Synthesis and characterization of some new heterocyclic compounds with studying the biological activityfor some of them.

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Abstract:

A series of new compounds including heterocyclic units have been synthesized. The chemical structures for these compounds were characterized by using FT-IR ,H-NMR, spectroscopy and the melting points were recorded, the purity were checked and the end of reaction by TLC with evaluated the biological activity for some of them.

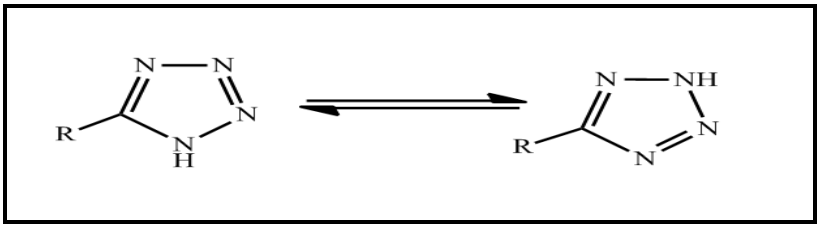
Keywords : Heterocyclic compounds, Schiff base, oxazepines.

Inroduction :

The azole moiety is an important and frequent insecticidal, agrochemical structural feature of many biologically active compounds[1-3]. Also, 1,3,4-oxadiazoles exhibit relevant biological properties and a wide varieties of applications, in particular as active compounds in both medicine and agriculture [4]. Most of the aromatic Schiff bases are sparingly soluble in water, while solubility of those having carbohydrate moiety is increased [5] .

Biologically , Shiff's bases having gained importance in medicinal and pharmaceutical fields due to a broad spectrum of biological activities like anti-inflammatory,analgesic and antimicrobial[6]. Schiff's bases undergo addition reactions of azomethian, the reagents add to polarized double bond of imine group (C=N), therefor nucleophilic reagents attack the carbon atom of the azomethian linkage[7], like Alkyl halid, Carboxylic acid chloride, Grignared reagents, Hydrogenation and Cyclic anhydride .

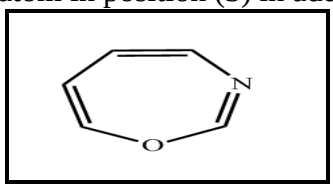
Tetrazoles are class of synthetic organic heterocyclic compounds consisting of five-member ring of four nitrogen and one carbon atom [8]. Although a great deal of the scientific literature concerning tetrazoles is in the area of medicinal chemistry, tetrazoles have also found use in other biological and non-biological applications. In agriculture tetrazoles serve as plant growth regulators, as herbicides and as fungicides [9] .



Two tautomers of tetrazole.

The simplest is tetrazole itself CN_4H_2.It is white to pale yellow crystalline solid with weak characteristic odour, soluble in water and alcohol. It is acidic in nature due to presence of four nitrogen atoms.

1,3-Oxazepine is unsaturated seven-membered hetrocycle containing oxygen atom in position (1), nitrogen atom in position (3) in addition of five carbons[10].



1,3-Oxazepine structure

Oxazepine derivative introduced in 1965 for use in relief of the psychoneuroses characterized by anxiety and tension[11]. Oxazepine derivatives showed various biological activities such as antibacterial and inhibitor for some enzymes action, some of oxazepine derivatives are used in another applied fields[12],

For a long time, the synthesis of 1,3- and 1,4-oxazepine rings was based on two limited classical types of reactions, the first reaction is called Valence-bond isomerization which is carried out via irradiation of polyaryl pyridine Noxides.This irradiation results in ring expansion to 1,3-oxazepine in high yield and some deoxygenation to the parent amines[13]. The second reaction is called Enamines condensation which is carried out by reaction of Erythro 1,2-diphenyl-2-phenylaminoethanol with dimethyl acetylene dicarboxylate in methanol at room temperature to give a mixture of the Michael adduct and tetrahydro-1,4-oxazepin-7-one[13,14].

Experimental part:

1- Synthesis of ethyl benzoate (2):

This compound was prepared by using ethanol absolute and sulfuric acid as described previously [15].

2-Synthesis of Acid hydrazide(3) [16].

Acid hydrazide was synthesized by addition of the hydrazine monohydrate (80%) (0.01mol.) to ester compound (1) (0.01mol.) with stirring, then ethanol absolute (10ml) was added and refluxed until the precipitate formed (1.5hrs). After cooling, the precipitate was filtered and re crystallized from ethanol.

3-Synthesis of 1-N-(benzoyl)-1,2-dihydro-pyridazin—3,6-dione (4)[17]:

Compound (3) (0.01mol) was mixed with maleic anhydride (0.01mol) in acetic acid (20ml), the mixture was refluxed for 7hrs., then cooled and added onto crushed ice, the precipitate was filtered off, washed with water and re-crystallized to give the final product, yield(60%).

4- **Synthesis of 1- N-(benzoyl)-1,2-dihydro-phthalazin-3,8- dione (5) [18].**

Compound (3) (0.01mol) was mixed with phthalic anhydride (0.01mol) in acetic acid (20ml), the mixture was refluxed for 5hrs., then cooled and added onto crushed ice, the precipitate was filtered off, washed with water and re-

crystallized, yield(75%).

5- Synthesis of 1- N-(benzoyl)- 3,5-dimethylpyrazole (6) [19]:

A mixture of compound (3) (0.01mol) was treated with acetyl acetone (0.01mol) and acetic acid (0.5ml) in absolute ethanol (15ml) was heated under reflux for 7hrs., after concentration and cooling , the solid product that formed was filtered off, and re-crystallized from ethanol, yield (65%).

6- Synthesis of 1-(benzoyl)-3-methylpyrazol-5-one (7)( ) :

A mixture of carbohydrazide (3) (0.01mol) and ethyl acetoacetate (0.01mol) in absolute ethanol (20ml) was heated at reflux temperature for (5hours), the reaction mixture was cooled and the precipitate was filtered off and re-crystallized to give the final product ,yield (65%):

7- Synthesis of 2-nitro phenyl semicarbazone (9)( ) :

To a hot ethanolic solution of compound (8) (0.01mol), a solution of semicarbazide hydrochloride and (0.03mol) of sodium acetate ,the reaction mixture was refluxed for 3 hrs. after cooling the mixture was poured in (100ml) of distilled water ,filtered and dried. The yield is (80%).

8- Synthesis of thiazolidine 2-nitro phenyl semicarbazone (10)( ) :

2- mercptoacetic acid (0.01) mole was added dropwise to(0.01)mole of Schiff base(9) in(20 ml)of dry benzene ,the mixture was refluxed for (24) hours then the solvent was evaporated and then the formed precipitate was re crystallized from ethylacetate and benzene,yield (75%).

9- Synthesis of tetrazole 2-nitro phenyl semicarbazone (11)[ ] :

A mixture of (0.01mol) of Schiff bases [9] tetrahydrofuran (THF) (15ml) and sodium azide (0.01mol) was heated on a water bath, the temperature of the water bath was controlled between (50-55)°C. The end of the reaction was checked by (TLC) which showed the disappearance of the starting material.

10- Synthesis of 2-amino-1,3,4-oxadiazole 2-nitro phenyl (12)[ ] :

Bromine (1ml) in acetic acid (5ml)was added to a stirred slurry of [11],(2gm) and anhydrous sodium acetate (6gm) in acetic acid (10ml). The mixture became colorless. The mixture was poured in water, solid which separated was filtered and dried. Re crystallized from a mixture of alcohol and acetic acid.

11- Synthesis of oxazole 2-nitro phenyl semicarbazone (13)[ ] :

A mixture of compound (9) (0.01 mol) and absolute ethanol (15ml) ,***p***-phenyl phenacyl bromide (0.01mol) was added. The mixture was refluxed for (8hrs)., cooled and neutralized with ammonium hydroxide solution. The precipitate was filtered off, washed with water, and petroluim ether was used for re-crystallization, yield (80%).

12- Synthesis of 2-(2-nitro phenyl semicarbazone)-3-alkyl)-2,3-dihydroquinazoline-4(1H) one (14)() :

A solution of 2-aminobenzoic acid (anthranilic acid) ((0.01mol) was added to Schiff bases (9) (0.01mol) in dioxane. The solution was heated under reflux for 16hrs. the solvent was evaporated under reduced pressure and the residue was treated with 10% of sodium bicarbonate, then filtered and re-crystallized by benzene-petroleum spirit (60-40),yield 76%).

Results and discussion:

Compound (2) was characterized by the appearance of carbonyl of ester compound at 1735 cm^{-1} (FT-IR spectrum), besides the disappearrance of carbonyl group of carboxylic acid() . Compound (3) was prepared from the reaction of ester compound and hydrazine hydrate in presence of absolute ethanol and characterized by the appearance of $NHNH_2$ group at 1650 cm^{-1},and disappearance of carbonyl of ester group at 1728 cm^{-1} besides the appearance of carbonyl of amide at 1645 cm^{-1}.

The FTIR spectrum of compound [4] indicated the appearance of (N-H) band at (3122) Cm^{-1} and appearance of aromatic (C-H) at (3008) Cm^{-1}, alph (C-H) at (2891,2968)Cm^{-1} and (C=C) band at (1490,1554) Cm^{-1} . The FTIR spectrum of compound [5] , shows the disappearance of the two bands of (N-H) group in the region (2935) Cm^{-1} and appearance of band due to aromatic (C-H) group at the region (2750)Cm^{-1} . carbonyl groups appeared at (1697)Cm^{-1} .

Comp. No	IR , KBr , v , CM-1									
	(N-H)	(C-H) Ar	(c-h) Alih	C=o	C=N	C-N	CH_2 bend	C=C	C-CO	Others Bands
4	3341	3027	2764 , 2621	1715	1638	1342	1422	1485 , 1530	1213 , 1003	
5	3122	3008	2891 , 2968	1662	1647	1330	1467	1490 , 1544	1226 , 1282	
6	2935	2750	2648 , 2542	1697	1595	1309	1493	1520 , 1375	1201 , 1045	C-OH 3203
7	3170	3039	2968 , 2910	1817	1761	1356	1493	1603 , 1547	1211 , 1113	C-NO_2

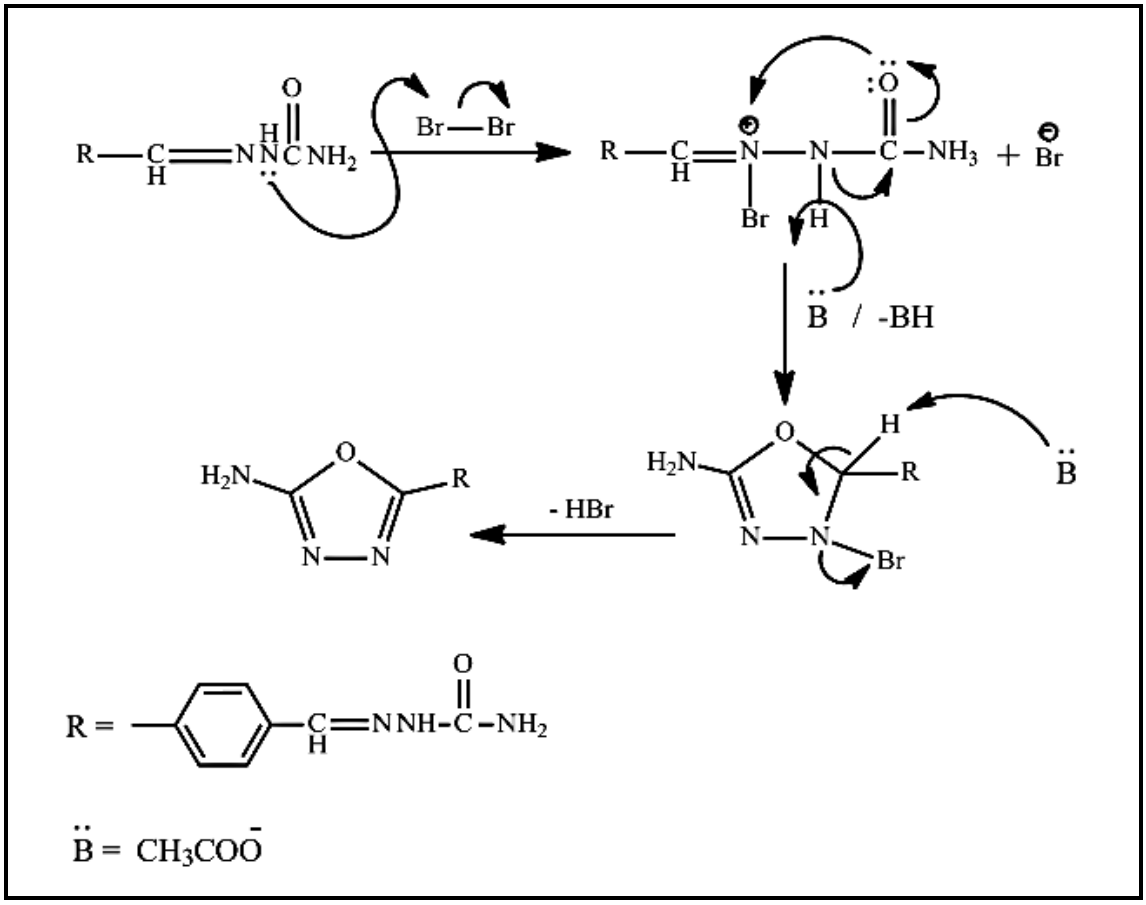
Table(1) The IR characteristic bands of compounds [4-7].

HNMR spectrum of compound [7] a signals at & (3.3) (2H,CH_2) , and & (11.9) (1H,NH) , and a multiplet signals at (8.05-8.5) (1H) that could be assigned to benzene ring protons figure (5).

Also, nitrobenzylidene semicarbazone (9) and 2-amino oxadiazole(10).

The condensation of 3-nitozbenaldehyde with semicarbazide hydrochloride which is one of the most common reaction to synthesize semicarbazone derivative [9] and synthesized 3-nitrophenyl–(1,3,4–oxadiazol-2-amine)[10] from [9] using bromine in sodium acetate[].

The suggested mechanism[] of the reaction is shown in below scheme:



Mechanism steps of [9] synthesis.

The FTIR spectrum of [9], indicated the appearance of νNH_2 band at 3332 cm^{-1} and the band of νNH at 3265 cm^{-1} in addition to stretching vibration of $\nu C=O$ at about 1732 cm^{-1}another bands due to, $\nu C=N$ at about 1612 cm^{-1} and $\nu(=CH)_{aromatic}$ at position 3100 cm^{-1}.

The FTIR spectrum of [10], shows the appearance of stretching vibration of amine group νNH_2 at about 3302 cm^{-1}. The band of $\nu C=N$ at 1658 cm^{-1}. Also some bands shows at (1284- 1246) cm^{-1} due to symmetrical and asymmetrical vibration of (C-O-C) group .

The title compound was synthesized from the reaction between compound [8] and semicarbazide hydrochloride in absolute ethanol and glacial acetic acid(86).

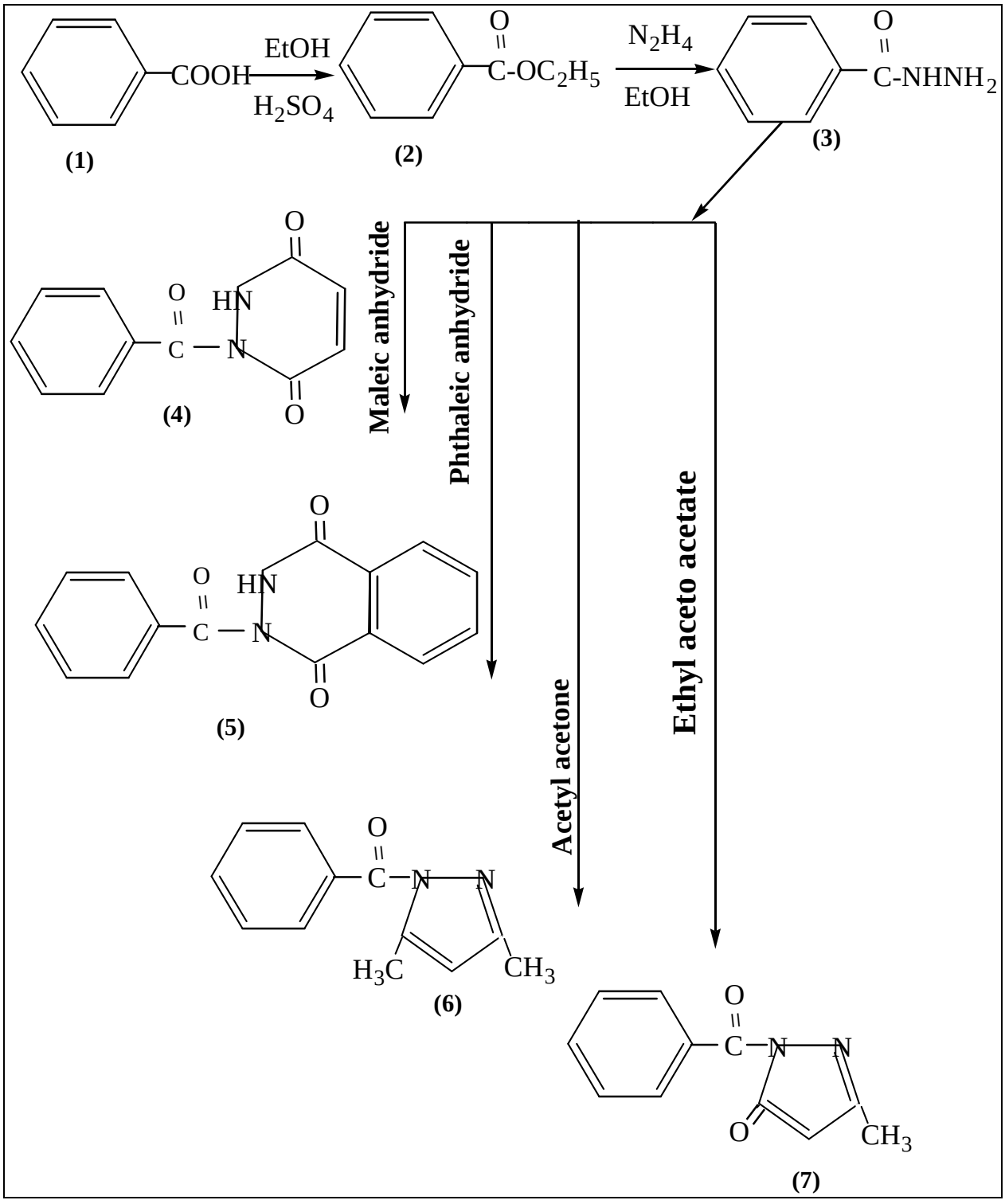
Compounds [4-7] were synthesized from the reaction of compound [5] with maliec anhydride , phthalic anhgydride , succinic anhydride and 3-nitro phthalic anhydride respectively in the presence of acetic acid as asolvent and catalyst.

Compounds [9], containing imine bond have been synthesized for preparing another derivatives like thiazolidin, tetrazolo and quinazoline ….etc, because these derivatives have a wide range of biological activity and industry. The title compounds were characterized by their melting points and FT-IR and ^{1}H-NMR spectra.

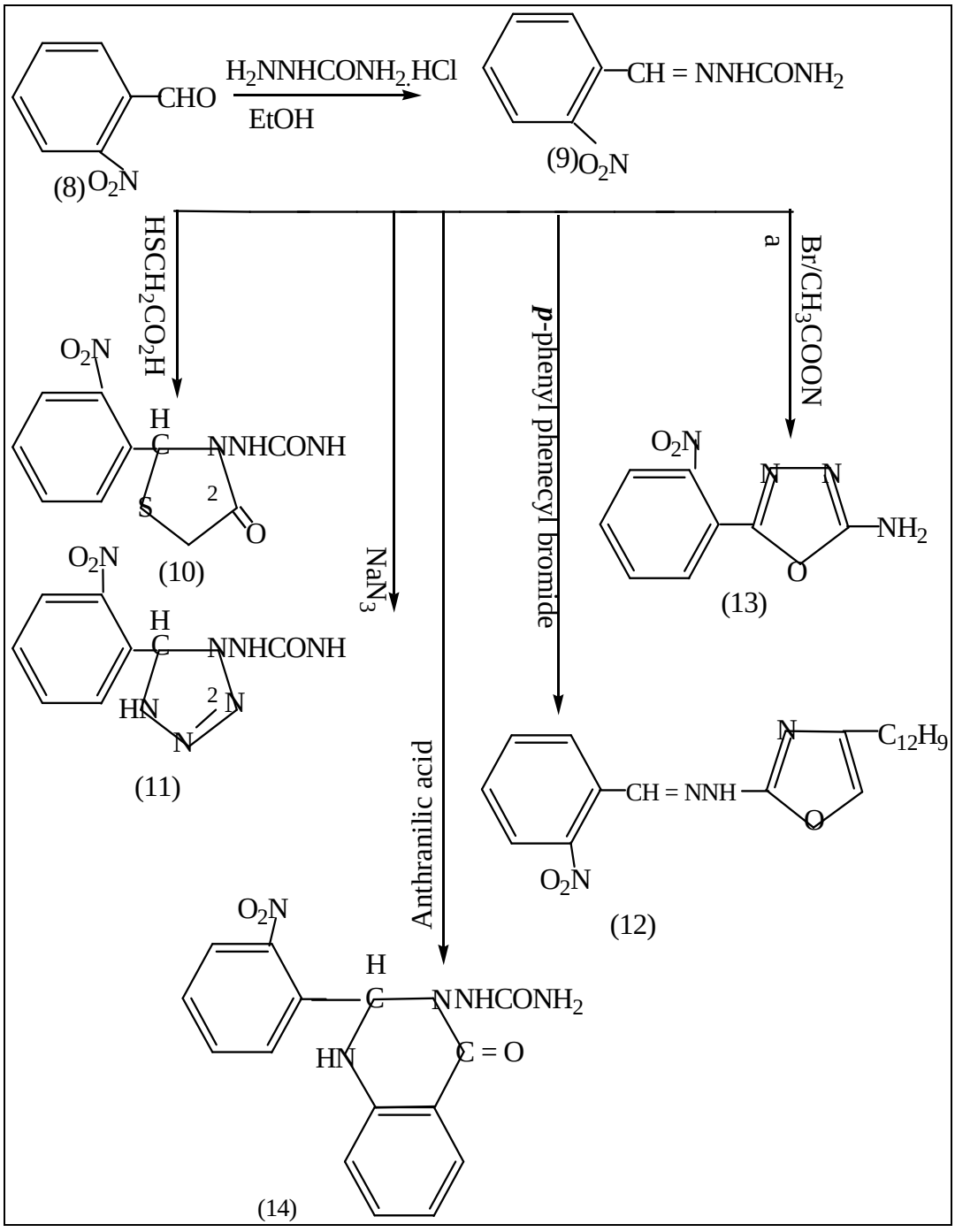
^{1}H-NMR spectrum ,fig (7),of compound (11), shows the following characteristic chemical shifts (DMSO-d_6, ppm). The aromatic protons appeared at: δ (7.6-8.5)ppm, besides the band at δ (10,5) ppm was appeared due to (-NH).

^{1}H-NMR spectrum of compound [13], shows the following characteristic chemical shift, (DMSO-d_6) ppm. The aliphatic protons present at (δ 4.2), aromatic ring protons appeared at (δ 7.0 – 8.1) ppm. Furthermore, the signal at (δ 10.1) attributed to (N-H) proton. ^{1}H-NMR spectrum ,fig (8),of compound (13), shows the following characteristic chemical shifts (DMSO-d_6, ppm). The aromatic protons appeared at: δ (7.0-8.0)ppm,(-CH)proton at δ (0.9)ppm, besides the band at δ (10,5) ppm was appeared due to (-NH), a two protons of (-CH_2) group gave a signal at δ (4.2)ppm[(11)].

The quinazoline compound (14) , Pyrimidine derivativesare prepared by heating of Schiff bases derivatives with anthranilic acid (o-aminobenzoic acid) in dioxane. The product was identified by FT-IR spectrum which shows the appearance of N-H vibration in (3361-3373) $cm^{-1}$and the disappearance of (C=N) band in (1600-1618) cm^{-1} . Also (C=C Ar.) band at 1595 cm^{-1} ,(C=O) at 1676 cm^{-1} and for (NO_2) at 1530 and at 1303 cm^{-1}.


COOH
EtOH
H_2SO_4
C-OC_2H_5
N_2H_4
EtOH
C-$NHNH_2$
(1)
(2)
(3)
Maleic anhydride
Phthaleic anhydride
Acetyl acetone
Ethyl aceto acetate
HN
(4)
(5)
H_3C
CH_3
(6)
(7)

SCHEME (1).


H2NNHCONH2.HCl
EtOH
CHO
CH = NNHCONH2
(8) O2N
(9) O2N
HSCH2CO2H
NaN3
Anthranilic acid
p-phenyl phenecyl bromide
a Br/CH3COON
O2N
H
C
NNHCONH
2
S
O
(10)
HN
N
(11)
N
N
NH2
O
(13)
CH = NNH
C12H9
(12)
C = O
(14)

SCHEME (2).

Biological activity

A few pathogenic species are known to be almost sensitive to certain antimicrobial agents, although in some parts of the world the situation is changing. As strains of pathogenic organism differ from one to another within their species in their antibiotic sensitivities, sensitivity tests are required as a routine.

Heterocyclic rings are considered an important class of compounds having a wide spectrum of biological activity, the heterocyclic compounds are well known for their antibacterial and antifungal activities**.**

In this work, the antibacterial test was performed according to the disc diffusion method [(14)]. Compounds (1, 3, 10, 13) were assayed for their antimicrobial activity in *vitro* against one strain of Gram negative bacteria (**E.coli**) and one strain of Gram positive bacteria (**Staphylococcus aureus**).

The previous bacteria were activated in a Nutrient Growth medium at 37 ^{o}C for 24 hour. The prepared agar and Petri dishes were sterilized by autoclaving for 15min at 121^{o}C. The agar was surface inoculated uniformly from the broth culture of the tested microorganisms.

Conclusions:

1- Compounds [1] showed moderately active on E.coli and no effect on E.coli, and Staphylococcus.

2- Compounds [1] showed moderately active on E.coli.

3- Compounds [10 and 12] showed no effect on E.coli a, and Staphylococcus.

Table (2): Antibacterial activities of the prepared compounds.

Comp.no.	Staph.	E.Coli.
1	_	+
10	+	+
12	++	++
3	+	+

Key to symbols:

Highly active = +++ (inhibition zone > 20 mm).

Moderately active = ++ (inhibition zone 11-20 mm).

Slightly active = + (inhibition zone 5-10 mm).

Inactive = - (inhibition zone <5 mm.

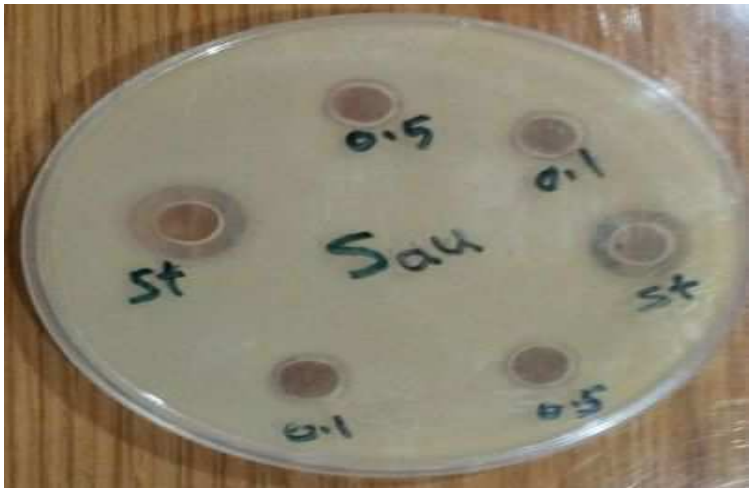


fig.(1): Effect of compound (13) on *staphylococcus.*

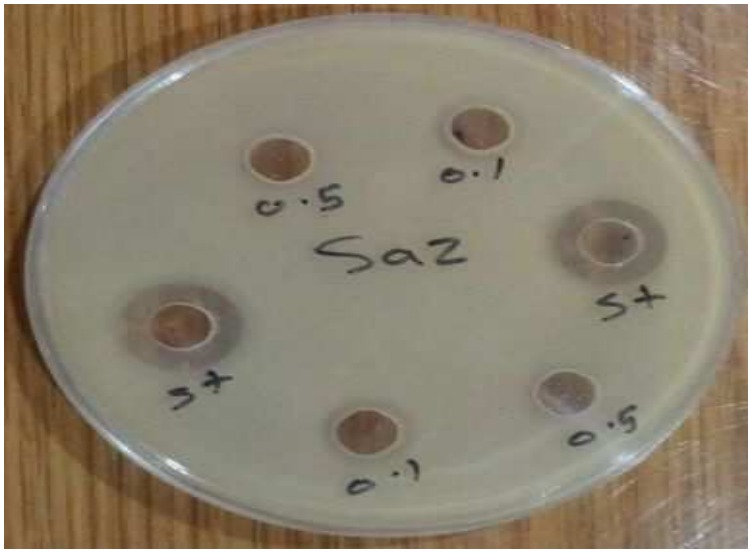


fig.(2): Effect of compound (10) on *staphylococcus.*

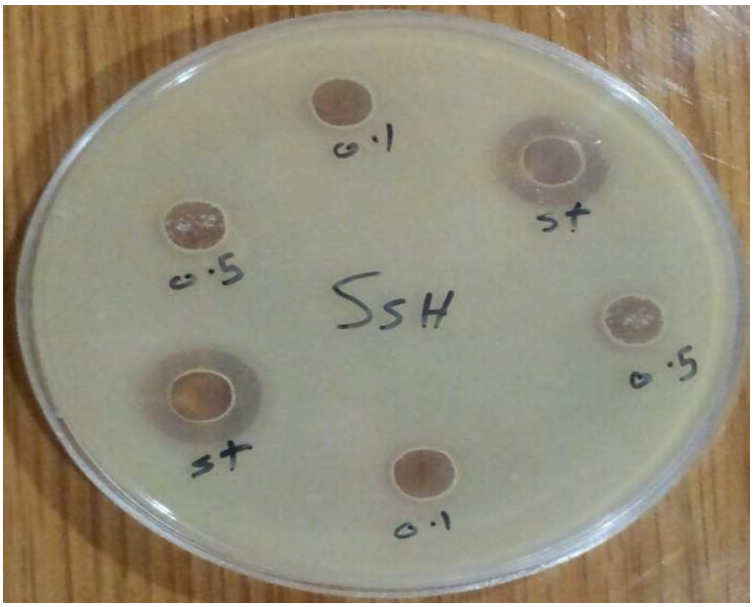


fig.(3): Effect of compound (11) on staph.

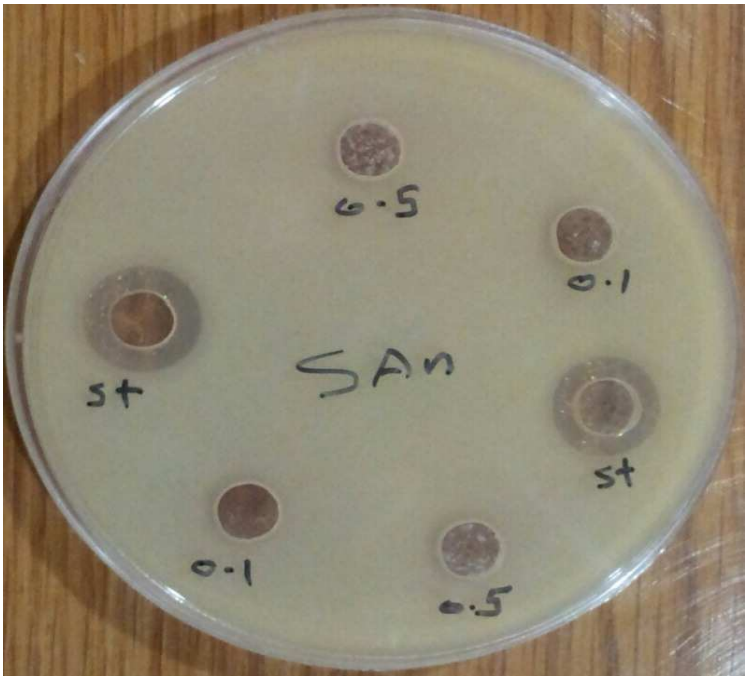


fig.(4): Effect of compound (14) on staph.

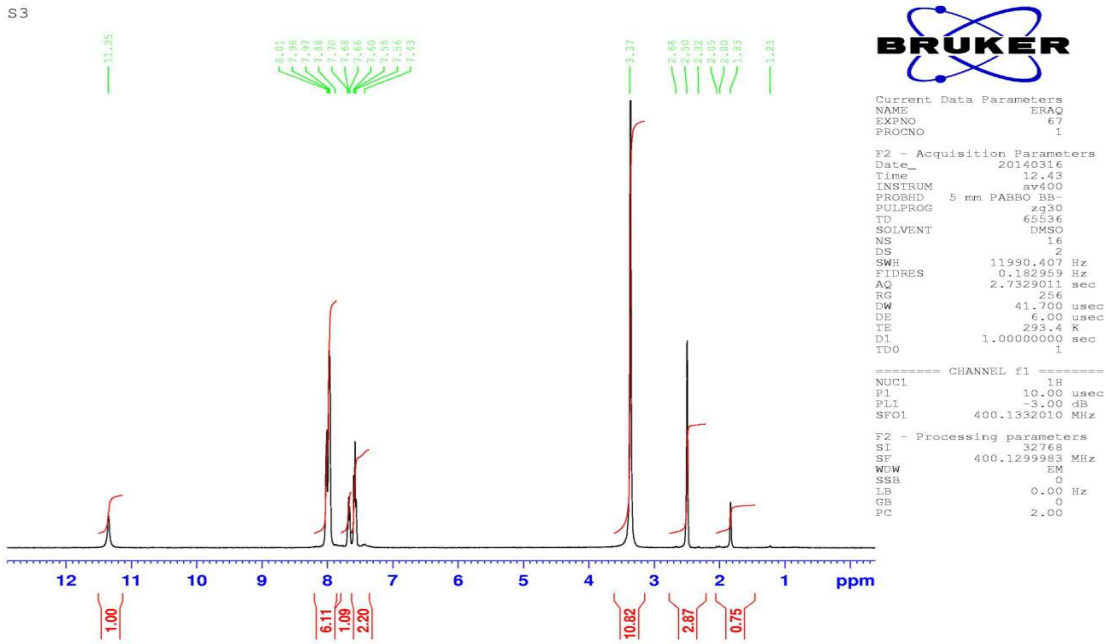


Fig (5): H-NMR spectrum of compound (5).

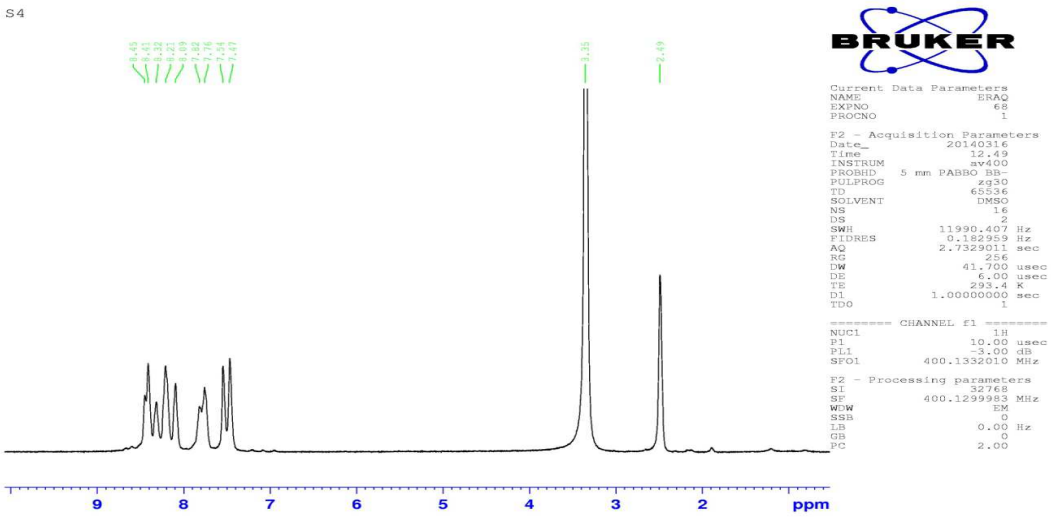


Fig (6): H-NMR spectrum of compound (13).

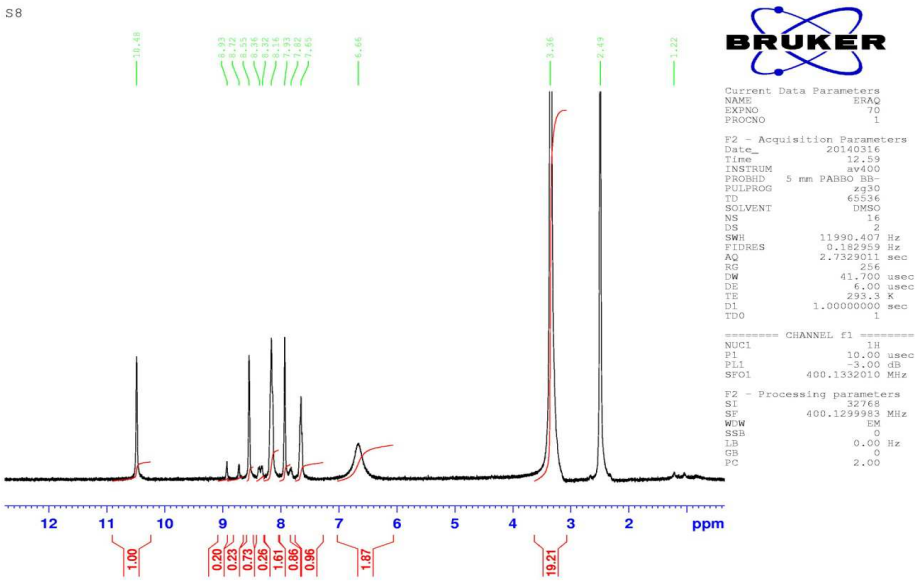


Fig (7): H-NMR spectrum of compound (11).

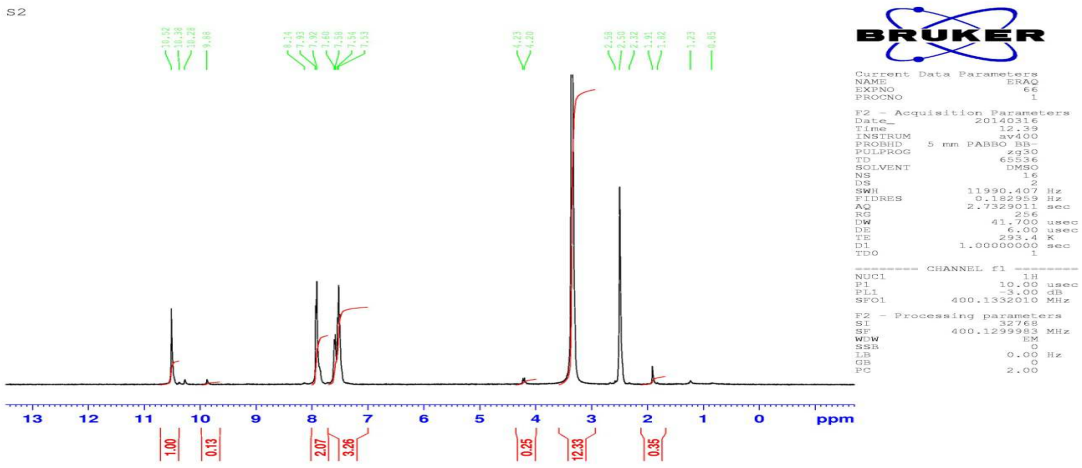


Fig (8): H-NMR spectrum of compound (12).

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