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# Synthesis of some Quinazolin One Derivatives for Their Antimicrobial Activity

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**Abstract**

A series of derivatives for compound 2-(4-chlorophenyl)-4H-benzo[d] [1,3] oxazin-4-one with different aromatic substitution were proved. The newly synthesized derivatives have been supported by spectral data FTIR and $H^1$ NMR. All the synthesized compounds were screened for their antimicrobial activity and compared with drug Amoxicillin as reference. [DOI: 10.22401/ANJS.00.1.03]

**Keywords:** Quinazolinone, Antimicrobial activity, 2-Azetidinone, 4-thiazolidinone.

## 1. Introduction

Quinazolinone (nitrogen containing heterocyclics) are considered to be important versatile pharmacophore in the fields of pharmacy and organic *Synthesis*. The derivatives of quinazolinone have gain importance as an antiinflammatory [1,2] antioxidant [3,4], Antimicrobial [5], antitubercular [6], anticancer [7.8] and enzyme inhibitors [9]. Derivatives of Cyclic imides have been found to be an important moiety in creation of novel Medical drugs and they encompass pharmacological activities [10].

Furthermore, compounds containing an azomethine group (imine) are a class of important compounds in medicinal chemistry and pharmaceutical field. The biological applications of these compounds have attracted remarkable regard [11,12]. The 2-azetidinones are of immense attention in diverse areas of clinically used drugs because of their different pharmacological activities [13,14].

The 4-thiazolidinone scaffold is very versatile and has featured in a number of medicinal chemistry. They have found uses as antitubercular, antimicrobial and anticancer [15,16]. In this project, we aimed to synthesize new heterocyclic compounds derivative from anthranilic incorporating with cyclic imide, 2-azetidinones and 4-thiazolidinone moieties with the hope to get better antimicrobial activity**.**

## 2. Experimental

### 2.1 Materials and measurement

The melting points were determined by an electrical thermal melting point apparatus and are uncorrected. All reagents have been commercially available at (Aldrich Co.) and have been used without further Purity of the derivatives have been checked on silica coated Merck-TLC plates by using water, acetone, benzene and chloroform as mobile phase. FT-IR measurements have been recorded by Shimadzu model FT-IR-8400S. $^1$H NMR spectra were registered by using a Bruker spectrophotometer model Ultra Shield at 300 MHz as solvent using DMSO-d6 and as internal standard using the TMS.

#### 2.1.1 Synthesis of 2-(4-chlorophenyl)-4H-benzo[d][1,3]oxazin-4-one(1)

Chlorobenzoylchloride (0.01 mol) was added dropwise to stirred solution of anthranilic acid (0.01 mol) in pyridine (20 ml), then the mixture was stirred at room tempearture for 4h. poured into ice-water. The solid was filtered washed with water and recrystallized from ethanol

#### 2.1.2 Synthesis of 3-(2-aminoethyl)-2-(4-chlorophenyl) quinazolin-4(3H)-one(2)

Compound 1(0.01 ml) was added to a mixture of Ethylenediamine (0.01 mL) in pyridine (20 mL), then refluxed for 12 h. The reaction mixture then poured into ice-water. The solid was filtered and recrystallized.

#### 2.1.3 Synthesis of 1-(2-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl) ethyl)-3-phenylthiourea (3)

A mixture of compound 2 (0.01mole) and phenyl isothiocyanate (0.01 mole) in (30 ml) dry dioxan was refluxed for 8hrs. The reaction mixture was concentrated and the obtained solid was filtered off, and recrystallized from ethanol. The physical properties are listed in Table (1).

**2.1.4 Synthesis of 4-((2-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl) ethyl) amino)-4-amic acids (4-6)**

Succinic anhydride or maleic anhydride orphthalic anhydride (0.01 mole) in (30 mL) acetone was added to compound (2), (0.01 mole) and the reaction was refluxed for 8-10 hrs. Then the mixture was poured on crushed ice, the resulted was filtered off and recrystallized.

**2.1.5 Synthesis N-(2-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl) ethyl)-4-methylbenzenesulfonamide(7)**

Toluene-4-Sulfonyl chloride (tosyl chloride) (0.01 mole) was added to mixture of compound 2 (0.01 mole) in (0.01 mole) pyridine in dry benzene (20 ml).was refluxed for 6h. The excess of solvent was evaporated and the product was filtered off, recrystallized.

**2.1.6 Synthesis of 3-(2-((2-substituted benzylidene) amino) ethyl)-chlorophenyl) quinazolin-4(3H)-one (8,9)**

To a solution of compound 2 (0.001mole) in (25 mL) of absolute ethanol, the aromatic aldehyde (0.001 mole) was added with 2-3 drops of glacial acetic acid. The mixture has been refluxed for 7 hours, reaction mixture was cooled then the mixture was filtered and recrystallized from chloroform. The physical properties are listed in table (1).

**2.1.7 Synthesis of 3-(2-((3-chloro-2-(2-substituted phenyl)-4-oxoazetidin-1-yl) ethyl)-2-(4-chlorophenyl) quinazolin-4(3H)-one (10,11)**

The mixture of Schiff base (8,9) (0.01 mol) and triethyl amine (0.02 mol) was dissolved in Dioxane (20 mL). Chloroacetyl chloride (0.02 mol) was added in portion wise with vigorous shaking at room temperature for 25 min. The reaction mixture was heated under reflux for 4 h and the content was kept at room temperature for 24 h and poured into ice-cold water. The product obtained was filtered, washed several times with water.

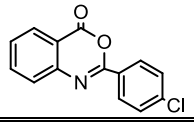
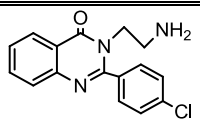
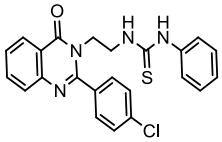
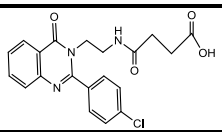
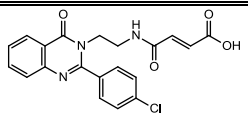
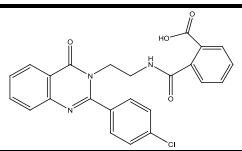
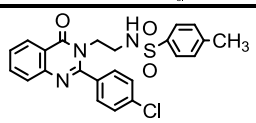
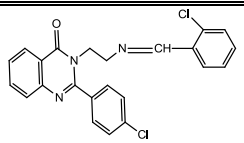
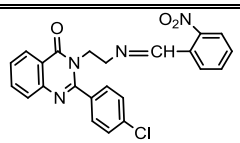
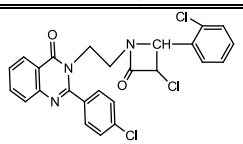
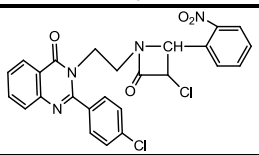
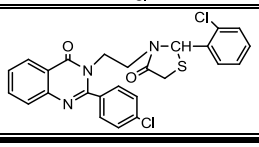
**2.1.8 Synthesis of 2-(2-substituted phenyl)-3-(2-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl)ethyl) thiazolidin-4-one (12,13)**

A mixture of compounds 8,9(0.01 mole) in DMF (40 mL), thioglycolic acid (0.02 mole) was added in presence of anhydrous ZnCl. The mixture have been refluxed for 12h then cooled and poured into ice cold water. The solids were filtered, and recrystallized.

**2.2 Antimicrobial Activity**

The antimicrobial activity of the quinazolinone derivatives (3-13) were tested by the agar disc-diffusion method against two Gram positive Staphylococcus aureus and Streptococcus pyogenes and two gram negative bacteria E. Coli, Klebsielllaspp micro organisms and fungal strains namely Candida albicans [17]. Dimethyl sulfoxide DMSO was used as a control and as solvent. The test was performed at 100mg/mL concentration. The bacteria and fungi were carried out in agar and potato dextrose agar medium and these plates were incubated for 24 h for bacteria and 48 h for fungi at 37 °C.

***Table (1)***
***Physical properties of the compounds (1-13)***

| Comp. No. | Comp. structure | M. p. C° | Yield % | Color | Rec. Solvent |
|---|---|---|---|---|---|
| 1 |  | 142-144 | 92 | Light yellow | Ethanol:$H_2O$ |
| 2 |  | 188-190 | 66 | Yellow | Ethanol |
| 3 |  | 200-202 | 50 | Yellow | Chloroform |
| 4 |  | 220-222 | 50 | Yellow | Dioxane |
| 5 |  | 95-97 | 54 | Yellow | Dioxane |
| 6 |  | 162-165 | 76 | Yellow | Ethanol:H2O |
| 7 |  | 182-184 | | | Acetone |
| 8 |  | 155-157 | 58 | Yellow | Ethanol |
| 9 |  | 184-187 | 47 | Light yellow | Chloroform |
| 10 |  | 167-169 | 54 | Yellow | Ethanol |
| 11 |  | 198-200 | 65 | Brown | Ethanol:H2O |
| 12 |  | 256-258 | 67 | Light brown | Ethanol:H2O |

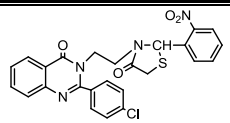
| | | | | | |
|---|---|---|---|---|---|
| 13 |  | 228-230 | 54 | Light yellow | Ethanol |

***Table (2)***
***Spectral data of the compounds (1-13)***

| Comp. No. | Characteristic bands of FT-IR (ATR, υ, cm-1) | | | | | |
|---|---|---|---|---|---|---|
| | $(C-H)_{ali}$ | $(C-H)_{arom}$ | (C=O) | (C=N) | $(C=C)_{arom}$ | Others |
| 1 | – | 3099 | 1768 | 1620 | 1591<br>1572 | 1253 (C–O–C) |
| 2 | 2950<br>2890 | 3090 | 1683 | 1639 | 1589<br>1562 | $NH_2$(3404,3329<br>NH(3223) |
| 3 | 2916<br>2847 | 3080 | 1664 | 1633 | 1599<br>1556 | NH(3282) |
| 4 | 2965<br>2837 | 3054 | 1720<br>1683 | 1628 | 1548<br>1542 | OH(3450-2843)<br>NH(3282) |
| 5 | 2986<br>2842 | 3014 | 1710<br>1676 | 1631 | 1610<br>1564 | OH(3300-2950)<br>NH(3275) |
| 6 | 2954<br>2865 | 3074 | 1703<br>1680 | 1639 | 1591<br>1556 | OH(3500-3000)<br>NH(3) |
| 7 | 2966<br>2854 | 3082 | 1666 | 1620 | 1600<br>1554 | $SO_2$ (1344,1155) |
| 8 | 2925<br>2874 | 3058 | 1685 | 1637<br>1630 | 1589<br>1552 | Cl (1115) |
| 9 | 2928<br>2891 | 3078 | 1699 | 1642<br>1626 | 1572 | $NO_2$(1527,134) |
| 10 | 2912<br>2880 | 3068 | 1722<br>1695 | 1653 | 1587<br>1568 | Cl(1122) |
| 11 | 2966<br>2845 | 3099 | 1730<br>1686 | 1630 | 1602<br>1584 | $NO_2$(1556,136) |
| 12 | 2958<br>2868 | 3052 | 1710<br>1676 | 1623 | 1594<br>1534 | Cl(1114) |
| 13 | 2920<br>2854 | 3076 | 1714<br>1664 | 1635 | 1597<br>1519 | $NO_2$(1527,134) |

## Results and discussions

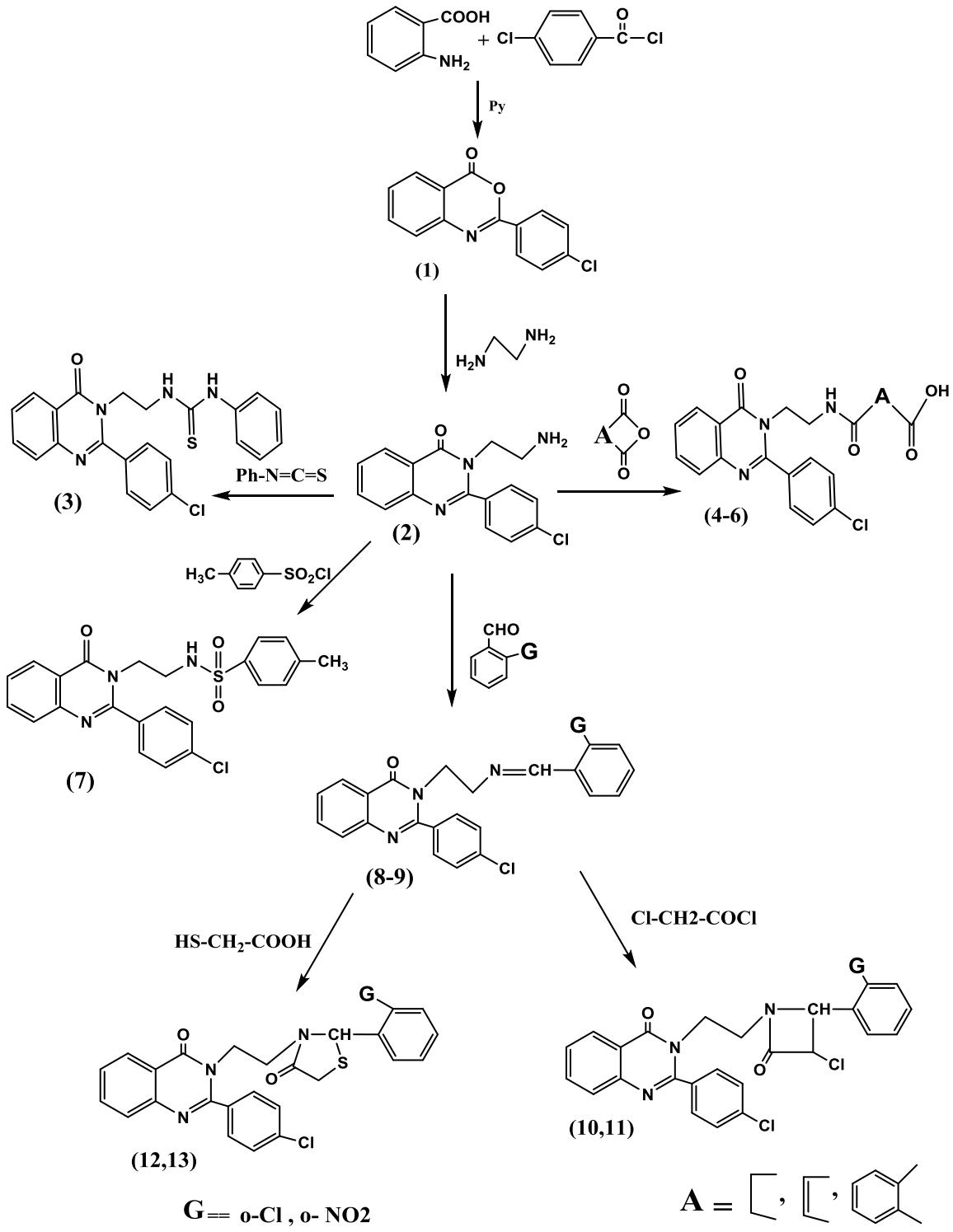
### Synthesis

The new quinazolinone derivatives were prepared following the reaction sequences depicted in scheme (1). The 4H-1,3-benzoxazin-4-one core used as key intermediates for the synthesized of compounds.

Compound (1) has been prepared by the condensation of the anthrnilic acid with p-chlorobenzoylchloride. The structure of all compounds were proven based on the melting point, thin layerchromatography, FTIR and $^1$HNMR spectroscopy.

The FTIR spectrum of this compound showed the disappearance of $NH_2$in the anthrnilic acid and appearance a sharp new absorption stretching bands at 1768 cm due to C=O oflacton in quinazolinone, Table (2).

Compound (1) was reacted successfully with ethylene diamine to give of 3-(2-aminoethyl)-2-(4-chlorophenyl) quinazolin-4(3H)-one(2) in good yield.




**Scheme (1)**

The FTIR spectrum Fig.(1) indicated the appearance two bands in the region (3404,3329) cm which could be attributed to asymmetric and symmetric stretching vibration of $NH_2$. $^1$H-NMR spectrum of compound (2) exhibited triplet signals at 3.5ppm and at 3.8 ppm was assigned to $2CH_2$ protons, signal at 4.8 ppm was attributed protons of $NH_2$, aromatic protons were appeared at 8.1-7.2 ppm.

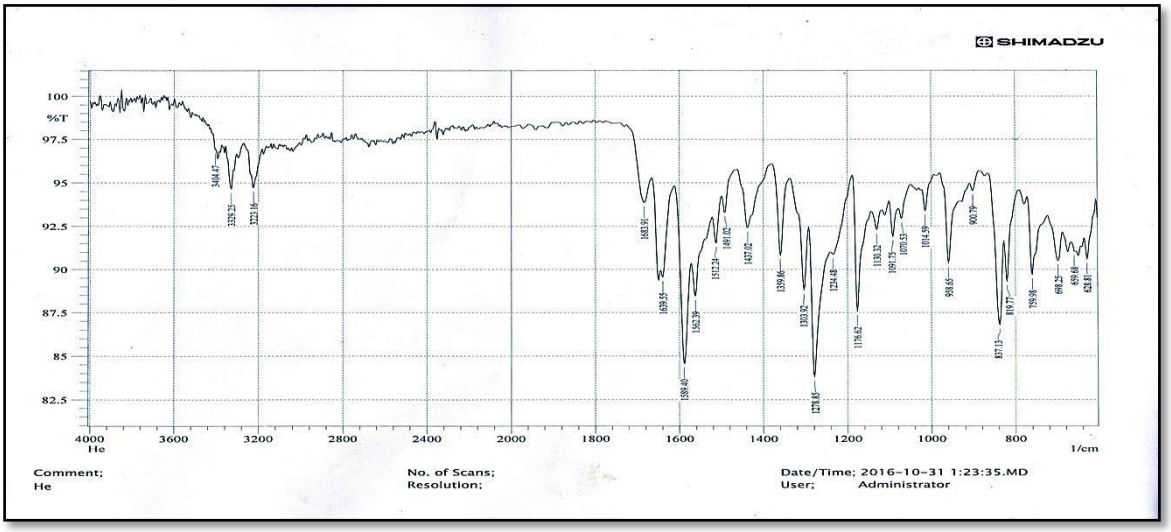



***Fig. (1) The FT-IR spectrum of compound (2).***

Thiourea derivatives (3) was synthesized by reacting compound (3) withphenyl isothiocyanate in dry dioxan. The FTIR spectrum showed NH stretching absorption in 3282 $cm^{-1}$ and C=S at 1240 $cm^{-1}$ while $^1$H-NMR spectra of compound (3) exhibited triplet signals 3.5 ppm, 3.8ppm elong to $2CH_2$. Singlet signals 5.2 ppm was assigned to NH proton and 12.8 ppm belong to (SH–NH tautomeric)state. The aromatic protons were appeared at 8.4-7.1 ppm[18].

Compound (4-6) were prepared via reaction of equimolar amounts of *Succinic anhydride or maleic anhydride or* phthalic anhydride and compound (2) in acetone. The reaction was carried out via nucleophilic attack of amino group on carbonyl group in acid anhydride. FT-IR spectra of compound (5) showed abroad absorption bands at 3300- 2950 $cm^{-1}$ due to (O–H) carboxylic and at 3275 $cm^{-1}$ due to (N–H) amide. Other absorption bands appeared at 1710 and $cm^{-1}$ 1676 a $cm^{-1}$ due to (C=O) carboxylic, (C=O) amide respectively. $^1$H-NMR spectrum Fig. (2) of this compound showed triplet signals at 3.0 ppm and at 4.2 ppm due to $2CH_2$, signals at 8.5-7.2 ppm due to aromatic protons and (N–H) proton and a clear signal at 10.7 ppm due to (O–H) carboxylic proton.

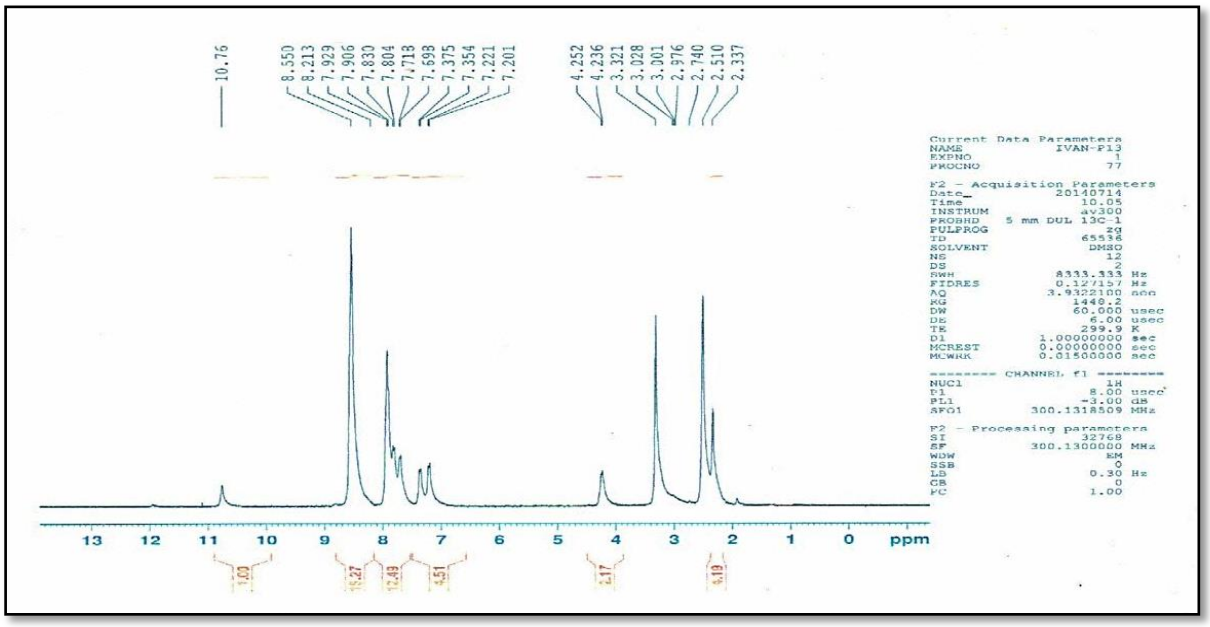



***Fig.(2) The $^1$H- NMR spectrum of compound (5).***

Reaction between toluene-4-Sulfonylchloride and compound (2) and pyridine *in* dry benzene afforded of N-(2-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl) ethyl)-4-methylbenzenesulfonamide (7). FT-IR spectrum of compound (7) shows the characteristic bands at 3246 and 1344, 1155 $cm^{-1}$ which due to NH, and ($SO_2$).

While the $^1$H-NMR spectrum indicated singlet signal at 2.24 ppm due to for proton ($CH_3$) group and singlet at 6.1 ppm connected to NH proton, while a signal as multiplet at 7.5-6.4 ppm due to aromatic protons.

Condensation of the compound (2) with aryl aldehydes in absolute ethanol afforded the Schiff bases (8,9).

The formation of these Schiff bases was indicated by the presence in their FTIR spectra of azomethine (CH=N) stretching band at (1630,1626) $cm^{-1}$, combined with the disappearance of the $NH_2$ stretching band Table (2).

The $^1$HNMR of derivative (9) showed triplet signal at 3.5 ppm due to $CH_2$ proton and at 3.7 ppm related to $CH_2$, while aromatic protons and proton of CH=N appears as multiplet signals at 8.5-7.2 ppm.

On the other hand, reaction of compounds (8,9) with triethyl amine and chloroacetyl chlorideafforded azetidinyl derivatives (10,11). The structure of compound (10) was obtained by FT-IR spectral data which was showed the disappearance band of azomethine in the region 1604 $cm^{-1}$ beside this the appearance of absorption band at 1722 $cm^{-1}$ (C=O β lactam).

The $^1$H-NMR of compound (10) showed doublet signals at 5.7-5.3ppm due to azetidinyl ring proton, a multiplet signals at 8.5 -6.7 (m,12H, Ar-H) belong to aromatic protons.

Moreover, cyclization of Schiff bases (8,9) with thioglycolic acid in the presence of anhydrous $ZnCl_2$ afforded compounds (12,13).

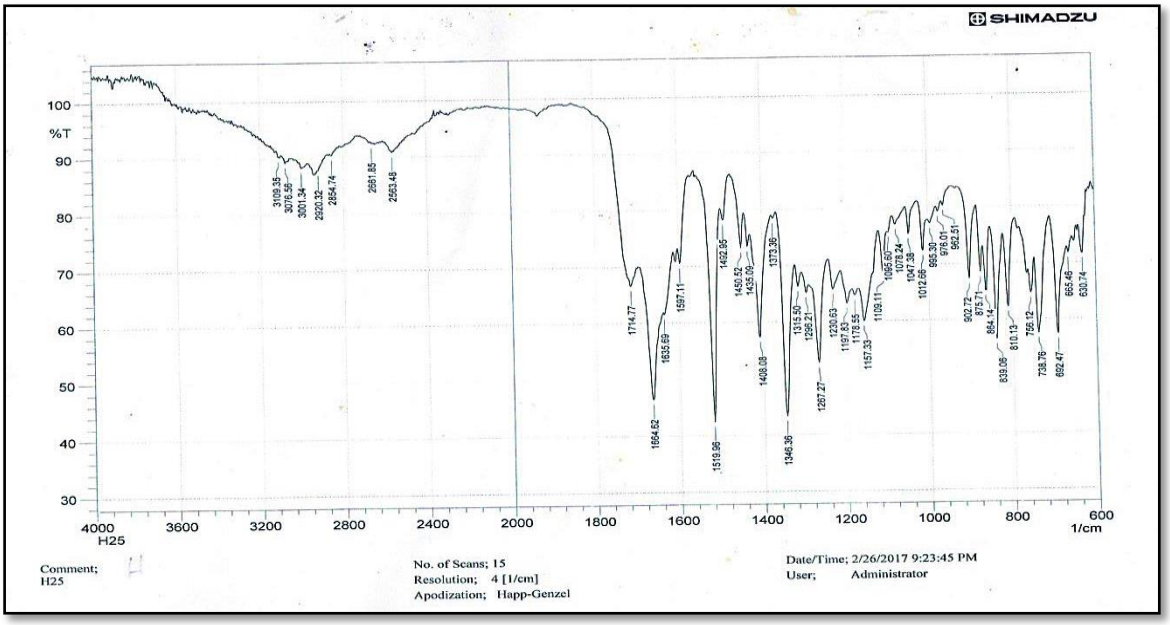



***Fig. (3) The FT-IR spectrum of compound (13).***

The structure of compound (13) established by FT IR spectral data, Fig.(3) which was showed the disappearance band of azomethine in the region 1626 $cm^{-1}$ combined with the appearance of absorption band at 1714 $cm^{-1}$ (C=O) of thiazolidinone. $^1$H-NMR spectrum of compound (11) showed singlet signals at 4.2 ppm and 5.3 ppm was attributed to protons ring of thiazolidinone.

### 3.2 Antimicrobial activity

The zone inhibition observed around the cups after respective incubation was measured in mm. It seems that the connected heterocyclic rings such as quinazolinone, azetidinone, thiazolidinone have improved the antimicrobial activities. Quinazolinone derivatives (10-13) showed high inhibition toward all kinds. The results of these studies are summarized in Table (3).

*Table (3)*
*Antimicrobial evaluation of compounds.*

| Heterocyclic derivatives | inhibition zone (mm) at 100 mg/mL | | | | |
|---|---|---|---|---|---|
| | Grampositive | | Gram negative | | Fungi |
| | S. aureus | S. epidermidis | E. coli | Klebsiellaspp | C. albicanus |
| **3** | – | – | 10 | 13 | 9 |
| **4** | 9 | 14 | 10 | 8 | 15 |
| **5** | – | 10 | 12 | – | 16 |
| **6** | – | 10 | 8 | – | 12 |
| **7** | 13 | 15 | 18 | 15 | – |
| **8** | – | 12 | 15 | 10 | 12 |
| **9** | 19 | 13 | 16 | 18 | – |
| **10** | 13 | 10 | 18 | 19 | 16 |
| **11** | 20 | 14 | 16 | 18 | 15 |
| **12** | 19 | 18 | 16 | 15 | 17 |
| **13** | 22 | 15 | 14 | 19 | 14 |
| **Amoxicillin** | 17 | 19 | 16 | 19 | 21 |

## 4. Conclusion

The newly quinazolinone derivatives are synthesized and characterized on the basis of analytical and spectral data.Screening of these compounds against pathogenic microorganism reveals that these compounds have the capacity of inhibiting metabolic growth of some microorganisms to different extent. It can be concluded that the antimicrobial activity of the compounds depends on the nature of substituent present on the quinazolinone ring.

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