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DOCKING, SYNTHESIS AND ANALYSIS OF 5-CHLORO-1-ISOPROPYL-2-[1-(4-ALKYL/ARYLPIPERAZIN-1-YL) ETHYL]-1H BENZIMIDAZOLES.

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ABSTRACT

Objective: The objective of this research was to docking, synthesis and analysis of new benzimidazole derivatives. **Methods:** The methods used were divided as Docking study, Preparation of structural library, Synthetic work and Spectral analysis of benzimidazole derivatives. On the basis of active site of Candida albicans, Structural Library of new series of benzimidazole were prepared and docked on Cytochrome p450 (CYP51) and five compounds were selected for synthesis showing highest docking score and Analyzed with NMR, IR, Mass Spectroscopy. Designed compound interact with Cytochrome p450 through hydrophobic and van der walls interactions. **Results:** Synthesized different substituted aryl Piperazines, 1-alkyl-2-[4-(alkyl/aryl) piperazin-1-yl] ethyl benzimidazole nucleus and condensed them to offer targeted compounds. The final compounds and intermediate were purified and their structures were established by Infra-red, mass spectroscopy. All important intermediate and final compounds were monitored by TLC, gas chromatography and the structure confirmed by mass spectroscopy with molecular ion peak and NMR spectra which are given in spectral analysis. **Conclusion:** A new class of 5-Chloro-1-isopropyl-2-[1-(4-alkyl/aryl piperazin-1-yl)-ethyl]-1H benzimidazole derivatives were synthesized and Analyzed. This investigation opens new area of antifungal agents, which are cheaper and simple and very selective than the existing azoles antifungal agents.

KEYWORDS: Docking, Benzimidazole, Synthesis, NMR, IR, Mass Spectroscopy.

INTRODUCTION

A **fungus** is a member of a large group of eukaryotic organisms that includes microorganisms such as yeasts and molds (British English: moulds), as well as the more familiar mushrooms. These organisms are classified as a kingdom, **Fungi**, which is separate from plants, animals, and bacteria. One major difference is that fungal cells have cell walls that contain chitin, unlike the cell walls of plants, which contain cellulose. Fungi lack chloroplasts and are heterotrophic organisms, requiring preformed organic compounds as energy sources Fungi contain unicellular, multinucleate, and multicellular forms.[1]

Fungal infections are important causes of morbidity and mortality in hospitalized patients, candidacies is the fourth most common blood cultures isolate at US hospitals, pulmonary aspergillosis is the leading cause of death in bone marrow transplant recipients, and Pneumocystis carinii pneumonia is the leading cause of death in AIDS patients in North America and Europe. Currently many antifungal drugs are available to treat the life threatening infections with good antifungal activity, but suffer from a number of drawbacks such as water solubility, narrow spectrum, and serious toxic side effects like pruritis, gastrointestinal upset, thrombonephebitis, drug interference, bioavailability and hepatotoxicity. Along with this the cost of treatment for such infections is also on a high. So an ideal, which has a broad spectrum of activity and has a low on side effects, is to be found having a cheaper cost of treatment. The use of amphotericin B, known as the 'gold standard' is limited because of its infusion related reactions and nephrotoxicity. Also the use of azoles, such as fluconazole, econazole and miconazole, has resulted in clinically resistant strains of Candida species. A 3.6–7.2% of vaginal isolates of Candida albicans from women with candidal vaginitis is resistant to fluconazole. This situation highlights the need for advent of safe, novel and effective antibacterial and antifungal compounds.

It is generally recognized that drug discovery and development are very time and resources consuming processes. There is an ever growing effort to apply computational power to the combined chemical and biological space in order to streamline drug discovery, design, development and optimization. In biomedical arena, computer-aided or *in silico* design is being utilized to expedite and facilitate hit identification, hit-to-lead

selection, optimize the absorption, distribution, metabolism, excretion and toxicity profile and avoid safety issues. Commonly used computational approaches include ligand-based drug design (pharmacophore) a 3D spatial arrangement of chemical features essential for biologicalm activity), structure-based drug design (drug-target docking), and quantitative structure– activity and quantitative structure–property relationships. Regulatory agencies as well as pharmaceutical industry are actively involved in development of computational tools that will improve effectiveness and efficiency of drug discovery and development process, decrease use of animals, and increase predictability.[2]

MATERIALS AND METHODS

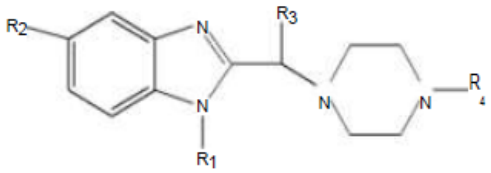
Experimental work

1. Docking study

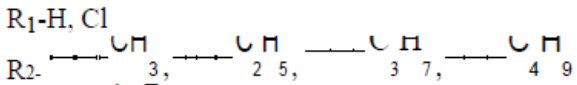
Maestro 9.2(Schrodinger software) was used for docking

2. Preparation of structural library

Following different substituent were considered according to previous study in our department.

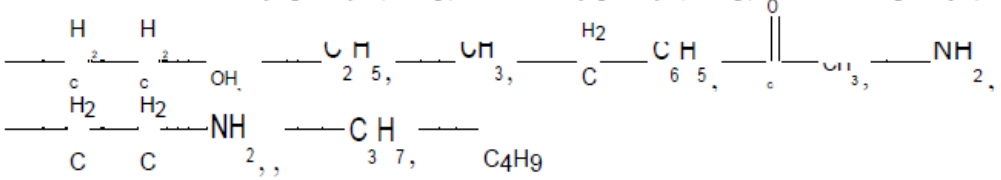


R1-H, Cl



R3- C_6H_5, CH_3

R4- C_6H_5,- Methyl phenyl (o,m,p), -Methoxy phenyl(o,m,p), -Chloro phenyl(o,m,p),



Library of all combination was made and docked these structures on Cytochrome P450 and following compounds were selected for synthesis on the basis of docking score and receptor interactions.

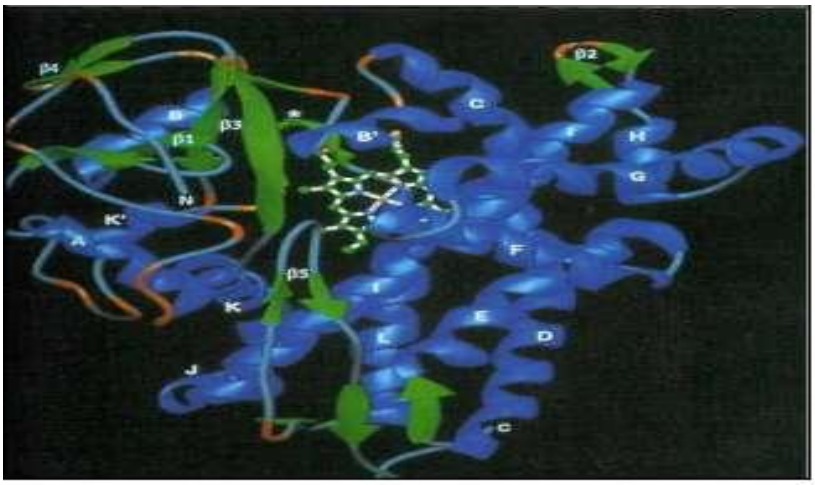


Fig .1: Cytochrome P450 general protein structure

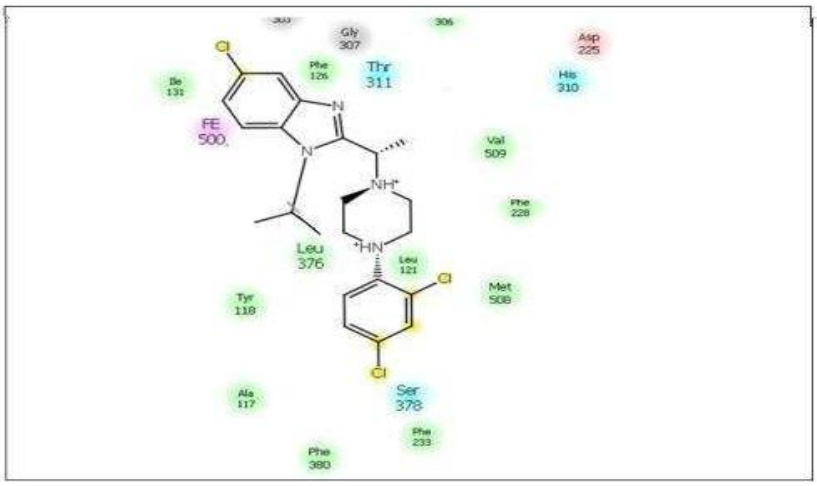
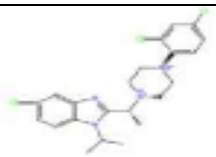
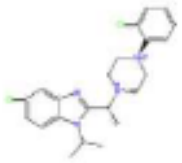
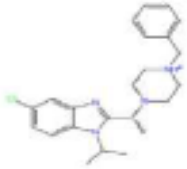
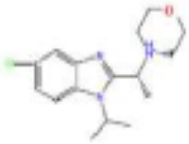
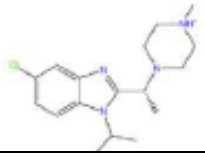


Fig.2: Interaction of VM2

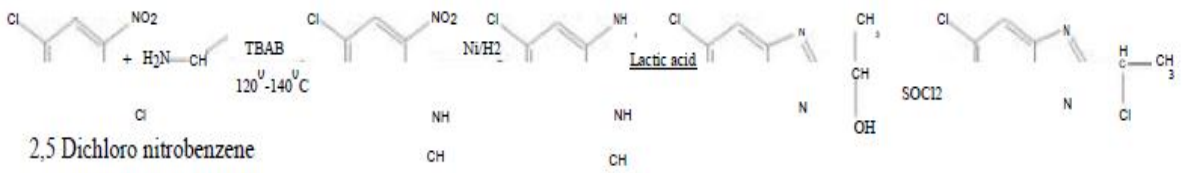
Fig.3: Drug receptor interaction

Table 1: Following compounds were selected for synthesis.

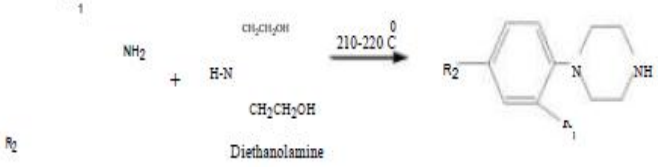
Sr.No	Structure	Docking score
1.		**-8.811**
2.		**-8.658**
3.		**-8.531**
4.		**-7.590**
5.		**-6.987**

3. Synthetic work.

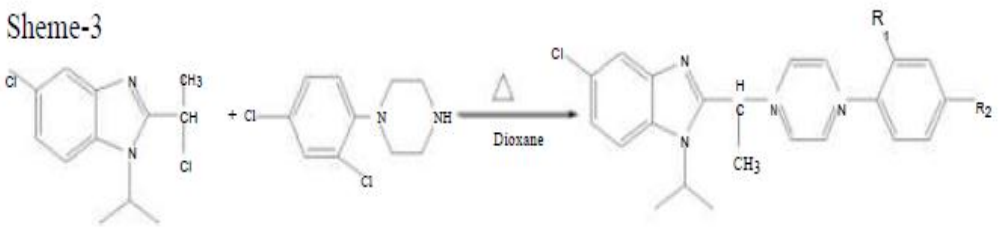
Sheme-1



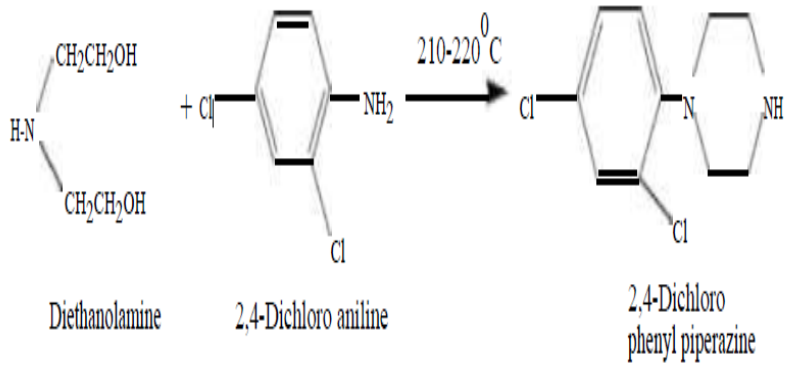
Sheme-2



Sheme-3



1) Synthesis of aryl Piperazines.



The following general procedure was adopted for the synthesis of various aryl Piperazines.

In a typical experiment, a mixture of 10.5 gm (0.1mol) diethanolamine and 48.6gm (0.3mol) of 2, 4-chloroaniline and 50 ml (0.6 mol) hydrochloric acid, in a three necked RBF, and it was distilled and solid mass remaining at bottom was heated at 215-225^{0}C on oil bath, then the mixture was treated with 50% sodium hydroxide and oily layer was separated and distilled with high vacuum to get pure product. Product was then precipitated in acetone with hydrochloric acid. Reaction was monitored by gas chromatography and product was confirmed by mass spectrometry.[3]

M^+-229.

NMR peaks-δ 7.10(s CH), 6.97(d,CH),6.47(d,CH),3.47(t CH_2),2.78(t CH_2).

Yield: gm (53%)

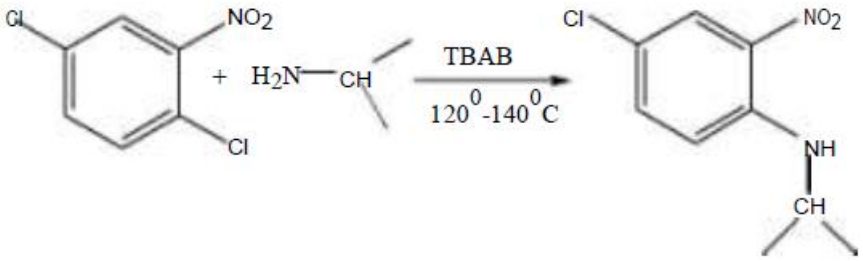
Following various Piperazine derivatives are prepared by same procedure and %purity was checked by gas chromatography.

Table 2: Various Piperazine.

Sr.No.	R	Yield (%)	GC	
			Purity (%)	Ret.time (min)
1.	2, 4 dichlorophenyl	76	90	8.2
2.	Benzyl	74	88	8.6
3.	N-Methyl piperazines	83	96	3.1
4.	2-chlorophenyl	80	97	4.9

(Ov101, 10%, 10^{0}C/min, 300^{0}C, injection temp. 280^{0}C)

2) Synthesis of 4-chloro N-isopropyl-2-nitroaniline.



Following general method was used for synthesis.

In autoclave reactor vessel ,384 gm(2 mole) of 2,5 dichloro nitrobenzene 354 gm(6 mole) of isopropylamine in 1-2 litres of water,40 gm of TBAB(Tetra butyl ammonium bromide) phase transfer catalyst was added ,then reaction was well maintained between temperture range of 120-140^{0}C and pressure of 3-4 Kg for 7-8 hrs.completion of reaction is monitored by gas chromatography and TLC.Reaction mixture was acidified with conc.HCl and precipited by conc.ammonia solution and above solid was collected and purified with pet.ether and hexane,purified orange solid was collected.and product confirmed by GC-MS.

M^+-214,216.IR peaks (cm^-)-1550, 1355, and 3300.

NMR 1H -δ 7.98(s,CH),7.44(d,CH),6.63(d,CH),2.97(septet,CH),1.18(d,CH_3)

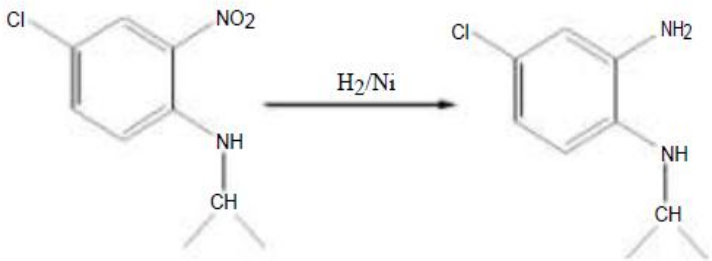
GC purity- 99.45%.

Melting point-60-650^{0}C

Yield- 150gm **(**50%)

R_f- 0.86 [benzene:cloroform(8:2)]

3) Synthesis of N^1-Isopropyl-o-Phenylenediamine**.**



Following general procedure was adopted for N^1-Isopropyl-o-Phenylenediamine.

In a typical expriment,30 gm of 4-chloro N-isopropyl-2-nitroaniline(0.13 mole) was dissolved in methanol .to the clear solution 5-6 gm of Raney Ni W-2 catalyst(Wet cake) was suspended. The reaction mixture was hydrogenated in 2 liters stainless steel container at pressure of 3 Kg till the hydrogen uptake is complete(4-5hrs).The completion of reaction was checked by TLC.The catalyst was filtered on hyflow bed washed with 50 ml methanol. The solvent was distilled under diminished pressure to get the product. And dark brown liquid (25 ml) was collected and used for next step. And product was confirmed by GC-MS.

M^+-183,185.

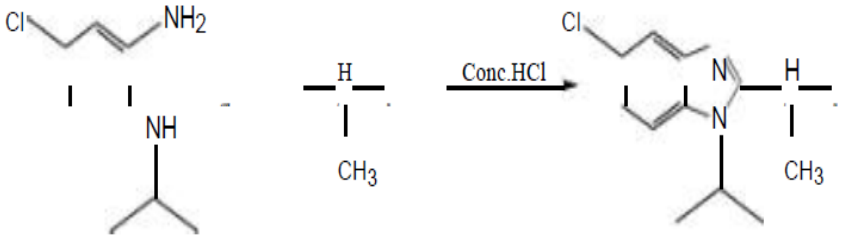
IR peaks (cm^-)-3419, 3352, 1660, and 3018

NMR 1H-δ 6.12(s,CH),6.3(d,CH),6(d,CH),3(sep.CH),1.2(d,CH_3).

Yield-50%

R_f- 0.50 [benzene:chloroform(8:2)

4) Synthesis of 1-(5-chloro-1-isopropyl-1*H*-benzoimidazol-2-yl) ethanol**.**



Following general procedure was adopted for Synthesis of 1-(5-chloro-1-isopropyl-1*H*-benzoimidazol-2-yl) ethanol. In a typical experiment, 15gm (0.08moles), 4-chloro-N^1- isopropyl phenylenediamine, 8 gm (0.08 moles) of lactic acid and 40 ml of conc. HCl was taken in a RBF and refluxed for 4 hrs. The reaction was monitored by TLC. A test portion was dumped in water and basified with sodium bicarbonate. The solid was extracted with) diethyl ether .and TLC of this extract was checked for the completion of reaction. After completion of the reaction, the reaction mixture was poured in ice-cold water. It was then basified with conc. ammonia solution. Product was sticky, extracted with diethyl ether. Ether was evaporated to get product.

Mass specra-238,240

IR peaks (cm^{-})-3462, 3018, and 2912.

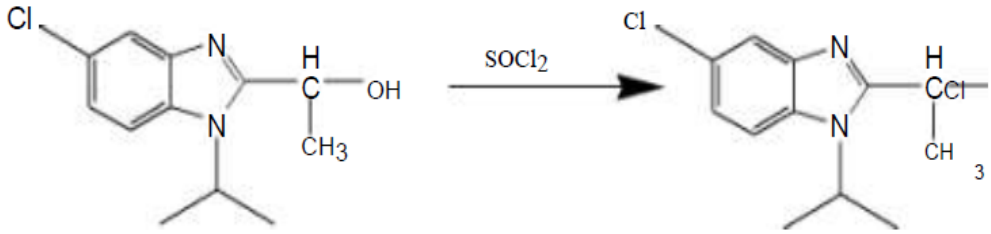
NMR-

1H-δ 7.71(s,CH),7.2(d,CH),7.6(d,CH),4(sep.CH),1.56(d,CH_3),4.6(s,CH),1.4(d,CH_3)

Yield: 80%

R_F: 0. 61[Benzene: acetone (8:2)]

5) Synthesis of 5-chloro-2-(1-chloro ethyl)-1-Isopropyl -1H-benzimidazole.



Following general procedure was adopted for Synthesis of 5-chloro-2-(1-chloro ethyl)-1-Isopropyl -1H-benzimidazole.

In a 250 ml three necks RBF, 60 ml thionyl chloride was transferred to a RBF and placed in an ice cold water bath. To it 10gm of 1-(5-chloro-1-isopropyl-1*H*-benzoimidazol-2-yl) ethanol was added slowly with occasionally shaking. Then placed RBF on heating mantel, fitted with a condenser and refluxed for 4 hrs. Excess thionyl chloride was recovered under vacuum on water bath. To the residue dry dioxane was added and stirred for half hour. Dioxane was recovered under vacuum to get product.

Mass spetra-M^{+}-256,258

IR peaks-(cm^{-}) 759,1650,3020,2975.

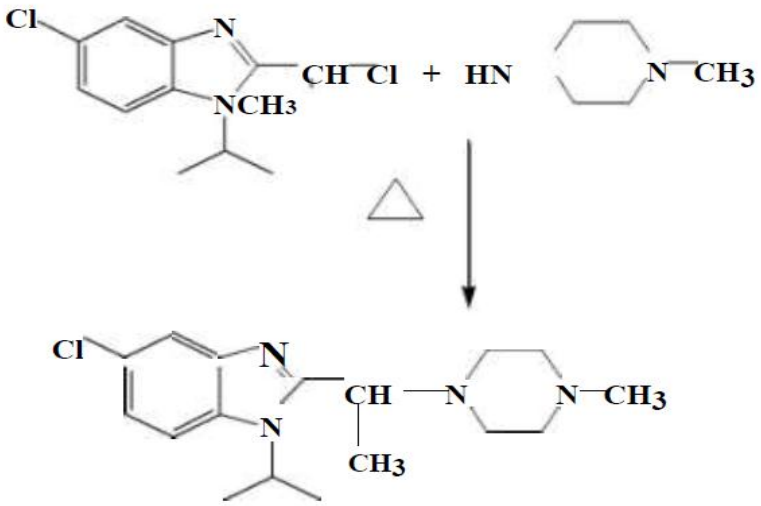
NMR 1H-δ 1.6(t.CH_3), 2(d, CH3), 5(sep.CH), 5.9(quar.CH), 7.3(d,CH),

Melting point: 126-128^{0}C

Yield: 12gm (71%) R_f: 0. 42 [Chloroform: Acetone (8:2)]

The following procedure was adopted for the synthesis of 5-chloro -1- isopropyl-2-[1-(4-alkyl/aryl piperazin-1-yl) ethyl]-1H Benzimidazole

6) 5-chloro -1- isopropyl-2-[1-(4-methylpiperazin-1-yl) ethyl]-1H Benzimidazole.



In a typical experiment, 1.3gm (0.005mol) of 5-chloro-2-(1-chloro ethyl)-1-Isopropyl -1H-benzimidazole,1.96gm (0.01mol) of N-methyl piperazine were dissolved in dry dioxane and mixed in an RBF. The reaction mixture was refluxed for 8 hrs. The reactions was monitored by TLC. The reaction mixture was then dumped in ice cold water and the product was collected by extraction with chloroform and dried.

IR peaks-(cm^{-})-752, 1515, 3020, and 1458.

NMR

1H-δ 7.71(s,CH),7.27(d,CH),7.6(d,CH),4(quar.CH),1.38(d,CH_3),2.46(t,CH_2),2.27(s,CH_3).

Yield: 50%

Rf: 0.5 [Chloroform: Acetone (8:2)]

Melting point: 107-110^{0}C

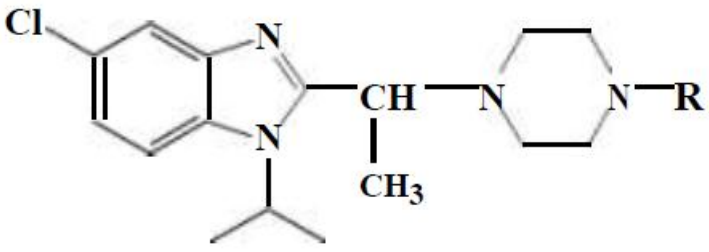


Table 3.

Sr.No	R	M.P (^{0}C)	Yield (%)	R_f ♣	(%)purity
1.	2,4 dichloro Phenyl	170-175	82	0.7	99.20
2.	2-chloro phenyl	145-150	65	0.52	98.38
3.	Benzyl	115-120	71	0.5	98.02
4.	N-methyl	107-110	50	0.5	98
5.	Morpholine	137-140	75	0.64	97

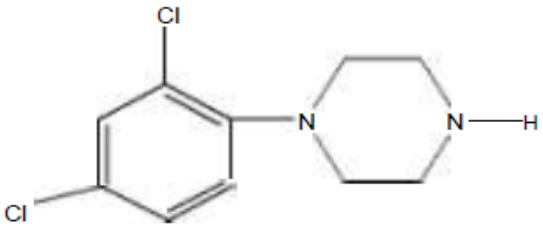
Solvent system: Chloroform: acetone (8:2)

+ Non-aqueous assay by using standard 0.1 N Perchloric acid.

4. Spectral analysis

A) Mass spectrometry.

1) 2, 4 dichlorophenyl piperazine.



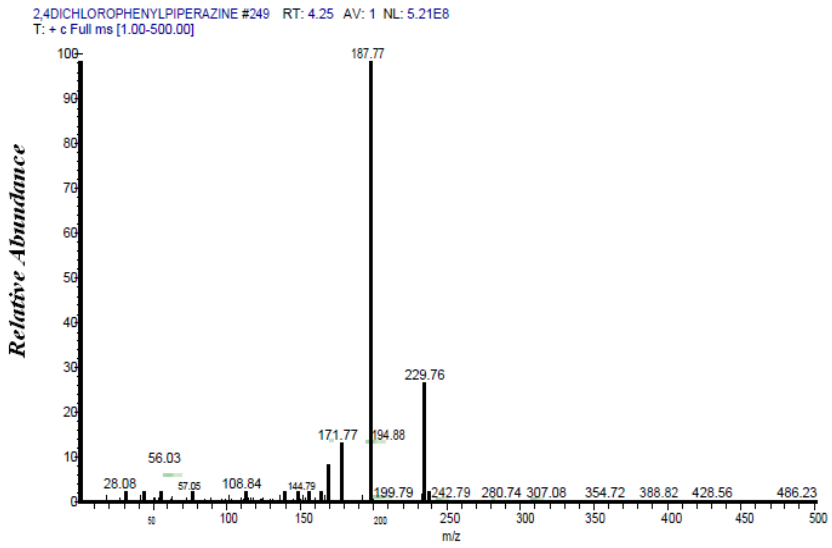
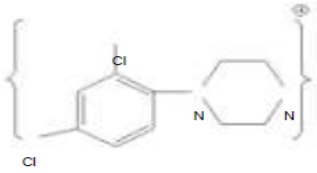
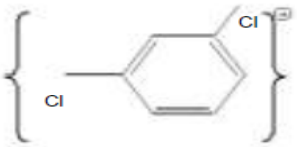
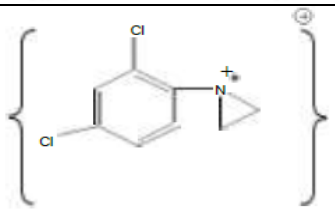


Fig. No.4: Mass Spectrum of 2, 4 dichlorophenyl Piperazine.

Table 4: Mass interpretation of 2, 4 dichlorophenyl Piperazine.

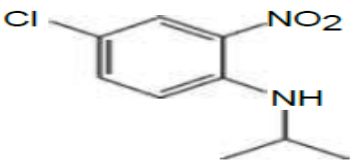
Molecular formula	Fragment	m/e
C10H12N2Cl2		**229.78** (Molecular ion peak)
C6H3Cl2		☆ ☆ ☆ **145,147,149**
C8H6NCl2		☆ ☆ ☆ **188,190,192** (Base peak**)**

☆ Cl35+Cl37=190

Cl37+Cl37=192

Cl35+Cl35=188

2) 4-chloro N^1 isopropyl-2-nitroaniline.



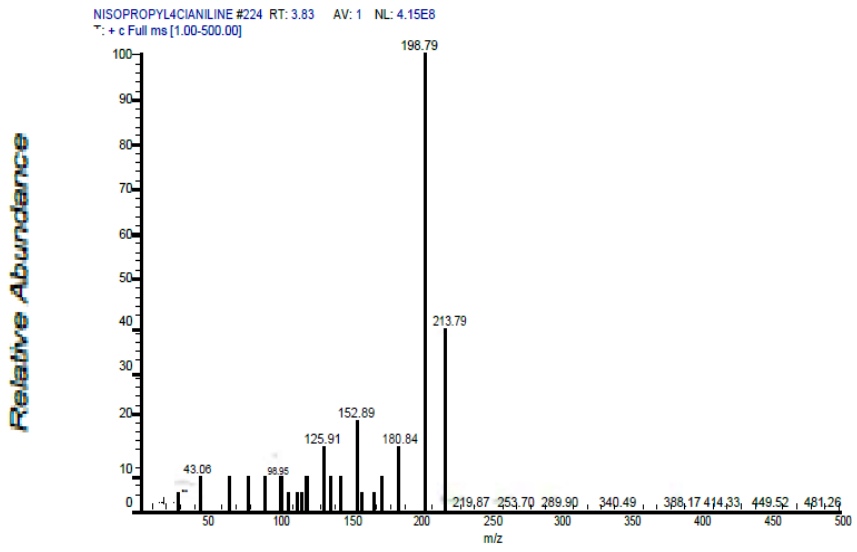
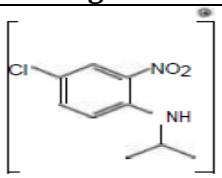
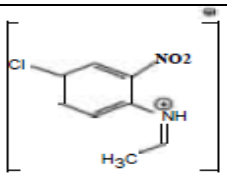
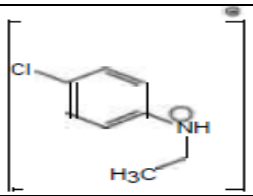
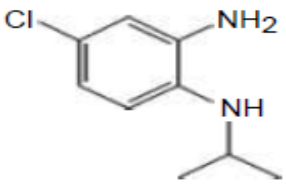


Fig.5: Mass Spectrum of 4-chloro N1isopropyl-2-nitroaniline.

Table 5: Mass interpretation of Mass Spectrum of 4-chloro N1isopropyl-2-Nitroaniline.

Molecular formula	Fragment	m/e
C9H11N2O2Cl		214,216 (Molecular ion peak)
C8H8N2O2Cl		199,201 (Base peak**)**
C8H8NCl		153,155
——C3H7	——C3H7	43

3) 4-chloro N1isopropyl-o Phenylene diamine.



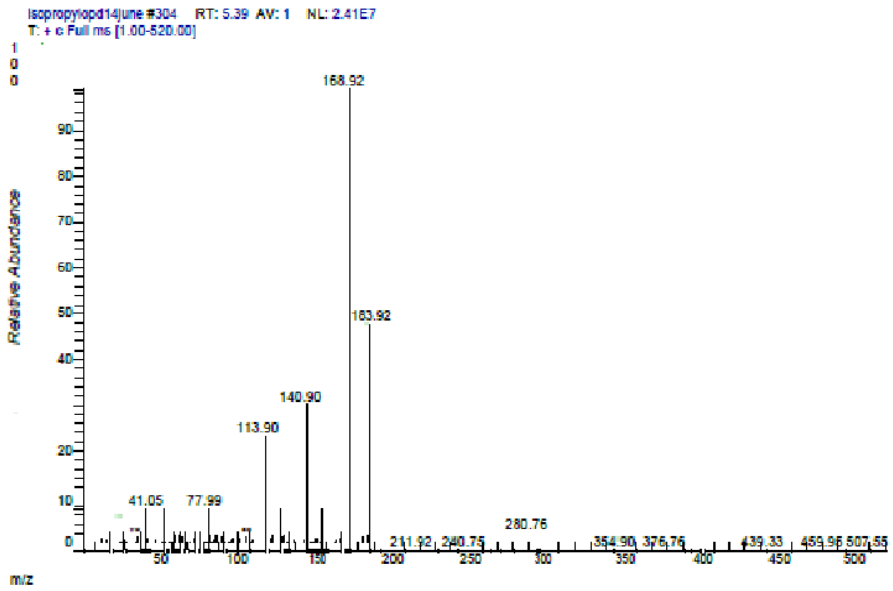
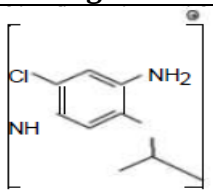
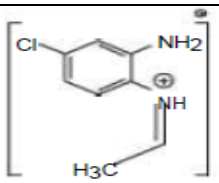
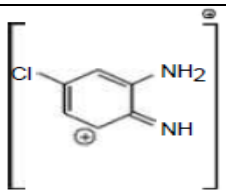
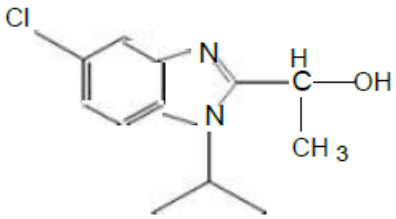


Fig.6: Mass Spectrum of 4-chloro N1isopropyl-o Phenylene diamine.

Table 6: Mass interpretation of 4-chloro N1isopropyl-o Phenylene diamine.

Molecular formula	Fragment	m/e
$C^9H^{13}N2Cl$		183,185 (Molecular ion peak)
$C^8H^{10}N2Cl$		169,171(Base peak)
C6H6N2Cl		140,142

4) 2- -hydroxy ethyl-N1-isopropyl benzimidazoles**.**



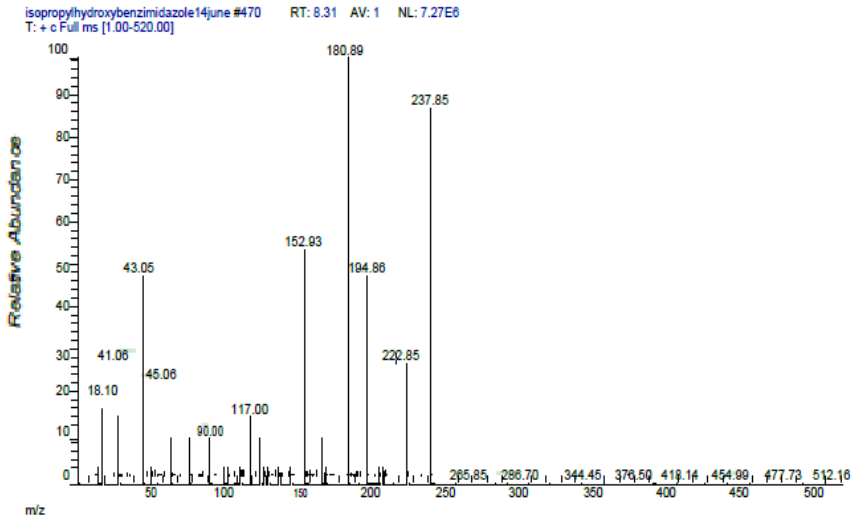
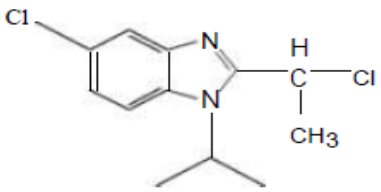


Fig. 7: Mass Spectrum of 2- -hydroxy ethyl-N1-isopropyl benzimidazole

5) 5-chloro-2-(1-chloro ethyl)-1-Isopropyl -1H-benzimidazole**.**



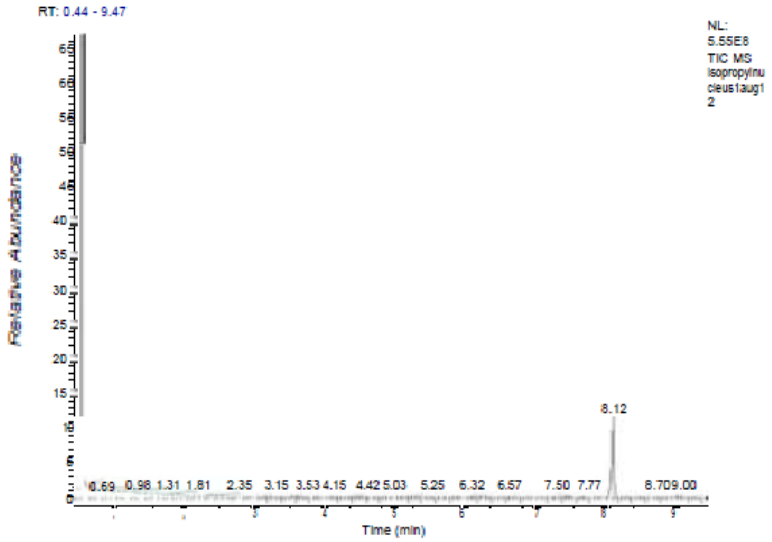


Fig.8: Mass Spectrum of 5-chloro-2-(1-chloro ethyl)-1-Isopropyl -1H-benzimidazole

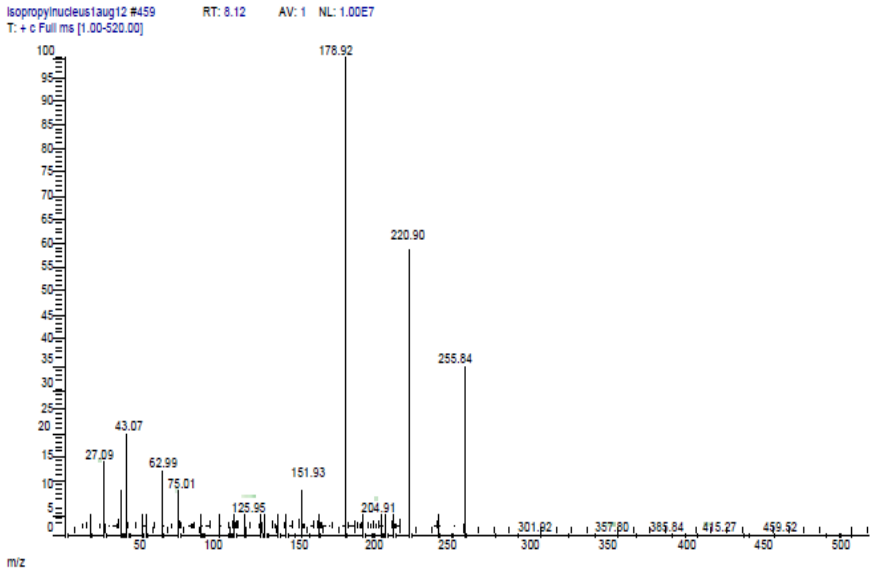
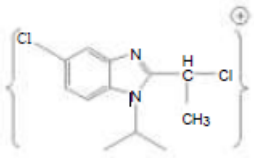
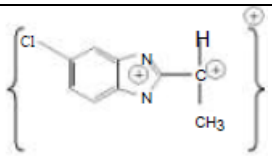
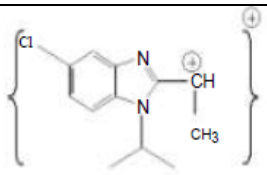
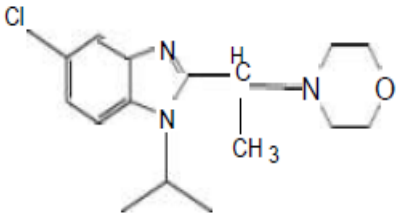


Table7: Mass interpretation of 5-chloro-2-(1-chloro ethyl)-1-Isopropyl -1Hbenzimidazole

Molecular formula	Fragment	m/e
C12H14N2Cl2		256,258 (Molecular ion peak)
C9H7N2Cl		178,180 (Base peak)
C12H14N2Cl		220,222

6) 5-chloro -1- isopropyl-2-[1-(4- morphonilyl) -1- yl) ethyl]-1H benzimidazole



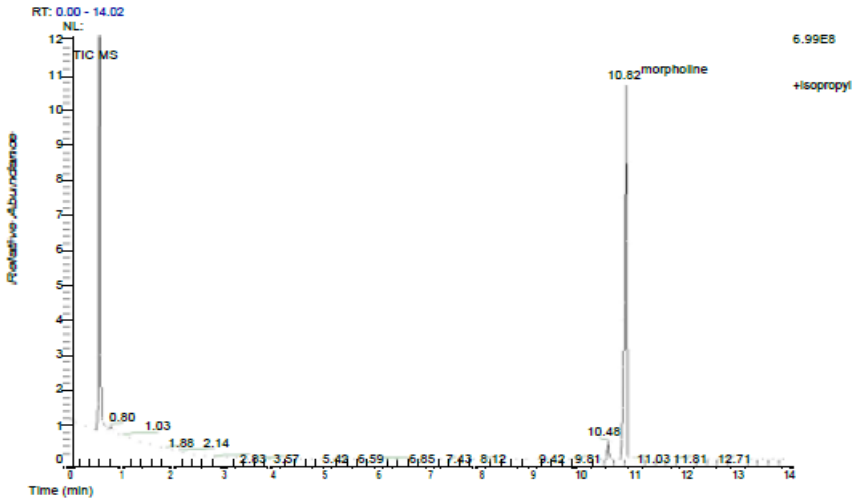


Fig .9: Mass Spectrum of 5-chloro -1- isopropyl-2-[1-(4- morphonilyl) -1- yl) ethyl]-1H benzimidazole

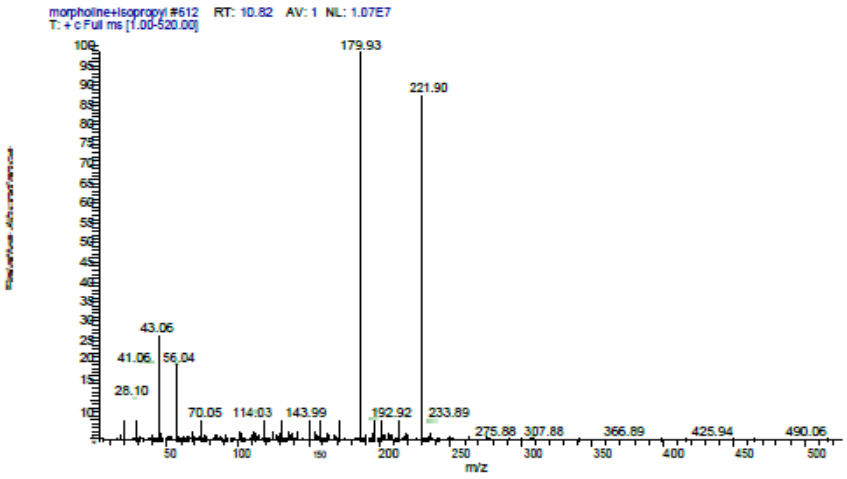


Fig.10: Mass Spectrum of 5-chloro -1- isopropyl-2-[1-(4- morphonilyl) -1- yl) ethyl]-1H benzimidazole

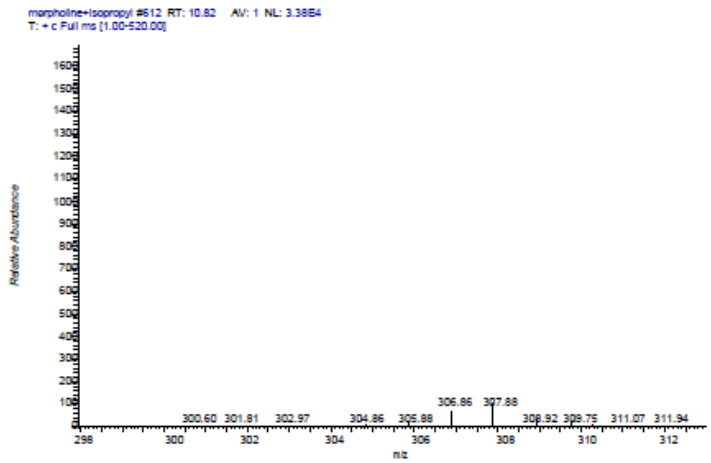
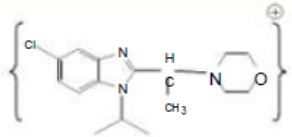
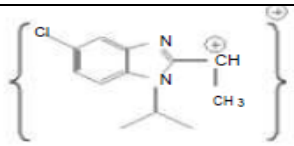
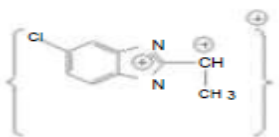
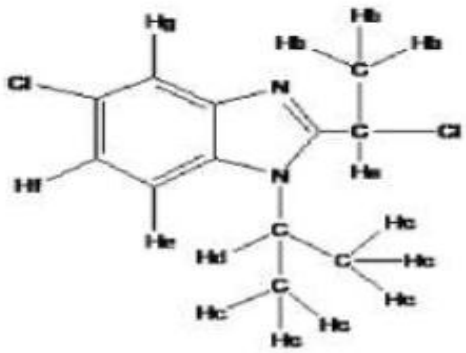


Table 8: Mass interpretation of 5-chloro -1- isopropyl-2-[1-(4- morphonilyl) -1- yl)ethyl]-1H benzimidazole.

Molecular formula	Fragment	m/e
C16H22N3OCl		307 (Molecular ion peak)
C11H14N2Cl		221
C9H8N2Cl		179

B) NMR Spectroscopy

1) 5-chloro-2-(1-chloro ethyl)-1-Isopropyl -1H-benzimidazole



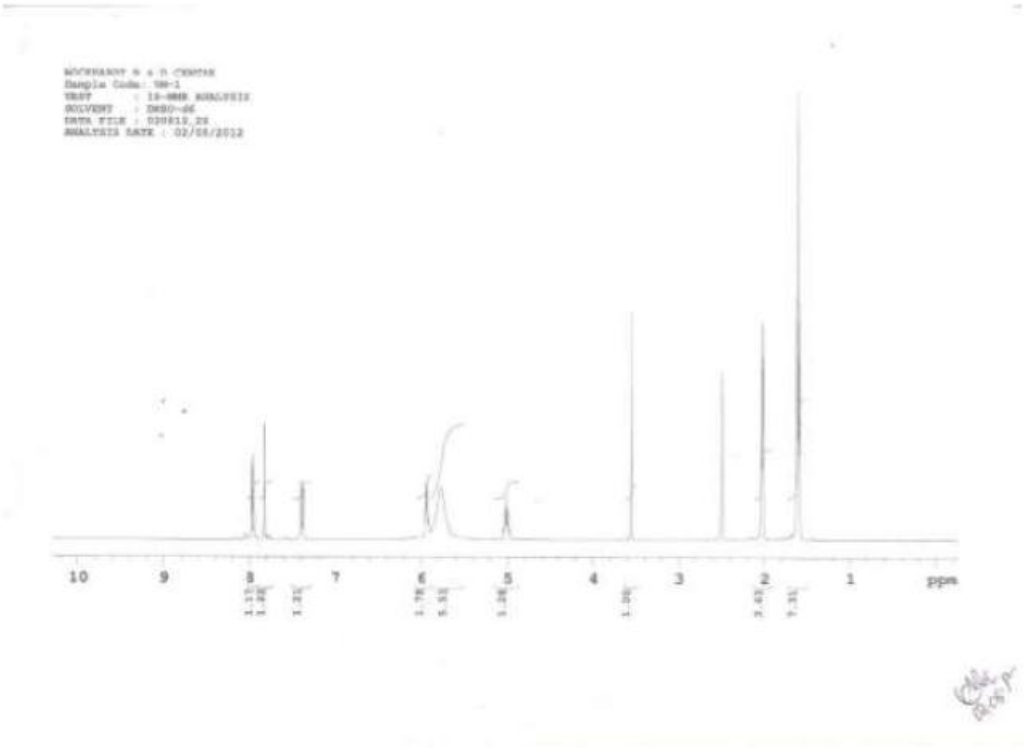
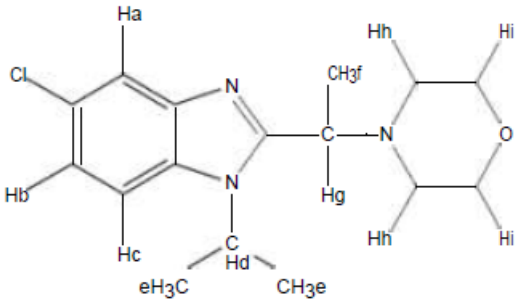


Table 9: PMR Interpretation of 5-chloro-2-(1-chloro ethyl)-1-Isopropyl -1 Hbenzimidazole.

Sr. No.	δ ppm	Splitting	Assignment
1.	1.6	Triplet	Hc
2.	2.028	Doublet	Hb
3.	5.00	Septe	Hd
4.	5.93	Quartet	Ha
5.	7.38	Doublet	He
6.	7.95	Doubet	Hf
7.	7.82	Singlet	Hg

2) 5-chloro -1- isopropyl-2-[1-(4- morphonilyl) -1-yl) ethyl]-1H benzimidazole



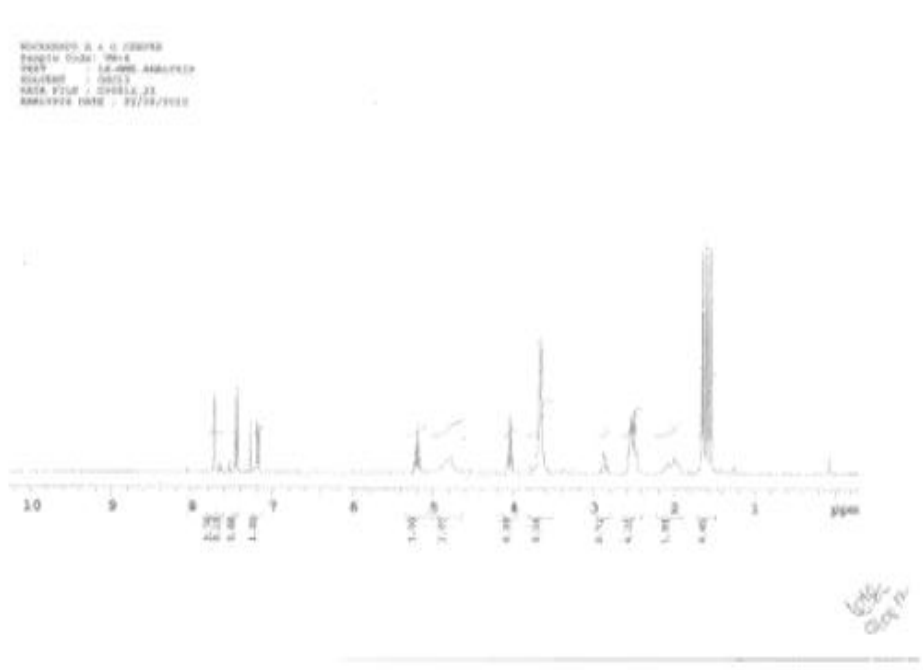
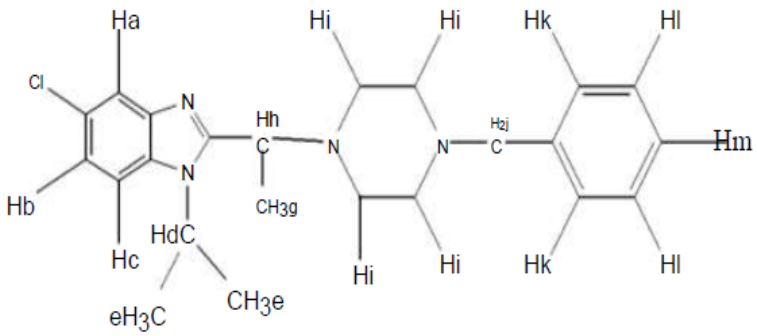


Table10: PMR Interpretation of 5-chloro -1- isopropyl-2-[1-(4- morphonilyl) -1-yl) ethyl]- 1H benzimidazole

Sr. No.	δ ppm	Splitting	Assignment
1.	1.6	Triplet(Doublet splitted to triplet due to long range coupling) (j=6)	He
2.	1.4	Doublet	Hg
3.	2.5	Triplet	Hh
4.	3.6	Triplet	Hi
5.	4.3	Quartet	Hg
6.	5.202	Septet	Hd
7.	7.275	Singlet	Ha
8.	7.4	Doublet	Hc
9.	7.7	Doublet	Hb

3) 5-chloro -1- isopropyl-2-[1-(4-benzylpiperazin-1-yl) ethyl]-1H benzimidazole:



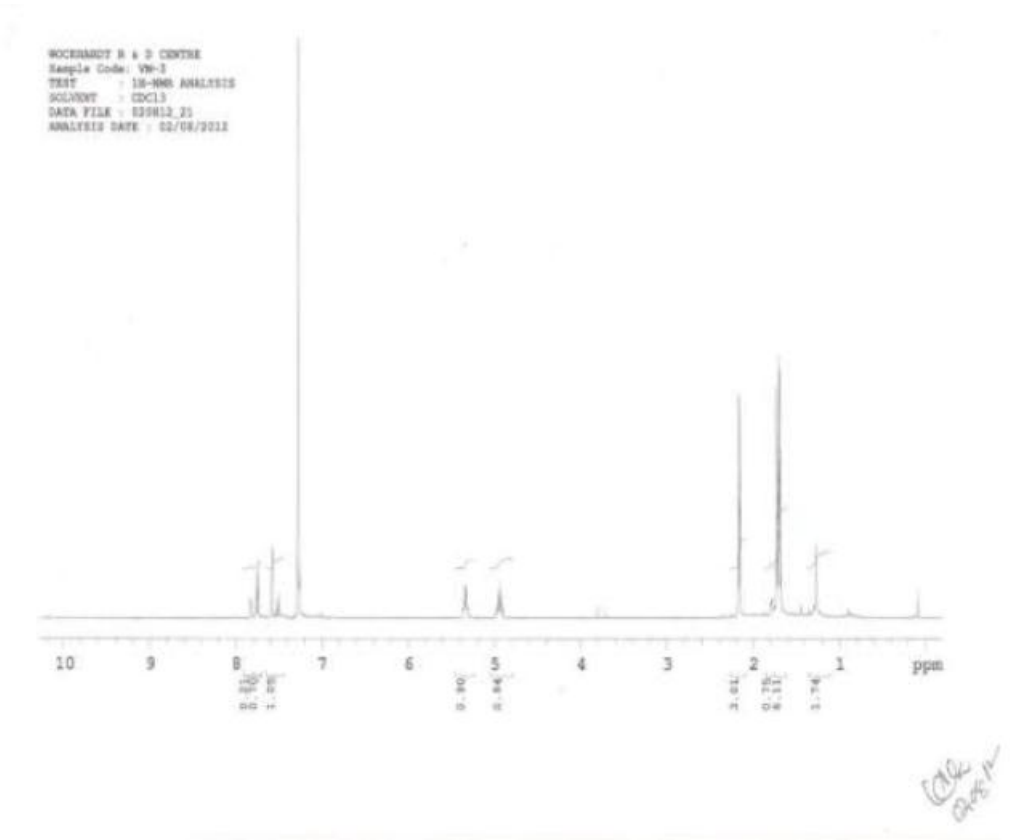
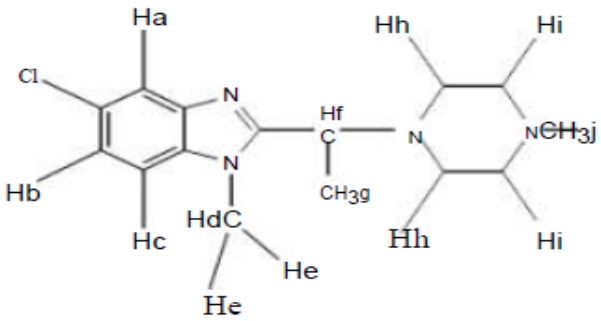


Table 11: PMR Interpretation of 5-chloro -1- isopropyl-2-[1-(4-benzylpiperazin-1-yl) ethyl]-1H benzimidazole

Sr. No.	δ ppm	Splitting	Assignment
1.	7.7	Singlet	Ha
2.	7.2	Doublet	Hb
3.	7.6	Doublet	Hc
4.	4	Septet	Hd
5.	1.56	Doublet	He
6.	4	Quartet	Hh
7.	2.46	Triplet	Hi

4) 5-chloro -1- isopropyl-2-[1-(4-methylpiperazin-1-yl) ethyl]-1H benzimidazole.



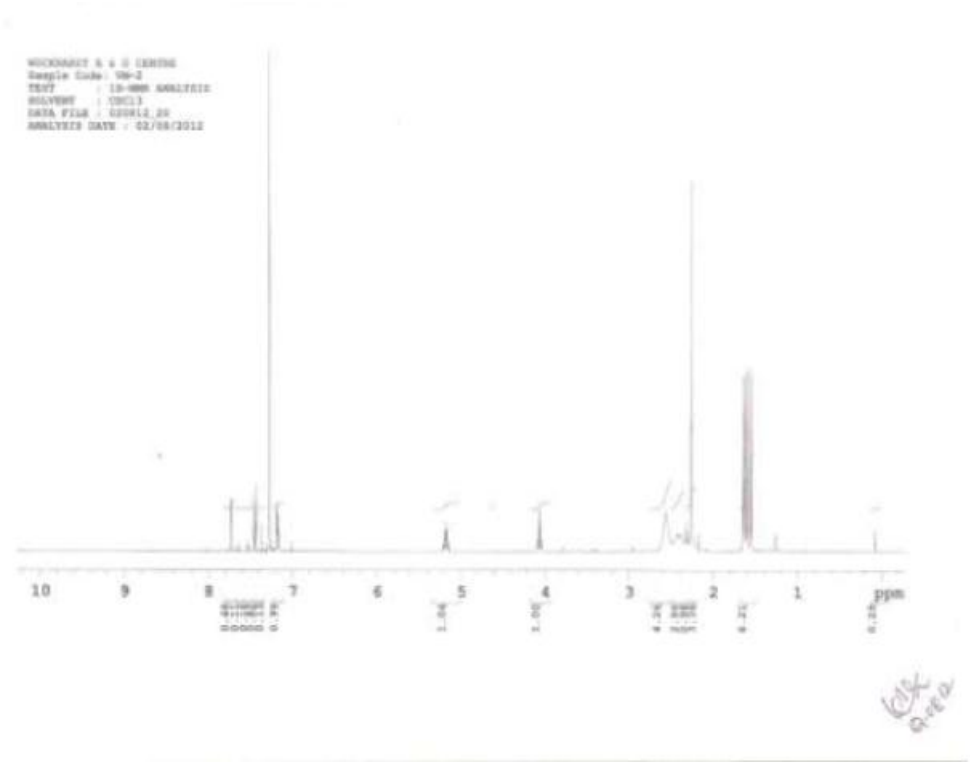


Table 12: PMR Interpretation of 5-chloro -1- isopropyl-2-[1-(4-methylpiperazin-1-yl) ethyl]-1H benzimidazole.

Sr. No.	δ ppm	Splitting	Assignment
1.	7.5	Singlet	Ha
2.	7.2	Doublet	Hb
3.	7.5	Doublet	Hc
4.	4	Septet	Hd
5.	1.56	Doublet	He
6.	3.12	Quartet	Hf
7.	1.29	Doublet	Hg
8.	2.6	Triplet	Hh
9.	2.27	Singlet	Hj

RESULTS AND DISCUSSIONS

The availability over the past 2 decades of the azoles antifungal agents represents a major advance in management of systemic fungal infections. Miconazole, the first azole drug approved and now recently withdrawn from the market, was available only as a highly toxic IV formulation; consequently, it was only rarely used. By contrast, the three oral azoles, ketoconazole, an imidazole, and, especially, itraconazole and fluconazole (both triazoles), have become frequently used therapeutic alternatives to amphotericin B.

The relative broad spectrum of activity of the azoles against common fungal pathogens, ease of administration and limited toxicity are highly attractive features. Fluconzole and itraconazole are better tolerated and more effective than ketoconazole.

These agents have several drawbacks and limitations also. One potential limitation of the azole antifungal agent is the frequency of their interaction with co administered drugs, which results in adverse consequences. A second limitation of the azoles is the emergence of resistance of fungal organisms, especially *Candida* species, to fluconazole. These limitations of the azoles will become more problematic if fluconazole and other azoles continue to be used injudiciously.

The present investigations were based upon following observations.

1. Unexploited substituted 1-alkyl benzimidazoles.
2. Attractive biological profile of N-aryl /alkyl piperazines.
3. Novel medicinal applications of simple N-alkyl-2-piperazinyl Benzimidazoles.
4. Enantiomer selectivity towards antifungal activity.

Many benzimidazoles derivatives substituted with piperazines have been synthesized and evaluated for antifungal activity in our department previously. From the limitations of therapeutically available benzimidazole containing antifungal agents and previous experiences of our department, we have synthesized different substituted aryl Piperazines, 1-alkyl-2-[4-(alkyl/aryl) piperazin-1-yl] ethyl benzimidazoles nucleus and condensed them to offer targeted compounds.

The investigation was designed in following manner

- Synthesis of various substituted aryl Piperazines.
- Synthesis of 5-Chloro-2-(1-chloro ethyl)-1-isopropyl -1H-benzimidazole

- Synthesis of targeted compounds
- Establishment of structures of targeted compounds on the basis of Infra-red spectra, NMR spectra and mass spectra. We have already described synthetic schemes in experiment work.

Spectral Analysis

The final compounds and intermediate were purified and their structures were established by Infra-red, mass spectroscopy.

Formation of 5-chloro-2-(1-chloro ethyl)-1-isopropyl -1H-benzimidazole was confirmed by the absence of –OH group with IR spectra(Fig no.14).The major functional groups observed are C=N near 1670cm^{-1},C-N near 1153cm^{-1},C-HAr near 3016cm^{-1},C-Cl near 681cm^{-1}.

All important intermediate and final compounds were monitored by TLC, gas chromatography and the structure confirmed by mass spectroscopy with molecular ion peak and NMR spectra which are given in spectral analysis.

CONCLUSION

A new class of 5-Chloro-1-isopropyl-2-[1-(4-alkyl/aryl piperazin-1-yl)-ethyl]-1H benzimidazole derivatives were synthesized and Analyzed. The logic behind the condensation of piperazines with Benzimidazoles was the role of Benzimidazoles nitrogens (the three nitrogens on C_2 are isosteric to triazole residue of conazoles) towards cytochrome P_{450} isoenzymes and the selectivity of Piperazine Towards fungal cytochrome P_{450} isoenzymes, in view of the conformational stability of the drug-receptor complex. In present investigation, there is one asymmetric carbon as shown in structure which will help to increase the selectivity of the compound. Ketocoanzole is complex molecule and needs a lengthy synthetic sequence to achieve the final product. This makes bulk drug expensive, which indirectly increases the cost of the treatment, also development of resistance and selectivity are problems associated with it. Therefore, producing a simple, inexpensive molecule with more or less identical activity to patented drug molecule has become a need.

Our prediction for the use of substituted benzimidazole is based on the hypothesis that the benzimidazole nucleus interact with receptor having hydrophobic, hydrogen, polar interactions. and the aryl piperazine fragment aids in selectivity towards inhibition of fungal Cytochrome P_{450} isoenzymes. From 600 molecules studied for interactions with Cytochrome P_{450} isoenzymes, 5 molecule were selected for synthesis out of the 25 Molecule with good

docking score. This investigation opens new area of antifungal agents, which are cheaper and simple and very selective than the existing azoles antifungal agents.

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