Synthesis and characterization of four novel compounds based on acridine

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ABSTRACT

selective acetylation of acridine using anhydrous aluminum chloride as catalyst and acetyl chloride as acylating agent are effective routes for the preparation of mono- and di-acetyl-acridine.

A novel pyrazoline derivative was synthesized by the reaction of an α,β- unsaturated ketone with hydrazine hydrate and formic acid. The structures of these compounds were characterized by ^{1}H NMR, IR and LC-MS spectra.

Key words: Acridine, Chalcone, Hydrazine hydrate, Pyrazoline.

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اصطناع وتشخيص أربعة مركبات جديدة أساسها الأكريدين

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الملخص

تعدُّ الأستلة الانتقائية للأكريدين باستخدام كلوريد الألمنيوم اللامائي وسيطاً وكلوريد الأستيل كعامل أستلة طريقة فعالة لتحضير أحادي وثنائي أستيل الأكريدين.
حُضّر مشتق بيرازوليني جديد بتفاعل كيتون β،α-غير مشبع مع هيدرات الهيدرازين وحمض النمل (الفورميك). وعُيِّنت بنى المركبات الناتجة بأطياف ^{1}H-NMR وIR وLC-MS.

الكلمات المفتاحية: أكريدين، شالكون، هيدرات الهيدرازين، بيرازولين.

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Introduction

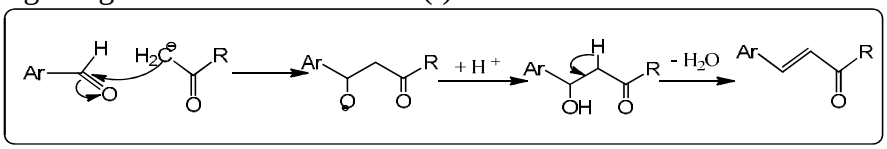
Acridine is an alkaloid structurally related to anthracene with one of the CH groups replaced by nitrogen. Acridine is obtained from high boiling fraction of coal tar. Acridine is also obtained from plant and marine sources. Acridine plays an important role in various medicines. A number of therapeutic agents are based on acridine nucleus such as quinacrine (antimalarial), acriflavine and proflavine (antiseptics), ethacridine (abortifacient), amsacrine and nitracine (anticancer), and tacrine. Acridine undergoes a number of reactions such as nucleophilic addition, electrophilic substitution, oxidation, reduction, reductive alkylation and photoalkylation. Acridine has an irritating odor.It crystallizes in colorless to light yellow needles with melting point of 105-107°C and boiling point of 346°C[1-4].

Friedel-Crafts Acetylation of Acridine:

The Friedel-Crafts acylation reaction is one of the most significant one-step routes for the synthesis of mono and di aromatic ketones, which are of special importance for the preparation of intermediates in manufacturing fine chemicals, polymers, semiconductors and pharmaceuticals. Friedel-Crafts reaction can be characterised in a general sense as acid-catalysed irreversible electrophilic substitution reaction of high selectivity and without rearrangements taking place although isomerization has occasionally been observed. It is essentially a reaction between an acyl component and an aromatic substrate, occurring in the presence of a catalyst, to give an aromatic ketone. Using acetylchloride as the reagent and aluminium chloride as the lewis acid catalyst. The effect of the solvent polarity, temperature, reaction time and the mode of addition on the reactivity-selectivity pattern was investigated (Perrier and Bouveault). Acetylation in 1,2-dichloroethane using an excess of acetyl chloride and aluminium chloride at reflux temperature, gives diacetyl derivatives. 1:4:4 (substrate: acetylating agent: catalyst) molar ratio is the best ratio to get a high yield of diacetylacridine. When acetylation was carried out in the non-polar solvents theconversion moderate to high depending on the temperature and reaction time without notable formation of polymeric materials. On the other hand, using a polar solvents, the conversion is only low to moderate (9–38 %) owing to the additional formation of dark polymeric materials. In the polar solvents the solutions are considered to be homogeneous and the solvent dissolves and solvates not only the $AlCl_3$, but also the $[CH_3CO^+.AlCl_3X^-]$ complex usually also the $AlCl_3$ complex of the resulting ketones [5,14].

Aldol Condensation reaction:

The **aldol condensation** is an important reaction in organic chemistry, primarily because this reaction is one of a limited number of reactions that result in the formation of a new carbon-carbon double bond. The aldol reaction requires two molecules, both of which may or may not be the same. The first molecule must contain a C-H bond next to a carbonyl (C=O) group, which is referred to as an α-hydrogen. The second molecule must contain a carbonyl group. The Aldol condensation is the coupling of an enolate ion with a carbonyl compound to form a β-hydroxycarbonyl, a simple case is addition of an enolate to an aldehyde to afford an alcohol, thus the aldol reaction is used extensively for the synthesis of new C=C bonds and to form larger organic molecules Scheme (I).



Scheme (I)

Pyrazolines:

Substituted pyrazolines are fluorescent compounds with high quantity yields and are used as optical brighteners and whiteners [6]. 2-Pyrazolines exhibit good characteristics of blue photoluminescence and electroluminescence. Pyrazoline derivatives are used as hole-transporting materials and as fluorescence probes in chemosensors [7]. These are five-membered nitrogen-containing heterocyclic compounds and various procedures have been developed for their synthesis [8]. Diarylpyrazolines are stable compounds and α,β-unsaturated ketones are convenient and versatile materials for the synthesis of pyrazolines. One special significance of pyrazolines lies in their use as synthetic intermediates for preparing cyclopropane and pyrazole derivatives[10-13].

2. Experimental

2.1. Materials and apparatus

Acridine and 1,2-dichloroethane (Merck-Schuchardt), Acetylchloride (Riedel-DeHaenag Seelze-Hannover), Aluminium chloride (Qualikems), 3-nitrobenzaldehyde (Sigma-Aldrich), formic acid (98% fluka), hydrazinehydrate and methanol 99.5%, and ethanol 99.5%were obtained from Panreac.Silica gel (ASTM) 70-230mesh (63-200 μm)

Melting points were obtained on a Stuart SMP-30 capillary melting point apparatus and are uncorrected (<390˚C). IR spectra were recorded as KBr discs using a Shimadzu 8300 FTIR spectrophotometer in the range (4000-400) cm^{-1}. NMR spectra (^{1}H-NMR) was acquired in $CDCl_3$ solution using Brucker AMX400 MHz spectrometer with tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a Finnegan-MAT model 8430 LC MS-DS spectrometer.

2.2. synthesis of 9-acetylacridine (I) (scheme II)

To a stirred solution of acetyl chloride (0.392 g; 0.005 mol) and aluminium chloride (0.668 g; 0.005 mol) in 1,2-dichloroethane (20 ml), acridine (1.176 g; 0.005 mol) in the same solvent (20 ml) was added (5 min), and the mixture was stirred at 25 ˚C and then heated under reflux for 72 h. The obtained residue was purified by column chromatography (silica gel–benzene). The ketone (1.33 g; 92 %) was obtained as a light yellow solid. M.p = 245 – 246˚C,

2.3. Synthesis of 1,8-diacetylacridine (II) (scheme III)

To a stirred solution of acetyl chloride (1.568 g; 0.02 mol) and aluminium chloride (2.668 g; 0.02 mol) in 1,2-dichloroethane (20 ml), acridine(1.176 g; 0.005 mol) in the same solvent (20 ml) was added (5 min), and the mixture was stirred at 25 ◦C for 1 h and then heated under reflux for 22 h. The obtained residue was purified by column chromatography (silica gel–benzene).The ketone (1.5 g; 87 %) was obtained as a yellow solid and dissolves in water.

2.4. Synthesis of 1,8 – bis - [3- (3 - nitrophenyl) – 1 – oxo – 2 – propen – 2 - yl] acridine (III) (scheme IV)

(2.265 gr ; 0.015 mol) of 3-nitrobenzaldehyde and (7.908 gr ; 0.030 mol) of diacetylacridine were dissolved in (50 ml) ethanol. The round-bottomed flask was placed in an ice bath and the mixture was stirred for 3 h with addition of 11% NaOH (cold ethanolic solution) drop by drop. The resultant mixture was allowed to stand for 24 h. The yellow residue was crystallized from methanol to giving the chalcone**.** Yield 90%, m.p.=280-283°C.

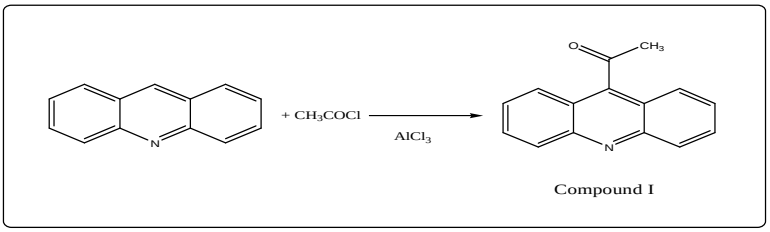
2.5.Synthesis of 1,8-bis-[(1-formyl-5-(3-nitrophenyl)-4,5-dihydro-3-pyrazolinyl] acridine (IV) (scheme IV)

To a mixture of (7.941gr; 0.015mol) of the chalcone (III) in 30 ml of formic acid, (3gr; 0.060mol) of hydrazine hydrate in 15 ml of ethanol were added dropwise. The reaction mixture was refluxed for

24 h with constant stirring, the resultant solution was cooled and poured onto crushed ice to obtain the crude product. The reaction product was recrystallized from ethyl acetate to give the title compound in 69% yield as white crystals, m.p =320-322°C. IR(KBr, Cm^{-1}) 1635.7 (C=O) cm^{-1}, 3097.3 (aromatic C-H stretch).

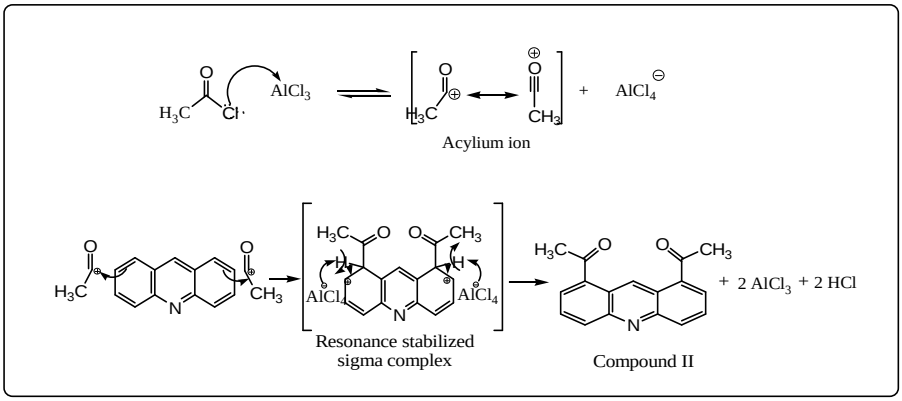
3. Results and discussion

The symmetry of the acridine molecule limits the number of isomeric mono-substituted derivatives. Systematic investigations of the Friedel-Crafts acetylation of Acridine have now been undertaken in detail in an attempt to prepare the mono and di-ketones by direct electrophilic substitution reaction in good yield. Mono and di-acetylation of acridine were carried out using the appropriate molar proportions of the hydrocarbon (substrate), acetyl chloride (acylating agent) and aluminium chloride (catalyst) in the chosen solvent applying Perrier addition method unless otherwise stated. Diacetylation of the substrate using four times excess of the acetylating agent and catalyst gives only one diketone.

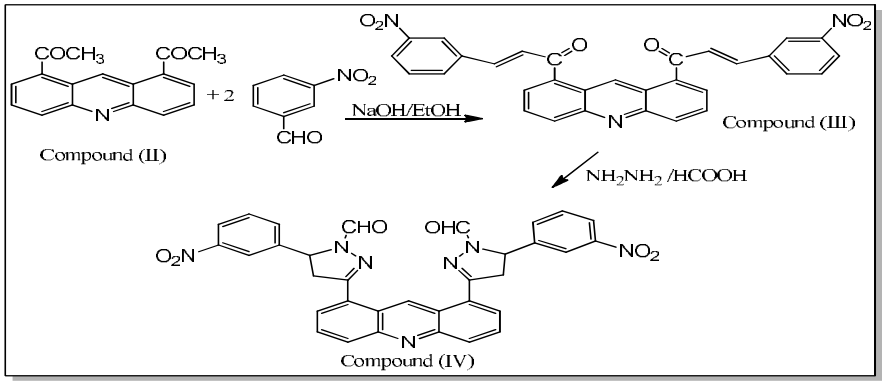


Scheme (II)

Mechanism of diacetylation:



Scheme (III)



Scheme (IV)

Four new acridine derivatives were synthesized:

9-acetyl acridine (compound I) was synthesized by the reaction of acridine with (1 mol) of acetyl chloride in 1,2-dichloroethane in presence of $AlCl_3$ (1 mol) as catalyst. IR (KBr bellets,cm^{-1}) shows $(C=O)_{str}$ at 1641.6cm^{-1}.Mass spectrum shows a molecular peek at m/z = 221.0 which corresponds to molecular weight of compound (I). The ^{1}H-NMR spectrum exhebits signals at 7.8-8.6ppm due to aromatic protons and signal at 3.71 ppm due to CH_3 protons.

1,8-diacetyl acridine (compound II) was synthesized by reaction of (1 mol) acridine with (4 mol) of acethylchloride in 1,2-dichloroethane in presence of (4 mol) $AlCl_3$. IR (KBr bellets, cm^{-1}) shows ν(C=O) peak at (1640.0 cm^{-1}). MS spectrum shows molecular peak at (m/z =263.6) corresponding to compound (II). This result confirmS the formation of (II), which differ from structure of (I) by additional acetyl group.^{1}H-NMR exibits signal at (2.65 ppm) due to the CH_3 group, and signals at 7.8 – 8.6 ppm due to aromatic protons.

1,8-bis-[3-(3-nitrophenyl)-1-oxo-2-propenyl] acridine (compound III) was synthesized by reaction of 1,8-diacethylacridine with 3-nitrobenzaldehyde in ethanol (Aldol condensation). IR (KBr bellets,cm^{-1}) shows (-CH=CH-) group at 1630.7cm^{-1}which indicates to formation of chalcone, $\nu(C=O)_{str}$ 1678.2cm^{-1}, This indicates to conjugation with new formed double bond. LC-MS: m/z = 529.4 and this corresponds to molecular weight of compound (III). ^{1}H-NMR spectrum shows signals at 7.439-7.929ppm due to (CH=CH-) group and signals at 7.0–8.0 atributed to aromatic protons. The disappearance of CH_3 signals refer to chalcone formation.

1,8-bis-[(1-formyl-5-(3-nitrophenyl))-4,5-dihydro-3-pyrazolinyl] acridine (compound IV) was synthesized by the reaction of chalcone (compound III) with formic acid and hydrazine hydrate in ethanol. IR spectrum of (IV) shows $\nu(C=N)_{str}$ at (1519cm^{-1}) and $\nu(C=O)_{str}$ at (1635.7cm^{-1}), MS spectrum shows peak at m/z=613.6 corresponds to suggested formula of (IV). We also suggested the mechanism of pyrazolinic derivative of acridine (scheme V).

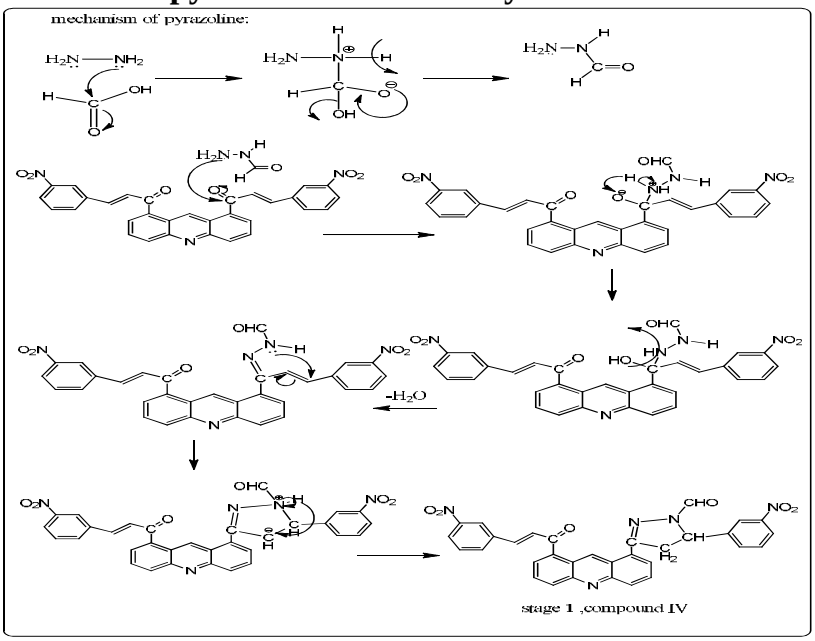
Table 1- The characterization data of the prepared compounds

Compound	formula	M_W(g/mol)	Colour	M.P (C)	Yield (%)	Solvent
I	$C_{15}H_{11}NO$	221.0	Light yellow	218-220	92	Water
II	$C_{17}H_{13}NO_2$	263.6	Yellow	245-246	87	Water
III	$C_{31}H_{19}N_3O_6$	529.4	Light yellow	280-283	90	DMSO
IV	$C_{33}H_{23}N_7O_6$	613.6	white	320-322	69	DMF

Table 2- Infrared data of the prepared compounds (cm^{-1})

Compound	formula	$\nu(C=O)$	$\nu(C=C)_{Ar}$	$\nu(C=N)_{Ar}$	$\nu(C-H)_{str}$	$\nu(N=O)$	$\nu(CHO)_{str}$
I	$C_{15}H_{11}NO$	1641	1421.3	1485	3007.6	-	-
II	$C_{17}H_{13}NO_2$	1640.0	1419.5	1471.1	2658.1	-	-
III	$C_{31}H_{19}N_3O_6$	1632.7	1386.3	1430.4	-	1500	-
IV	$C_{33}H_{23}N_7O_6$	1635.7	1415	1465.9	3097.3	1519	2624

Mechanism of pyrazoline derivative synthesis:



Scheme (V)

4. Conclusions

The main aim of the present work was to investigate in detail the activity and selectivity of Friedel-Crafts acetylation of acridine as well as to prepare the mono and diacetyl isomers in good yield. The best conditions to obtain the mono-acetyl compound were found to be 1:1:1 molar ratio of the Acridine: acylating agent: catalyst, 25 ˚C and 72 h, in dichloroethane. In the case of the diacetyl derivativ, the best-suited condition is 1:4:4 molar ratio in 1,2-dichloroethane at 45 ˚C (reflux) for 23 h with 100% selectivity.

Also we have successfully synthesizeda new chalcone, 1,8-bis-[3-(3-nitrophenyl)-1-oxo-2-propenyl-yl]acridine and pyrazoline,1,8-bis-[(1-formyl-5-(3-nitrophenyl))4,5-dihydro-3-pyrazolinyl]acridine and the prepared compounds were characterized by spectral methods.In this research the mechanism of the formation of acridine derivative containing pyrazoline moiety (IV) was suggested.

Acknowledgments

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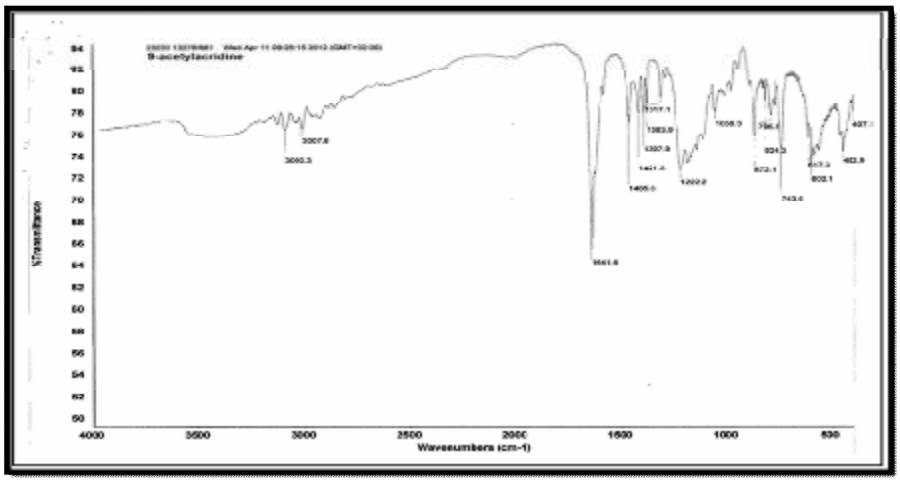

Fig 1, IR spectra compound (I)

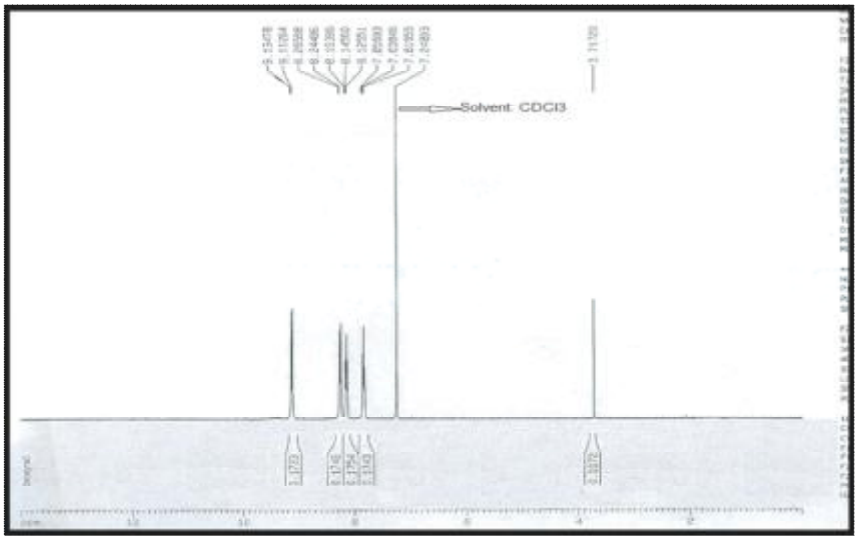

Fig II,^{1}H-NMR compound (I)

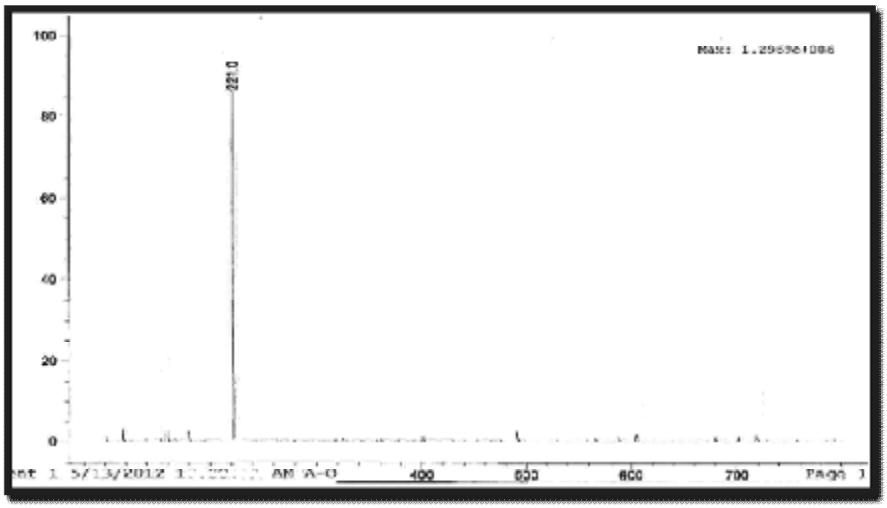

Fig III, LC-MS compound (I)

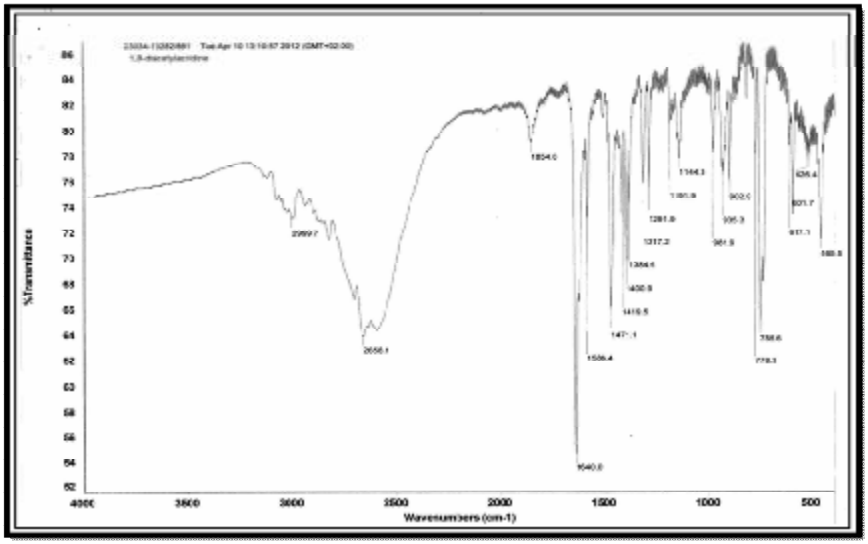

Fig IV, IR spectra compound (II)

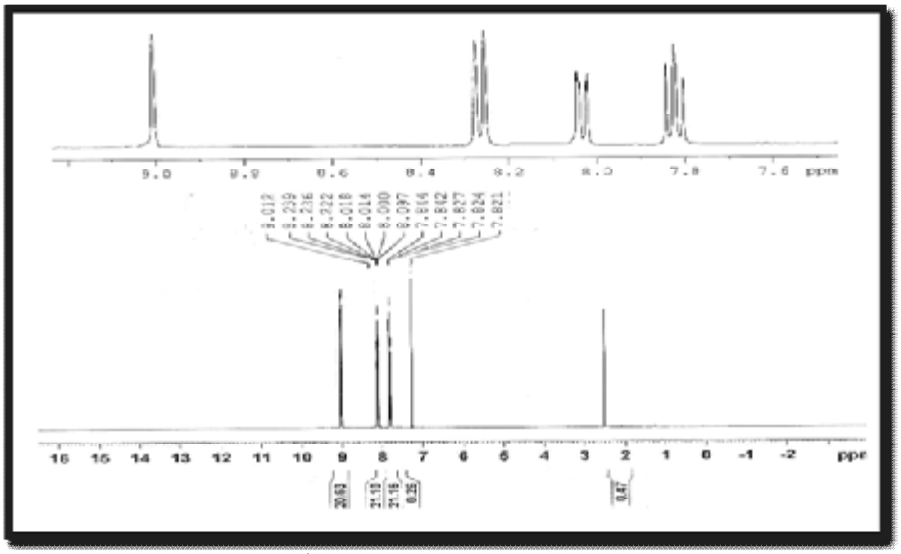

Fig V,^{1}H-NMR spectra compound (II)

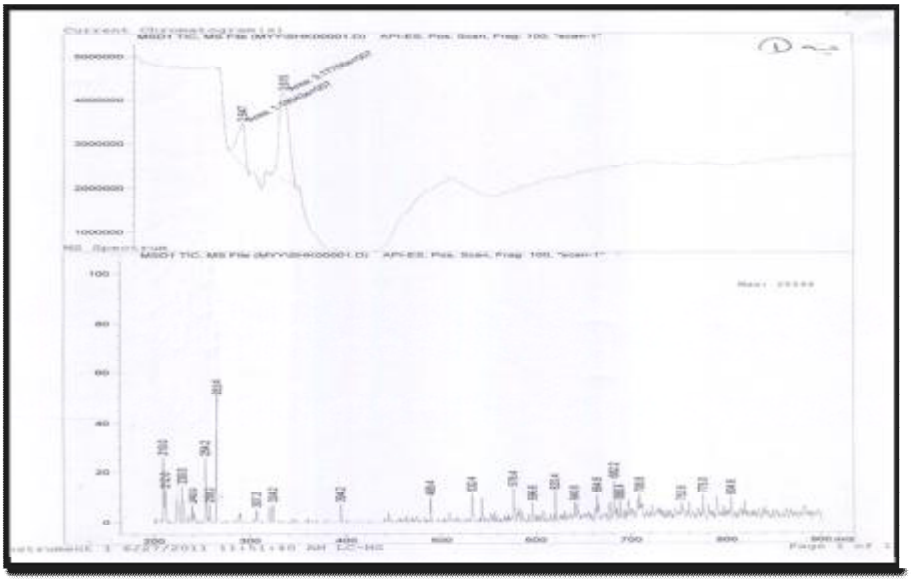

Fig VI- LC-MS compound (II)

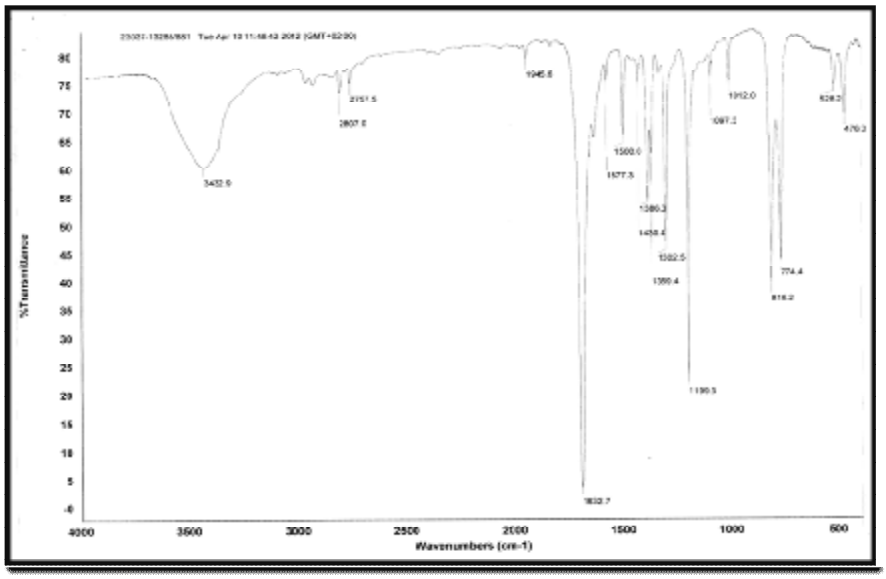

Fig VII, IR Spectra Compound (III)

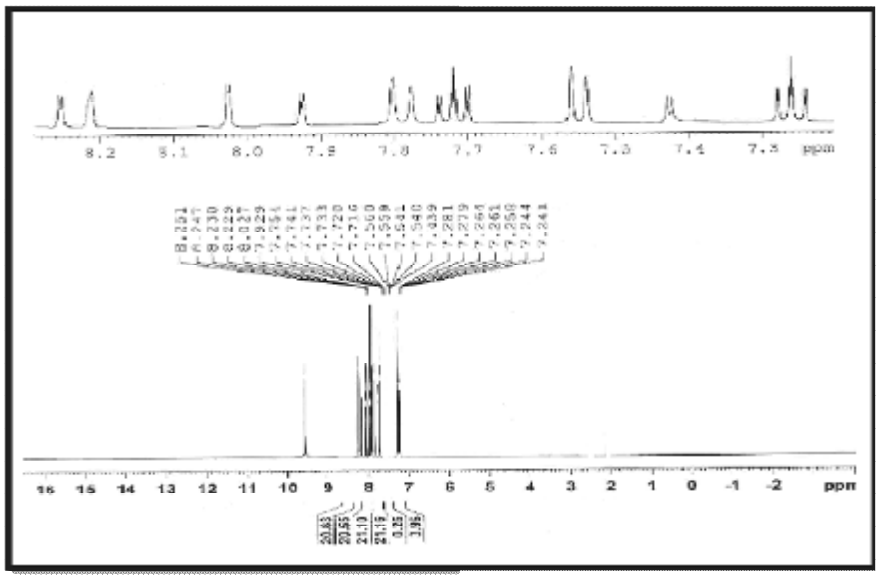

Fig VIII, ^{1}H-NMR spectra –compound (III)

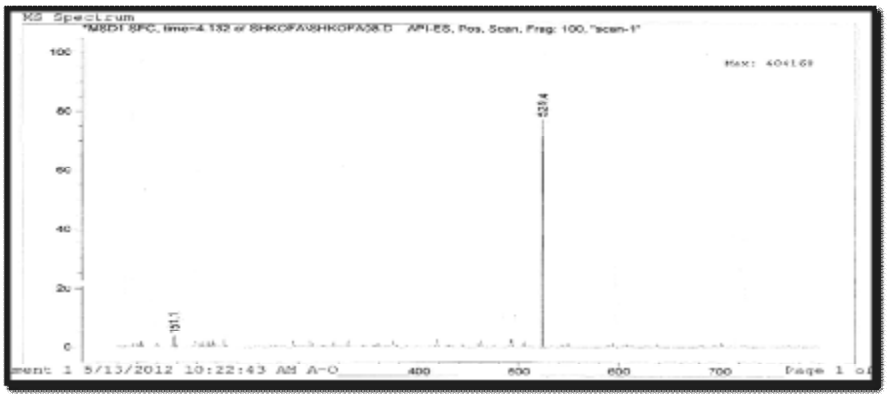

Fig IX, LC-MS Compound (III)

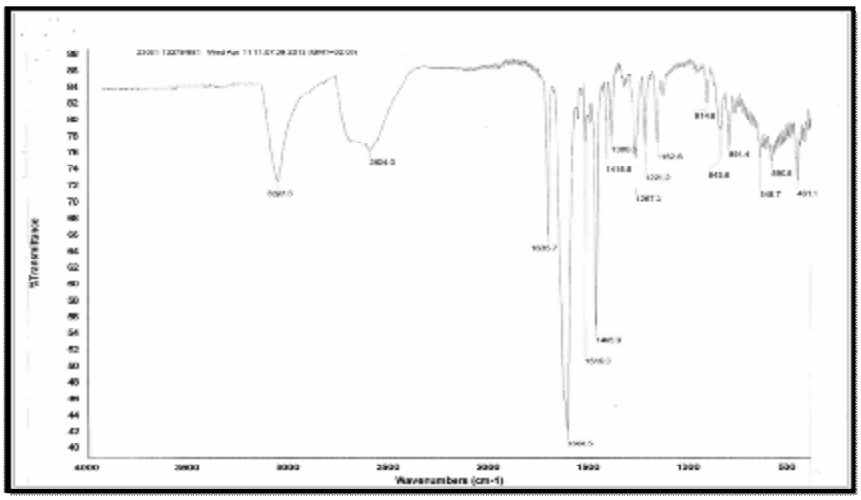

Fig X,IR Spectra compound (IV)

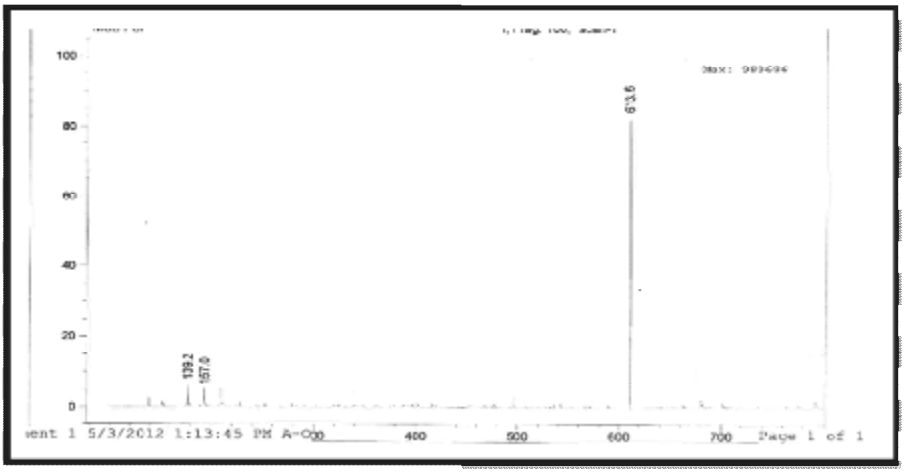

Fig XI, LC-MS compound (IV)

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