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ORIGINAL ARTICLE **OPEN ACCESS**

Synthesis, Characterization, DFT and antimicrobial studies of some azomethine and β-amino derivatives

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ABSTRACT
In the present work, three phenol derivatives Schiff and Mannich Bases were prepared and characterized using analytical and spectral methods such as FT-IR, [1]H-NMR, [13]C-NMR and Mass Spectral Studies. The molecular structure, vibrational frequencies and intensity vibrational bands were analyzed for Schiff base derived by treating 2-ethoxy-4-(((2-(trifluoromethyl)phenyl)imino)methyl)phenol and interpreted with the help of Density Functional Theory (DFT) method with basis set 6-311++G(d,p). Further all the compounds are screened for Anti-microbial activity by disc diffusion method. Synthesized compounds such as (1-phenyl-ethyl)-amine(MA1), (3-trifluoromethyl phenyl)-amine (MA2) and 4-nitro-2-(trifluoromethyl) aniline(MA3) compounds found to have antibacterial and antifungal activity
Key words: *Mannich Bases- Imines-azomethine compounds-DFT*

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INTRODUCTION

A reaction in which two molecules combine to form a single molecule is called condensation reaction. Usually a small molecule water is removed in this reaction [1]. Formation of peptide bond during the combination amino acid is because of condensation reaction, a covalent bond forms between the amine nitrogen of one amino acid and the carboxyl carbon of the second amino acid. Condensation reaction proceeds in a step-wise fashion to produce the addition product. It is a versatile class of reactions that can occur in acidic or basic conditions or in the presence of a catalyst. There are several type of condensation reactions exist, viz., aldol condensation, Claisen condensation, Knoevenagel condensation, Dieckman condensation (intramolecularClaisen condensation), Schiff Condensation and Mannich Condensation [2]. Of these several condensation reaction studied, the products of Schiff and Mannich reactions gained much attention among the researchers in the fields like Organic, Organometallic and Pharmaceutical chemistry due to their wide biological applications. The present research work focused on synthesis of organic compounds via. Schiff and Mannich reactions. Hence, it is essential to highlight the importance of Schiff and Mannich Bases. German chemist, Hugo Schiff in 1864 produced Schiff bases by reacting primary amines and carbonyl compounds [3-5]. Schiff base is also known as imine or azomethine group. Schiff bases are active against a wide range of organisms since they play an important role in living organisms, such as decarboxylation, transamination and C-C bond cleavage. Biological Properties Azomethine group of these compounds has a great attention as precursor in huge organic synthesis due to their biological applications such as, anticancer, CNS depressant, antibacterial, anti-inflammatory [6-8], anticonvulsant, anti-tumor, analgesic [9-11], anti- hypertensive activity, anti HIV activity, antimicrobial activity[12,13], anticovelcent [14], anti-tubercular [15], anti-cancer [16], anti-oxidant [17], plant growth inhibitors, and insecticidal properties. Schiff base ligands are essential in the field of coordination chemistry, especially in the development of complexes of Schiff bases because these compounds are potentially capable of forming stable complexes with metal ions. Metal-imine complexes have been widely investigated due to antitumor and herbicidal use. They can work as models for biologically important species. Ligands and complexes that include sulfur and nitrogen have wide applications for the synthesis of drugs. Drug resistances properties of Schiff base against antibacterial agents may be enhanced by the preparation of metal complexes, using a process of chelation with the coordination of transition metal ions. Schiff bases

have N atoms as their basic elements. Schiff base derivatives containing donor atom can act as good chelating agents for the transition of metal ions [18].

Photo- and thermochromic properties of Schiff bases find used in the following modern technolgies: optical computers, to measure and control the intensity of the radiation, in imaging systems, in the molecular memory storage, as organic materials in reversible optical memories and photodetectors in biological systems [19, 20]. Photochromic properties of Schiff compounds make them as photo stabilizers, dyes for solar collectors, solar filters. They are also exerted in optical sound recording technology [19]. Among others, worthy of interest in the properties associated with Schiff rules include: properties of liquid crystal [20], chelating ability [21], thermal stability [22], optical nonlinearity [23] and the ability to create the structure of a new type of molecular conductors using electrical properties to proton transfer [24]. Because of its thermal stability Schiff bases can be used as stationery phase in gas chromatography. The optical nonlinearity of these compounds allows us to use them as electronic materials, opto-electronic (in optical switches) and photonic components [25]. Imine derivatives can be exerted to obtain conductive polymers. Schiff bases as an electrical conductor possess a variety range of uses: as catalysts in photo electrochemical processes, electrode materials and micro-electronic equipment, organic batteries or electrochromic display device (graphical output devices).Due to the presence of the imine group, the electron cloud of the aromatic ring and electronegative nitrogen, oxygen and sulfur atoms in the Schiff bases molecules [26], these compounds effectively prevent corrosion of mild steel, copper, aluminium and zinc in acidic medium.Carl Mannich developed a product by reacting formaldehyde and a primary or secondary amine or ammonia and a compound containing acidic proton, the final product formed is a β-amino-carbonyl compound also known as a Mannich base [27, 28]. The Mannich reaction is an example of nucleophilic addition of an amine to a carbonyl group followed by dehydration to the Schiff base. The Mannich-Reaction is employed in the organic synthesis of natural compounds such as peptides, nucleotides, antibiotics, and alkaloids (e.g. tropinone). Mannich compounds are used to possess potent activity like anti-inflamatory, anticancer, antibacterial, antifungal and antimicrobial activities [29].

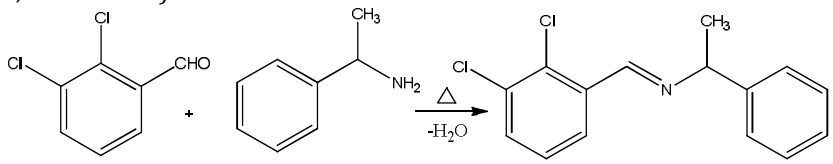
MATERIAL AND METHODS

Synthesis of azomethine compounds via Schiff reaction (MA1-MA3)

Melting points were measured in an open capillary on Mel-Temp apparatus and are uncorrected. IR spectra were recorded on Perkin Elmer spectrometer using KBr pellets.^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer for solution in DMSO-d_6 with tetramethylsilane (TMS) as an internal standard. All the chemical shifts values were recorded as δ ppm. Mass spectra were recorded by EI method and HRMS was measured on a JEOL GC mate II mass spectrometer. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with silica gel-G coated plates.

Synthesis of (2, 3-Dichloro-benzylidene)-(1-phenyl-ethyl)-amine (MA1)

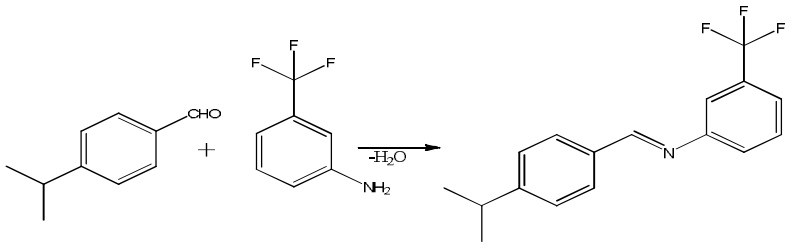
To the ethanolic solution of 1-phenylethanamine (12.8 mL, 0.1 M), 2,3-dichlorobenzaldehyde (17.5 g, 0.1 M) was added and refluxed for 6 h. The mixture was poured into a beaker contain crushed ice. The solid separated out was washed, filtered and dried over vacuum and recrystallized using ethanol. (Colour: Deep Brown solid; M.P: 171 ^{0}C)



Scheme:1 - Synthesis of (2, 3-Dichloro-benzylidene)-(1-phenyl-ethyl)-amine (MA1)

Synthesis of (4-Isopropyl-benzylidene)-(3-trifluoromethyl phenyl)-amine (MA2)

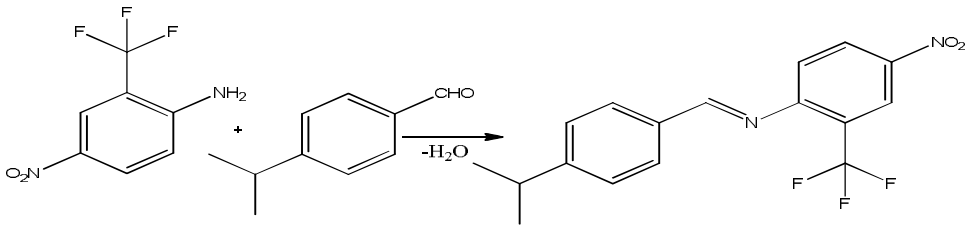
To the ethanolic solution of 4-isopropyl benzaldehyde (14.8 mL, 0.1 M), 3-amino benzotrifluoride. (16.0 mL, 0.1 M) was added. The reaction mixture was taken in a RB flask and kept over a magnetic stirrer and stirred for 6 h. The solid separated out was washed, filtered, and dried over vacuum and recrystallized using absolute ethanol. (Colour: Colourless solid; M.P: 180 ^{0}C)



Scheme: 2- Synthesis of (4-Isopropyl-benzylidene)-(3-trifluoromethyl phenyl)-amine (MA2)

Synthesis of N-(4-isopropylbenzylidene)-4-nitro-2-(trifluoromethyl) aniline (MA3)

To the ethanolic solution of 2-amino-5-nitrobenzenetrifluride (20.4 g, 0.1 M), 4-isopropylbenzaldehyde (15.0 mL, 0.1M) was added. The reaction mixture was taken in a RB flask and kept over a magnetic stirrer and stirred for 6 h. The solid separated out was washed, filtered, and dried over vacuum and recrystallized using absolute ethanol. (Colour: Brown solid; M.P: 106 ^{0}C)



Scheme: 3- Synthesis of N-(4-isopropylbenzylidene)-4-nitro-2-(trifluoromethyl) aniline (MA3)

Antimicrobial study

Antibacterial activity evaluated against *E.coli* and *S.aureus* and antifungal activity performed against *Aspergillusniger* by disc diffusion method. Known concentration of compound at 100µg/disc were preloaded and placed over the agar surface seeded with test pathogen. Zone of inhibition for bacteria recorded after 24 h and antifungal activity confirmed after 5 days.oflaxacin and cyclohexamide used as positive control DMSO used as negative control.Relative inhibitory zone was calculated as follows

RIZD= Zone of Test-Zone of negative control/zone of PC X 100

RESULT AND DISCUSSION

Spectral and Antimicrobial studies of (MA1)

The FT-IR spectrum of MA1 is presented in the **Fig. 1.** Aromatic C-H stretching in phenyl ring exhibits a band at 3068 cm^{-1}. A strong absorption band appeared at 2964 cm^{-1} is due to C-H stretching. An absorption band at 1562 cm^{-1} indicates C=N stretching. A band appeared at 719 is due to C-Cl stretching.^{1}H- NMR spectrum of MA1 in the **Fig 2.** The peaks ranges from 7.2-7.5 are due to aromatic protons. Presence of azomethine and methine protons revealed from the peaks exhibited at 6.9 ppm and 5.9 ppm respectively. Methyl protons exhibited peak at 1.5 ppm. **Fig. 3** represents the ^{13}C-NMR spectrum of MA1. Azomethine carbon exhibits a peak at 162 ppm. Aromatic carbons show signals from 120 to 128 ppm. A peak appeared at 72 ppm shows the presence of methine carbon. A peak obtained at 22 ppm is due to methyl carbon. Mass spectrum of (2, 3-Dichloro-benzylidene)-(1-phenyl-ethyl)-amine (MA1) is shown in the **Fig 4.** Exact mass of MA1 has been confirmed by its m/z appeared at 277.04.

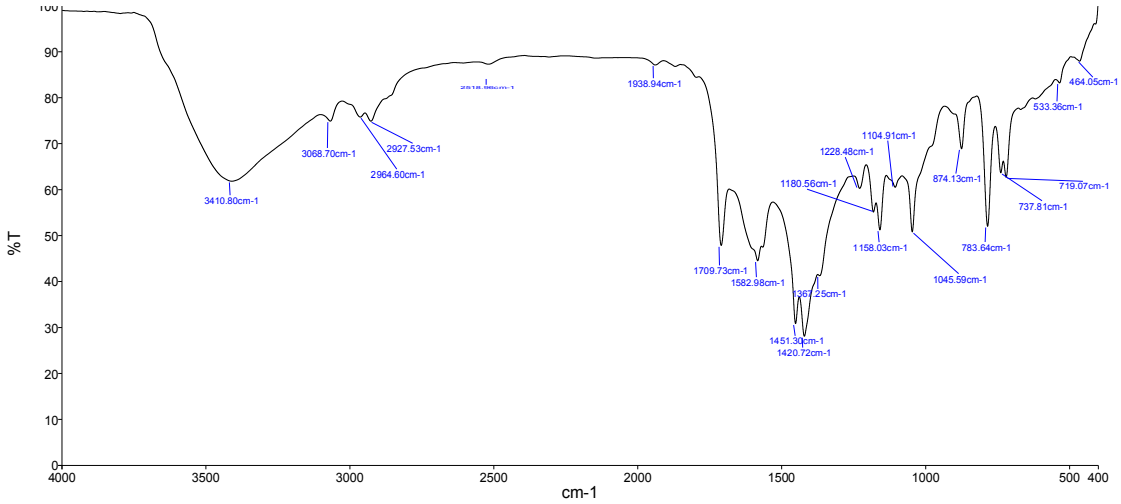


Fig. 1. FTIR spectrum of (2, 3-Dichloro-benzylidene)-(1-phenyl-ethyl)-amine (MA1)

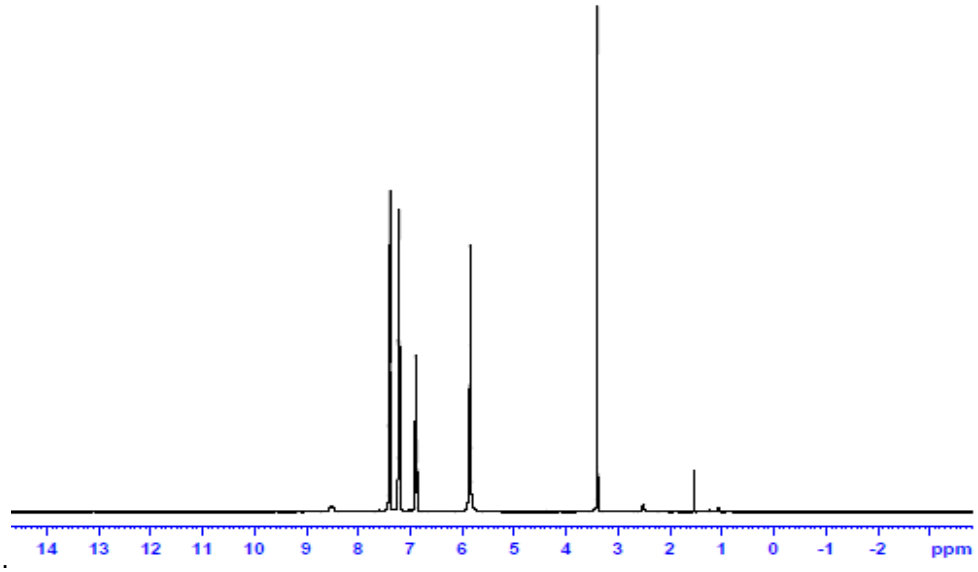


Fig. 2.[1]H-NMR spectrum of (2, 3-Dichloro-benzylidene)-(1-phenyl-ethyl)-amine (MA1)

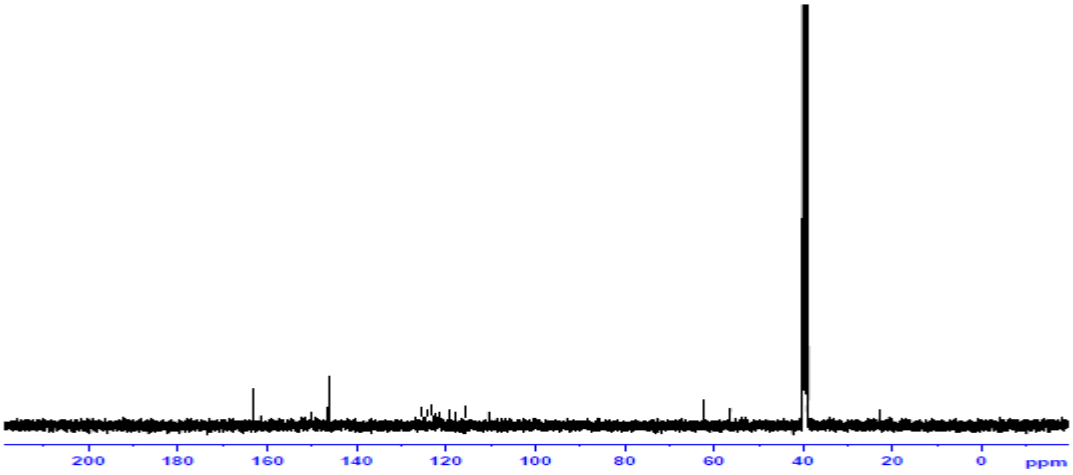


Fig. 3.[13]C-NMR spectrum of (2, 3-Dichloro-benzylidene)-(1-phenyl-ethyl)-amine (MA1)

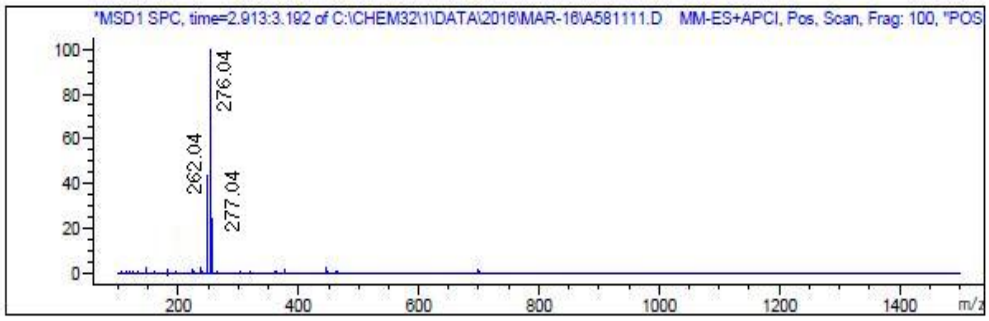


Fig. 4. Mass spectrum of (2, 3-Dichloro-benzylidene)-(1-phenyl-ethyl)-amine (MA1)

Spectral and Antimicrobial studies of (MA2)

The FT-IR spectrum of MA2 is presented in the **Fig. 5.** Aromatic C-H stretching in phenyl ring exhibits a band at 2965 cm^{-1}. A strong absorption band appeared at 2876 cm^{-1} is due to C-H stretching. An absorption band at 1631 cm^{-1} indicates C=N stretching. A band appeared at 660 is due to C-F stretching. ^{1}H-NMR spectrum of MA2 has been given in the **Fig. 6.** A peak at 8.5 ppm indicates the azomethine proton. The signals ranges from 6.9 to 7.5 ppm are assigned to aromatic protons. A peak observed at 2.5 ppm indicates methine protons. Methyl protons are assigned by the signal obtained at 1.1 ppm. ^{13}C-NMR of the compound MA2 has been presented in the **Fig. 7.**Azomethine carbon shows a peak at 161 ppm. The peaks ranging from 124-138 indicate the aromatic carbons. CF_3 carbon is indicated by a peak at 122 ppm. Mass Spectrum of (4-Isopropyl-benzylidene)-(3-trifluoromethyl phenyl)-amine. (MA2) given in **Fig. 8** represents the mass spectrum of the compound MA2. The peak appearing at m/z 291.12 confirms the calculated molecular mass of the compound. The intense peak at m/z 248.12 is the base peak.

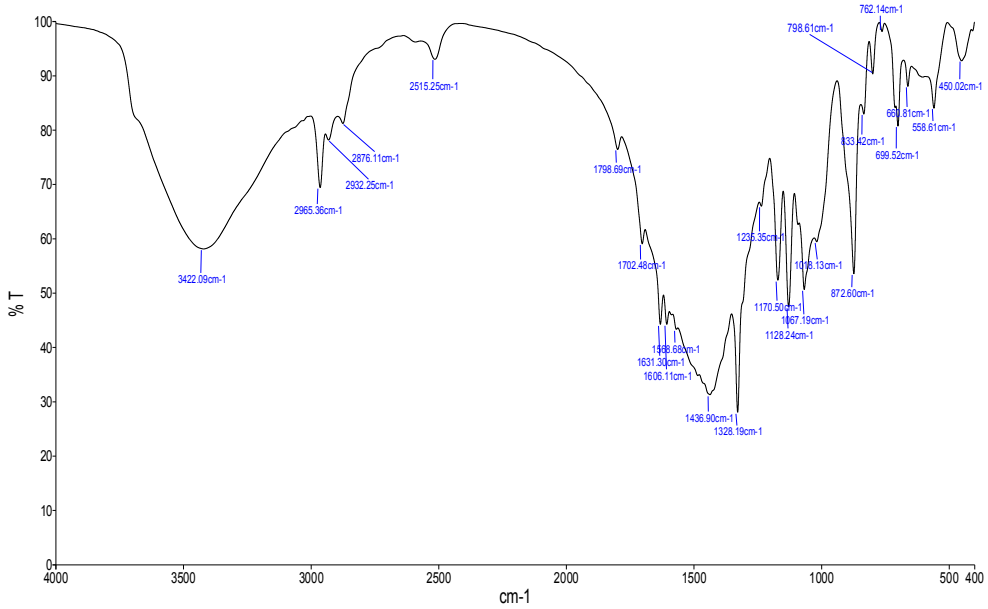


Fig. 5. IR Spectrum of (4-Isopropyl-benzylidene)-(3-trifluoromethyl phenyl)-amine (MA2)

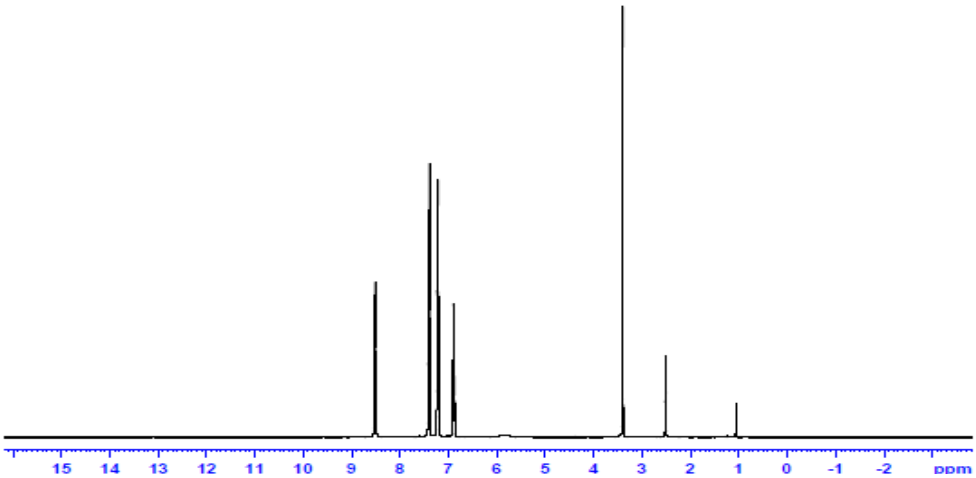


Fig. 6[1]H-NMR Spectrumof(4-Isopropyl-benzylidene)-(3-trifluoromethylphenyl)amine (MA2)

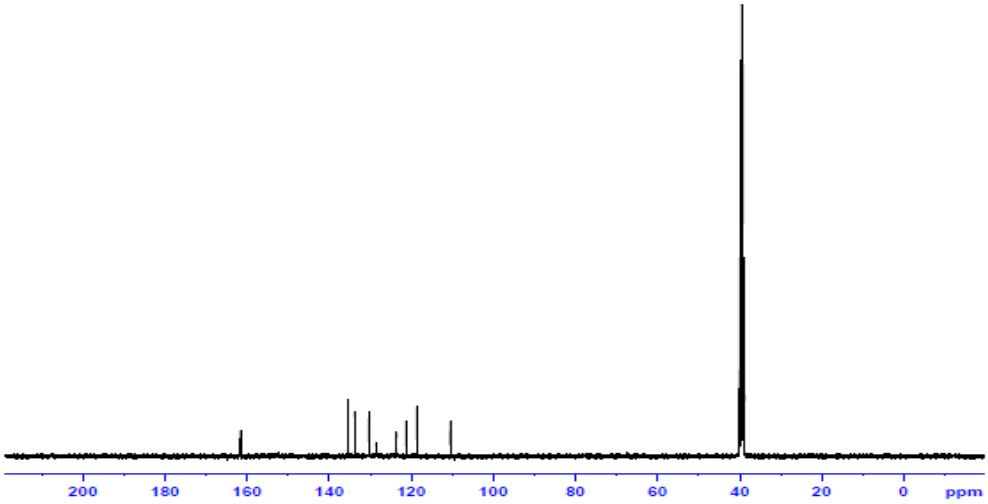


Fig.7.[13]C-NMR Spectrum of (4-Isopropyl-benzylidene)-(3-trifluoromethyl phenyl)-amine. (MA2)

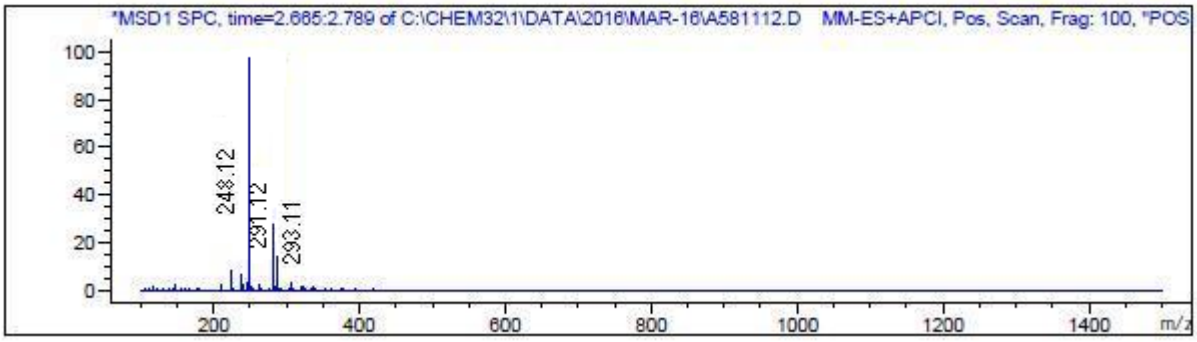


Fig.8 Mass Spectrum of (4-Isopropyl-benzylidene)-(3-trifluoromethyl phenyl)-amine. (MA2)

Spectral and Antimicrobial studies of (MA3)

FT-IR spectrum of MA3 is shown in the **Fig. 9**. The band appears at 3314 cm^{-1} is due to NH stretching. Aromatic C-H and C=C stretching frequencies are indicated by the bands at 2988 and 1492 cm^{-1} respectively. Carbonyl stretching frequency of ester is noticed by a band at 1697 cm^{-1}, ^{1}H-NMR spectrum of N-(4-isopropylbenzylidene)-4-nitro-2-(trifluoromethyl)aniline(MA3) given in the **Fig. 10**. A peak at 8.5 ppm indicates the azomethine proton. The signals ranges from 6.9 to 7.5 ppm are assigned to aromatic protons. A peak observed at 2.5 ppm indicates methine protons. Methyl protons are assigned by the signal obtained at 1.2 ppm.[13]C-NMR of the compound MA3 is presented in the **Fig. 11**. Azomethine carbon

shows a peak at 162 ppm. The signal appeared at 146 ppm is due to nitro group carbon bonded in aromatic ring. The peaks ranging from 122-135 indicate the aromatic carbons. CF_3 carbon is indicated by a peak at 121 ppm.**Fig. 12**represents the mass spectrum of the compound MA3. The molecular ion peak appearing at m/z 336.31 confirms the calculated molecular mass of the compound. The peak appearing with high intensity at m/z 293.11 is the base peak.

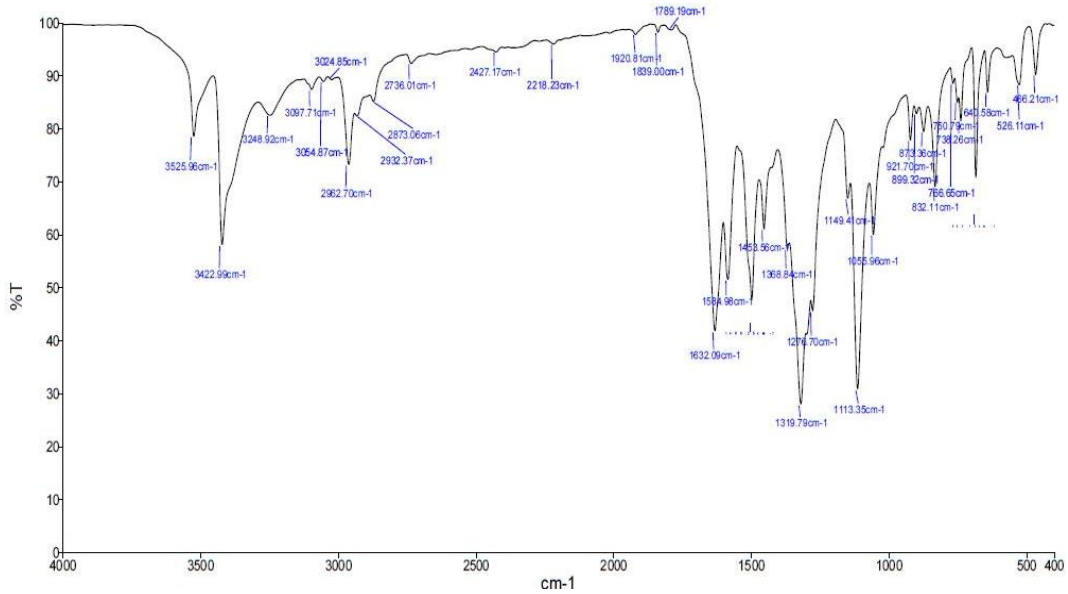


Fig. 9. IR spectrum of N-(4-isopropylbenzylidene)-4-nitro-2-(trifluoromethyl)aniline (MA3)

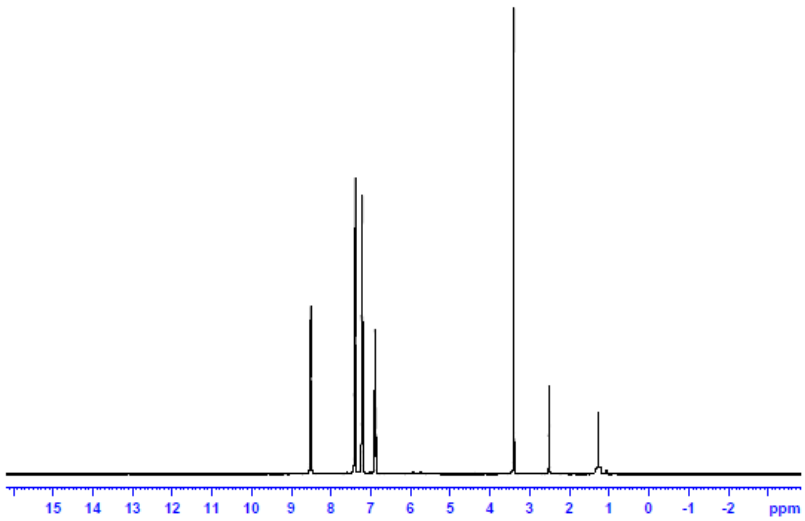


Fig. 10.^{1}H-NMR spectrum of N-(4-isopropylbenzylidene)-4-nitro-2-(trifluoromethyl)aniline(MA3)

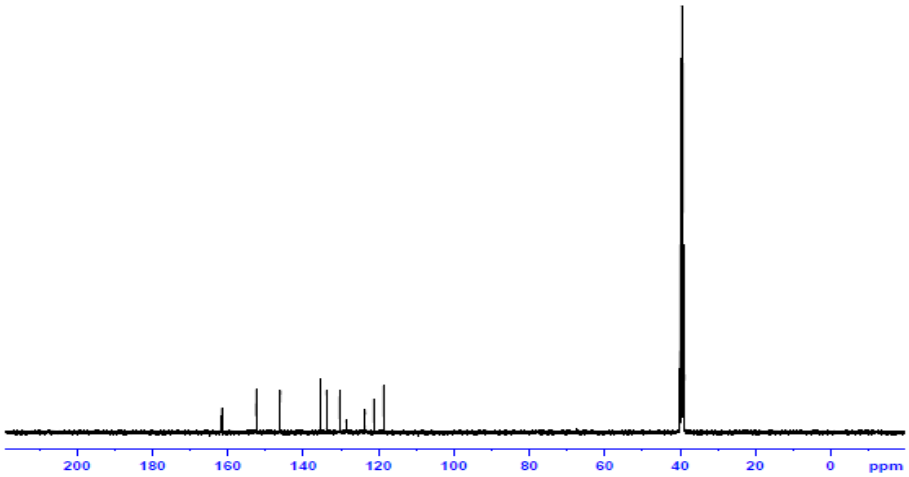


Fig. 11.^{13}C-spectrum of N-(4-isopropylbenzylidene)-4-nitro-2-(trifluoromethyl)aniline (MA3)

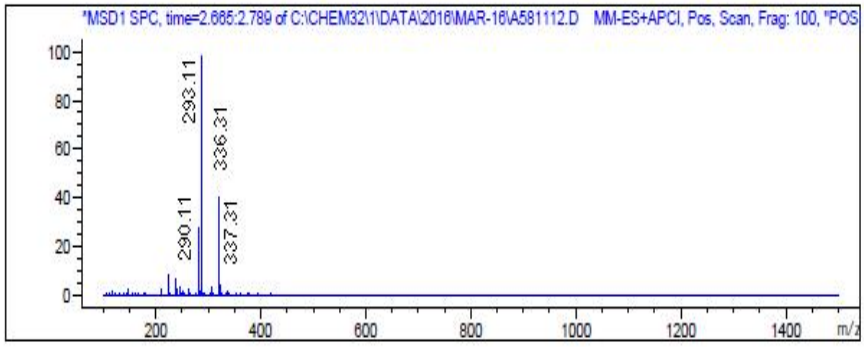


Fig. 12. Mass spectrum of N-(4-isopropylbenzylidene)-4-nitro-2-(trifluoromethyl)aniline

Antibacterial effect

Zone of inhibition of the compound MA1 –MA3 is given in the Table 1 reveals that the compound exhibits very less activity against *E.coli*. It shows moderate activity against *A. niger*. Potency of the compound is found to be high against *S. aureus*. All the three compound is found to be potent against gram positive bacteria and less active against gram negative bacteria and moderate against fungi strain when compared to the standard drug employed. All the test pathogens were highly sensitive to MA3 than MA1 and MA2. The compound MA2 possesses very high activity against *S. aureus*, less activity against *E.coli* and considerable activity against the fungi strain, *A. niger* when compared to the positive standard. In general the compound exhibit moderate activity against fungi pathogen and potent against gram positive bacteria. **Fig. 13**represent the results of the antimicrobial evaluation of the compound MA1 to MA3 Compared with standard. MA1 found 76% RIZD against fungi but moderate against bacterial pathogen. Similarly MA2 found better against Staphylococcus and It shows 50 % RIZD against E.coli and A.niger. the another derivative MA3 is found to posses greater activity than standard against *S. aureus* and *E. coli*but moderate activity against *A. niger*. The compound is more active against bacterial stain than the fungi when compared to the positive standard.Many investigators have observed the importance of azomethines for their antibacterial and antifungal [30]

Table 1.Zone of inhibition mm in diameter

TEST PATHOGEN	MA1	MA2	MA3	STANDARD	NC
S. aureus	20	19	30	20	2
E. coli	18	16	30	24	3
A. niger	25	18	20	30	3

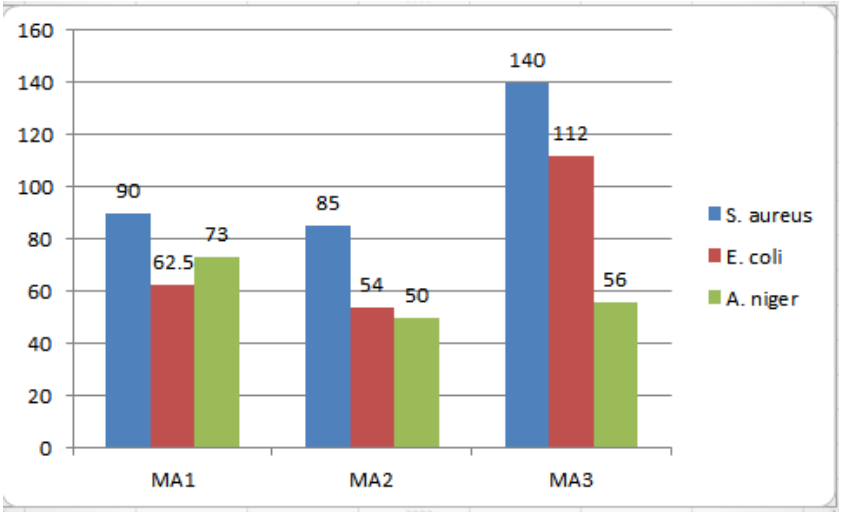


Figure . Relative inhibitory zone of diameter

CONCLUSION

Biologically potent compounds having more Nitrogen in their structure wereeffected through condensation Schiff and Mannich base reactions.FT-IR, 1H-NMR, 13C-NMR and Mass Spectral data of all the compounds corroborated with the structure proposed in the scheme concerned. The results of the antimicrobial studies reveal that, the compounds have found to possess highest activity at 100 µg for all the selected microorganism.

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