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# Synthesis and Antimicrobial Screening of Some Potent 2, 4, 5-Triaryl Substituted Imidazoles Analogues

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## ABSTRACT

Present study circumspects synthesis of some 2, 4, 5-triaryl substituted analogues of imidazole and their spectral characterization by means of IR and $^{1}$H NMR. The compounds were screened for antibacterial activity against standard strains of both Gram positive and Gram negative bacteria. Results obtained establishes compounds IM3 and IM4 to be significantly responsive against different bacterial strains and as such these compounds can pave the way for development of potent antibacterial agents.

**Keywords:** Imidazole, Aryl aldehydes, Antibacterial, Cup-plate method.

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## INTRODUCTION

Over the century, the importance of imidazoles in biological system has attracted much interest due to their chemical and biochemical properties. Compounds with imidazole ring system have exhibited diverse pharmacological properties and can play important role in biochemical processes[1,2] as glucagon receptor anagonists[3], inhibitors of P38 MAP kinase[4], B-Raf kinase inhibitor[5], plants growth regulators[6], antibacterial[7] and antitumour[8] agents. The potency and wide applicability of the imidazole pharmacophore can be attributed to its hydrogen bond donor-acceptor capability as weak as its high affinity for metals which are present in many protein active sites[9]. 2,4,5-Triaryl-1H-imidazole compounds have gained remarkable importance due to their widespread biological activities and their use in synthetic chemistry. Due to their immense importance, many synthetic strategies have been developed. In 1882, Radziszewski and Japp reported the first synthesis of the imidazole from 1,2-dicarbonyl compound, various aldehydes and ammonia, to obtain the 2,4,5-triphenylimidazoles[10,11]. Also, Grimmett et al. proposed the synthesis of the imidazole using nitriles and esters[12]. Recently, there are several methods reported in the literature for the synthesis of 2,4,5-triaryl-1H-imidazoles from benzil/benzoin, aldehydes and ammonium acetate using different catalyst such as zeolite HY/silica gel[13], $ZrCl_4$[14], $NiCl_2.6H_2O$[15], ionic liquid[16], iodine[17], sodium bisulfite[18], acidic $Al_2O_3$[19], AcOH[20], $NH_4OAc$[21] , $Yb(OTf)_3$[22]. In recent years, boric acid ($BO_3H_3$) has gained special attention as catalyst in organic synthesis because of many advantages such as excellent solubility in water, uncomplicated handling, inexpensiveness and eco-friendly nature. Recently, several synthetically useful organic transformations using boric acid as a catalyst have been reported in the literature[23]. The present study encompasses refluxing of benzil with aryl aldehydes in presence of ammonium acetate and catalyst boric acid to form some 2,4,5 –triaryl substituted derivatives of imidazoles followed by their antibacterial screening.

## MATERIALS AND METHOD

The uncorrected melting points ($^OC$) of the synthesized compounds were determined using an electric melting point apparatus by open capillary method. The progress of reactions and purity of synthesized compounds were checked on silica gel-G TLC plates using various solvent combinations of different polarity. The spots were detected with iodine vapors as visualizing agent. The $\lambda_{max}$ (in nm) of the synthesized compounds was recorded on *Elico SL 164* UV-visible spectrophotometer using acetone as solvent. The FT-IR spectra of the synthesized compounds were recorded on a FT-IR *Perkin Elmer Spectrum RX-I* spectrometer using KBr disc in the range

of 4000-400 $cm^{-1}$ . The Proton NMR ($^1$H NMR) spectra were recorded in *Bruker AC-F 400* FT-NMR spectrometer at a frequency of 400 MHz. Spectra were obtained in deuterated acetone (acetone-$d_6$) using TMS (δ 0.00 ppm) as an internal standard at room temperature. Chemical shift (δ) values are expressed in ppm relative to internal standard.

**Synthetic Scheme**

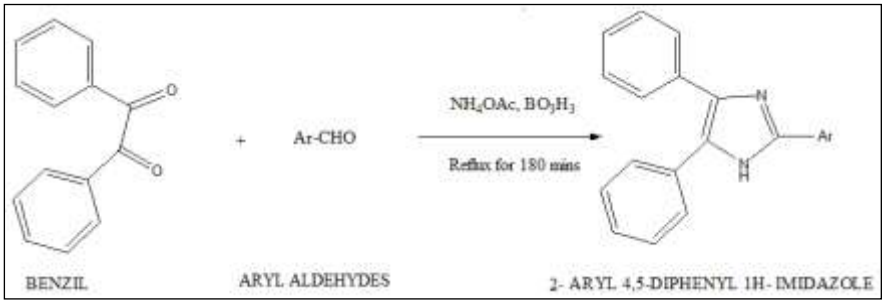
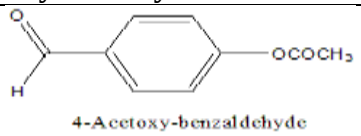
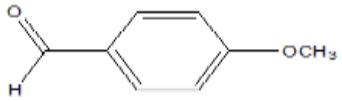
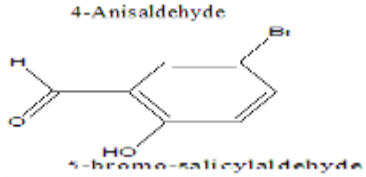
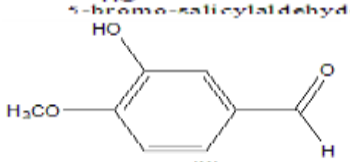



**Figure 1: Synthetic scheme for 2, 4, 5 –triaryl imidazoles**

**Table 1: Aryl aldehydes used**

| Compound | Aryl Aldehyde Used |
|---|---|
| IM1 ($C_{23}H_{18}N_2O_2$) Mol. Wt = 354.04 |  4-Acetoxy-benzaldehyde |
| IM2 ($C_{22}H_{18}N_2O$) Mol. Wt = 326.39 |  4-Anisaldehyde |
| IM3 ($C_{21}H_{15}BrN_2O$) Mol. Wt = 391.26 |  5-bromo-salicylaldehyde |
| IM4 ($C_{22}H_{18}N_2O_2$) Mol. Wt = 342.39 |  Vanillin |

**General method for synthesis of 2-Substituted benzimidazoles**

5 mol% of boric acid ,1 mmol of benzil, 3 mmol of ammonium acetate were dissolved in equal volumes of water and ethanol (5:5 ml) in single neck round bottom flask and to it equimolar aryl aldehyde was added. The reaction mixture was refluxed in a water bath for 3 hours. The progress of the reaction was monitored using TLC. Finally, the reaction mixture was poured into ice water (50ml) and the precipitated solid was filtered, washed with water, dried and recrystallized from ethanol to get corresponding 2,4,5-triaryl-1H-imidazoles. The products were confirmed by IR, $^1$H NMR analysis and melting point determination[24].

**Antibacterial Evaluation**

The antibacterial activity of the synthesized compounds was evaluated systematically against different strains of Gram-positive bacteria like *Staphylococcus aureus* and *Bacillus subtilis* and Gram-negative bacteria like *E.Coli* and *Pseudomonas aeruginosa*. The inhibition zones (in mm) of synthesized compounds were determined by cup-plate method[25]. The sterilized medium (autoclaved at 121°C for 20min) was inoculated using 18 hr slant cultures of the test organisms and transferred into sterile Petri dishes and allowed to the media to solidify. Cups of 8mm diameters were made on solidified media. Solutions of the synthesized compounds at a concentration of 50µg/ml and 100µg/ml were prepared in acetone. 50µl of each solution was placed in cups by means of sterile pipette. In each plate one cup was used for standard and other two for test solutions. The plates thus prepared were left for 90 min in a refrigerator for diffusion. The plates were incubated at 37°C for 24 hrs and examined for inhibition zones. The experiment was performed in duplicate and the average diameter of the zones of inhibition was recorded Amikacin (50µg/ml) was used as standard.

## RESULTS AND DISCUSSON

**Physico-chemical properties and spectral data of the synthesized compounds**

The yields of all the synthesized compounds were found to be satisfactory within the range of 55 to 60%. The spectral data generated upon analysis were found in accordance with the anticipated structure of the synthesized compounds.

**IM1: 2-(4-acetoxyphenyl)-4,5-diphenyl-1H-imidazole:**

Yield: 60%; Melting point: 227-231ºC; $R_f$ value: 0.84; IR (KBr $cm^{-1}$): 1474 (-C=C stretching), 1650 (-C=N stretching), 3016 (=C-H stretching), 3279 (aromatic –NH stretching); $^1$H NMR (400 MHz, acetone-$d_6$), δ (ppm): 3.84(3H,s,$CH_3$);7.0(2H,d,2CH);7.39-7.54(10H,m,10CH),6.87(2H,d, 2CH); 9.02 (s, 1H; broad, NH)

**IM2: 2-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazole:**

Yield: 58%; Melting point: 226-227ºC; $R_f$ value: 0.82; IR (KBr $cm^{-1}$): 1457 (-C=C stretching), 1634 (-C=N stretching), 3090 (=C-H stretching), 3279 (aromatic –NH stretching); $^1$H NMR (400 MHz, acetone-$d_6$),δ(ppm):3.72(3H,s,CH3);6.91(2H,d,2CH);7.24-7.54(10H,m,10CH),7.12(2H,d, 2CH); 9.21 (s, 1H; broad, NH)

**IM3: 2-(5-bromo-2-hydroxyphenyl)-4,5-diphenyl-1H-imidazole:**

Yield: 59%; Melting point: 250.5ºC- 252ºC; $R_f$ value: 0.91; IR (KBr $cm^{-1}$): 1521 (-C=C stretching), 1640 (-C=N stretching), 3090 (=C-H stretching), 3342 (aromatic –NH stretching), 3459 (-OH

broad); $^1$H NMR (400 MHz, acetone-$d_6$), δ (ppm): 4.12(3H,s,CH3); 7.26-7.70(10H,m,10CH), 6.91(4H,d, 4CH); 9.22 (s, 1H; broad, NH), 4.69 (s, 1H; OH)

**IM4: 2-(3-methoxy-4-hydroxyphenyl)-4,5-diphenyl-1H-imidazole:**

Yield: 55%; Melting point: 239-242ºC; $R_f$ value: 0.87; IR (KBr $cm^{-1}$): 1490 (-C=C stretching), 1642 (-C=N stretching), 3045 (=C-H stretching), 3274 (aromatic –NH stretching), 3556 (-OH broad); $^1$H NMR (400 MHz, acetone-$d_6$), δ (ppm): 3.66(3H,s,CH3);7.21(2H,d,2CH);7.24-7.54(10H,m,10CH),7.32(2H,d, 2CH); 9.34 (s, 1H; broad, NH) 4.72 (s, 1H; OH)

**Antibacterial activity data of the synthesized compounds**

Antibacterial screening of the synthesized compounds against different strains of Gram positive and Gram negative bacteria show compounds IM3 and IM4 exhibiting marked inhibition of both Gram positive and negative strains.

**Table 2: Antibacterial activity data**

| **Compound** | **Zone of Inhibition (mm)** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Gram positive bacteria** | | | | **Gram negative bacteria** | | | |
| | ***S.Aureus*** | | ***B.Subtilis*** | | ***E.Coli*** | | ***P.aeruginosa*** | |
| | 50 | 100 | 50 | 100 | 50 | 100 | 50 | 100 |
| IM1 | 13 | 15 | 15 | 21 | 16 | 19 | 15 | 18 |
| IM2 | 17 | 20 | 13 | 20 | 15 | 19 | 16 | 18 |
| IM3 | 17 | 19 | 21 | 26 | 17 | 21 | 17 | 21 |
| IM4 | 19 | 20 | 22 | 23 | 18 | 22 | 19 | 24 |
| **Control | - | - | - | - | - | - | - | - |
| *Amikacin | 17 | - | 23 | - | 18 | - | 20 | - |

*Amikacin (50 µg/ml) was used as positive control; **Acetone was used as negative control

## CONCLUSION

Stressing on the structural influence on the activity of the synthesized novel analogues, it can be observed that the hydroxyl group (-OH) present in both IM3 (from salicylaldehyde) and IM4 (from vanillin) may have a vital role in the activity of the compounds. On the other hand IM2 and IM1 too showed notable inhibitory activity to a considerable extent. It is evident from the research work that this series of synthesized and screened compounds along with further explored ones following the above mentioned convenient synthetic procedure may pave the way for development of some very potent antibacterial agents.

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