SYNTHESIS AND BIOLOGICAL ACTIVITY OF IMIDAZOLE DERIVATIVE OXICONAZOLE ANALOGUES

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ABSTRACT:

In the current study I have made an effort to synthesize imidazole derivative oxiconazole analogue and evaluate them for antifungal activity. By using different method for determining antifungal activity of a compound, by adding it in varying concentration to a culture of test organism. Most of the target compounds had broad spectrum antifungal activity, which showed excellent to moderate inhibitory activity against the tested strains. By using UV, IR and 1H NMR the structures of these compounds were confirmed.

Keywords: Imidazole, Oxiconazole, Anti-fungal activity

1. INTRODUCTION:

Health, one of the most fundamental human needs, is the condition of whole mental, bodily, and social well-being and goes beyond just being free from pain or illness. It has always been a source of concern. Human proactive endeavours to prevent or treat health issues prompted the search for new drugs or appropriate variants on existing medications.

The antifungal, anticancer, and antioxidant medications now on the market are insufficient to address this issue. Their minimal activity level, quick resistance-building, and negative side effects outweigh their benefits.

It is standard practice to alter a known compound's structural characteristics in an attempt to improve correlation and provide advice for more pharmacological research, with the goal of shedding lighter on the link between chemical structure and physiological activity. It is generally known that significant changes in biological activity may be caused by structural modifications to certain molecules. In medicinal chemistry, the synthesis of derivatives has been a major area of study. The goal of synthesizing drug derivatives has been to alter the way that medications work, especially to lessen their adverse effects. [1] The prevalence of fungal infections has considerably grown throughout the last 20 years. High rates of morbidity and mortality are the outcome. Bacteria and fungi cause a wide range of ailments in mammals and humans alike. A portion of them pose a threat to life. Fungi are heterophilic creatures that thrive by consuming other live or dead organisms. [2]

1.1.1 Fungi and Fungal Infections

Eukaryotic creatures with one or more cells are known as fungi. They feature a cytoplasmic membrane composed of sterols, mainly ergosterol, and a distinct cell wall structure. [3] Microscopic organisms that have the ability to penetrate epithelial tissue are the source of fungal infections. Among the kingdom of fungi are molds, rusts, yeasts, and mushrooms. Similar to mammals, fungi are heterotrophic, meaning they get their nutrition from outside sources rather than from inside (like plants with photosynthesis). The majority of fungi are helpful and engaged in biodegradation, but some can lead to opportunistic infections when they enter the skin through wounds or enter the lungs and nasal passages through inhalation. [4] An estimated one million people die annually from fungal infections, mostly from those caused by the Aspergillus, Candida, and Cryptococcus species. Even with antifungal medications, these underdiagnosed illnesses are difficult to cure and have a high associated death rate. [5]
Different human mycosis is-

1. Superficial

The most prevalent infections are onychomycosis (nail), keratomycosis (eye), and otomycosis (ear). [3] Candida, Malassezia spp., and dermatophytes infections are the causes of superficial fungal infections. Aerobic fungi known as dermatophytes are the most frequent culprits behind superficial fungal infections. These dermatophytes may reproduce and proliferate in the outermost layers of the epidermis by physiologically breaking down keratin. Thus, in clinical practice, protein rich body fragments are most commonly impacted by dermatophytic infection. Arthroconidia that are lodged in skin and hair scales can survive there for years, causing relapses and recurrences to occur often. The three genera that the causing dermatophytes are from are Trichophyton, Microsporum, and Epidermophyton. Depending on the infection location and the patient's immune system reaction, dermatophyte infections might present with different clinical signs. The susceptibility to dermatophyte infections is also known to be influenced by genetic susceptibility. [6] The most common manifestation is tinea pedis, also known as dermatophytosis of the foot, which is most usually brought on by Trichophyton rubrum. [7]

2. Deep/invasive

In organs of human body, fungi are specific and proliferate. Some times in deep tissues also remarkable. These infections are hard to identify, have a convoluted clinical history, and a dismal prognosis. The most common causes of them are fungus belonging to the Aspergillus and Candida genera. [3,8,9] Candida genus yeasts are the source of the infection known as candidosis. Candida most commonly causes superficial infections of the skin and mucous membranes. [7]

1.2 Antifungal agents

As their names imply, antifungal pharmaceuticals and antimitotic medications are therapies that target and eliminate fungal infections that pose minimal harm to the host. Major systemic fungal infections are treated and/or prevented with the use of these substances. [10] Depending on how they function, antifungals are divided into seven different types. Targeting the synthesis

of ergo sterol, fungal cell walls, sphingolipids, proteins, nucleic acids, microtubules, and fungal membranes are some of these types. [11] With the development of imidazole derivatives like clotrimazole, miconazole, and oxiconazole, azoles became known as a class of antifungal medications. [12]

1.2.1 Mechanism of action of antifungals

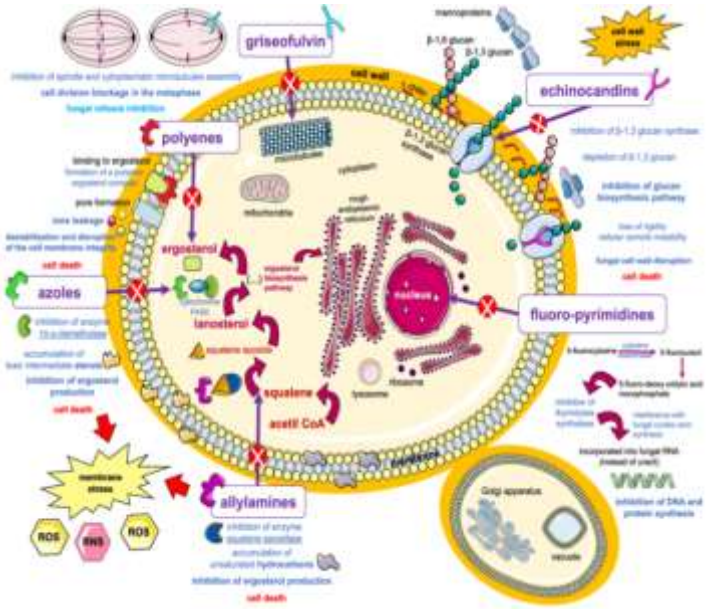


Fig. 1.2.1 Mechanism of action of antifungals

Azoles are a class of antifungals that work by preventing the production of ergo sterol, a vital constituent of membranes. To be clear, the azole class of antifungal medications inhibits the lanosterol 14-α-demethylase enzyme, which is dependent on cytochrome P450 (CYP450). When the so-called enzyme is suppressed, ergosterol is consumed and accumulates, which impairs the fungal membrane's ability to perform a number of its activities and ultimately encourages fungal growth. [13] Many azoles have been effectively utilized for more than 35 years to treat invasive fungal infections caused by dermatophytes and Candida species strains. [14]

1.3 Heterocyclic Compounds

Carbocyclic chemicals, such as benzene, are cyclic molecules that have just carbons as ring members. Because all of the ring's backbone contains carbon, it is also a hemicyclic molecule. Heterocyclic compounds, on the other hand, are cyclic substances that contain at least one element other than carbon in their ring. These atoms are known as heteroatoms.

Compounds that consist of one heteroatom and five heterocyclic components. In these cases, non-bonding lone pairs of electrons in sulfur, nitrogen, and oxygen have an impact on the alternate π bond in rings contain five carbon atoms in their structures. There are around five different types of heterocyclic compounds: tetrazole, oxizole, pyrazole, imidazole’s, and triazoles.

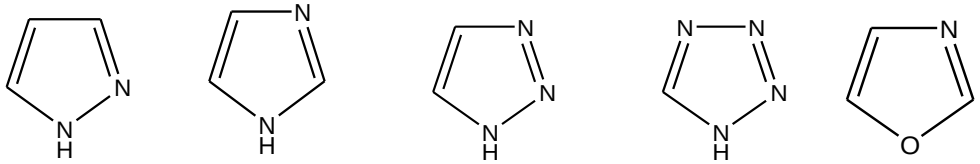


Fig. 1.3.1 some examples of five membered heterocyclic compounds

Nitrogen, oxygen, and sulphur are included in the ringed structures of pyridine, pyran, and thiopyran, three of the heterocyclic compounds having six members. Approximately six single-member heterocyclic compounds:

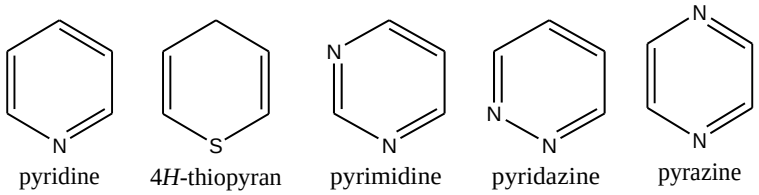


Fig. 1.3.2 Some examples of six membered heterocyclic compounds

One of the two cyclic chemicals that condense to produce them is a heterocyclic compound. [15]

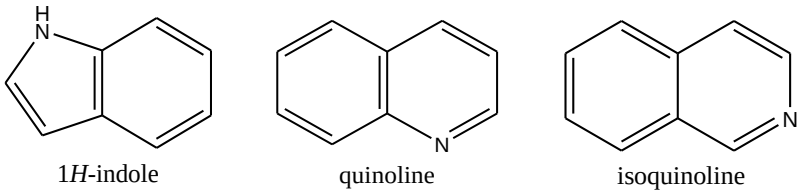


Fig. 1.3.3 Some examples of fused heterocyclic compounds

1.4 Azoles

A type of five-membered heterocyclic compounds known as azoles has a nitrogen atom as well as at least one additional non-carbon atom (such as oxygen, sulfur, or nitrogen) attached to the ring. [16]

While griseofulvin, the first drug having antifungal action, was identified in 1939, Woolley (1944) introduced the first azole compound; nonetheless, it was a coincidental finding that first revealed the antimycotic impact of the benzimidazole moiety.

The azole antifungals have been used in clinical practice to treat a variety of fungal infections for more than 20 years. They are divided into the imidazoles and triazoles, two separate groups. [17]

1.5 Imidazole

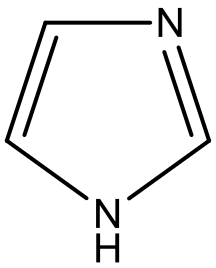


Figure. 1.5 Structure of Imidazole

The chemical formula for imidazole, a five-membered heterocyclic ring, is C3H4N2, as shown in Figure 1.5. This formula indicates that there are two N and three C atoms within its structure. Since glyoxal and ammonia were used in the first synthesis to create imidazole, it was formerly known as glyoxaline. [18]

Planar five-membered rings come in two tautomeric forms, which is imidazole. Figure 1.5 illustrates the two 1, 3-diazole ring's comparable tautomeric forms that arise when one of the two nitrogen atoms has a positive charge. Imidazole is a very polar molecule that dissolves entirely in water, with an estimated dipole of 3.61D. [19]

Heinrich Debus created imidazole for the first time in 1858. Its production began with the combination of formaldehyde and glyoxal in ammonia, which resulted in the end product, imidazole-originally known as glyoxaline. [20,21]

The heterocyclic aromatic organic compound imidazole has the following chemical characteristics:

- **Basicity:** Because the N-atom in a cyclic ring containing five carbons has a single pair of electrons, imidazole may receive a proton and acts as a weak base.
- **Nucleophilicity:** In some processes, including nucleophilic substitution and addition reactions, the nitrogen atom in imidazole can function as a nucleophile.
- **Coordination:** Because of its nitrogen atom, imidazole may coordinate with metal ions to create metal complexes.
- **Electrophilicity:** In some processes, especially those involving the electrophilic substitution of aromatic compounds, imidazole can also function as an electrophile.
- **Tautomerism:** Imidazole displays tautomeric equilibrium, in which the hydrogen atom's location on the nitrogen atom varies, between its 1H-imidazole and 3H-imidazole forms. [22,23]

1.6 Overview of oxiconazole

Oxiconazole, an oxime O-ether, is the 2,4-dichlorobenzyl ether of the oxime that is produced by formal acetophenone carbonyl group condensation with hydroxylamine. In this procedure, a 1H-imidazol-1-yl group is used to replace one of the hydrogens in the methyl group, and chlorines are used to replace the phenyl groups at positions 2 and 4. It is an antifungal medication that is applied topically to treat fungal skin infections. It is frequently found in creams and powders as the nitrate salt. It serves as an agent with anti-infective properties. It is

a member of the class of substances known as dichlorobenzenes, oxime O-ethers, imidazoles, and conazole antifungal medications. It is an oxiconazole (1+) conjugate base. [45]
It is used to treat numerous types of skin diseases, such as ringworm, jock itch, and athlete's foot. [46]
Although its exact route of action is yet unknown, oxiconazole, like other azole antifungals, most certainly inhibits the cytochrome P450-dependent demethylation of lanosterol. This stops the synthesis of ergosterol, which is necessary for the fungal cell membrane. Oxiconazole alters the permeability of fungal cell membranes, encourages the loss of vital intracellular components, and ultimately inhibits fungal cell development by interfering with the formation and integrity of fungal cell membranes. [47]

2. Experimental Section

2.1 Materials and methods

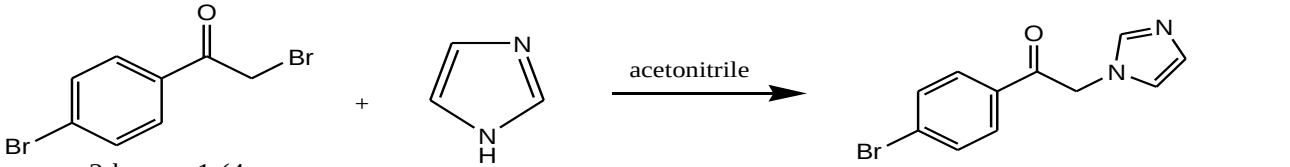
All the chemicals and solvent procured from CDH (P) Ltd., Qualigens Fine Chemicals, Loba Cheme Pvt. Ltd. and otto kemi and used without further purification. The melting points of all synthesized compounds were determined in open capillary tubes and are uncorrected. The purity of all compounds was checked by TLC on silica gel plates. IR spectra were recorded on Jasco FT-IR-4100 in KBr disc. H1 NMR spectra were recorded on a Varian 400 MHz spectrometer in DMSO-d6 and CDCl3; chemical shifts (δ) were in ppm relative to TMS and coupling constant (J) were expressed in hertz (Hz) using tetramethylsilane as an internal standard.

2.2 Synthesis

The compounds of the synthetic protocol scheme were obtained in the following steps
General procedure for synthesis of compounds PS1-PS5 [38]

STEP-1

1. 4-bromophenacyl bromide (10gm), acetonitrile (10ml) and imidazole (7.6gm).
2. Cool reaction mass to 30-35℃. Stir and maintain reaction mass for 3.0 hrs. at same temperature.
3. Charge 30ml methanol at 30-35℃, stir at same temperature for 30min.
4. Cool the reaction mass at 10℃ slurry wash with chilled methanol.

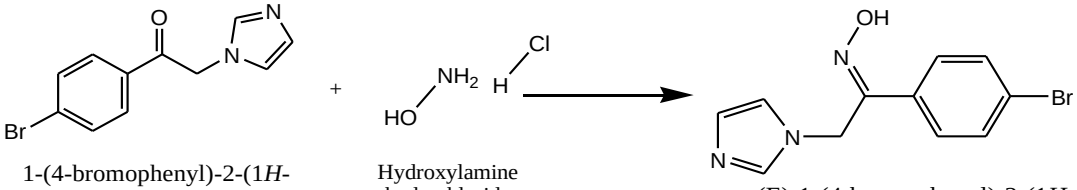


2-bromo-1-(4-bromophenyl)ethanone + 1*H*-imidazole → 1-(4-bromophenyl)-2-(1*H*-imidazol-1-yl)ethanone

STEP-2

1. Take stage-1 material, methanol (7.3ml) and pyridine (7.3ml) in round bottom flask. Heat to 60℃ to dissolve the material.
2. Add hydroxylamine HCl (4.0gm) in reaction mass and heat reaction mass to reflux.

3. Maintain reaction mass to reflux for 3hrs.
4. Add 30ml distilled water and adjust pH with aq. Ammonia.
5. Stir for 30min at 25-30℃ and filter the reaction mass.



1-(4-bromophenyl)-2-(1*H*-imidazol-1-yl)ethanone

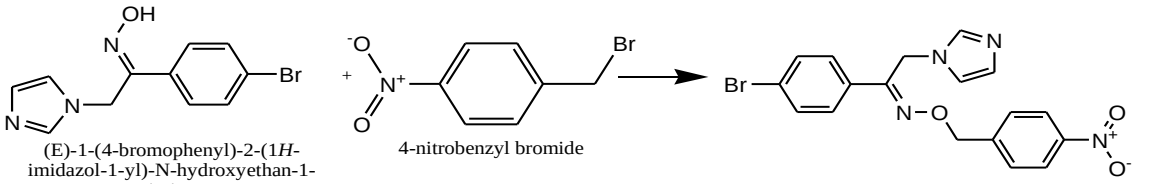
Hydroxylamine hydrochloride

(E)-1-(4-bromophenyl)-2-(1*H*-imidazol-1-yl)-N-hydroxyethan-1-imine

STEP-3

1. Take stage-2 material, dimethyl formamide (30ml) and 4-nitrobenzyl bromide (5gm)/ 4-chlorobenzyl cyanide (5ml)/ benzyl chloride (5ml) and stir for 30min at 30-35℃.
2. Add sodium hydride (3gm).
3. Exotherm observed temp. rises, stir reaction mass for 30min.
4. Add isopropyl alcohol (30ml) stir reaction mass to 30-35℃ for 30min.

From 4-nitrobenzyl bromide-

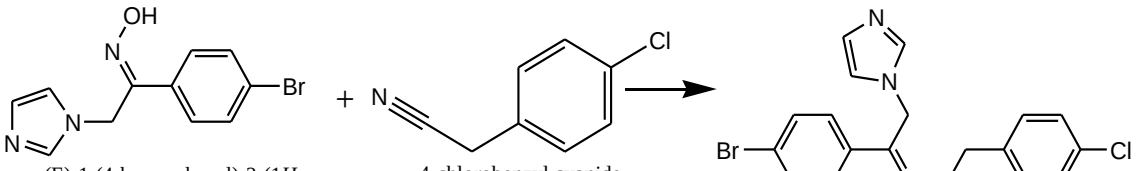


(E)-1-(4-bromophenyl)-2-(1*H*-imidazol-1-yl)-N-hydroxyethan-1-imine

4-nitrobenzyl bromide

Ethanone, 1-(4-bromophenyl)-2-(1H-imidazole-1-yl)-,O-[(4 nitrophenyl)methyl]oxime,(1Z)-

From 4-chlorobenzyl cyanide-

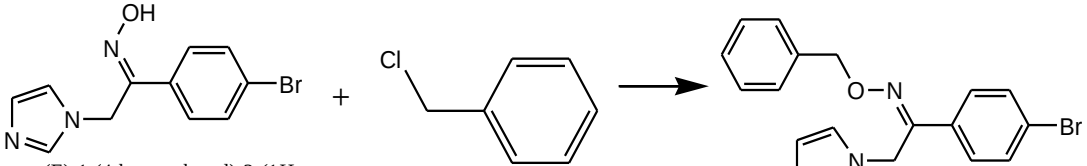


(E)-1-(4-bromophenyl)-2-(1*H*-imidazol-1-yl)-N-hydroxyethan-1-imine

4-chlorobenzyl cyanide

PS2

From benzyl chloride-



(E)-1-(4-bromophenyl)-2-(1*H*-imidazol-1-yl)-N-hydroxyethan-1-imine

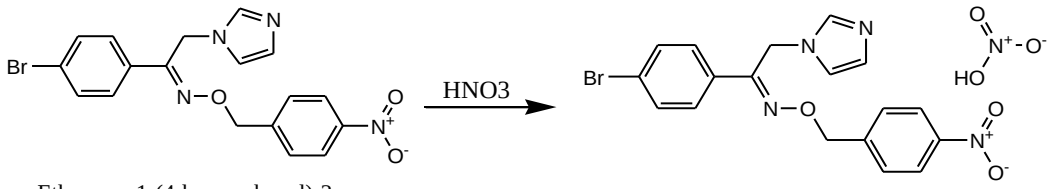
benzyl chloride

PS4

STEP-4 (Only for compound PS1, PS3, PS5)

1. Take stage-3 material and add 2N HNO3 (20ml) slowly.
2. Stir reaction mass for 3hrs. at 30-35℃.
3. Filter and dry.

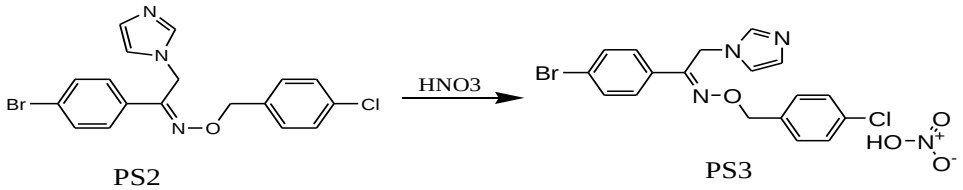
From Ethanone, 1-(4-bromophenyl)-2-(1H-imidazole-1-yl)-,O-[(4-nitrophenyl)methyl]oxime,(1Z)-



Ethanone, 1-(4-bromophenyl)-2-(1H-imidazole-1-yl)-,O-[(4 nitrophenyl)methyl]oxime,(1Z)-

PS1

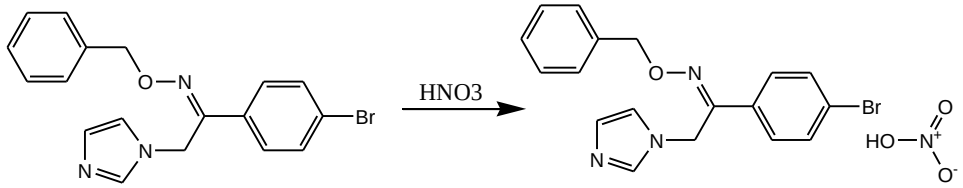
From derivative PS2



PS2

PS3

From derivative PS4



PS4

PS5

Synthesis of Ethanone, 1-(4-bromophenyl)-2-(1H-imidazole-1-yl)-,O-[(4 nitrophenyl)methyl]oxime,(1Z)-nitrate (PS1)

% yield= 67.5%, Rf= 0.65, Melting Point: 208-210°C

^{1}H NMR Spectra (400MHz; DMSO-d6/ppm): 8.16-8.31 (3H, m, Ar), 7.10-7.92 (8H, m, Ar), 6.62 (1H, s, Ali), 6.04 (1H, s, Ali), 2.49 (1H, s, -OH)

FTIR (KBr, cm^{-1}): 528.0 (C-Br), 2856.6 (N=C), 1383.7 (N=O), 3438.5 (C-H, Ar.), 1636.5 (C=C, Ar.), 2923.7 (C-H, Ali.).

Synthesis of Ethanone, 1-(4-bromophenyl)-2-(1H-imidazole-1-yl)-,O-[(4 chlorophenyl)methyl]oxime,(1Z)- (PS2)

% yield= 65.6%, R_f = 0.58, Melting Point: 212-214°C.

^{1}H NMR Spectra (400MHz; DMSO-d6/ppm): 7.53-7.62 (8H, m, Ar), 7.50-7.53 (3H, m, Ar), 5.30 (1H, s, Ali), 4.05(1H, s, Ali)

FTIR (KBr, cm^{-1}): 829.7 (C-Cl), 568.7 (C-Br), 2855.3 (N=C), 1388.1 (N=O), 3455.4 (C-H), 1438.8 (C-C), 1622.6 (C=C), 3139.9 (N-O).

Synthesis of Ethanone, 1-(4-bromophenyl)-2-(1H-imidazole-1-yl)-,O-[(4 chlorophenyl)methyl]oxime,(1Z)-nitrate (PS3)

% yield= 67.7%, R_f = 0.95, Melting Point: 222-225°C.

^{1}H NMR Spectra (400MHz; DMSO-d6/ppm): 7.41-7.98 (8H, m, Ar), 5.99-6.20 (3H, m, Ar), 5.82 (1H, s, Ali), 5.78 (1H, s, Ali), 2.48(1H, s, -OH)

FTIR (KBr, cm^{-1}): 823.8 (C-Cl), 564.9 (C-Br), 2855.9 (N=C), 1384.9 (N=O), 3421.5 (C-H), 3113.4 (N-O), 1455.4 (C-C), 1637.4 (C=C).

Synthesis of Ethanone, 1-(4-bromophenyl)-2-(1H-imidazole-1-yl)-,O [(phenyl)methyl]oxime,(1Z)- (PS4)

% yield= 66.4%, R_f = 0.91, Melting Point: 230-232°C.

^{1}H NMR Spectra (400MHz; DMSO-d6/ppm): 6.53-7.64 (9H, m, Ar), 6.83-7.33 (3H, m, Ar), 5.30 (1H, s, Ali), 3.789 (1H, s, Ali)

FTIR (KBr, cm^{-1}): 567.2 (C-Br), 1445.0 (C-C), 1624.0 (C=C), 1570.6 (C-N), 1387.0 (N=O), 2856.0 (N=C), 3454.5 (C-H).

Synthesis of Ethanone, 1-(4-bromophenyl)-2-(1H-imidazole-1-yl)-,O [(phenyl)methyl]oxime,(1Z)-nitrate (PS5)

% yield= 64.4%, R_f = 0.74, Melting Point: 201-205°C.

^{1}H NMR Spectra (400MHz; DMSO-d6/ppm): 7.84-7.98 (9H, m, Ar), 7.65-7.72 (3H, m, Ar), 5.99 (1H, s, Ali), 2.87 (1H, s, Ali)

FTIR (KBr, cm^{-1}): 567.8 (C-Br), 1458.4 (C-C), 1694.3 (C=C), 1582.9 (C-N), 1383.4 (N=O), 2856.2 (N=C), 3047.9 (C-H).

Pharmacological Evaluation

The produced chemicals were biologically tested using spectrum analysis. The agar diffusion method was adopted in this study to assess the antifungal efficacy of various newly synthesized drugs. The in-vitro antifungal activities of the synthesized compounds were carried out by

microdilution susceptibility test using cup-plate technique. The anti-fungal activity was screened against fungal strains viz. Candida albicans. The MIC (minimum inhibitory concentration) values were determined in compare to standard drug oxiconazole (anti-fungal). The MIC is considered to be the lowest drug concentration for which there is no microbial growth.

Antifungal Activity

Experimental Procedure

In vitro antifungal screening by agar diffusion method

Using the agar diffusion method at various doses, several newly synthesized compounds were tested for their antifungal efficacy against fungal strain. DMF served as a solvent control and the commercial antifungal Oxiconazole was utilized as the standard.
The process for conducting an activity test based on agar diffusion was as follows. The approach followed the strategies on condition that by the NCCLS.
Microorganisms used: C. albicans

Procedure:
A. Media Preparation:
Filled a sterile plastic flat-bottomed Petri dish with a 90 mm diameter and 20 ml of newly produced and sterilized Muller Hinton Agar (Difco, USA) on a level surface. [For fungal strains, complemented with.2% glucose and 0.5 mcg/ml Methylene blue].
For full solidification, let the agar medium cool to room temperature.
(i) The plates were chilled at 4℃ for 25–30 minutes.
B. Inoculum Preparation:
Prepared saline suspension of isolated colonies.
C. Inoculation of Test Plates:
In between 15 minutes subsequently the inoculum preparation, dipped a germ-free cotton swab into the adjusted suspension and rotated several times. By pressing the swab against the test tube's interior wall above the fluid level, the excess inoculum was removed.
The sterile agar surface was streaked with the swab to inoculate the dried portion of the pre-cooled agar plates.
D. Application of Compound
After the medium was established, a single well or hole was created in each plate, and various test substance concentrations were added to each cavity.
Within five minutes of loading the material, the plates were placed in an incubator that was adjusted to 35°C.
E. Reading the plates
Following 16–18 hours of incubation, confluent lawns of growth were checked on the plates. Measurements were made of the discs' diameter as well as the diameters of the zones of total inhibition. A ruler was used to measure zones to the closest whole millimeter, and the ruler was held against the back of the inverted Petri plate.

Broth dilution assay (Minimum inhibitory concentration)

The broth dilution technique was utilized to ascertain the antifungal activity of the produced compounds. The agar disc diffusion experiment was used to regulate the minimum inhibitory concentration (MIC) values for bacteria that shown sensitivity to the chemicals.

i. The compounds were produced at 1.5 mg/mL, which is the greatest concentration. The rack held the two rows of twelve sterile capped tubes. The serial double dilution approach was used to achieve different chemical dilutions.
ii. The compounds were diluted in increments of 100µg/mL.
iii. 5 mL of each solution were placed in a sealed tube, and 5 mL of double strength media were added.
iv. Tubes were injected with a 0.2 mL fungus spore solution. At the end of each row, a blank 2 mL of compound-free soup was added.
v. The tubes were incubated at 37 °C for 48 hours.
vi. To determine full inhibition, an organism was inoculated into a tube containing 2 mL of broth and it was refrigerated overnight at +4 °C.

The lowest chemical concentration (MIC) that did not exhibit any discernible fungal growth during the incubation period was defined. [39-41]

3. Result and Discussion

3.1.1 Chemistry

The imidazole derivative oxiconazole analogues were prepared in several steps summarized in scheme. At initial step the 4'-bromophenacyl bromide react with hydroxylamine hydrochloride in refluxing ethanol pyridine resulting corresponding oxiconazole analogues (PS1-PS5). Which is then condensed with the benzyl halides by means of sodium hydride in hot DMF. The oxiconazole analogues (PS-1, PS3 and PS5) reacts with nitric acid to form a desired compound. The conformation of structure of compounds were performed by TLC, IR, NMR, Melting point and solubility.

3.1.2 Biological evaluations of synthesized compounds

Using the region of embarrassment method, the antifungal action of currently synthesized imidazole derivatives was investigated against Candida albicans and oxiconazole as a standard drug. **Compound PS3** was originate to be more powerful against Candida albicans, with minimal inhibitory concentration, while the remaining compounds demonstrated moderate antifungal activity.

Table 3.1.2 Antifungal Activities of the Compounds

Compounds	**Candida albicans (conc. 100µg/ml)**
PS1	0.9

PS2	1.7
PS3	3.11
PS4	0.8
PS5	1.4

4. Conclusion

This study was designed to synthesize and analyse several new imidazole derivative oxiconazole analogues, as well as to investigate their antifungal properties. The above-mentioned procedure for synthesizing all derivatives yields high-quality products. UV, IR and 1H NMR analyses were accomplished to corroborate the structures of the recently synthesized substances. When compared to traditional medications, some of the synthetic compounds had moderate to good antifungal efficacy.

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