World Journal of
Experimental Biosciences

Volume 4, Number 2: 98-107
ISSN: 2313-3937
2016

Research article

Identification of new heterocyclic compounds synthesized from 4-aminopyridine and evaluation their antibacterial effect

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ABSTRACT

Diazotization of pyridine-4-amine (1) to form diazonium chloride salt (2): pyridine-4-diazonium chloride which undergo coupling reaction with various anions in DMF, and EtOH to give: 2-(pyridine-4-yldiazonium) isoindoline-1,3-dione (3), 2-(pyridine-4-yldiazonium) isoindoline-1-one-3-sulphoxide (4), and ethyl 2-(pyridine-4-yldiazonium) acetate (5). The last ester was converted to the acid hydrazide: 2-(pyridine-4-yldiazonium) acetohydrazide (6) which was condensed with 4-chlorobenzaldehyde in absolute ethanol and some drops of glacial acetic acid to give the Schiff's base: *N* -_(4-chlorobenzylidene) -2-(pyridine-4-yldiazonium) acetohydrazide (7). Schiff's base was reacted with benzoic acid derivatives (2-aminobenzoic acid, 2-hydroxybenzoic acid, and 2-mercaptobenzoic acid) in ethanol to give: *N*-[2-(4-chlorophenyl)-4-oxo-1,2-dihydroquinazoline-3-(4*H*)-yl]-2-(pyridine-4-yldiazonium)acetamide (8), *N*-[2-(4-chloro-phenyl)-4-oxo-2*H*-benzo[*e*][1,3]oxazine-3-(4*H*)-yl-2- (pyridine-4-yldi azonium)acetamide (9), and *N*-[2-(4-chlorophenyl)-4-oxo-2*H*-benzo[*e*][1,3]thiazine-3-(4*H*)-yl]-2-(pyridine-4-yldiazonium)acetamide (10). The spectral methods of the prepared compounds were characterized by FT.IR, ^{1}HNMR (for compounds (4, and 10), and Uv-Vis (for compounds (3,4,8,9, and 10), besides melting points were recorded and the purity was checked through T.L.C. technique. Antibacterial activity for some of the synthesized compounds was screened.

Keywords: 4-Aminopyridine, Acid hydrazide, Diazonium salt, Dihydroquinazoline, Heterocyclic compounds, Oxazine, Schiff's, Thiazine.

Citation: Tawfiq MT. (2016) Identification of new heterocyclic compounds synthesized from 4-aminopyridine and evaluation their antibacterial effect. *World J Exp Biosci* **4**: 98-107.

Received April 17, 2016; Accepted June 9, 2016; Published July 8, 2016.

INTRODUCTION

Heterocyclic synthesis has emerged as a powerful technique for generating new chemical entities useful for drug discovery [1]. Synthetic heterocyclic compounds especially containing hetero atom N, O, S have enormous potential primarily as agrochemicals, drugs [2]. Isoindoline-1,3-dione derivatives have structural feature –CO-N(R)-CO- and an imide ring which help them to be biologically active and pharmaceutically useful [3]. Phthalimides have received much attention due to their anti bacterial, anti fungal [4], analgesic [5], anti-tumor [6], anti-HIV activities [3], anti-inflammatory [7], antioxidant, anti-proliferative [8], acetyl cholinesterase inhibitors [9] and inhibitor of human

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neuronal nitric oxide synthase [10]. 1,2- Dihydroquinazolinone (DHQZ) derivatives are used as chemotherapeutic agents for the treatment of diseases resulting from different microorganisms and now there has been a major expansion in the number of quinazolinone derivatives as drugs [11]. DHQZ is a privileged scaffold because of its extensive pharmacological activities including anti-bacterial, anti-fertility, anti-tumor, anti-fungal, analgesic efficacy [12], hypnotic, sedative, analgesic, anticonvulsant, anti-tussive, antibacteria, anti-diabetic, anti-inflammatory, and anti-tumor agents [13]. In addition to this, some therapeutic agents containing the structure of quinazolinone have been on the market or are in clinical trials for the treatment of cancer [14]. 1,3- Oxazine derivatives have played a crucial role in the theoretical development of heterocyclic chemistry and are also used extensively in organic synthesis[15]. Due to the rapid development of bacterial resistant to antibacterial agents, it is vital to discover novel scaffold for the design and synthesis of the new antibacterial agents to help in the battle against pathogenic microorganisms [16]. In the last few years oxazine derivatives have proved to be valuable synthetic intermediates and also possess important biological activities like sedative, analgesic, antipyretic, anti conversant, anti-tubercular, anti-tumor, anti-malarial, anti-fungal, anti-bacterial, anti-viral, and analgesic activity. Due to the rapid development of bacterial resistant to antibacterial agents, it is vital to discover novel scaffold for the design and synthesis of the new antibacterial agents to help in the battle against pathogenic microorganisms [17].
1,3- Thiazine derivatives are used in various organic synthesis and transformation as reaction intermediates. They have been used as anti tubercular, anti bacterial, anti microbial, anti tumor, insecticidal, fungicidal, herbicidal agent, tranquilizers anti radiation agents and various dyes [18]. The study aims to prepare and characterize some of new heterocyclic derivatives starting from 4-amino- pyridine by using some strategies. The methods used offer some advantages such as good yields, simple procedure, low cost, and ease of work up, and were expected to have a biological activity.

EXPERIMENTAL

Instruments

All melting points are uncorrected in degree centigrade and determined on Gallen kamp electric melting point apparatus. FTIR spectra were recorded (KBr disk) on a SHIMADZU FTIR 8300 spectrophotometer in the range (4000 - 400)/ cm. UV/Vis spectra were recorded on UV /Vis Varian Uv-Cary-100 spectrophotometers in DMSO as solvent. HNMR spectra were determined on a BRUKER-400 MHz operating 300 MHZ spectrometer with tetramethyl-silane (TMS) as an internal standard, and the chemical shifts are in δ ppm using deuterated dimethylsulfoxide (DMSO-d6) as a solvent, measurements were done in Chemistry Department, AL-Al-Bayt University-Jordan. The reactions progress was monitored by thin-layer chromatography (TLC) using Fertigfollen precoated sheets type Polygram Silg, and the plates were developed with iodine vapor. The biological activity was performed by environmental laboratory, University of Baghdad, Baghdad, Iraq.

Synthesis of diazonium salt (2) [19]

Pyridine-4-amine (1) (0.02 mol, 1.8822 gm) was added to hydrochloric acid (10 ml, HCl +10 ml water) and cooled in ice-salt bath at (0-5) 0C with stirring and then added to cold sodium nitrite solution (1.38 gm in 5 ml) water was added slowly with stirring at 5 ^{0}C for 1 h to form diazonium salt. The mixture was diluted with water, neutralized by addition of ammonia.

Synthesis of 2-(pyridine-4-yldiazonium) isoindoline-1, 3-dione (3) [20]

To get stirred solution of formed, diazonium chloride salt (2) was added gradually (0.02 mol, 3.382 gm) of sodium phthalimide in DMF (20 ml) and stirring was continued for 30 min at 5 ^{0}C. The reaction temperature was then gradually raised to room temperature, then to 50 ^{0}C and after 15 min a clear yellow solution was obtained. The yielded mixture was refluxed with continuous stirring and then left to crystallize. Crystals were collected by filtrations, washed with 2% sodium bicarbonate solution and then with excess distilled water and re-crystallized from ethanol to give bright yellow crystals.

Synthesis of 2-(pyridine-4-yldiazonium) isoindoline-1-one-3-sulphoxide (4) [21]

To get stirred solution of formed diazonium chloride salt (2) was added gradually (0.02 mol, 4.103 gm) of sodium saccharin in DMF (20 ml) and stirring was continued for 30 min at 5 0C. The reaction temperature was then gradually raised to room temperature, then to 40-50 ^{0}C and after 15 min a clear yellow solution was obtained. The solution was then refluxed with continuous stirring, and then left to form crystals. Crystals were collected by filtrations, washed with (2%) sodium bicarbonate solution then with excess distilled water and re-crystallized from ethanol to give pale yellow crystals.

Synthesis of ethyl 2-(pyridine-4-yldiazonium) acetate (5) [22]

To get a stirred solution of formed diazonium chloride salt (2) was added gradually a solution of 0.02 mol, 1.76 gm of ethyl acetate and 0.02 mol, 1.64 gm of sodium acetate into 25 ml ethanol with stirring for 30 min at 5 0C. The reaction temperature was then gradually raised to room temperature. The resulted mixture was refluxed with continuous stirring then cooled to room temperature. The formed precipitate was filtered, washed with (2%) sodium bicarbonate solution then with distilled water, dried and purified by re-crystallization from ethanol to give light brown crystals.

Synthesis of 2-(pyridine-4-yldiazonium) acetohydrazide (6) [23,24]

To get a solution of 0.006 mol, 1.159 gm of ethyl 2-(pyridine-4-yldiazonium) acetate (5), absolute ethanol (20 ml) was added (0.01 mol, 0.5 gm, 0.5 ml) to hydrazine hydrate (90%). The mixture was refluxed under anhydrous conditions for 6-7 h. Excess solvent was distilled off. The resulting solid was separated out on cooling filtered and re-crystallized from ethanol. The compound was separated as shining light yellow needle shaped crystals.

Synthesis of N -_(4-chlorobenzylidene)-2-(pyridine-4-yldiazonium) acetohydrazide (7) [25]

Schiff's bases (7) have been prepared accordance to standard method. In absolute ethyl alcohol (20 ml), solution of 2-(pyridine-4-yldiazonium) acetohydrazide (6) (0.005 mol, 0.895 gm) were slowly added to a solution of 4-chlorobenzaldehyde (0.005 mol, 0.702 gm) + 2 drops of glacial acetic acid in absolute ethanol (20 ml). After stirring for 1h, the mixture was refluxed for 4-5 h with stirring. The mixture was filtered after cooling and washed with cold ethanol and re-crystallized from ether.

Synthesis of N- [2-(4-chlorophenyl)-4-oxo- 1,2 -dihydroquinazoline-3-(4H)-yl] -2-(pyridine-4-yldiazonium) acetamide (8) [26]

To a solution of Schiff base N -_(4-chlorobenzylidene)-2-(pyridine-4-yldiazonium) acetohydrazide (7) (0.002 mol, 0.602 gm) in absolute ethanol (20 ml) was added slowly to the solution (0.002 mol, 0.274 gm) of 2-aminobenzoic acid into absolute ethanol (15 ml). The mixture was stirred for 1 h then the mixture was refluxed for 9 h with stirring. The reaction mixture was poured into crushed ice water. The separated crystals were filtered, washed with ethanol, dried and re-crystallized using ethanol.

Synthesis of N-[2-(4-chlorophenyl)-4-oxo-2H-benzo[e][1,3]oxazine-3-(4H)-yl -2-(pyridine-4-yldiazonium) acetamide (9) [27]

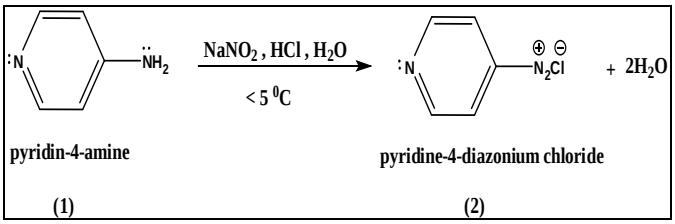
To a solution of schiff base: N -_ (4-chlorobenzylidene)-2-(pyridine-4-yldiazonium) acetohydrazide (7) (0.002 mol, 0.602 gm) in absolute ethanol (20 ml) was added slowly to solution (0.002 mol, 0.276 gm) of 2-hydroxybenzoic acid in absolute ethanol (15 ml). The mixture was stirred for 1 h then the mixture was refluxed for 9 h with stirring. The reaction mixture was poured into crushed ice water. The separated oxazine was filtered, washed with ethanol, dried and re-crystallized using ethanol.

Synthesis of N-[2-(4-chlorophenyl)-4-oxo-2H-benzo[e][1,3]thiazine-3-(4H)-yl]-2-(pyridine-4-yldiazonium) acetamide (10) [28]

To a solution of Schiff base: N -_(4-chlorobenzylidene)-2-(pyridine-4-yldiazonium) acetohydrazide (7) (0.002 mol, 0.602 gm) in absolute ethanol (20 ml) was added slowly to solution (0.002 mol, 0.308 gm) of 2-mercaptobenzoic acid in absolute ethanol (15 ml). The mixture was stirred for 1 h then the mixture was refluxed for 9 h with stirring. The reaction mixture was poured into crushed ice water. The separated thiazine was filtered, washed with ethanol, dried and re-crystallized using ethanol.

RESULTS and DESCUSION

The infrared study of the important methods in identification of absorbed peaks of the result functional groups effective which found within the structural formula of the compounds prepared. The difference in the intensity of the main functional groups of absorption peaks indication of the occurrence of interaction. Aromatic diazonium salt: pyridine-4-diazonium chloride (2) was obtained by diazotization of pyridine-4-amine (1) with NaNO2 in dilute hydrochloric acid according to a published procedure [19,29] (**Table 1**).



Scheme -1

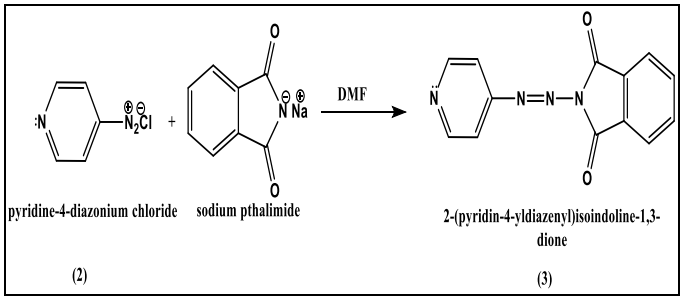
The suggested mechanism of the diazotization reaction is known [30,31]. Compound (2) represents a stable aryl diazonium ion source and is a class of nitrogen-containing compounds useful for synthetic transformations [32]. Diazonium ions are weak electrophiles, however, they undergo coupling with activated aromatic nuclei such as aryl amines, phenols and aromatic heterocyclic compounds. However, the careful control of the pH of the reaction medium is necessary for the success of the process [33]. It is well-known classical synthesis of aromatic diazoamino system is formed in the reaction between a diazonium cation and the nucleophilic nitrogen atom of an amine or amide. Usually, the diazonium salt involved is not isolated, and an acidic aqueous solution of this reagent is exposed directly to the amine at low temperature in the presence of an excess of base to neutralize the acid used for diazotation [34].

Table 1. Physical properties of the synthesized compounds.

Compo-und No.	Molecular formula	Molecular Weight (gm/mol.)	Yield %	M.P. C^0	Color
3	$C_{13}H_8O_2N_4$	252	74	127-129	Light yellow
4	$C_{12}H_8O_3N_4S$	288	69	117-120	Brown
5	$C_9H_{11}O_2N_3$	193	75	191-193	Light brown
6	$C_7H_9ON_5$	179	61	153-155	Yellow
7	$C_{14}H_{12}ON_5Cl$	301.5	54	173-175	Dark yellow
8	$C_{21}H_{17}O_2N_6Cl$	420.5	59	219-221	Yellow
9	$C_{21}H_{16}O_3N_5Cl$	421.5	55	235-237	Brown
10	$C_{21}H_{16}O_2N_5SCl$	437.5	56	241-143	Greenish brown

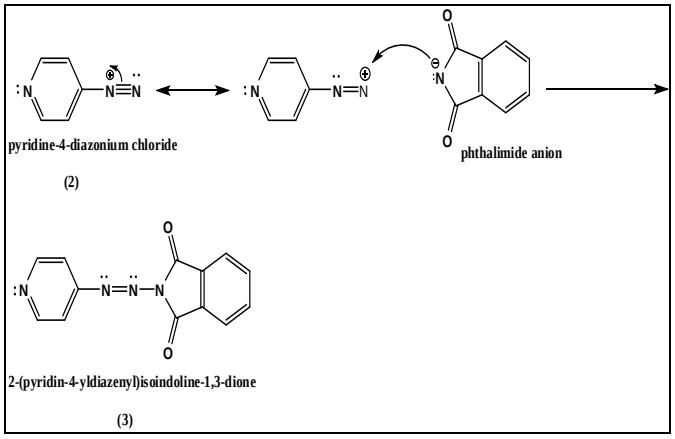
Nitrogen containing nucleophiles that are not amines are known as amine surrogates like phthalimide, which reacted with diazonium cations to give covalent diazo-compounds. This nucleophile (N -) can be reacted with electrophiles to produce an N-substituted phthalimide [35-38]. Among the bicyclic nitrogen heterocycles phthalimides which classified as cyclic imides are an interesting class of compounds with a large range of applications, their molecules contain an imide ring and the general structure (-CO-N(R)-CO-) [39].

These cyclic imides are an important functionality which have important biological effects similar or even higher than known pharmacological molecules and so their biological activity is being a subject of biomedical research [40,41]. The reaction of aromatic diazonium salt with sodium phthalimide (the first step in the Gabriel synthesis of amines) in DMF is a nucleophilic substitution reaction type second order (SN2) to form 2-(pyridine-4-yldiazonium) isoindoline-1,3-dione (3) via a straightforward SN2 displacement [42].



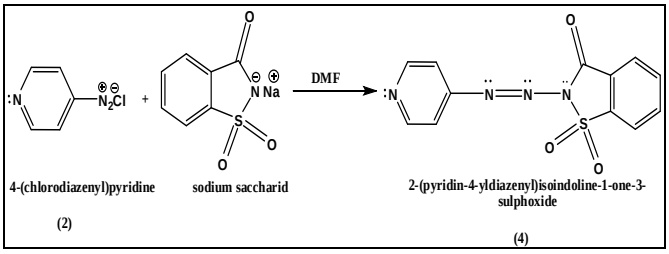
Scheme -2

The suggested mechanism of the reaction is shown in scheme 3 The FT.IR spectrum of compound (3), showed disappearance of (-NH2) stretching bands at υ (3437, 3379)/ cm, and (NH) bending at υ (1587)/ cm of the starting material, and appearance stretching bands of (C=O cyclic amide) at υ (1651)/ cm, (N=N trans azo) at υ (1586)/ cm, (**Table. 2**) (**Fig 1**).

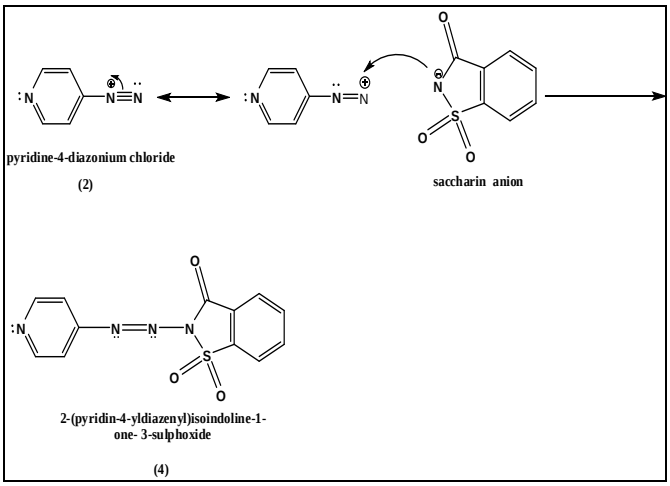


Scheme - 3

The artificial sweetener, saccharin, is an imide. Saccharin is approximately 500 times sweeter than sugar at one time, which represents the most important non caloric sweetener use in foods. At the present time, the most wide use non-caloric artificial sweetener is aspartame (NutraSweet). For the structure of aspartame [43], sodium saccharin reacted with aromatic diazonium salt in DMF to form: 2-(pyridine-4-yldiazonium) isoindoline-1-one-3-sulphoxide (4) via a straight forward SN2 nucleophilic substitution reaction [44]. The suggested mechanism of the reaction is shown in scheme 5. The FT.IR spectrum of compound (4), showed disappearance of (-NH2) stretching bands at υ (3437, 3379)/ cm, and (NH) bending at υ (1587)/ cm of the starting material and appearance stretching bands of (C=O cyclic amide) at υ (1659)/ cm, (N=N trans azo) at υ (1639)/ cm, and strong stretching band at υ (1356,1063)/ cm due to (S=O) group in cyclic sulfonamide (**Table 2**) (**Fig. 2**).

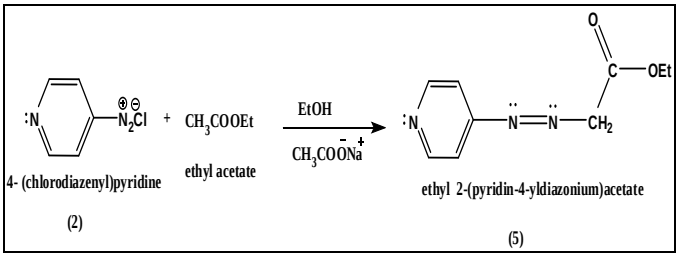


Scheme - 4



Scheme - 5

The 1HNMR spectrum of compound (4) shows the several characteristic chemical shifts; protons of pyridine ring at δ (7.736-7.887) ppm, and protons of benzene ring appeared at the range δ (7.457-7.647) ppm (Fig 9). However, such diazoamino couplings are frequently accompanied by side reactions e.g. (C -) couplings, leading to formation of product in a good yield [45]. Ethyl acetate suffered coupling reaction with aromatic diazonium salt in absolute ethanol in presence of sodium acetate to form the ester: ethyl 2-(pyridine-4-yldiazonium) acetate (5) via a straight forward SN2 nucleophilic substitution reaction [46].



Scheme - 6

The suggested mechanism of the reaction is shown in scheme 7. The FT.IR spectrum of compound (5), showed disappearance of (-NH2) stretching bands at υ (3437, 3379)/ cm, and (NH) bending at υ (1587)/ cm of the starting material and appearance stretching bands of C=O cyclic amide at υ (1765)/ cm, (N=N trans azo) at υ (1576)/ cm, (C-H aliphatic) at υ (2986,2947) (**Table 2**) (**Fig 3**).

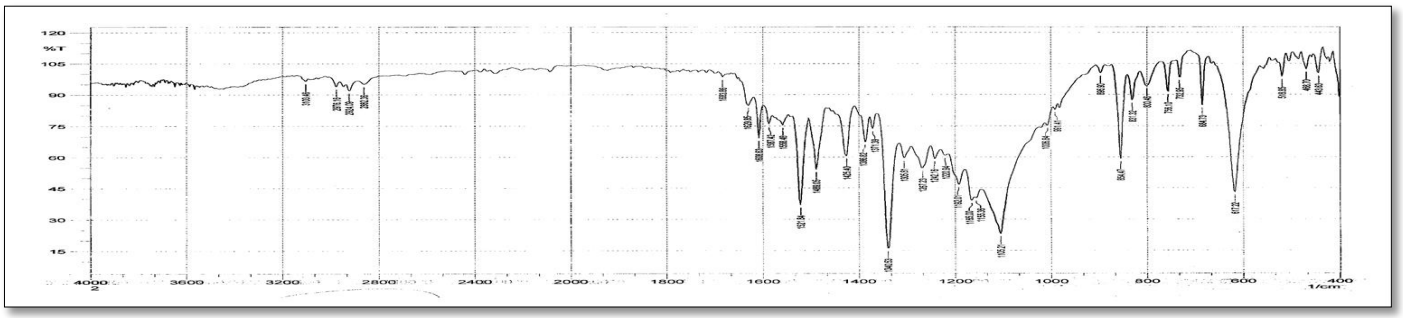


Fig 1. FT.IR spectrum of compound (3).

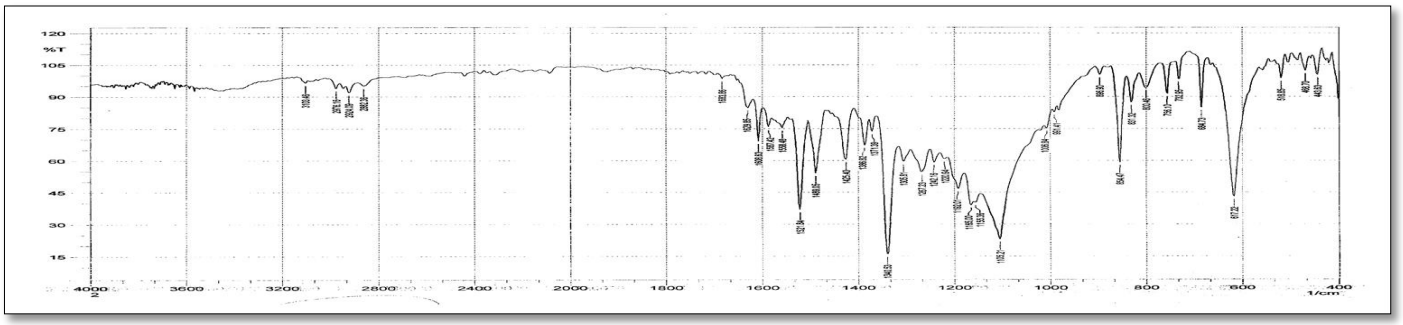


Fig 2. FT.IR spectrum of compound (4).

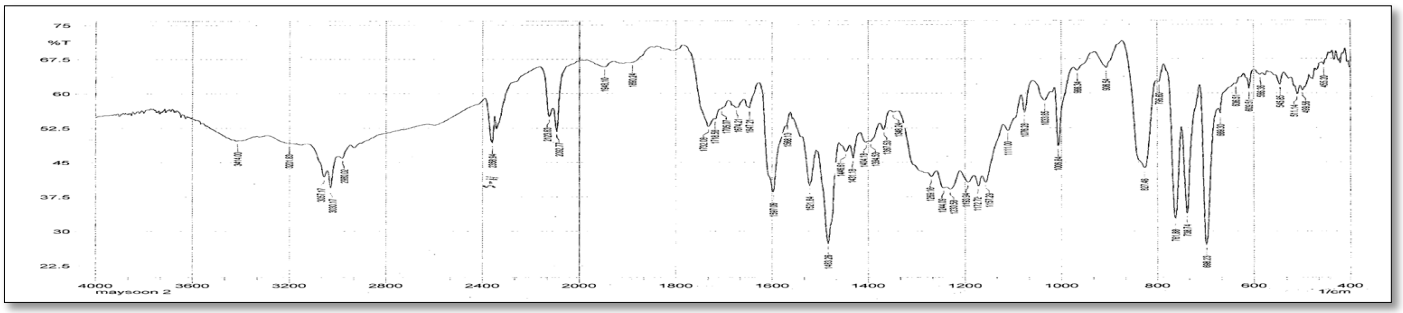
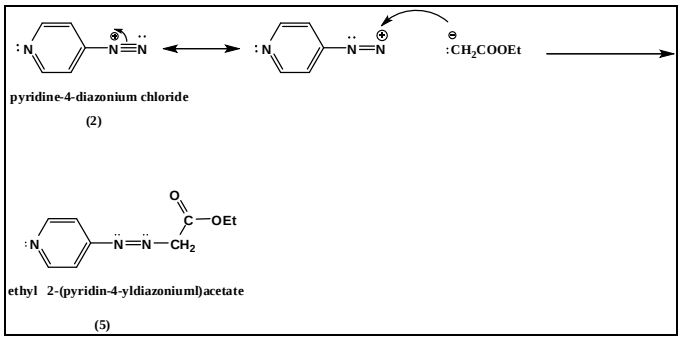


Fig 3. FT.IR spectrum of compound (5).

Table 2. FT.IR spectral data of the synthesized compounds (3-10).

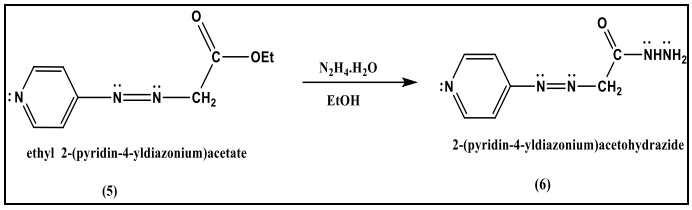
Comp.	ᵛCH aro.	ᵛCH ali.	ᵛC=O	ᵛS=O	ᵛNH₂ , NH	ᵛC=C aro.	ᵛN=N trans azo	Others ᵛ
3	3054	-	1651	-	-	1534, 1589	1586	C-N 1254
4	3082	-	1659	1356, 1063	-	1556, 1585	1639	C-N 1269
5	3068	2986, 2947	1765	-	-	1529	1576	C-O 1247
6	3057	2976	1710	-	3443-3351	1527	1579	N-H bend 1625.
7	3054	2926, 2859	1684	-	3346	1553	1563	C=N imine 1675 C-Cl 856 N-H bend. 1565
8	3082	2924	1763	-	3418	1567	1527	C-N 1253 C-Cl 867 N-H bend. 1622
9	3091	2982, 2856	1767	-	3447	1585	1536	C-N 1251 C-O 1237 C-Cl 871 N-H bend. 1627
10	3064	2931	1735	-	3422	1559	1531	C-N 1254 C-S 1271 C-Cl 874 N-H bend. 1623

The reaction of hydrazine hydrate with ester is one of the most common reaction to synthesize the acid hydrazide , it is a tetrahedral nucleophilic substitution reaction[47,48] .



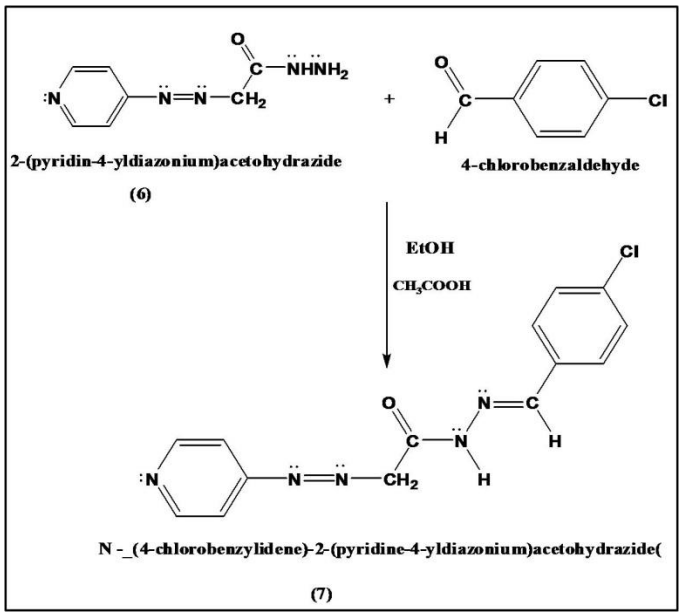
Scheme - 7

The mechanism of this reaction is known [47]. FT.IR spectra of the hydrazide derivative compounds (6) showed



Scheme - 8

the appearance of the characteristic absorption bands in the region υ (3443-3351) cm-1 due to the asymmetric and symmetric stretching vibration of the (-HN-NH2) group , and disappearance of absorption bands at υ (1765) cm-1 due to the stretching vibration of carbonyl group of ester , while showed appearance of absorption band at υ (1710) cm-1 of the compound (5) due to stretching vibration of amide II band [47] (**Table 2**) (**Fig 4**). The treatment of acid hydrazides (6) with 4-chlorobenzaldehyde afforded the corresponding Schiff base that was identified as compound (7) on the basis of its spectral data (scheme-8).



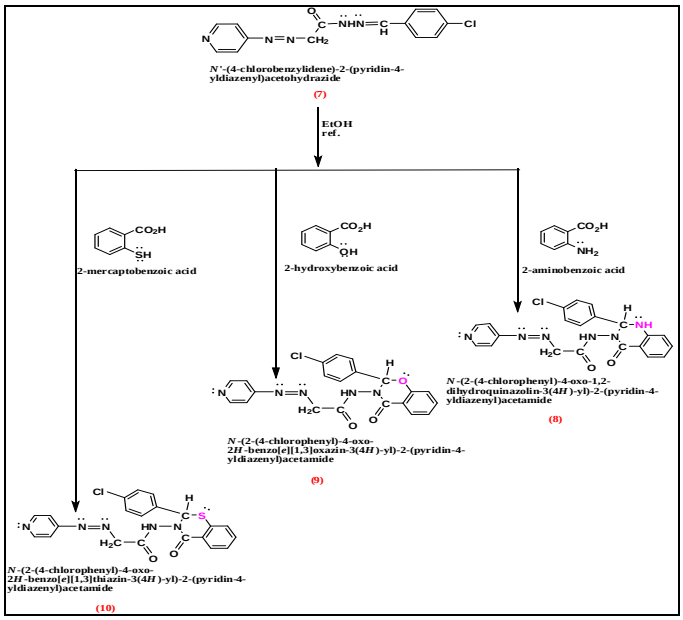
Scheme - 9

The titled compounds were synthesized from the condensation reaction of equimolar quantity of acid hydrazide (6) with 4-chlorobenzaldehyde in absolute ethanol and drops of glacial acetic acid; It is the major method to prepare Schiff bases [49-51]. The mechanism of this condensation is known and is acid catalyzed [52]. The FT.IR spectrum of compound (7), showed disappearance of (-NH2) stretching band, and appearance stretching band of imine (C=N) at υ (1675) cm-1 , and stretching band of aromatic (C-Cl) at υ (856) cm-1 (**Table. 2**) (**Fig 5**).

For a long time imines have been used successfully in the synthesis of nitrogen containing heterocyclic [53]. Guinazoline (8), oxazine (9), and thiazine (10) were synthesized by refluxing equimolar amounts from the imine (7) with benzoic acid derivatives in absolute ethanol. Cyclization occur where functional group in (2-aminobenzoic acid, 2-hydroxybenzoic acid and 2-mercaptobenzoic acid) attack as a nucleophile the carbon of (C=N) bond [54,55]. These compounds were characterized by FT.IR, 1HNMR spectra, besides the TLC and physical properties (**Table 2**).

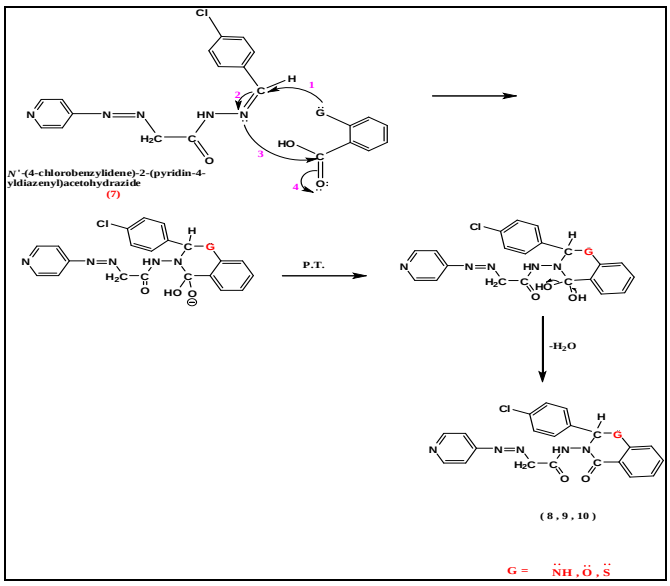
The FT.IR spectrum of compounds (8,9, and 10), showed the appearance of stretching band of carbonyl group at υ (1767-1735) cm-1 due to Guinazoline , oxazine , and thiazine rings and this was the most characteristic evidence for the success of cyclization step.

The FT.IR spectra of compounds (8,9, and 10), showed disappearance of (C=N) stretching band of imine, and appearance stretching band at υ (1237) cm-1 due to (C-O) bond in oxazine ring , and stretching band at υ (1271) cm-1 due to (C-S) bond in thiazine ring, (table-2) (figs.-6-8). The 1HNMR spectrum of compound (10) (**Fig.10**) shows the following characteristic chemical shifts (DMSO-d6) ppm., Protons of methylene (CH2) appeared at δ(2.046), Proton of methine (CH) appeared at (δ 2.467), Proton of (NH) of secondary amide group appeared at(δ 3.301); Protons of aromatic rings appeared at the range δ (7.436-8.133) as a multiple overlapping peaks.



Scheme 10

The proposed mechanism of this reaction is shown in scheme 11, UV-Vis absorption peaks values for compounds (3,4,8,9, and 10) were shown in (Table 3). The physical properties of all synthesized compounds are shown in (Table 1).



Scheme 11

Table 3. Ultra violate (UV)- Visible spectral data for some synthesized compounds.

Compounds No.	λMax (nm)
3	236
4	298 , 306
8	345 , 368
9	329 , 361
10	340 , 359

Microbiological examination

The disc diffusion method was used for study the antibacterial activity in this work. The prepared compounds (3,4,8,9, and 10) were assayed for antimicrobial activity in vitro against Gram negative bacteria (*Escherichia coli*) and Gram positive bacteria (*Staphylococcus aurous*). The sterilized petri dishes and agar were prepared by autoclaving for 15 min at 121 ^{0}C. The solvent DMSO was used for dissolving the compounds. Both bacteria were inoculated onto sterile plates and incubated at 37 ^{0}C for 24 h. The various prepared compounds which were examined cause inhibition zones. **Table 4** shows results of the initial examination tests. Biological effectiveness test showed that prepared compounds sulpher (S) have high antibacterial effect on both used bacteria (*E. coli* and *S. aureus*). In case of *S. aureus*, compounds (4,8and 9) showed slightly anti-bacterial activity, and compound 10 showed highly activity, while compound 3 showed no activity. For *E. coli,* compound 9 have no effect on this bacteria because this bacteria is highly resistant to wide spectrum of antibiotic, their slim polysaccharides blocks antibiotics from enter the bacterial cells and also there are genetic factor, while compounds 3, 4, and 8 have no effect on this bacteria, compound 10 showed the highest antibacterial activity.

Table 4. Antimicrobial activity of some synthesized compounds. **-,** no inhibition = inactive; **+,** 5-10mm = slightly active; **++,** 11-20 mm = moderately active.

Comp. No.	*Escherichia coli*	*Staphococcus aureus*
3	+	-
4	+	+
8	+	+
9	-	+
10	++	++

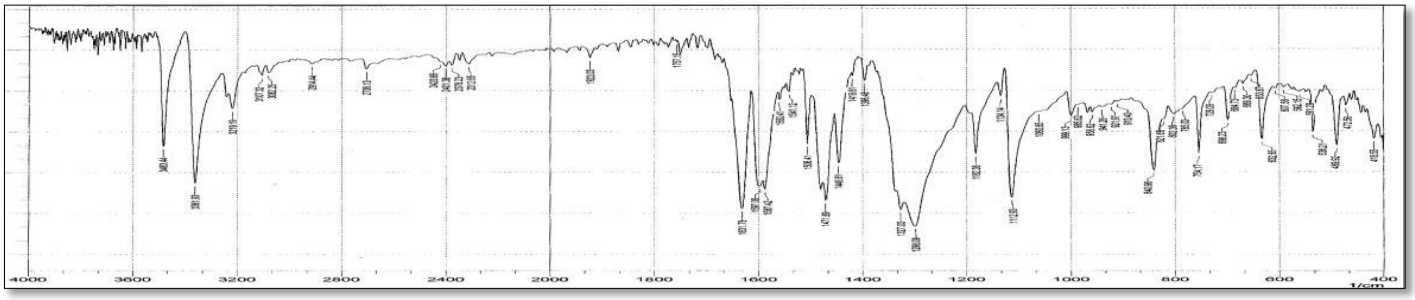


Fig 4. FT.IR spectrum of compound (6).

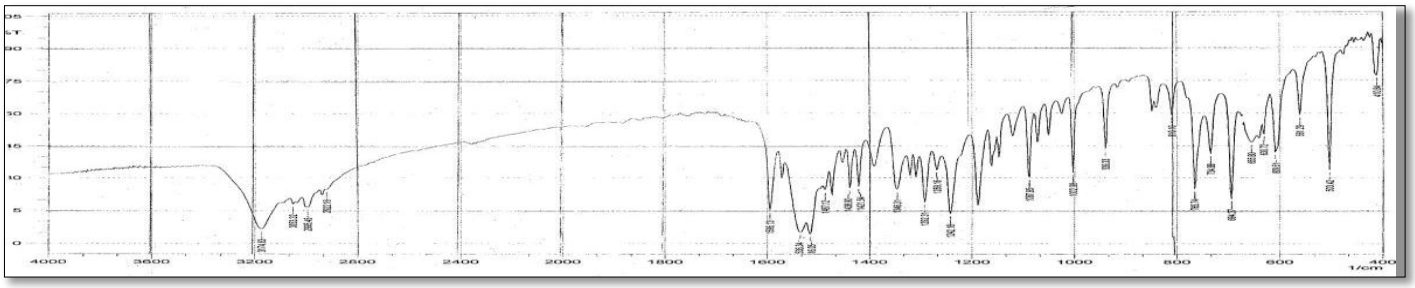


Fig 5. FT.IR spectrum of compound (7).

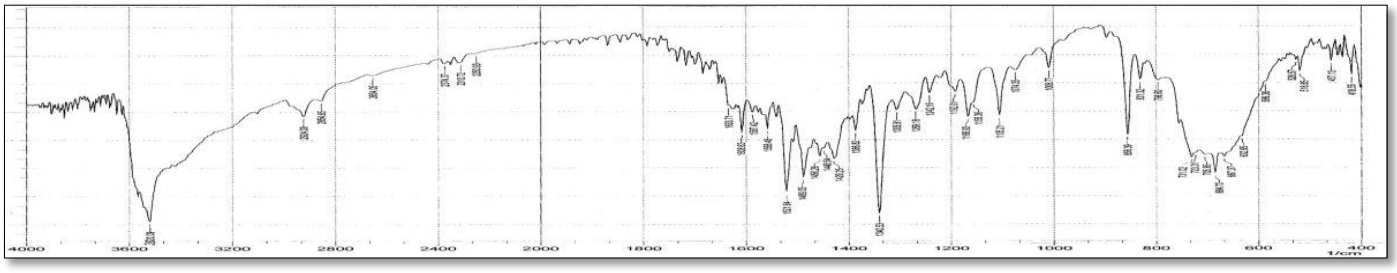


Fig 6. FT.IR spectrum of compound (8).

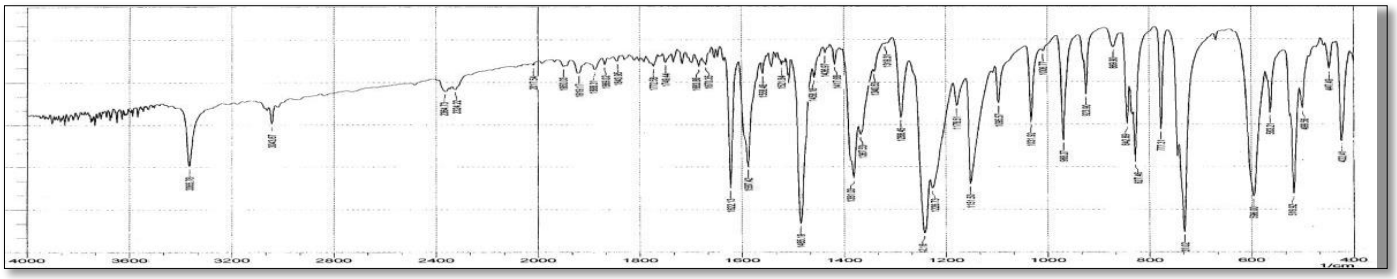


Fig 7. FT.IR spectrum of compound (9).

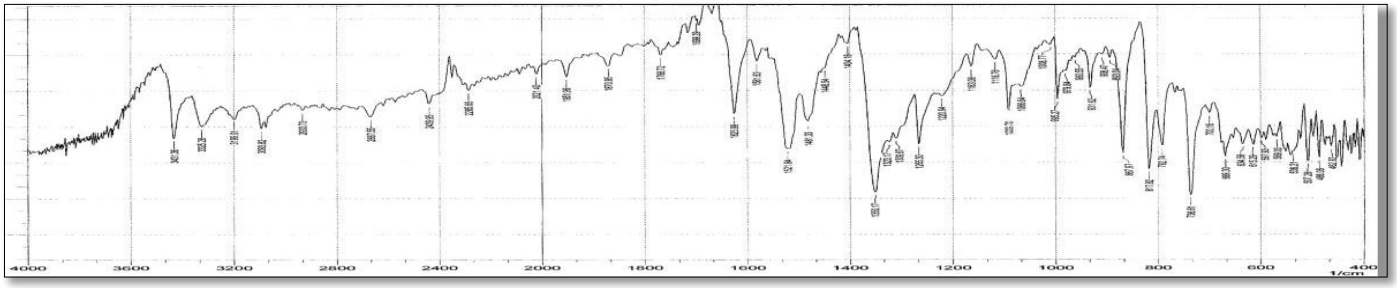


Fig 8. FT.IR spectrum of compound (10).

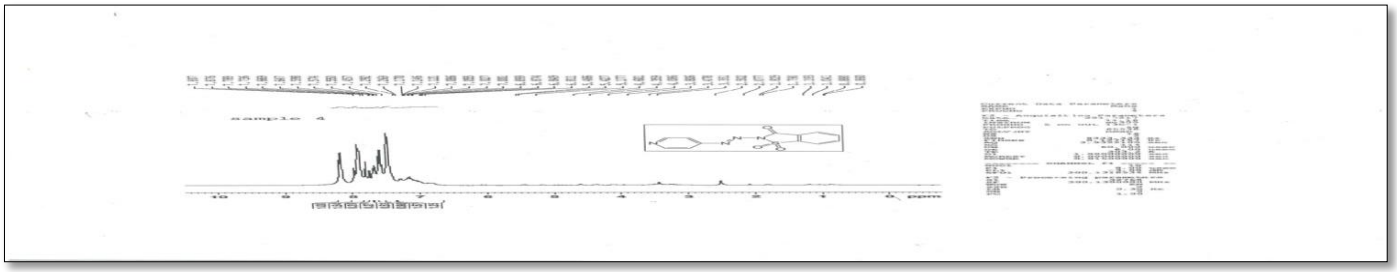


Fig 9. [1]HNMR spectrum of compound (4).

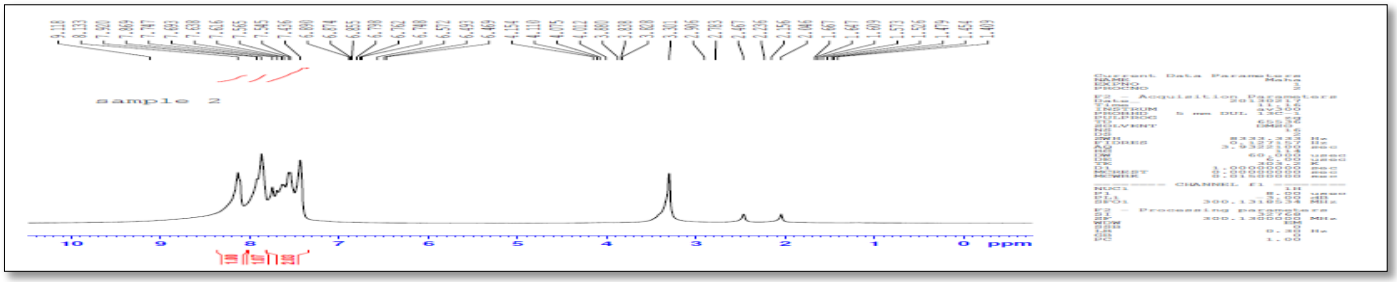


Fig 10. [1]HNMR spectrum of compound (10).

Conflict of interest

The authors declare that they have no conflict of interests.

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