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Synthesis and evaluation of Biological activity of new cyclic Imides derived from 4-amino phenazone

تحضير و تقييم الفعالية البايولوجية لايمايدات حلقية جديدة مشتقة من 4 - امينوفينازون

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Abstract

A series of new cyclic imides containing phenazone heterocycle were prepared via following three different methods.
The first one involved direct reaction of different cyclic anhydrides with 4-amino phenazone producing the corresponding amic acids which subsequently introduced in dehydration reaction to afford the desirable imides while the second method involved treatment of 4-amino phenazone with chloro acetyl chloride affording 4-(2-chloro acetamido) phenazone which introduced in reaction with potassium salts of both phthalimide and succinimide producing N-(2-acetamido phenazone -4-yl)phthalimide and succinimde respectively .
The third method involved reaction of 4-(2-chloro acetamido) phenazone with N- (hydroxy phenyl) phthalimides producing three new N-(oxy acetamido phenazone-4-yl) phenyl phthalimides.
Antibacterial activity of the prepared new imides against two types of bacteria were evaluated and the results showed that the new imides exhibit good to moderate antibacterial activity.
Antifungal activity of the new imides were also tested against *candida albicans* fungi and most imides showed slight activity against this fungi.

الخلاصة

تضمن البحث تحضير سلسلة من ايمايدات حلقية جديدة معوضة بحلقة الفينازون وذلك بإتباع ثلاثة طرق مختلفة.
تضمنت الطريقة الأولى إجراء تفاعل مباشر بين الانهيدريدات الحلقية المختلفة ومركب4-امينو فينازون لإنتاج حوامض الاميك المقابلة والتي بدورها تفقد جزيئة ماء متحولة إلى الايمايدات المطلوبة.
اما الطريقة الثانية فقد تم فيها معاملة المركب 4-امينو فينازون مع كلورو كلوريد الاستيل للحصول على المركب 4-(2-كلورو اسيتاميدو) فينازون والذي بتفاعله مع ملح البوتاسيوم للفثال ايماید او السكسن ايماید انتج ايمايدات جديدة هي N-(2-اسيتاميدو فينازون-4-يل) فثال ايماید و سكسن ايماید على التوالي.
اما الطريقة الثالثة فقد تضمنت تفاعل المركب 4-(2-كلورو اسيتاميدو) فينازون المحضر مع مركبات N-(هيدروكسي فنيل) فثال ايماید مما اسفر عن تكوين ثلاث ايمايدات جديدة هي N-(اوكسي اسيتاميدو فينازون -4-يل) فنيل فثال ايماید .
تم تقدير الفعالية البايولوجية للايمايدات الجديدة ضد نوعين من البكتريا هي ستافيلوكوكاس اوريس (الموجبة لصبغة كرام) و سيدوموناس اريجينوزا (السالبة لصبغة كرام) حيث اوضحت النتائج بان اغلب الايمايدات المحضرة ذات فعالية بايولوجية ضد انواع البكتريا المشار اليها.
كذلك فقد درست الفعالية البايولوجية للايمايدات الجديدة ضد احد انواع الفطريات هو *Candida albicans* حيث اظهر غالبيتها فعالية قليلة كمضاد لهذه الفطريات.

Introduction

Cyclic imides are important family of organic compounds which exhibit a great variety of biological activities such as antifungal , antibacterial, antispasmodic and analgesic properties [1-3] Some cyclic imides are used as plant growth regulators while others used as insecticides and some have important applications in medical field [4-6] .

On the other hand 4-amino phenazone is an important heterocyclic compound which its derivatives have a variety of potential biological activities.

Keeping these above facts in view we considered it of interest to synthesize a series of new cyclic imides containing phenazone moiety in their structures by following different methods and to evaluate the new compounds for their antibacterial activity.

Experimental

All chemicals used in this work were from BDH, Merk,Fluka and were used without further purification.

Melting points were determined on Gallen Kamp capillary melting point apparatus and were uncorrected.

FTIR spectra were recorded using KBr discs on Shimadzu FTIR-8400 Fourier Transform Infrared spectrophotometer.

^{1}H-NMR spectra were recorded on near magnetic resonance Bruker, ultra shield 300 MHz using tetra methyl silane as internal standard and $CDCl_3$ as solvent in

Al al-.Bayt University in Jordan, C.H.N analysis were determined on Perkin- Elmer 240 Elemental analyzer. Incubator Hetashi model was used for incubation samples in biological study.

1. Preparation of N-(phenazone -4-yl)maleamic, Citraconamic, phthalamic and succinamic acids[1-4]

Literature procedures [7,8] were followed in the synthesis of the titled amic acids with minor modifications:

(0.01mol) of cyclic anhydride(maleic , citraconic, phthalic or succinic) anhydride was dissolved in (25mL) of dry acetone then (0.01 mol)of 4-amino phenazone dissolved in (20 mL)of acetone was added drop wise with cooling and stirring .

Stirring was continued for two hours then the obtained precipitate was filtered and recrystallized from ethanol or dioxane .

Table(1) lists physical properties and FTIR spectral data of the prepared amic acids.

2. Preparation of N-(phenazone-4-yl)Maleimide, citraconimide, phthalimide or succinimide[5-8]

The titled imides were prepared according to literature procedures with some modifications [8,9]:

A mixture of (0.01 mol) of N-(phenazone-4-yl) amic acids [1-4], (30 ml) of acetic anhydride and(5%)by weight of amic acid from anhydrous sodium acetate was refluxed for 3 hrs with stirring.

The resulted homogeneous solution was cooled to room temperature then poured into cold water with vigorous stirring .

The obtained precipitate was filtered , washed with water then purified by recrystallization from hexane.

3. Preparation of N-(phenazone -4-yl)3,4-dimethyl malimide[9]

Compound [9] was prepared according to literature procedures [10] .

A solution of (0.01 mol) of 4-amino phenazone in (20 ml) of ether was added drop wise to a solution of (0.01 mol) of 3,4-dimethyl maleic anhydride in (30 mL) of ether with stirring and cooling.

The mixture was stirred for 3 hrs at room temperature then was left overnight.

The resulted precipitate was filtered and purified by recrystllization from dioxane.

4. Preparation of N-(phenazone -4-yl) 1,8-Naphthalimide [10]

A mixture of (0.01 mol) of 1,8- naphthalic anhydride , (0.01 mol) of 4-amino phenazone , 20 mL of acetone and 5ml of glacial acetic acid was refluxed for 6 hrs with continuous stirring [11] .

The obtained mixture was poured into crushed ice with stirring and the resulted precipitate was filtered then purified by recrysallization from petroleum ether b.p. (60-80) ^{0}C.

Physical properties and FTIR spectral data of the prepared imides [5-10] are listed in Table (2).

5. Preparation of4-(2-chloro acetamido) phenazone [11]

The titled compound was prepared according to literature procedures [12]:

(0.01 mol) of 4-amino phenazone was dissolved in (30 mL) of dry ether then a solution of (0.01 mol) of chloro acetyl chloride in (30 mL) of dry ether was added in portions with stirring and cooling .

After 30 minutes of additional stirring the solid product was separated then filtered , washed with dilute $NaHCO_3$ solution then with water.The product was purified by recrystallization from dioxane.

6.Preparation of N-(4-acetamido phenazonyl)phthalimide [12]

a- Preparation of potassium phthalimide

(0.01 mol) of phthalimide was dissolved in (20 mL) of absolute ethanol then was heated in water bath.'

The obtained clear solution was added to alcoholic potassium hydroxide solution with continuous stirring and cooling then the resulted precipitate was filtered and dried [13] .

b. Preparation of N-(4-acetamido phenazonyl)phthalimide [12]

(0.01 mol) of compound [11] was dissolved in (25mL) of absolute ethanol then (0.01 mol) of the prepared potassium pthalimide was added gradually with stirring.

The resulted mixture was refluxed for six hours with continuous stirring then was cooled to room temperature.

The formed precipitate was filtered, washed with $NaHCO_3$ solution then with water, and finally purified by recrystallization from acetone.

7. Preparation of N-(4-acetamido phenazonyl) succinimide[13]

The titled compound was prepared via reaction of equimolar amounts of potassium succinimide with compound [11] following the same steps used in the preparation of compound [12].Potassium succinimide was prepared by following the same procedure used in the preparation of potassiumphthalimide.

Physical properties and FTIR spectral data of compounds [11],[12] and [13] are listed in Table (3).

8-Preparation of N-(4-oxyacetamido phenazone-4-yl)phenyl phthalimide[14]

(0.01 mol) of N-(4-hydroxy phenyl) phthalimide was dissolved in (15 mL)of aq. NaOH solution then (0.015 mol)of compound [11] dissolved in (30ml) of acetone was added in portions with stirring and keeping temperature below (40 C^0).

The mixture was refluxed for three hours with continuous stirring then was cooled to room temperature and poured into excess cold water with vigorous stirring.

The obtained precipitate was filtered, washed with water and dried then recrystallized from cyclohexane.

9-Preparation of N-(3-oxyacetamido phenazone-4-yl)phenyl phthalimide[15]

The titled compound was prepared by following the same procedure used in the preparation of compound [14] except using of N-(3-hydroxy phenyl) phthalimide instead of N-(4-hydroxy phenyl) phthalimide.

10-Preparation of N-(2-oxyacetamido phenazone-4-yl)phenyl phthalimide[16]

The titled compound was prepared by following the same procedure used in the preparation of compound [14] except using of N-(2- hydroxy phenyl) pthalimide instead of N-(4-hydroxy phenyl) phthalimide.

Physical properties and FTIR spectral data of the prepared compounds [14] , [15], and [16] are listed in Table (4).

11. Antibacterial activity

The cup plate method using nutrient agar media was employed in studying the antibacterial activity of the prepared compounds against *staphylococcus aureus* and *Pseudomonas aeruginosa* and antifungal activity against candida albicans.

Using a sterilized cork borer cups were scooped out of agar media contained in a Petri dish which was previously inoculated with the microorganisms.

The test compound solution (0.1 mL) was added in the cups and the Petri dishes were subsequently incubated at 37 ^{0}C for 48 hrs.

Zones of inhibition produced by each compound was measured in mm and the results are listed in Table (6).

Results and Disscution

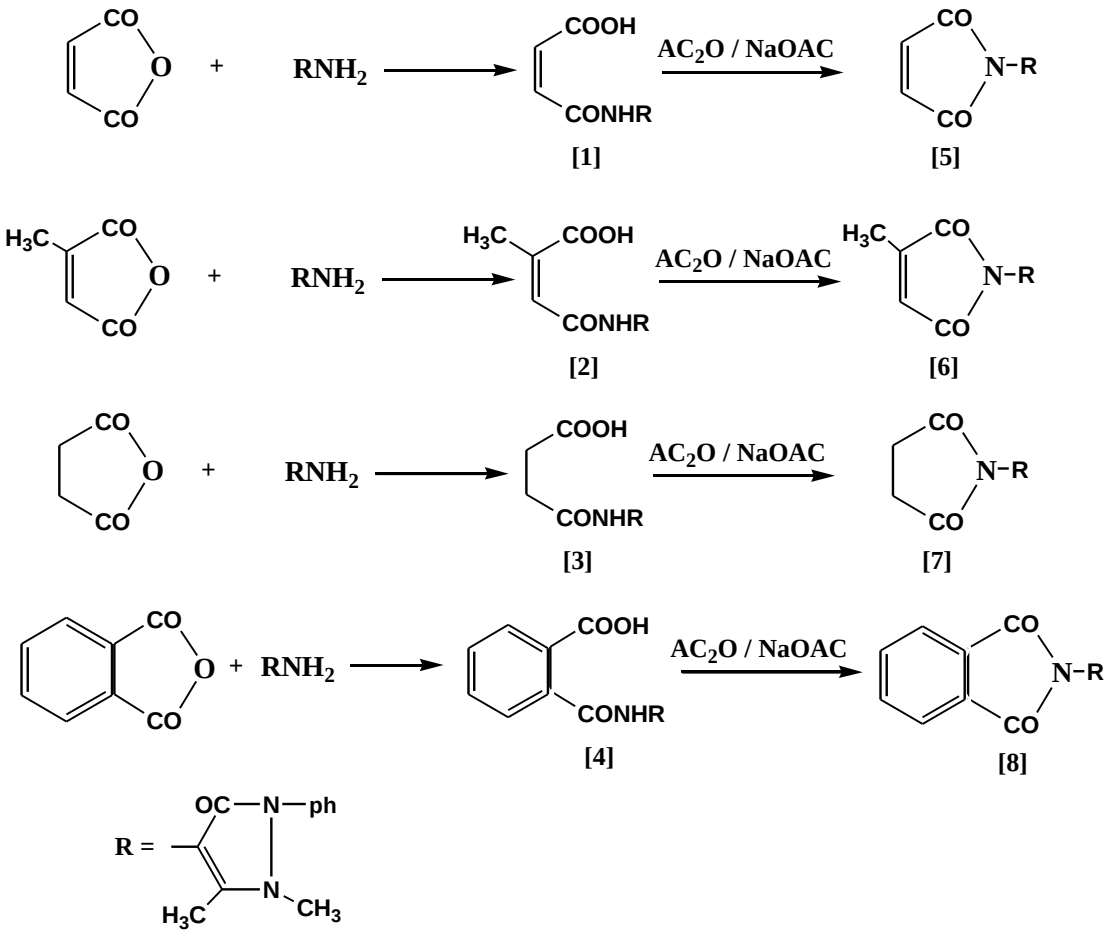
Cyclic imides are important family of organic compounds that posses wide spectrum of biological activities.

Also phenazone is an important ring system for many substances of biological and medical interest.

All these facts encouraged us to synthesize new compounds containing the two biologically active moieties cyclic imide and phenazone with expected biological activity.

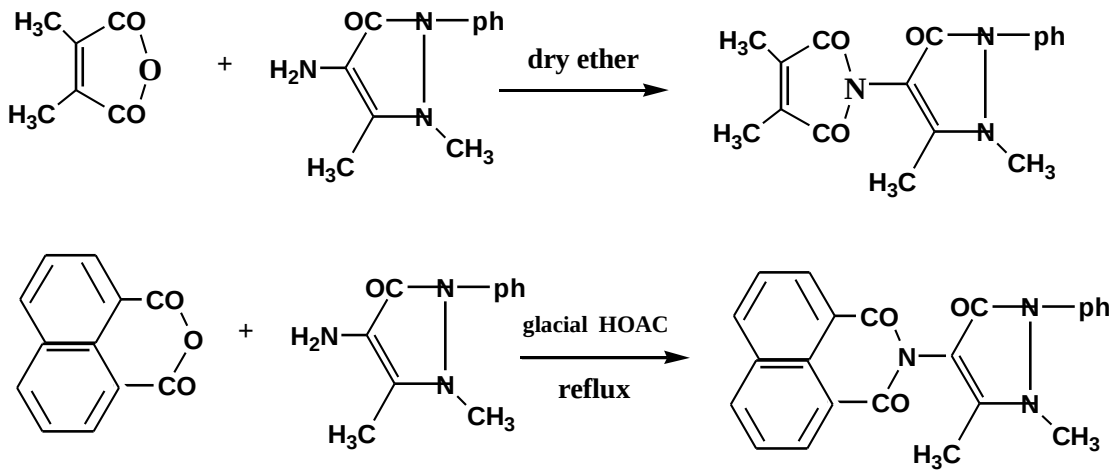
Three different strategies were followed to perform this target the first one involved synthesis of various cyclic imides including maleimide, citraconimide , phthalimide and succinimide substituted with phenazone ring via reaction of 4-amino phenazone with different cyclic anhydrides to produce the corresponding amic acids which in turn were dehydrated by using acetic anhydride and anhydrous sodium acetate to afford the desirable imides.

This strategy can be summarized in Scheme (1).



Scheme (1)

On the other hand synthesis of N-(phenazone -4-yl)-3,4-dimethyl maleimide was performed by direct reaction of equimolar amounts of 3,4-dimethyl maleic anhydride and 4-amino phenazone in dry ether at room temperature, while synthesis of N-(phenazone -4-yl)-1,8 - naphthalimide was performed via reflux of 1,8- naphthalic anhydride and 4-amino phenazone in acetone in the presence of suitable volume of glacial acetic acid as described in Scheme (2).



[10]

Scheme (2)

Structures of the prepared amic acids[1-4]and cyclic imides [5-10] were confirmed by FTIR and HNMR spectroscopy.

FTIR spectra of the prepared amic acids showed clear absorption bands at (3220- 3420) cm^{-1}due to υ(O-H) carboxylic and υ (N-H) amide [14] .

The spectra showed also other bands at (1704-1712) cm^{-1} , (1630-1670) cm^{-1} and (1566-1643) cm^{-1}due to υ (C=O) amide , υ (C=O) amide in phenazone ring and υ (C=C) respectively.

While FTIR spectra of cyclic imides showed disappearance of υ(O-H) carboxylic and υ (N-H) amide due to dehydration and cyclization and this proved success of imide formation [9,10] .

Also the spectra showed many clear bands at (1720-1740) cm^{-1}, (1635-1681) cm^{-1}, (1550-1630) cm^{-1} and (1350-1395) cm^{-1}which were attributed to υ(C=O) imide , υ(C=O)amide in phenazone ring, υ (C=C) and υ(C-N)imide respectively.

Moreover FTIR spectra of imides [7] and [10] showed shoulder absorption band at (1775-1780) $cm^{-1}$and this is a characteristic band for imide.

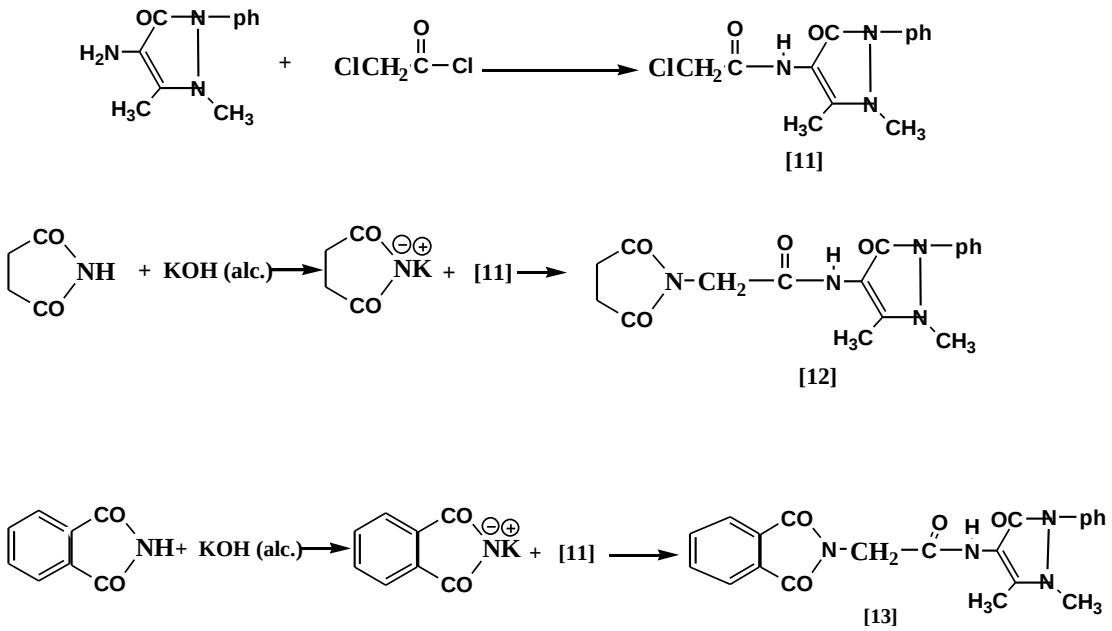
On the other hand HNMR spectrum of compound [1] showed signals at δ=2.2 and 3.07 ppm belong to CH_3 group and (-N-CH_3) respectively , signals belong to vinylic protons appeared at δ=6.3 and 6.5 ppm while signals at δ=(7.3-7.6)ppm belong to aromatic protons [15] .

HNMR spectra of the prepared imides [5] and [9] showed signals at δ=(2.1-2.15) ,3.2 and (7.3-7.5)ppm belong to CH_3, (-N-CH_3) and aromatic protons.

Moreover HNMR spectrum of compound [5] showed signals at δ=6.2 and 6.45 ppm due to 2H vinylic while compound [9] spectrum showed signals at δ=2.05 ppm belong to two methyl groups attached to imide ring.

The second strategy used in this work involved building of new cyclic imides connected to phenazone ring through acetamido bridge depending on Gabrial reaction.

Performing this strategy involved two steps the first one involved preparation of 4-(2-chloro acetamido) phenazone via reaction of 4-amino phenazone with chloroacetyl chloride and this in turn react with potassium salt of phthalimide or succinimide producing the new imides [12] and [13] as described in scheme (3).



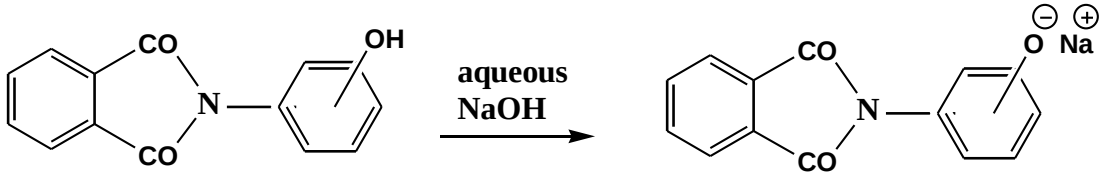
Scheme (3)

FTIR spectra of the new imides [12] and [13] showed clear absorption bands at (3363- 3394) cm^{-1}, (1704-1728) cm^{-1} and (1635-1690) cm^{-1} due to υ(N-H)amide , υ(C=O) imide and υ(C=O) amide respectively, also a clear shoulder band due to υ(C=O) imide was appeared at(1775-1780) cm^{-1} .

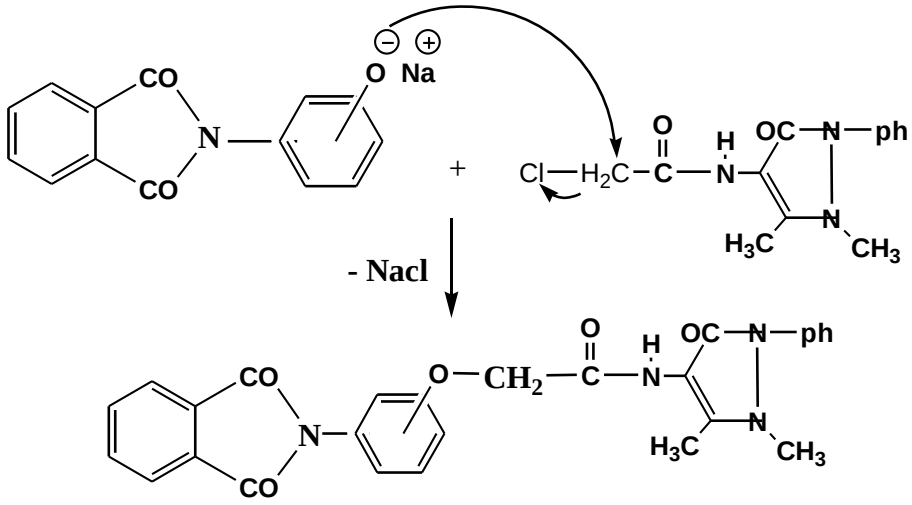
HNMR spectrum of compound[13]showed clear signals which proved its structure including signals at δ=2.2 ,3.05 ppm belong to (CH_3) and (-N-CH_3) and signals at δ=(7.2-7.8) ppm due to aromatic protons while the signal at δ=3.45 ppm belong to two protons in ($-\underset{\underset{O}{\|}}{C}\cdot CH_2\,NH-$) proving the presence of acetamido bridge [13] .

The third strategy used in this work involved building of new cyclic imides connected to phenazone ring through phenoxy acetamido bridge.

This strategy was performed via reaction of N-(hydroxy phenyl) phthalimide with 4-(2- chloro acetamido) phenazone in aq. sodium hydroxide solution as described in scheme(4).



N-(hydroxy phenyl) phthalimide



Compounds [14,15,16]

Scheme (4)

The three N-(hydroxy phenyl) phthalimides were synthesized as reported in literature [7] via dehydration of the corresponding N-(hydroxy phenyl) phthalamic acids by fusion .

FTIR spectra of the prepared imides [14-16] showed absorption bands at (3384-3400) cm^{-1},(1705-1712) cm^{-1} and (1665-1680) cm^{-1} due to υ (N-H) amide, υ(C=O imide and υ(C=O) amide respectively.

Moreover the spectra revealed a characteristic absorption band at (1140-1170) cm^{-1} due to υ(C-O-C) ether.

HNMR spectrum of imide [14] showed clear signals at δ=2.1,3.15 and(6.75-7.45)ppm belong to (CH_3), (-N-CH_3) and aromatic protons respectively, while the signal at δ=4 ppm belong to two protons in (—C(=O)—CH_2—O—).

All details of FTIR and H-NMR spectral data of the prepared compounds in this work are listed in Tables(1-5) while C.H.N analysis for some of them are listed in Table (6) and Figures (1-11) showed FTIR and H-NMR spectra for some of the prepared compounds .

Since the prepared new imides were built from two biologically active components we expected these imides to posses biological activity ,so the synthesized imides were screened for their antibacterial activity against two types of bacteria *Staphylococcus aureus* (Gram positive) and *Pseudomonas aeruginosa* (Gram negative).

Also antifungal activity of the prepared imides against candida albicans fungi were evaluated..

The test results presented in Table (7) showed that imides [6],[9] and [15] were highly active against *Staphylococcus aureus* but moderately active against *Pseudomonas aeruginosa* .

Other imides were found to be either moderately active or slightly active against *Staphylococcus aureus* but they showed slight activity against *Pseudomonas aeruginosa* except imides [5,8,10,12] which were inactive against this bacteria .
On the other hand all the prepared imides were found to be slightly active against candida albicans fungi except imides [10] and [12] which were inactive.

Table(1) physical properties and FTIR spectral data of N-(phenazone -4-yl) amic acids

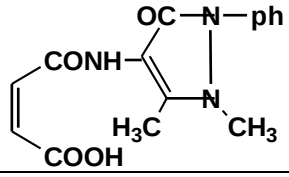
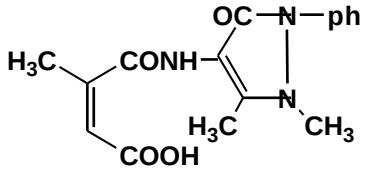
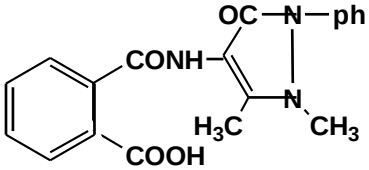
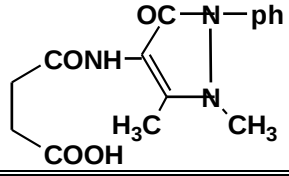
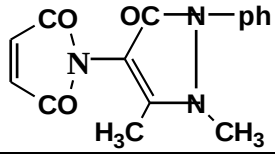
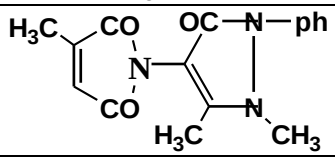
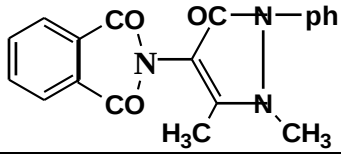
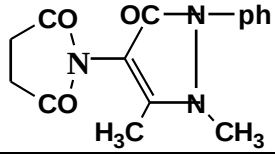
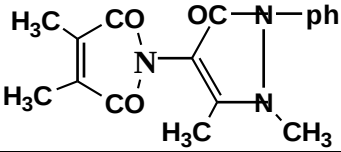
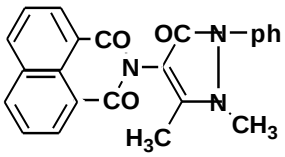
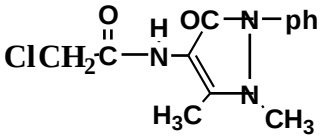
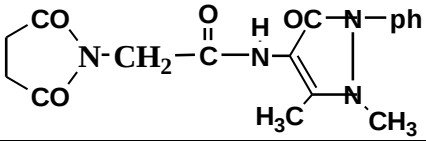
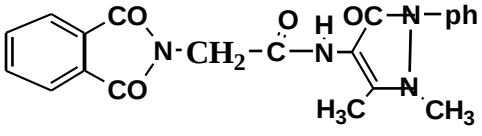
Compd. No.	Compound structure	Color	Yield %	Melting Point C^0	Major FTIR absorptions cm^{-1}			
					υN-H υO-H	υ C=O Amide	υ C=O Phenazone	υ C=C Aliphatic
1		Pale yellow	95	138-140	3300 3220	1712	1650	1566
2		Yellow	77	120-122	3400 3240	1710	1670	1643
3		Dark Brown	70	165-166	3420	1704	1630	1590
4		Light Brown	82	152-153	3360 3290	1710	1655	1589

Table (2) Physical properties and FTIR spectral data of N-(phenazone-4-yl) imides

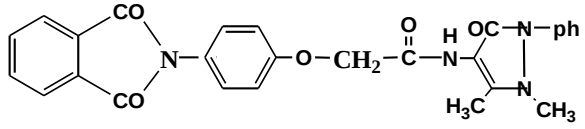
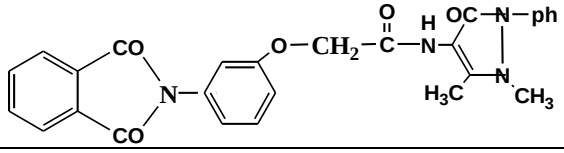
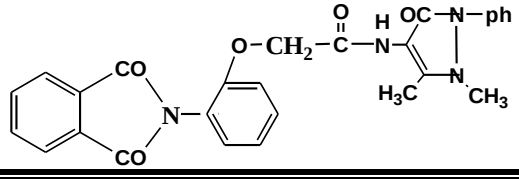
Compd. No.	Compound structure	Yield %	Color	Melting Point C^0	Major FTIR absorptions cm^{-1}			
					υ C=O Imide	υ C=O Amide	υ C=C Aliphatic	υC-N Imide
5		82	Dark Yellow	84-86	1720	1635	1550	1350
6		86	Yellow	70-72	1720	1674	1580	1395
7		74	Brown	123-124	1780 1730	1670	1580	1350
8		71	Brown	96-97	1720	1681	1589	1388
9		80	Pale Brown	162-164	1730	1682	1630	1388
10		90	White	216-218	1755 1740	1666	1589	1350

Table(3) Physical properties and FTIR spectral data of compounds[11],[12]and [13]

Compd. No.	Compound structure	Color	Yield %	Melting Point C^0	Major FTIR absorptions cm^{-1}				
					υ C=O Imide	υ C=O Amide	υC=C	υC-N Imide	υN-H
11		Pink	88	72-74	-----	1690	1635	-----	3410
12		Brown	81	84-86	1780 (sh*) 1704	1666	1573	1404	3394
13		Black	85	89-90	1776 (sh*) 1728	1635	1589	1373	3363

(Sh*)= Shoulder

Table (4) physical properties and FTIR spectral data of N-(oxyacetamido phenazone-4- yl)phenyl phthalimides

Compd. No.	Compound structure	Yield %	Melting Point C^0	Major FTIR absorptions cm^{-1}				
				υN-H	υ C=O Imide	υ C=O Amide	υ C=C	υC-O-C Ether
14		86	94-96	3390	1712	1665	1604	1155
15		78	103-104	3384	1705	1680	1590	1170
16		80	99-100	3400	1710	1671	1602	1140

Table(5) H-NMR spectral data for some of the prepared compounds

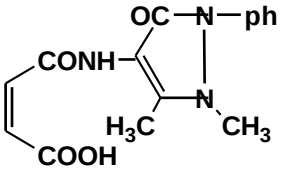
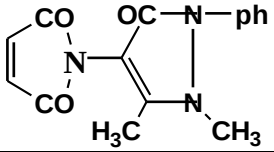
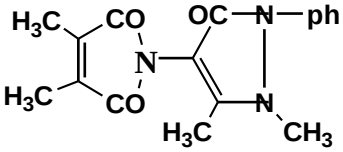
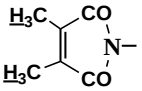
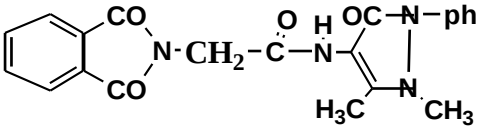
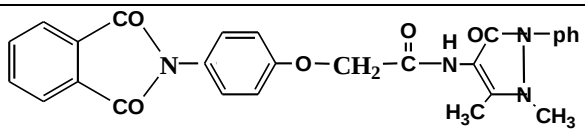
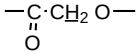
Compd. No.	Compound structure	Chemical shifts in ppm
1		δ= 2.2, 3H (CH_3), δ= 3.07 ,3H ($C\underline{H}_3$-N-) δ=6.3 and δ=6.5 2H vinylic δ= 7.2 NH amide, δ=(7.3-7.6) 5H aromatic δ= 9.8 OH carboxylic
5		δ= 2.1, 3H (CH_3) , δ= 3.2 ,3H ($C\underline{H}_3$-N-) δ=6.2 and δ=6.45 2H vinylic δ=(7.3-7.4) 5H aromatic
9		δ=2.05 6H, 2CH_3  δ=2.15 3H ,CH_3 δ=3.2 3H, -CH_3-N- δ=(7.3-7.5) 5H aromatic
13		δ=2.2,3H CH_3, δ=3.05 3H, $C\underline{H}_3$-N- δ= 3.45 ,2H δ= (7.2-7.8) NH and 9H aromatic
14		δ= 2.1,3H CH_3, δ=3.15 3H, $C\underline{H}_3$-N- δ=4, 2H  δ= (6.75-7.45)13 H aromatic and δ = 8.62 NH proton

Table (6) C.H.N analysis for some of the prepared compounds

Compd. No.	Calculated			Found		
	% C	%H	% N	%C	%H	%N
3	64.95	4.84	11.96	64.88	4.99	12.24
7	68.46	4.50	12.61	68.21	4.32	12.78
9	65.59	5.46	13.50	65.71	5.26	13.29
10	72.06	4.43	10.96	71.92	4.38	11.22
12	59.64	5.26	16.37	59.55	5.49	16.18
13	64.61	4.61	14.35	64.39	4.53	14.45
14	67.22	4.56	11.61	67.10	4.40	11.79
16	67.22	4.56	11.61	66.99	4.51	11.41

Table(7) Antibacterial and antifungal activity of the prepared compounds

Compd. No.	Gram positive	Gram negative	Candida albicans Fungi
	Staphylococcus aureus	*Pseudomonas aeruginosa*	
1	+	-	-
2	+	+	+
3	+	-	+
4	-	-	-
5	++	-	+
6	+++	++	+
7	++	+	+
8	+	-	+
9	+++	++	+
10	+	-	-
12	+	-	-
13	+	+	+
14	++	+	+
15	+++	++	+
16	++	+	+

Key to symbols: Inactive = (-) inhibition zone < 6mm
Slightly active = (+) inhibition zone 6-9 mm
Moderately active = (++) inhibition zone 9-12 mm
Highly active = (+++) inhibition zone > 12mm

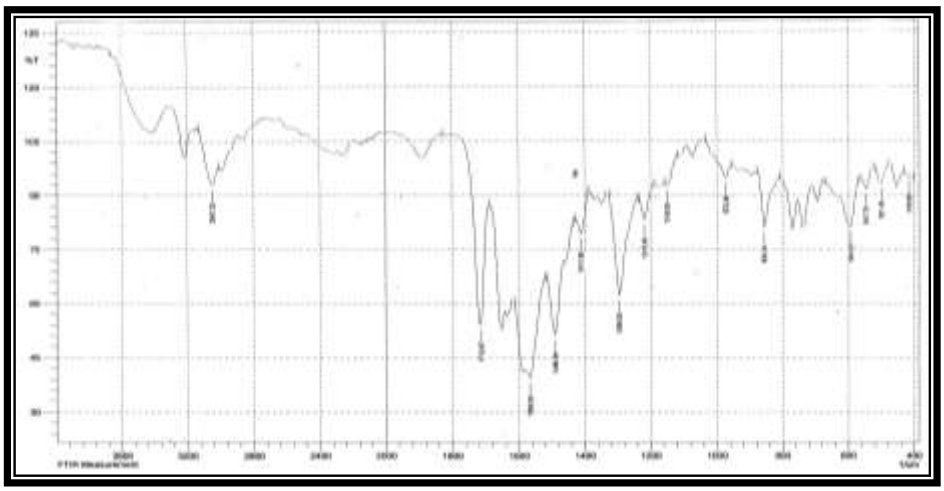


Fig.(1) FTIR spectrum of compound [1]

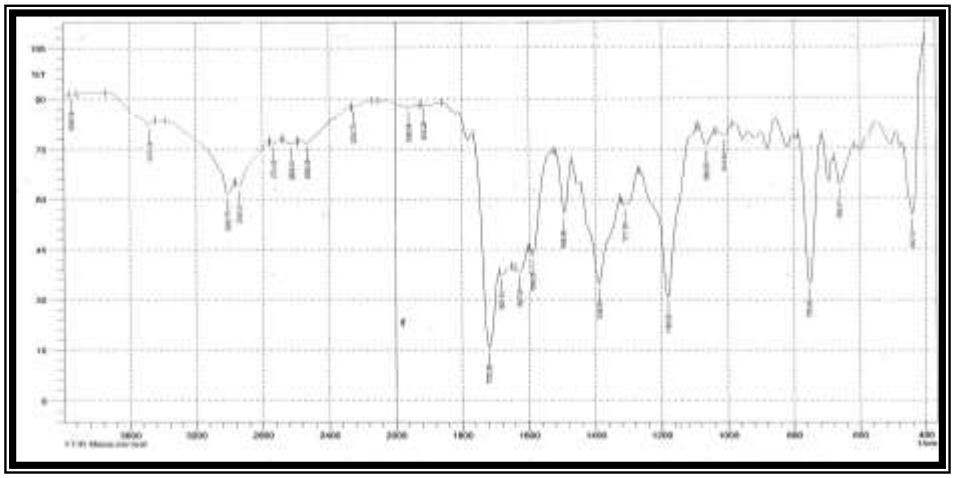


Fig. (2) FTIR spectrum of compound [8]

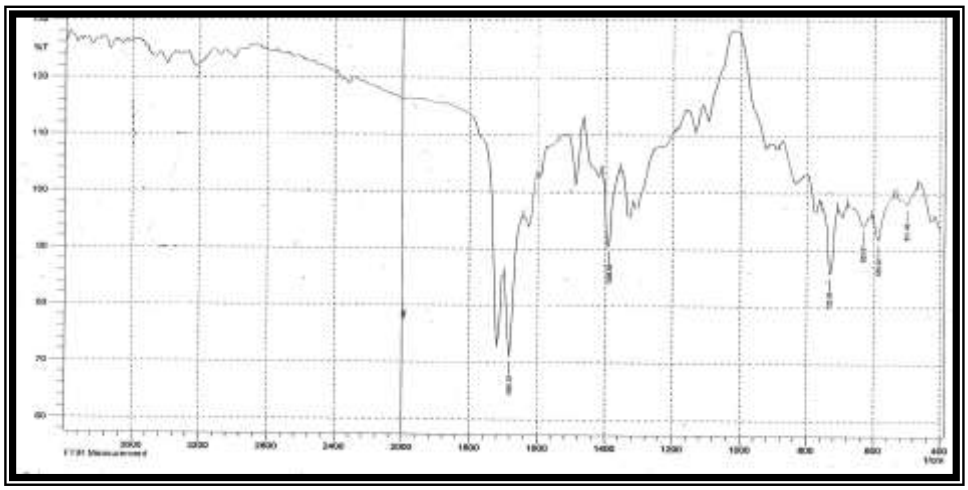


Fig. (3) FTIR spectrum of compound [9]

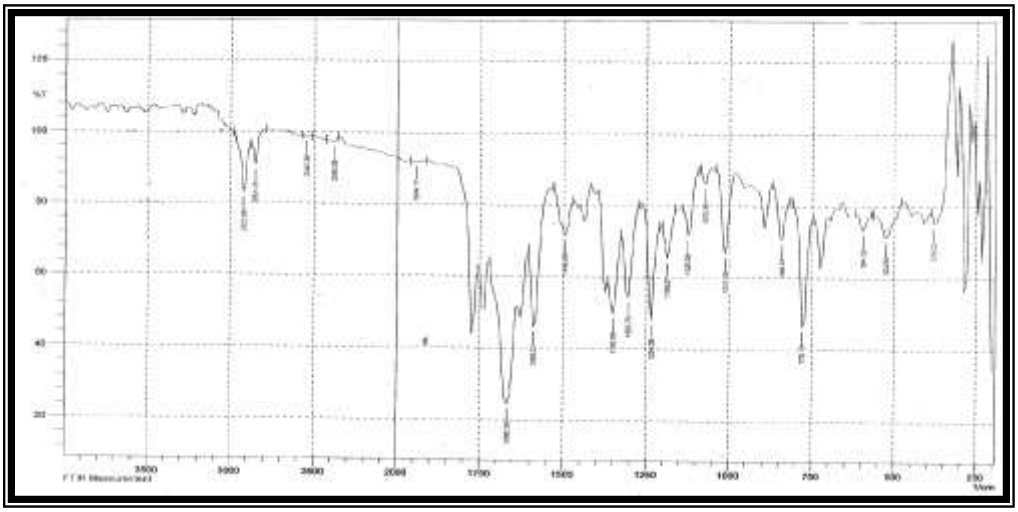


Fig.(4) FTIR spectrum of compound [10]

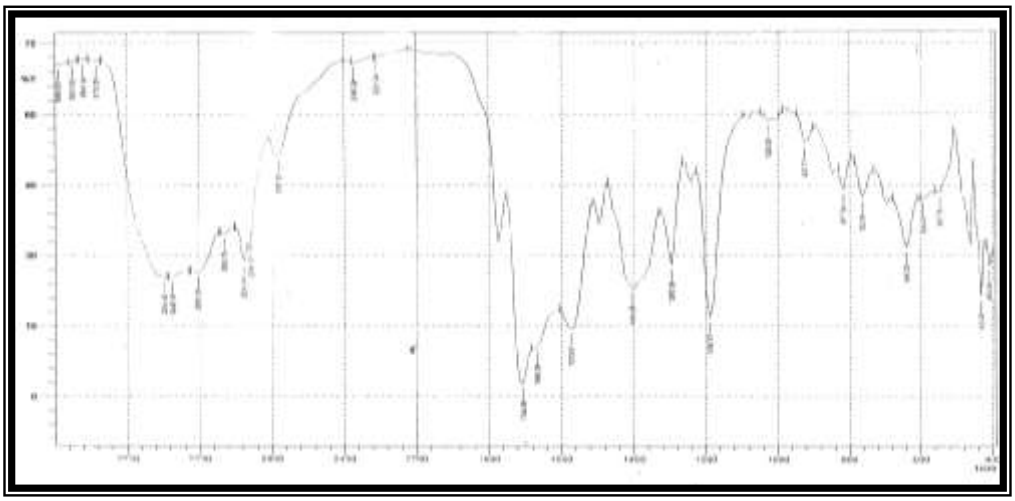


Fig. (5) FTIR spectrum of compound [12]

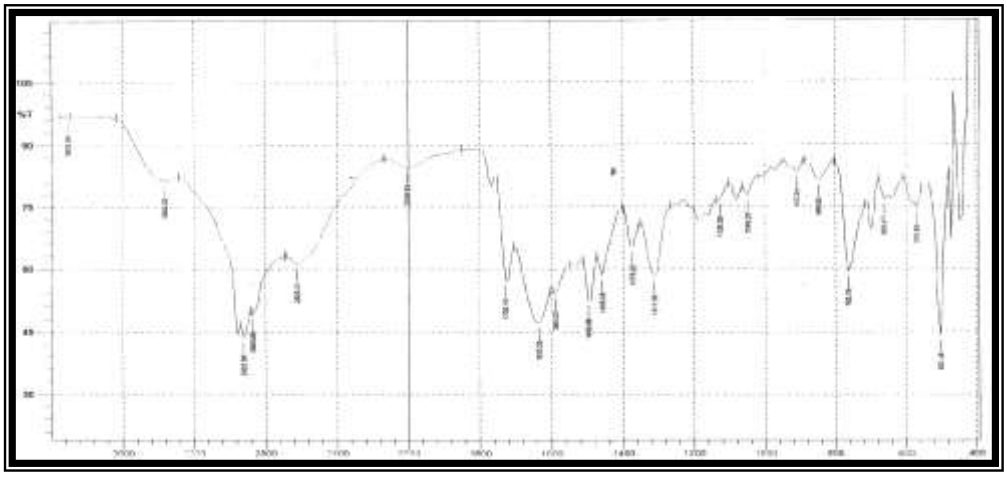


Fig. (6) FTIR spectrum of compound [13]

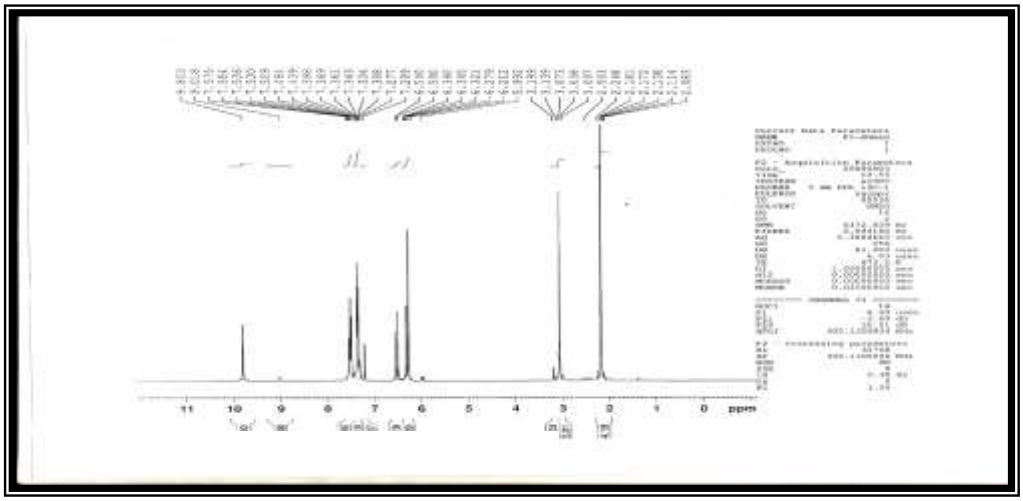


Fig. (7) H-NMR spectrum of compound [1]

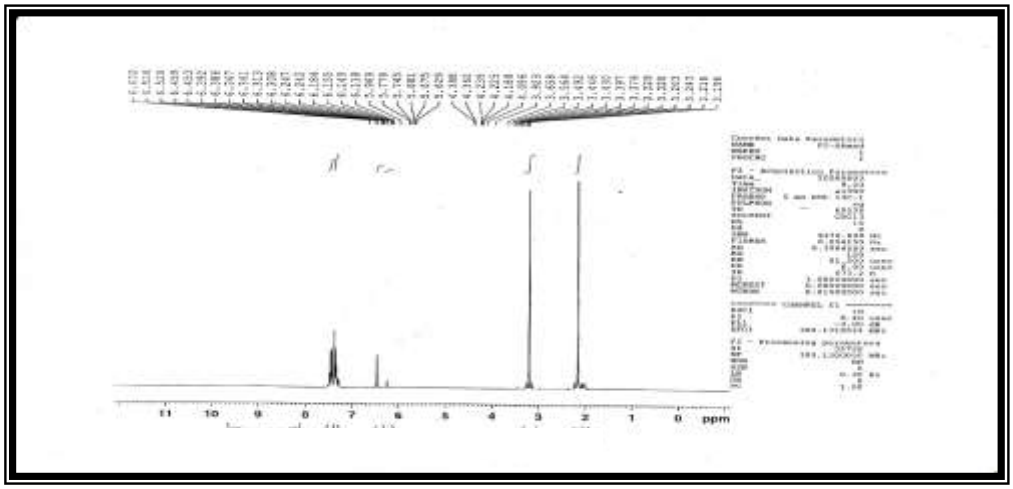


Fig. (8) H-NMR spectrum of compound [5]

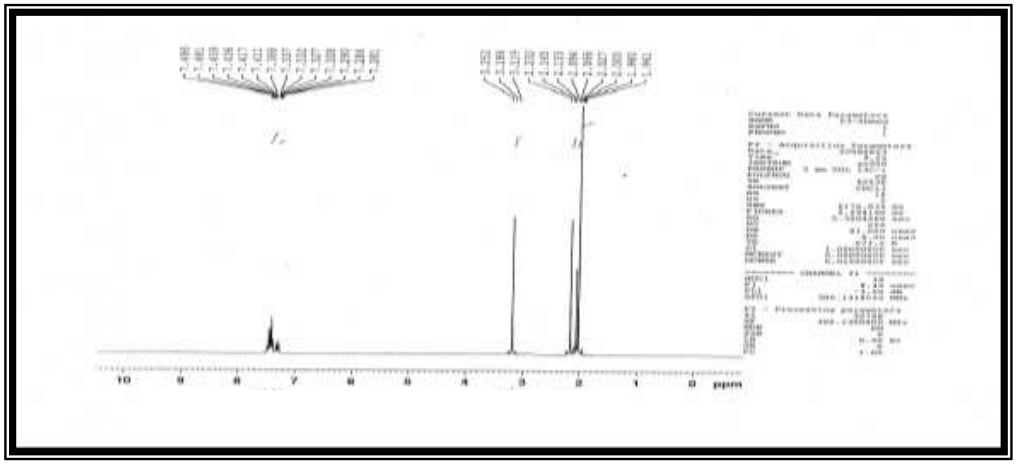


Fig. (9) H-NMR spectrum of compound [9]

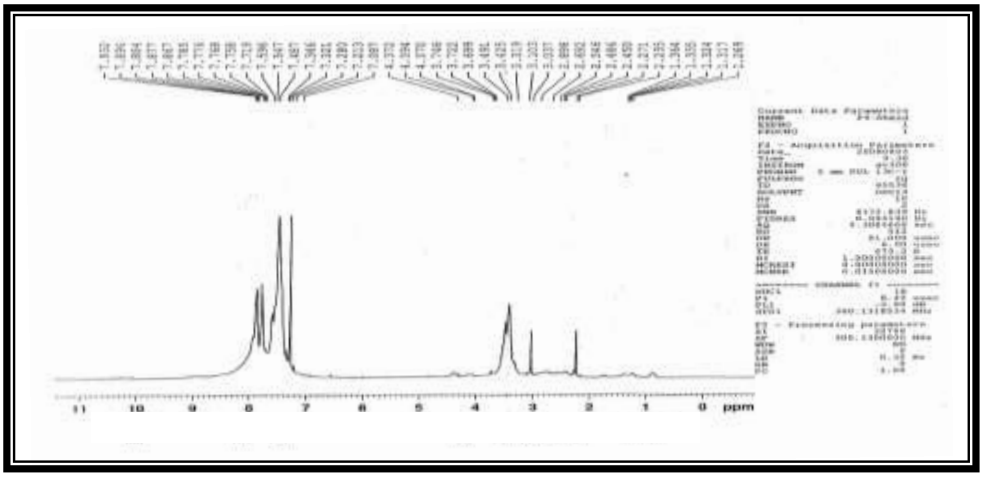


Fig. (10) H-NMR spectrum of compound [13]

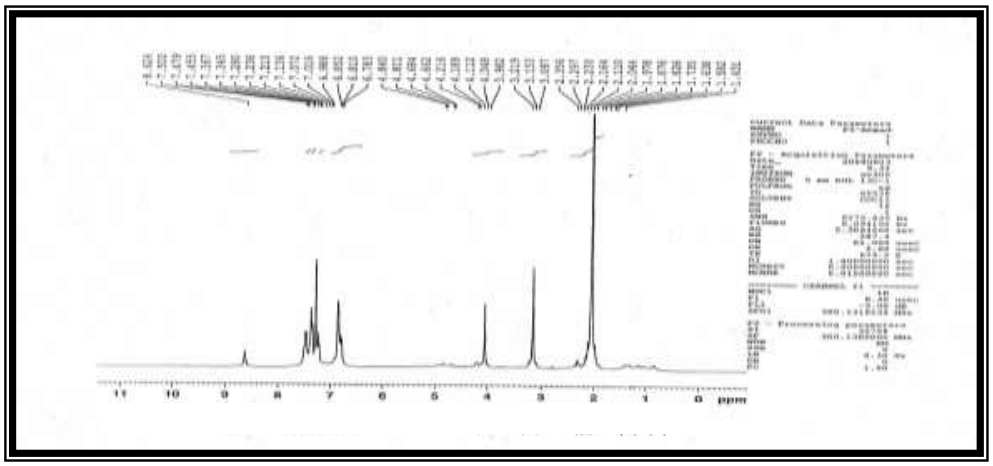


Fig. (11) H-NMR spectrum of compound [14]

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