ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at www.jgpt.co.in

RESEARCH ARTICLE

Synthesis and Spectroscopic Studies of Some Heterocyclic Compounds (Oxazepane -4, 7-Dione, Azetidin-2-one) Derived from 2-Chloro -1, 8-Naphthyridine-3-Carbaldyhyd and Studying their Bacterial Activity

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Abstract

Some new 2-chloro -1,8-Naphthyridine-3-carbaldyhyd (K_1) has been synthesized using N-acetyl-2-amino pyridine with through Vilsmeier-Haack cyclization to preparation the compounds of Synthesis of 3-chloro-4-(2-chloro1,8-Naphthyridine-3-yl)-1-phenylenazetidin-2-one by ring closer reaction through the reaction of the compound (K_{5-7}) with chloro acetyl chloride in presence of drops of tri ethyl amine in 1,4-dioxane ,andas has been prepared (R) 2-(2-chloro1,8-Naphthyridine-3-yl)-1-phenyl-1,3-oxazepane-4,7-dione from reaction the compound (K_{8-10}) with of Malic anhydride ,The newly synthesized compounds were characterized by spectroscopic evidences such as IR and ^{1}H NMR. The synthesized compounds were screened for their in vitro antibacterial activity, compounds were shown good activity.

Keywords: *1, 8-naphthyridine, Vilsmeier-Haack, Azetidine, Oxazepane-4, 7-Dione.*

Introduction

Naphthyridine is the name commonly given to the fused-ring system resulting from the fusion of two pyridine rings through two adjacent carbon atoms, each ring thus containing only one nitrogen atom. The first naphthyridine derivative was obtained and named by Arnold Reissert 1893 [(1)] as the pyridine like analogue to naphthalene. There are six different types of naphthyridines which are defined through the position of the nitrogen atoms in the bicyclic system(1-6).(1,5-Napthyridine, 1,6-Napthyridine,1,7-Napthyridine, 1,8-Napthyridine, 2,6-Napthyridine 2,7-Napthyridine).

The first un substituted naphthyridines synthesized,1,5-naphthyridine[(2)] and 1,8-naphthyridine [(3)] were published in1927 by Bobranski, Suchard and Koller.1,6-Naphthyridine, 1,7-naphthyridine and 2,7-naphthyridine were reported by Ikekawa in 1958.[(4)] 2,6-Naphthyridine was independently reported by Gicacomello *et al* and Tan *et al* in 1965.[(5)]Among different types of naphthyridines, 1,8-naphthyridine derivatives have received significant attention due to their exceptionally broad spectrum of biological activity. The 1,8-naphthyridine skeleton is present in many compounds that have been isolated from natural substances, with wide spectrum of biological activities such as antibacterial,[(6.7.8)] antimycobacterial,[(9)] antitumor,[(10)] anti-inflammatory,[(11)] anti-platelet,[(12,13)] gastric anti-secretary,[(14)]anti-allergic,[(15)] local anesthetic,[(16)] anti-HIV,[(17)] anticancer,[(18)] and benzodiazepine receptor activity.[(19)]Nalidixic acid (7), for example, possesses strong antibacterial activity and used mainly for the treatment of urinary tract infections with gram negative pathogens.[(20)] In addition, Gemifloxacin (8) is an oral broad-spectrum quinolone antibacterial agent used in the treatment of acute bacterial exacerbation of chronic bronchitis and mild-to-moderate pneumonia.[(21)] One recent study showed that Gemifloxacin possess anti-metastatic activities against breast cancer in vitro and in vivo (in mice).[(22)]

Material and Methods

- Infrared Spectrophotometer model Shimadzu 8400, Type (KBR) Scale [400-4000 cm^{-1}].
- Melting Point Electro thermal 9300 melting point Apparatus.

- ^{1}H- NMR spectrometer for proton (^{1} H-NMR) Bruker400MHz, has measurements using DMSO-d6 as a solvent was to measure in Ahl-Albate University.by a device Ultra shield 400 MHz. Bruker 2003.

Chemical Materials Of the following companies: (Fluka, BDH, GHK, Aldrich, Merck) and materials used directly without recrystallization.

Synthesis of 2-Chloro-1, 8-Naphthyridine-3-Carbaldyhyd (K_1) [23]

To solution of (0.01mole) of N-(pyridine-2-yl) acetamides in (0.15 mole) DMF, at (0-5C^o) with stirring POCl3 (0.06mole) was added drop wise. The reaction mixture was heated at (80Co) for about (16hrs) with stirring. The reaction mixture was poured into crushed ice for (30 Min), and the resulting solid filtered, washed well with water and dried and re-crystallized from ethyl alcohol to give pure compound. as shown in Table (1).

Synthesis of (E)-N-(2-chloro-1, 8-Naphthyridine-3-yl) (methylene) aniline (K_{2-4})[24]

(0.01mole) 2-chloro -1,8-Naphthyridine-3-carbaldyhyd was dissolved in (10 ml) absolute ethanol in added with stirring aryl amine (0.01mole), and the mixture was refluxed for 6 hrs. On cooling, the precipitate was formed, filtered off, washed with ethanol, dried and re-crystallized from ethanol or benzene. As shown in Table (2).

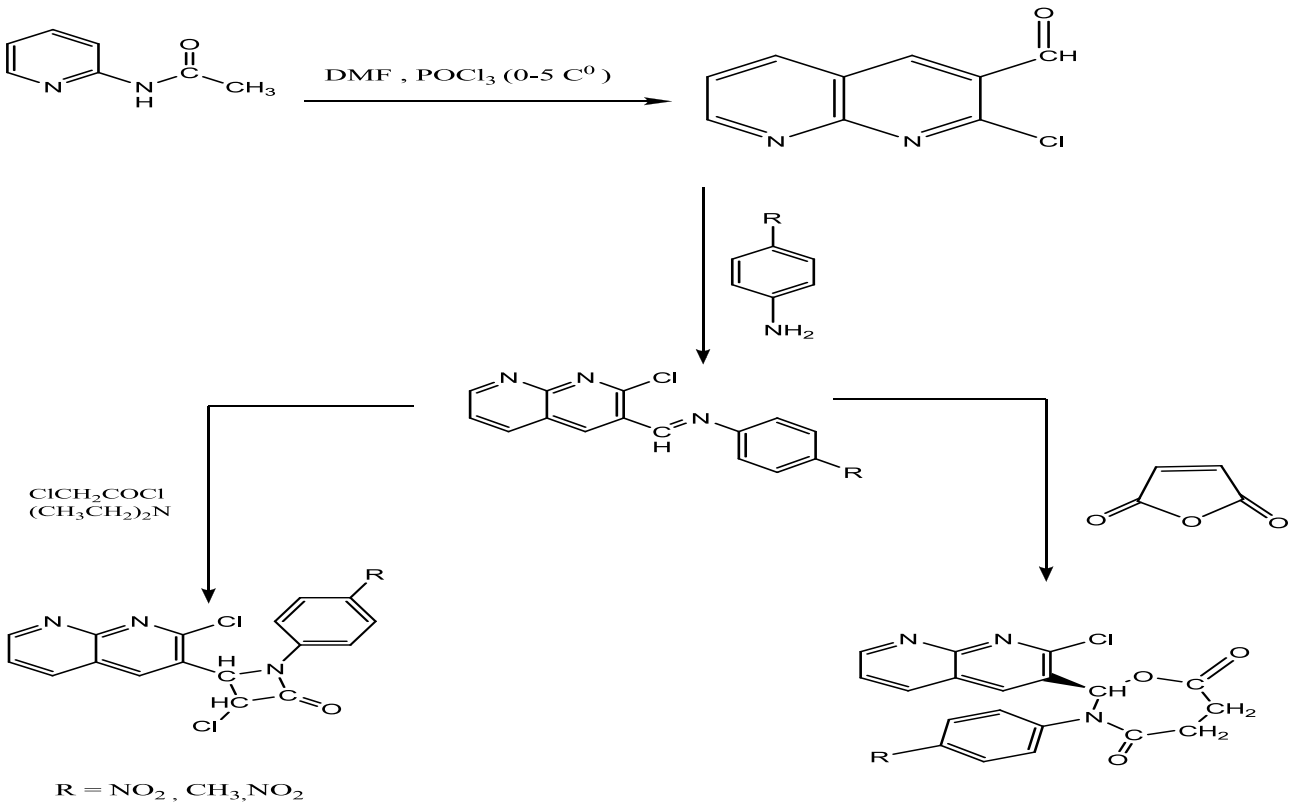
Synthesis of 3-Chloro-4-(2-Chloro1, 8-Naphthyridine-3-yl)-1-Phenylenazetidin-2-One (K_{5-7}) [25]

Mixture of (0.01mole) of chloro acetyl chloride dissolved in(10ml) of cold 1,4-dioxane at (0 -5 C^0) with (0.01mole) tri ethyl amine dissolved in (10ml) 1,4-dioxane, Then add (0.01 mole) from 2-chloro -1,8-Naphthyridine-3-carbaldyhyddissolved in (10 ml) DMF. was refluxed for 6 hrs. Then poured into crushed ice, the resulting solid was filtered washed with cold water and re-crystallized from Ethanol. .as shown in Table (3)

4-Synthesis of (R) *2*-(2-Chloro1, 8-Naphthyridine-3-yl)-1-Phenyl-1,3-Oxazepane-4,7-Dione (K_{8-10})[26]

Solution (0.01mole)2-chloro -1,8-Naphthyridine-3-carbaldyhyd which was synthesized in (10 mL) from benzene then mixture with (0.01mole) of Malic anhydride dissolved in(10 mL) of dry benzene , was refluxed for (6 hr.) with stirring .Cooling at room temperature, The solid Material separated, filtered, and Recrystallized in Dioxane or benzene. As shown in Table (4)

Scheme 1: Path ways for prepared compounds



Biological Studies

Antibacterial activity of these compounds was determined. Using Escherichia Coli and Streptococcus, then 10mM and 5mM of these compounds were placed on an agar seeded with the test organism. The plate was incubated at (37 C0) for (24 hr), I read the after (24 hr) and was compared with standard tables installed by (NCCLS.1993) to determine whether the isolates were sensitive or resistant life to antibiotics, [27].

Results and Discussion

Synthesis of 2-Chloro -1, 8-Naphthyridine-3-Carbaldyhyd

N-(pyridine-2-yl) acetamideswithPOCl3, shown in Scheme (1).sure to get follow-up reaction change the physical properties of the melting point and color. And then were identified by FT-IR and some of them by 1HNMR. FT-IR spectra of Schiff bases (K1) showed clear absorption bands at (1734cm-1) due to (C=O) ,and showed clear absorption bands at range of (3050cm-1), and (2731-2865 cm-1) which belong to both (C-H) aromatic and aliphatic respectively. While (C=N) appeared at (1600 cm-1), beside that the (C=C aromatic) appeared at range of (1482–1590 cm-1), While (C-Cl) appeared at (686 cm-1). As shown in the Table (4).

Synthesis of (E)- N- ((2-chloro-1, 8-Naphthyridine - 3-yl) (Methylene)

New Schiff bases were synthesized from the reaction of) 2-chloro-1,8-Naphthyridine -3-carbaldyhyd with aryl amine, shown in scheme (1).sure to get follow-up reaction change the physical properties of the melting point and color. and then were identified by FT-IR, and some of them by ^{1}HNMR. FT-IR spectra of Schiff bases (K_{2-4}) showed clear absorption bands at (1620cm^{-1}) due to (C=N) ,and showed clear absorption bands at (3084cm^{-1}), and (2933-2985 cm^{-1}) which belong to both (C-H) aromatic and aliphatic respectively.

While (C=C aromatic) appeared at (1502-1581 cm^{-1}), beside that the (C-Cl) appeared at (748 cm^{-1}). As shown in the Table (4) and Figure (1).On the other hand of ^{1}H-NMR in DMSOd6 , showed , at δ=(2.667) ppm (C-H Aliph),at δ =(3.409)ppm (OCH_3),at δ =(6.710-8.761)ppm (C=C) of aromatic ring , and at δ=(8.778)ppm(CH-N), the Compound (K_4) . It was a matching packet of the literature [28] .as shown in Figure (4).

Synthesis of 3-Chloro-4-(2-Chloro1, 8-Naphthyridine-3-yl)-1-Phenylenazetidin-2-one

New azetidin-2-one were synthesized from the reaction of chloro acetyl chloride with E)-N-((2-chloro-1, 8-Naphthyridine-3-yl) (methylene**)**, shown in scheme (1). sure to get follow-up reaction change the physical properties of the melting point and color. and then were identified by FT-IR, and some of them by ^{1}HNMR. FT-IR spectra of Schiff bases (K_{5-7})) showed clear absorption bands at (1793cm^{-1}) due to (C=O), and showed clear absorption bands at (1645cm^{-1}) due to (C=N), and showed clear absorption bands at (3062cm^{-1}), and (2832-2900 cm^{-1}) which belong to both (C-H) aromatic and aliphatic respectively. While (C=C aromatic) appeared at (1415-1541 cm^{-1}), beside that the (C-Cl) appeared at (680 cm^{-1}), and at (1170 cm-^{1}) due to (C-O-C), and at (1307 cm-^{1}). As shown in the Table (4) and Figure (2). On the other hand of ^{1}H-NMR in DMSOd6 , showed , at δ=(6.673) ppm (C – H Aliph),at δ =(6.713.8.766)ppm (C=C) of aromatic ring , and δ=(8.778)ppm(CH-N) the Compound (K_6) . as shown in Figure (5).

Synthesis of (R) 2- (2-Chloro1, 8-Naphthyridine- 3-yl)-1-Phenyl- 1,3-Oxazepane-4, 7-Dione

New oxazepane were synthesized from the reaction of E)-N-((2-chloro-1,8-Naphthyridine-3-yl) (methylene) with of Malic anhydride, shown in scheme (1) sure to get follow-up reaction change the physical properties of the melting point and color. and then were identified by FT-IR , and some of them by 1HNMR. FT-IR spectra of Schiff bases (K8-10) showed clear absorption bands at (1737cm-1) due to (-COO-) ,beside that the (-CO-N-) appeared at(1650cm-1),and showed clear absorption bands at range of (3064cm-1), and (2848-2900 cm-1) which belong to both (C-H) aromatic and aliphatic respectively.

While (C=N) appeared at (1600 cm-1), beside that the (C=C aromatic) appeared at range of (1504-1552 cm-1) ,and at (746 cm-1) due to (C-Cl) . As shown in the table (4) and Figure (3). On the other hand of 1H-NMR in DMSOd6 , showed ,at δ =(3.452)ppm (OCH3),at δ =(7.678-8.667)ppm (C=C) of aromatic ring , atδ=(8.984)ppm(CH-N).the Compound (K10) . It was a matching packet of the literature [28] .as shown in Figure (6).

Biological Study

The biological studies of compounds (K_1, K_2, K_6, k_{10}) were evaluated against *(Eschershia Coli, Staphylococcus Epidermidis , Staphylococcus)* Table (5) the results showed that these compounds (K_1, K_2, K_6, k_{10}) have a good activity against.

Table 1: Physical Constant of Compound (K1)

Comp. No.	R	Molecular formula	Color	M.P(°C)	Yield (%)	Recryst. Solvent
K_1	/	C9H5ClN2O	Yellow	162-164	60	ethyl alcohol

Table 2: Physical Constant of Compound (K_2-K_4)

Comp. No.	R	Molecular formula	Color	M.P(°C)	Yield (%)	Recryst. Solvent
K_2	CH_3	$C_{16}H_{12}ClN_3$	Brown	194-196	87	Ethanol
K_3	NO_2	$C_{15}H_9ClN_4O_2$	Orang	221-223	54	Ethanol
K_4	OCH_3	$C_{16}H_{12}ClN_3O$	Yellow	165-167	72	Benzene

Table 3: Physical Constant of Compound (K_5-K_7)

Comp. No.	R	Molecular formula	Color	M.P(°C)	Yield (%)	Recryst. Solvent
K_5	CH_3	C18H13Cl2N3O	Dark Yellow	252-254	57	Ethanol
K_6	NO_2	$C_{17}H_{10}Cl_2N_4O_3$	Orang	214-216	63	Ethanol
K_7	OCH_3	$C_{18}H_{13}Cl_2N_3O_2$	Pale Yellow	245-247	60	Ethanol

Table 4: Physical Constant of Compound (K_8-K_{10})

Comp. No.	R	Molecular formula	Color	M.P(°C)	Yield (%)	Recryst. Solvent
K_8	CH_3	$C_{20}H_{16}ClN_3O_3$	Pale Yellow	173-175	70	Dioxane
K_9	NO_2	$C_{19}H_{13}ClN_4O_5$	Brown	222-224	**76**	Benzene
K_{10}	OCH_3	$C_{20}H_{16}ClN_3O_4$	Pale red	250-252	51	Dioxane

Table 5: Biological study of the prepared compounds

Comp. No.	R	*G-Escherichia coli*		*Streptococcus Pyogene*	
		5mM	***10mM***	***5mM***	***10mM***
k_1	/	++	++	+++	+
K_2	3-CH_3	++ + ++		+ - +	+ - -
K_6	2-Br	++	++	-	+
K_{10}	3-OCH_3	++	+	-	-

Key (-) Inactive (< 5m), (+) slightly active (10-12m), (++) moderately active (15-20m) (+++) highly active (>20mm)

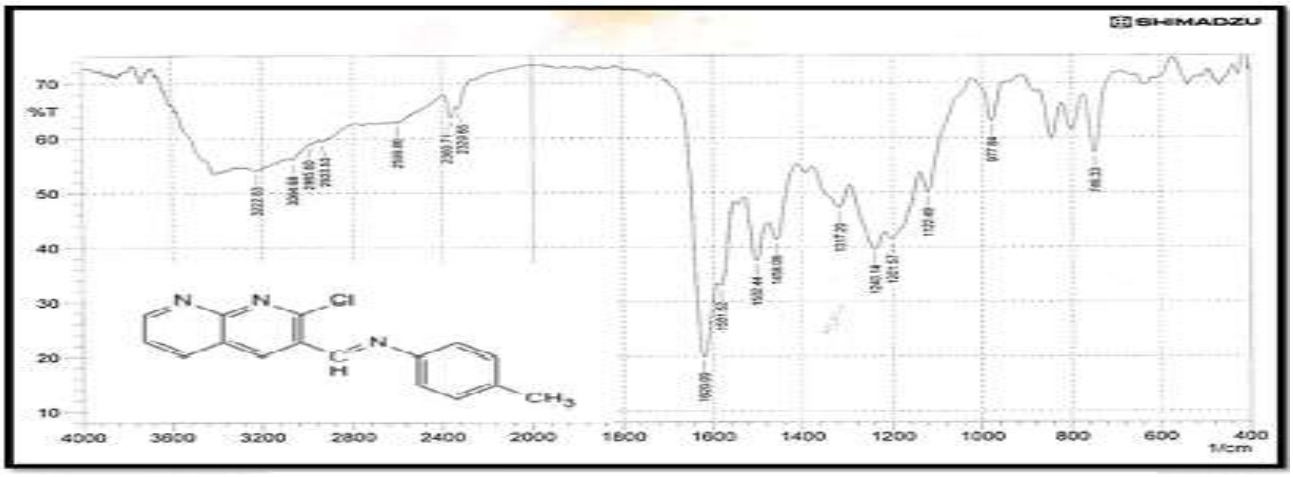


Fig.1: IR spectrum of synthesized compound (K2)

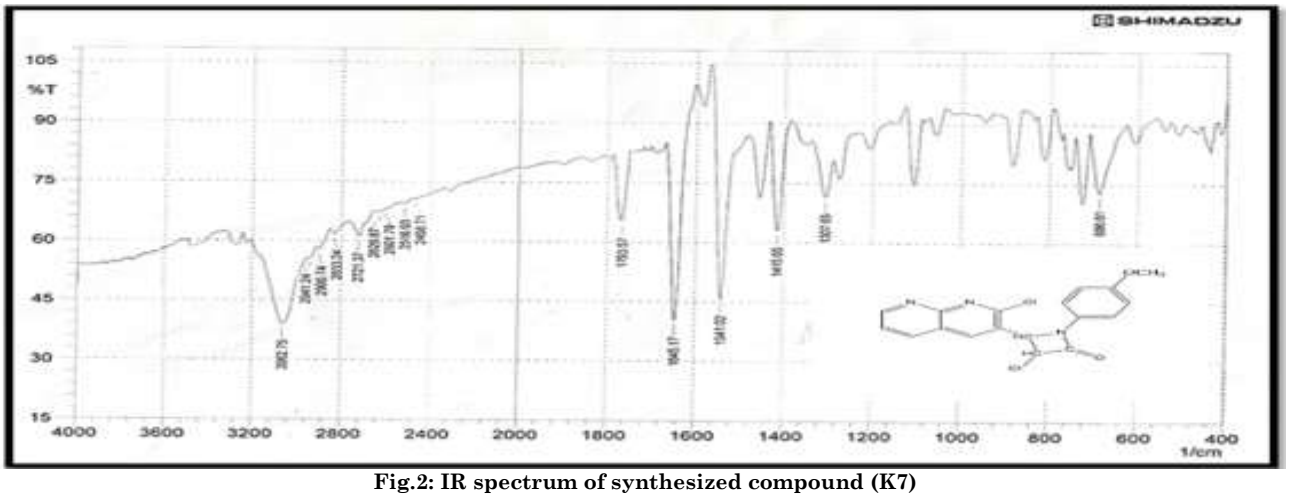


Fig.2: IR spectrum of synthesized compound (K7)

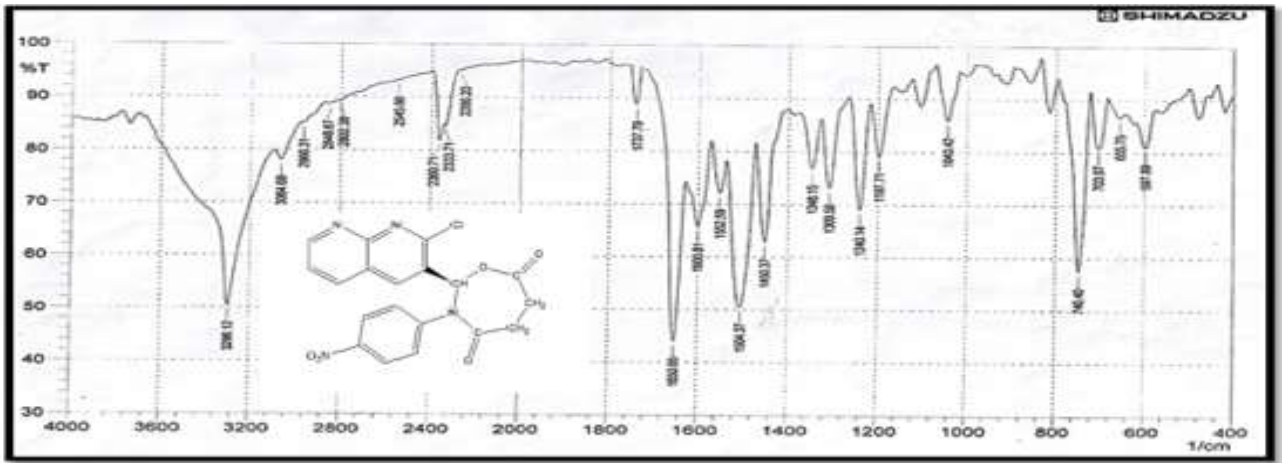


Fig.3: IR spectrum of synthesized compound (K9)

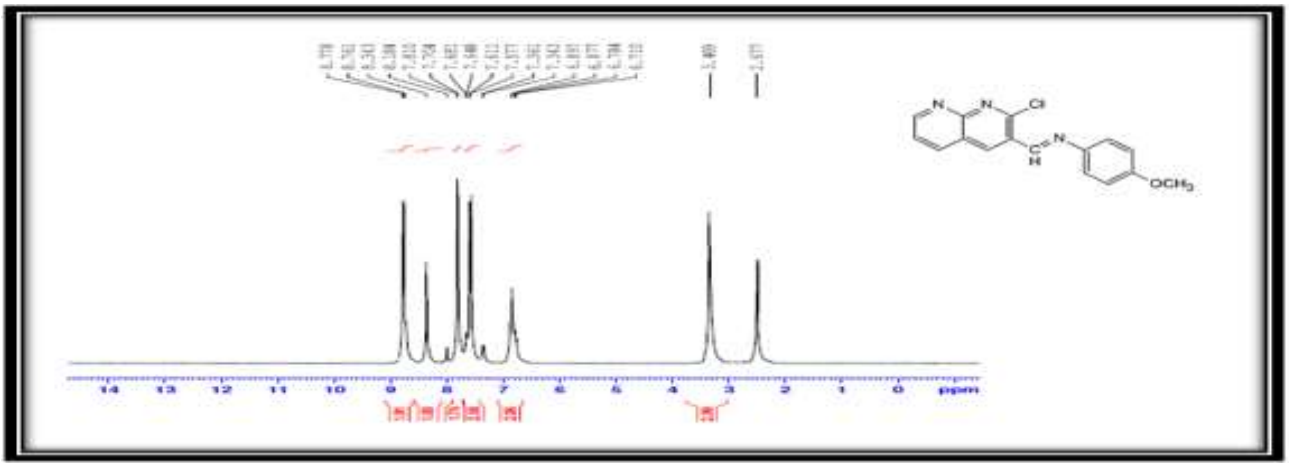


Fig.4: 1H-NMR. Spectrum of synthesized compound (K4)

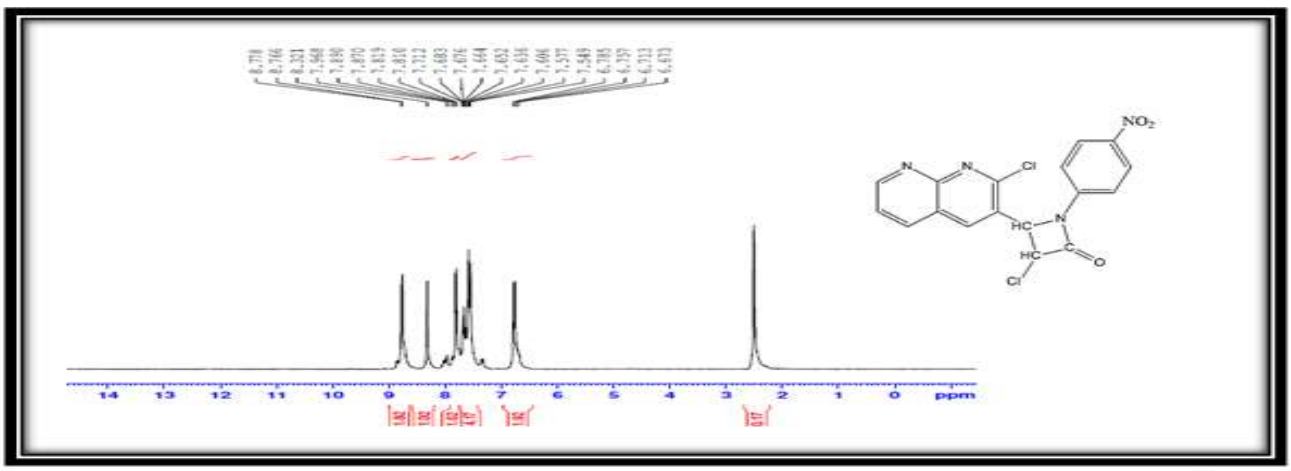


Fig 5: 1H-NMR Spectrum of synthesized compound (K6)

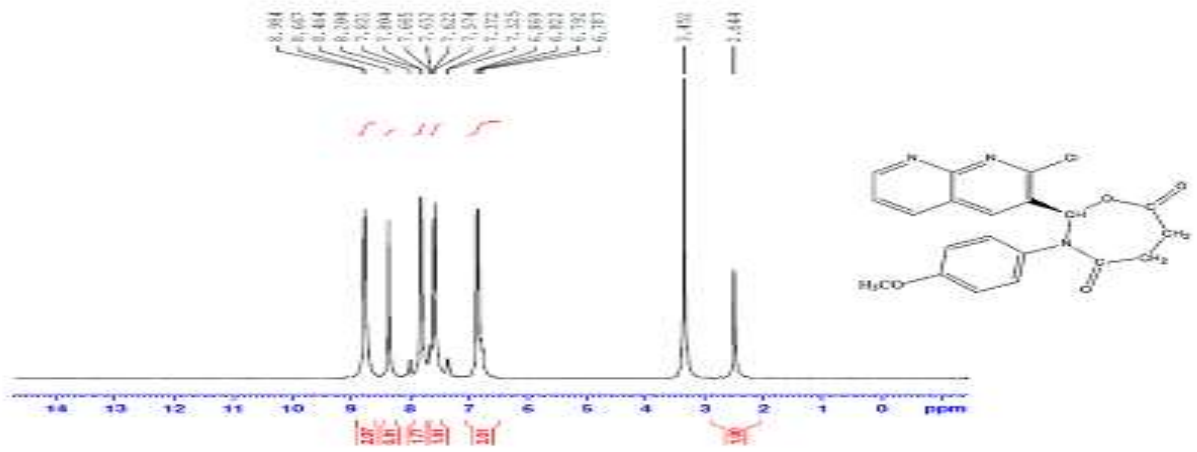


Fig.6: 1H-NMR. Spectrum of synthesized compound (K10)

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