiazole were synthesized and characterized by analytical and spectral techniques. These compounds exhibited significant activity against all the tested microorganisms.

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