Saeed and Al-Majidi *Iraqi Journal of Science, 2026, Vol. 67, No. 3, pp: 1249-1270*
DOI: 10.24996/ijs.2026.67.3.1

ISSN: 0067-2904

Synthesis, Identification and Screened anti-microbial activity of some new N-substituted quinazoline-4-one, oxazine-4-one and thiazine-4-one derivatives bearing a 4(3H)-quinazolinone moiety

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Received: 6/12/2024 Accepted: 4/3/2025 Published: 30/3/2026

Abstract

This work includes synthesis of new heterocyclic derivatives of quinazoline-4-one, oxazine-4-one and thiazine-4-one and studying their application as anti-microbial. The preparation process commenced with the reaction of para methoxybenzoyl chloride with anthranilic acid to give 2-(4-methoxy benzamido) benzoic acid **(compound 1). This compound then reacts with** acetic anhydride under dry conditions, resulting in the formation of benzoxazinone compound **2**. Following this, compound 2 undergoes a reaction with ethyl glycinate hydrochloride under basic conditions, yielding in compound **3** serves as the starting material for the synthesis of some heterocyclic compounds by reaction with nitrogen nucleophiles. The nucleophilic addition of 80% hydrazine hydrate to compound **3** yields the corresponding hydrazide **4**. Subsequently, the condensation of compound **4** with various para-substituted aromatic aldehydes in the presence of glacial acetic acid leads to the synthesis of Schiff base derivatives **5-9**. Finally, the compound **5-9.** These compounds (5-9) can undergo three distinct reactions. The first reaction involves treating compounds **5-9** with anthranilic acid to obtain 1,4 dihdroquinazoline -4- one **10-14.** The second reaction entails reacting compounds **5-9** with salicylic acid to obtain oxazine-4-one **15-19**. The third reaction involves the interaction of compounds **5-9** with 2-mercapto benzoic acid to obtain thiazine -4-one **20-24**. The newly synthesized compounds were characterized via spectral techniques; their [FT-IR, ^{1}H-NMR and ^{13}C-NMR]. Additionally, we evaluated the antibacterial effects of some synthesized compounds against Grame-negative ***Escherichia coli***, ***Pseudomonas aeruginosa,*** Grame-positive bacteria ***Staphylococcus***, and ***Bacillus cereus*** and two kinds of fungi ***Candida albicans*** and ***Rhizopus microrhizosporium***. The result showed that some of the compounds were very effective against ***Escherichia coli, Pseudomonas aeruginosa, Staphylococcus, and Bacillus cereus***. Furthermore, strong activity is observed ***in Rhizopus microrhizosporium and Candida albicans.*** On the other hand, some of the compounds were effective against ***Candida albicans and Rhizopus microrhizosporium*** and not effective against all strains of bacteria***: Escherichia coli, Pseudomonas aeruginosa, Staphylococcus, and Bacillus cereu***

Keywords: quinazoline-4-one, oxazine-4-one, thiazine-4-one Schiff's bases, antibacterial, antifungal

تحضير وتشخيص وتقدير الفعالية الميكروبية لبعض المشتقات الجديدة ل Nمعوضات كوينازولين – 4-أون، أوكسازين-4-أون وثايازين -4-أون والمحملة على مركب 4-(3H) كوينازولين.

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الخلاصة

يتضمن هذا العمل تخليق مشتقات حلقية غير متجانسة جديدة من الكينازولين-4-ون، والأوكسازين-4-ون، والثيازين-4-ون ودراسة تطبيقها كمضادات للميكروبات. بدأت عملية التحضير بتفاعل كلوريد البارا ميثوكسي بنزويل مع حمض الأنثرانيليك لإعطاء حمض 2-(4-ميثوكسي بنزاميدو) بنزويك (المركب **1**). يتفاعل هذا المركب بعد ذلك مع أنهيدريد الأسيتيك في ظل ظروف جافة، مما يؤدي إلى تكوين مركب بنزوكسازينون **2**. بعد ذلك، يخضع المركب **2** للتفاعل مع هيدروكلوريد إيثيل جليسينات في ظل ظروف قاعدية، مما ينتج عنه مركب **3** يعمل كمادة أولية لتخليق بعض المركبات الحلقية غير المتجانسة عن طريق التفاعل مع نواة النيتروجين. إن الإضافة النيوكليوفيليه لـ 80% من هيدرات الهيدرازين إلى المركب **3** تعطي الهيدرازيد المقابل **4**. بعد ذلك، يؤدي تكثيف المركب **4** مع مختلف الألدهيدات العطرية المستبدلة بارا في وجود حمض الأسيتيك الجليدي إلى تخليق مشتقات قاعدة شيف **5-9**. وأخيرًا، المركب **5-9**. يمكن أن تخضع هذه المركبات (**5-9**) لثلاثة تفاعلات مميزة. يتضمن التفاعل الأول معالجة المركبات **5-9** بحمض الأنثرانيليك للحصول على 1،4 ديهيدروكينازولين -4- ون **10-14**. يتضمن التفاعل الثاني تفاعل المركبات **5-9** مع حمض الساليسيليك للحصول على أوكسازين-4- ون **15-19**. يتضمن التفاعل الثالث تفاعل المركبات **5-9** مع حمض 2-مركابتو بنزويك للحصول على الثيازين -4- ون **20-24**. تم توصيف المركبات المصنعة حديثًا من خلال التقنيات الطيفية؛ [FT-IR، 1H-NMR و13C-NMR] بالإضافة إلى ذلك، قمنا بتقييم التأثيرات المضادة للبكتيريا لبعض المركبات المصنعة ضد البكتيريا سلبية الجرام ***العصيات*** **القولونية، والزائفة الزنجاريه**و البكتيريا إيجابية الجرام ال**مكورات العنقودية الذهبية والعصوية الشمعية** ونوعين من الفطريات **فطريات المهبل وفطرالرايزوبس**. أظهرت النتيجة أن بعض المركبات كانت فعالة جدًا ضد **العصيات القولونية، والزائفة الزنجاريه، المكورات العنقودية الذهبية والعصوية الشمعية**. علاوة على ذلك، لوحظ نشاط قوي في **فطريات المهبل فطرالرايزوبس** من ناحية أخرى، كانت بعض المركبات فعالة ضد **فطريات المهبل فطرالرايزوبس** ولم تكن فعالة ضد جميع سلالات البكتيريا: **العصيات القولونية، والزائفة الزنجاريه والمكورات العنقودية الذهبية والعصوية**.

1. Introduction

Quinazolinone-containing heterocyclic compounds represent an important class of pharmaceuticals with diverse biological activities [1] including anti-microbial [2] anti-inflammatory [3], anti-bacterial, and antiviral effects [4]. Dihydroquinazolinones are a class of nitrogen heterocyclic compounds recognized for their prominent structural units [5]. In recent decades, the chemistry and pharmacology of dihydroquinazolinones have captured the attention of scientists because their derivatives show numerous biological activities [6]. Heterocyclic thiazine derivatives play a crucial role as they are integral components of various biomolecules and pharmaceuticals [7-8] such as anticancer [9], antimicrobial [10], anti-inflammatory [11], anti-tumor agents [12]. Benzofused heterocycles with a wide range of biological action include benzoxazinone-based chemicals, [13], an important class of them. 1, 4-Benzoxazinone and 1, 3-Benzoxazinone derivatives [14] are examples of such heterocycles and exhibit a wide range of biological activities such as antioxidant [15], anti-cytotoxic and Antitumor [16], anti-inflammatory [17-18], antimalarial [19], antibacterial [20], and anticancer [21-22]. Heterocyclic compounds containing oxygen and nitrogen are highly significant due to their presence in various natural products and their potential biological activities. Because of their immediate biological actions, quinazolinone derivatives have recently drawn a lot of interest from researchers in organic and medicinal chemistry. The primary objective of this research is to synthesize a new some new N-substituted quinazoline-4-one, oxazine-4-one and thiazine-4-one derivatives bearing a 4(3H)-quinazolinone moiety and evaluate its anti-microbial activity.

2. Experimental part

2.1 Material and instrument

The chemicals and solvents used in the experiment were obtained from Sigma Aldrich, Merck, Fluka, and BDH businesses without additional purification processes. The melting points were measured using an open-ended capillary tube on a Gallena Kamp electro-thermal melting point instrument (variable heater) from England. The FTIR measurements were conducted using a Shimadzu (8400s) Fourier Transform Infrared Spectrometer from Japan. The samples were prepared as KBr disks and the measurements were taken in the range of 4000-600 cm-1. The Department of Chemistry is located at the College of Science at the University of Baghdad in Iraq. The 1H-NMR and 13C-NMR spectra were obtained using a Bruker spectrometer operating at frequencies of 500 and 600 megahertz. The solvents employed were DMSO-d6 and CDCl3, with TMS serving as the internal standard. The Sharif University of Technology is located in Iran. The antimicrobial activity was conducted in the Central Service laboratory, located in the College of Education for Pure Science at the University of Baghdad. The College of Science at the University of Baghdad includes all the equipment and instruments necessary for the determination of the structural composition of synthesized compounds.

2.2 Methods of the synthesis of compound

*2.2.1 Synthesis 2-(4-methoxy benzamido) benzoic acid **I** [23]*

A mixture of anthranilic acid (1.37 g, 0.01 mol) and dry acetone (5 mL) was cooled in an ice bath. A solution of para-methoxy benzoyl chloride (0.98 mL, 0.01 mol) and dry pyridine (0.5 mL) was then added dropwise while maintaining cooling. The mixture was refluxed for three hours in a water bath at (50-60) °C, after which it was allowed to cool to room temperature and poured into ice-cold diluted (1:1) HCl. The pale-yellow solid precipitate was filtered, washed with distilled water, and recrystallized from ethanol water. Table (1) presents the structural physical properties and FT-IR spectra of compound **1**.

*2.2.2 Synthesis 2-(4-methoxy phenyl)-4H-benzo [3, 1] oxazine- 4-one. **2** [23]*

Compound **1** (2 g, 0.008 mol) was dissolved in acetic anhydride (1.5 mL, 0.016 mol) and refluxed for 4 hours under dry conditions. The solution was cooled to room temperature, solution was poured into cold petroleum ether to obtain the desired crystals, which were recrystallized from ethanol & water. Table (1) presents the structural physical properties and FT-IR spectra of compound **2**

*2.2.3 Synthesis 2-(4-methoxyphenyl)-3-ethylacetate)-quinazoline-4(3H) - one. **3** [24]*

Compound **2** (1 g, 0.004 mol) was dissolved in 3 mL of dry dimethylformamide (DMF). Ethyl glycinate hydrochloride (0.5 g, 0.004 mol) was dissolved in 1 mL of dry DMF was added along with 0.5 mL of 1% NaOH in ethanol. The mixture was then refluxed for 4 hours and subsequently poured into ice cold to produce the solid crystals. The crystalline precipitate was filtered, washed with distilled water, and then recrystallized from ethanol. Table (1) includes the physical properties and FT-IR spectra.

*2.2.4 Synthesis 2-(4-methoxyphenyl)-3-(2-aceto hydrazide)-quinazoline-(3H)-one. **4** [25].*

For compound **3**, 0.5 g (0.001 mol) was dissolved in absolute ethanol (15 mL) and reacted with hydrazine hydrate (80%) (0.15 mL, 0.002 mol). The mixture was refluxed for (8) hours and then cooled overnight in the refrigerator. A solid crystalline formed upon adding the mixture to ice-cold water. The product was filtered, washed with distilled water, and recrystallized from acetone. Table (1) shows the structural physical properties and FT-IR spectra of compound **4**

*2.2.5 General synthesis of N- [(4-substituted benzylidene) acetohydrazone] 2-(4-methoxyphenyl) quinazoline3 (4H)-one. **5-9** [25]*

The compound **4** (1.1 g, 0.002 mol) was combined with 10 mL of absolute ethanol, along with 2-3 drops of a catalyst glacial acetic acid, and an equimolar amount of various substituted aromatic aldehydes (0.002 mol) in a 50 mL round-bottom flask. The mixture refluxed for 6 - 8 hours. After refluxing, the final product was left to sit until the solvent had completely evaporated. The compound was washed using distilled water, then dried and recrystallized using a suitable solvent. Table (2) shows the structural physical properties and FT-IR spectra of compound **5-9**

*2.2.6 General procedure for the synthesis 2-(4-methoxyphenyl)-N-acetamido [4-oxo-2-substituted phenyl -1, 4-dihydroquinazoline-3-(2H)-yl)] - quinazoline3 (4H)-one.**10-14** [26]*

A mix of Schiff bases **5–9** (0.0042 mol) and anthranilic acid (0.57 g, 0.0042 mol) dissolved in 15 mL of THF in a 50-mL round-bottom flask and refluxed for (14–16) hours. After refluxing, the mixture was evaporated [30]. The next step involved neutralizing the solution by adding 15 mL of a 5% sodium bicarbonate solution. The crude sample underwent filtration and recrystallization using ethanol. Table (4) shows the structural physical properties and FT-IR spectra of compounds **10-14**

*2.2.7 General procedure for the synthesis 2-(4-methoxyphenyl)-N-acetamido [4-oxo-2-substituted phenyl -2H-benzo[e] [1,3] oxazine-3 (4H)-yl)]- quinazoline3(4H)-one.**15-19***

A mixed solution of Schiff bases **5–9** (0.0042 mol) and salicylic acid (0.58 g, 0.0042 mol) dissolved in THF solvent 15 mL in a 50-mL round-bottom flask was refluxed for (12-13) hours. Then the mixture was evaporated [26]. The next step involved neutralizing the solution by adding 15 mL of a 5% sodium bicarbonate solution. The crude sample underwent filtration and recrystallization using ethanol. Table (6) shows the structural physical properties and FT-IR spectra of compounds **15-19**

*2.2.8 benzo[e] [1,3] thiazin-3 (4H)-yl)]- quinazoline3(4H)-one .**20-24***

A mixture of Schiff bases **5–9** (0.0042 mol) and 2-mercapto benzoic acid (0.64 g, 0.0042 mol) was dissolved in 15 mL of THF in a 50-mL round-bottom flask and refluxed for (10-12) hours. Then the mixture was evaporated [26]. The next step involved neutralizing the solution by adding 15 mL of a 5% sodium bicarbonate solution. The crude sample underwent filtration and recrystallization using ethanol. Table (8) shows the structural physical properties and FT-IR spectra of compounds **20-24**.

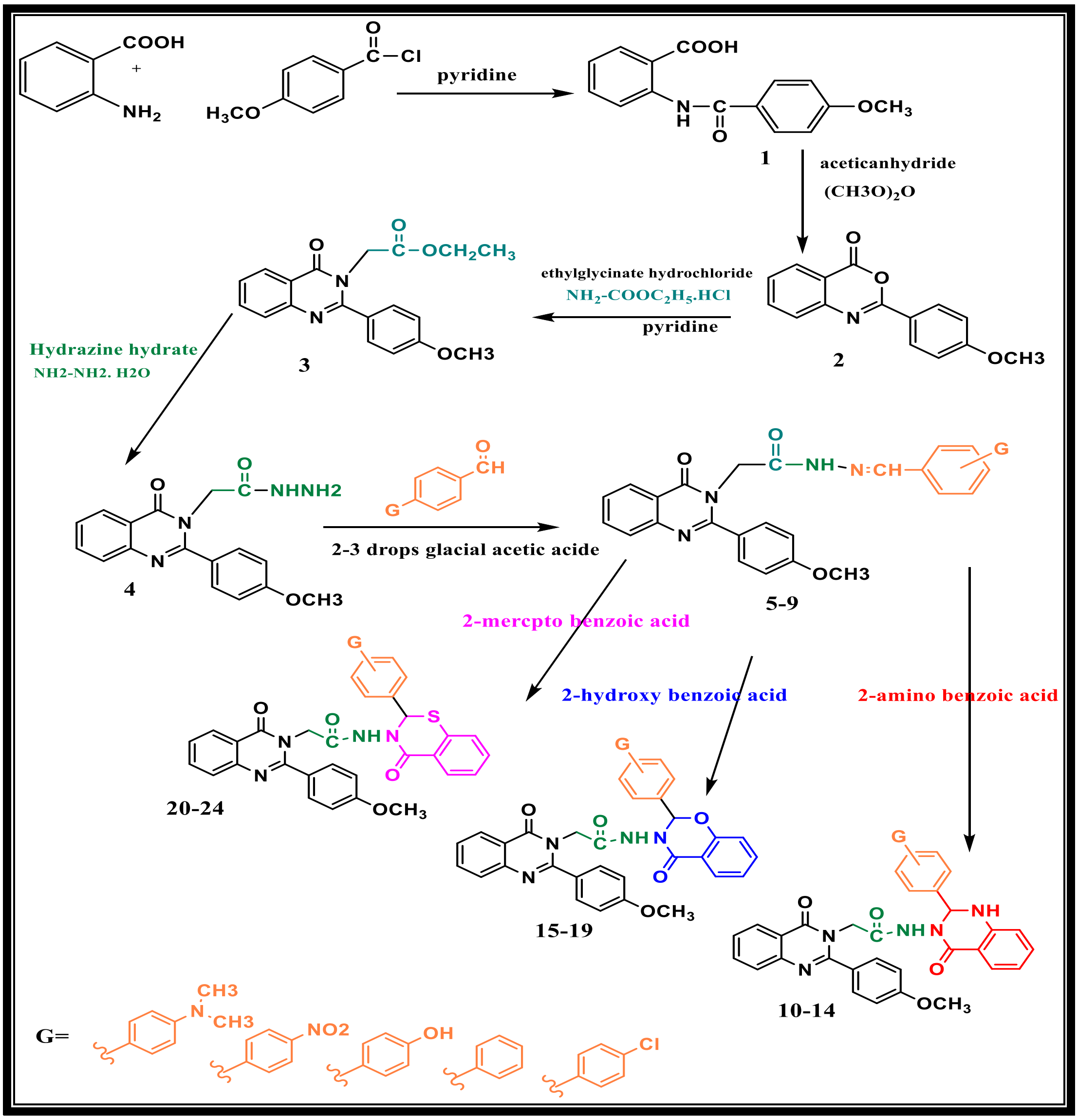
All physical properties and FT-IR spectra are summarized in Tables 1, 2, 3, 4, 6 and 8, while the 1H-NMR and 13C-NMR spectra are included in Tables 3, 5, 7 and 9.

2.3 Anti-bacterial and Anti-fungal activity [27-29]

The anti-microbial activity of the synthesized compounds was tested using the "disk diffusion method". The synthesized compounds were evaluated on four bacterial strains, including two gram-positive bacteria (Bacillus subtilis, Staphylococcus aureus) and two gram-negative bacteria (Escherichia coli, Pseudomonas aeruginosa). The samples were placed on Muller Hinton agar medium and incubated at a temperature of 37 °C for 24 hours. The results obtained for certain substances were good and satisfactory. They evaluated two fungal strains, Rhizopus microrhizosporium and Candida albicans, for investigation. The samples were placed on PDA medium and incubated at 28 °C for 3-5 days, following standard procedures. Several of the findings resulted in a good outcome. The tested compounds were dissolved in DMSO, and a specific concentration of each compound (80 µg/ml) was introduced into the cups. The petri dishes were placed in an incubator set at a temperature of 37 ºC for a duration of 24 hours. The measurement of the inhibition zone for each compound was recorded in millimetres, and the complete results can be found in Figure 9 & Table (10). The investigations were conducted at the B.P.C. analysis laboratory.

3. Results and Discussion

The sequence of reactions for the preparation 1,4-dihydro quinazoline-4- one, Oxazine-4-one and thiazine-4-one from quinazolinone- 4(3H) is illustrated in the scheme (1). The structures of the synthesized compounds were confirmed using the IR, and NMR spectroscopic studies [30]



Scheme (1)

Compound **1** is synthesized by acylating anthranilic acid with 4-methoxy benzoyl chloride in the presence of pyridine as catalyst and acetone as solvent, under dry and cold conditions. The FT-IR spectrum data of compound **1** displays several distinctive absorption bands, including a broad absorption band at (3448-2700) cm^{-1} attributed to ν (O-H), 3257 cm^{-1} for ν (N-H), and 3068 cm^{-1} due to ν (C-H) in the aromatic group. Additionally, two bands were observed at 1710 cm^{-1} and 1672 cm^{-1}, corresponding to ν (C=O acid) and ν (C=O amide), respectively. The FT-IR spectral data of compound **1** are listed in table (1). Compound **2** synthesis by cyclization reaction of compound **1** in acetic anhydride. The FT-IR spectrum of compound **2** included a stretching vibration band at 3066 cm^{-1} corresponding to ν (C-H) in the aromatic group, 1760 cm^{-1} for ν (C=O) in the lactone, and 1641 cm^{-1} due to ν(C=N). In addition, the bands at 1600 cm^{-1} and 1568 cm^{-1} were associated with ν (C=C) in the aromatic structure, while 1218 cm^{-1} and 1168 cm^{-1} represented ν (C-O-C). The FT-IR spectral data of compound 2 are listed in table (1). Compound **2** reacted with (1% NaOH in ethanol) with ethyl glycinate hydrochloride) to yield compound **3**. The positive test of compound **3** with hydroxamic acid is proof of the formation of ester. The FT-IR spectrum shows a band at 3072 cm^{-1} corresponding to the ν (CH) aromatic vibration. Bands at 2977 cm^{-1} and 2937 cm^{-1}, are attributed to the ν (C-H) aliphatic vibrations. Two strong stretching vibration bands at 1749 cm^{-1} and 1668 cm^{-1}, arising from the (C=O ester) and (C=O amide) functional groups, respectively. A band at 1641 cm^{-1} associated with the ν (C=N) vibration. Bands at 1606 cm^{-1} and 1571 cm^{-1}, which characterize the ν (C=C) aromatic vibrations. The FT-IR spectral data of compound 3 are listed in Table (1). While 1H-NMR spectral data show a t triplet signal at 1.34 ppm, attributed to methyl protons. A singlet signal at 3.85 ppm, corresponds to ($-OCH_3$) protons. A quartet signal at 4.14 ppm, arising from ($O-CH_2$) protons. Another singlet signal at 4.67 ppm, is associated with ($N-CH_2$) protons. A multiplet signal, representing aromatic protons, spanning the range 7.08-8.60 ppm. The ^1H-NMR and 13 C-NMR spectral data for compound **3** have been compiled in Table (3). Compound 3 is treated with an excess of hydrazine hydrate to produce compound 4. The FT-IR spectrum data of compound **4** show the disappearance of absorption band ν (C=O) of the ester and there was a new band 1668 cm-1 appeared instead of the previous band belonging to υ (C=O) of amid, and also two bands appeared at 3436 and 3290 cm-1 belong to υ (-NH2) Asym. And Sym. Respectively. the FTIR spectral data of compound 4 are listed in table (1). While 1H-NMR spectral data show a signal appeared in δ= 4.70 ppm belong to 2H of (NH2), δ= 8.79 ppm belong to (NH). 1H-NMR and 13C-NMR spectral data for compound 4 are shown in table (3). Compounds **5-9** were synthesized by the reaction of compound **4** with different substituted aromatic aldehyde to yield Schiff bases derivatives. Compounds 5-9 showed the disappearance of absorption band 3436, 3290 cm-1 belonging to υ ($-NH_2$) Asym. And Sym. and appearing anew absorption band 1659- 1636 cm-1 due to stretching of υ (C=N) of Schiff base. The FT-IR spectra of compounds 5-9 are presented in Table (2). 1H-NMR spectral data for compounds **5** and **7** show a singlet signal at δ=9.15 ppm for compound **5** and at δ=9.12 ppm for compound **7** due to 1H of functional group (-NH). 1H-NMR and 13C-NMR spectral data for compounds **5**, and **7** are shown in table (3).

Table 1: physical characteristics and FT-IR spectral data for compounds 1-4

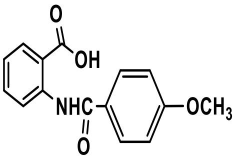
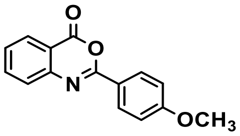
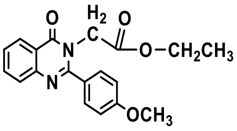
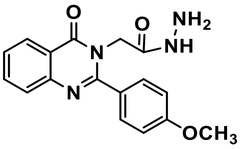
Com no	structure	m.p ^0C	Color	Yield%	Solvent recryst.	FT-IR(νcm^{-1})
1		212-214	pale yellow	90	Ethanol-water	3448-2700(OH), 3257(NH),3068(Ar-H),2974,2929(CH aliph), 1710(C=O acid),1672, (C=O amide), 1203,1176 ν(C-O-C),Ȣ (p-position) 776
2		158-159	white	90	Ethanol	3028(Ar-H),2952,2873(CH aliph),1760 (C=O lactone),1641 (C=N),1218,1168 ν(C-O-C), Ȣ (p-position) 773
3		98-100	Pale orang	80	Ethanol	3072 (Ar-H),2977,2937(CH-aliph),1749(C=O) ester ,1668, (C=O) amide, (C=C) 1606,1571 ν(C-O-C) 1213,1182 , Ȣ (p-position) 757
4		180-181	White	75	Acetone	3436, 3290(NH2), 3182(NH),3002(Ar-H),2977,2939(CH aliph),1668 overlap(C=O) amide with (C=Oquinaz.)

Table 2: physical characteristics and FT-IR spectral data for compounds 5-9

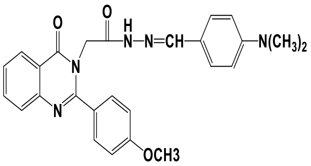
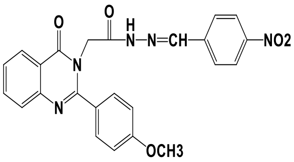
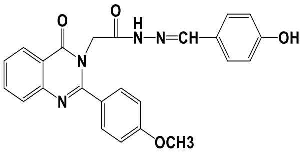
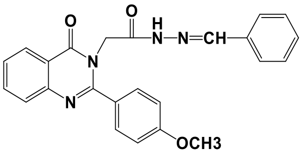
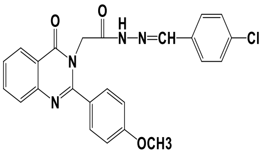
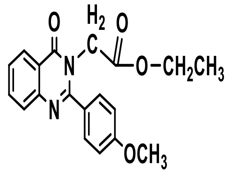
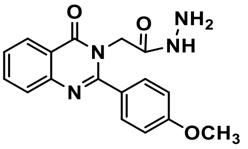
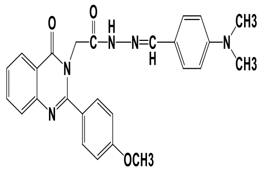
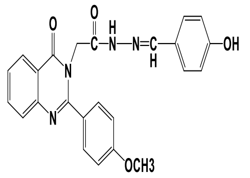
Com no	Com. Structure	m.p ^0C	Color	Yield %	Solvent recryst.	FT-IR(νcm-1)
5		238-239	dark yellow	92	dioxan	3419 (NH), 3070 (Ar-H), 2960, 2910(CH aliph.), 1679 (C=O) overlap quinaz. with amide,1639 (C=N), 838Ȣ(p-position)
6		215-216	yellow	70	Acetone	3296(NH), 3072 (Ar-H), 2987, 2912(CH aliph.) 1681 (C=O) overlap quinaz. with amide ,1633 (C=N), ν(NO_2) 1542,1357,823Ȣ(p-position)
7		198-200,	purple	70	dioxan	3434(OH), 3213(NH), 3033 (Ar-H), 2937(CH aliph.), 1647 (C=O) amid overlap with (C=O) quinaz,1639 (C=N), ν(C-O-C)1242,1172, Ȣ (p-position) 842
8		205-207	White	75	Acetone	3332(NH), 3068 (Ar-H), 2968, 2933(CH aliph.), 1683 (C=Oquinaz),1652(C=O amid) 1631 (C=N), ν(C-O-C)1253,1178, Ȣ (p-position) 840
9		230-232	light brown	75	Acetone	3390(NH), 3076, (Ar-H), 2979,2933(CH aliph.), 1652 (C=O quinaz.) overlap with (C=O amide),1622 (C=N),1101(Ar-Cl), 838Ȣ(p-position)

Table 3: ^{1}H-NMR and ^{13}C-NMR data spectrum of novel synthesized compounds 5-9

Com.no	Structure	^{1} H-NMR spectral data (Ȣ ppm)	^{13}C-NMRspectral data (Ȣ ppm)
3		1.34 (t,3H, CH_3);3.85 (s,3H, OCH_3),4.17 (q,2H, OCH_2); 4.67 (s,2H -NCH_2); 7.08-8.60 (m,8H, H aromatic)	14.52(CH_3),48.12(NCH_2), 55.82(OCH_3), 61.12(OCH_2),114.47-156.85(Ar-C), 162.68(C=N), 164.67(C=O) quinaz., 169.93 (C=O) ester
4		3.85 (s,3H, -OCH_3) 4.34(d,2H, -NH_2); 4.70 (s,2H, NCH_2), 7.01-8.51 (m,8H, H aromatic); 8.79(t,1H, NH)	46.81 (NCH_2);55.91(OCH_3), 112.21-152.16(Ar-C), 162.68(C=O) quinaz, 164.55(C=O) amide
5		2.92 (s,6H, -CH_3) ;3.82 (s,3H, -OCH_3); 4.83 (s,2H, -NCH_2); 6.71-8.64 (m,12H, H aromatic), 8.10(s,1H, HC=N), 9.15(s,1H,NH)	41.84(N$(CH_3)_2$ 46.81(NCH_2), 55.91(OCH_3), 114.62-156.82(Ar-C), 146.81(C=N) imine,162.74(C=N) quinaz 165.82(C=O) quinaz., 170.63 (C=O) amid
7		3.80 (s,3H, -OCH_3); 4.87 (s,2H, NCH_2); 6.82-8.31 (m,12H, H aromatic); 8.11(s,1H, HC=N), 9.12(s,1H, NH);10.01(s,1H,OH)	44.86(NCH_2), 55.91(OCH_3), 112.21-148.46(Ar-C), 146.81(C=N) imine,162.68(C=N) quinaz 165.82(C=O) quinaz., 169.65 (C=O) amid

The initial synthetic route involves reacting 2-amino benzoic acid to produce 1,4-dihydroquinazoline-4-one derivatives (compounds 10-14). The FTIR spectra of all compounds **10-14** exhibited the disappearance of absorption bands that represent imine groups ν (N=CH) at (1639-1622) cm^{-1}, whereas absorption bands corresponding to dihydroquinazolinone rings ν(N-H) appeared at (3433-3319) cm^{-1}. Furthermore, at (1711-1668) cm^{-1}, the absorption bands of amide groups overlap with those of dihydroquinazolinone rings at ν(C=O). The results of the study are presented in Table (4). However, the ^{1}H-NMR spectrum of compound **10** showed the disappearance of the singlet signal of (N=CH-) proton of Schiff's base **5** and the appearance a singlet signal at δ = 2.98 ppm for the (-NCH_3) protons. Another singlet signal at δ = 3.83 ppm corresponds to the (-OCH_3) protons. The (NCH_2) proton results in a singlet signal at δ = 4.69 ppm. The (C-H) proton in the dihydroquinazolinone ring exhibits a singlet signal at δ = 5.17 ppm. The (-N-H) proton in the dihydroquinazolinone ring is represented by a singlet signal at δ = 6.43 ppm. While multiple signals in the range of δ = 7.03-8.36 ppm correspond to the aromatic ring protons. Finally, the (O=C-NH) amide proton produce a singlet signal at δ=9.50 ppm. The ^{1}H-NMR spectral data for compound **10** are presented in Table (5). In addition to, ^{1}H-NMR for compound **11** indicated the absence of signal singlet of imine group (N=CH-) proton of Schiff bases **6** and observed a singlet signal at δ = 3.80 ppm corresponds to the (-OCH_3) protons. The (NCH_2) proton results in a singlet signal at δ = 4.69 ppm. The (C-H) proton in the dihydroquinazolinone ring exhibits a singlet signal at δ = 5.23 ppm. The (-N-H) proton in the dihydroquinazolinone ring is represented by a singlet signal at δ = 6.39 ppm. Finally, multiple signals in the range of δ = 7.06-8.33 ppm correspond to the aromatic ring protons. Also, the (O=C-NH) amide proton produces a singlet signal at δ=9.74 ppm. The ^{1}H-NMR spectral data and ^{13}C-NMR for compound **10 & 11** show in table (5)

Table 4: physical characteristics and FT-IR spectral data for compounds

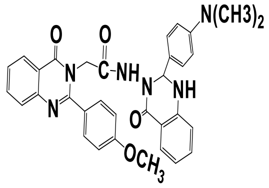
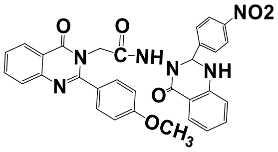
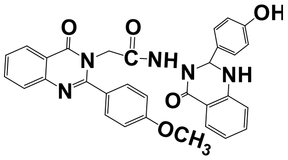
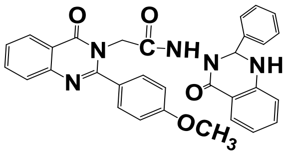
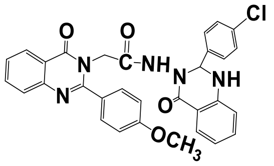
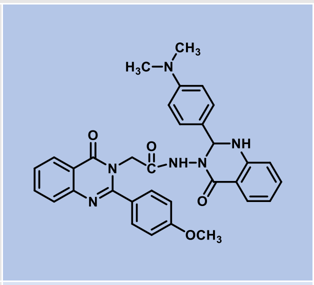
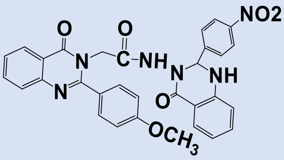
Com. no	Structure	m.p °C	Color	Yield%	FT-IR(νcm-1)
10		213-215	orang	75	3307, 3217(NH), 3064(Ar-H), 2975,2935(CH aliph.), 1687 (C=O cyclic) overlap with (C=O quinaz.), 1645(C=O amide), 842ẟ(p-position)
11		160-162	deep orang	82	3433 (NH), 3082(Ar-H), 2964,2931(CH aliph.) 1674, overlap (C=O cyclic) overlaps with (C=O quinaz.),1641(C=O amide) 1523&1361(NO_2),817ẟ(p-position)
12		122-124	Light red	78	3461 (OH), 3375, 3257(NH), 3068(Ar-H), 2964, 2935(CH aliph.), 1666 (C=O cyclic) overlaps with (C=O amid), 846 ẟ(p-position)
13		137-139	Brown	75	3398, 3215(NH), 3060(Ar-H), 2974,2935 (CH aliph), 1660 (C=O cyclic) overlaps with (C=O quinaz.), 1641(C=O amide) ,840ẟ(p-position)
14		165-167	Pale brown	90	3319,3209(NH),3070(Ar-H), 2970,2937(CH aliph),1668 (C=O cyclic) overlaps with (C=Oquinaz.), 1649(C=O amide) ,1116 (Ar-Cl), 844ẟ(p-position)

Table 5: ^{1}H-NMR and ^{13}C-NMR data spectrum of novel synthesized compounds 10,11

Com.no	Structure	^{1} H-NMR spectral data (ẟ ppm)	^{13}C-NMR spectral data (ẟ ppm)
10		2.98(s,6H, NCH_3) 3.83 (s,3H, -OCH_3); 4.69 (s,2H, NCH_2); 5.12(s,1H, -NCH) pyrimidine 6.43(s,1H, -NH) pyrimidine 7.03-8.36 (m,16H, H aromatic); 9.50(s,1H, NH)	41.48(NCH_3)2 48.46(NCH_2), 55.95(OCH_3), 73.53(NCH) pyrimidine 114.64-147.07(Ar-C), 156.50(C=N) quinaz 159.44(C=O) pyrimidine., 165.82(C=O) quinaz 170.63 (C=O) amid
11		3.80 (s,3H, -OCH_3); 4.69 (s,2H, NCH2);5.23(s,1H, -NCH) pyrimidine 6.39(s,1H, -NH) pyrimidine, 7.06-8.33 (m,16H, H aromatic); 9.74(s,1H, NH)	47.77(NCH2), 55.35(OCH3), 71.52(NCH) pyrimidine 114.51-148.72(Ar-C), 155.19(C=N) quinaz 161.42(C=O) pyrimidine., 162.34(C=O) quinaz 171.25 (C=O) amid

The second synthetic pathway involves the reaction with 2-hydroxy benzoic acid, yielding oxazine-4-one derivatives (compounds 15-19). The IR spectra show the disappearance of the Schiff base C=N absorption band at 1639-1622 cm-1 and the appearance of a new band at

1714-1668 cm-1 corresponding to the C=O stretch of the oxazine ring. The FT-IR spectrum data of compounds **15-19** is shown in table (6). The 1H-NMR spectrum of compound **15** showed the disappearance of the singlet signal of imine (N=CH-) proton of Schiff's base **5** and the appearance a singlet signal at δ = 3.01 ppm for the (-NCH_3) protons. Another singlet signal at δ = 3.79 ppm corresponds to the (-OCH_3) protons. The (NCH_2) proton produces a singlet signal at δ = 4.50 ppm. The (C-H) proton in the benzoxazinone ring exhibits a singlet signal at δ = 6.76 ppm. Also, multiple signals in the range of δ = 7.13-8.63 ppm correspond to the aromatic ring protons. Finally, the (-N-H) proton in amide is represented by a single signal at δ = 9.67 ppm. In addition, 1H-NMR for compound **17** indicated the absence of signal singlet of imine group (N=CH-) proton of Schiff bases **7** and observed a singlet signal at δ = 3.82 ppm corresponds to the (-OCH_3) protons. The (NCH_2) proton results from a singlet signal at δ = 4.35 ppm. The (C-H) proton in the benzoxazinone ring exhibits a singlet signal at δ = 6.86 ppm. Multiple signals in the range of δ = 7.06-8.33 ppm correspond to the (Ar-C) aromatic ring protons. Also, the (O=C-NH) amide proton produce a singlet signal at δ=9.74 ppm. The ^{1}H-NMR spectral data & ^{13} C-NMR for compounds **15, and 17** are presented in Table (7)

Table 6: physical characteristics and FT-IR spectral data for compounds 15-19

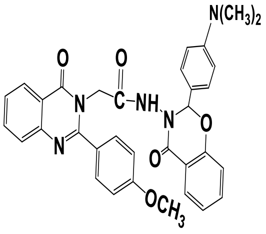
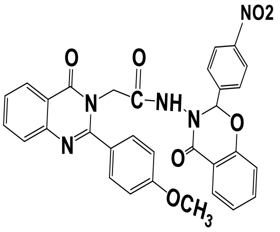
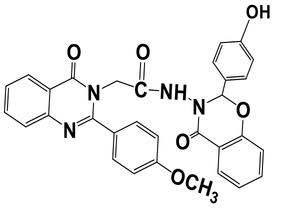
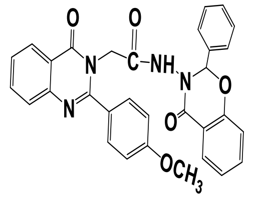
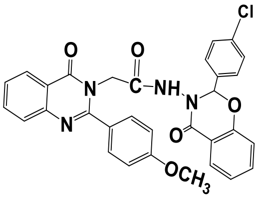
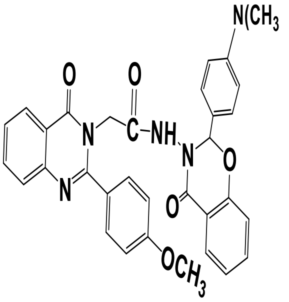
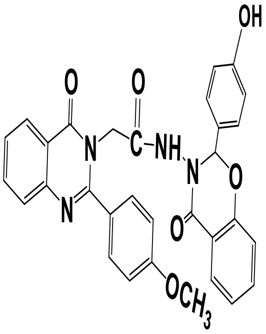
Com. no	Structure	m.p 0C	Color	Yield %	FT-IR(νcm^{-1})
15		119-121	Pale pink	85	3323 (NH), 3029(Ar-H),2975, 2933 (CH aliph.),1668(C=O cyclic) overlap with (C=O quinaz.),1649 (C=O amide),844ȣ(p-position)
16		77-79	yellow	80	3413(NH),3060(Ar-H),2975,2935(CH aliph.), 1714(C=O cyclic.) ,1666 (C=O quinaz.), 1641 (C=O amide),1527&1363 (NO_2),842ȣ(p-position)
17		87-89	Pale brown	75	3448(OH), 3386(NH), 3064(Ar-H), 2983, 2840 (CH aliph.), 1687(C=O cyclic) overlap with (C=O quinaz) 1647 (C=O amide),846ȣ(p-position)
18		180-182	red	80	3394(NH), 3070(Ar-H),2943,2887(CH aliph) 1685 (C=O cyclic) overlap with (C=O quinaz.), 846ȣ(p-position)
19		165-167	deep orang	75	3259(NH), 3097(Ar-H),2987,2914 (CH aliph.), 1687 (C=O cyclic),1670 (C=O quinaz) overlap with C=O amid),1108 (Ar-Cl),846ȣ(p-position)

Table 7: ^{1}H-NMR and ^{13}C-NMR data spectrum of novel synthesized compounds 15&17

Com. no	Structure	^{1} H-NMR spectral data (ȣ ppm)	^{13}C-NMR spectral data (ȣ ppm)
15		3.01(s,6H, -NCH$_3$),3.79 (s,3H, -OCH$_3$); 4.50 (s,2H, NCH$_2$); 6.76(s,1H, -NCH), benzoxazinone 7.13-8.63 (m,16H, H aromatic); .67(s,1H, NH)	41.48(NCH$_3$)2 ,48.46(NCH$_2$), 55.95(OCH$_3$),87.31(NCH) benzoxazinone 114.64-147.07(Ar-C), 156.85(C=N) quinaz.,165.82(C=O) quinaz, &benzoxazinone,170.63 (C=O) amid
17		3.82 (s,3H, -OCH$_3$); 4.35 (s,2H, NCH$_2$); 6.86(s,1H, -NCH) benzoxazinone, , 7.15-8.62 (m,16H, H aromatic); 9.74(s,1H, NH), 10.04(s,1H. OH)	45.87(NCH$_2$), 55.21(OCH$_3$), 86.10(NCH) benzoxazinone, 113.21-155.73(Ar-C),160.82 (C=N) quinaz,164.34(C=O) quinaz. & benzoxazinone, 170.26 (C=O) amid

The final method involves the reaction with 2-mercaptobenzoic acid to produce thiazine-4-one derivatives (compounds 20-24). This reaction also results in the disappearance of the absorption band at 1639-1622 cm^{-1}, which corresponds to the (C=N) of the Schiff base, while a new band appears at 709-648 cm^{-1}, associated with ν (C=O) in the thiazine ring. The FT-IR spectrum data of compounds **20-24** is shown in table (8). The 1H-NMR spectrum of compound **20** is listed the disappearance of the singlet signal of imine (N=CH-) proton of Schiff's base **5** and the appearance a singlet signal at $\delta = 2.88$ ppm for the (-NCH$_3$) protons. Another singlet signal at $\delta = 3.81$ ppm corresponds to the (-OCH$_3$) protons. The (NCH$_2$) proton produces a singlet signal at $\delta = 4.47$ ppm. The (C-H) proton in the thiazine ring exhibits a singlet signal at $\delta = 6.12$ ppm. Also, multiple signals in the range of $\delta = 6.84$-8.57 ppm refer to the aromatic ring protons. Finally, the (-N-H) proton in amide is represented by a single signal at $\delta = 8.74$ ppm. While the ^{1}H-NMR spectrum of compound **22** is listed the disappearance of the singlet signal of imine (N=CH-) proton of Schiff's base **7** and the appearance of a singlet signal at $\delta = 3.82$ ppm corresponds to the (-OCH$_3$) protons. The (NCH$_2$) proton results in a singlet signal at $\delta = 4.12$ ppm. The (C-H) proton in the thiazine ring exhibits a singlet signal at $\delta = 6.47$ ppm. Also, multiple signals in the range of $\delta = 7.13$-8.64 ppm correspond to the aromatic ring protons. The (-N-H) proton in amide is represented by a single signal at $\delta = 8.74$ ppm. Finally, a singlet signal at $\delta = 9.67$ ppm corresponds to the (-OH) protons. The ^{1}H-NMR spectral data & ^{13} C-NMR for compounds **20,** and **22** are presented in Table (9). The FTIR spectra and ^{1}HNMR for compounds **5, 7, 10**, and **11** are shown in Figures 1–8.

Table 8: physical characteristics and FT-IR spectral data for compounds 20-24

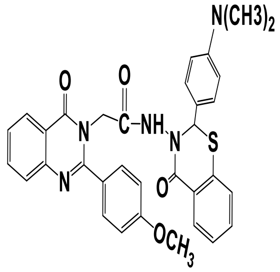
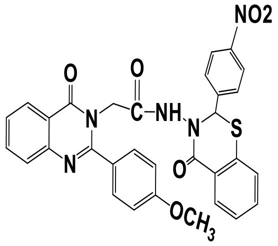
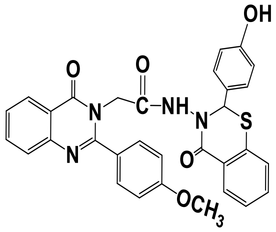
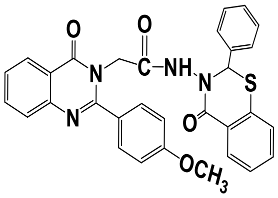
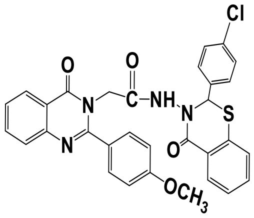
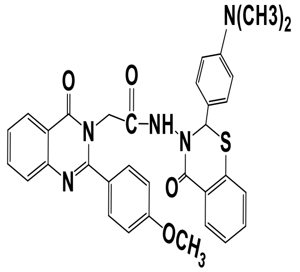
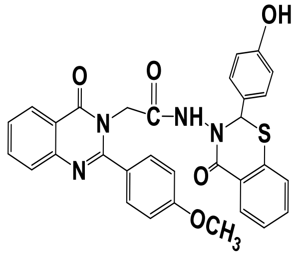
Com. No	Com. Structure	m.p 0C	Color	Yield%	FT-IR(νcm-1)
20		219-221	Light yellow	70	3323, (NH),3070(Ar-H), 2975,2840(CH aliph.),1668 (C=O cyclic.) overlaps (C=O quinaz.), 1649(C=O amide), 844Ȣ(p-position) Ȣ(p-position) 844, ν(C-S) 698
21		200-202	Green	80	3404(NH), 3060(Ar-H), 2977,2910(CH aliphatic), 1672 (C=O cyclic, 1531&1367 (NO_2), Ȣ (p-position) 842, ν(C-S) 649
22		87-89	Deep yellow	77	3421(OH),3228 (NH), 3072(Ar-H),2977, 2871(CH aliph.), 1662 (C=O cyclic), Ȣ (p-position) 836, ν(C-S) 649
23		174-176	white	75	3247(NH), 3066(Ar-H), 2962,2837 (CH aliph.), 1694 (C=O cyclic). 1679 (C=O quinaz) ,1648 (C=O amide), Ȣ (p-position) 846,ν(C-S) 649
24		190-192	Pele yellow	80	3259(NH), 3097(Ar-H) 2987, 2935(CH alph.), 1687 (C=O cyclic), 1670 (C=O quinaz), overlap with (C=O amid),ν(C-O-C) 1251,1188, (Ar-Cl) 1108 Ȣ(p-position),846,ν(C-S) 649

Table 9: ^{1}H-NMR and ^{13}C-NMR data spectrum of novel synthesized compounds 20&22

Com.no	Structure	^{l} H-NMR spectral data (Ȣ ppm)	^{3}C-NMR spectral data (Ȣ ppm)
20		3.01(s,6H, N-CH$_3$) 3.85(s,3H, -O-CH$_3$) 4.50(s,2H, -N-CH$_2$) 6.76(s,1H, -SCH thaizin ring),7.13-8.63 (m,16H, Ar-H); 9.67 (s,1H, -NH)	41.48(-NCH$_3$) 47.75(N-CH$_2$) ,55.92(-O-CH3) 65.12(S-CH thiazine ring), 114.23-156.85(Ar-C) 162.80(C=O thiazine) 164.67.20(C=Oquinazoline) 169.86(C=O amide)
22		3.82(s,3H, -O-CH$_3$), 4.12 (s,2H, -N-CH$_2$), 6.74(s,1H, -SCH thaizin ring),6.75-8.63 (m,17H, Ar-H);8.74(s,1H, -OH), 9.67 (s,1H, -NH)	47.28(N-CH$_2$), 55.73(-O-CH$_3$); 65.24 (S-CH thiazine ring). 113.21-152.71 (Ar-C), 162.69(C=O thiazine) 164.34 (C=O quinazolinone), 170.26 (C=O amide),

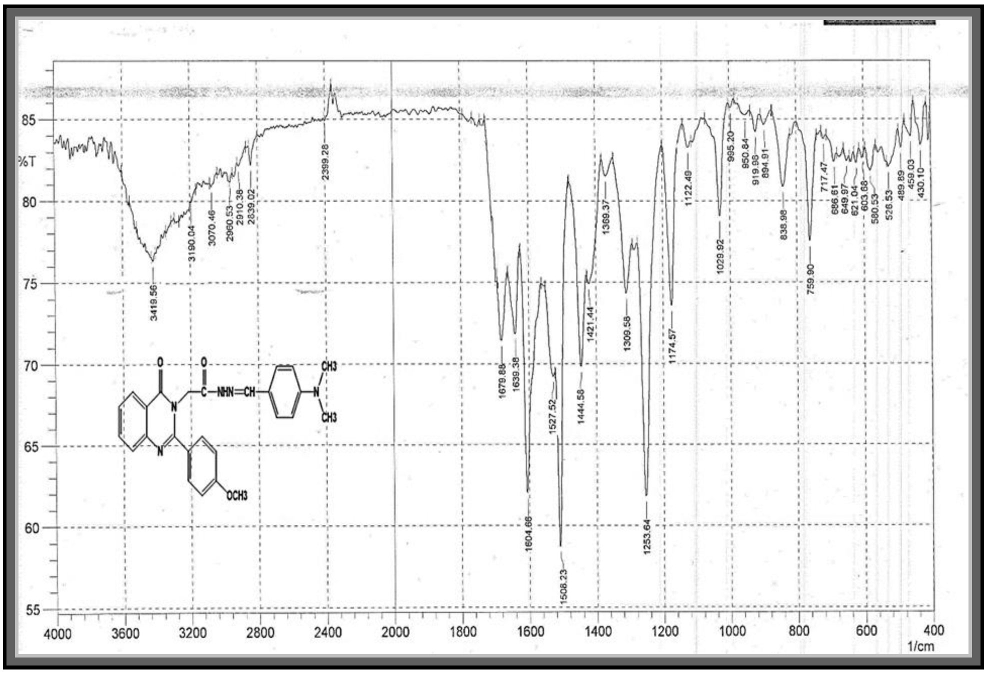


Figure 1: FT-IR for compound 5

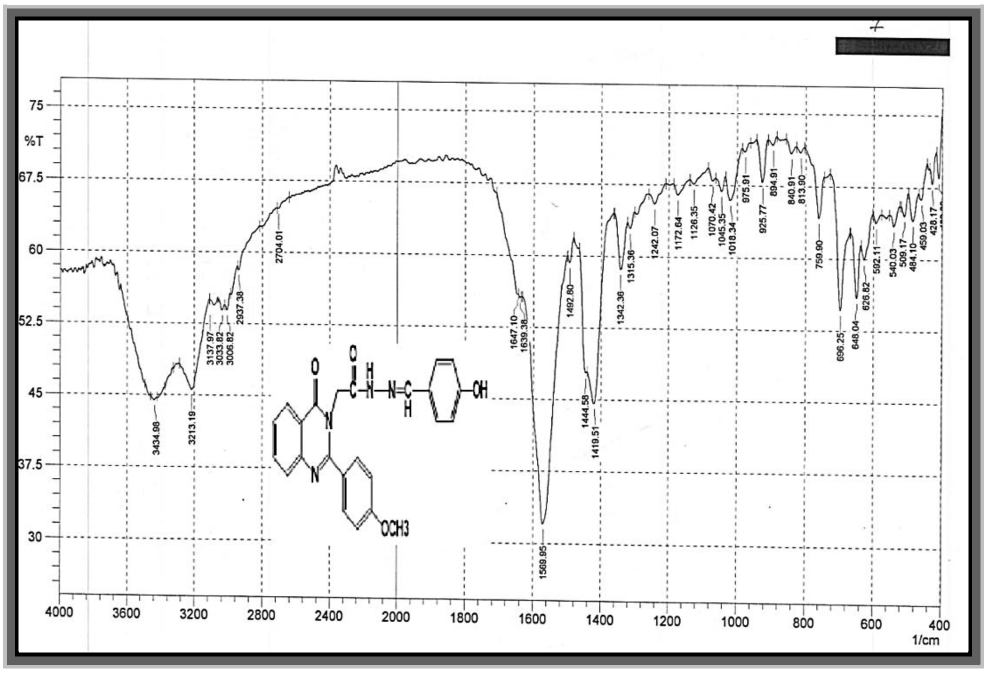


Figure 2: FT-IR for compound 7

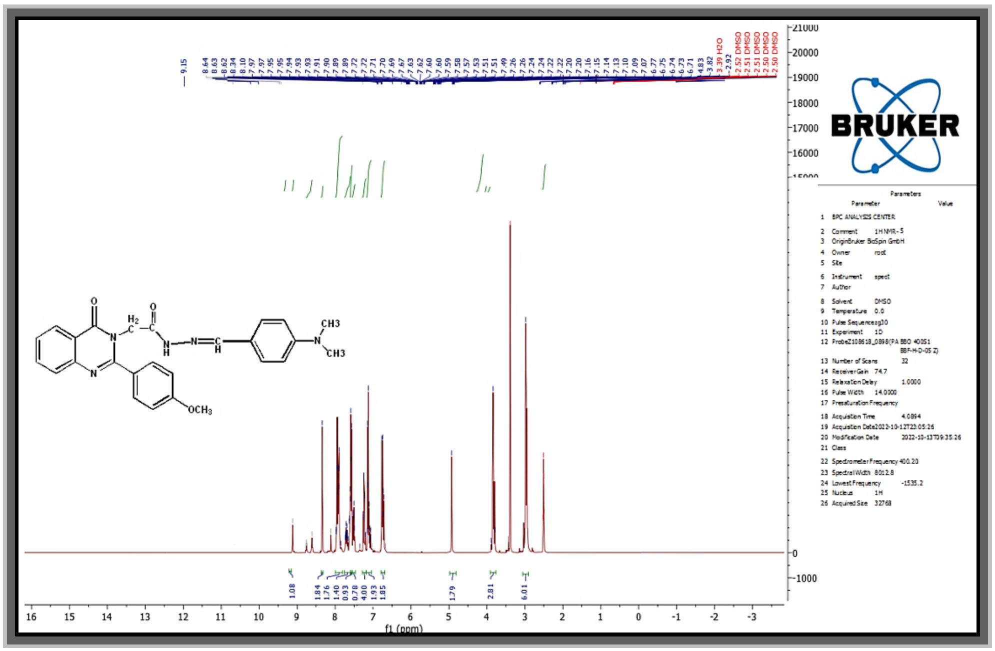


Figure 3 : ^{1}H-NMR spectrum of compound 5

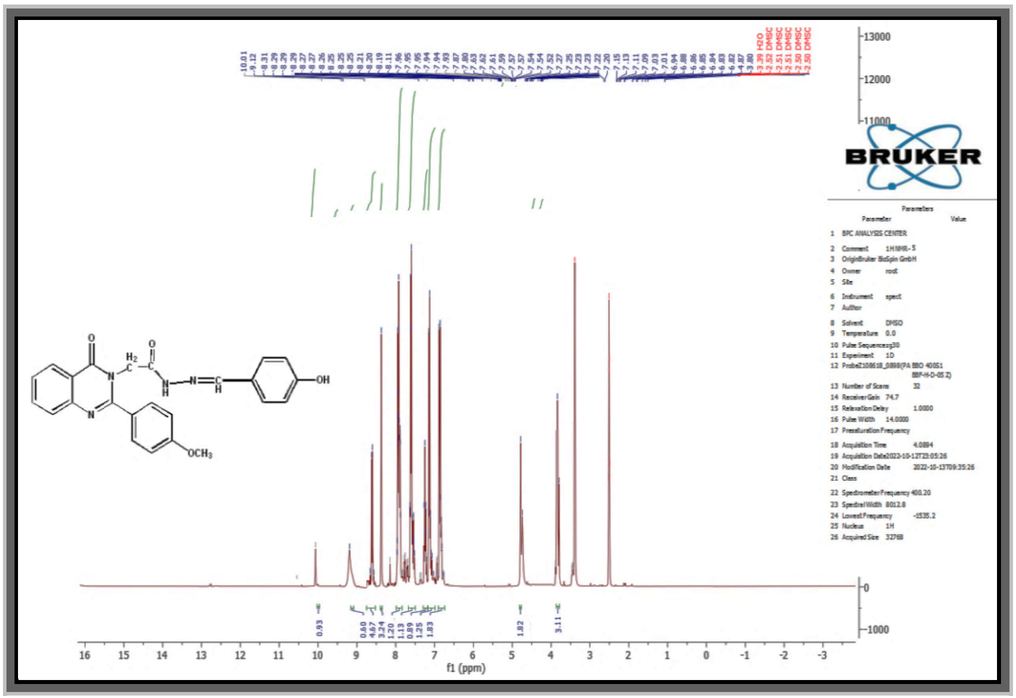


Figure 4: ^{1}H-NMR spectrum of compound 7

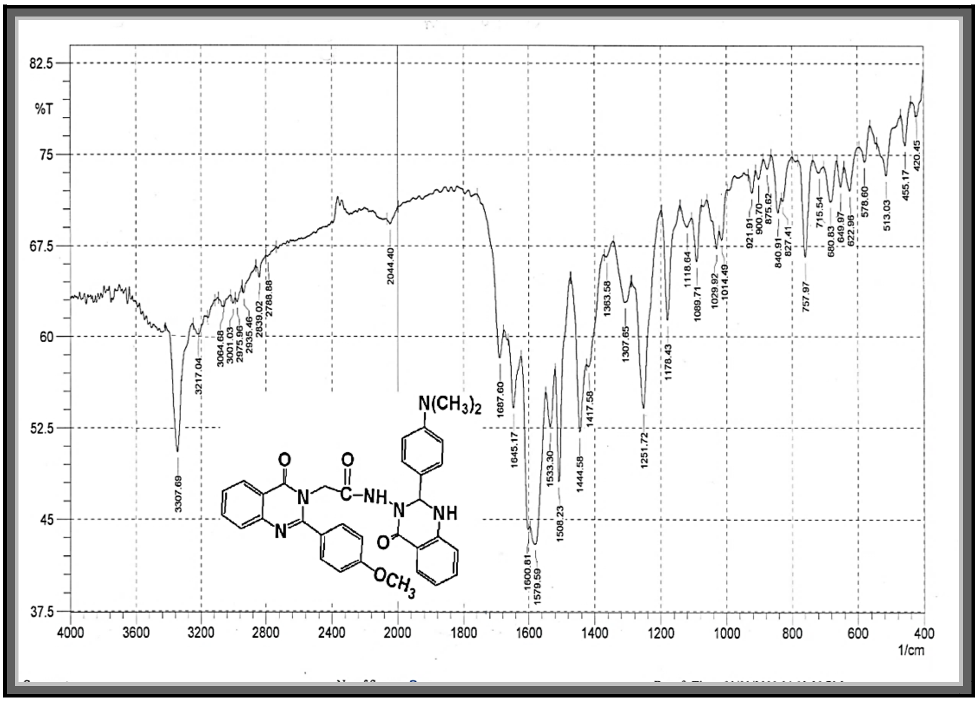


Figure 5 : FT-IR for compound 10

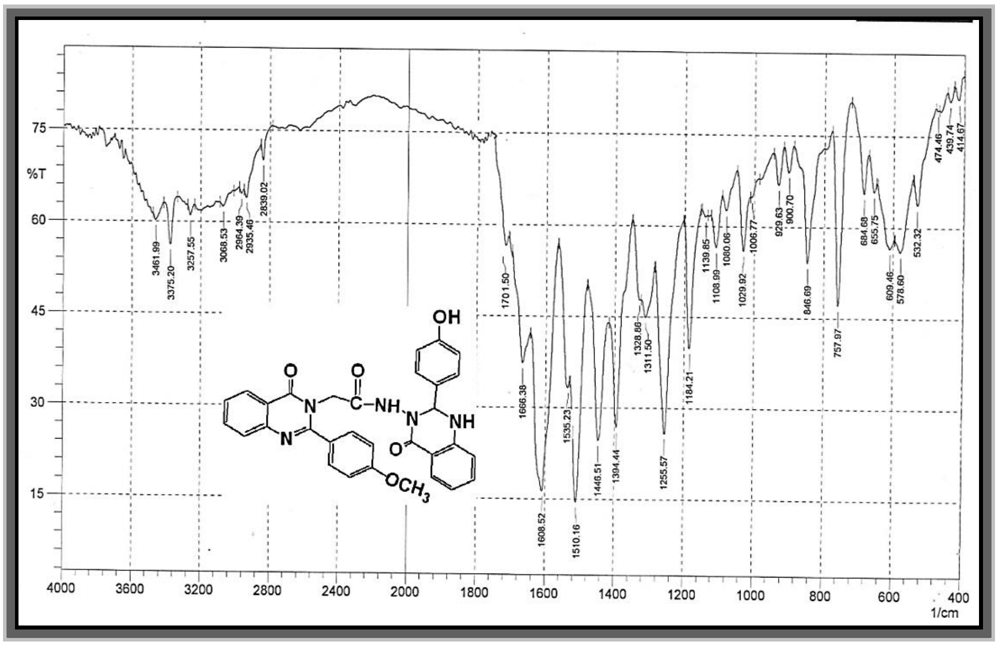
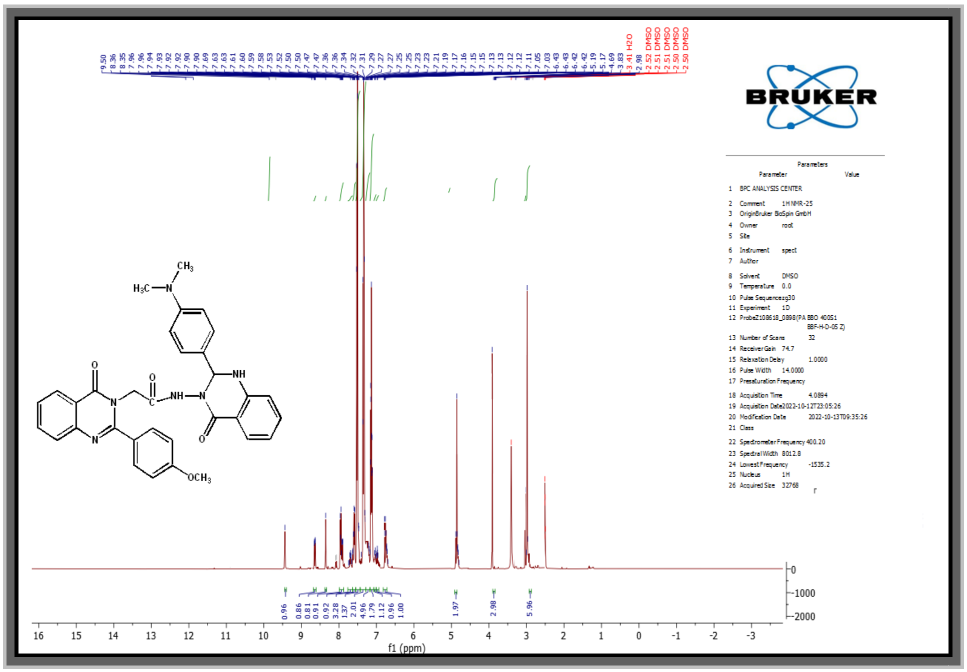


Figure 6 : FT-IR for compound 12



Parameters

	Parameter	Value
1	BPC ANALYSIS CENTER	
2	Comment	1H NMR-25
3	Origin	Bruker BioSpin GmbH
4	Owner	root
5	Site	
6	Instrument	spect
7	Author	
8	Solvent	DMSO
9	Temperature	0.0
10	Pulse Sequence	zg30
11	Experiment	1D
12	Probe	Z108618_0898 (PA BBO 400S1 BBF-H-D-05 Z)
13	Number of Scans	32
14	Receiver Gain	74.7
15	Relaxation Delay	1.0000
16	Pulse Width	14.0000
17	Presaturation Frequency	
18	Acquisition Time	4.0894
19	Acquisition Date	2022-10-12T23:05:26
20	Modification Date	2022-10-13T09:35:26
21	Class	
22	Spectrometer Frequency	400.20
23	Spectral Width	8012.8
24	Lowest Frequency	-1535.2
25	Nucleus	1H
26	Acquired Size	32768

Figure 7 : ^{1}H-NMR spectrum of compound 10

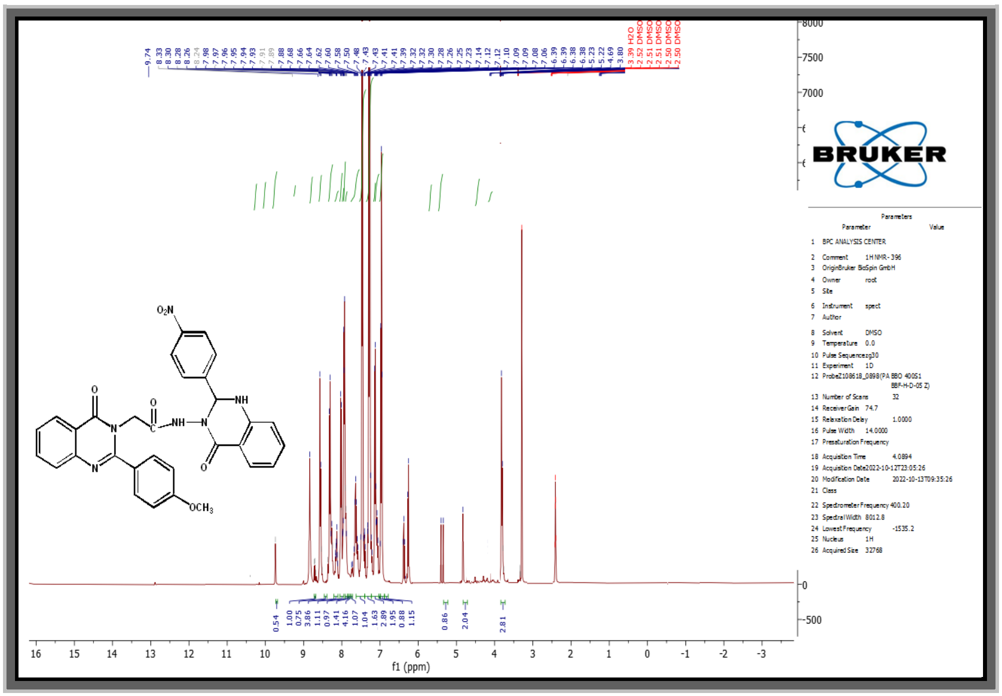


Figure 8 : ^{1}H-NMR spectrum of compound 11

Anti-microbial activity

Some of the synthesized compounds 4(3H) quinazolinone derivatives (1,4-dihydro quinazoline -4-one, Oxazine -4-one and Thiazine -4-one derivatives) were screened for anti –microbial activities against two grams negative (***Escherichia coli*** and ***Pseudomonas auroginosa)*** and two grams positive (***Staphylococcus aureus*** and **Bacillus** ***cereus***) bacteria and two strain of fungi (***Candida albicans*** and ***Rhizopus Microrhizosporium***). The results indicated that compounds 3, 4, 5, 6, 7, 12,17 and 19 exhibited moderate activity against gram-positive ***Staphylococcus aureus*.** Additionally, compounds 3, 4, 5, 6, 7, 12, and 17 demonstrated good activity against gram-negative ***Escherichia coli*** except 19 had a moderate activity against ***Escherichia coli***. Compounds 4,5,17 and 19 have a good activity against gram-negative ***Pseudomonas auroginosa*** but 3,6,7 and 12 have a moderate activity against ***Pseudomonas auroginosa.*** Compounds 7 and 19 have moderate activities against gram-positive ***Bacillus cereus*** but the other compounds have a good activity against the same bacteria. On the other hand, the test compounds 3,4,6,7,12,17 and 19 have good activity against ***Candida albicans*** but 5 and 6 have moderate activity against this strain of fungi [31-35]. Compounds 3,12 and 19 have very good activity against ***Rhizopus Microrhizosporium*** also the other compounds 4,5,6,7 and 17 have good activity against ***Rhizopus Microrhizosporium.*** Compounds 21 and 22 have good activity against the fungus Candida albicans and ***Rhizopus Microrhizosporium*** but are not effective against all species of bacteria. ***Escherichia coli, Pseudomonas auroginosa and Staphylococcus aureus and Bacillus cereus.***

Table 10: The antimicrobial activity of the synthesized compounds tested
[Control]: 80 µg/mL; solvent: dimethylsolfoxide; Inhibition Zone: (-) no inhibition; (1-6) weak; (7-11) moderate; (12-19) good; ≤ 20 very good

Com No.	Diameter of inhibition zone (mm)					
	Escherichia coli -ve	***Pseudomonas auroginosa -ve***	***Staphylococcus aureus +ve***	***Bacillus cereus +ve***	***Candida albicans***	***Rhizopus Microrhizosporium***
Control\ DMSO	–	–	–	–	–	–
Amoxillin	9	8	10	8	8	9
3	15	11	11	15	12	20
4	14	16	10	17	15	17
5	12	19	10	12	10	13
6	13	8	9	12	9	17
7	14	9	9	9	12	16
12	12	11	9	12	12	20
17	14	16	8	13	13	15
19	11	12	8	11	14	22

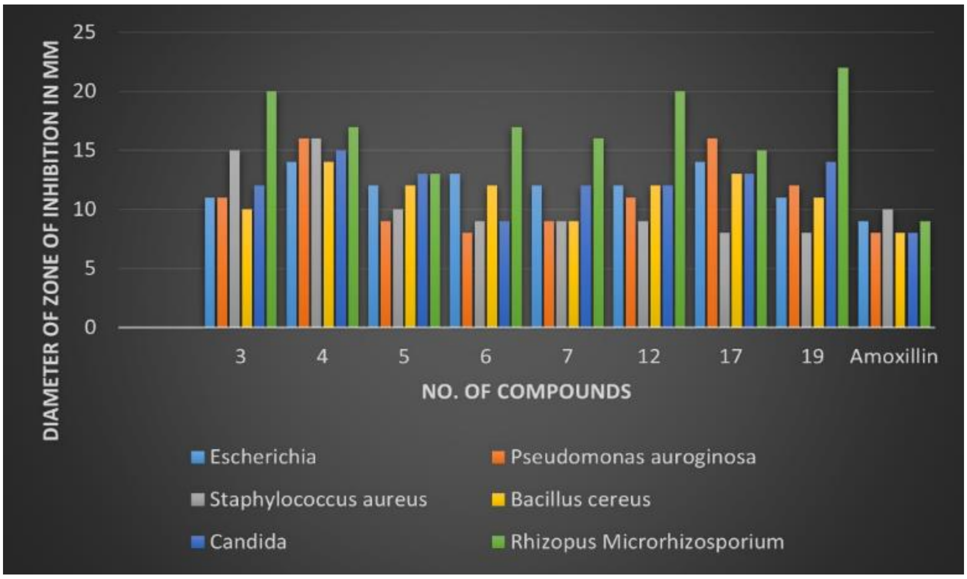


Figure 9: Inhibition of the test compounds with drug

Conclusion

This study aimed to synthesize a series of novel six-member rings bearing 4(3H)-quinazolinone derivatives (1,4-dihydro quinazoline -4-one, Oxazine -4-one and Thiazine -4-one derivatives) and to evaluate their antimicrobial activities. The results indicated that the tested compounds 3, 4, 5, 6, 7, 12,17 and 19 exhibited moderate to good activity against Gram-negative bacteria ***Escherichia coli***, Pseudomonas aeruginosa and against Gram-positive Bacteria **Staphylococcus,** and ***Bacillus cereus***. Additionally, compounds 3, 4, 6, 7, 12,17 and 19 demonstrated good activity against ***Candida albicans*** but 5 and 6 had moderate activity against this strain of fungi. But compounds 3,12 and 19 have very good activity against **Rhizopus Microrhizosporium** also compounds 4,5,6,7 and 17 have good activity against ***Rhizopus Microrhizosporium***. Compounds 21and 22 have good activity against two strains of fungus: ***Candida albicans*** and ***Rhizopus Microrhizosporium*** but not effective against all strains of bacteria: ***Escherichia coli, Pseudomonas aeruginosa*** and against Bacteria ***Staphylococcus, and Bacillus cereus***.

5. Acknowledgements

I begin by giving thanks to the great Allah, who bestowed upon me the strength and health necessary to accomplish my studies. Also, I would like to thank the Department of Chemistry for providing all chemicals and certain equipment.

6. Conflict of Interest

The authors declare that they have no conflict of interest.

7. Compliance with ethical standards

This section states that none of the authors have examined animals or people.

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