



Synthesis of Novel Imidazoles as Potent Antimicrobial Agents

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ABSTRACT: Imidazole is a heterocyclic compound with five membered unsaturated ring structure composed of 3 carbons and 2 nitrogen atoms at non-adjacent positions. Imidazole drugs have broad applications in many areas of clinical medicine. These are currently used as tools in pharmacological studies. The important therapeutic properties of imidazole related drugs have encouraged the medicinal chemists to synthesize and test a large number of novel molecules. In this investigation, it was of interest to synthesize 1-(2-bromophenyl)-2-phenyl-1H-phenanthro[9,10-d]imidazole, by reaction of substituted imidazole with bromine in the presence of acetic acid. Various derivatives i.e. 1-(2-bromophenyl)-2-phenyl-1H-phenanthro[9,10-d]imidazole, 1-(2-bromophenyl)-2-(2-nitrophenyl)-1H-phenanthro [9,10-d]imidazole, 1-(2-bromophenyl)-2-(4-chlorophenyl)-1H-phenanthro [9,10-d]imidazole, 1-(2-bromophenyl)-2-(4-styryl-phenyl)-1H-phenanthro [9,10-d]imidazole and 1-(2-bromophenyl)-2-(4-styryl-phenyl)-1H-phenanthro [9,10-d]imidazole were formed with respective yield of 74, 64, 73, 79 and 72%. The structures of the compounds have been established on the basis of spectral analytical data. All the derivatives have been screened for their antimicrobial activities at the 100µg/ml and 200µg/ml against *Candida albicans*. © 2011 IGJPS. All rights reserved.

KEYWORDS: Imidazole; Antimicrobial Activity; Medicinal Chemistry.

INTRODUCTION

Medicinal chemistry is the discipline concerned with determine the influence of chemical structure on biological activity and in the practice of medicinal chemistry developed from an empirical one involving organic synthesis of new compound based largely on the modification of structure and then identifies their biological activity [1, 2]. Medicinal chemistry concerns with the discovery, development, interpretation and the identification of mechanism of action of biologically active compounds at the molecular level [3]. Various biologically active synthetic compounds have five-membered nitrogen-containing heterocyclic ring in their structures [4]. Structural frameworks have been described as privileged structures and in particular, N containing polycyclic structures has been reported to be associated with a wide range of biological activity. In the field of five membered heterocyclic structures imidazole

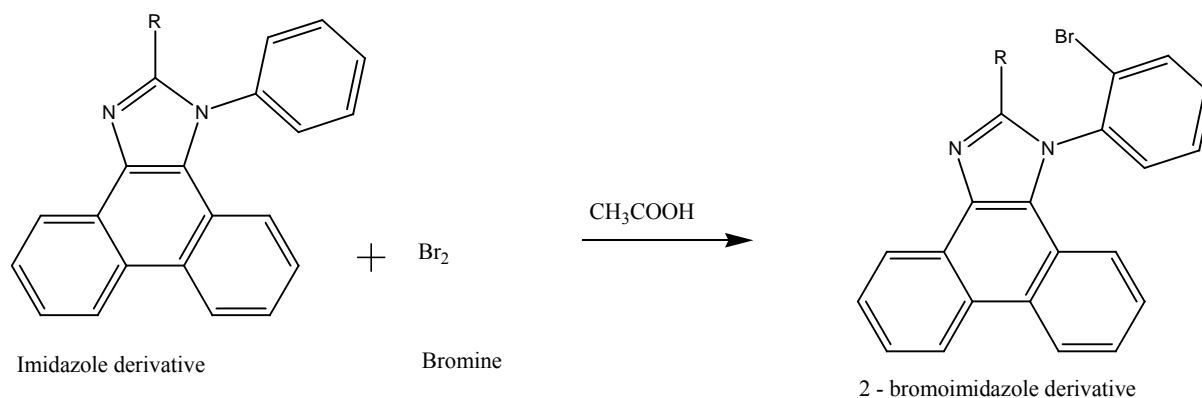
nucleus shows various properties. The high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Imidazole drugs have broadened scope in remedying various dispositions in clinical medicines. Medicinal properties of imidazole include anticancer, b-lactamase inhibitors, 20-HETE (20-Hydroxy-5,8,11,14-eicosatetraenoic acid) synthase inhibitors, carboxypeptidase inhibitors, hemeoxygenase inhibitors, antiaging agents, anticoagulants, anti-inflammatory, antibacterial, antifungal, antiviral, antitubercular, antidiabetic and antimalarial [5-18]. This group presents in azoles antifungal which inhibit the accumulation of methylated sterols destroy the composition of the lipid bilayer of membranes. Some imidazole drugs, at high concentrations, could exert direct inhibitory action on membranes, without interference with sterols and sterol esters [19, 20]. Infectious microbial disease causes worldwide problem, because microbes have resisted prophylaxis or therapy longer than any other form of life. In recent decades, problems of multidrug-resistant microorganisms have reached an alarming level in many countries around the world. Resistance of anti-microbial agents such as β -lactam antibiotics, macrolides, quinolones and vancomycin etc. and different species of bacteria causes increased important global problem [21,22]. Imidazole and its derivatives are reported to be physiologically and pharmacologically active and find applications in the treatment of several diseases.

MATERIALS & METHODS

The chemicals and reagents used in this were of AR and LR grade. They were procured from Spectro Chem, Hi-Media, Merck, Sigma Aldrich and Ranbaxy. . The IR spectra were recorded on Perkin Elmer BX FTIR 882 spectrometer using KBr pellet method in the range of 4000–400 cm^{-1} . NMR spectra were recorded on Bruker Avance II 400 Spectrometer. In ^1H -NMR, chemical shift values were reported in parts per million on the scale in dimethyl- d_6 sulfoxide with tetramethylsilane as the internal standard.

SYNTHESIS OF BROMINATED IMIDAZOLE

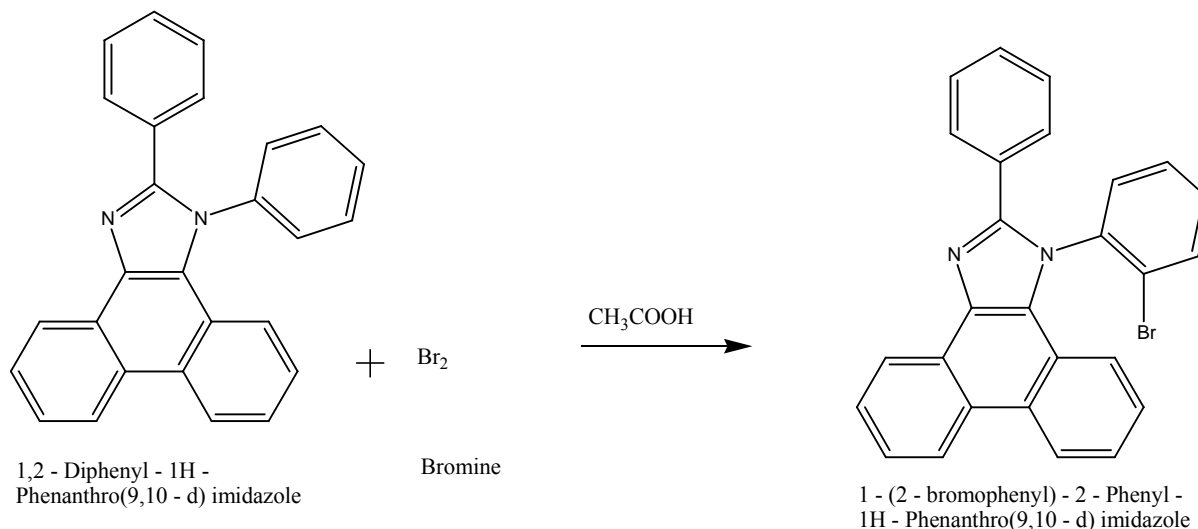
Took 500 mg of the imidazole derivatives and 15 ml of glacial acetic acid in a conical flask. Placed the flask in ice bath and added to it 5 ml of bromine water dropwise through burette with constant stirring. The mixture was heated on the hot plate with occasional shaking for 3 hrs. The completion of reaction was checked by TLC. Poured the reaction solution in to a beaker having access of water and purified by recrystallizing with hot ethanol. Noted down the % yield and melting point of the compound.



SYNTHESIS OF BROMOIMIDAZOLE DERIVATIVE

I SYNTHESIS OF 1-(2-BROMOPHENYL)-2-PHENYL-1H-PHENANTHRO[9,10-D]IMIDAZOLE

Took 500 mg of 1,2-Diphenyl-1H-phenanthro[9,10-d]imidazole and 15 ml of glacial acetic acid in a conical flask. Placed the flask in ice bath and added to it 5 ml of bromine water drop wise through burette with constant stirring. The mixture was heated on the hot plate with occasional shaking for 3 hrs. The completion of reaction was checked by TLC. Poured the reaction solution in to a beaker having access of water and purified by recrystallizing with hot ethanol.

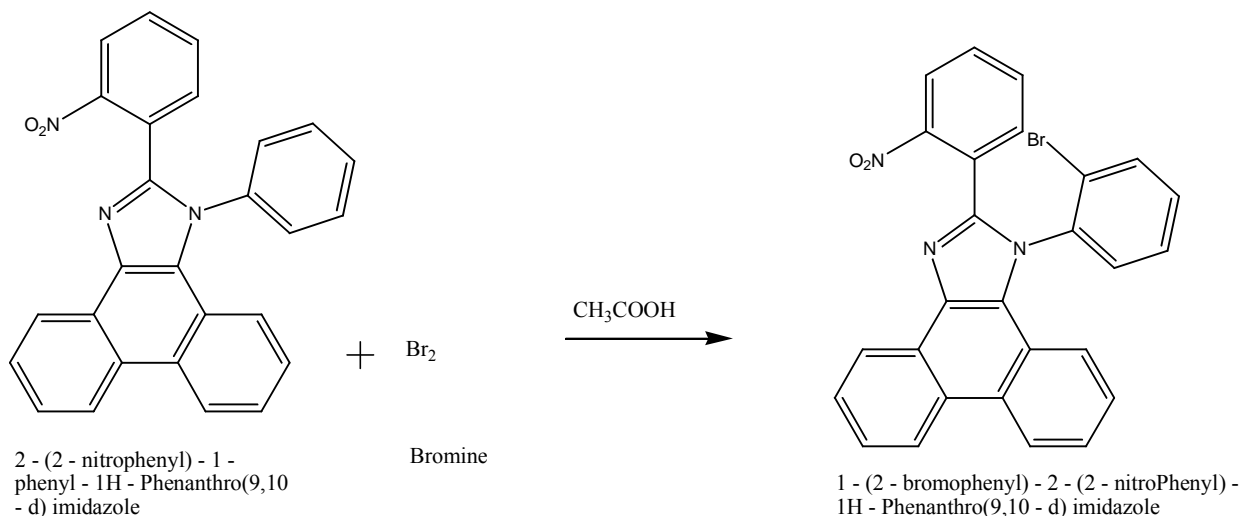


IR (KBr cm^{-1}): 1720 (C=N), 1564.54 (C=C), 2978 (C-H str.), 728.76 (C-H aromatic)

^1H NMR (DMSO- d_6) δ ppm: δ 7.95 (5H, s, Ar-H). δ 7.74 (4H, s, Ar-H) δ 8.54 (8H, d, A phenantherene- H), and as the expected structure show absorption in the region, the reaction is deemed to be successful.

II SYNTHESIS OF 1-(2-BROMOPHENYL)-2-(2-NITROPHENYL)-1H-PHENANTHRO [9,10-D]IMIDAZOLE

Took 500 mg of 2-(2-nitrophenyl)-1H-phenanthro[9,10-d]imidazole and 15 ml of glacial acetic acid in a conical flask. Placed the flask in ice bath and added to it 5 ml of bromine water drop wise through burette with constant stirring. The mixture was heated on the hot plate with occasional shaking for 3 hrs. The completion of reaction was checked by TLC. Poured the reaction solution in to a beaker having access of water and purified by recrystallizing with hot ethanol.

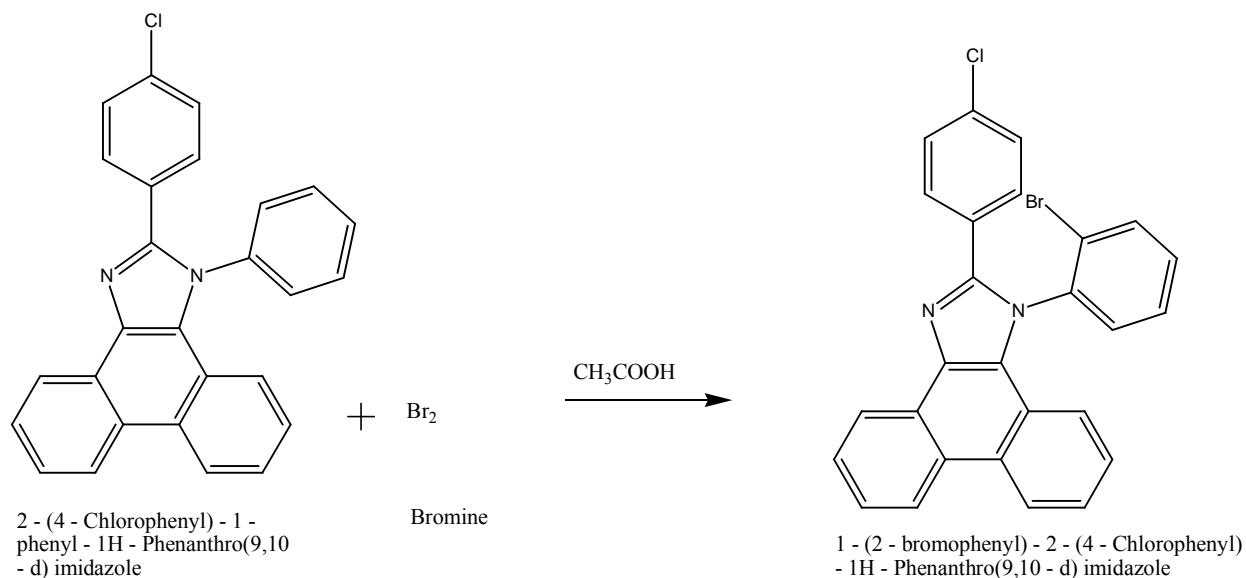


IR (KBr cm^{-1}): 1679 (C=N), 1580 (C=C), 2850 (C-H str.), 750 (C-H aromatic)

^1H NMR (DMSO- d_6) δ ppm: δ 7.2- 7.4 (4H, m, Ar-H). δ 7.82- 7.88 (4H, m, Ar-H) δ 8.25 (8H, d, A phenantherene- H)

III SYNTHESIS OF 1-(2-BROMOPHENYL)-2-(4-CHLOROPHENYL)-1H-PHENANTHRO [9,10-D]IMIDAZOLE

Took 500 mg of 2-(4-chlorophenyl)-1H-phenanthro[9,10-d]imidazole and 15 ml of glacial acetic acid in a conical flask. Placed the flask in ice bath and added to it 5 ml of bromine water drop wise through burette with constant stirring. The mixture was heated on the hot plate with occasional shaking for 3 hrs. The completion of reaction was checked by TLC. Poured the reaction solution in to a beaker having access of water and purified by recrystallizing with hot ethanol.

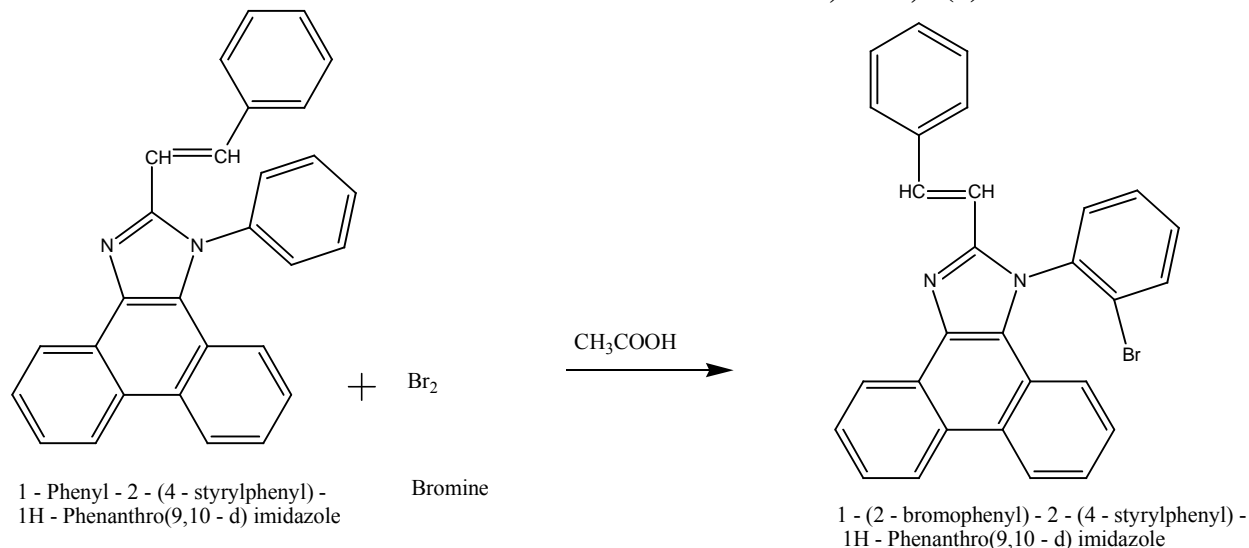


IR (KBr cm^{-1}): 1742 (C=N), 1565 (C=C), 2930 (C-H str.), 710 (C-H aromatic)

^1H NMR (DMSO- d_6) δ ppm: δ 7.35- 7.53 (4H, m, Ar-H), δ 7.9 (4H, s, Ar-H), δ 8.3 (8H, d, A phenantherene- H)

IV SYNTHESIS OF 1-(2-BROMOPHENYL)-2-(4-STYRYL-PHENYL)-1H-PHENANTHRO [9,10-D]IMIDAZOLE

Took 500 mg of 1 phenyl-2-(4-styryl-phenyl)-1H-phenanthro [9,10-d]imidazole and 15 ml of glacial acetic acid in a conical flask. Placed the flask in ice bath and added to it 5 ml of bromine water drop wise through burette with constant stirring. The mixture was heated on the hot plate with occasional shaking for 3 hrs. The completion of reaction was checked by TLC. Poured the reaction solution in to a beaker having access of water and purified by recrystallizing with hot ethanol.

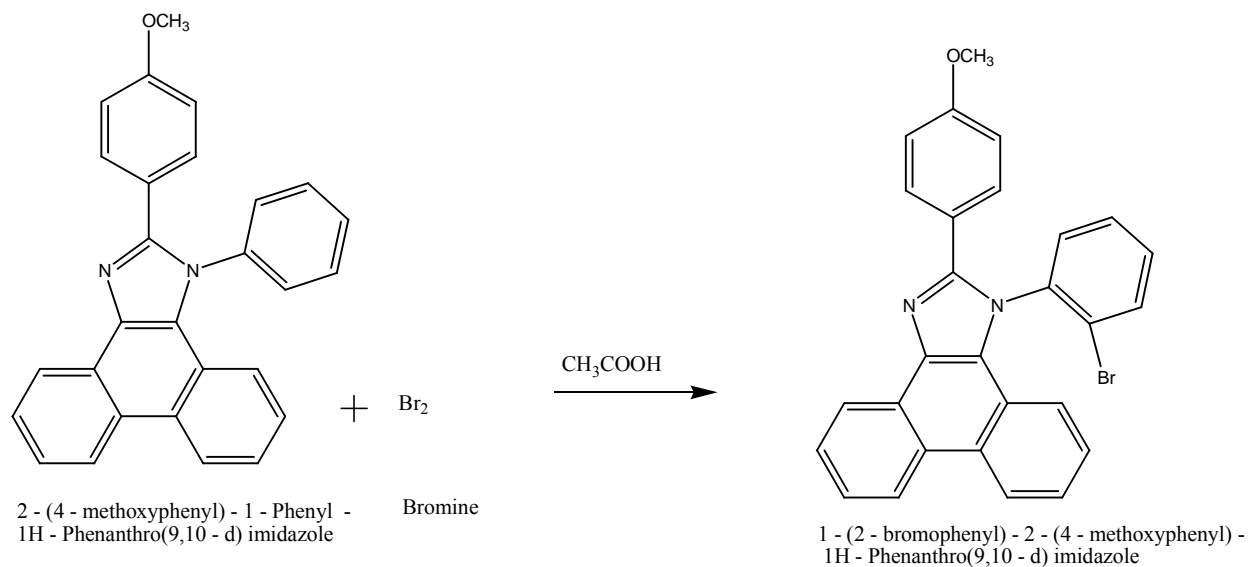


IR (KBr ^{cm-1}): 1795 (C=N), 1570 (C=C), 2880 (C-H str.), 705 (C-H aromatic)

¹H NMR (DMSO- d₆) δppm: δ7.4- 7.75 (4H, m, Ar-H), δ7.6 (4H, s, Ar-H), δ8.6 (8H, d, A phenantherene- H)

V SYNTHESIS OF 1-(2-BROMOPHENYL)-2-(4-STYRYL-PHENYL)-1H-PHENANTHRO [9,10-D]IMIDAZOLE

Took 500 mg of 1 phenyl-2-(4-phenoxyethyl)-1-phenyl-1H-phenanthro [9, 10-d]imidazole and 15 ml of glacial acetic acid in a conical flask. Placed the flask in ice bath and added to it 5 ml of bromine water drop wise through burette with constant stirring. Mixture was heated on the hot plate with occasional shaking for 3 hrs. The completion of reaction was checked by TLC. Poured the reaction solution in to a beaker having access of water and purified by recrystallizing with hot ethanol.



IR (KBr ^{cm-1}): 1820 (C=N), 1650 (C=C), 2870 (C-H str.), 725 (C-H aromatic)

¹H NMR (DMSO- d₆) δppm: δ7.35- 7.78 (4H, m, Ar-H), δ7.9 (4H, s, Ar-H), δ8.20 (8H, d, A phenantherene- H)

ANTI MICROBIAL ACTIVITY

CHOICE OF MEDIA FOR ANTI MICROBIAL ACTIVITY

There is no one medium satisfactory for all compounds against all organism using different assay procedure. Sabourad's dextrose agar (SDA) has for long been the most widely used medium for growing pathogenic fungi other media include kimmigs agar media and casein yeast extractglucose media. One remedy to the problem of selection of the media only was altering the method of MIC determination but it was not successful sinciet grossly influences the result.

METHODS OF SCREENING:

AGAR DIFFUSION METHOD

In the agar diffusion assay each plate is seeded with a single organism wells are cut: in the agar, or stainless steel cylinders are placed on the agar and each reservoir is charged, with test substance. Following incubation the zone of inhibition of growth round the reservoirs are measured, the more active the compound the large the zone. Although only a single organism is incorporated in each plate, one plate can be used to test several compounds and their relative potencies determined from the respective zone sizes.

BROTH DILUTION METHOD:

In a broth dilution assay the compound is incorporated in a liquid medium, which is then inoculated with the fungus and incubated. After a specified time, growth or absence of growth can be determined by visual observation and an MIC determined or the level of growth quantified by nephelometer or spectrophotometer. Although each compound and each organism require a separate tube, the broth dilution system is capable of miniaturization and automation. Each system has its advantage and disadvantage and since it is desire to have an indication of the activity with a wide range of the fungal organism the most practicable and adaptable system at the screening stage is the agar dilution assay.

RESULTS & DISCUSSION

Table 1. Physical properties of boromoimidazole derivatives

| Sr.no. | Comp. | R | m.p.(⁰ C) | % Yield | Rf value |
|--------|-------|--|-----------------------|---------|----------|
| 1 | I | -C ₆ H ₅ | 242 | 74 | 0.87 |
| 2 | II | -2-NO ₂ -C ₆ H ₅ | 209 | 64 | 0.84 |
| 3 | III | -4-Cl-C ₆ H ₅ | 281 | 73 | 0.96 |
| 4 | IV | -CH=CH-C ₆ H ₅ | 219 | 79 | 0.81 |
| 5 | V | -4-OCH ₃ -C ₆ H ₅ | 197 | 72 | 0.76 |

The sterilized agar medium was poured into petridishes and allowed to solidify for 30 min. On the surface of media fungus was spread with the help of sterlized cotton swab. After 10 min. punching into agar surface a sterile cork bored made cup or cavity and scooping out the punched part of agar. 2 cups were made into each petridish and into these caps were added the test compound (200µg/ml, 100µg/ml) are well filled with pure solvent DMF and another well was filled with standard antibiotic (voriconazole 200µg/ml,

100µg/ml), against candida albicans organism. The plates were kept in cold for 1 hr and then incubated at 37-38⁰c for 24 hrs. The zone of inhibition formed around the cups after overnight incubation was measured and percentage inhibition of the compound evaluated.

Table 2: Percent zone inhibition at the 100 µg/ml and 200 µg/ml.

| S.No. | Compound | Zone of Inhibition (100 µg/ml) | Zone of Inhibition (200 µg/ml) |
|-------|-------------------------|-----------------------------------|-----------------------------------|
| 1 | I | 06 | 10 |
| 2 | II | 19 | 21 |
| 3 | III | 18 | 25 |
| 4 | IV | 15 | 17 |
| 5 | V | 16 | 22 |
| 6 | Control | 00 | 00 |
| | Standard (Voriconazole) | 32 | 43 |

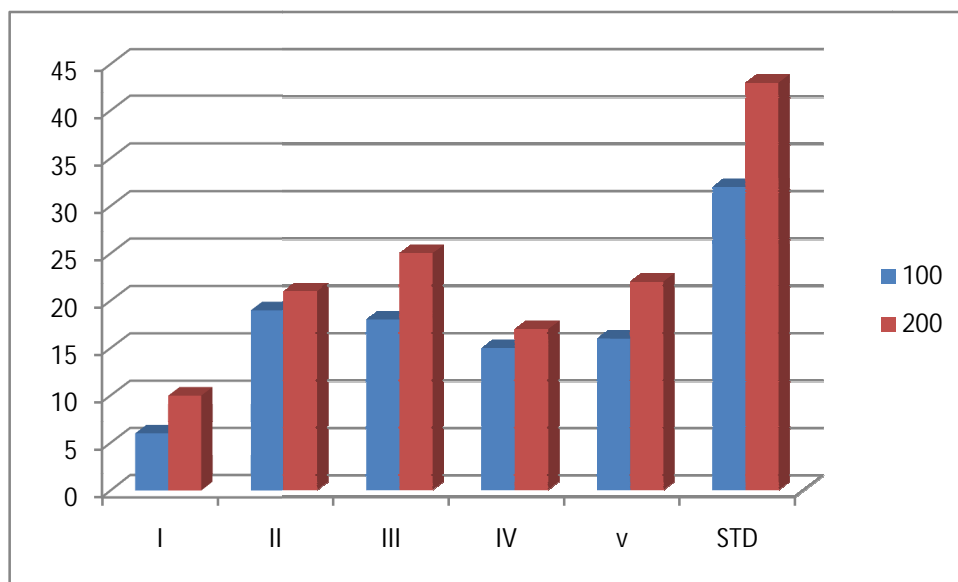


Figure Indicates the Zone of inhibition at the 100 and 200µg/mg conc. of I-V compound.

The structures of synthesized imidazole derivatives were confirmed from their respective spectral data such as IR, ¹H NMR studies. The antimicrobial activity of compounds I- IV were tested and it has been found that 200µg/ml dose of every compound has better activity as compare to 100µg/ml. As we consider all all results obtained from antimicrobial activity, we can say that all the compounds active antimicrobial agents.

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