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1-Abstract

In this study, phenylquinazoline-4-(3H)one, one of the significant heterocyclic compounds, is chosen to prepare many of its derivatives, which are considered Schiff bases, by reacting the heterocyclic compound with a number of aromatic aldehyde derivatives, including salicyaldehyde, piperonal, and vanillin, as well as ketone derivatives, including acetophenone, o-hydroxyacetophenone, p-nitroacetophenone, 2-bromoacetophenone, p-chloroacetophenone, and m-nitroacetophenone to prepare many Schiff bases, which are considered very important in organic and inorganic reactions, to prepare derivatives that have pharmaceutical, industrial, and agricultural applications. These prepared compounds were characterized using multiple techniques, including physical and functional techniques, to obtain their expected composition.

Keyword: quinazolinone, Schiff base, hydrazone, transition metal complexes.

2- Introduction

Quinazolinone is one of the most common heterocyclic compounds used in medical and pharmaceutical research. It is a heterocyclic compound whose structural formula consists of two aromatic rings, namely benzene and a pyrimidine, which contain two nitrogen atoms. It was first called benzodiazine, then Weddige called it quinazoline, derived from the German word (Chinazoline) [1]. Quinazolinone derivatives have medicinal properties, including analgesic, anti-inflammatory and anti-cancer activities, as well as antimicrobial [2,3]. Quinazoline is mostly found in the form of alkaloids in the stems and leaves of some medicinal plants called Chinese quinine, examples of which include Dichroq febrifuga [4]. Quinazolinone is considered more distinguished as an intermediate compound for developing and exploring new pharmaceutical formulations or as a basic nucleus for natural product compounds [5,6], it is characterized by its high melting points and being a crystalline solid that does not dissolve in water or in most organic solvents, but it dissolves in alkaline aqueous solutions and does not dissolve in aqueous solutions of dilute acids, but sometimes it dissolves in concentrated solutions, as the simple quinazolines can dissolve in hydrochloric acid solution, where they form stable salts of monohydrochloride. It is also possible to form chlorurate and chloroplatinate, as they are salts with some metals such as copper, mercury, and zinc [5]. It is relatively easy to prepare and most of its derivatives are often prepared to obtain biologically active compounds in chemistry. Series of compounds containing a quinazoline nucleus were designed by linking their nucleus to a group that increases their effectiveness or linking them to compounds with known pharmacological activity, taking advantage of innovative and advanced preparation methods [7,8], and through their effectiveness, they receive great attention in a variety of properties [9]. It has been proven that aromatic quinazoline has tyrosine kinase inhibitor, which is beneficial for controlling tumor growth [10]. The quinazoline compound is one of the important compounds that is considered the building block for many heterocyclic compounds that have important effectiveness [11,12]. Also, quinazoline ring is the main key to most anti-convulsant drugs in pharmaceutical chemistry because it possesses analgesic and anti-inflammatory activity [13,14,15], as the interactions associated with the tonic nature of quinazolinones are often very complex and unpredictable. In general, it is most likely in the form of a keto or enol, while the stability of the ring system in quinazoline is very stable towards redox reactions and hydrolysis, and there is no report on the degradation of quinazoline by simple chemical oxidation [16]. Quinazoline-4-(3H)one derivatives have shown different ranges of effectiveness from mild to moderate, i.e. possibility of mild ulcer, compared to aspirin [17,18,19] and are considered a successful anti-inflammatory agent in the treatment of the lower back, i.e. a centrally acting muscle relaxant [20], and quinazoline derivatives have shown that they have many potential antimicrobial activities, as there is a large group of active biological agents such as antibacterial, antifungal, antiviral, plasma, and others [21, 22]. Research has continued to prepare Quinazoline-4-(3H) one derivatives using the microwave method [23]. In some reactions, ultrasound has been used to carry out some reactions that require high temperature and high pressure, for example the Bischler cyclization method, which is one of the most prominent conventional methods that is carried out at a temperature of (120 C°) [24,25]. In this research, compounds containing the following were prepared: [26]

 M_1 : 2-aryl-4H-1,3-benzoxazine-4-one

M2: 3-amino-2-aryl-4-quinazoline

M₃: (E)-2-phenyl-3-((1-phenylethylidene)amino)quinazolin-4(3H)-one)

 $M_4: (E) - 3 - ((1 - (2 - hydroxyphenyl) ethylidene) amino) - 2 - phenylquinazolin - 4(3H) - one$

 $M_5: (E) - 3 - ((1 - (4 - nitrophenyl) ethylidene) amino) - 2 - phenylquinazolin - 4(3H) - one$

M7:(E)-3-((1-(2-bromophenyl)ethylidene)amino)-2-phenylquinazolin-4(3H)-one

M8:(E)-3-((benzo(d)(1,3)dioxol-5-ylmethylene)amino)-2-phenylquinazolin-4(3H)-one

M₉:(E)-3-((1-(3-nitrophenyl)ethylidene)amino)-2-phenylquinazolin-4(3H)-one

M₁₀:(E)-3-((1-(4-chlorophenyl)ethylidene)amino)-2-phenylquinazolin-4(3H)-one

M₁₁:(E)-3-((1-(4-hydroxy-3-methoxyphenyl)ethylidene)amino)-2-phenylquinazolin-4(3H)-one

M₁₃:(E)-3-((2-hydroxybenzylidene)amino)-2-phenylquinazolin-4(3H)-one

3- Materials and devices

The chemicals used are all of high purity and were used without any purification process. The melting points of the prepared compounds were recorded using a Stuart Melting Point /30 SMP device of British origin in the laboratories of the Chemistry Department, College of Education for Girls / University of Mosul.

Infrared measurements were carried out using a Japanese-made FT-IR 8400 S Shimadzu Spectrophotometer in the region between 400-4000 cm⁻¹ in terms of wavenumber in the laboratories of the Chemistry Department / College of Science / University of Tikrit.

The ¹H-NMR spectrum of the compounds was also measured using a 400 MHz Bruker DRX system device, using Tetramethylsilane (TMS) as an internal standard reference, and dimethyl sulfoxide (DMSO-d⁶) solvent at the College of Science/University of Basra.

The mass spectrum was measured to determine the molecular weight of the compounds using a GAS Chromatography Mass Spectrometry Measurement Gas device, type GC-MS-QP2010Ultra, equipped by the Japanese company Shimadzu, in the Central Laboratory/ College of Applied Sciences/ Samarra University.

CHN was measured by an Italian manufacturer EuroVector S.p.A. - EuroEA3000 CHNS-O Analyzer, which is based on Turbo Flash Combustion Technology, which provides the highest levels of speed and performance at the University of Tehran.

As for the device to sterilize the agricultural medium and dishes from bacteria, using a device of the type (Hirayama) of Japanese origin in the Department of Biology / College of Education for Girls / University of Mosul.

4- Practical part

4.1- Synthesis of (M1) 2-aryl-4H-1,3-benzoxazine-4-one

(1.71g, 0.0125mol) of anthranilic acid was taken in a round flask to which (15 ml) of pyridine was added in an ice bath using a magnetic stirring device, then (3.50g, 0.025mol) of benzoyl chloride was placed in a baker, cooled for half an hour in ice bath and add drop by drop to the round flask for half an hour. Stir the mixture for three hours until a precipitate forms, then the precipitate is filtered, washed well with water, recrystallized from ethanol, and dried under vacuum pressure, as in the chemical equation:



2-aryl-4H-1,3-benzoxazine-4-one (M₁)

4.2- Synthesis of (M₂) 3-amino-2-aryl-4-quianzolone

(1.11g, 0.005mol) of M₁ compound was taken in a round flask and (4 ml) of hydrazine hydrate (85%) was added drop by drop, then (10ml) of ethanol was added. The mixture was stirred with a magnetic stirrer and heated (117C°) for three hours, then cooled. The resulting precipitate is filtered, recrystallized from ethanol, and then dried under vacuum pressure, as in the chemical equation:



3-amino-2-aryl-4-quian: (M2)

4.3- Synthesis of (M₃)

(E)-2-phenyl-3-((1-phenylethylidene)amino)quinazolin-4(3H)-one)

(1.18g, 0.005mol) of compound M₂ was added to (0.60g, 0.005mol) of acetophenone, then 20 ml of absolute ethanol and drops of glacial acetic acid were added in a round flask. The mixture was heated for (6 hours), then the mixture was cooled in an ice bath, until the precipitate appears, then it is filtered, dried, and the precipitate is recrystallized from ethanol.

4.4- Synthesis of (M₄)

((E)-3-((1-(2-hydroxyphenyl)ethylidene)amino)-2-phenylquinazolin-4(3H)-one

(1.18g, 0.005mol) of compound M₂ was added to (0.68g, 0.005mol) of orthohydroxyacetophenone, then the same steps as paragraph (4-3) are followed.

4.5- Synthesis of (M₅)

(E)-3-((1-(4-nitrophenyl)ethylidene)amino)-2-phenylquinazolin-4(3H)-one

(1.18g, 0.005mol) of compound M₂ was added to (0.82g, 0.005mol) of para-nitroacetophenone, then the same steps as paragraph (4-3) are followed.

4.6- Synthesis of (M₇)

(E)-3-((1-(2-bromophenyl)ethylidene)amino)-2-phenylquinazolin-4(3H)- one

(1.18g, 0.005mol) of compound M₂ was added to (0.99g, 0.005mol) of 2-bromoacetophenone, then the same steps as paragraph (4-3) are followed.

4.7- Synthesis of (M₈)

(E)-3-((benzo(d)(1,3)dioxol-5-ylmethylene)amino)-2-phenylquinazolin-4(3H)-one

(1.18g, 0.005mol) of compound M₂ was added to (0.75g, 0.005mol) of piperonal, then the same steps as paragraph (4-3) are followed.

4.8- Synthesis of (M₉)

(E)-3-((1-(3-nitrophenyl)ethylidene)amino)-2-phenylquinazolin-4(3H)-one

(0.6g, 0.005mol) of compound M₂ was added to (0.82g, 0.005mol) of meta-nitroacetophenone, then the same steps as paragraph (4-3) are followed.

4.9- Synthesis of (M10)

(E) - 3 - ((1 - (4 - chlorophenyl) ethylidene) amino) - 2 - phenylquinazolin - 4(3H) - one

(0.6g, 0.005mol) of compound M₂ was added to (0.77g, 0.005mol) of para-chloroacetophenone, then the same steps as paragraph (4-3) are followed.

4.10- Synthesis of (M11)

(E)-3-((1-(4-hydroxy-3-methoxyphenyl)ethylidene)amino)-2-phenylquinazolin-4(3H)-one

(0.6g, 0.005 mol) of compound M₂ was added to (0.76g, 0.005 mol) of vanillin, then the same steps as paragraph (4-3) are followed.

4.11- Synthesis of (M₁₃)

(E)-3-((2-hydroxybenzylidene)amino)-2-phenylquinazolin-4(3H)-one

(0.6g, 0.005mol) of compound M₂ was added to (0.61g, 0.005mol) of salicyaldehyde, then the same steps as paragraph (4-3) are followed.

Table (1) shows some physical properties of the prepared compounds, and Scheme (1) shows the method for preparing Schiff bases (hydrazones) (M_3 - M_5 - M_7 - M_{11} , M_{13}).

(M2)

Compd	M.P.	yield	Colour	Analysis Calc. (Found)			
compu.	(C°)	(%)	Colour	С%	Н%	N%	
M1	118-	87%	Yellow	(75.33)	(4.03)	(6.27)	
141	120	0770	Tenow				
Ma	190-	81%	White	(70.88)	(4.64)	(17.72)	
1412	192						
Ma	232-	85%	White	(77.87)	(5.01)	(12.38)	
1413	235	0570	white	78.47	4.37	12.66	
M4	227-	90%	White	(74.36)	(4.78)	(11.83)	
	230	<i>J</i> 070	white	73.91	4.62	12.16	
M	225-	90%	White	(68.75)	(4.16)	(14.58)	
1015	228						
M-	114-	75%	Yellow	(63.17)	(3.82)	(10.05)	
1 v1 7	117						
Ma	220-	0.0%	Paiga	(71.54)	(4.06)	(11.38)	
1018	223	9070	Deige	70.68	4.47	10.46	
M.	239-	010/	White	(68.75)	(4.16)	(14.58)	
1019	242	91/0	white				
Mia	226-	800/	White	(70.70)	(4.28)	(11.24)	
14110	228	0070	winte				
M	253-	0.5%	White	(73.90)	(4.39)	(12.31)	
101	255	95/0	white				
Mia	227-	95%	White	(71.15)	(4.58)	(11.32)	
1 v1 13	230		w mite	70.75	4.65	12.25	

Table (1) Elemental analysis and some physical properties of Schiff base compounds (hydrazones)



 R_4

 \mathbf{R}_1



 R_2





 M_2



M_{13} : R_1, R_3, R_4 -H , R_2 =OH

Scheme (1) The method for preparing Schiff bases (hydrazones) (M₃-M₅, M₇-M₁₁,M₁₃)

Some physical properties and elemental analysis data of the compounds (quinazolinone and Schiff bases, hydrazones) are summarized in (Table 1) The results confirm the proposed composition.

Synthesis of Schiff bases (hydrazones): The reaction occurs through the mechanism of nucleophilic addition, which is accompanied by the loss of a water molecule to form hydrazones, as in the following mechanism:



Scheme (2): Mechanism of nucleophilic addition to form hydrazones

5- Results and discussion

New 3-amino-2-phenyl-(3H)-4-quinazolinone derivatives synthesis by reaction between 3-amino-2-aryl-4-aquinazolone (M_2) and aldehyde or ketone derivatives yielded only one product (Scheme 1). [26]

5.1- Infrared spectrum

The prepared compounds were identified using the infrared spectrum in Table (2) and Figures (1-11), where the compound M_1 showed the stretching frequency of the carbonyl group v (C=O) at (1764 cm⁻¹) and the stretching frequency of the bond v (C=N) at (1614 cm⁻¹) As for the bond v (C-O), it showed a stretch value of (1062 cm⁻¹)

Compound M₂: The appearance of the v (N-H) band at (3317 cm⁻¹) in the IR spectrum of this compound is considered evidence of the formation of compound M₂. Likewise, the shift of the frequency of the carbonyl group band from 1750 cm⁻¹ to 1658 cm⁻¹ is another evidence of the formation of the compound M₂ because it is carbonyl amide.

Likewise, the prepared hydrazones (M_{3} , M_{5} , M_{7} , M_{11} , M_{13}) were characterized by the infrared spectrum. These compounds showed distinct bands at frequencies (1651-1680 cm⁻¹) attributed to the stretching vibration of the bond v (C=O) for the carbonyl group, and the high value is sometimes due to the fact that the hydrazide carbonyl group sometimes appears fused with it. As for the stretching frequency of the bond v (OH) for compounds (M_{4} , M_{11} , M_{13}), it appears at (3315-3282 cm⁻¹).

It also showed bands at the frequencies range (1514-1651 cm⁻¹) and (1572-1606 cm⁻¹) that are due to the union of the bond stretching v (C=N) and the bond stretching frequency v (C=C) in the compound, respectively.

Bands also appeared at frequencies (3068-3028 cm⁻¹) that correspond to the symmetrical stretching frequencies of the (CH)_{ar} group of the prepared compounds.

Bands of symmetrical and asymmetrical stretching of the nitro group appeared in compounds M_5 and M_9 at (1344, 1346 cm⁻¹) and (1518, 1523 cm⁻¹), respectively.

A band appeared at (549 cm⁻¹), (540, 780 cm⁻¹) for the (C-Cl) bond in compound M_{10} , and a band appeared at (646 cm⁻¹) for the (C-Br) bond in compound M_7 . [27]

comp	(C=N) v	(C=O) v	v (C=N) _{ring}	v (C=C) ar	v(N-N)	(CH)ar v	v(CH ₃) sy	v(CH3) as	v(NO ₂)	Others
M1	-	1746	1614	1572	-	3034	-	-	-	v (C-O) _{ring} 1471
M ₂	-	1658	1529	1602	934	3064	-	-	-	v (NH) 3317
M ₃	1649	1664	1529	1602	1024	3028	1319	1446	-	-
M4	1584	1654	1527	1602	1024	3030	1330	1446	-	v (OH) 3315
M5	1647	1680	1581	1599	980	3030	1311	1442	1518as 1344s	-
M ₇	1589	1662	1523	1606	1024	3032	1369	1448	-	v (C-Br) 646
M ₈	1649	1658	1589	1604	1033	3068	1316	1450	-	v (CH) _{al} 2895 v (C-O) _{ring} 1261
M9	1651	1672	1581	1602	1035	3034	1318	1446	1523as 1346s	-
M ₁₀	1647	1672	1583	1602	976	3030	1311	1448	-	v (C-Cl) 549
M ₁₁	1514	1651	1587	1600	1031	3051	1315	1425	-	v (CH) _{al} 2839 v (OH) 3302
M ₁₃	1651	1666	1583	1606	1030	3053	-	-	-	v (CH) _{al} 2880 v (OH) 3282

Table (2) : Infrared spectrum bands for the prepared compounds



Figure (1): Infrared spectrum of compound M₁



Figure (2): Infrared spectrum of compound M₂



Figure (3): Infrared spectrum of compound M₃



Figure (4): Infrared spectrum of compound M₄



Figure (5): Infrared spectrum of compound M5



Figure (6): Infrared spectrum of compound M7



Figure (7): Infrared spectrum of compound M8



Figure (8): Infrared spectrum of compound M9



Figure (9): Infrared spectrum of compound M₁₀



Figure (10): Infrared spectrum of compound M₁₁



Figure (11): Infrared spectrum of compound M₁₃

5.2-¹H-NMR spectrum

the prepared compounds.

The ¹H-NMR spectrum of the proton in DMSO-d⁶ solvent and the measurement reference is tetramethylsilane (SiMe₄) for the compound M₁ aromatic proton showed a multiple signal at (δH7.55-8.21ppm9H) due to nine protons. The ¹H-NMR spectrum of compound M_2 protons of two aromatic rings showed a multiple signal at (δ H7.15-8.68ppm9H) due to nine aromatic protons. A single signal appeared at (8H4.70ppm2H) due to two protons of the amino group NH2. As for compound M₃, the ¹H-NMR spectrum showed a multiple signal at (δ H7.37-8.65ppm14H) due to 14 protons belonging to the aromatic rings, and a signal appeared at (δ H2.61ppm3H) due to three protons of the CH₃ methyl group. Table (3) and Figures (12-22) show the chemical shifts of the aromatic protons and the important groups for the rest of

Table (3): 'H-NMR spectrum data for the prepared compounds						
Compd.no.	¹ H-NMR (DMSO-d ⁶ , δ, ppm)					
M1	7.55-8.21 (m.9H,Ar-H)					
M ₂	4.70 (s.2H. NH ₂), 7.15-8.69(m, 9H,Ar-H)					
M ₃	2.61 (s.3H, CH ₃), 7.37-8.65 (m, 14H, Ar-H)					
M4	2.53 (s.3H, CH ₃), 6.95-8.20 (m,13H, Ar-H) ,12.94(s.1H,OH)					
M5	2.79 (s.3H, CH ₃), 7.27-8.43 (m, 13H, Ar-H)					
M ₇	2.87 (s.3H, CH ₃), 7.44-8.21 (m, 13H, Ar-H)					
M ₈	6.13(s.2H, CH ₂), 7.02-8.00 (m, 12H, Ar-H), 8.39(s.1H, CH)					
M9	2.78 (s.3H, CH ₃), 7.27-8.63 (m, 13H, Ar-H)					
M ₁₀	2.81 (s.3H, CH ₃), 7.39-8.64 (m, 13H, Ar-H)					
M ₁₁	3.84(s.3H, CH ₃), 6.78-8.60 (m, 12H, Ar-H), 9.65(m.1H, OH)					
M ₁₃	11.15 (s.1H, OH), 6.83 -8.59 (m, 13H, Ar-H), 8.70 (s.1H, CH=N-)					



Figure (12): ¹H-NMR spectrum of compound M₁



Figure (13): ¹H-NMR spectrum of compound M₂



Figure (14): ¹H-NMR spectrum of compound M₃







Figure (16): ¹H-NMR spectrum of compound M₅



Figure (17): ¹H-NMR spectrum of compound M₇



Figure (18): ¹H-NMR spectrum of compound M₈



Figure (19): ¹H-NMR spectrum of compound M₉



Figure (20): ¹H-NMR spectrum of compound M₁₀



Figure (21): ¹H-NMR spectrum of compound M₁₁



Figure (22): ¹H-NMR spectrum of compound M₁₃

5.3- GC. Mass

spectral data of compounds (M_3, M_4, M_8, M_{13}) is given in Fig (23-26) Mass spectra of the compounds show molecular ion peaks with different relative abundances, which are in good agreement with expected values.



Figure (23): Mass spectrum of compound M₃



Figure (24): Mass spectrum of compound M₄

2023







Figure (26): Mass spectrum of compound M13

5.4- Biological activity

The effect of the compounds (M₁, M₅, M₇, M₁₁, M₁₃) was studied in this research on two species of bacteria: *Escherichia coli*, which is gram-negative and *Staphylococcus aureus*, which is gram-positive, using dimethyl sulfoxide (DMSO) as a solvent in this study. The *E.coli* bacteria treat many infections, including the colon, especially those that affect the bladder and urinary tract. As for the *Staphylococcus aureus* bacteria, they are used to treat skin infections. A control model for the solvent was conducted and its effect on bacterial growth was studied under the same conditions to avoid solvent

interactions. A comparison was made with a type of antibiotic that affects the compounds and Schiff bases (hydrazones) prepared on the two mentioned types of bacteria, Table (4).

The compounds showed varying biological activity against the two species of bacteria (*E.coli*, gram-negative and *Staphylococcus aureus*, gram-positive). Measurements showed that the best compound was M_7 , followed by M_2 . [28]

	Name of	Inhibito	ory effect	on <i>E.coli</i>		Inhibitory effect on staph. aureus				
No.	compound	12.5 mg/ml	25 mg/ml	50 mg/ml	100 mg/ml	12.5 mg/ml	25 mg/ml	50 mg/ml	100 mg/ml	
1	M1	0	0	0	0	0	0	0	8	
2	M ₂	10	11.5	13	15	10	11.5	13.5	15	
3	M ₃	0	0	7	9	0	0	0	0	
4	M4	8.5	9	10	11	0	0	0	0	
5	M ₅	0	0	0	0	0	7	8	10	
6	M ₇	8.5	14	17.5	20	9.5	13.5	15	17	
7	M ₈	0	0	0	8	6.5	7	8	9	
8	M ₉	9.5	10	11.5	12	7.5	8	8.5	10	
9	M ₁₀	8	8.5	9.5	11	7.5	8.5	9.5	12	
10	M ₁₁	0	0	7	8	0	6.5	8	9	
11	M ₁₃	7.5	8	9.5	10.5	6.5	7.5	8	9	
12	imipinium	12	12	12	12	13	13	13	13	
13	nitrofurantion	13	13	13	13	13	13	13	13	
25 -									- 42 5	
15 -								 12.5 25 50 		
10 -		T	đ			đ	1		100	
5 -										
0 -	1 2	3	4	5	6 7	8	9	10		
12.5	0 10	0	8.5	0 8	3.5 0	9.5	8	0		

 Table (4) : Inhibitory activity of the prepared compounds on two species of the studied bacteria

Scheme (3): The inhibitory effect of ligands and some prepared complexes on the growth of *E.coli* bacteria

17.5

11.5

8.5

9.5

11.5



Scheme (4): The inhibitory effect of ligands and some prepared complexes on the growth of E.coli bacteria



Scheme (5): The inhibitory effect of ligands and some prepared complexes on the growth of *Staphylococcus aureuse* bacteria.



Scheme (6): The inhibitory effect of ligands and some prepared complexes on the growth of *Staphylococcus aureuse* bacteria.





Figure (27): Inhibitory activity of the prepared compounds on the growth of bacteria E.coli, Staph. aureus.

Conclusion

In this work we have characterized synthesis of eleven new phenyl quinazoline-4-(3H) one, Schiff bases (hydrozones) M_1 , M_5 , M_7 , M_{11} , M_{13} .

The ¹HNMR, elemental analysis (CHN), FT-IR spectra, GC. Mass spectra and antibacterial properties of the prepared compounds were recorded and investigated.

The Synthesized compounds shows good biological activity against two types of bacteria.

ACKNOWLEDGMENTS

The researchers are thankful to Department of Chemistry / College of Education for Girls, University of Mosul for providing laboratory facilities during this research.

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