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Research Article

CHEMISTRY

Synthesis and Characterization of Some Quinazolone Derivatives

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ABSTRACT Reaction of compound 1 with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (ABG) afforded 2. Deplocking of 2 with sodium methoxide gave 1. Alkylation of 1 led to the formation of 3a-c. Fusion of 1 with ethyl chloroformate and/or ethyl chloroacetate gave 4a,b. Similarly, boiling of 1 with ethyl chloroacetoacetate gave 5. Refluxing of 1 with diphenyl diazomethane gave 6. Compound 7 reacted with some aromatic aldehydes and triethyl- and/or triphenyl– phosphite in glacial acetic acid to furnish the amino phosphonates 8a-d. Treatment of 7 with 4-aminobenzoic acid gave 9. Boiling 7 and triethylorthoformate in glacial acetic acid gave 10. Condensation of 7 with 4-benzylidene-2-phenyloxazol-5(4H)-one furnished 11. Reaction of 7 with 4-chlorophenyl isocyanate and/or phenyl isothiocyanate in boiling anhydrous pyridine gave 12 and/or 14. Refluxing 7 with chloroacetaldehyde in ethanol yielded 15. Fusion of 7 with some sultones afforded the corresponding sultams 18a,b. All the new compounds were tested for their potential antibacterial activates and the results indicated that some of them showed activity against different types of bacteria.

Key words: *quinazolonones, alkylation, aminophosphonates, sultams, biological activity.*

Introduction:

As our research group for some time ago is involved in the chemistry of quinazolone derivatives[1-3] due to their importance in biological activity as antihypertensive,[4] antifibrillatory, choleretic, antiphlogistic,[5] antimitotic anticancer,[6] antifungal[7, 8] and anticonvulsant agents.[9] Quinazolinones were reported to possess diverse pharmacological activities such as CNS depressant,[10] hypnotic, antiinflamatory,[11] antitumor,[12] muscle relaxants[13] and for their antineoplastic activity.[14] So, it is our goal to extend our study in this area to explore the reactivity of 3-phenylquinazoline-2,4(1H,3H)-dithione **(1)**[15] and 3-amino-6,8-dibromo-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one (**7**) towards different reagents to synthesize some new derivatives for testing their biological activities.

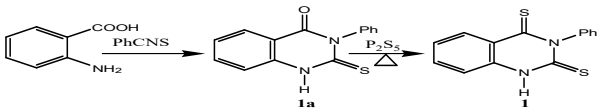
RESULTS AND DISCUSSION

Reaction of 3-phenylquinazoline-2,4(1H,3H)dithione **(1)**[15] with (2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)bromide (□-ABG) in the presence of triethyl amine in DMF at room temperature afforded the corresponding S-nucleoside **2**. Deblocking of **2** using sodium methoxide at r.t. yielded the starting aglycone,[1,16] and not the desired deblocked compound 3-phenyl-2-((2R,3S,4R,5R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-ylthio)quinazoline-4(3H)-thione (**2a**). Its IR spectrum showed the C=O at 1748 cm^{-1} and its ^{1}H-NMR spectrum showed a singlet (12H, $4CH_3$) at 1.96 ppm and its MS showed the EI (M^+) at 600.25. S-alkylation of compound **1** could be achieved by its treatment with alkylating agents namely: methyl iodide, benzyl chloride and /or phenacyl

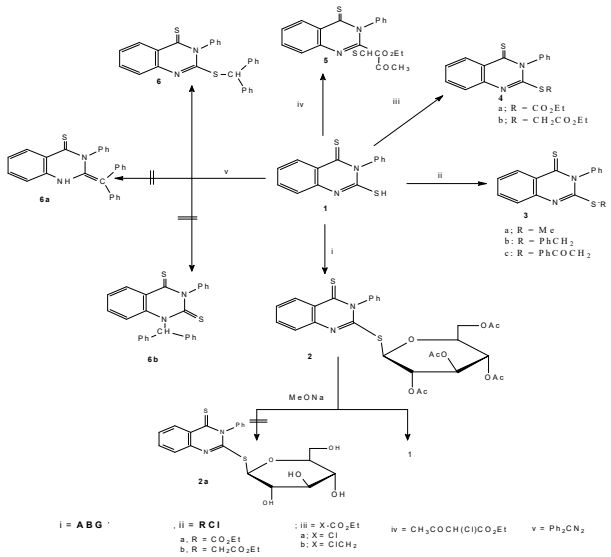
chloride at room temperature to yield the corresponding 2-alkylthio derivatives **3a-c,** respectively (Scheme **2**). The ^{1}H-NMR spectrum of compound **3a** showed a singlet (CH_3) at 2.75 ppm.

Fusion of compound **1** with ethyl chloroformate and / or ethyl chloroacetate yielded the corresponding 2-alkylthio derivatives (**4a, b**) (Scheme **2**). The IR spectrum of compound **4a** showed the carbonyl (C=O) ester at 1760 cm^{-1}.

By the same manner refluxing compound **1** with ethyl chloroacetoacetate in methanol for 4 hr afforded ethyl-3-oxo-2-(3-phenyl-4-thioxo-1,2,3,4-tetrahydro- quinazolin-2-ylthio) butanoate (**5**) (Scheme **2**). Its IR spectrum showed the (C=O) ketone at 1665 and the (CO) ester at 1742 cm^{-1}, its ^{1}H-NMR spectrum showed a triblet 3H of (CH_3) at 1.64, quartet 2H (CH_2) at 3.41 and a singlet (CH) at 3.95 ppm. Refluxing of compound **1** with diphenyl diazomethane (prepared according to known method)[17] in anhydrous benzene for 6 hr gave 2-(benzhydrylthio)-3-phenyl quinazoline-4(3H)-thione (**6**) as the sole product (tlc) and not 6**a** or 6**b** (Scheme **2**). The structures 6**a** and 6**b** were ruled out based on different spectroscopic data. The IR spectrum of **6** showed the disappearance of SH at 1653 cm^{-1} , while appearance of SCH at 2927 cm^{-1} and its ^{1}H-NMR spectrum showed a singlet (CH) at 3.51 ppm. and its MS showed the m/z (M^+) at 436.59.



Scheme **1**



Scheme **2**

In our earlier work [1] we found that 3-amino-6,8-dibromo-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one (**7**) was a versatile compound due to its biological activity as **Accaros:** Spider mite (Tetranychus- urticae),(Koch), Fungicides (Rhizoctonia solani, Fusarium oxysporium, Fusarium solani, Verticillium dahliae and Verticillium sulphurellium)and Bactericides (Psedomonas solaniserum, Erwinia carotovora and Ralstonia salanceanum).[1]

So, we found it is worthy to extend our study on the chemistry of compound **7** to get new derivatives of expected biological activity.

Accordingly, Compound **7** reacted with a mixture of aromatic aldehydes(benzaldehydeand4-chlorobanzaldehyde)andtriethyl-and/or triphenyl–phosphite in glacial acetic acid at 100°C for 4-6 hr (tlc) to furnish the amino phosphonates **(8a-d),** respectively. The IR spectrum of compound **8a** showed the (CH) at 2849 and (NH) at 3300 cm^{-1}. The ^{1}H-NMR spectrum of compound **8b** showed the triplet ($2CH_3$) at 1.20, (CH) at 3.94 and ($NH_{acyclic}$) at 2.51 ppm.. The ^{13}C-NMR spectrum of compound **8c** showed the (CH) at 53.55, (P-O-C) at 154.33 and (C=O) at 169.22 ppm.

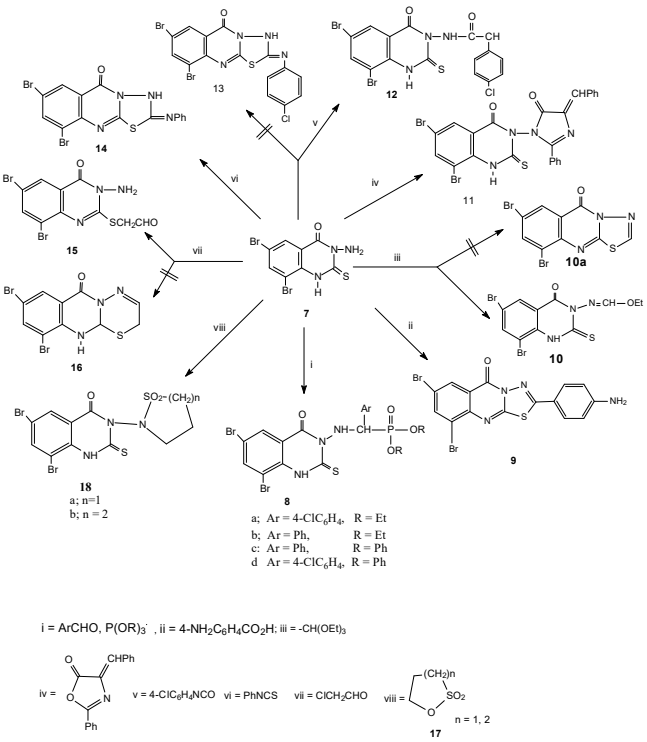
Treatment of compound **7** with 4-aminobenzoic acid in boiling phosphorus oxychloride for 8 hr gave 2-(4-aminophenyl)-7,9-dibromo-10,10a-dihydro-[1,3,4]thiadiazolo[2,3-b]quinazolin-5-one (**9**) through the elimination of two molecules of water. Its ^{13}C-NMR spectrum showed the (C=C) at 153.15, (C=O) at 164.32 and (C=N) at 170,31ppm.

Boiling amixture of compound **7** and triethylorthoformate in glacial acetic acid for 3 hr (tlc) gave ethylN-6,8-dibromo-4-oxo-2-thioxo-1,2-dihydroquinazolin-3(4H)-ylformimidate(**10**).ItsIR spectrum showed the (CH) at 2950 cm^{-1} and Its ^{13}C-NMR spectrum showed the (CH_3) at 14.19 and (CH_2) at 61.52 ppm.

Condensation of compound **7** with 4-benzylidene-2-phenyloxazol-5(4H)-one in boiling glacial acetic acid furnished3-(4-benzylidene-5-oxo-2-phenyl-4,5dihydroimi-dazol-1-yl)-6,8-dibromo-2-thioxo-1,2,3,8atetrahydroquin-azolin-4(4a*H*)-one (**11**). Its IR spectrum showed a sharp signal at 2970 cm^{-1} for ($CH_{ar.}$) and its MS spectrum showed the m/z at (581, 14%), (M^+, $C_{24}H_{15}Br_2N_4O_2S_2$).

Reaction of compound **7** with 4-chlorophenyl isocyanate and/or phenyl isothiocyanate in boiling anhydrous pyridine for 4-5 hr gave 1-(4-chlorophenyl)-3-(6,8-dibromo-4-oxo-2-thioxo-1,2-dihydroquinazolin-3(4H)-yl)urea (**12**) and/or 7,9-dibromo-2-(phenylimino)-2,3-dihydro-

[1,3,4]thiadiazolo[2,3-b]quina-zolin-5-one(**14**), respectiv-eely. The IR spectrum of compound **12** showed the (C=O-NH) at 1660, (CH) at 2961 cm^{-1}. The ^{13}C-NMR spectrum of compound **14** showed the (C=N) at 147.17, (C=O) at 156.86 and (C-S) at 160.66 ppm.



Scheme **3**

Refluxing a mixture of compound **7** and chloroacetaldehyde in ethanol for 3 hr yielded 2-(3-amino-6,8-dibromo-4-oxo-1,2,3,4-tetrahydroquinazolin-2-ylthio)acetalde-hyde (**15**). Its IR spectrum showed the disappearance of C=S at 1120 cm^{-1} , while appearance of C=N at 1560 cm^{-1} and its ^{1}H-NMR spectrum showed signal (2H, CH_2) at 4.43 and a single (1H, CHO) at 9.70 ppm.

Fusion of compound **7** with 1,3-propane-and/or 1,4-butane-sultone at 180 °C for 9-11 hr afforded the corresponding sultams: 6,8-dibromo-2-thioxo-2,3-dihydro-quinazolinoyl-propane-1,3-sultam **(18a)** and 6,8-dibromo-2-thioxo-2,3-dihydroquinazolinoyl-butane-1,4-sultam **(18b)**, respectively (Scheme **3**). The ^{1}H-NMR spectrum of compound **18a** showed the (m, 2H, CH_2) at 1.20, (d, 2H, CH_2) at 3.01 and (d, 2H, CH_2) at 3.20 ppm. The IR spectrum of compound **18b** showed the (SO_2) at 1156, 1350 cm^{-1} and (C=S) at 1120 cm^{-1}.

EXPERIMENTAL

All melting points were uncorrected and performed by the open capillary melting point apparatus. Microanalyses were performed by Microanalysis Unit, Faculty of Science, Cairo University and Microanalysis Unit, Central Laboratory, Tanta University. IR spectra recorded with a Perkin-Elmer 1720 spectrometer. The NMR spectra were recorded on a Brüker AC 250 FT NMR spectrometer at 250 MHz for ^{1} H and 62.9 MHz for ^{13}C, Varian UNITY 500 NMR spectrometer at 500 MHz for ^{1} H or 125.7 MHz for ^{13}C, Bruker 200 MHz And Bruker 90 MHz spectrometer using TMS as an internal standard DMSO as a solvent. Chemical shifts (δ) are reported in parts per million (ppm) and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br (broad). Mass spectra (MS) were recorded using electron ionization (E.I.) on a Varian Mat 311A spectrometer.

Compounds **1a**[15], **1**[15] and **7**[1] were prepared according to recommended methods.

Coupling of 1 with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (ABG). Formation of 2.

A solution of compound **1** (0.27 g, 0.001 mol) was dissolved in a mixture of triethyl amine (2 ml) and DMF (15 ml) and added to a solution of ABG (0.41g, 0.001 mol). The reaction mixture was stirred at r. t. for 4 hr (tlc). The reaction mixture was pourd onto cold water, the solid formed was filtered off, washed with water, dried, and recrystallized from ethanol to afford **2**[16].

2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl-thio)-3-phenyl-2,3dihydro-quinazoline-4(1H)-thione (2)

IR: *v* (cm^{-1}) 1227 (C=S $_{cyclic}$), 1610 (C=N), 1748 (C=O, acetyl), 2925 (CH); **^{1}H-NMR** (DMSO-d_6): δ 1.96 (s, 12H, 4CH_3), 4.01-4.30 (s, 2H, CH_2), 4.96 (dd, 1H, *J* = 5.63 Hz, H-5`), 5.10 (t, 1H, *J* = 3.04 Hz, H-4`), 5.36 (dd, 1H, *J* = 4.98 Hz, H-3`), 5.58 (dd, 1H, *J* = 3.85 Hz, H-2`), 5.97 (dd, 1H, *J*` = 4.16, H-1`), 7.39 – 8.55 (m, 9H, $H_{ar.}$)ppm; **^{13}C-NMR** (DMSO-d_6): δ 20,19 (CH_3, C′6), **2**0,35(CH_3, C′4), 20.36 (CH_3, C′2), 20.38 (CH_3, C′3), 61.65, 67.94, 68.50, 73.01, 75.06, 81.90 (C′6, C′4, C′2, C′3, C′5, C′1$_{anomeric}$), 127.19, 128.84, 129.04, 129.84, 130.20 ($C_{ar.}$), 153.51 (C=N_{cyclic}), 169.08, 169.20, 169.20, 169.72, 169.87 (C = O, $_{acetyl}$), 189.08 (C=S_{cyclic})ppm.; **MS** (EI) m/z = 600.25 (M^+, $C_{28}H_{28}N_2O_9S_2$, 100%).

Deblocking of Compound 2.

Compound **2** (0.60 g, 0.001 mol) was dissolved in (20 ml) methanol and two drops of sodium methoxide solution (0.001 N) were added. The reaction mixture was left at room temperature for 4 hr (tlc). The solvent was evaporated under vacuum and the residual solid was dissolved in water neutralized with dill HCl. The solid formed was filtered off, washed with water, dried, recrystallized from ethanol to give the starting material **1**[16]. Yield 0.93 g (62%); m.p. 180-182 °C. mp and mixed mp of the product with authentic sample of **1** gave no depression.

Alkylation of 1. Formation of 3a-c.

Compound **1** (0.81g, 0.003 mol) was dissolved in methanol (20 ml) and sodium hydroxide (0.5 g). The appropriate alkyl halide (0.003 mol) was added, and the reaction mixture was stirred at r.t. for 4-5 hr (tlc). The solid product formed was filtered off, recrystallized from ethanol, filtered, and dried to afford **3a-c**.Table **1**and Scheme **2**.

2-(Methylthio)-3-phenylquinazoline-4(3H)-thione (3a).

IR: *v* (cm^{-1}) 1188 (C=S_{cyclic}), 1665 (C=N), 2925 (CH); **^{1}H-NMR** (DMSO-d_6) (fig. 9): δ 2.75 (s, 3H, CH_3), 6.88 – 7.88 (m, 9H, $H_{ar.}$)ppm; **^{13}C-NMR** (DMSO-d_6): δ 14,16 (CH_3), 122.09, 124.14, 126.18, 128.91, 136.81, 143.12

and 149.12 ($C_{ar.}$), 163.26 ($C=N_{cyclic}$), 179.12 (C=S) ppm; **MS** (EI) m/z = 284,05 (M^+, $C_{15}H_{12}N_2S_2$, 1.7%).

2-(Benzylthio)-3-phenylquinazoline-4(3H)-thione (3b).

IR: *v* (cm-1) 1200 ($C=S_{cyclic}$), 1690 (C=N), 2875 ($CH_{aliph.}$), 3037 ($CH_{ar.}$); **^{1}H-NMR** (DMSO-*d6*): δ 4.51 (s, 2H, CH_2), 7.25 – 8.57 (m, 14H, $H_{ar.}$) ppm; **^{13}C-NMR** (DMSO-*d6*) (fig. 14): δ 39.29 (CH_2), 126.83, 127.38, 128.46, 129.02, 129.41, 129.84, 129.94 and 135.45 ($C_{ar.}$), 156.68 ($C=N_{cyclic}$), 188.99 (C=S) ppm.

1-Phenyl-2-(3-phenyl-4-thioxo-3,4-dihydroquinazolin-2-ylthio)ethanone (3c).

IR: *v* (cm^{-1}) 1193 (C=S), 1635 ($C=N_{cyclic}$), 1728 (C=O Ph), 2979 ($CH_{aliph.}$), 3088 ($CH_{ar.}$); **^{1}H-NMR** (DMSO-*d6*): δ 4.76 (s, 2H, CH_2), 7.20– 8.51(m, 14H, $H_{ar.}$)ppm.; **^{13}C-NMR** (DMSO-*d6*) (fig.17): δ 43.71 (CH_2CO), 126,21, 128.20, 128.77, 128.93, 129.90, 130.06, 133.47 and 135.28 ($C_{ar.}$),186.11 ($C=S_{cyclic,}$), 193.50 ($C=OC_6H_5$) ppm.

Table **1**: Physical and analytical data of compounds **3a-c**

Cpd.	M.P. (°C)	Yield (%)	M.F. (M. wt.)	M.A. (%); Calcd/Found		
				C%	H%	N%
3a	192-4	82	$C_{15}H_{12}N_2S_2.1/10H_2O$ (284.4)	63.35 62.96	4.25 4.46	9.85 9.31
3b	122-4	75	$C_{21}H_{16}N_2S_2.1/10H_2O$ (360.08)	69.97 69.63	4.47 4.42	7.77 7.73
3c	181-3	86	$C_{22}H_{16}N_2OS_2$ (389.07)	68.01 67.48	4.15 3.93	7.21 6.45

Reaction of compound 1 with ethyl chloroformate and/or ethyl chloroacetate. Formation of 4a,b.

Compound **1** (0.81g, 0.003 mol) was fused in ethyl chloroformate and / or ethyl chloroacetate (0.003 mol) for 4-5 hr (tlc). The excess of the reagent was evaporated till dryness under vaccum. The residual solid was crystallized from ethanol to give compounds **4a** and/or **4b**, respectively.

Ethyl-2-(3-phenyl-4-thioxo-1,2,3,4tetrahydroquinazolin-2-ylthio)formate (4a).

IR: *v* (cm^{-1}) 1235 (C=S), 1690 (C=N), 1760 (C=O), 2945 ($CH_{aliph.}$); **^{1}H-NMR** (DMSO-*d6*) (fig.19): δ 1.25 (t, 3H, *J* = 3.61 Hz, CH_3), 3.65 (q, 2H, *J* = 2.96 Hz, CH_2), 7.20 – 8.55 (m,18H, $H_{ar.}$) ppm.; **^{13}C-NMR** (DMSO-*d6*): δ 22.50 (CH_3), 58.11 (CH_2), 115.58, 115.93, 125.20, 127.90, 127.95, 128.51, 129.06, 129.19, 131.70, 131.76, 135.23, 125.31 and 135.73 ($C_{ar.}$), 144.16 (COO), 172.81 (C=S), 189.77 (C=S)ppm.

Ethyl-2-(3-phenyl-4-thioxo-1,2,3,4tetrahydroquinazolin-2-ylthio)acetate (4b).

IR: *v* (cm^{-1}) 1197 (C=S), 1610 (C=N), 1675 (C=O), 2930 ($CH_{aliph.}$); **^{1}H-NMR** (DMSO-*d6*) (fig. 22): δ 1.25 (t, 3H, *J* = 4.71 Hz, CH_3), 3.57 (d, 2H, *J* = 3.14 Hz, CH_2S), 4.21 (q, 2H, *J* = 2.83 Hz, CH_2CO), 6.20 – 7.85 (m, 18H, $H_{ar.}$) ppm; **^{13}C-NMR** (DMSO-*d6*): δ 14.02 (CH_3), 33.45 (CH_2CO), 61.45 (CH_2), 110.12, 119.89, 129.80, 130.01, 136.01, 137.98, 139.32, 143.32, 151.02 and 154.34 ($C_{ar.}$), 173.02 (C=N), 179.23 (C=O), 203.98 (C=S) ppm.

Reaction of compound 1 with ethyl chloroacetoacetate. Formation of 5.

To a solution of compound **1** (0.81g, 0.003 mol) in methanol (15 ml) and potassium hydroxide (0.56 g, 0.01 mol), ethyl chloroacetoacetate (0.49 g, 0.003 mol) was added. The reaction mixture was stirred at r. t. for 5 hr (tlc). The solid product that formed was recrystallized from ethanol to give **5**.

Ethyl-3-oxo-2-(3-phenyl-4-thioxo-1,2,3,4tetrahydroquinazolin-2-ylthio)-butanoate (5).

IR: *v* (cm^{-1}) 1250 (C=S), 1610 (C=N), 1742,1665 (2C=O) 2940 ($CH_{aliph.}$); **^{1}H-NMR** (DMSO-*d6*) (fig. 25): δ 1.64 (t, 3H, *J* = 4.91 Hz,CH_3CH_2), 2.55 (s, 3H, CH_3CO), 3.4 (q, 2H, *J* = 2.53 Hz, CH_2), 3.95 (s, 1H, CH), 7.00-7.9 (m, 9H, $H_{ar.}$) ppm; **MS**: (EI) m/z = 398.8 (M^+, $C_{20}H_{18}N_2O_3S_2$, 2.2 %).

Reaction of compound 1 with diphenyl diazomethane. Formation of 6.

Compound **1** (0.81 g, 0.003 mol) was refluxed with diphenyl diazomethane (0.5 ml, 0.004 mol) in anhydrous benzene (30 ml) for 6 hr (tlc). After cooling to r. t. the formed solid product was filtered off, recrystallized from methanol, filtered, and dried to afford **6**.

2-(Benzhydrylthio)-3-phenylquinazoline4(3H)thione(6)

IR: *v* (cm^{-1}) 1240 (C=S), 1690 (C=N), 2927 ($CH_{aliph.}$), 3090 ($CH_{ar.}$). **^{1}H-NMR** (DMSO-*d6*) (fig. 28): δ 3.51 (s, 1H, SCH), 6.32-8.51 (m, 19H, $H_{ar.}$) ppm; **^{13}C-NMR** (DMSO-*d6*): δ 55.29 (CH), 127.28, 128.20, 128.52, 128.61, 128.94, 129.53, 129.86 and 140.07 ($C_{ar.}$), 156.12 (C=N), 190.01 (C=S) ppm; **MS** (EI) m/z = 436.59 (M^+, $C_{27}H_{20}N_2S_2$, 31.9 %).

Table**2**. Physical and analytical data of compounds **4a,b, 5** and **6.**

Cpd.	M.P. (°C)	Yield (%)	M.F. (M. wt.)	M.A. (%); Calcd/Found		
				C%	H%	N%
4a	184-6	87	$C_{17}H_{14}N_2O_2S_2.1/10H_2O$	59.63	4.12	8.18

			(342.44)	59.26	4.06	8.13
4b	210-12	89	$C_{18}H_{16}N_2O_2S_2$. 1/10H_2O (356.46)	60.65 60.29	4.52 4.46	7.86 7.81
5	190-2	78	$C_{20}H_{18}N_2O_3S_2$. 1/10H_2O (398.5)	60.28 59.95	4.55 4.49	7.03 6.99
6	196-8	85	$C_{27}H_{20}N_2S_2$. 1/10H_2O (436.59)	74.28 73.90	4.62 4.56	6.42 6.38

Reaction of compound 7 with a mixture of triethyl- and/or triphenyl–phosphite and aromatic aldehydes. Formation of 8a-d.

A mixture of **7** (0.98 g, 0.0028 mol), benzaldehyde and 4-clorobanzaldehyde (0,003 mol) and triethyl- or triphenyl–phosphite (0.003 mol) in glacial acetic acid (30 ml) was heated at 100 °C for 4-6 hr (tlc). The reaction mixture was concentrated to 1/4 volume and poured onto ice. The solid formed was filtered off, washed by petroleum ether followed by recrystalliztion from methanol to give the amino phosphonates **(8a-d),** respectively. The data are listed in table 3.

Diethyl(6,8-dibromo-4-oxo-2-thioxo-1,2dihydroquinazolin3(4*H*)-ylamino)- (phenyl)-methylphosphonate (**8a**).

IR: *v* (cm^{-1}) 680 (C-Br), 745 (C-Cl), 1260 (C=S_{cyclic}), 1310 (P=O), 1687 (C=O), 2849 (CH), 3197, 3300 (2NH); **^{1}H-NMR** (DMSO-d_6): δ 1.22 (s, 6H, $2CH_3$), 2.52 (s, 1H, $NH_{acyclic}$), 3.94 (s, 1H, CH), 4.15 (s, 4H, $2CH_2$), 7.42-8.05 (m, 6H, $H_{ar.}$), 8.55 (s, 1H, NH_{cyclic}) ppm. **^{13}C-NMR** (DMSO-d_6): δ 14.17 ($2CH_3$), 39.29 (CH), 61.12 ($2CH_2$), 126.59, 127.44, 129.00, 129.96, 130.15, 130.50, 135.50 and 139.93 ($C_{ar.}$), 168.20 (C=O), 188.86 (C=S) ppm.

Diethyl(4-chlorophenyl)(5,7-dibromo-1-oxo-3-thioxo-3,4-dihydroisoquinolin-2(1*H*)ylamino)methylphosphonate (**8b**).

IR: *v* (cm^{-1}) 695 (C-Br), 1172 (C=S), 1280 (P=O), 1663 (C=O), 2955 ($CH_{aliph.}$), 3065 ($CH_{ar.}$), 3231, 3410 (2NH); **^{1}H-NMR** (DMSO-d_6): δ 1.20 (s, 6H, $2CH_3$), 2.51 (s, 1H, $NH_{acyclic}$), 3.94 (s, 1H, CH), 4.15 (s, 4H, $2CH_2$), 7.40-8.05 (m, 6H, $H_{ar.}$), 8.55 (s, 1H, NH_{cyclic}) ppm.; **^{13}C-NMR** (DMSO-d_6): δ 14.61 ($2CH_3$), 39.49 (CH), 62.16 ($2CH_2$), 127.71, 127.84, 129.82, 129.94, 130.24, 131.63, 136.11 and 138.51 ($C_{ar.}$), 167,18 (C=O), 186.14 (C=S) ppm. **Diphenyl(6,8-dibromo-4-oxo-2-thioxo-1,2dihydroquinazolin-3(4*H*)ylamino) (phenyl)methylphosphonate** (**8c**).

IR: *v* (cm^{-1}) 680 (C-Br), 1120 (C=S), 1260 (P=O), 1640 (C=O), 2849 (CH), 3321 (NH); **^{1}H-NMR** (DMSO-d_6): δ 2.50 (s, 1H, $NH_{acyclic}$), 4.01 (s, 1H, CH), 6.45-8.05 (m, 17H, $H_{ar.}$), 8.55 (s, 1H, NH_{cyclic}) ppm.; **^{13}C-NMR** (DMSO-d_6): δ 53.55 (CH), 125.51, 126.35, 128.29, 129.18, 131.73, 133.92, 134.56 and 140.73 (2Ph, $C_{ar.}$), 154.33 (P-O-C), 169,22 (C=O), 185.92 (C=S) ppm.

Diphenyl(4-chlorophenyl)(5,7-dibromo-1-oxo-3thioxo-3,4-dihydroisoquinolin-2(1*H*)ylamino)methylphosphonate (**8d**).

IR: *v* (cm^{-1}) 603 (C-Br), 692 (C-Cl), 1185 (C=S), 1265 (P=O), 1640 (C=O), 2845 (CH), 3321 (NH);**^{1}H-NMR** (DMSO-d_6): δ 2.53 (s, 1H, $NH_{acyclic}$), 4.12 (s, 1H, CH), 6.45-8.05 (m, 16H, $H_{ar.}$), 8.55 (s, 1H, NH_{cyclic}) ppm.; **^{13}C-NMR** (DMSO-d_6): δ 53.15 (CH), 127.00, 128.84, 129.34, 129.98, 130.33, 131.91, 136.23 and 138.85 ($C_{ar.}$), 152.10 (P-O-C), 169.46 (C=O), 189.09 (C=S) ppm.

Table **3**. Physical and analytical data of compounds **8a-d.**

Cpd.	M.P. (°C)	Yield (%)	M.F. (M. wt.)	M.A. (%); Calcd/Found		
				C%	H%	N%
8a	215-17	87	$C_{19}H_{19}Br_2ClN_3O_4PS$. 1/5$H_2O$ (611.67)	37.31 37.05	3.13 3.08	6.87 6.82
8b	195-17	89	$C_{19}H_{20}Br_2N_3O_4PS$.1/25MeOH.1/20H_2O (437.11)	39.53 39.51	3.49 3.37	7.28 5.96
8c	220-22	80	$C_{27}H_{20}Br_2N_3O_4PS$. 1/20H_2O (673.31)	48.16 48.05	2.99 2.96	6.24 6.22
8d	189-91	77	$C_{27}H_{19}Br_2ClN_3O_4PS$. 1/20$H_2O$ (707.76)	45.82 45.72	2.71 2.68	5.94 5.92

Reaction of compound 7 with 4-aminobenzoic acid. Formation of 9.

A mixture of **7** (0.7g, 0.002 mol) and 4-aminobenzoic acid was heated in boiling phosphorus oxychloride (10 ml) for 8 hr (tlc.). The reaction mixture was cooled to r. t. and neutralized by NaOH (20%). The solid formed was filtered off, recrystallized from ethanol to give **9,** yield 77%, m. p. 180 °C.

2-(4-Aminophenyl)-7,9-dibromo-10,10a-dihydro[1,3,4]-thiadiazolo[2,3-b]quina-zolin-5-one (9)

IR: *v* (cm^{-1}) 695 (C-Br), 1617 (C=N), 1655 (C=O, cyclic), 3338 ($NH_{2\ sym}$), 3460 ($NH_{2\ asym}$). **^{1}H-NMR** (DMSO-d_6): δ 4.09 (s, 2H, NH_2), 6.65-8.55 (m, 6H, $H_{ar.}$) ppm.; **^{13}C-NMR** (DMSO-d_6): δ 115.14, 118.64, 128.55, 128.65, 129.89, 129.96, 131.70, 133.41 and 138.81 ($C_{ar.}$), 153.15 (C=C), 164.32 (C=O), 170,31 (C=N) ppm.

Analysis for $C_{15}H_8Br_2N_4OS$. 1/20 H_2O (M.wt.452)

Calcd: C, 39.85%; H, 1.78%; N, 12.39%.. Found: 39.12%; 1.57%; 11.75%.

Reaction of compound 7 with triethylorthoformate. Formation of 10.

A mixture of compound **7** (0.7g, 0.002 mol) and triethylorthoformate (0.43g, 0.003 mol) in glacial acetic acid (25 ml) was refluxed for 3 hr (tlc). The reaction mixture was cooled to r.t. The solid product that formed was filtered off, recrystallized from ethanol and dried to give **10**. yield 76%, m. p. 192 °C.**Ethyl N-6,8-dibromo-4-oxo-2-thioxo-1,2dihydroquinazolin-3(4H)-ylformimidate (10)**

IR: *v* (cm^{-1}) 670 (C-Br), 1630 (C=N), 1740 ($C=O_{cyclic}$), 1180 ($C=S_{cyclic}$), 2950 (CH), 3498 (NH); **^{1}H-NMR** (DMSO-d_6): δ 1.61 (t, 3H, *J* = 4.11 Hz, CH_3), 4.10 (q, 2H, *J* = 2.17 Hz, CH_2), 1663($C=S_{cyclic}$) ppm.; **^{13}C-NMR** (DMSO-d_6): δ 14.19 (CH_3), 61.52 (CH_2), 126.59, 127.44, 129.00, 130.15, 135.50 and 140.91 ($C_{ar.}$), 155.61 (C=N), 167.85 (C=O), 186,72 (C=S) ppm.

Analysis for $C_{11}H_9Br_2N_3O_2S$. 1/25EtOH. 1/20H_2O (407.08)

Calcd: C, 32.45%; H, 2.23%; N, 10.32%. Found: 32.35%; 2.20%; 10.29%.

Reaction of compound 7 with 4-benzylidene-2-phenyloxazol-5(4H)-one. Formation of 11

A mixture of compound **7** (0.7g, 0.002 mol) and 4-benzylidene-2-phenyloxazol-5(4H)-one (**a**) (0.5g, 0.002 mol) was boiled in glacial acetic acid for 5 hr (tlc.), The reaction mixture was cooled to r.t. The solid product that formed was filtered off, recrystallized from ethanol and dried to give **11**. yield 60%, m. p. 210 °C.

3-(4-Benzylidene-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)-6,8-dibromo-2-thioxo-1,2,3,8atetrahydroquinazolin-4(4a*H*)-one (11).

IR: *v* (cm^{-1}) 705 (C-Br), 1160 ($C=S_{cyclic}$), 1590 (C=N), 1610 (C=O-N), 1665 ($C=O_{cyclic}$), 2970 (CH), 3490 (NH);**^{1}H-NMR** (DMSO-d_6): δ 4.22 (s, 1H, NH), 7.19 (s, 1H, CH), 7.20-8.54 (m, 12H, $H_{ar.}$) ppm.; **^{13}C-NMR** (DMSO-d_6): δ 115.58 (CH), 125.20, 127.90, 127.95, 128.51, 129.06, 129.19, 131.70, 135.23, 135.31, 135.73 ($C_{ar.}$), 163.01 ($C=O_{cyclic}$), 172.81 (C=O), 189.77 (C=S) ppm.; **MS** (EI) m/z = (582.27, $C_{24}H_{14}Br_2N_4O_2S$, 10%).

Analysis for $C_{24}H_{14}Br_2N_4O_2S$. 1/20H_2O (582.27)

Calcd: C, 49.51%; H, 2.42%; N, 9.62%. Found: 49.38%; 2.40%; 9.60%.

Reaction of compound 7 with 4-chlorophenyl isocyanate and/or phenyl isothyocyanate. Formation of 12 and 14.

To a solution of compound **7** (0.35g, 0.001 mol) in anhydrous pyridine (25 ml) was added 4-chlorophenyl isocyanate and / or phenyl isothyocyanate (0.006 mol). The reaction mixture was refluxed for 4-5 hr (tlc). The solvent was evaporated to dryness under vacuum, and the residual solid was recrystallized from methanol and dried to give **12** and / or **14**, respectively.

1-(4-Chlorophenyl)-3-(6,8-dibromo-4-oxo-2-thioxo1-,2-dihydroquinazolin-3(4*H*)-yl)urea (**12**).

IR: *v* (cm^{-1}) 1190 ($C=S_{cyclic}$), 1610 ($C=O_{cyclic}$), 1660 (C=O-NH), , 2961 (CH), 3450 (NH);**^{1}H-NMR** (DMSO-d_6): δ 7.30-8.21 (m, 7H, $H_{ar.}$), 8.81 (s, 1H, $NH_{cyclic.}$) 11.72 (s, 2H, $2NH_{acyclic}$) ppm.; **^{13}C-NMR** (DMSO-d_6): δ 119.81, 128.61, 128.87, 129.40, 130.96, 137.78, 138.54 and 139.02 ($C_{ar.}$), 149.80 (C=O), 161.08 ($C=O_{cyclic}$), 179.01 (C=S) ppm.

7,9-Dibromo-2-(phenylimino)-2,3dihydro[1,3,4]thiadiazolo[2,3-b]quinazolin-5-one (**14**).

IR: *v* (cm-1) 678 (C-Br), 1610 (C=N), 1690 (C=O), 3450 (NH); **^{1}H-NMR** (DMSO-d_6): δ 2.41 (NH), 7.45-8.25 (m, 7H, $H_{ar.}$)ppm. **^{13}C-NMR** (DMSO-d_6): δ 125.93, 126.02, 127.24, 128.34, 128.41, 129.26, 129.31, 129.40 and 137.25 ($C_{ar.}$), 147.17 (C=N), 156.86 (C=O), 160.66 (C-S) ppm.

Table **4**. Physical and analytical data of compounds **12 and 14.**

Cpd.	M.P. (°C)	Yield (%)	M.F. (M. wt.)	M.A. (%); Calcd/Found		
				C%	H%	N%
12	192-4	57	$C_{15}H_9Br_2ClN_4O_2S$. 1/20H_2O (504.58)	35.70 35.60	1.80 1.78	11.10 11.07
14	122-4	71	$C_{15}H_8Br_2N_4OS$. 1/20H_2O (452.12)	39.85 39.73	1.78 1.76	12.39 12.36

Reaction of compound 7 with chloroacetaldehyde. Formation of 15

A mixture of compound **7** (0.35 g, 0.001mol) and chloroacetaldehyde (0.15g, 0.002 mol) in ethanol (20 ml) was refluxed for 3 hr (tlc). The reaction mixture was cooled to r.t.. The solid product that formed was filtered off, recrystallized from ethanol and dried to give **15**. yield 88%, m. p. 185 °C.

2-(3-Amino-6,8-dibromo-4-oxo-1,2,3,4tetrahydroquinazolin-2-ylthio)acetaldehyde (15).

IR: *v* (cm^{-1}) 730 (C-Br), 1560 (C=N), 1620 ($C=O_{cyclic}$), 1690 (C=O), 2850 ($CH_{ar.}$), 3300 ($NH_{2\ sym}$), 3490 ($NH_{2\ asym}$); ^{1}H-NMR (DMSO-d_6): δ 2.50 (s, 2H, NH_2), 4.43 (s, 2H, CH_2), 8.15 – 8.4 (dd, 2H, *J* = 1.95 Hz, $H_{ar.}$) 9.70 (s, 1H, CH) ppm.

Analysis for $C_{10}H_7Br_2N_3O_2S$. 1/20H_2O (393.05)

Calcd: C, 30.56%; H, 1.80%; N, 10.69%. Found: 30.46%; 1.77%; 10.66%.

Reaction of 7 with some Sultones. Formation of 18a,b.

Compound **7** (0.35g, 0.001mol) was fused with 1,3-propane- and/or 1,4-butane-sultone (0.002 mol) at 180°C for 4-6 hr (tlc). The residual solid was recrystallized from ethanol and afforded the corresponding sultams **18a and 18b**, respectively.

6,8-Dibromo-2-thioxo-2,3dihydroquinazolinoylpr-opane -1,3-sultam (18a).

IR: *v* (cm^{-1}) 685 (C-Br), 1120 (C=S), 1151-1360 (SO_2), 1710 ($C=O_{cyclic}$), 3390 (NH); **^{1}H-NMR** (DMSO-d_6): δ 1.20 (m, 2H, CH_2), 3.01(d, 2H, *J* = 2.01 Hz,CH_2), 3.20 (d, 2H, *J* = 2.21 Hz, CH_2), 4.15 (NH), 7.80 – 8.51 (dd, 2H, *J* = 2.75 Hz, $H_{ar.}$) ppm. ; **^{13}C-NMR** (DMSO-d_6): δ 14.17 (CH_2), 39.29 (CH_2), 61.12 (CH_2), 126.59, 127.49, 129.00, 130.15, 139.93 ($C_{ar.}$), 168.20 (C=O), 188.86 (C=S) ppm.

6,8-Dibromo-2-thioxo-2,3dihydroquinazolinoylb-utane-1,4-sultam (18b).

IR: *v* (cm^{-1}) 690 (C-Br), 1120 (C=S), 1156-1350 (SO_2), 1670 ($C=O_{cyclic}$), 3400 (NH); **^{1}H-NMR** (DMSO-d_6): δ 1.21 (m, 2H, CH_2), 2.01 (m, 2H, CH_2), 2.95 (d, 2H, *J* = 2.14 Hz, CH_2), 3.15 (d, 2H, *J* = 2.71 Hz, CH_2), 4.70 (NH), 7.90 – 8.53 (dd, 2H, *J* = 2.99 Hz, $H_{ar.}$) ppm.; **^{13}C-NMR** (DMSO-d_6): δ 19.17 (CH_2), 21.29 (CH_2), 47.51 (CH_2), 50.51 (CH_2), 126.69, 129.96, 130.15, 135.35, 139.93 ($C_{ar.}$), 160.27 (C=O), 186.45 (C=S) ppm.

Table **5**. Physical and analytical data of compounds **18a,b.**

Cpd.	M.P. (°C)	Yield (%)	M.F. (M. wt.)	M.A. (%); Calcd/Found		
				C%	H%	N%
18a	192-4	61	$C_{11}H_9Br_2N_3O_3S_2$. 1/20H_2O (455.15)	29.03 28.94	1.99 1.97	9.23 9.20
18b	122-4	89	$C_{12}H_{11}Br_2N_3O_3S_2$. 1/20H_2O (469.17)	30.72 30.63	2.36 2.34	8.96 8.93

BIOLOGICAL ACTIVITY

Antimicrobial activity of some selected compounds (**4a** and **5)** were determined against *Escherichia coli (NCIM2065)* as gram-negative bacteria, *S. ureus* as gram-positive bacteria and *Candida albicans* as fungi. The inhibition zones were measured in triplicates by standard methods using Cut plug method.[18,19] It was found compound **5** exhibited the highest inhibition zone against *E. coli*.

Conclusion

In this work. It is reported the preparation of some new quinazoline-4-ones derivatives for testing their biological activity bactericides. The results indicated that some of them showed activity against different types of bacteria.

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الملخص باللغة العربية

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تم تحضير بعض مشتقات الكينازولونات وهما المركبان 1و 7 كمواد أوليه

تم تكاثف المركب **1** مع الاسيتو برومو جلوكوز فى وجود **DMF** وثلاثى ايثيل أمين عند درجة حرارة الغرفة معطيا مشتق الجلوكوبيرانوزيل المقابل على الموضع **S** (**2**).

عند تقليب المركب **1** مع بعض هاليدات الاكيل تتكون مشتقات الالكيل ثيو المقابلة (3a-c). عند صهر المركب (1) مع كل من الايثيل كلوروفورمات والايثيل كلوراسيتات والايثيل اسيتو اسيتات يتكون مركبات الالكيل ثيو المقابلة

5 and **4a,b** . عند غليان المركب (**1**) مع ثنائي فينيل ثنائي أزو الميثان فى البنزين اللامائي فانه يعطي **6.** يتكاثف المركب (**7**) مع بعض الالدهيدات فى وجود ثلاثي (ايثيل –فينيل) الفوسفايت فانه يعطي **8a-d**. وعند معالجة المركب (7) مع 4-أمينو حمض البنزويك فانه يعطي مشتق ثياديازولوكينازولينون المقابل (**9**) .

وعند غليان المركب (**7**) مع ثلاثي ايثيل الفورمات فى وجود حمض الخليك الثلجي فانه يعطي (**10**).

عند تفاعل المركب (**7**) مع4-بنزيليدين-2-فينيل اوكزازولون ليعطي (**11**). عند تفاعل المركب (**7**) مع 4-كلوروفينيل ايزوسيانات وفينيل ايزوثيوسيانات ليعطي **14,12** .

عند غليان مخلوط من المركب (7) و كلورو اسيتالدهيد فى وجود الايثانول فانه يعطي **15** .

عند صهر المركب (**7**) مع(3,1-بروبان /1،4- بيوتان) سالتون عند درجة حرارة 180م° فانه يعطي السالتامات المقابلة(**18a**,**b**) .

تم اختبار الفاعلية البيولوجيه لبعض المركبات تجاه بعض أنواع من البكتيريا ووجد لها فاعلية مناسبة.