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RESEARCH ARTICLE

A GREEN SYNTHESIS AND BIOLOGICAL STUDIES OF NOVEL N-(SUBSTITUTED-BENZYLIDENE)-4-(5-(4-CHLOROPHENYL)-1-PHENYL-4, 5-DIHYDRO-1H-PYRAZOL-3-YL) ANILINE.

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Manuscript Info

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4-Amino acetophenone, Green synthesis, Schiff base, 2-Pyrazoline

Abstract

Green synthesis of novel schiff base compounds bearing 2-pyrazoline moiety and their biological activities have been described. All the products were obtained in very good yield within 5-10 mins by using grinding method. The structures were confirmed with the help of various spectral studies and observed very good inhibition zone against tested bacterial strains.

Background:-

Imine is first reported by Schiff in 1864 which containing carbon-nitrogen double bond and are formed by condensation reaction between carbonyl compounds and amines [1-4]. These compounds plays important role in the realm of organic chemistry as synthons in the preparation of a number of industrial and biologically active compounds like formazans, 4-thiazolidinines and benzoxazines [5-6]. Schiff bases have gained importance in medicinal and pharmaceutical fields due to a broad spectrum of biological activities like anti-bacterial [7], Anti-fungal [8] anti-inflammatory [9-12], analgesic [13], anticonvulsant [14], antitubercular [15], anticancer [16-17], antioxidant [18] and anthelmintic [19].Apart from that, they have been found to posses applications in various field such as analytical, industrial and inorganic chemistry [20-21]. Pyrazoline are well known nitrogen-containing 5-membered heterocyclic compounds and displays a broad spectrum of pharmacological activities [22-26]and are present in a number of pharmacologically active molecules such as phenazone, amidopyrene, methampyrone (analgesic and antipyretic), azolid, tandearil (anti-inflammatory), indoxacarb (insecticide) and anturane (uricosuric). The applications of Schiff bases and 2-pyrazoline derivatives promoted me to design novel heterocyclic schiff bases for development of new therapeutic agents. With this concern and from our previous work [27-30], I attempted to synthesize a series of novel heterocycles by connecting these two moieties in order to improve their microbial activities.

Methods:-

All the required chemicals for research were purchased from Avra, Loba, and S.D fine chemicals (India). Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer as KBr pellet. ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a Brucker (300MHz) instrument in $CDCl_3$ solvent using tetramethylsilane (TMS) as an internal standard and chemical shift values are given in δ ppm. Anti-bacterial studies were performed by using disc diffusion method where the inhibition values are given in mm in diameter and Gentamicin (20 µg) used as standard.

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Experimental Procedure:-

General procedure to synthesis of chalcone (3):

A mixture of 0.01mol of *p*-NH_2-acetophenone **1**, (1 equiv) and p-Cl-benzaldehyde**2** (1 equiv) with 40% aqueous NaOH solution (2 mL) was stirred in ethanol (20 mL) for 3 hrs at room temperature. After completion of the reaction indicated by TLC, mixture was poured in to crush ice and acidified with dilute hydrochloric acid. The solid formed was filtered, dried and recrystalyzed from ethanol.

General procedure to synthesis of 2-Pyrazoline (5):

A mixture of substituted chalcone**3** (1 equiv) and phenyl hydrazine hydrochloride **4** (1 equiv) was refluxed for 3 hr in distilled ethanol (20 mL) with catalytic amount of AcOH. After completion of the reaction indicated by TLC, the mixture was poured in to ice-cold water. The solid formed was filtered, washed repeatedly with water, dried and finally recrystalyzed from ethanol.

General procedure to synthesis of2-Pyrazoline incorporatedschiff bases (7a-e):

One equivalent of **5** and one equivalent of p-Cl -benzaldehyde were taken in pestle and morter. To this 3-5 drops of glacial acetic acid was added and mixture was grinded up to 10-20 mins. During the grinding, the solid compounds were started to melt and again solidified. Formation of products was identified using TLC and the solid formed was filtered and recrystalyzed from ethanol. The same procedure was followed to prepare remaining derivatives.

FT-IR, ^{1}H-NMR and ^{13}C-NMR data of selected 2-Pyrazoline incorporatedSchiff base derivatives:-

N-(4-chlorobenzylidene)-4-(5-(4-chlorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)aniline (7a):

FT-IR (KBr, cm^{-1}): 3390.48, 2958.83 (Ar-CH str), 2827.32 (Aliphatic-CH str), 1597.91 (HC=N str), 1359.15 (C-N str) 1090.78 (Ar-Clstr), ^{1}H-NMR ($CDCl_3$, δ): 3.01-3.09 (dd, 1H, C_4-H), 3.86-3.91 (dd, 1H, C_4-H), 5.28-5.40 (dd, 1H, C_5-H), 6.70-8.23 (m, 17Ar-CH), 8.45 (s, 1H, CH=N); ^{13}C-NMR ($CDCl_3$,δ), 42.86 (C_4), 58.89 (C_5), 113.96, 114.63, 124.49, 124.84, 126.71, 127.80, 128.07, 128.22, 128.61, 128.79, 128.98, 129.21, 131.043, 131.26 (17Ar-CH), 131.40, 131.48, 135.70, 136.72, 142.55, 144.27, (7-Ar-C), 149.38, 156.65 (2CH=N).

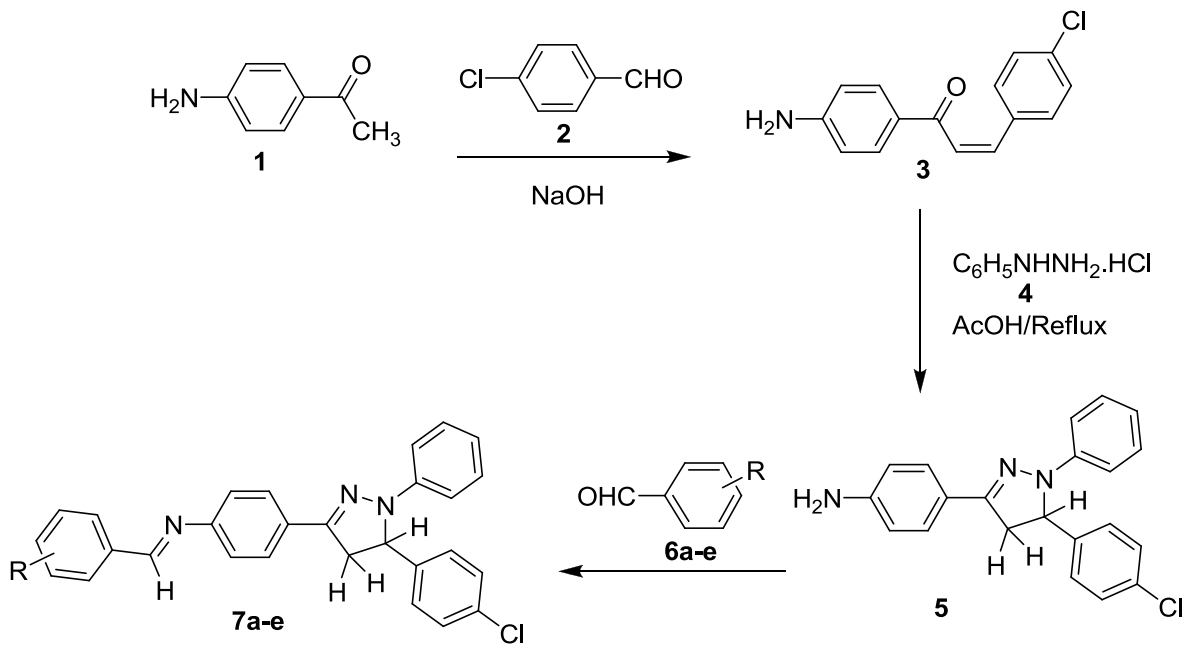
4-(5-(4-chlorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-N-(3-nitrobenzylidene)aniline (7b):

FT-IR (KBr, cm^{-1}): 3347.51, 2928.81 (Ar-CH str), 2828.76 (Aliphatic-CH str), 1596.39 (HC=N str), 1483.85 (NO_2asym), 1339.46 (C-N str) 1011.18 (Ar-Clstr), ^{1}H-NMR ($CDCl_3$, δ): 3.20-3.28 (dd, 1H, C_4-H), 3.72-3.82 (dd, 1H, C_4-H), 5.42-5.46 (dd, 1H, C_5-H), 6.69-7.92 (m, 17Ar-CH), 8.40 (s, 1H, CH=N); ^{13}C-NMR ($CDCl_3$,δ), 44.17 (C_4), 60.54 (C_5), 112.80, 113.75, 113.97, 114.89, 119.26, 120.32, 120.85, 124.02, 124.76, 126.97, 127.27, 127.41, 128.15, 128.25, 128.82, 129.35, 131.04 (17Ar-CH), 131.48, 133.92, 135.82, 140.79, 144.44, 147.27, (7-Ar-C), 148.07, 151.19 (CH=N).

(E)-4-(5-(4-chlorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-N-(4-methoxybenzylidene)aniline (7c): FT-IR (KBr, cm^{-1}): 3390.38, 2958.80 (Ar-CH str), 2827.48 (Aliphatic-CH str), 1593.11 (HC=N str), 1352.10 (C-N str) 1090.52 (Ar-Clstr), ^{1}H-NMR ($CDCl_3$, δ): 3.11-3.21 (dd, 1H, C_4-H), 3.86 (OCH_3), 3.88-3.94 (dd, 1H, C_4-H, It is not clear merged with OCH_3 signal), 5.40-5.50 (dd, 1H, C_5-H), 6.67-8.24 (m, 17Ar-CH), 8.41 (s, 1H, CH=N); ^{13}C-NMR ($CDCl_3$,δ), 40.28 (C_4), 52.65 (OCH_3), 54.37(C_5), 112.97, 114.15, 117.13, 119.75, 120.73, 126.09, 126.87, 127.53, 128.19, 128.52, 129.59, 129.64, 130.40, 133.00 (17Ar-CH), 133.37, 133.93, 136.59, 136.97, 141.06 (7-Ar-C), 151.86, 155.51 (CH=N).

Results and Discussion:-

Present work begins with 4-NH_2-Acetophenone (**1**) which react with 4-Cl-Benzaldehyde aldehyde (**2)** produced corresponding chalcone (**3**). This chalcone further react with phenyl hydrazine hydrochloride (**4**) afforded 2-pyrazoline derivative (**5**). Final products (**7a-e**) were obtained by reaction between **5** and various substituted benzaldehydes (**6a-e**) in the presence of catalytic amount of AcOH. Here in, Aldol condensation reaction was utilized to obtain the chalcone, Michael type addition reaction was performed to get 2-pyrazoline and imine formation reaction was used to produce schiff bases. The physical data such as, melting point, Color, Rf value (Table-1) and spectral data such as, FT-IR, ^{1}H-NMR and ^{13}C-NMR were well supported the formation of the desired products by the agreement of observed signals with expected signals. Antimicrobial activities of compounds **7a-e** were examined by using disc diffusion method and obtained results revealed that their very good activities than standard (Table-2).



Scheme: Synthesis of Novel 2-Pyrazoline incorporated Schiff bases (**7a-e**)

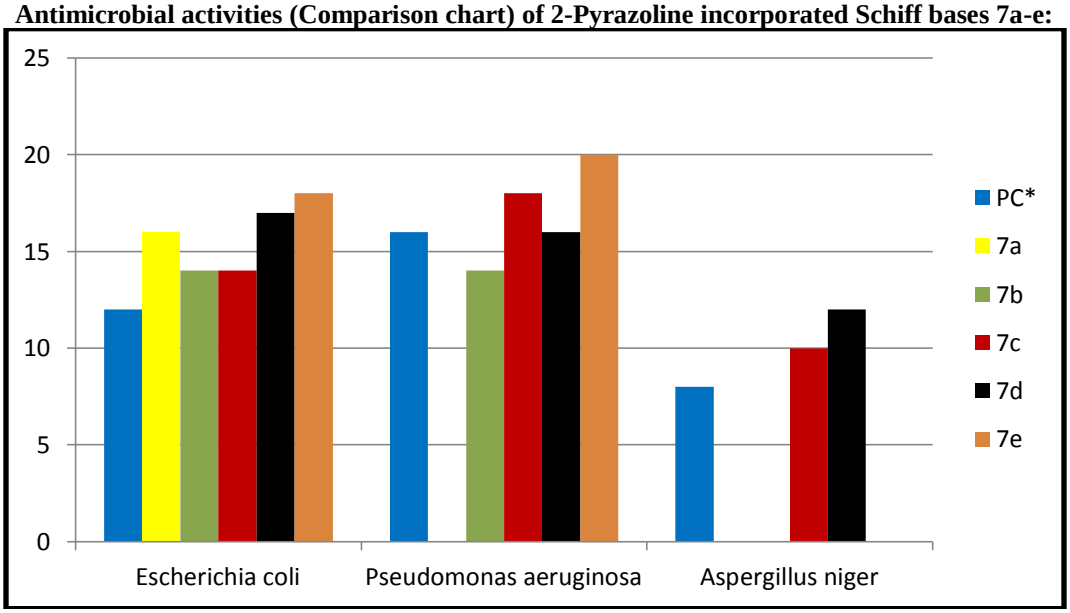
Table-1:- Physical data of 2-Pyrazoline incorporated Schiff bases **7a-e**

Comp.code	X	Yield (%)	Mp (^oC)	Color	Rf value (Hex:EA, 2:1)
7a	*p*-Cl	86	156-160	Light Yellow	0.52
7b	*m*-NO_2	90	170-174	Orange	0.48
7c	*P*-OCH_3	70	132-134	Dark yellow	0.60
7d	*P*-CH_3	58	114-118	Pale yellow	0.58
7e	*p*-NO_2	80	158-162	Orange	0.46

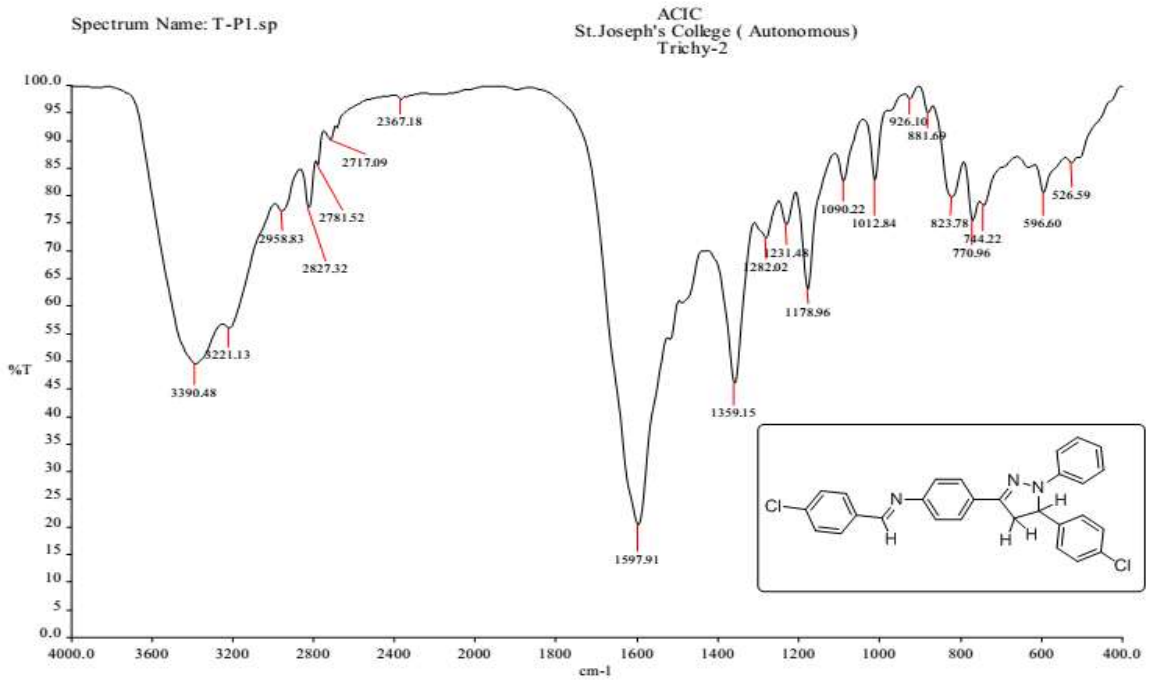
Table-2:- Antimicrobial activity data of 2-Pyrazoline incorporated Schiff bases **7a-e**:

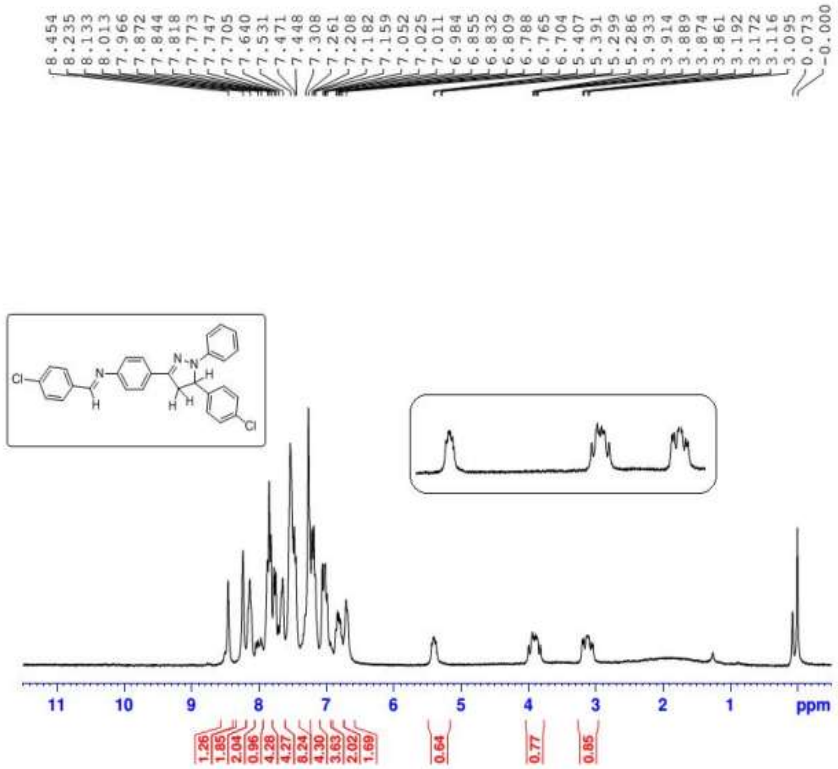
Sample	Zone of Inhibition (mm in diameter, 20 µg/disc)		
	Escherichia coli	*Pseudomonas aeruginosa*	*Aspergillusniger*
PC*	12	16	08
7a	16	-	-
7b	14	14	-
7c	14	18	10
7d	17	16	12
7e	18	20	-

Antimicrobial activities (Comparison chart) of 2-Pyrazoline incorporated Schiff bases 7a-e:



FT-IR, ^{1}H-NMR and ^{13}C-NMR Spectral images of selected 2-Pyrazoline incorporatedSchiff base derivatives



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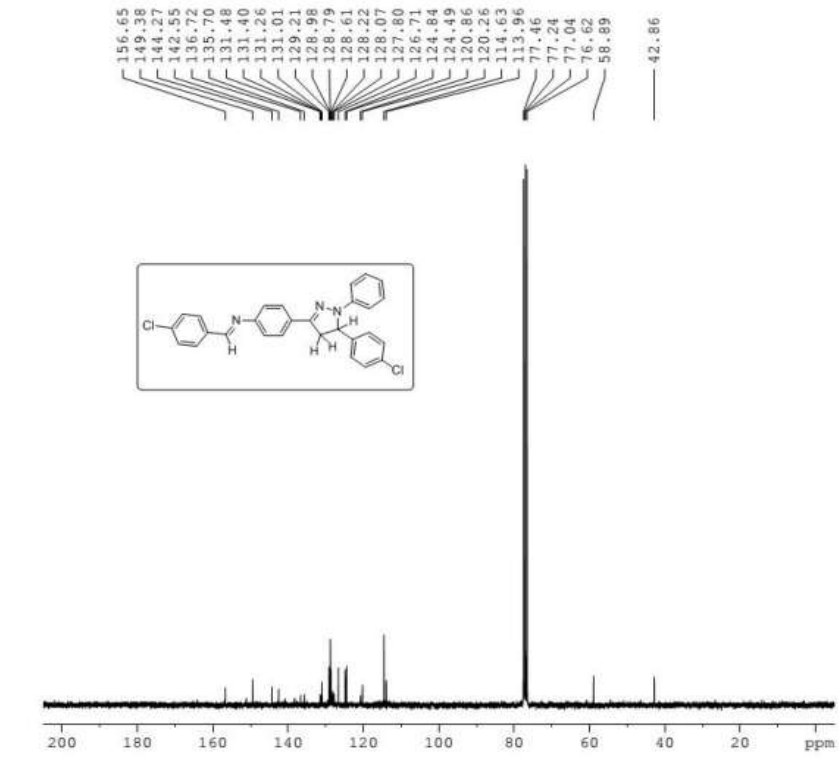


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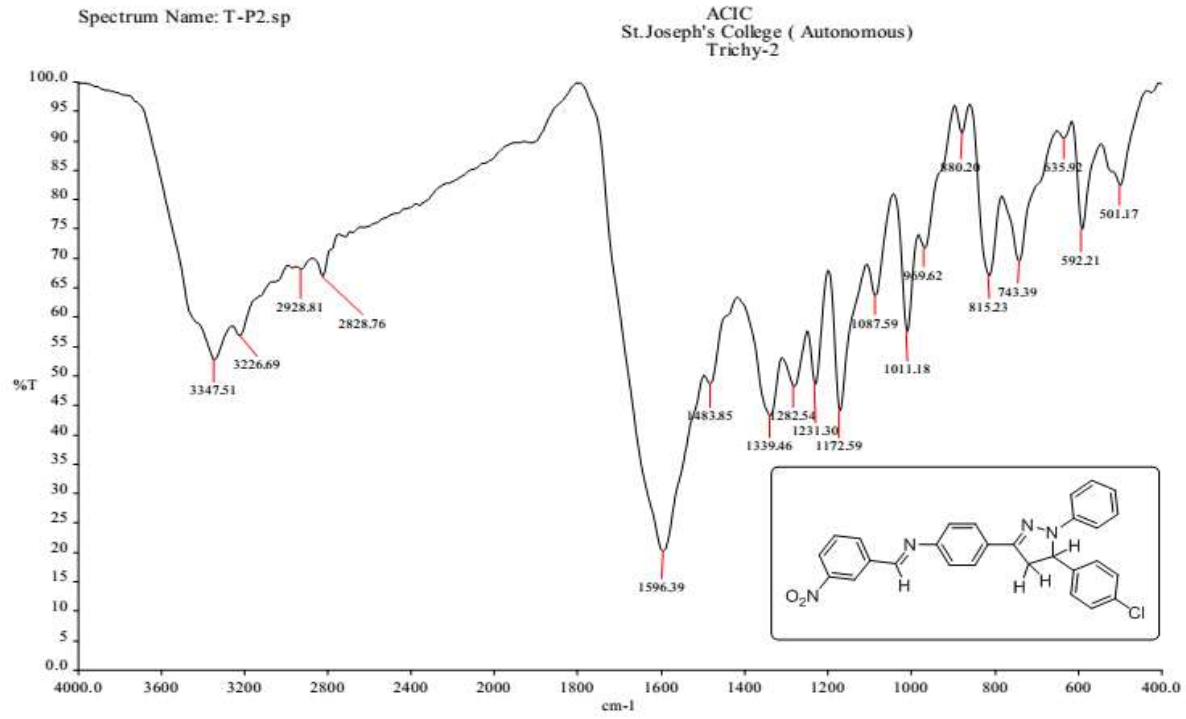

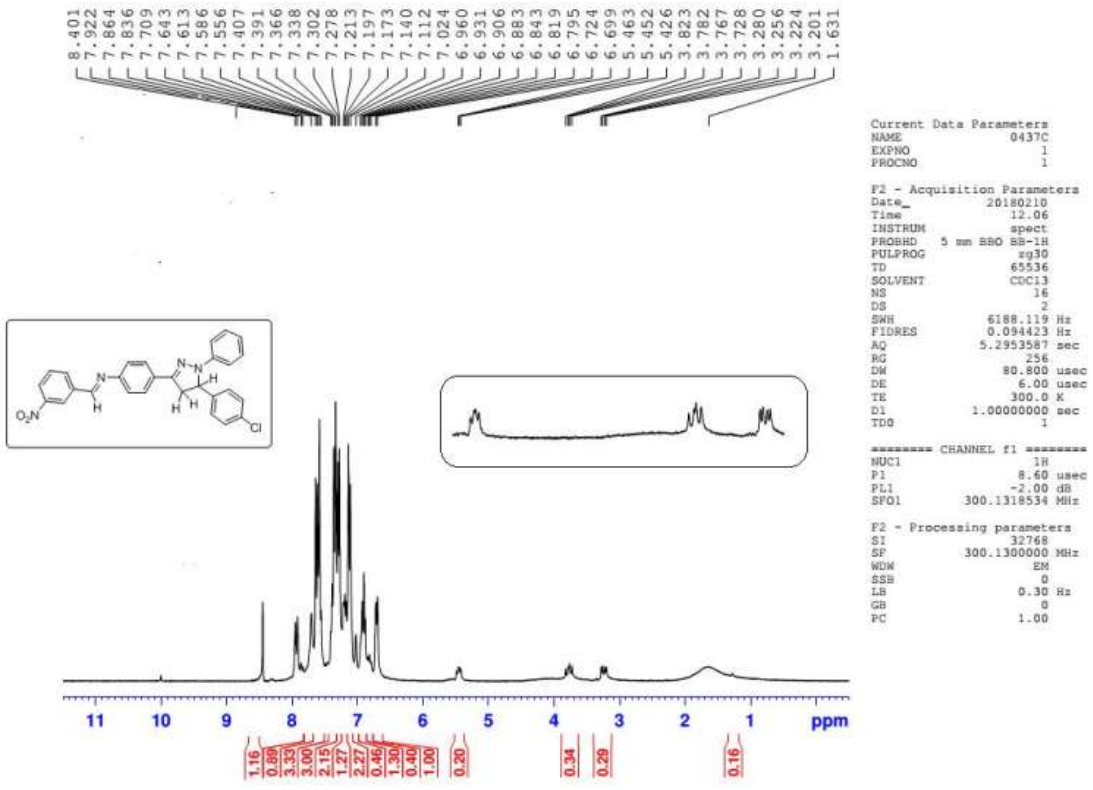


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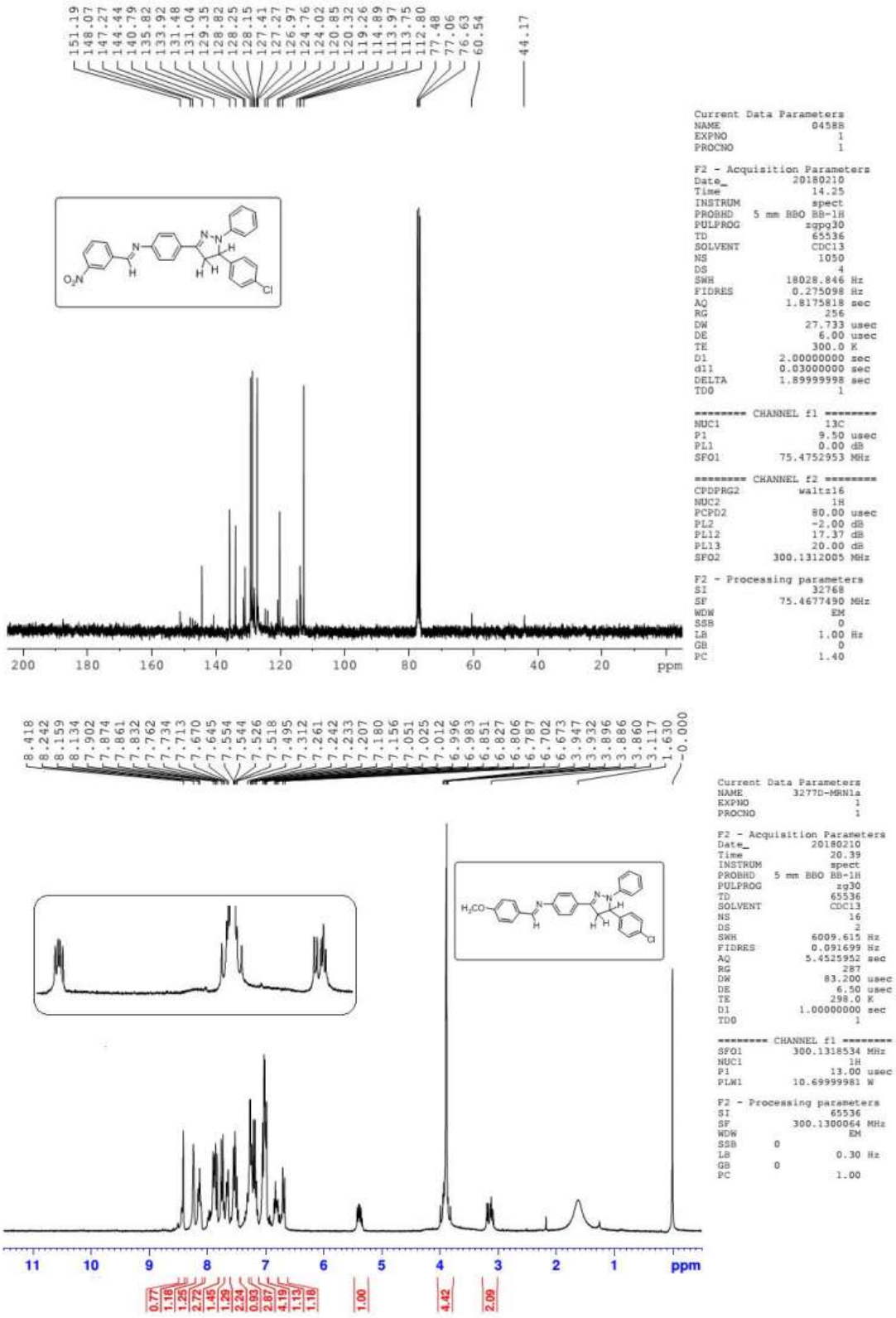
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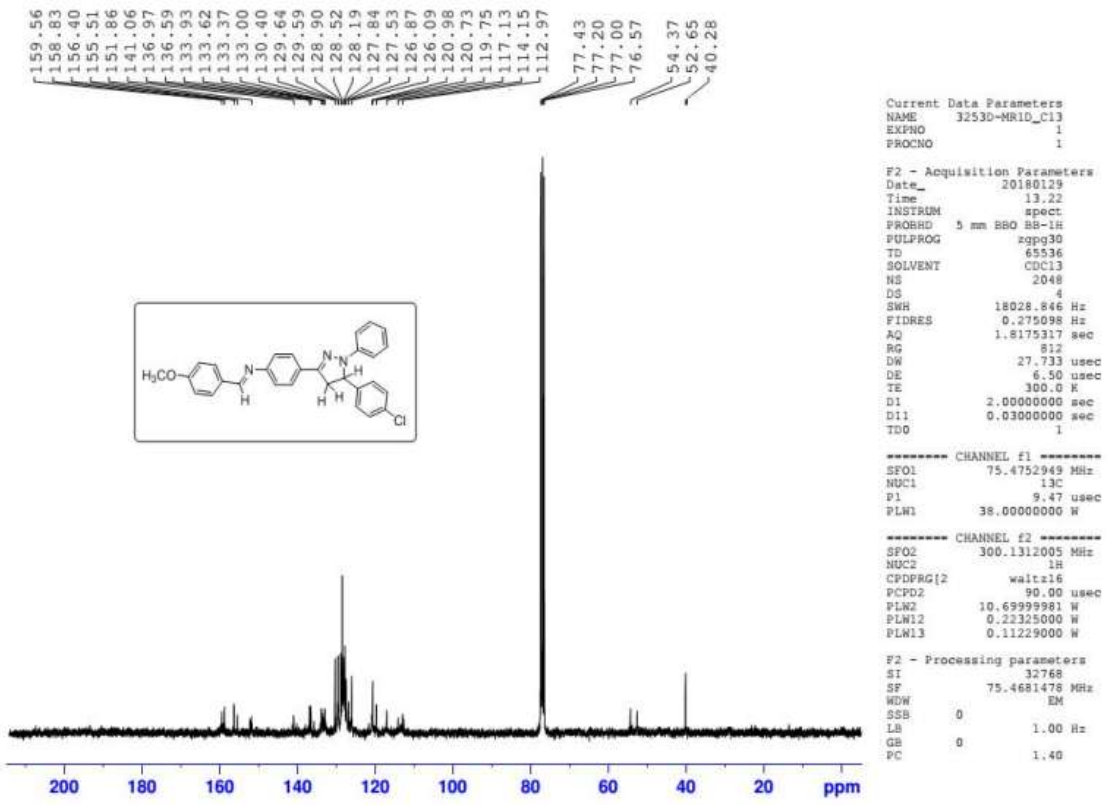

Conclusion:-

I have reported synthesis of some novel schiff base derivatives comprising 2-pyrazoline moiety in a green manner with very good yield. All the synthesized compounds were characterized by using analytical and spectral data. The very good antibacterial activities were observed against selective bacterial strains than fungal strain.

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