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Synthesis and Evaluation of Antibacterial and Antifungal Activity of New Series of Thiadiazoloquinazolinone derivatives

A.A. Aly*, AbdelmotaalAbdelmajeid*, and Eman M. Zahran

Chemistry Department, Faculty of Science, Benha University, Benha, P. O. Box 13518. Egypt

Abstract

A facile and convenient synthesis of 1,3,4-thiadiazolyl quinazolinone derivatives is described via cyclization of anthranilic acid with maleic anhydride, which upon reaction with glycine afforded 3-glycinyl quinazolinone derivative (2), then treated with thiosemicarbazide and produced 1,3,4-thiadiazolyl quinazolinone derivative (3).Moreover, benzoxazinoneisothiocyanate (13) is used as a key compound in synthesizing of triazolyl-(14), oxazolidinyl-(15) and triazinanyl-(16a,b) benzoxazinoneheterocyclesby reaction with phenyl hydrazine, glycine and urea and/ or thiourea, respectively.
Evaluation of antimicrobial activity of some of the synthesized compounds against selected bacteria and fungi strains in comparison with Ampicillin as antibacterial agent and Amphotericin B as antifungal agent exhibited promising activity as compared to the references. The structures of the synthesized compounds were confirmed on the basis of their elemental analyses as well as spectral data (IR, MS and 1H NMR).

Keywords: N-heterocycles, thiadiazolylquinazolinones, isothiocyanatobenzoxazinone, antibacterial activity, antifungal activity.

1. Introduction

N-containing heterocyclic compounds such as quinazoline derivatives have significant and extensive concern due to their widely and distinct pharmaceutical activities. They occur extensively in nature with a broad range of natural activities in variety of natural building blocks as alkaloids, and found across the plant and animal kingdoms as well as various microorganisms [1-4].

Quinazolines have already determined diverse pharmacological activities and found in the several applications as anti-inflammatory [5], analgesia [6], anti-virus [7], anti-cancer [8,9], anti-cytotoxin [10], anti-tuberculosis [11], anti-oxidant [12], antimalarial [13], anti-hypertension [14], anti-obesity [15], anti-psychotic [16], anti-diabetes [17]. Moreover, they act as bactericides [18], fungicides [19], herbicides [20] and pesticides [21] in addition to helpful synthetic block in the several alkaloids. Thus, researchers have a great attention in the synthesis and pharmacological evaluation of quinazoline/quinazolinone hybrids by installing various active groups to the quinazoline moiety due to their diverse biological activities.

Furthermore, during the last decades, 1,3,4-thiadiazole derivatives have drawn much attention due to their biological and pharmaceutical activities and have been investigated increasingly due to their numerous therapeutic and industrial applications, which is supposed due to the presence of =N−C−S− moiety [22,23].

A brief survey on the biological activities of 1,3,4-thiadiazole scaffolds showed antiviral [24], antidepressant [25], anti-HIV [26], antimicrobial [27], anti-inflammatory [28], anti-tuberculosis [29], anti-bacterial [30], antioxidant [31], anticancer [32], as well as CNS depressant and anticonvulsant [33,34].

In the view of high biological and pharmacological activity of quinazoline derivatives, we reported in our previous work certain substituted quinazoline derivatives [35-39], and we aimed to continue our ongoing interest on synthesis of these scaffolds, and converge our progress in synthesizing some thiadiazolylquinazolinone derivatives. Herein,

*Corresponding author e-mail:*aly.maboudaly@fsc.bu.edu.eg*; (**A.A. Aly**).

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we demonstrated an efficient synthesis of 1,3,4-thiadiazolyl quinazolinone, and benzoxazinone scaffolds with evaluation of their antibacterial and antifungal activity.

2. Experimental

2.1. Materials

Melting point are uncorrected and determined by the opencapillary method using Gallen Kamp melting point apparatusMicroanalysis as well as 1H NMR, IR and Mass spectra carried out by the Micro Analytical Unit atCairoUniversity.

IR-Spectra (KBr disk) of the synthesized compounds were recorded on FT/IR-BRUKER,Vector 22 (Germany).1H NMR Spectra were recorded in deuterated chloroform (CDCl3) or dimethylsulphoxide (DMSO-d6) as a solvent on a Varian Mercury VX-300 MHz and/or on a Varian Germini-200 MHz using (TMS as internal reference). And mass spectra were recorded on Shimadzu GCMS-QP-1000EX mass spectrometer at 70 e.v. All reaction carried out monitored by thin layer chromatography TLC on 0.1 mm silica gel 60f254 mark plates. Antimicrobial activities were carried out at the Micro Analytical Center, Faculty of Science, Cairo University.

2.2. Methods

Synthesis of 3-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)acrylic acid (1)

To a solution of anthranilic acid (0.01mol) in pyridine (30 mL), maleic anhydride (0.01mol) was added, thenthe mixture was refluxed for 4h, and then concentrated. The solid product that separated on cold was filtered off, dried and crystallized from pet-ether (40-60). (c.f. Table 1).

Synthesis of 3-(3-(carboxymethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)acrylic acid (2).

A (0.01mol) of 3-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)acrylic acid (1) was fused with (0.01mol) of glycine on sand bath above the melting point for 4h in presence of an air condenser, then cooled, water is added.The solid obtained after filtration was crystallized from n-butanol. (c.f. Table 1).

Synthesis of 3-((5-amino-1,3,4-thiadiazol-2-yl) methyl)-2-(2-(5-amino-1,3,4-thiadiazol-2-yl)) quinazolin-4(3H)-one (3).

A mixture of 3-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)acrylic acid(2) (0.01mol) and thiosemicarbazide (0.02 mol) in POCl3 (15 mL) was heated under reflux for 6h, left to cool, then poured into ice/ HCl with stirring. The solid product that separated out was filtered off, washed with water, dried and then recrystallized from methanol. (c.f. Table 1).

General procedure of Synthesis of compounds (4) and (5).

To solution of compound (3) (0.01 mol) in ethanol (15 mL), acetyl chloride and/ or acetic anhydride (0.02 mol) was added and refluxed for 6h. After that, left to cool, poured into cold water with stirring, the crude product that separated out was filtered off under suction, washed with cold water, dried and recrystallized from proper solvent and give compound (4) and (5).

Synthesis of N-(5-((2-(2-(5-acetamido-1,3,4-thiadiazol-2-yl) vinyl)-4-oxo quinazolin-3(4H)-yl)methyl)-1,3,4-thiadiazol-2-yl) acetamide (4). (c.f. Table 1).

Synthesis ofN,N-(5-((2-(2-(5-acetamido-1,3,4-thiadiazol-2-yl)vinyl)-4-oxoquinazolin- 3(4H)-yl)methyl)-1,3,4-thiadiazol-2-yl) (5).(c.f. Table 1).

Synthesis of1-(5-(2-(3-1,3,4-thiadiazol-2-yl)-3-phenylurea-4-oxo-3,4-dihydroquinazolin-2-yl)vinyl)-1,3,4-thiadiazol-2-yl)-3-phenylurea(6)

A (0.01mol) of compound (3) and phenyl isocyante (0.02 mol) in dry benzene (20 mL) was heated under reflux for 5 h in presence of catalytic amount of triethylamine. The reaction mixture was left to cool and the solid that deposited was filtered off, washed several times with light petroleum, dried and recrystallized from n-butanol. (c.f. Table 1).

Synthesis of 2-(2-(5-(4-chlorobenzylideneamino)-1,3,4-thiadiazol-2-yl) vinyl)-3-(2-(5-(4-chlorobenzylideneamino)-1,3,4-thiadiazol-2-yl) quinazolin-4(3H)-one (7).

To solution of compound (3) (0.01 mol) in absolute ethanol (20 mL), 4-chlorobenzaldehyde was added, and the reaction mixture was heated under reflux for 5 h, left to cool, the precipitated solid that separated out was filtered off, washed with cold water, dried and recrystallized from ethanol. (c.f. Table 1).

General procedure for synthesis of compounds (8) and (9):

A mixture of compound (3) (0.01 mol) and (0.02 mol) of N-tosylglycine, and/or N-methyl alanine in THF (15 mL) and in presence of DCCI was allowed to stir for 24 h. The produced solid was filtered off, washed with water and recrystallized from a proper solvent. (c.f. Table 1).

Synthesis of (E)-2-(methylamino)-N-(5-(2-(3-((5-(2-(methylamino)propanamido)-1,3,4-thiadiazol-2-yl)methyl)-4-oxo-3,4-dihydroquinazolin-2-yl)vinyl)-1,3,4-thiadiazol-2-yl)propenamide (8).(c.f.Table 1**).**

Synthesis of 2-((4-methylphenyl)sulfonamido)-N-(5-((2-(2-(5-(2-((4-methylphenyl) sulfonamido)acetamido)-1,3,4-thiadiazol-2-yl) ethyl)-4-oxoquinazolin-3(4H)-yl) methyl)-1,3,4-thiadiazol-2-yl) acetamide (9).(c.f.Table 1).

Table (1). Physical data of compounds (1-9)

Compd. No	M.F. M. wt.	M. P. °C Colour	Yield (%)	Solvent	Analysis Calc. (Found) %		
					C	H	N
1	$C_{11}H_7NO_4$ 217.18	178-180 Yellow	88	pet-ether	60.83 60.80	3.25 3.21	6.45 5.41
2	$C_{13}H_{10}N_2O_5$ 274.23	220-222 Yellow	79	n-butanol	56.94 56.90	3.68 3.65	10.22 10.18
3	$C_{15}H_{12}N_8OS_2$ 384.44	256-259 Pale Yellow	92	methanol	46.86 46.82	3.15 3.10	29.15 29.11
4	$C_{19}H_{16}N_8O_3S_2$ 468.51	250-253 Pale Yellow	82	n-butanol	48.71 48.68	3.44 3.40	23.92 23.89
5	$C_{23}H_{20}N_8O_5S_2$ 552.59	260-263 Brown	75	ethanol	49.99 49.95	3.65 3.60	20.28 20.25
6	$C_{29}H_{22}N_{10}O_3S_2$ 622.68	252-254 Yellow	90	n-butanol	55.94 55.90	3.56 3.52	22.49 22.45
7	$C_{29}H_{18}Cl_2N_8OS_2$ 629.54	263-265 Brown	70	ethanol	55.33 55.30	2.88 2.85	17.80 17.75
8	$C_{33}H_{30}N_{10}O_7S_4$ 806.91	255-258 Brown	65	ethanol	49.12 49.09	3.75 3.70	17.36 17.30
9	$C_{23}H_{26}N_{10}O_3S_2$ 554.65	260-262 Brown	67	ethanol	49.81 49.77	4.72 4.69	25.25 25.20

General procedure for synthesis of 10a,b:

A solution ofcompound **3** (0.01 mol) in n–butanol (30 mL) was treated with *N*- phathaloyl glycine, and/ or *N*-Phathaloyl phenylalanine (0.02 mol) and refluxed for 5h. The produced solid was filtered off, and recrystallized from a proper solvent.

Synthesis of 2-(1,3-dioxoisoindolin-2-yl)-N-(5-((2-(2-(5-(2-(1,3-dioxoisoindolin-2-yl)acetamido)-1,3,4-thiadiazol-2-yl)ethyl)-4-oxoquinazolin-3(4*H*)-yl)methyl)-1,3,4-thiadiazol-2-yl)acetamide (10a) (*c.f.* Table 2).

Synthesis of (1,3-dioxoisoindolin-2-yl)-N-(5-((2-(2-(5-(2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanamido)-1,3,4-thiadiazol-2-yl)ethyl)-4-oxoquinazolin-3(4*H*)-yl)methyl)-1,3,4-thiadiazol-2-yl)-3-phenylpropanamide (10b) *(c.f.* Table 2).

Synthesis of (E)-2-(5-(2-(3-2-(5-(2-(3-methyl-4-oxo-3,4-dihydro quinazolin-2-yl)-1,3,4-thiadiazol-2-yl)isoindoline-1,3-dione-4-oxo-3,4-dihydroquinazolin-2-yl)vinyl)-1,3,4-thiadiazol-2-yl)isoindoline-1,3-dione (11).

A (0.01 mol) of compound **(3)** was treated with (0.02 mol) of phthalic anhydride in (20 mL) benzene and in presence of catalytic amount of triethylamine. The reaction mixture was heated under reflux for 4 h, the solid that separated out filtered off, washed, dried and purified by recrystallization from ethanol. (*c.f.* Table 2).

Synthesis of 1-(5-(2-(3-((5-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-1,3,4-thiadiazol-2-yl)methyl)-4-oxo-3,4-dihydroquinazolin-2-yl)vinyl)-1,3,4-thiadiazol-2-yl)-1H-pyrrole-2,5-dione (12).

A mixture of 3-((5-amino-1,3,4-thiadiazol-2-yl)methyl)-2-(2-(5-amino-1,3,4-thiadiazol-2-yl)vinyl)quinazolin-4(3H)-one **(3)**and maleic anhydride (0.02 mol) in ethanol (20 mL) was heated under reflux for 6 h, left to cool, poured into cold water with stirring. The crude product that separated out, filtered off, washed with cold water, dried and recrystallized from ethanol. (*c.f.* Table 2).

Synthesis of 3-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)prop-2-enoyl isothiocyanate (13).

To a stirred solution of the acid chloride (0.01 mol) in dry acetone (50 mL), a solid ammonium thiocyanate (0.01 mol) was added, and allowed tostir for one hour at room temperature. Ammonium chloride precipitated during the progress of the reaction, and separated by filtration leaving a clear solution of isothiocyanatobenzoxazinone.

Synthesis of 2-(2-(2-phenyl-5-thioxo-2,5-dihydro-1H-1,2,4-triazol-3-yl)vinyl)-4H-benzo[d][1,3]oxazin-4-one (14).

A mixtureof isothiocyanatobenzoxazinonederivative **(13)**and phenylhydrazine (0.01mol) in 30 mL of benzene and in presence of catalytic amount of pyridine was heated under refluxed for 3h. After removing the excess benzene, a crude solid obtained filtered off, dried and recrystallized from ethanol. (*c.f.* Table 2).

Synthesis of 3-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)-N-(5-oxooxazolidin-2-yl)propenamide (15).

A mixture of compound**(13)** (0.01 mol) and glycine (0.01mole) in dry acetone (30 mL).A few drops of pyridine were added as a catalyst, and the reaction heated under reflux for 3h.Removal of excess benzene afforded a crude solid after cooling. The obtained solid was filtered off, dried and recrystallized from methanol. (*c.f.* Table 2).

General procedure for synthesis of 16a,b:

To a stirred solution of isothiocyanatobenzoxazinone**(13)** (0.01 mol) in dry acetone (30 mL), Urea and /or thiourea (0.01 mol) was added, and in presence of catalytic amount of pyridine heated under reflux for 5h. The solid precipitated filtered off, dried and crystallized from proper solvent to give compounds **16a,b**.

2-(2-(4-oxo-6-thioxo-1,3,5-triazinan-2-yl)vinyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (16a). (*c.f.* Table 2).

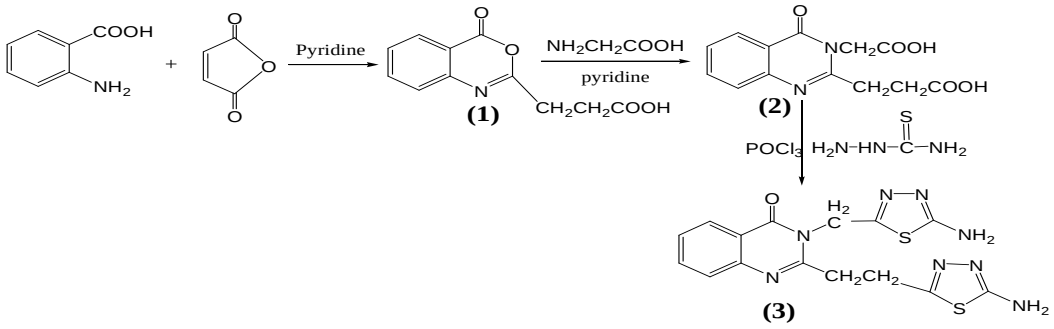
2-(2-(4,6-dithioxo-1,3,5-triazinan-2-yl)vinyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (16b). (*c.f.* Table 2).

Table (2). Physical data of compounds (10-16).

Compd. No	M.F. M. wt.	M. P. °C Colour	Yield (%)	Solvent	Analysis Calc. (Found) %		
					C	H	N
10a	$C_{35}H_{22}N_{10}O_7S_2$ 758.13	188-190 White	82	ethanol	55.76 (55.69)	2.88 (3.92)	18.52 (18..45)
10b	$C_{49}H_{22}N_{10}O_7S_2$ 938.22	180-182 Yellow	79	n-butanol	62.84 (62.55)	3.01 (3.21)	14.68 14.59
11	$C_{31}H_{16}N_8O_5S_2$ 644.64	253-255 Yellow	78	ethanol	57.76 57.70	2.50 2.44	17.38 17.35
12	$C_{23}H_{12}N_8O_5S_2$ 544.52	255-257 Yellow	91	ethanol	50.73 50.69	2.22 2.18	20.58 20.55
14	$C_{18}H_{12}N_4O_2S$ 348.38	144-147 Yellow	77	ethanol	62.06 62.02	3.47 3.41	16.08 16.05
15	$C_{14}H_{11}N_3O_5$ 301.25	153-155 Pale yellow	83	methanol	55.82 55.77	3.68 3.65	13.95 13.91
16a	$C_{13}H_{10}N_4O_3S$ 302.31	158-160 Pale yellow	89	n-butanol	51.65 51.61	3.33 3.30	18.53 18.50
16b	$C_{13}H_{10}N_4O_2S_2$ 318.37	156-158 Yellow	87	n-butanol	49.04 49.01	3.17 3.13	17.60 17.56

3. Results and discussion:

3,1-benzoxazin-4-one-3-acrylic acid **(1)**was synthesized by reaction of anthranilic acid with maleic anhydride in refluxed pyridine, which upon treatment with glycine yielded 3-glycinyl quinazolinone derivative **(2)** in good yield.**(Scheme 1)**. This reaction may be proceeds by the following mechanism in Figure **1**.



Scheme 1. Synthesis of compounds (1–3)

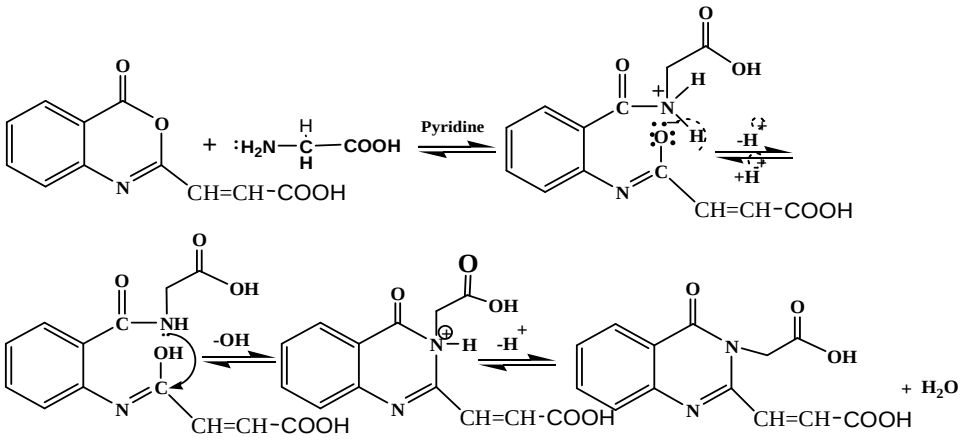


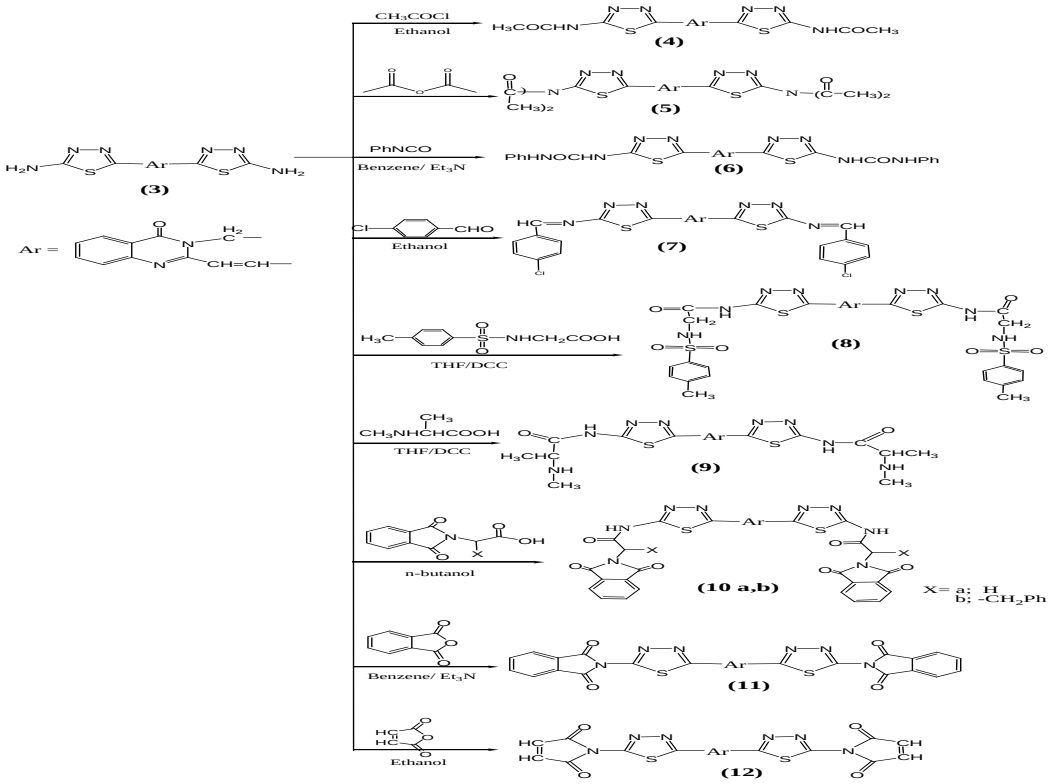
Figure 1. Illustrative mechanism for synthesis of compound **(2)**

IR-spectrum of compound **(1)** showed νOH at 3384 cm^{-1}, νC-H aromatic centered at 3090 cm^{-1}, in addition to νC=O'^{S} at 1765, 1711 cm^{-1}.

The structure of quinazolinone derivative **(2)** was inferred from its IR-spectrum which showed νOH at 3418 cm^{-1}, νC-H aromatic at 3047, and frequency due to acid, and quinazolinone carbonyls νC=O'^{S} at 1705, and 1693cm^{-1}, respectively.

Furthermore, the key compound thiadiazolylquinazolinone derivative **(3)** was obtained via treatment of the quinazolinone derivative **(2)** with thiosemicarbazide in $POCl_3$,which elucidated clearly from disappearance of hydroxyl and carbonyl of acid in its IR spectrum. The amino group ofthiadiazolyl quinazolinone derivative **(3)** has been used for alternate synthesis of some other derivatives **(4-12)**. **(Scheme 2)**

The amino group ofthiadiazolyl quinazolinone derivative **(3)** has been used for alternate synthesis of some other derivatives **(4-12)**. **(Scheme 2)**



Scheme (2). Synthesis of compounds (4–12)

Acetyl chloride and / or acetic anhydride used for acetylation of the thiadiazoloquinazolinone derivative **(3)**and produced the acetylated products **(4)** and **(5)**,respectively. Compound **(4)** was elucidated on the basis of its IR-spectrum which showed νNH'^{S} at 3308 cm^{-1}, νC-H aromatic at 3050, and νC-H aliphatic at 2928 cm^{-1}, besides the frequency due to carbonyls at 1700, and 1693 cm^{-1}, respectively, and its ^{1}H NMR spectrum showed signals δ'^{S} ppmat 1.3 (s, 3H , CH_3), 4.2 (dd, 2H, CH=CH), 7.2-8.4 (m, 4H, Ar-H), and 8.6 (s, 2H, NH$^{'S}$), while IR-spectrum of compound **(5)** showed νC=O'^{S} in range of 1720-1672cm^{-1} and disappearance of absorption bands due to NH$^{'S}$and ^{1}H NMR spectrum showed signals at δ'^{S} ppm at at 1.9 (s, 4CH_3 ,12H), 2.8 (t, 4H, 2CH_2), 3.4 (s, 2H, 1CH_2), 7.4-8.2 (m, 4H , Ar-H). Its Mass spectrum showed molecular ion peak ($M^{\cdot+}$-1) at 553 (0.18%), ($M^{\cdot+}$-2) at 552(0.43%), and the base peak at 57(100%).

Also, 1-(5-(2-(3-1,3,4-thiadiazol-2-yl)-3-phenylurea-4-oxo-3,4-dihydroquinazolin-2-yl)vinyl)-1,3,4-thiadiazol-2-yl)-3-phenylurea **(6)** was obtainedvia treatment thiadiazoloquinazolinone derivative **(3)** with phenyl isocyanate. The structure of this compound was inferred from its IR-spectrum which νNH'^{S} at 3407 cm^{-1}, νC-H aromatic at 3049, and νC-H aliphatic at 2922 cm^{-1}, and νC=O'^{S} at 1710, and 1693 cm^{-1}. and ^{1}H NMR spectrum which showed signals δ'^{S} ppm at 2.4 (s, 2 H, CH_2), 4.2 (dd, 2H, CH=CH), 6.6-8.4(m, 14H, Ar–H), 8.6 (s, 2H, 2NH) and 11.4 (s, 2H, 2NH).

Moreover, condensation of thiadiazoloquinazolinone derivative **(3)** with 4-chlorobenzaldehde demonstrated the schiff's base derivatives **(7)** andin good yields. IR-spectrum of compound **(7)** showed νC=O at 1695, and νC=N at 1635 cm^{-1}, in addition to the other characteristic peaks of the compound. A suggested mechanism for Schiff's base formation is illustrated in Figure **2**.

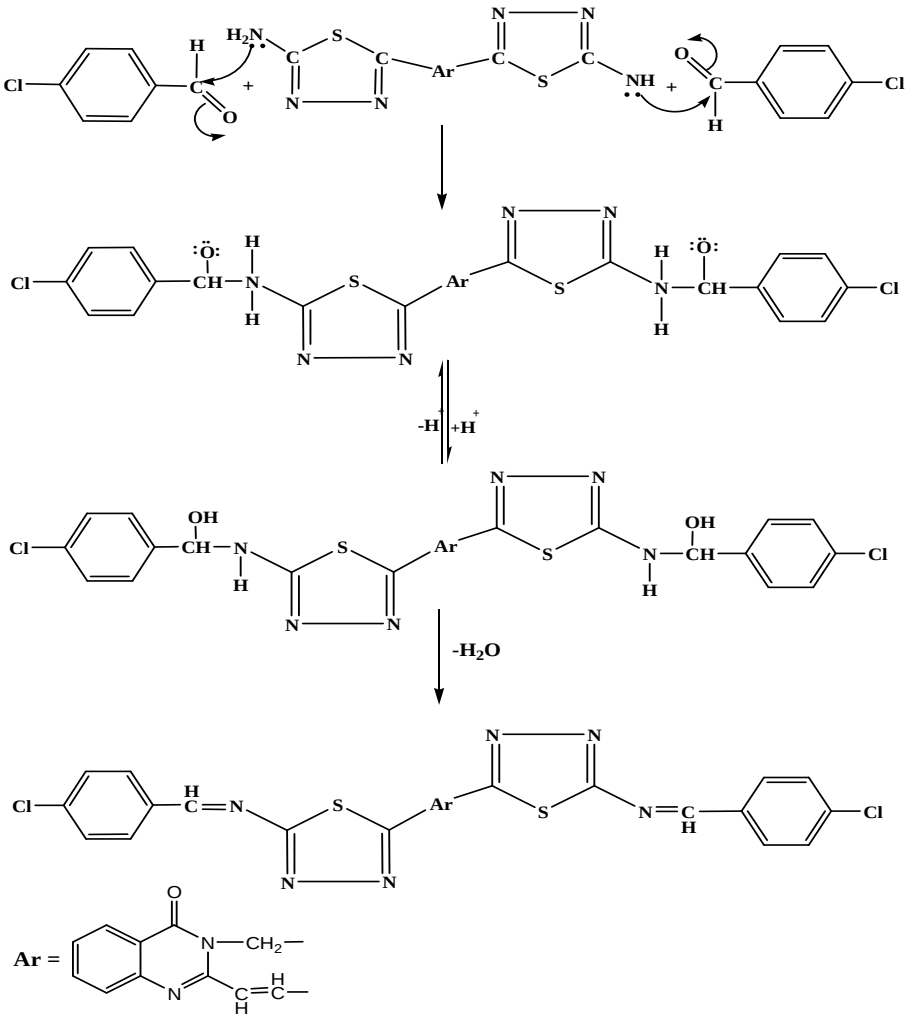


Figure 2. Illustrative mechanism for synthesis of compound **(7)**

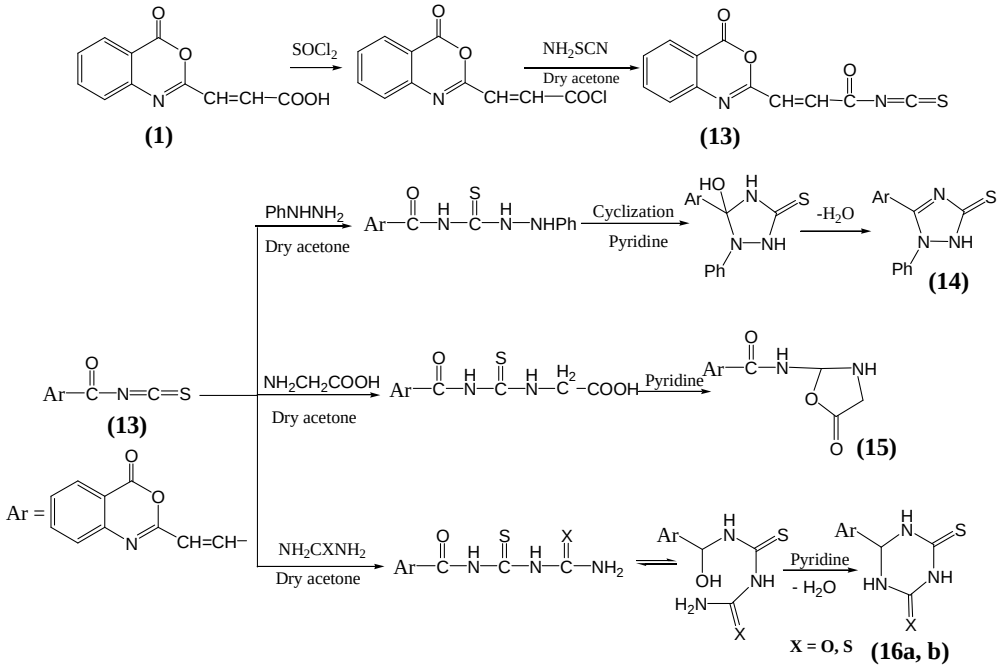
Besides, *N*-tosylglycine and/ or *N*-methyl alanine was allowed to react with thiadiazoloquinazolinone derivative **(3)** in refluxed THF and in presence of DCC to obtain the amino acid derivatives of thiadiazolo quinazolinone, and furnished compound **(8)**, and **(9)**, respectively. IR-spectrum of compound **(8)** showed νNH'^{S} at 3385 cm^{-1}, νC-H aromatic at 3050 cm^{-1}, and νC-H aliphatic at 2950 cm^{-1}, νC=O'^{S} at 1705, and 1685 cm^{-1}, νC=N at 1630 cm^{-1}, while IR-spectrum of compound **(9)** showed νNH'^{S} at 3382cm^{-1}, and νC=O at 1712 and νC=N at 1632 cm^{-1}, in addition to other characteristic peaks of the compound.

Thiadiazoloquinazolinone **(3)** was also incorporated with *N*- phathaloylglycine, and/ or *N*-Phathaloyl phenylalanine in boiling n-butanol,in order to obtain dioxoisoindoline derivatives**10a** and **10b**, respectively. IR-spectrum of **(10a)** showed νNH'^{S} at 3432cm^{-1}, and νC=O'^{S} at 1775, 1722 and 1685 cm^{-1}.

Bis-(1,3-dioxoisoindolinyl/(2,5-dioxo-2,5-dihydro-pyrrolyl)thiadiazolyl quinazolinone derivatives **(11)** and**(12)** were also synthesized, respectively, via reaction of the thiadiazoloquinazolinone derivative **(3)** with phthalic anhydride and / or maleic anhydride. IR-spectrum of compound **(11)** showed disappearance of aldehydic carbonyl absorption bands, and appearance of νC=O'^{S} in range of 1708-1693cm^{-1}, νNH'^{S} at 3307 cm^{-1} besides the other characteristic peaks of the compound. Its ^{1}H NMR spectrum showed signals δ'^{S} ppm at 2.1 (s, 2H, CH_2), 4.8 (dd, 2H, CH=CH), and 7.4-8.6 (m, 12H, Ar-H).

IR spectrum of compound **(12)** showed νO-H at 3326 cm^{-1}, νC-H aromatic at 3050, νC-H aliphatic at 2922 cm^{-1}, and νC=O'^{S} in range of 1720-1685cm^{-1}, besides the other characteristic peaks of the compound. Its ^{1}H NMR spectrum (DMSO-*d6*) showed signals δ'^{S} ppm at 4.3 (s, 2H, 3CH_2), 5.5 (dd , 4H , 2CH = CH), 7.4-8.2 (m ,12H, Ar-H).

On the other hand, treatment of benzoxazinone isothiocyanate **(13)** solution in acetone (prepared in situ) with phenyl hydrazine gave intermediate, which unpon cyclization followed by dehydration furnished 2-(2-(2-phenyl-5-thioxo-2,5-dihydro-1H-1,2,4-triazol-3-yl)vinyl)-4H-benzo[d][1,3] oxazin-4-one **(14)**. **(Scheme 3).**



Scheme (3). Synthesis of compounds (13–16)

IR-spectrum of compound **(14)** showed absorption bands for νNH'^{S}~OH at 3468, 3211, and 3168 cm^{-1}, νC-H aromatic at 3049, νC-H aliphatic at 2926 cm^{-1}, νSH at 2063 cm^{-1}, νC=O at 1765, 1685 cm^{-1}, νC=N at 1628cm^{-1}, and νC=S at 1402 cm^{-1}, respectively. Moreover, treatment of 3,1-benzoazinone isothiocyanate **(13)**with glycine produced the thiourea derivative, which upon cyclization in the presence of pyridine furnished3-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)-N-(5-oxooxazolidin-2-yl)propenamide **(15)**.IR-spectrum showed absorption bands for νNH'^{S} at 3350-3200 cm^{-1}, νC-H aromatic at 3040, νC-H aliphatic at 2928 cm^{-1}, νSH at 2066 cm^{-1}, νC=O'^{S} at 1767, 1720, and 1662 cm^{-1}, and νC-O-C (ether) at 1185, 1085cm^{-1}.^{1}H NMR spectrum ofcompound **(15)** showed signals δ'^{S} ppm at 3.3 (s, 2H, 1CH_2), 4.8 (dd , 4H , 2 CH = CH), 7.4-8.2 (m ,4H, Ar-H), and 8.6 (s, 2H, 2NH).

Finally, Addition of urea and/or thiourea to the isothiocyanato benzoxazinone **(13)** afforded thioxo/ dithioxo-1,3,5-triazinanyl benzoxazinone **(16a)** and **(16b)**, respectively, which may be proceeds by the following suggested mechanismFigure **3**.

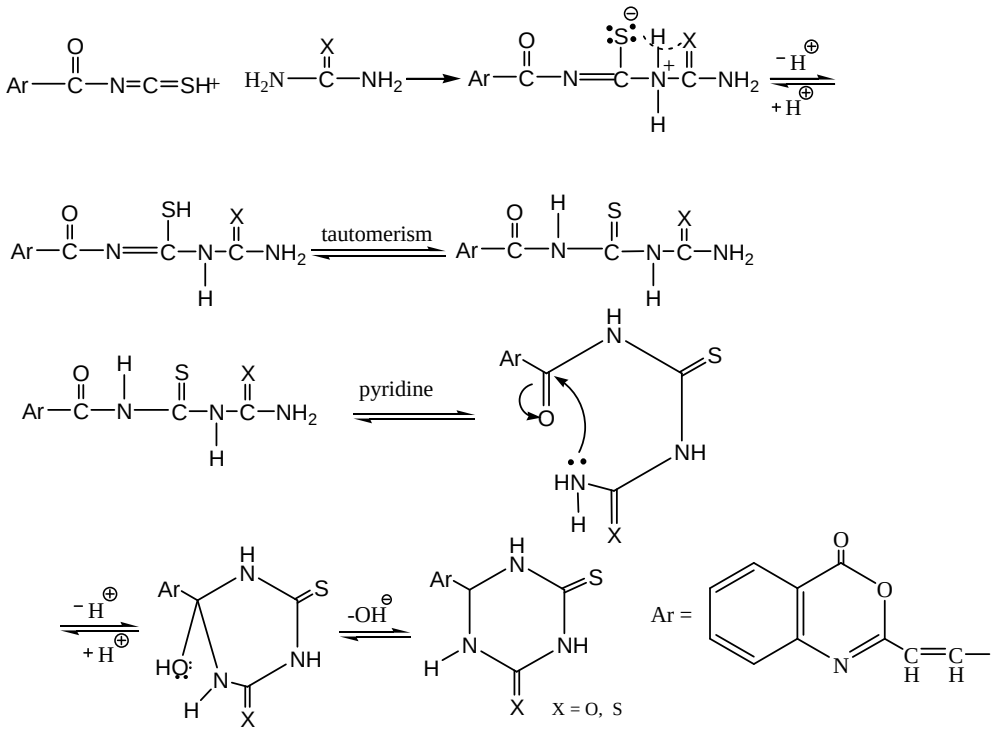


Figure 3. Illustrative mechanism for synthesis of compound **(16a,b)**

IR-spectrum of **(16a)** revealedνNH~OH at 3410-3259 cm^{-1}, νC=O's in range 1760-1673 cm^{-1}, νC=N at 1630 cm^{-1}, and νC=S at 1384cm^{-1}beside the other characteristic peaksof the compound, while IR-spectrum of **(16b)** showed absorption bands forνNH's at 3410, 3256 cm^{-1}, νSH at 2068 cm^{-1}, νC=N at 1629, and νC=S at 1400 cm^{-1} besides the other characteristic bands of the compound.

3.2 Biological Activity:

Antimicrobial activity of the tested samples was determined using a modified Kirby-Bauer disc diffusion method **[40-42].**In brief, 100 µl of the test bacteria/fungi were grown in 10 ml of fresh media until they reached a count of approximately 10^8 cells/ml for bacteria or 10^5 cells/ml for fungi. 100 µl of microbial suspension was spread onto agar plates corresponding to the broth in which they were maintained.

Biological activity screened of some of the synthesized compounds led to the fact that these outlined derivatives are biologically active against the tested microorganisms. The results are depicted in Table **(3)**.

Table (3): Antimicrobial activity of some of the synthesized compounds

	Inhibition zone diameter (mm / mg Sample)			
	Bacterial species		**Fungi**	
Compound No.	**G-**	**G+**		
	Escherichia coli	***Staphylococcus aureus***	***Aspergillus flavus***	***Candida albicans***
Control : DMSO	0.0	0.0	0.0	0.0
Ampicillin Antibacterial agent	25	21	--	--

Amphotericin B Antifungal agent	-	--	17	21
1	14	14	15	15
2	12	13	13	12
3	16	15	0.0	0.0
4	0.0	0.0	16	16
5	17	16	0.0	0.0
6	0.0	0.0	0.0	0.0
7	18	15	0.0	0.0
11	13	12	12	14
12	12	14	0.0	0.0
14	0.0	0.0	0.0	0.0
15	13	16	15	12
16a	15	12	13	18
16b	14	18	14	16

The results of biological activity of the synthesized compounds depicted in table **(3)** showed that most of the synthesized compounds exhibit from moderate to good antimicrobial activity.

The synthesized quinazoline derivatives, **3, 5,** and **7** showed good activity against ***Escherichia coli,*** and ***Staphylococcus aureus.*** while compounds **1, 2, 11, 12, 15** and **16b** showedmoderate activity against ***Escherichia coli***. On the other hand, compounds **1, 4 ,15, 16b** exhibited good activity against ***Aspergillus flavu***,whilecompounds **2 , 11, 16a** showedmoderate activity against ***Aspergillus flavu***, andcompounds **3 , 5, 6, 7, 12, 14** showed no activity against ***Aspergillus flavu***.

Furthermore, compounds **1, 4, 16a, 16b** and **2, 11, 15** showed good to moderate activity against ***Candida albicans***,as compared with the standard antifungal agent **Amphotericin B**.Thus, most of the synthesized compounds exhibited a promising activity against both tested bacterial and fungal strains compared to the starting quinazolinyl acrylic acid **(2)**. The biological activity of these quinazoline series were enhanced by incorporation of thiadiazol moiety.

Conclusions

We have used simple and convenient methods with simple work up and producing clean productsfor the synthesis of novel thiadiazolyl quinazolinone series **(3-12)** and heterocycles such as triazolyl-**(14)**, oxazolidinyl-**(15)** and triazinanyl-**(16a,b)** benzoxazinone. Most of the synthesized compoundstested for antibacterial and anti-fungi activity and showed higher activity than **Ampicillin**

and **Amphotericin B**used as reference drugs, thus they are promising lead compounds for the development of antimicrobial agents.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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تشييد وتقييم النشاط البكتيرى والفطرى لسلسلة جديدة من مشتقات الثيادیازولوكينازولينون

الملخص العربى

فـى هـذا البحـث تـم تشـييد مشـتقات4,3,1-ثيادیازولیـل كينـازولينون (1)وذلكبحلقنـة حمـض الأنثرانيليـك مـع انهيدريـد حمـض المـاليكثم بتفاعل الناتج مع الجلايسين حصلنا على مشتقات 3- جلايسينيل كينازولينون (2) والتـى تـم معالجتـه بعـد ذلـك بالثيوسـيميكاربازيد لينـتج مشـتق -1,3,4 ثيادیازوليـــل كينـــازولينون (3). كـــذلك تـــم تحضيرمشـــتق البنزواكزازينونايزوثيوسـيانات (13)والـذى اسـتخدم لتشـييد مركبـات مثـل الترايازوليـل بنزواكزازينـون (14) والأوكزازوليـدنيل بنزواكزازينـون (15) وكـذلك الترايازينيل بنزواكزازينـون (16 أ ، ب) وذلـك بتفاعلـه مـع الفينيـل هيدرازين والجلايسين واليوريا والثيويوريا على التوالى.

ايضا تم تقييم النشاط البكتيرى والفطرى للمركبات المحضرة تجاه بعض سلالات من البكتريا والفطريات المختارة ومقارنتها بعقاقير موجودة بالسوق كمرجع لتلك المركبات وقد أظهرت بعض هذه المركبات نشاطا واعدا للاستفادة منها فى الأغراض الطبية.

كما تم اثبات التراكيب البنائية للمركبات المحضرة بواسطة التحليل المختلفة مثل التحليل الجزيئى للعناصر و طيف الاشعة تحت الحمراء والرنين النووى المغناطيسى وكذلك مطياف الكتلة.