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A Convenient Method of Synthesis of 3-(4, 5-diphenyl-1H imidazole-2-yl) From Benzil in Absence of Catalyst

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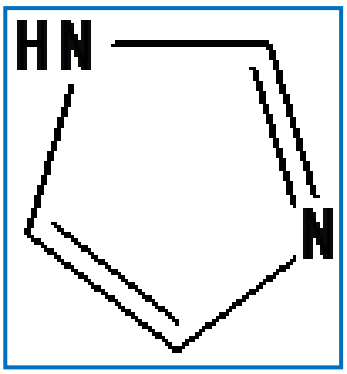
ABSTRACT: In this study new imidazoles derivatives were synthesized.The first stage involved preparation of 3-(4,5-diphenyl-1Himidazole-2-yl)phenol(AA1)by reacting Benzil with Substituted benzaldehyde in presence of sodium cyanide catalyst .The second stage involved the synthesis of Synthesis of 3-(4, 5 - diphenyl-1H imidazole-2-yl) sulfonamide(AA2) using TEA in glacial acetic acid. Finally the compound were synthesized using the three component system (Compound AA2), Substituted benzaldehyde and ammonium acetate. The structure of all compounds were confirmed by elemental analysis ,NMR and IR data and by melting point .In conclusion this method give some advantages such as good yield ,simple procedure , low cost of chemicals and easy work up .

Keywords: Benzil, ammonium acetate, substituted benzaldehyde, imidazole derivatives.

Introduction

Medicinal chemistry is the discipline concerned with deterring 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 [1-3]. Medicinal chemistry concerns with the discovery, development, interpretation and the identification of mechanism of action of biologically active compounds at the molecular level [4]. Various biologically active synthetic compounds have five-membered nitrogen-containing heterocyclic ring in their structures. Structural frameworks have been described as privileged structures and in particular, N-containing polycyclic structures have been reported to be associated with a wide range of biological activity [5-8]. In the field of five membered heterocyclic structures imidazole chemotherapeutics agents. Imidazole drugs have broadened scope in remedying various dispositions in clinical medicines.Imidazole (1, 3-diaza-2, 4-cyclopentadiene) is a planar five-membered ring system with three carbon and two nitrogen atom in 1 and 3 positions.



The simplest member of the imidazole family is imidazole itself, a compound with molecular formula

$C_3H_4N_2$. The systemic name for the compound is 1, 3 - diazole, one of the annular N bear a H atom and can be regarded as a pyrole type N. It is soluble in water and polar solvents. It exists in two equivalent tautomeric forms highly polar compound, as evidenced by a calculated dipole of 3.61D, and is entirely soluble in water.

Experimental section

Methods and Materials

4-hydroxybenzaldehyde,4-methylbenzaldehyde,4-methoxybenzal,chlorobenzaldehyde, benzil and triethylamine were purchased from Sigma Aldrich, India. Sodium hydroxide and PEG-400, ethanol, ammonium acetate, ethyl acetate and hexane were purchased from Avra, Chemicals, Hyderabad. Pre-coated Silica gel plate was purchased from Merck (TLC purpose).A variety of physio-chemical methods have been employed to characterize the synthesized compounds. A brief account of these methods was given below. The melting points were determined in open capillaries, using Boats melting apparatus, expressed in ºC (uncorrected).FT-IR spectra were recorded on Alpha-Bruker spectrophotometer (KBr pellets) scanning with the entire region of 4000-400 cm-1 with typical resolution of 1.0 cm^{-1}.UV spectra were recorded on Alpha Bruker UV spectrophotometer.^{1}H NMR spectra were recorded on Bruker AV400 spectrometer operating at 400 MHz for recording ^{1}H NMR spectra in DMSO solvent using TMS as internal reference (Chemical shifts in ppm).

Synthesis of imidazole consisting sulfonamides derivatives

The substituted imidazole consisting sulphanomides derivatives have been synthesized through two stages.

Stage 1: Synthesis of 3-(4, 5 - diphenyl-1H imidazole-2-yl) phenol (AA_1)

An equal molar quantities mixture of compound benzil (3g, 0.014mol), 3-hydroxybenzaldehyde (1.742g, 0.014mol), ammonium acetate (5.49g, 0.014mol) and amino acid (0.1g) were refluxed in ethanol (30mL) for 3 hours at room temperature. After completion of the reaction, the reaction mixture was poured into ice cold water and the off-white solid was obtained recrystallized with ethanol, filtered to get needles like off-white crystals of 3-(4, 5 - diphenyl-1H imidazole-2-yl) phenol (**AA_1**). The purity of the product and progress of reaction was monitored by TLC.

Stage 2: Synthesis of 3-(4, 5 - diphenyl-1H imidazole-2-yl) sulfonamide (AA2)

An equal molar quantities mixture of compound 3-(4, 5 - diphenyl-1H imidazole-2-yl) phenol (**AA1**) (1g, 0.003mol) and benzenesulfonyl chloride (0.42mL, 0.003mol) and dioxane (10mL) contains few drops of triethylamine were refluxed at 8 hours. The progress of the reaction maintained by TLC the reaction mixture allowed to cool in to room temperature and poured in to ice cold water.

A colorless solid was obtained, recrystallized with ethanol to get a crystals 3-(4, 5 - diphenyl-1H imidazole-2-yl) sulfonamide **(AA2)**. The structure of the compound confirms UV, FT-IR and ^{1}HNMR spectra region.the synthesized compounds of **AA1, AA2, AB1, AB2, AC1, AC2, AD1** and **AD2.** All synthesized compounds were characterized by UV (Fig.1 and 4), FT-IR (Fig.2 and 5), and ^{1}H NMR (Fig.3 and 6), spectroscopy techniques and were found to be in agreement with the chemical structures expected. The Compounds are Synthesized and characterization by following table 1 and 2.

Result and discussion

Initially, condensation of 1:1 mixture of benzil and Substituted benzaldehyde with excess of ammonium acetate in ethanol under reflux using catalytic amount of L-proline, resulted in excellent yield (95%). Condensation at room temperature using L-proline catalyst with stirring for 48 hours also gave 3(4, 5-diphenyl-1H- imidazole-2yl) phenol in comparable excellent yield. Keeping in view the successful result obtained from L-proline, various other aldehyde were used in the synthesis of 3(4, 5-diphenyl 1H-imidazole-2yl) phenol. In a stage 2, substituted sulfonamide containing imidazole derivatives have synthesized from substituted imidazole derivatives in the presence of catalytic amount of triethylamine.

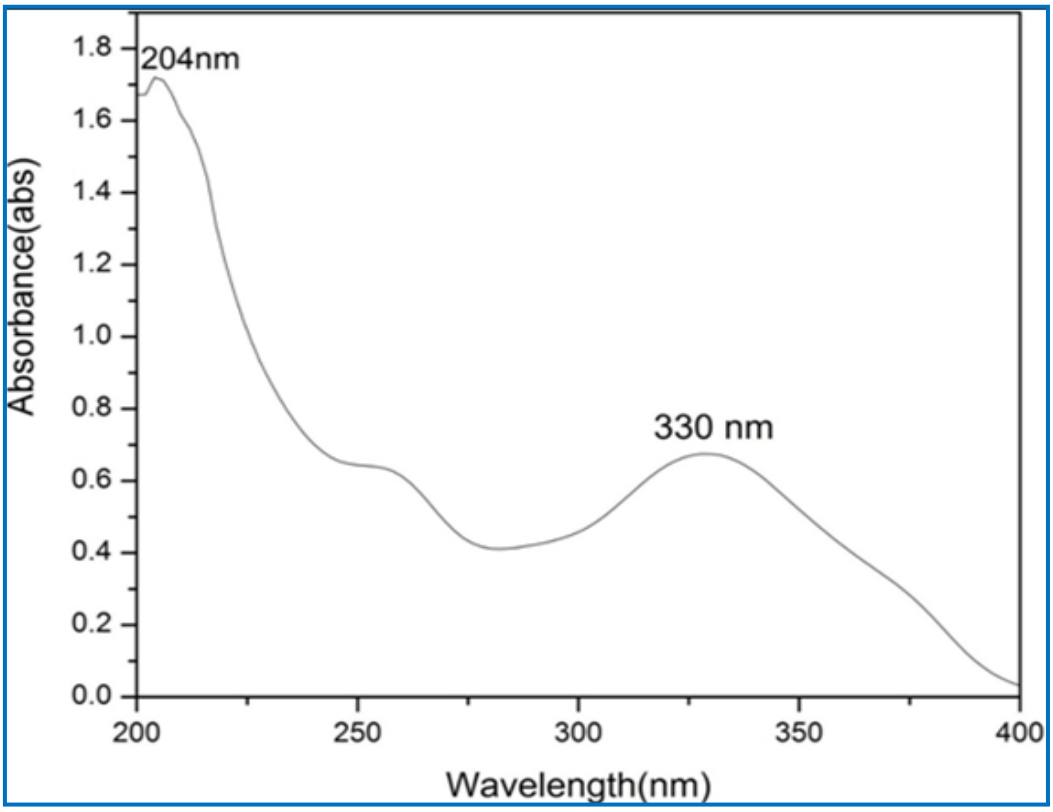


Fig 1 UV spectrum of 3-(4, 5 - diphenyl-1H imidazole-2-yl) phenol

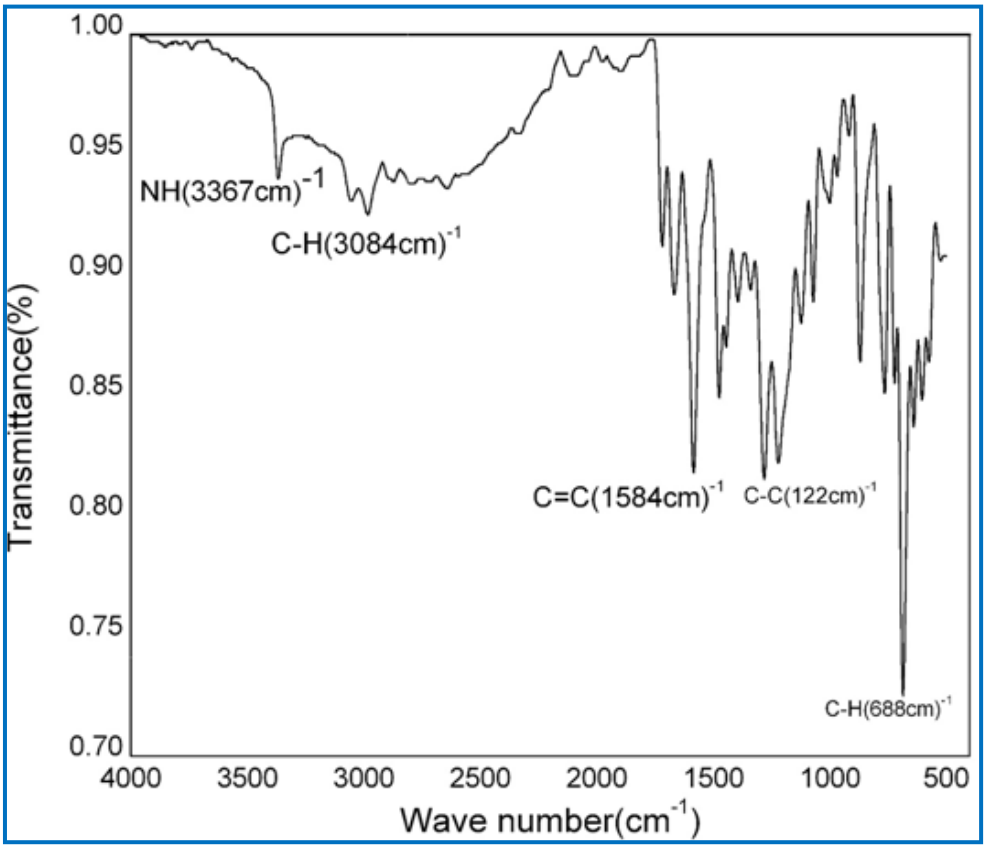


Fig 2 FTIR spectrum of 3-(4, 5 - diphenyl-1H imidazole-2-yl) phenol

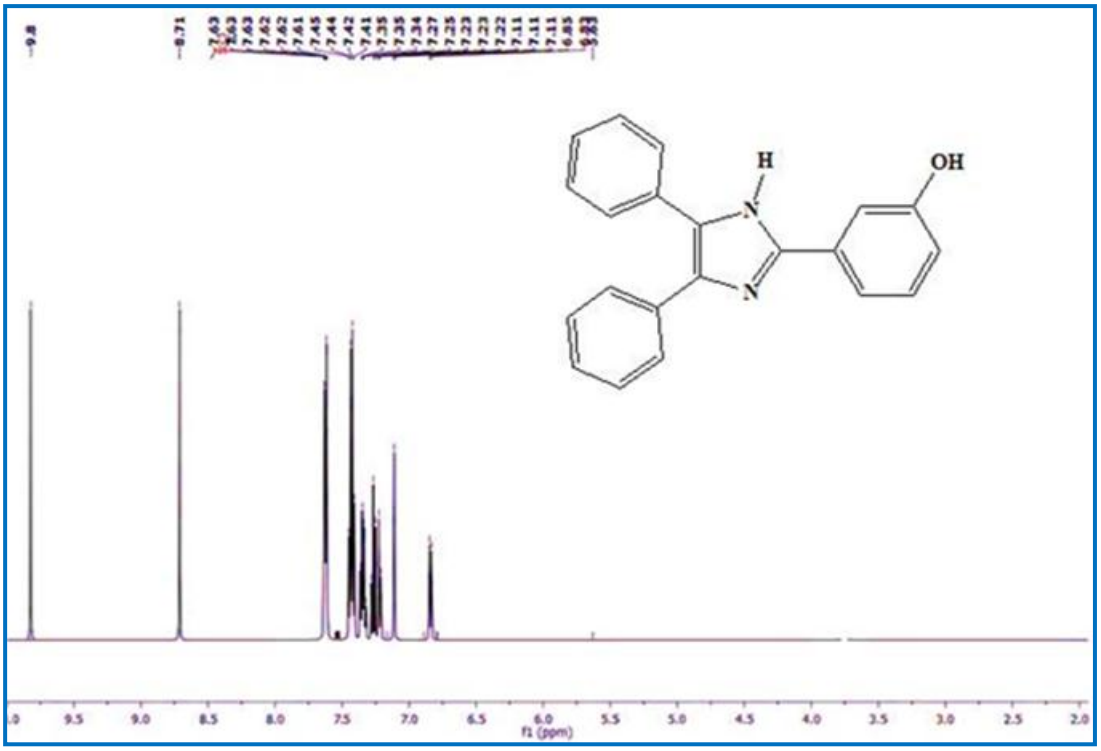


Fig 3 1H NMR spectrum of 3-(4, 5 - diphenyl-1H imidazole-2-yl) phenol

Table 1 Interpretation of spectrum of 3-(4, 5 - diphenyl-1H imidazole-2-yl) phenol

UV (λ max: nm):	(CH=CH) 204 & (C=O) 330
FTIR (Cm-1)	3367 (N-H str.vib), 3084 (Aromatic C-Hstr), 1583 (-C=N str), 1744 (C=O), 1584 (C=C str), 871C-H out plane bending)
^{1}H NMR (ppm)	8.71 (S,1H, N-H) ,6.8-7.63 (m, 11H, Ar-H), 9.8 (s, 1H, Ar-OH)

Sl.NO.	**Compound code**	**Substitution of the compound (Reactant 1)**	**Substitution of the compound (Reactant 2)**
1	AA1& AA2	Benzil	3-hydroxybenzaldehyde
2	AB1& AB2	Benzil	4-chlorobenzaldehyde
3	AC1& AC2	Benzil	4-methylbenzaldehyde
4	AD1& AD2	Benzil	Benzaldehyde

Table 2 Interpretation of spectrum of 3-(4, 5 - diphenyl-1H imidazole-2-yl) sulfonamide

UV (λ max: nm):	(CH=CH) 218 & 308
FTIR (Cm-1)	3040 (Aromatic C-Hstr), 1425 (-C=N str), 1358 (C=S), 1640 (C=C str), 871C-H out plane bending)
^{1}H NMR (ppm)	6.5-7.263 (m, 19H, Ar-H), 7.8 (s, 1H, Ar-OH)

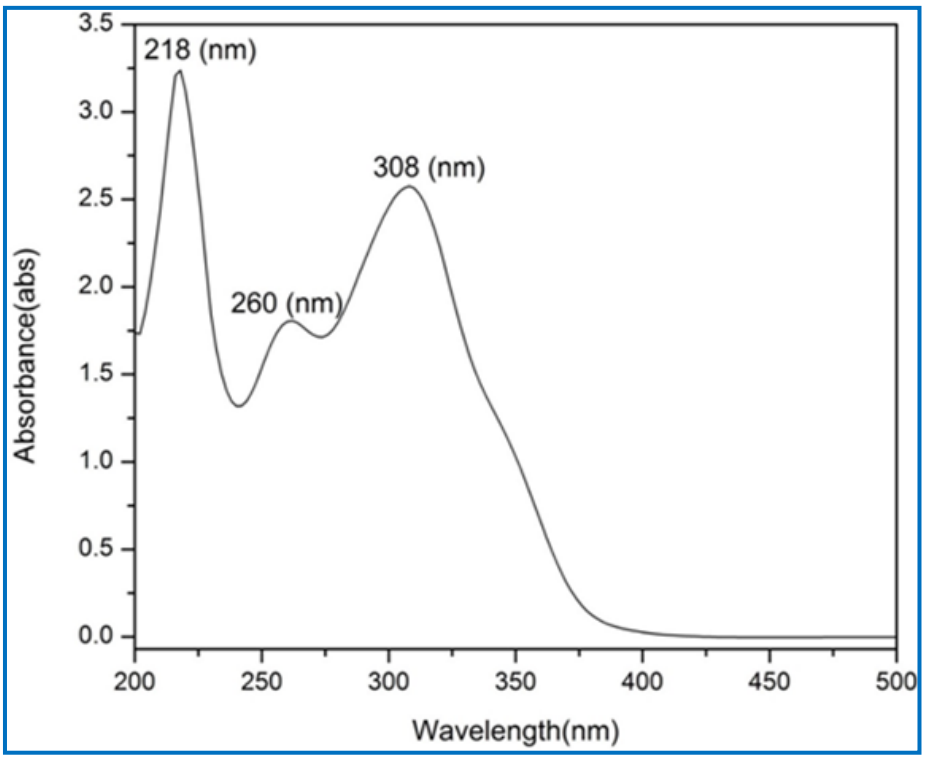


Fig 4 UV spectrum of 3-(4, 5 - diphenyl-1H imidazole-2-yl) sulphonamide

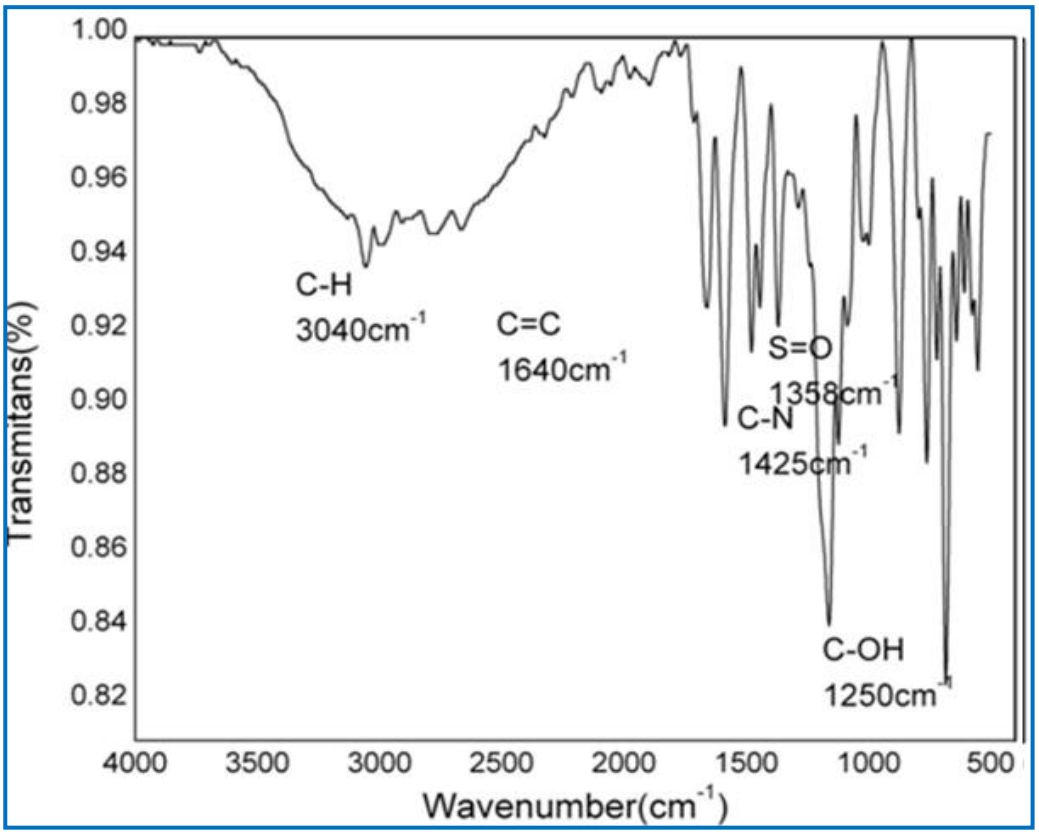


Fig 5 FTIR spectrum of 3-(4, 5 - diphenyl-1H imidazole-2-yl) sulphonamide

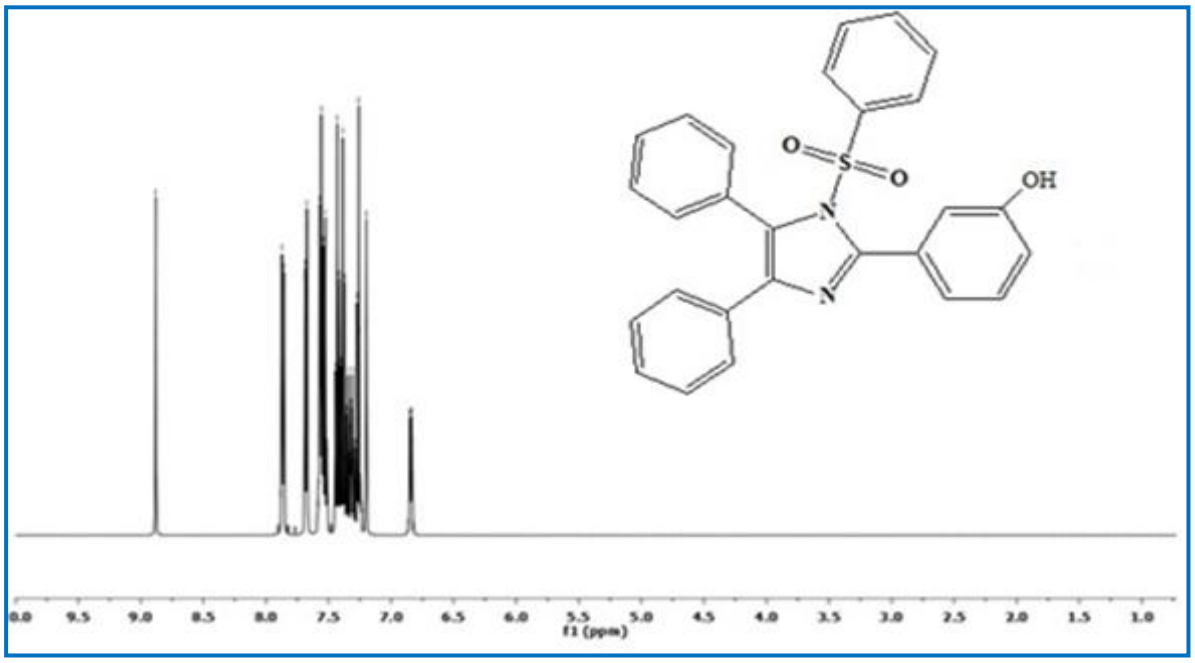
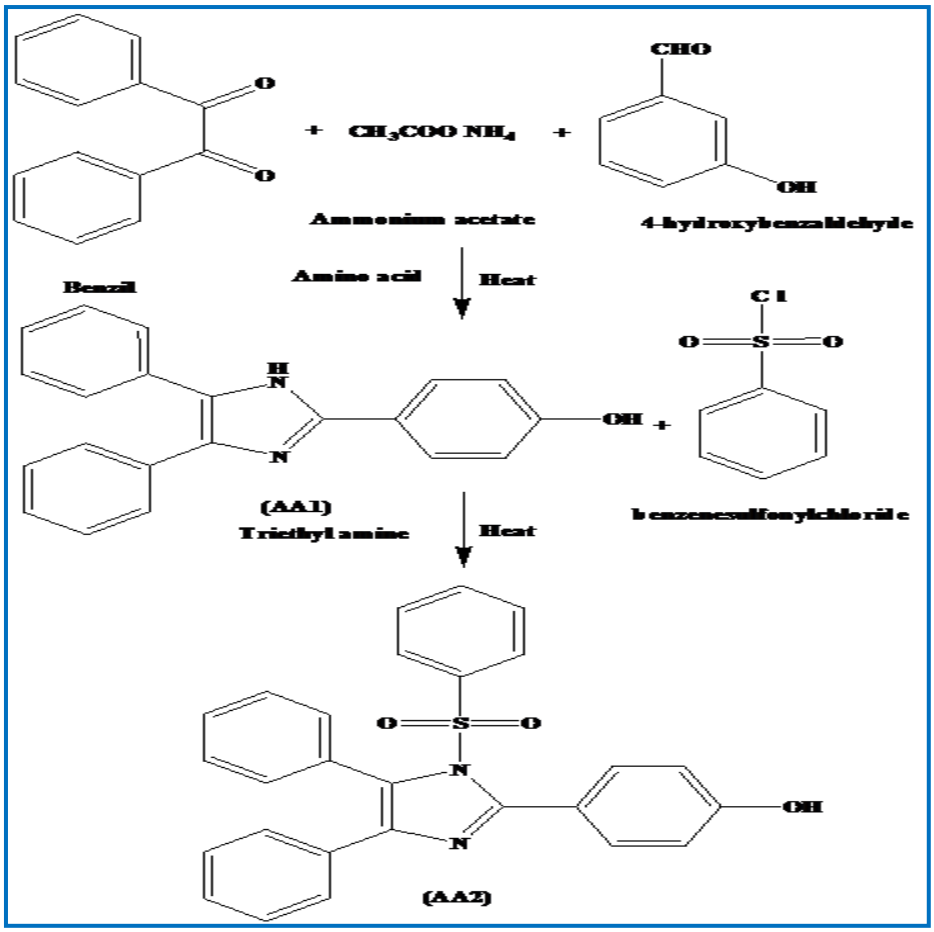


Fig 6 1H NMR spectrum of 3-(4, 5 - diphenyl-1H imidazole-2-yl) sulphonamide



Synthetic Scheme

Antibacterial activity

The compounds viz, **AA1, AA2, AB1, AB2, AC1, AC2, AD1** and **AD2** have been subjected to biological studies using few representative number of pathogenic organism like *Staphyloccocous aures* (MTCC 96) and *Escheriochia coli* (MTCC 443) using minimum inhibitory concentration (MIC) technique. According to MIC, if a small amount of compound is needed to control the growth of the pathogenic organism, such a compound known to possess better activity in controlling the microorganism than that of others, which is quite opposite to the technique called zone of inhibition.

Table 3 summarized the MIC of stage 1 and stage 2 compounds against the pathogenic organism. According to this among the synthesized compounds **AB1** and **AB2** shows excellent activity towards two tested bacterial strains of both *staphylococcus aureus and Escherichia coli* with lowest value of **15.50**&**7.25** (µg/mL) respectively (Fig. 7). The increasing activity of the compounds due to the chlorine and sulfonamide substituent. Among the two compound **AB2** showed superior activity due to the presence of sulfonamide and nitrogen atoms.

Methyl **(AC1 & AC2**) and methoxy **(**A**D1 & AD2**) substituted compounds also found to have very good activity due to the presence of electron donating substituent present in the imidazole and imidazole substituted sulfonamide derivatives.

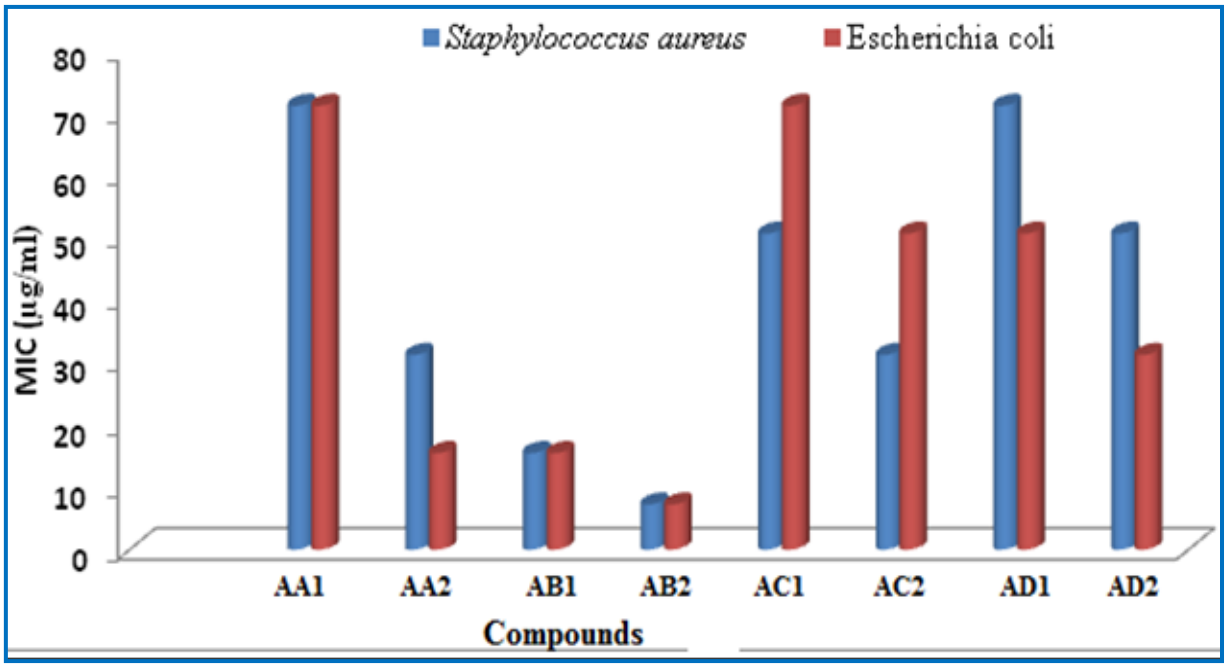


Fig 7 Bar Graph for comparison of antibacterial activities of synthesis compounds

Table 3 MIC values of all synthesized compounds

Compounds	Minimum Inhibiting Concentration (µg/ml)	
	Staphylococcus aureus	***Escherichia coli***
AA1	71.25	71.25
AA2	31.25	15.50
AB1	**15.50**	**15.50**
AB2	**7.25**	**7.25**
AC1	50.75	71.25
AC2	31.25	50.75
AD1	71.25	50.75
AD2	50.75	31.25

Without substituted imidazole and sulfonamide derivatives have moderate activity against both pathogenic organism than the compounds of **AB1, AB2, AC1, AC2, AD1** and **AD2**.

Conclusion

Discussion of the synthesized compounds of **AA1, AA2, AB1, AB2, AC1, AC2, AD1** and **AD2.** All synthesized compounds were characterized by UV, FT-IR and ^{1}H NMR spectroscopy techniques and were found to be in agreement with the chemical structures expected. Antibacterial activity of eight synthesized compounds tested against *Staphylococcus aureus*and *Escherichia coli.* from the antimicrobial evaluation of all the synthesized compounds sulfonamide consisting imidazole derivatives found to have excellent activity than the corresponding imidazole derivatives. Among all the synthesized compounds, out of eight compounds chloro substituted compound **AB2** showed excellent antibacterial activities against both *Staphylococcus aureus* and *Escherichia coli* with lowest value of **7.25**(μg/mL)respectively.

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