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Imidazole Derivatives From Benzoin Moiety

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CHAPTER 1
INTRODUCTION

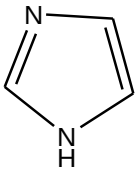
1.1 GENERAL

Medicinal chemistry or pharmaceutical chemistry is a specialty that encompasses identifying, analyzing and creating novel chemical substances for medicinal application at the intersection of chemistry. It may also involve the study of the biological properties of current drugs and their interactions quantitative structure-activity relationship (QSAR). The emphasis on safety aspects of medicinal products is on pharmaceutical chemistry and aims to ensure fitness for medical products (Smith, *et al*., 2009).

In other words, medicinal chemistry is classified as a discipline that deals with determining the control of the biological activity chemical structure. New compounds with a variety of modifications can be synthesized in medicinal chemistry and their biological processes identified subsequently (Williams *et al*, 2002 and Pandey, 2004).

The main aim of medicinal chemistry is to design and to invent new drug composites. This includes a team of staff from various disciplines, including chemical, biology, pharmacology and computing. (Thomas, *et al*., 2007).

1.1.1 Introduction To Imidazole



(1)

Imidazole (1) is the 5 member ring structure that comprises (1, 3-diaza-2, 4-cyclopentadiene) (1) is a planner of two atoms of nitrogen and one atomic carbon. Imidazole was renamed Glyoxaline for the first time. It is amphoteric and vulnerable to electrophillic and nuclear attack. It also exists naturally as a riboside in the purine nucleus and amino acid histidine, and (Finar, 2009).

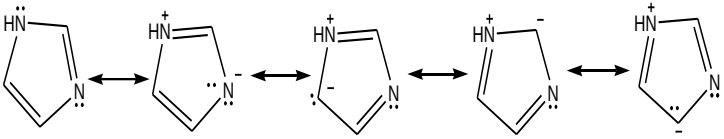
The C3H4N2 chemicals formulation, imidazole is the simplest component.

Imidazole derivatives have taken a special role in medicinal chemistry. These derivatives are an important heterocyclic class and contain a wide number of organic and chemical compounds. Imidazole is an alkaloid and an aromatic heterocyclic. Imidazole derivatives are widely used in a variety of clinical fields. Imidazole that contains drugs has a wide range of medicinal medicinal treatments for different diseases. The therapeutic properties of imidazole products have led to many new chemotherapeutic agents being produced by medicinal chemist. Imidazole derivatives are currently used in pharmacology studies as tools.

The biological and pharmaceutical synthesis of various 2-imidazoline forms is essential, because many imidazoline derived have various activities, including antidiabetic, antihypertensive and anti-inflammatory activities. It also has numerous uses in the industry, in addition to its use for medicinal purposes. In chromatography with invisible metal affinity immobilized is also used to immobilised metal affinity chromatography (IMAC).

In addition the use of these imidazolines in separate synthetic reactions is synthetic. There have recently been numerous syntheses of 2-imidazolin beginning primarily with NBS aldehydes and ethylenediamines (Fujioka, et al, 2005).

1.1.2 Properties of Imidazole

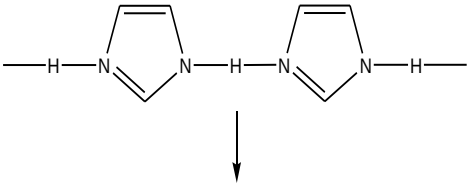


(2)

Imidazole is a monoacidic natural foundation that can form crystalline salts with acids (John Wiley and Sons, 2006). Imidazole is a five-member, water-soluble, planar ring like other polar solvents. On one of the two nitrogen atoms the hydrogen atom is located. It is of the same type: 1H-Imidazole and 3H-Imidazole. It is of equal form: Imidazole is a moderately polar and fully soluble compound in water, as is seen in a reported dipole of 3.61D. This is called aromatic. This mixture contains Some imidazole resonance structures as seen above (2) (Bhatnagar, *et al*, 2011).

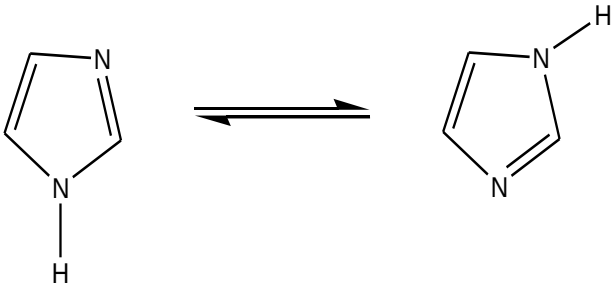
1.1.3 Physical Properties of Imidazole

It is a high B.P. colourless liquid. (Boiling point) of 256oC, where the linear molecular relation is formed, over all other 5-section heterocyclic compounds because of intermolecular H-bonding. Hydrogen attachment in the imidazole ring has been shown. (6).



(6)

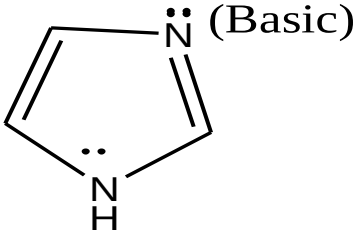
When the electrophillic substitution is in the nucleus, imidazol and nucleophillic substitution are often substituting. M.P. has imidazoles. 80-91oC, the basis is weak and tautomeric, with positions 4 and 5 being similar (7).



Tautomerism of imidazole

(7)

1.1.4 Chemistry of Imidazole



(Acidic)

(3)

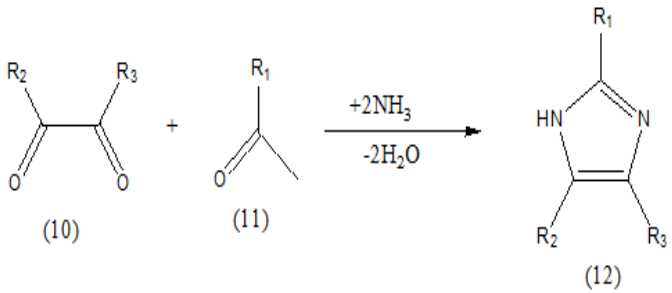
Imidazoles are similar to pyrrol as an acid and pyridine as a basis (3). The unidentified N-3 Electron Pair, but the Nitrogen 'pyrrol,' is not the electrophilic reagent, since it is part of an artificial flavoring sextet. Although the ring of the imidazole is more likely to attack an

electrophilic attack, it is much less present in an atomic replacement response except where there is a strong replacement of electron in the ring elsewhere. The fused benzene ring of benzimidazole offers ample electron extraction to allow many C-2 nuclear alternatives. The arrays of covalent associations of finite value to dipolar donors are evidence of the collective reactivity of imidazole. These predictions are electrophonic attack in N3 or any imidazole carbon ring, C-2 or C-1 nuclear strikes, which are molecular amphoteric characteristics. C-2 in benzimidazole is expected as a nucleophile attack. The benzimidazole ion reactivity at C-2 is improved by nucleophiles compared with the neutral atom.

1.2. PREPARATION

1.2.1 Debus Synthesis

First reported was imidazole in 1858, while some derivatives of imidazole had already been found in the 1840s. Heinrich Debus was first synthesised. He synthesised imidazole with ammonia with glyoxal (10) and formaldehyde (11). This synthesis is also used to generate C-substituted imidazoles while achieving very low yields (12) (Debus, 1858).



1.3 BIOLOGICAL ACTIVITY OF IMIDAZOLE

Imidazole shows various biological activities as it is utilized in the treatment of different diseases.

1.3.1 Antibacterial Activity

The term chemotherapy can be defined as a treatment of diseases caused due to the infective parasites and organisms with causing destruction to their host animal. Modern chemotherapy began with the work of Paul Ehrlich (1854-1915). Due to his pioneer discoveries in this field, he is regarded as 'Father of Chemotherapy'.

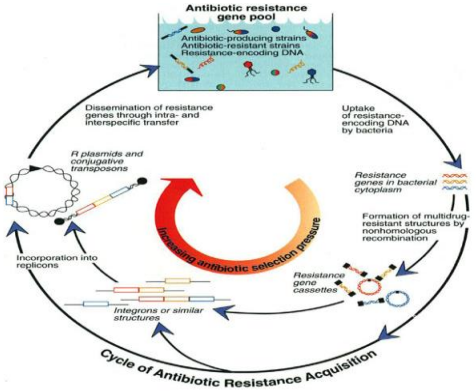
He expected the production of chemo agents that would rare diseases without damaging the host. The fact of antibiotics in 1877 was confirmed by Pasteur. Anthrax bacilli developments in the urine were inhibited by airborne bacteria. In 1930's, sulfa drugs became important; in 1929, the first antibiotic penicillin was discovered by Alexander Fleming. His first clinical experiments were carried out in 1940. By showing Prontosil a therapeutic effect of a sulfonamide dye on pyrene infections, Domagk initiated modern chemotherapy in 1935. Prontosil was found quickly to have p-aminobenzene sulfonamide as an active ingredient and did not require shading. The first sulfonamide was sulfa pyridine. Waksman and his colleagues periodically searched the actinomycetes as antibiotic source in 1940 and in 1944 found Streptomycin. This community of soil microbes proved rich in antibiotics and soon followed by Tetracyclines, Chloramphenicol, Erythromycin and many more. Amphotericin-B to cope with systemic mycosis and Grseiofulvin to help dermatophyte assaults were launched around 1960. Both of these antibiotic medications are available. Flucytosine was a well-known antifungal property in 1970. However, it could only act as an Amphotericin assessment drug. In the mid-1970s and 80s, the production of imidazoles advanced. (Kadam, *et al,* 2007)**.**

The earliest known antibiotic is pyocyanase produced before 1935 in Germany from the crude extract of *pseudomonas aeruginosa* cultures. It was for the treatment of meningitis, diphtheria and the grippe. These types of antibiotics contain 2-hydroxyquinolone as a nucleus, but other synthesized substances found toxic later (Parmioo, 2006).

In the past 40 years, importance has moved from the quest for antibiotics to the production, attractive or conflicting, of semisynthetic derivatives from older antibiotics.

The biggest contribution to therapeutics of the present century is antimicrobial medicines. The importance of infectious diseases is raised in developed countries. They are one of the most popular and misused drugs as a class (Jacob, *et al*., 1999).

Fig. 1.1 Mechanism of action of antibacterial agent



a. **Inhibition of cell metabolism:** Antimetabolites are classified as antibacterial agents that inhibit cell metabolism. This inhibits the synthesis, but not the host's metabolism. They do this by an inhibition of the bacterial cell's catalyzed process, but not in animal cells. Sulfonamides are considered to be the best-known examples of antibacterial agents.

b. **Inhibition of bacterial cell wall synthesis:** Bacterial cell lysis (bursting) can be caused by cell walled synthesis inhibition. Losses such as penicillins and cephalosporins are implicated because animal cells do not have a cell wall and these agents do not affect them.

c. **Interaction with the plasma membrane:** Some antibacterial agents interfere with the permeability of plasma membrane. This results in the cells being fatal. This is how polymyxins and tyrothricin function.

d. **Disruption of protein synthesis:** Disrupting protein synthesis ensures that agents that inhibit protein synethesis can no longer be made essential for cell survival, therifamycins, aminoglycosides, tetracyclines and chloramphenicol

e. **Inhibition of nucleic acid transcription and replication:** Cell division enzymes are prohibited from inhibiting the function of nucleic acid. Nalidixic acid is an agent that acts like this (Charles, *et al*., 1965).

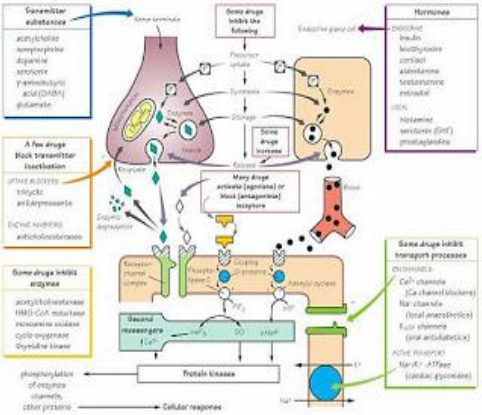


Fig. 1.2 Mechanism of action of antifungal agents

The fungal cell wall varies considerably from the bacterial cell wall and has no impact on antibacteria such as β-lactams or vancomycin. The cell wall is one of the most attractive targets in the fungal cell. It is composed of three polysaccharides; β-1, 3- glucan, chitin and mannoprotien.

Table No. 1.1 Mechanism of action of various antifungals (Kadam, *et al,* 2007)

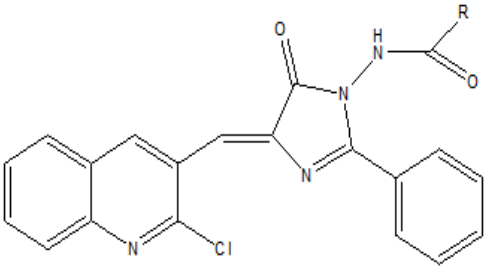
S. No.	Drug	Mechanism of action
1.	Polyene antibiotics	Interacts and changes the selective permeability of the fungal membrane with fungal membrane sterols.
2.	Griseofulvin	Interacts with fungal micro-tubules and prevents cell division.
3.	Imidazole derivative	Inhibits ergosterol synthesis in fungal cell membrane resulting into leakage of cell constituents.
4.	Flucytosine	Inhibits the formation of fungal nucleic acids.
5.	Tolnaftate	Inhibits transport of precursors for protein and nucleic acid in fungi.
6.	Cyclopirox	Inhibits transport of precursors needed for the synthesis of proteins and nucleic acid in fungi.
7.	Potassium iodide	Iodination of proteins in fungal cell-membrane.

1.4. LITERATURE REVIEW OF VARIOUS ACTIVITIES

1.4.1 Antimicrobial Activity

Salman *et al,* 2015 the two recent sequence S-alkyl-imidazolidin-4-one and S-alkyl-imidazole have been reported for the new form of antimicrobial and antioxidant agents. DPPH (1, 1-diphenyl-2-picrylhydrazyl) radical approach was used for measurement of their antioxidant potentials in vitro. Their antibacterial screens against Staphylococcus aureus, Bacillus subtilis, Pseudomonas Aeuroginose and Escherichia coli, and the antifungal activity of Aspergillus fumigates were evaluated, with most compounds showing solid, important results in contrast to the respective standards. Candida albicans, Syncephalastrum racemosum and Geotrichum candidum were also evaluated.

Desai *et al,* 2014 An approach has been established to synthesise N-(4-(2-chloroquinolin-3-yl)methylene)-5-oxo-2-phenyl-4, 5-dihydro-1-imidazole-1-yl)amides. In comparison with the conventional reaction during a solution step, we observes that solvent-free thermolysis is a simple, fast, high efficiency and environmentally friendly protocol for the synthesis of quinoline-based imidazole derivatives. In vitro, antimicrobial production is investigated of freshly synthesised microbial compounds of various organisms: Escherichia Coli (MTCC 443); Pseudomonas aeruginosa (MTCC 1688). (MMTCC 442). (MTCC 1323). Both bioactive synthesised molecules are tested with a bioassay, i.e. serial broth dilution, for their in vitro antifungal action.



R= different aryl substituents

1.5. IDENTIFICATION OF PROBLEMS AND ISSUES

Various literature review of imidazole derivatives shows that there is regular need of imidazole derivative which possess antimicrobial activity due to increasing infections and their distinct types. So there is a regular need to synthesize a new compound with better activity then previous synthesized compounds.

1.6. RATIONALE

Because of the strong biological activity and synthetic application, synthetic analysis of imidazole units is very significant. Imidazoles represent the central fragment of numerous natural products and biological systems as an essential class of heterocycles. Imidazole compounds have various pharmacological properties and have essential functions in biochemical processes. The strength and wide applicability of the imidazol pharmacophore is due to its donor-acceptor potential in hydrogen bonding and its high metal affinity (e.g., Zn, Fe, Mg).

Literature revels that Imidazoles have been identified as anthelmintic, anti-inflammatory (specific COX-2 inhibitor),

antiviral, anticancer, anti-bacterial, anti-fungal, anti tubercular, anti-depressant and now they are also known for their anti-ulcer activity.

In the previous year many 1, 2, 4, 5- tetra substituted imidazole derivatives were synthesized for the antimicrobial activity. Imidazole nucleus has a wide scope for research in future.

In the present work we want to synthesize newer derivatives of 1, 2, 4, 5- tetra substituted imidazole with minimum toxicities.

1.7. PLAN OF WORK

STAGE: 1

1) Literature survey
2) Synthesis and purification of substituted imidazole derivatives.
3) Analytical evaluation: Synthesized compound will be characterized by using-
    - Thin Layer Chromatography
    - Infrared spectroscopy
    - NMR spectroscopy
    - Mass spectroscopy

STAGE: 2

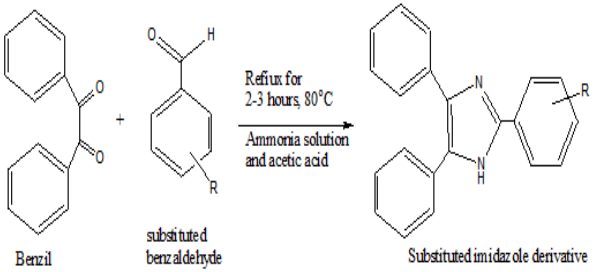
1) Biological screening: Synthesized compound will be Screened for biological screening:
    - Anti-bacterial activity
    - Anti-fungal activity

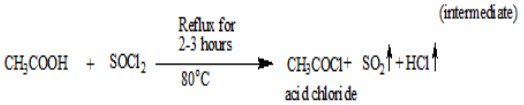
STAGE: 3

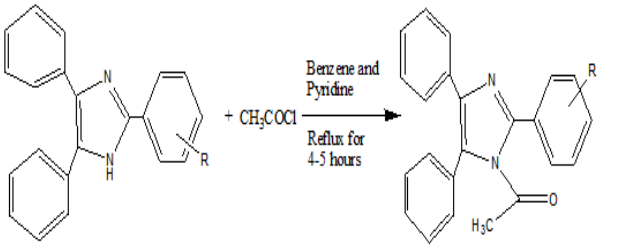
1) Compilation of data
2) Thesis writing

CHAPTER 2

2.1 REACTION SCHEME 1



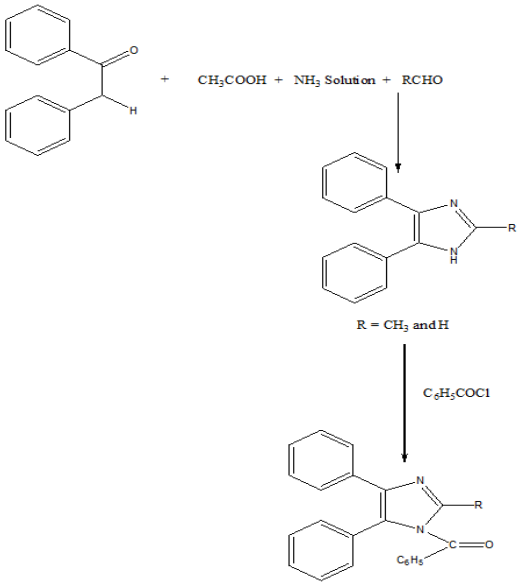




Where,

R= 2-chloro
4-chloro
2-methoxy
4-methoxy
2-nitro
3-nitro
4-nitro

2.2 REACTION SCHEME 2



2.3 SYNTHETIC WORK

Material and Methods

The melting points of the synthesized derivatives were estimated by the capillaries method and are uncorrected. Spectral analysis of newly synthesized compounds was done. IR Spectra (KBr), ^{1}H NMR ($CDCl_3$) and the mass spectra (dry helium) of synthesized compounds were recorded from CDRI, Lucknow.

Table No. 2.1 List of various substitutes

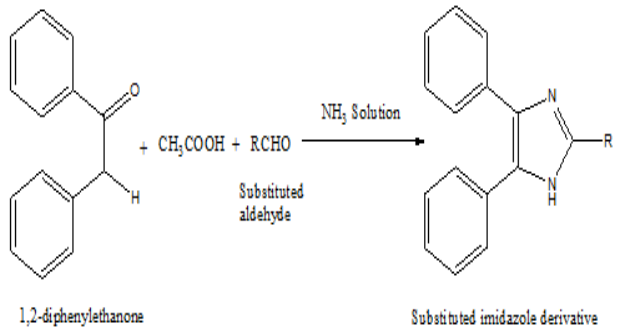
Compounds	R
IMD 1	2-Cl

IMD 2	4-Cl
IMD 3	2-OCH_3
IMD 4	4-OCH_3
IMD 5	2-NO_2
IMD 6	3-NO_2
IMD 7	4-NO_2

2.4 GENERAL PROCEDURE FOR COMPOUNDS IMD8 AND IMD9

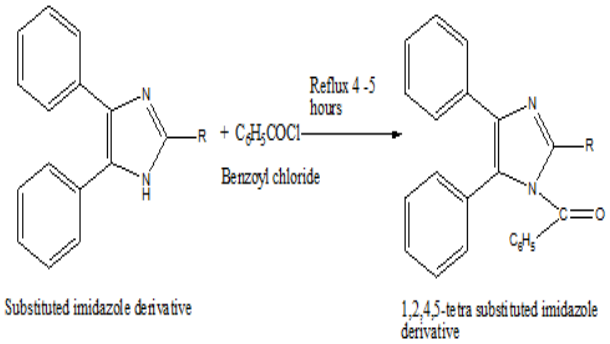
- **Step 1**

The amount of benzoin (2,65 gm), ammonia (5 mL), and substitution aldehyde (1,5 ml) was specifically weighed and dissolved in 50 ml of glacial acetic acid at RBF 100 ml. The reaction mixture was heated and often shaked for 5 hours on the heating mantle. 300 ml of cool water has been added to the reaction mixture after completion of the reaction resulting in product precipitation. The blend was kept overnight in the refrigerator. With 5% ammonium solution, the sample was immediately filtered and nullified. The compound was re-energized and cleansed of absolute ethanol to have a crystalline compound of pale or coloured yellow.



- **Step 2**

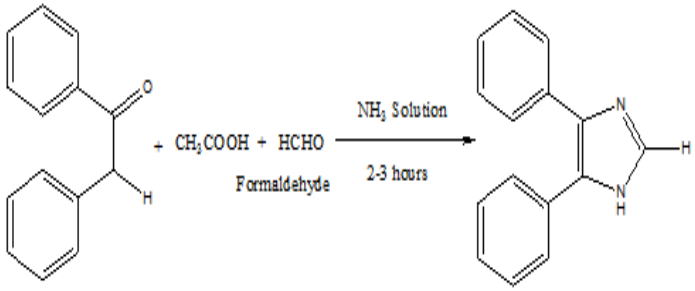
RBF was used for 4-5 hours as a solvent and pyridine (0.5 ml) as a catalyst in substituted (0.50 gm) imidozole derivatives and in freshly prepared benzoyl chloride solute (2.5 ml). A single spot on TLC investigated the completion of the reaction. Cool the reaktion mixture and drain it into ice water at room temperature. Shake the mixture in crushed ice and keep it cool for the night. The compounds have been isolated and purified. Ethanol recrypted the substance. There was an uncolored commodity.



Synthesis of IMD 8

- **Step 1**

Precise weighing of benzoin (2,65 g), of ammonia (5 mL) and of formaldehyde (1,5 mL) in 50 ml of glacial acetic acid in 100ml RBF was done in a processed manner. The reaction mixture was heated and often shaked for 5 hours on the heating mantle. 300 ml of cool water has been added to the reaction mixture after completion of the reaction resulting in product precipitation. The blend was kept overnight in the refrigerator. With 5% ammonium solution, the sample was immediately filtered and neutralised. The compound was recrystallized and purified to create a pale yellow crystalline compound from absolute ethanol.



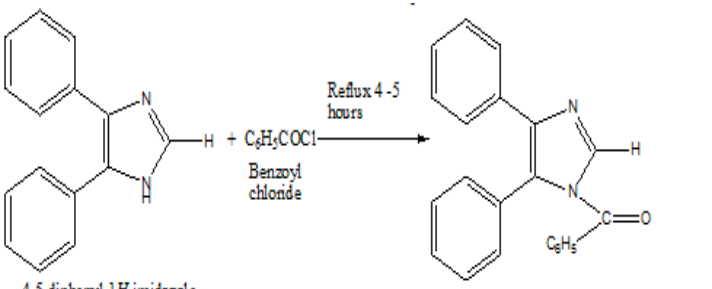
1,2-diphenylethanone

4,5-diphenyl-1*H*-imidazole

- **Step 2**

RBF was taken with the solvents benzene (30 mL) and pyridines (0.5 mL) as catalyst for four to five hours, with substituted imidazole derivatives (0.5 gm) and freshly prepared benzoyl chloride (2.5 ml). A single spot on TLC tested the completion of the reaction. Cool the reaction mixture and add in ice water at the room temperature. Shake the mixture well in crushed ice and hold it for overnight in cold weather. The compounds were isolated and

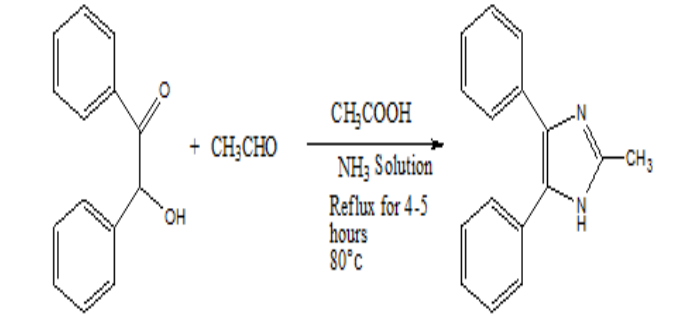
filtrated. Ethanol recrystallized the substance. There has been an uncolored commodity.



Synthesis of IMD 9

- **Step 1**

Accurately weighed concentrations were taken of benzoin and dissolved in 50 ml glacial acetic acid (5 ml), and aceltaldehyde (1.5 ml) of 100 ml RBF. The reaction mixture was heated and often shaked for 5 hours on the heating mantle. 300 ml of warm water has been added to the reaction mixture after completion of the reaction resulting in product precipitation. The blend was kept overnight in the refrigerator. With 5% ammonium solution, the sample was immediately filtered and neutralized. The compound was recrystallized and purified to create a pale yellow crystalline compound from absolute ethanol.

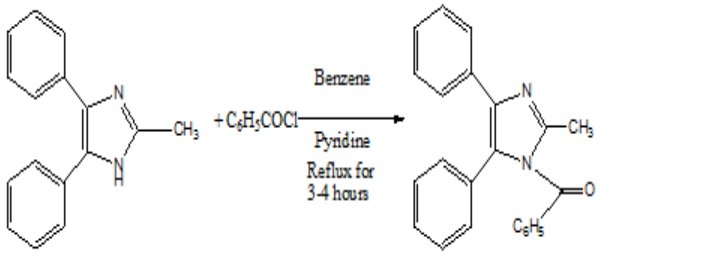


2-hydroxy-1,2-diphenylethanone

2-methyl-4,5-diphenyl-1*H*-imidazole

- **Step 2**

RBB has been taken with benzene (30 ml) as a solvent and pyridine (0.5 ml) as a 4-5-hour catalyst for replaced (0,5 grammes) and freshly prepared (2,5 ml) imidazole derivatives. as a catalyst. A single spot in TLC tested the completion of the reaction. Cool the mixture at room temperature and place it in ice water. Shake the blend well in crushed ice and hold it for the night at cold temperatures. These compounds were isolated and purified. The substance has been ethanol recrystallized. There was a colourless commodity.



2-methyl-4,5-diphenyl-1*H*-imidazole

(2-methyl-4,5-diphenyl-1*H*-imidazol-1-yl)(phenyl)methanone

Synthesis of IMD 10

- **Step 1**

Precise dissolution of the amounts of benzoin (2,65 gm), ammonia solution (5,0 ml) and propionaldehyde (1,5 ml) in a 100 ml RBF in 50 ml of glacial acetic acid was taken and dissolved. The reaction mixture was heated and often shaked for 5 hours on the heating mantle. 300 ml of cool water has been added to the reaction mixture after completion of the reaction resulting in product precipitation. The blend was kept overnight in the refrigerator. With 5% ammonium solution, the sample was immediately filtered and neutralised. The compound was recrystallized and purified to create a pale yellow crystalline compound from absolute ethanol str

- **Step 2**

RBB has been taken with benzene (30 ml) as a solvent and pyridine (0.5 ml) as a 4-5-hour catalyst for replaced (0,5 grammes) and freshly prepared (2,5 ml) imidazole derivatives. A single spot on TLC investigated the completion of the reaction.. Draw the reaction mixture into ice water and refill at room temperature. Shake the mixture well with crushed ice and keep it overnight cool. The compounds have been extracted and filtrated. Ethanol recrystalling the product. A substance was collected without colour.

Table No. 2.2 List of various substitutes

Compounds	R
IMD 8	H
IMD 9	CH_3

IMD 10	C_2H_5

2.5 PHARMACOLOGICAL SCREENING

Antimicrobial Activity

A continuing fight against humans and the various microorganisms causing pathogens and disease has been fought throughout history. Pandemic immunodeficiency syndrome, bubonic disease, tuberculosis, malaria and human immunodeficiency have infected substantive human population sections, causing significant disease and death. In the middle of the twentieth century, significant innovations in antibacterial antibiotics and other ways of infection helped make the tide a human one. Bacteria responded by manifesting different types of resistance almost until antibacterial antibiotics were deployed. The level and complexity of the resistance mechanisms indicating bacterial pathogens increased as the use of antimicrobial increased (Tenover, 2006). One of the biggest medical successes of the last 50 years has been the introduction of antibiotics for chemical treatment of bacterial infections. The advent of bacterial resistance to antibiotics however threatens current agents' therapeutic application, creating a search need for new antibacterial medicines. The most frequent source of antimicrobial agents is plants. Many of the synthetic medications currently in production cause different side effects. Thus, the drug production of herbal compounds may be useful if newer medications with reduced side effects are to satisfy this need. One of the most effective potential ways to contain antibiotic resistance and disease control tends to be antibacterial active concepts isolated from higher plants. Large-scale assessment of local flora used for various biological activities in conventional medicines is a crucial first step towards the isolation and characterisation of the theory and drug production (Satish et al., 2008).

Fungi are essential food and grain destroyers during their storage which makes their nutritional value insufficient for human consumption. There have been records of over 300 fungal metabolites being poisonous to humans and animals. Carcinogenic, genotoxicity, terratogenicity, nephrotoxic, hepatotoxic, hormonal and immunosuppressant are the major toxic results. Plant metabolites seem to be one of the safest options since them, when compared to conventional pesticides, have a limited environmental influence and risk on customers. (Satish *et al*.,2007).

2.6 MATERIAL AND METHODS

Antibacterial Activity

Preparation of Sample

Synthesized compounds where dissolved in the sterile water or (dimethyl formamide) DMF with various concentration like 400, 500 and 600μg/ml.

Preparation of Standard

50mg of the Ampicilin was dissolved in the 100 ml of sterile water.

Microorganisms used

Cultures of *Staphhylococcus aureus*(NCIM 2079), *Bacillus subtilius*(NCIM 2708), *Pseudomonas aeruginosa*(NCIM 2242) & *Escherichia coli*(NCIM 2685)were obtained from Pune. Different staining methods and biochemical reactions described the microorganisms. The microorganisms were sub-cultivated and used in a solution of nutrient agar at frequent intervals.

Preparation of standard inoculum

McFarland Constants

The bacterial suspension turbidity created by barium chloride with sulfuric acid-interacting reactions can be determined by a chemically inducted precipitation reaction.

Procedure

1. Ten test tubes of equal size were set up.
2. 1 % chemically pure sulphuric acid solution was prepared.
3. 1.175 % aqueous solution of barium chloride ($BaCl_2$) was prepared.
4. The sum of the two solutions shown in the table was applied slowly with continuous upheaval to the tubes to make 10 ml per tube in total.
5. The tube has been screened and the barium suspended sulphate (BaSO4) is almost equal to a homogenous cell density per ml.
6. The McFarland norm pipes have been stored in the dark for six months at room temperatures.

Table No. 2.23 Quantity required for the preparation of standard inoculum

Tube no.	0.5	1	2	3	4	5	6	7	8	9	10
$Bacl_2$ (ml)	0.05	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
H_2SO_4 (ml)	9.95	9.9	9.8	9.7	9.6	9.5	9.4	9.3	9.2	9.1	9.0
Cell density (1×10^8/ ml)	1.5	3	6	9	12	15	18	21	24	27	30

Table No. 2.24 Preparation of Assay Media*

S. no.	Ingredients	Weight (g)
1.	Beef extract	4.0
2.	Peptone	5.0
3.	Agar	20.0
4.	Distilled water	q. s. 1000 ml

***pH 7.4 was maintained for the assay media.*

In sufficient volumes of distilled water, the abovementioned quantities of various components were precisely weighed and dissociated. By autoclave at 1210C for 15 minutes, the prepared media was sterilised.

Procedure

In a heating air oven at 1600C the petrids were thoroughly washed and sterilised for one hour.30 ml of a sterile agar agar medium was applied to the inoculum and was poured onto sterile petridies. The medium was boroned with the sterile borer chemical. The bores of the respective test solution were 0.1 ml, and the normal reference was 0.1 ml Ampicillin at 100 mg/0.1 ml. Any platform retained a control with only DMSO in the cup.

The petridishes have been held 45 minutes in the refrigerator to be disseminated. The petridizes were incubated for 24 hours at 370 C after diffusion and inhibition areas were detected and measured on a scale.

Both four microorganisms have been antibacterial behaviour in all the compounds. Same media is used for both subculture and antibacterial activity estimation. The entire reading was tripled and is stated in the Normal Mean Error (± SEM).

Anti-Fungal Activity

Procedure: The method was carried out according to the NCCLS guidelines.

Anti-fungal Screening by Cup Plate method: This approach is based on the spread of antifungal components to the inoculated Saboraud dextrose medium from the reservoir hole in order for the growth of the fungus to be prevented as a field around the hole. Two mushrooms have been chosen viz. Candida albicans and Aspergillus niger.

Preparation of inoculum

The fungus suspension was prepared according to the standard Mac-Farland nephelometer. For the preparation of fungal suspension a 24 hour old culture was used. A sterile isotonic solution of sodium chloride has been suspensioned by fungus, and its turbidity has been modified to produce approximately 1.5 X 106 cells/ml. The optical density (650 nm) of 100 ml of 1 percent sulphuric acid was calculated equal to 1,175 percent barium chloride.

Sample preparation

The synthesised compounds have been dissolved to 400, 500 and 600 mg/ml in distilled water.

Culture medium

For preliminary antifungal operation, Saboraud dextrose Agar medium (Hi Media) was employed. The medium was dissolved for 15 minutes in water and autoclaving at 1210 C.

Standard preparation

The standard fluconazole was formulated in sterile distilled water at a concentration of 10 µg/ml.

Table No. 2.25 Nutrient Medium Sabouraud's Agarmedium*

S. no.	Ingredients	Weight in gm
1.	Dextrose	40
2.	Peptone	10
3.	Agar	20
4.	Distilled water	q. s. 1000 mL

***pH5.6 was maintained for nutrient media.*

It was used to quantify subculture as well as antibacterial behaviours. The medium's pH plays a major role in fungal growth. Medium acid favours growth, but excess acid cannot consolidate agar. Consequently, 0.1% lactic acid was used in the medium's pH.

Antifungal screening of compounds

By agar-gradient process, the synthesised compounds were standardised by antifungal research.

Preparation of assay medium

The quantities of the various ingredients listed above have been carefully weighed and water was dissolved. The so-called medium was sterilized for 15 minutes with autoclaving at 1210C.

Working procedure

The suspension of a single isolated colony in a standard saline of around 5 ml developed an inoculum. This is eventually incorporated to strengthen the suspension. The filamentous fungi are then diminished by 20 and the mould was badly weakened. In an inoculum suspension, the sterile cotton swab was hydrolyzed and the excess moisture was collected while the cotton swab had been rolling in the tube, and the hot Sabourauds agar medium had been inserted in the fluid at a height of 30 mL. The surface of Sabouraud's medium plate was strung in both directions by means of a moisture cotton swab.

280C has been dried out on the covering of Sabouraud's agar pan. Then the sterile cork borer was used to make 4 bores per platter. The aforementioned process was conducted in aseptic condition, and the respective trench was supplemented with 0.1 ml test solution and the normal reference was 0.1 ml fluconazole. Each plate was operated using DMSO. Plate incubation lasted 48 hours at 280C. Subsequently in Standard Error Mean (± SEM) the values of the inhibition zones were reported triplicate

CHAPTER 3

3.1. CHEMISTRY

3.1.1 Synthesized derivatives (IMD 1- IMD 10)

New imidazole derivatives were synthesized on the basis of **Radiszewski Synthesis.** In this research we synthesized imidazole derivatives by refluxing benzil with various substitutes of benzaldehyde. According to the literature reviews substitutes of benzaldehyde gives more active agents. Benzil was accurately weighed as required and dissolved in the little amount of solvent acetic acid and then substitute of benzaldehyde was dissolved in acetic acid with few percent of ammonia solution. The reaction was refluxed for 4-5 hours using heating mantle. Product was collected after pouring the reaction mixture into the ice water and then recrystallized and purified by ethanol.

In the first stage, the proliferation was conducted of 2 substituted phenyl, 4, 5 DP-1-H imidazole products which reacted with acid chloride further. In pyridine as a catalyst and benzene as a solvent, it was refluxed for 3-4 hours. The reaction mix was then cooled and shook and then held in the refrigerator or freezer. After one day it was extracted and recrystallized with ethanol after processing. Melting point, TLC, NMR, IR, Mass spectra, were used for the scheme. Subsequently antibacterial and antifungal substances were tested.

Table No. 3.1. Physicochemical data of intermediate substituted compounds

S. No.	Code no.	R	Molecular formula	M.W.	R_f Value	(%) yield	M.P.(˚C)
1	**IM 1**	2-chloro	$C_{21}H_{15}ClN_2$	330.81	0.79	65%	Not melted upto 250˚C
2	**IM 2**	4-chloro	$C_{21}H_{15}ClN_2$	330.81	0.84	67%	Not melted upto 250˚C
3	**IM 3**	2-methoxy	$C_{22}H_{18}N_2O$	326.39	0.72	47%	248 ˚C
4	**IM 4**	4-methoxy	$C_{22}H_{18}N_2O$	326.39	0.68	46%	250 ˚C
5	**IM 5**	2-nitro	$C_{21}H_{15}N_3O_2$	341.36	0.55	75%	235 ˚C
6	**IM 6**	3-nitro	$C_{21}H_{15}N_3O_2$	341.36	0.60	72%	221 ˚C
7	**IM 7**	4-nitro	$C_{21}H_{15}N_3O_2$	341.36	0.59	72%	220 ˚C
8	**IM 8**	H	$C_{15}H_{12}N_2$	220.1	0.55	76%	190 ˚C
9	**IM 9**	methyl	$C_{16}H_{14}N_2$	234.12	0.52	70%	201 ˚C
10	**IM 10**	ethyl	$C_{17}H_{18}N_2$	250.338	0.62	67%	210 ˚C

Table No. 3.2 Physicochemical data of finally synthesized compounds

S. No.	Code No.	R	Molecular formula	M.W.	R_f Value	(%) yield	M.P.(˚C)
1	**IMD 1**	2-chloro	$C_{23}H_{17}ClN_2O$	372.85	0.71	48.02 %	250 ˚C

2	**IMD 2**	4-chloro	$C_{23}H_{17}ClN_2O$	372.85	0.77	45.18 %	248 ˚C
3	**IMD 3**	2-methoxy	$C_{24}H_{20}N_2O_2$	368.43	0.83	35%	67.5 ˚C
4	**IMD 4**	4-methoxy	$C_{24}H_{20}N_2O_2$	368.43	0.79	32.13 %	69 ˚C
5	**IMD 5**	2-nitro	$C_{23}H_{17}N_3O_3$	383.4	0.68	71.42 %	170 ˚C
6	**IMD 6**	3-nitro	$C_{23}H_{17}N_3O_3$	383.4	0.68	70.58 %	168 ˚C
7	**IMD 7**	4-nitro	$C_{23}H_{17}N_3O_3$	383.4	0.65	72.13 %	170 ˚C
8	**IMD 8**	H	$C_{22}H_{16}N_2O$	324.13	0.68	68%	169 ˚C
9	**IMD 9**	methyl	$C_{23}H_{18}N_2O$	338.14	0.56	70.12 %	171 ˚C
10	**IMD 10**	ethyl	$C_{24}H_{22}N_2O$	354.44	0.77	69%	175 ˚C

3.2. PHARMACOLOGICAL SCREENING

3.2.1 Antibacterial Activity

Screening results of synthesized compounds shows that final compounds IMD2, IMD5 and IMD7 possess significant activity against gram negative *Escherichia coli*, IMD1, IMD2, IMD3 possess moderate activity against gram negative *Pseudomonas aureginosa*. IMD1, IMD2 and IMD10 possess significantactivity against grampositive *Staphhylococcus aureus*. IMD1 and IMD2 possess significantactivity against grampositive *Bacillus subtilis.* Antibacterial activity persists for the remaining substances in a whole sequence. Antibacterial debate and comparison with ampicillin antibiotics was carried out. Antibacterial activity data are provided in table no. 3.2.3.

3.2.2. Antifungal Activity

Screening results of antifungal activity showed that synthesized compounds IMD2 possess significant activity against *Candida albicans*. Remaining derivatives are mildly antifungal. Anti-fungal activity discussion and contrast is compared with fluconazole. Antifungal data are displayed in table no 3.3. Data are given.

Table No. 3.3 Antimicrobial activity of Synthesized Imidazole Derivatives (IMD 1-10)

S. no.	Compounds	Concentration (µg/ml)	Zone ofinhibition (mm)				
			Gram negativebacteria		Gram positivebacteria		Fungus
			E.coli	*P.auregin osa*	*S.aureus*	*B.subtilis*	*C.albicans*

1.	IMD 1	500	18.3	17.2	17.8	16.0	13.7
		600	19.1	18.5	20.3	17.0	14.9
2.	IMD 2	500	18.3	17	20.3	16.0	14.3
		600	19	17.9	21.3	17.0	15.7
3.	IMD 3	500	13.4	15.6	13.5	14.4	13.2
		600	14.8	16.3	14.7	14.8	13.7
4.	IMD 4	500	17.0	15.6	13.9	14.7	14.7
		600	17.9	15.9	14.3	15.3	15.1
5.	IMD 5	500	19.1	-	15.9	-	-
		600	19.9	-	16.8	-	-
6.	IMD 6	500	14.3	-	15.1	-	-
		600	15.0	-	16.5	-	-
7.	IMD 7	500	17.7	-	18.3	-	-
		600	18.9	-	19.9	-	-
8.	IMD 8	500	18.6	15.6	18.3	14.4	13.2
		600	19.9	15.9	19.5	14.8	13.7
9.	IMD 9	500	19.0	17.6	17.6	17.7	17.6
		600	19.9	17.9	18.3	18.2	18.1
10.	IMD 10	500	21.0	18.6	17.7	17.7	17.5
		600	21.9	18.8	18.3	18.3	18.0
8.	Ampic	500(	20.0	19.3	23.0	17.1	-

	illin	µg/ ml)					
9.	Flucon azole	500(µg/ ml)	-	-	-	-	16

Table No. 3.4 Antimicrobial activity of Synthesized Imidazole Derivatives (IM 1-10)

S. no.	Compounds	Concentration (µg/ml)	Zone of inhibition(mm)				
			Gram negativebacteria		Gram positivebacteria		Fungus
			E. coli	*P.auregin osa*	*S.aureus*	*B.subtilis*	*C.albicans*
1.	IM 1	500	15.2	15.2	15.4	14.2	12.7
		600	16.1	15.3	18.3	16.0	13.5
2.	IM 2	500	17.3	15	19.3	13.5	13.3
		600	18.6	16.5	18.3	14.0	14.4
3.	IM 3	500	11.3	12.6	12.4	12.4	11.2
		600	12.6	13.3	13.7	12.8	13.9
4.	IM 4	500	17.0	14.3	12.7	13.7	12.6
		600	17.9	14.9	13.3	14.3	13.1
5.	IM 5	500	17.3	-	14.9	-	-
		600	17.9	-	15.8	-	-

6.	IM 6	500	14.3	-	14.3	-	-
		600	14.9	-	15.4	-	-
7.	IM 7	500	15.7	-	15.3	-	-
		600	16.9	-	16.6	-	-
8.	IM 8	500	16.6	15.6	16.3	13.4	12.2
		600	17.9	15.7	17.5	13.8	13.7
9.	IM 9	500	17.0	16.6	15.3	15.7	14.6
		600	18.2	16.9	16.3	17.2	16.1
10.	IM 10	500	19.0	13.6	15.9	17.1	14.5
		600	20.9	18.3	16.2	17.8	14.8
8.	Ampicillin	500(µg/ml)	20.0	19.3	23.0	17.1	-
9.	Fluconazole	500(µg/ml)	-	-	-	-	16

Fig. 3.1 Antimicrobial activity of synthesized imidazole derivatives

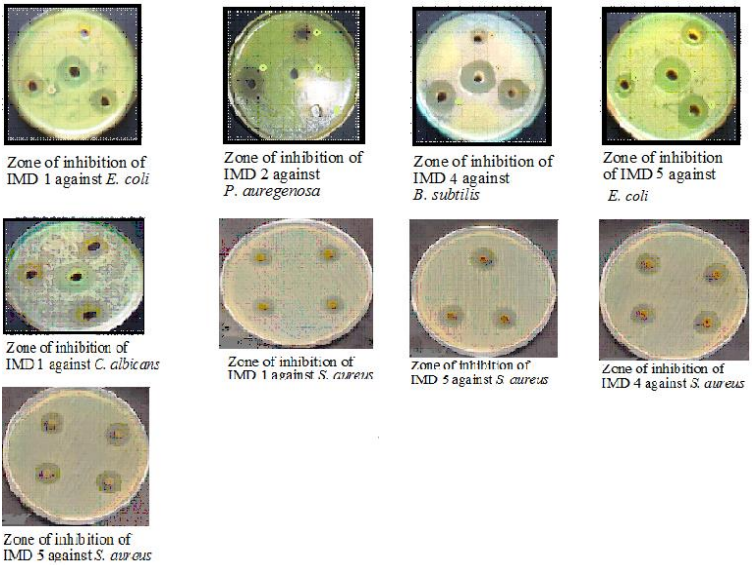
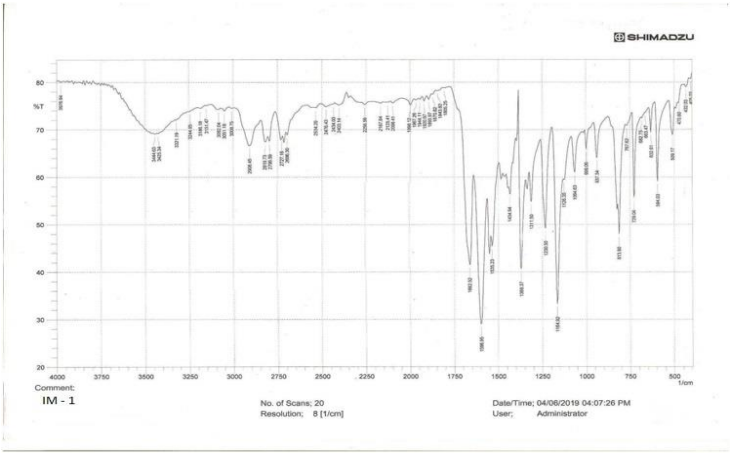
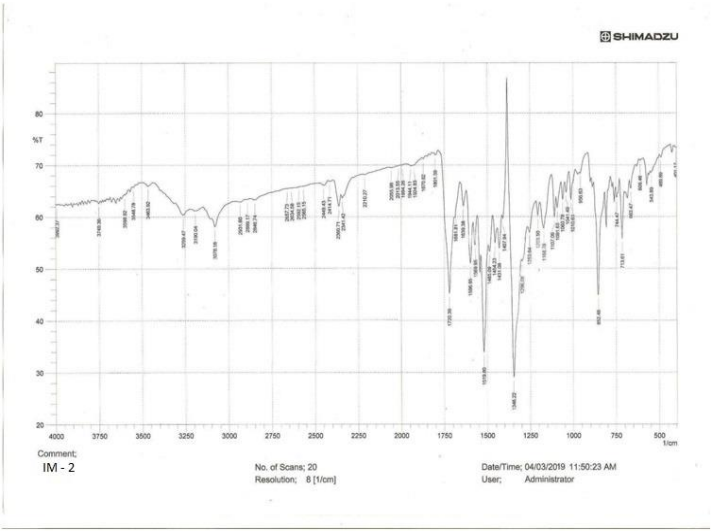
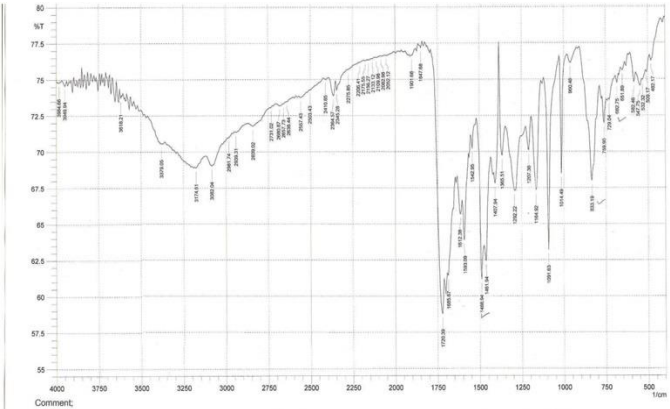


Fig. 3.1 Zone of inhibition of various derivatives against various species.

3.3 RESULT ANALYSIS GRAPH







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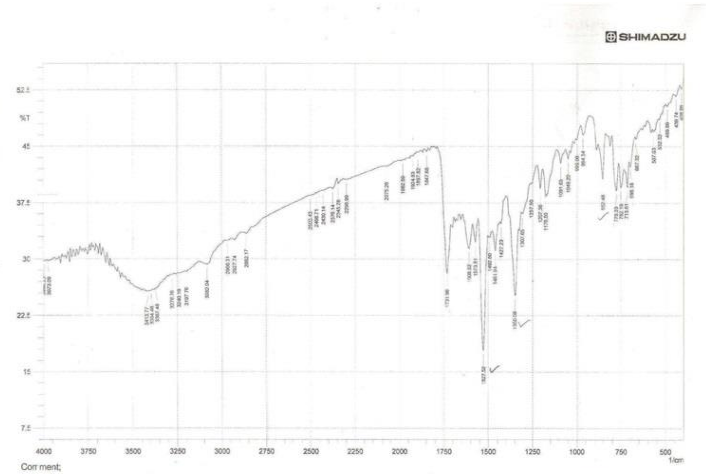

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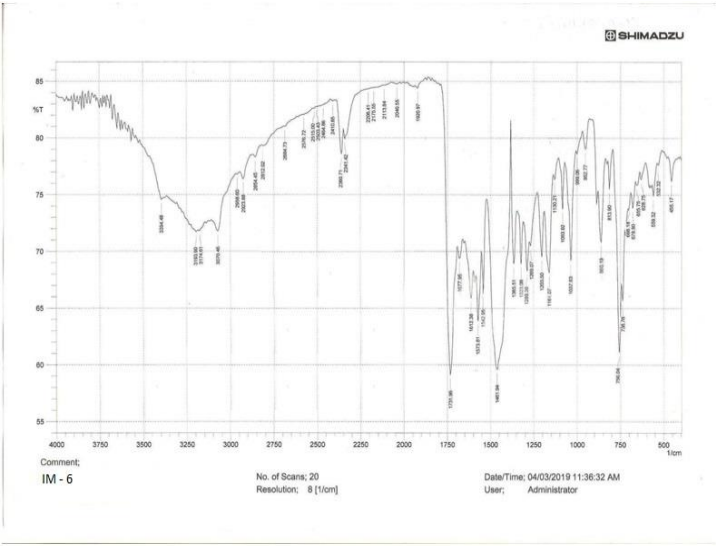
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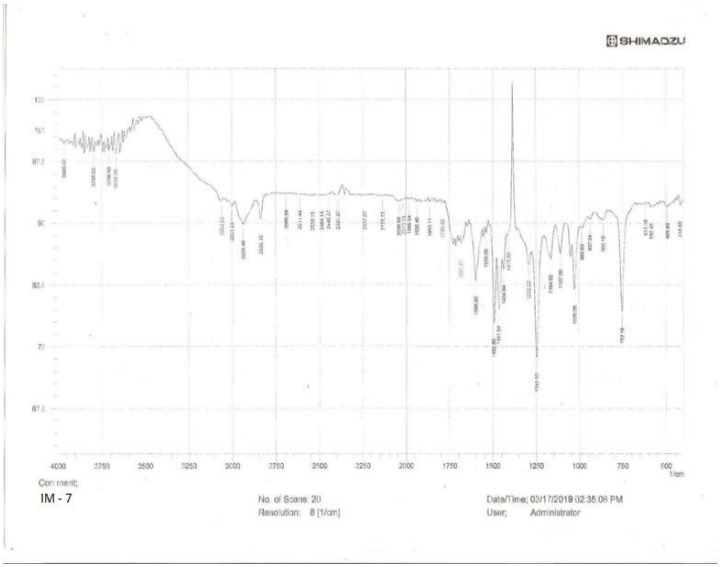
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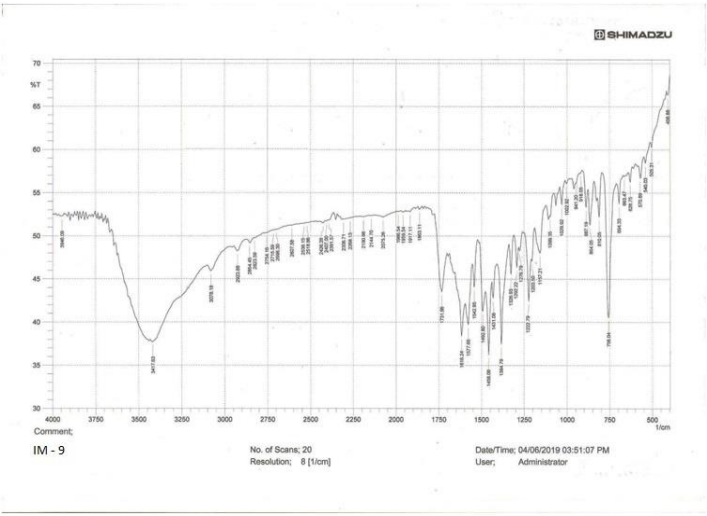
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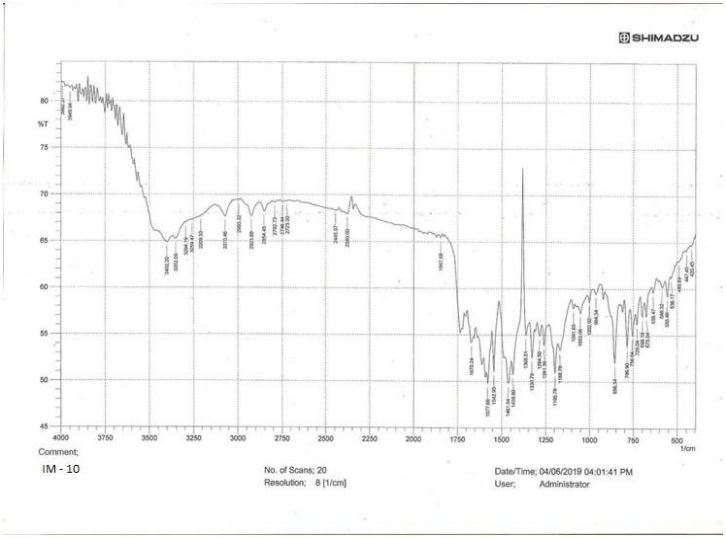
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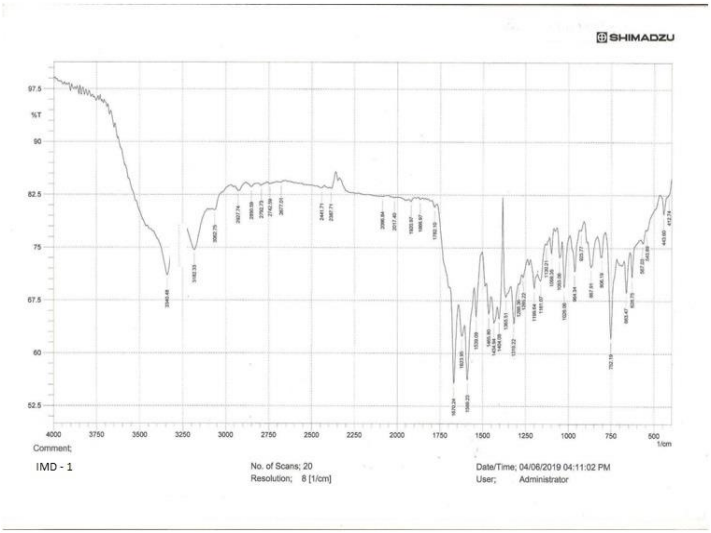
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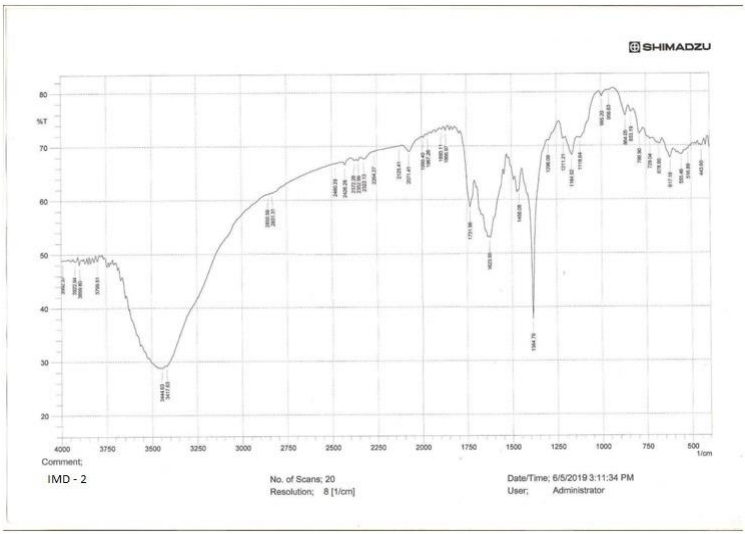
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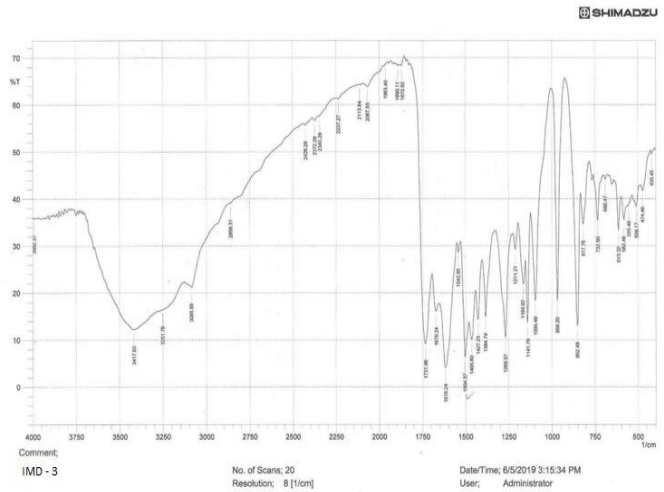

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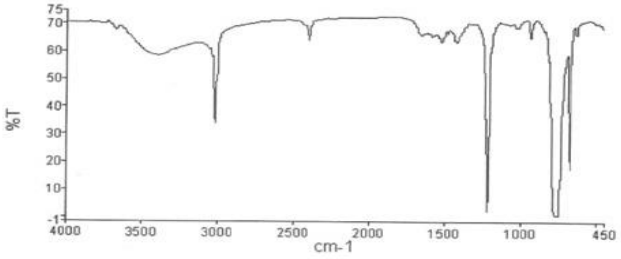

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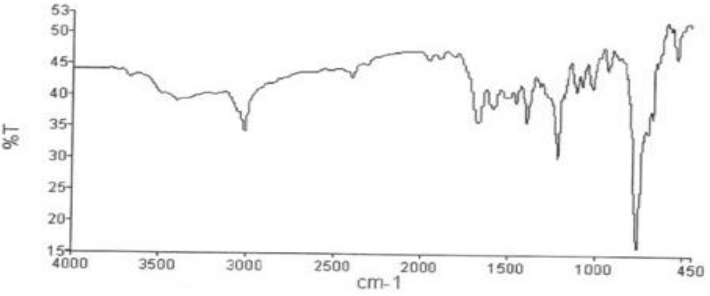

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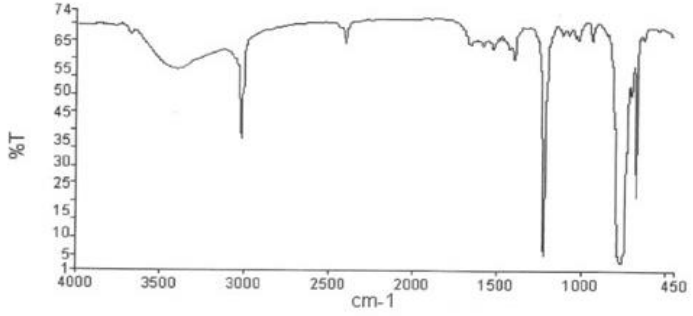

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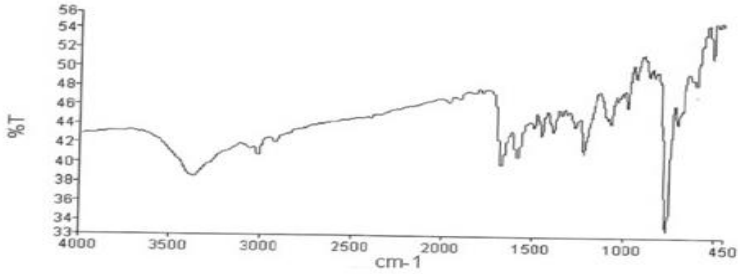

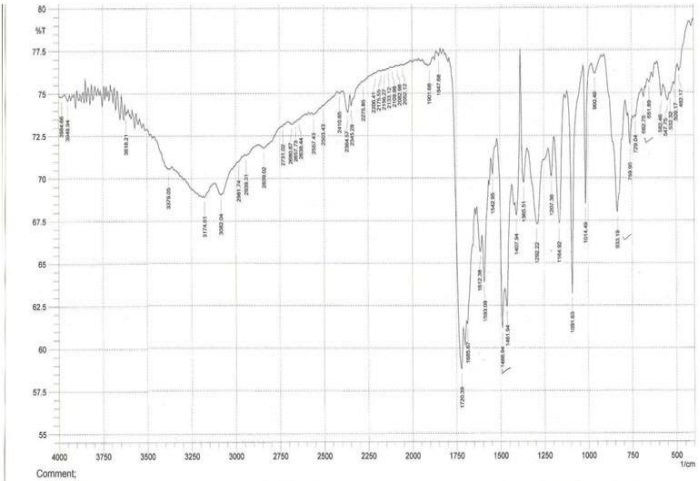

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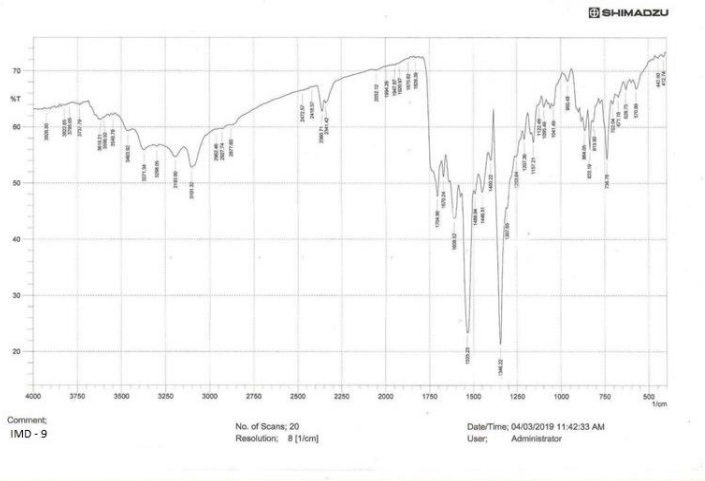
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1750
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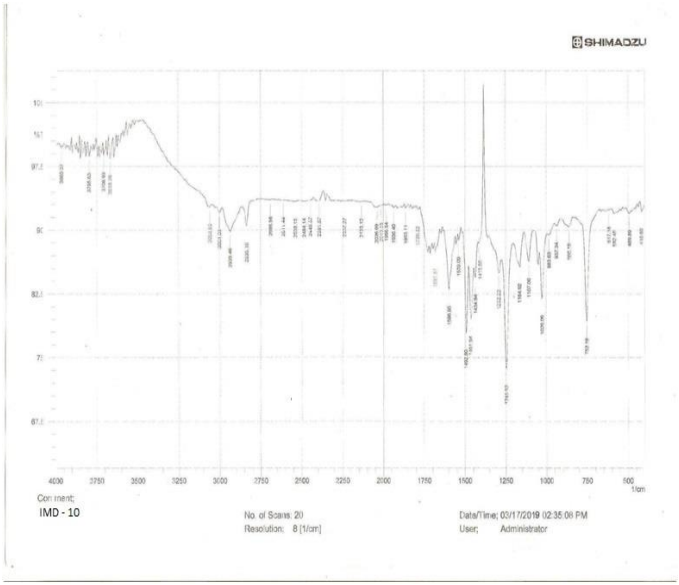
Comment;
IMD - 9
No. of Scans; 20
Resolution; 8 [1/cm]
Date/Time; 04/03/2019 11:42:33 AM
User; Administrator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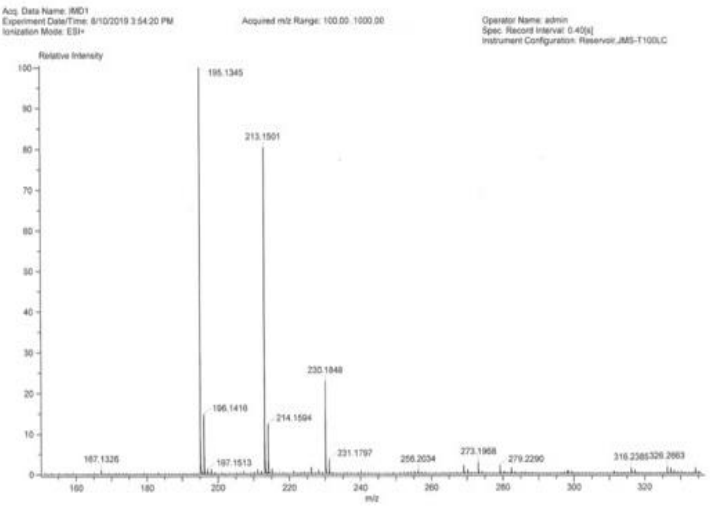
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Acquired m/z Range: 100.00..1000.00
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Spec. Record Interval: 0.40[s]
Instrument Configuration: Reservoir_IMS-T100LC
Relative Intensity
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213.1501
230.1848
196.1416
214.1594
231.1797
167.1326
197.1513
256.2034
273.1968
279.2290
316.2385328.2663
m/z

CHAPTER 4

4.1 CONCLUSION

Newly synthesized imidazole (1, 3-diaza-2, 4-cyclopentadiene) derivatives were found good antifungal and antibacterial agents. Some of them are promising and need to be further investigated to get better agents. Imidazole is a better nucleus which may be used further for good and improved antimicrobial activity in future. IR, 1H NMR and mass spectroscopy experiments have verified structures of imidazole derivatives. Antimicrobial screening findings have demonstrated that both chemicals are present in all species. The compounds demonstrate strong antibacterial activity against negative bacteria and bacteria. Nitro-imidazoles show activity against only anaerobes bacterias such as *Escherichia coli* and *Staphhylococcus aureus*. Other remaining compounds show moderate activity with reference compound Ampicillin and Fluconazole. Compounds which have halo-substitution show good antifungal activity. Together, we may assume that the imidazole derivatives examined are both active against bacteria and fungi, given the findings from antibacterial and antifungal studies.

4.2 RESEARCH APPLICATION

Significant synthetic technique in drugs discoveries is the insertion of the imidazole nucleus. The high therapeutic qualities of the medication imidazole have contributed to the synthesis of a wide variety of new chemical agents of strong biological action by medicinal chemists. In remedying numerous provisions of clinical

formulations the spectrum of imidazole products has expanded. In the field of medicinal chemistry several methods for imidazole synthesis and even their separate structural reactions offer huge scope.

The continuing increase in antibacterials in these recent years has highlighted the need to develop powerful antibacterial medicines that are highly antibacterial in ability and especially effective in fighting persistent bacilli. In the last two decades, the azole class has been one of the most widely researched. In the bioactive molecules, azoles are the most common heteroaromatic scaffolds. A central structure in numerous synthetic medicinal products, the benzimidazole ring mechanism displays a wide variety of biological function, including antibacterial and anti-fungal features.

As this class of derivatives also exhibit other activities such as anticancer, antilishmanial, antidepressant and anti-viral so above synthesized derivatives can also subjected to other activities for future research.

REFERENCES

- Achar, K.C.S., Hosamani, K.M., Seetharamareddy, H.R., 2010, *European Journal of Medicinal Chemistry*, 45, 2048–2054.

- Bhatnagar, A., Sharma, P.K. and Kumar, N., 2011. *Inter. J. Pharm Tech Res*., 3 (1), 268-282.
- Bredereck, H., Gompper, R. and Hayer, D., 1959. *Chem. Ber*, 92, 338.
- Boland, N.A., Casey, M., Hynes, S.J., Matthews, J.W. and Smyth, M.P., 2002. *J.Org. Chem*, 67, 3919.
- Congiu, C., Cocco, M. T. and Onnis, V., 2008. *Bioorganic & Medicinal Chemistry Letters*, 18, 989–993.
- Davood, A. and Alipour, E., 2008. A. Shafiee.*Turk J Chem*., 32, 389 – 395.
- Debus, H., 1858. *Annalen der Chemie and Pharmacie*, 107, (2), 199 – 208.
- Finlay, M.R.V., Acton, D.G., Andrews, D.M., Barker, A.J., Dennis, M., Fisher, E., Graham,
- M.A., Green, C.P.,Heaton, D.W., Karoutchi, G., Loddick, S.A., Morgentin, R., Roberts, A., Tucker, J.A. and Weir, H.M., 2008. *Bioorg. Med.Chem. Lett*, 18, 4442.
- Finar, I. L., 2009. *Organic Chemistry: Stereochemistry and the chemistry of natural products*, 5, 2, ELBS Longman Group Ltd., London, 614-615.
- Hill, A.J. and Johnston, J.V, 1954. *J. Am. Chem. Soc*, 76, 922.
- Hofmann, Klaus., 2013. Imidazole and Its Derivatives, *The Chemistry of Heterocyclic Compounds*, Volume 6, By, John Wiley and Sons.

- Lunt, E., Newton, C.G., Smith, C., Stevens, G.P., Stevens, M.F., Straw, C.G., Walsh, R. J., Warren, P. J., Fizames, C. and Lavelle, F., 1987. *J. Med. Chem*., Feb, 30 (2), 357- 66.
- Neef, G., Eder, U. and Sauer, G.J., 1981. *Org. Chem*, 46, 2824.
- Puratchikodya, A. and Doble, M., 2007. *Bio-organic & Medicinal Chemistry*, 15, 1083–1090.
- Purohit, M. and Shrivastava, S.K., 1991.*Indian J. Pharm. Sci*., 53**,** 162.
- Pandey K, Kali R, Bhalla T. N. and Barthwal J. P., 1987. *Pharmazie*, 42**,** 269.
- Pandeya Nath, S.N., 2004. *A Text Book of medicinal chemistry*, SG publisher, 1(3), 2-3.
- Robert, C. and Elderfield**.,** 1957, V-5, 744.
- Ramya, V., Shingalapur, Hosamani, K. M. and Keri, R.S., 2009. *European Journal of Medicinal Chemistry*, 44, 4244–4248.
- Sharma, D., Narasimhan, B., Kumar, P., Judge, V., Narang, R., Clercq, E. De. and Balzarini, J., 2009. *European Journal of Medicinal Chemistry*, 44, 2347–2353.
- Shin, G.I. and Lee, J.I., 1996. J.H. Kim, *Bull. Korean Chem. Soc*, 17, 29.
- Singh, H., and Kapoor, V.K., 2008. *Medicinal and Pharmaceutical Chemistry*, Vallabh Prakashan, 2, 1 -2.
- S. Baroniya, Z. Anwer, P. K. Sharma, R. Dudhe, N. Kumar.2010, *Der Pharmacia Sinica*.,1(3), 172-182.
- Sarasin, and Weymann, 1924. Helv.*Chim, Acta*, **7**,720.
- Sharma, P.S., Sharma, R., Tyagi, R., 2009. Curr. Cancer Drug Targets, 2008, 8,53
- Singh, I. P., Saxena, A. K., Sinha, J. N., Shanker, K., Eur. J. *Med. Chem*, 20**,** 283.
- Sawhney, S. N., Vir, D., Gupta, A., *Indian J. Chem*., 1990, 29b, 1107.

- Tafi, A., Anastassopoulou, J., Theophanides T., Botta, M., Corelli, F., Massa, S., Artico, M., Costi, R., Santo, RD., Ragno, R., *Molecular Modeling of Azole Antifungal Agents Active against Candida albicans*. 1. *A Comparative Molecular Field Analysis Study*, *Journal of Medicinal Chemistry*, 39, 1996, 1227-1235.
- Vorbriiggen, H. and Krolikiewicz, K., 1981. *Tetrahedron, Lett*., 22, 4471.
- Williams, D. A. and Lemke, T. L., 2002**.** *Foye's Principles of medicinal chemistry*, Lippincott Williams and Wilkins, 5, 36.
- Wallach, and Schuelze., 1881. *Ber*, 14,420-423.
- Wyler, R., Murbach, A., Mohl, H., An imidazolederivative (econazole)as an antifungal agent in cell culture systems, In Vitro,15,10,1979,745-750.
- Zampieri, D., Mamolo, M. G., Vio, L., Banfi, E., Scialino, G., Fermeglia, M., Ferrone, M., and
- Pricl, S., 2007. *Bioorganic & Medicinal Chemistry*. 15, 7444–7458.
- Ling, V., 1997. *Cancer Chemother. Pharmacol*., 40 (suppl), S3;
- Kaye, S., 1998**.** *Curr. Opin.Oncol.*,10 (suppl 1), S15.

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