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ORIGINAL PAPER

Synthesis and biological evaluation of some 3*H*-quinazolin-4-one derivatives

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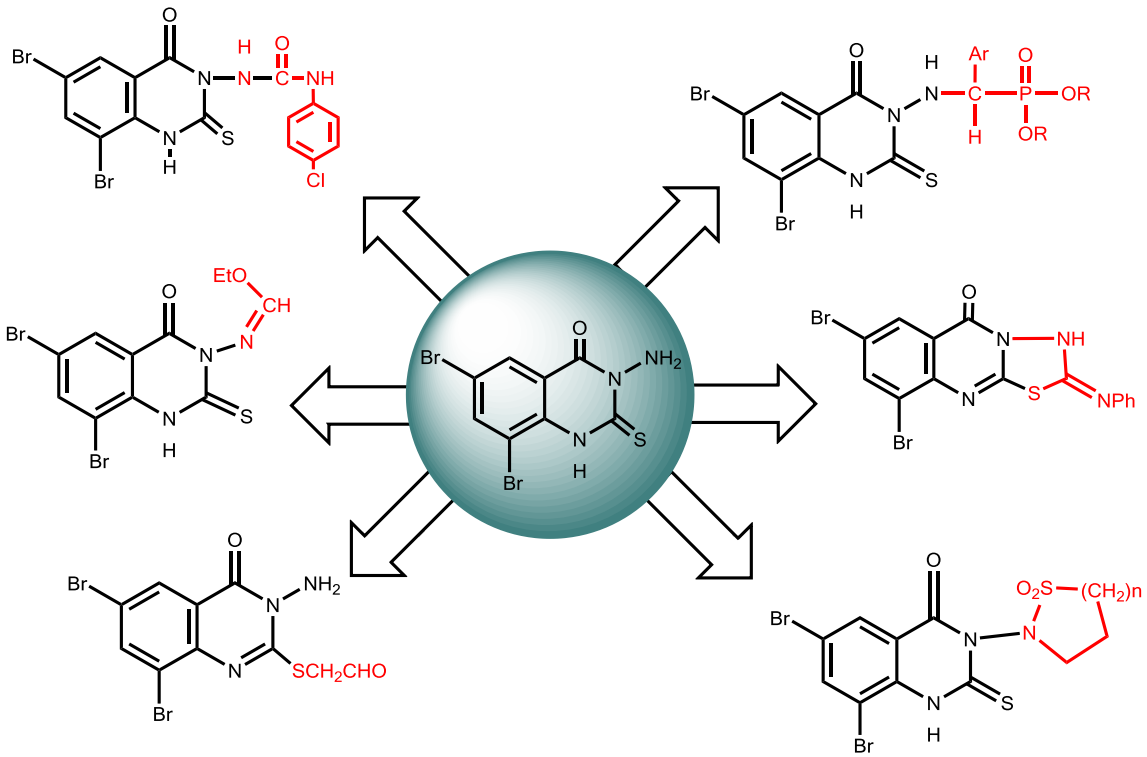
Abstract

Starting from 3-phenylquinazoline-2,4(1*H*,3*H*)-dithione, some new derivatives of 3*H*-quinazoline-4-ones were synthesized. The structures of all new compounds were inferred based on the mass spectral, infrared, and NMR spectral data as well as the elemental analytical data. Some compounds were chosen for testing their biological activities as antibacterial, antifungal, and anticancer agents.

Graphic abstract



Keywords Quinazolinones · Synthesis · Nucleosides · Biological · Antibacterial

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Introduction

The wide range of pharmacological activities of quinazolinones made them a major source of attraction during the last decades. They are essentially used as analgestic [1–3], antinflammatory [4, 5], diuretic [6–8], anticonvulsants [9–11], potential antispasmolytic [12], long active sedatives [1, 13], bronchodilators [14], and cholertic agents [15]. Additionally, 1,2,4-triazoloquinazoline derivatives [16, 17] were found to be promising biologically active compounds having potent antihypertensive [18, 19], antihistaminic [20, 21] with negligible sedation [22], and anticancer activities [23, 24]. Many derivatives of quinazolinone are patented and used in the market as potential drugs for different kinds of diseases (Scheme 1).

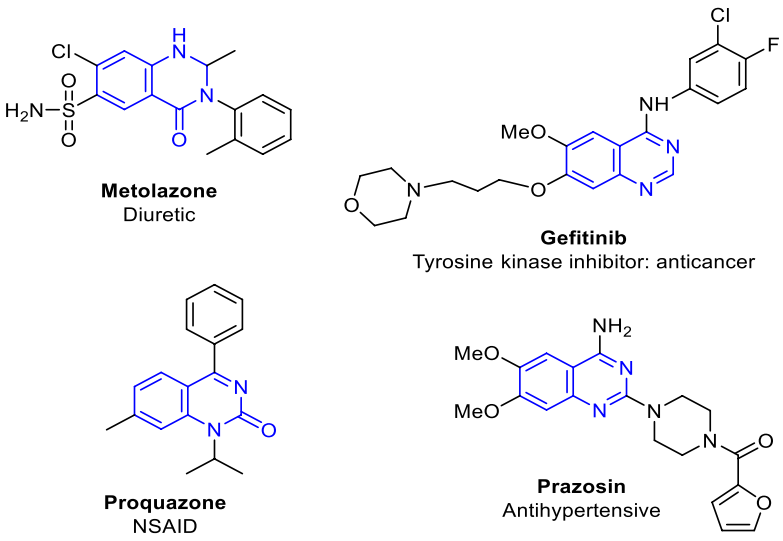
Accordingly, all these facts with our previous work [25–27] directed us to synthesize some new derivatives of 3*H*-quinazoline-4-ones for testing their biological activities as antibacterial, antifungal, and anticancer agents.

Results and discussion

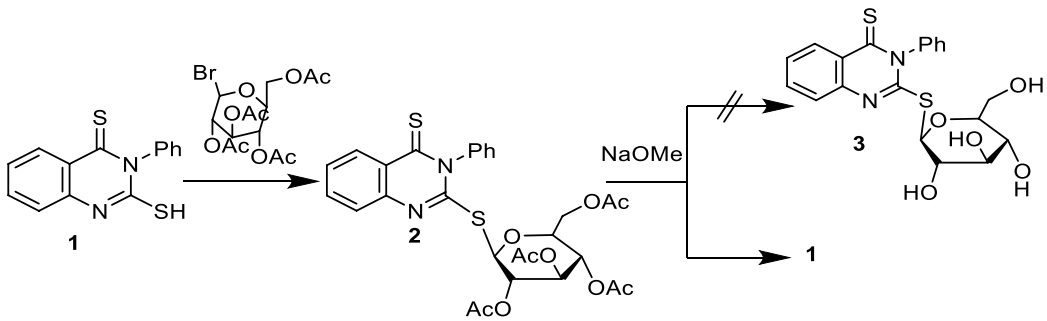
The starting 3-phenyl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one **1** was synthesized according to the reported procedure [28] by refluxing a mixture of 2-aminobenzoic acid and phenyl isothiocyanate and thiation of the produced compound with phosphorus pentasulphide in boiling anhydrous pyridine to yield **1** in good yield.

Coupling compound **1** with (2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)bromide (ABG) in the presence of Et_3N in DMF at r.t. afforded the corresponding *S*-nucleoside **2**. Attempt to deblock compound **2** using MeONa at room temperature afforded the starting aglycone **1** [29, 30] instead of the desired deblocked compound (**3**) (Scheme 2).

S-Alkylation of compound **1** was achieved by its treatment with some alkylating agents namely: MeI, BzCl, and/or phenacyl chloride at room temperature that yielded the corresponding 2-alkylthio derivatives **4a-c**, respectively. On treatment of the *S*-benzyl derivative (**4b**) with boiling NH_2NH_2 in MeOH afforded the corresponding hydrazino derivative (**5**) through SN_{Ar} reaction and replacing SBz



Scheme 1 Representative examples of quinazoline containing-drugs



Scheme 2 Synthesis of *S*-nucleoside **2** and attempt for deblocking

with NH_2-NH_2 (Scheme 3). Fusion of compound **1** with ethyl chloroformate and/or ethyl chloroacetate at the boiling point of each of the reactants yielded the corresponding 2-alkylthio derivatives (**6a,b**). By the same manner, refluxing compound **1** with ethyl chloroacetoacetate in MeOH for 4 h afforded ethyl-3-oxo-2-(3-phenyl-4-thioxo-1,2,3,4-tetrahydro-quinazolin-2-ylthio) butanoate **7** (Scheme 3).

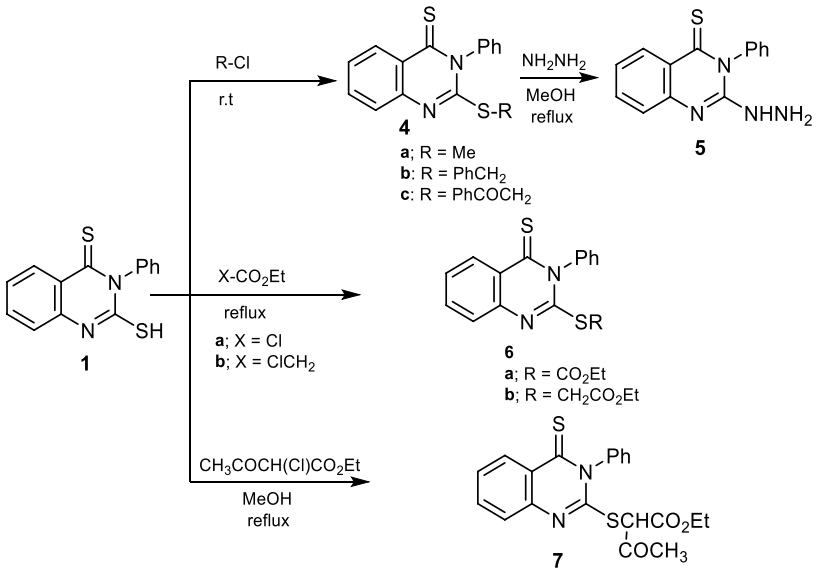
Refluxing compound **1** with diphenyl diazomethane (prepared according to known method [31]) in anhydrous benzene for 6 h gave 2-(benzhydrylthio)-3-phenylquinazoline-4(3H)-thione **8** via S–H insertion as the sole product (tlc) and not $\mathbf{8^i}$ (corresponding to SH elimination) or $\mathbf{8^{ii}}$ (corresponding to N–H insertion) (Scheme 4). The structures $\mathbf{8^i}$ and $\mathbf{8^{ii}}$ were ruled out based on different spectroscopic data. As the IR and ^{1}H-NMR spectra showed the absence of NH for $\mathbf{8^i}$ or SH for $\mathbf{8^{ii}}$, while in the ^{1}H-NMR spectrum of **8** there is a singlet peak centered at 3.51 ppm corresponding to one proton assigned to S-CH (Scheme 5).

The amino phosphonates (**10a-d**), which are phosphonic analogs of naturally occurring α–amino acids, could be synthesized when the starting compound **9** [30] was allowed to react with a mixture of triethyl- and/or triphenyl-phosphite and some aromatic aldehydes namely: benzaldehyde and 4-clorobenzaldehyde in boiling glacial AcOH for 4–6 h to afford the corresponding amino phosphonates (**10a-d**) (Scheme 6).

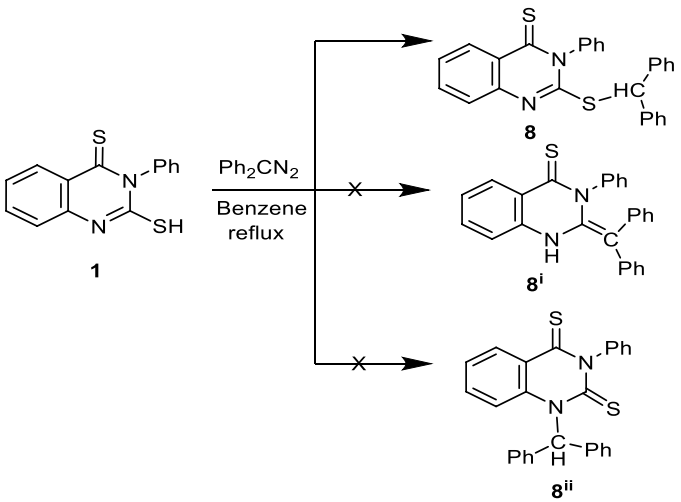
To understand how compounds **10a-d** were formed, the reaction pathway shown in (Scheme 7) was postulated:

Refluxing compound **9** with triethylorthoformate in glacial AcOH for 3 h yielded **11** as the sole product (as evidenced from tlc) through the elimination of EtOH without any formation of the cyclized one **12** (Scheme 8). Structure

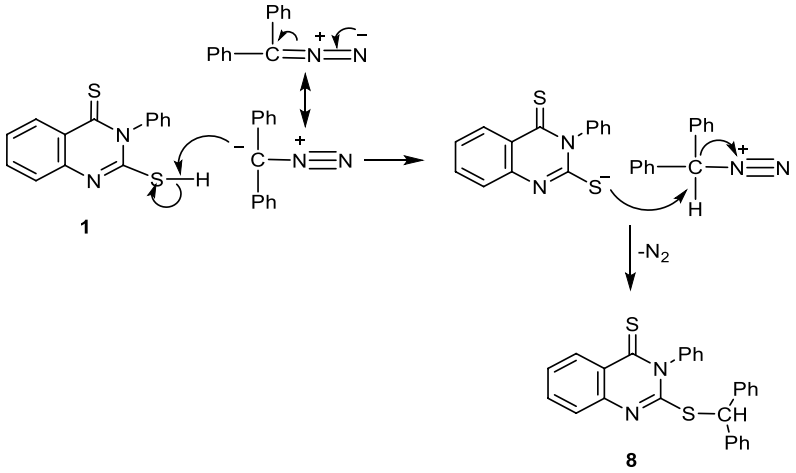
Scheme 3 Synthesis of compounds **4–7**



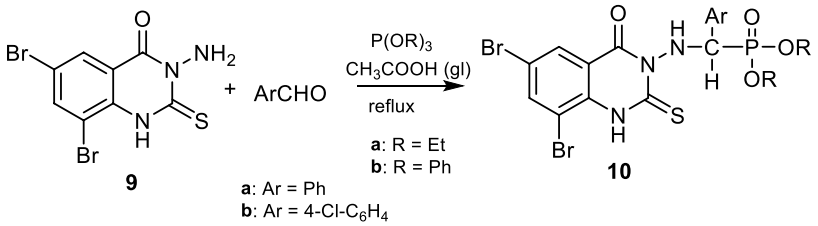
Scheme 4 Reaction of **1** with diphenyl diazomethane



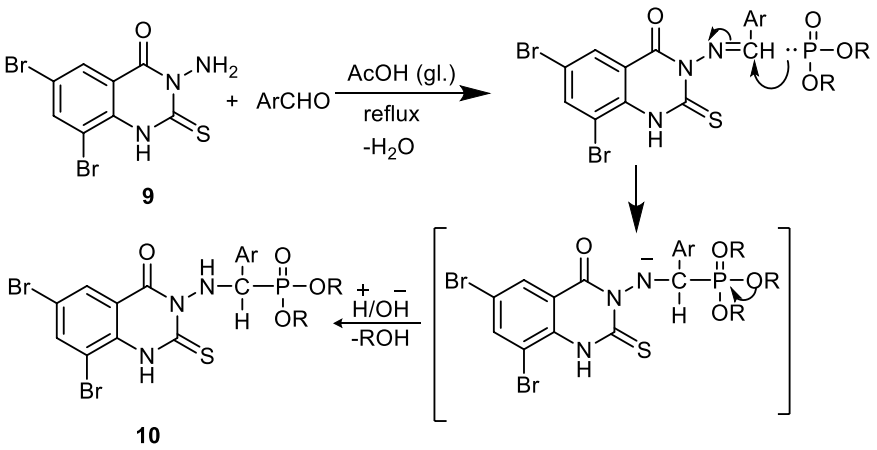
Scheme 5 Reaction pathway for synthesis of compound **8**



Scheme 6 Synthesis of amino phosphonates **10a-d**



Scheme 7 Reaction pathway for synthesis of compound **10**

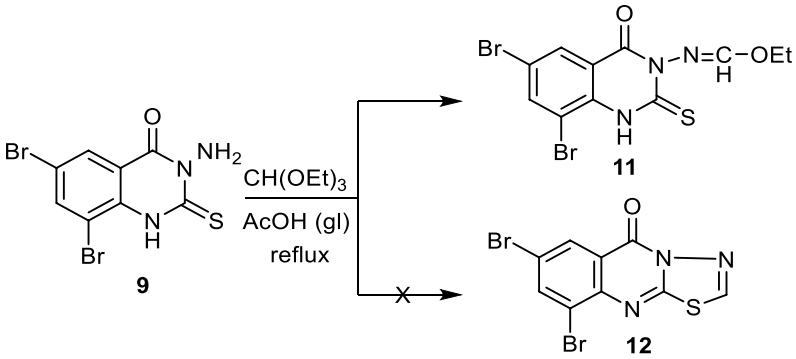


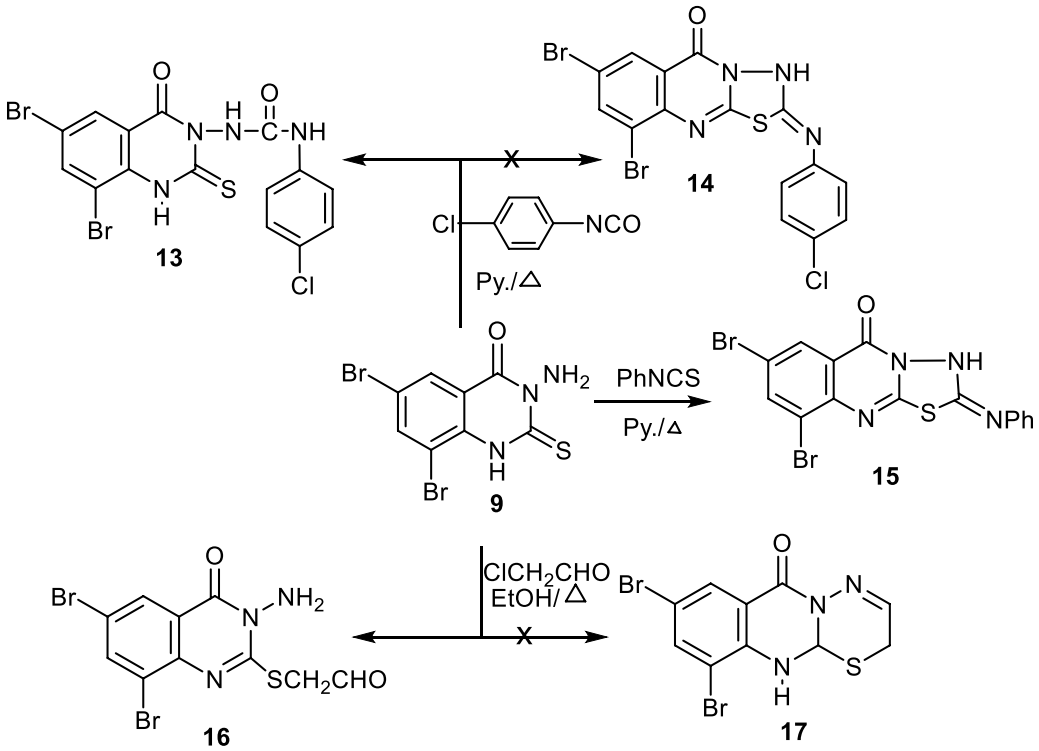
12 was ruled out based on the IR and ^{1}H-NMR spectral data, where the IR spectrum showed the characteristic NH stretching at 3448 cm^{-1}. Moreover, the ^{1}HNMR spectrum revealed the appearance of characteristic protons of ethyl group (a quartet peak for CH_2 at 4.10 ppm, and a triplet peak at 1.61 ppm for CH_3). The microanalytical data gave an additional evidence for the structure **11**.

Treatment of compound **9** with 4-chlorophenyl isocyanate in boiling pyridine for 5 h afforded the open ring structure **13** as the entire product (tlc) without any formation of the cyclized one (**14**). The cyclized structure **14** was ruled out according to the IR and MS spectral data. Its IR spectrum showed 2 CO groups at 1610 cm^{-1} and 1660 cm^{-1}. The microanalytical data gave an additional proof for this structure **13** (Scheme 9)**.** While reacting **9** with phenyl isothyocyanate under the same above reaction conditions for 3 h afforded the cyclized structure **15** as the sole product via elimination of H_2O (Scheme 9).

Reaction of compound **9** with chloroacetaldehyde in boiling EtOH for 3 h yielded

Scheme 8 Synthesis of compounds **12**





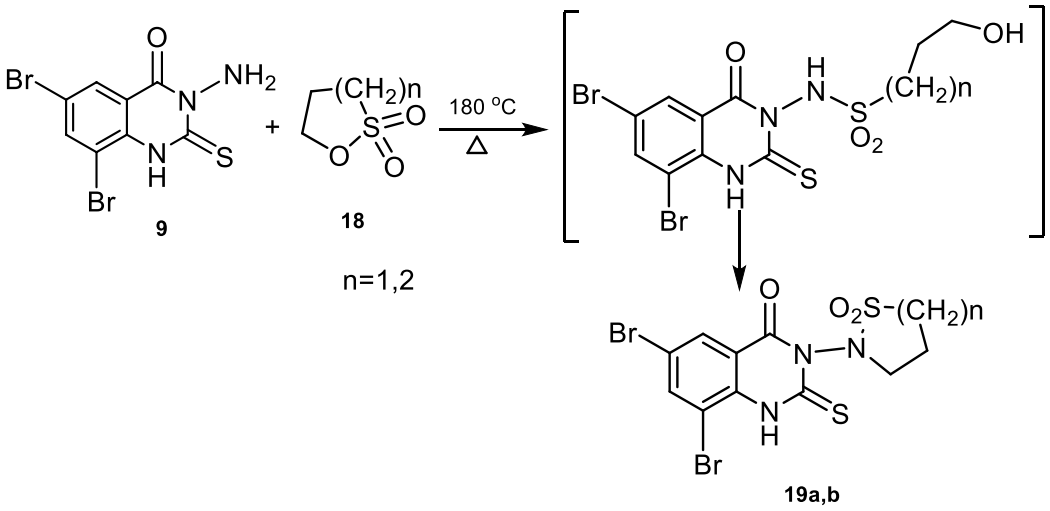
Scheme 9 Synthesis of compounds **14–17**

2-(3-amino-6,8-dibromo-4-oxo-1,2,3,4-tetrahydroquinazolin-2-ylthio)-acetaldehyde (**16**) as the sole product (tlc) without any traces of the cyclized structure **17**. While fusion of compound **9** with 1,3-propane- and/or 1,4-butane-sultone (**18a,b**) at 180 °C afforded the corresponding sultams **19a**,**b**, respectively (Scheme 10).

Biology

Antitumor activity

Quinazolinone derivatives have been found to exhibit a wide range of biological activities [32, 33]. Many research groups have focused on their synthesis and biological activities over the last 20 years. A considerable number of amino and/or ester group derivatives were reported to be antiviral, antibacterial, antifungal, and anticancer [34–45]. Producing new antimicrobial and anticancer safe agents is a great concern, and this is due to the increase in contamination and microbial infection by *microorganisms* and cancer diseases in the last few years. The aim of the present study is to investigate the antitumor activity of some newly synthesized quinazolinone derivatives.



Scheme 10 Synthesis of compounds **19a,b**

Table 1 Effect of compound 7 on PC3cell line

Conc. (µg/ml)	Surviving ratio
0.0	1.00
5.0	0.60
12.5	0.584
25.0	0.291
50	0.182

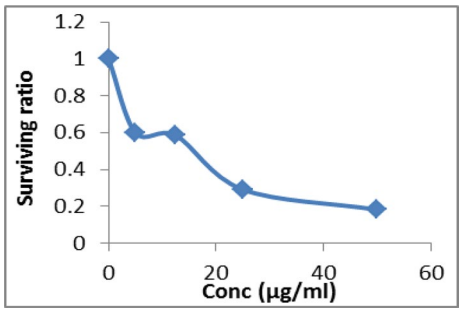


Fig. 1 Effect of compound (**7**) on **PC3** cell line ($\mathbf{IC_{50}}$ **= 16.3 µg/ml**)

Table 2 Effect of compound 7 on CACO cell line

Conc. (µg/ml)	Surviving ratio
0.0	1.00
5.0	0.820
12	0.568
25.0	0.386
50	0.299

Anticancer activity

In vitro potential cytotoxicities of the tested compounds were determined using the colorimetric method. Cytotoxic activity of ethyl-3-oxo-2-(3-phenyl-4-thioxo-1,2,3,4-tetrahydro-quinazolin-2-ylthio)butanoate (**7**) was tested against cancer cells (5 mg/mL in DMSO), obtaining medium inhibitory concentration ($\mathbf{IC_{50}}$) values in l g/mL, using a dilution method in a 96-well plate. After 72 h incubation, the absorbance was measured at 546 nm. DMSO was used as negative control and Doxorubicin (DOX) as positive control, both at the same concentration as the tested compounds. Compound **7** was dissolved in DMSO and subjected to cytotoxic evaluation against two cancer cell lines namely: **CACO** and **PC3** cell lines.

Anticancer activity of 7 against PC3 cell line

Quinazolinones were reported to possess diverse pharmacological activities such as CNS depressant [46, 47], hypnotic, antiinflammatory [31, 48], muscle relaxants [49] and for their antineoplastic activity [50]. In this study, these compounds and their modification clay with Na-MMT were examined as anticancer **PC3** cell line in vitro. Table 1 and Fig. 1 showed the anticancer activity of (**7**). From Table 1 and Fig. 1, the $\mathbf{IC_{50}}$ of compound **7** was 16.3 µg/ml. The lowest survival ratio was 0.182 and obtained from the highest concentration of **7**.

Anticancer activity of quinazolinones against CACO cell line

Ethyl-3-oxo-2-(3-phenyl-4-thioxo-1,2,3,4-tetrahydro-quinazolin-2-ylthio)butanoate (**7**) was tested against anticancer CACO cell line in vitro. The $\mathbf{IC_{50}}$ against **CACO** cell line was 17.3 µg/ml., c. f. Table 2 and Fig. 2. Its lowest survival ratio was 0.299 obtained from 50 µg/ml.

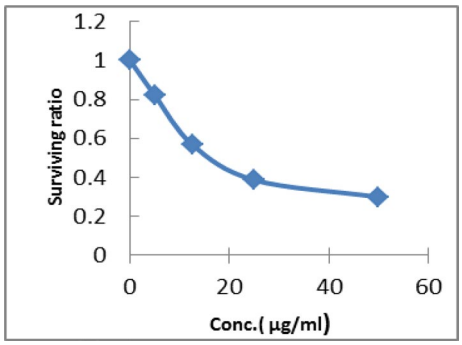


Fig. 2 Effect of compound (**7**) on **CACO** cell line (**IC_{50} = 17.3 µg/ml**)

Antimicrobial Activity

Antimicrobial activity of some quinazolinone derivatives

Our earlier work [46] showed that some quinazolinones did not give any antimicrobial activity with fungicides (*Fusarium solani*), and bactericides (*Pseudomonos solani*). Surprisingly, in our hands now we found that treatment of compounds **9**, **6b**, **7**, and **5** against another type of bacteria like *S.areous (MARSA)* gave high antimicrobial activity. The highest inhibition zone (25 mm) caused by compound **9** [51] (Table 3). On the other hand, testing compounds **9**, **6b**, **7**, and **5** as fungicides (*fusorium solani*), and bactericides (*psedomonos solani*) did not show any antimicrobial activity (Table 3). About 50 ul of streptomycin was used as antimicrobial standard, and about 50 ul from amphotrcin was used as standard and for antifungal.

Compound **9** showed the highest inhibition zone (25 mm) with *S.areous (MARSA)* only. Its containing amino group which might be the responsible group for inhibitory effect on growth of *S.areous MARSA*. The amino group bind with the organisms cell wall or cell membrane or cell constituents. While, compound **7** did not show any activity against all organisms.

Table 3 Antimicrobial activity of **9**, **6b**, **7** and **5**

Comp	Inhibition zone (mm)		
	S.areous MARSA	*E. coli*	*C. albicans*
9	25	−ve	−ve
6b	15	−ve	−ve
7	−ve	−ve	−ve
5	21	−ve	−ve
Streptomycin	**26**	**21**	**20**

Determination of minimal inhibitory concentrations (MICs)

MICs of different synthetic compounds were determined for each antimicrobial agent by using agar dilution method [52]. The inhibition zone was measured in triplicates in different concentrations (0.5, 1.0, 2.0 ug/ml), and the mean value of **MICs** is tabulated in the following tables.

MICs (µg/ml) of compounds (**9**, **6b**, **7** and **5**) were studied as shown in Table 4. Compounds **9**, **6b** and **5** showed antibacterial activities, and their *MICs* of these compounds were 1.0 µg/ml with different tested organisms. While, compound **7** did not show any activity against all organisms.

Experimental

All melting points were uncorrected and performed by the open capillary melting point apparatus. Microanalyses were performed by Microanalysis Unit, Central Laboratory, Tanta University, Tanta, Egypt. IR spectra were recorded with a PerkinElmer 1720 spectrometer. The NMR spectra were recorded on a Bruker 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 and $CHCl_3$ as solvents. 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.

Synthesis of 3-phenylquinazoline-2,4(1*H*,3*H*)-dithione (1) [28]

To a solution of 2-aminobenzoic acid (40 g., 0.2 mol) with phenyl isothyocyanate (0.2 mol) in anhydrous pyridine (25 ml). The reaction mixture was refluxed for 5 h (tlc). The solvent was evaporated to dryness under vacuum, and the residual solid was crystallized from methanol and dried to give 3-phenyl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one which was refluxed (0.02 mol) for 2 h (tlc) with phosphorus pentasulphide (0.03 mol) in anhydrous pyridine (15 ml).

Table 4 MICs (µg/ml) of compounds (**9**, **6b**, **7** and 5)

Comp	Inhibition zone (mm)		
	S. areous MARSA	*E. coli*	*C. albicans*
9	1.0	–	–
6b	1.0	–	–
7	–	–	–
5	1.0	–	–

The solvent was evaporated till dryness under vacuum. The residual solid was recrystallized from methanol and dried to give **1.** Yield 79%; m.p. 165–167 ºC [28].

2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl-thio)-3-phenyl-2,3-dihydro-quinazoline-4(1*H*)-thione (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 (0.001 mol). The reaction was complete within for 4 h at room temperature. Pouring onto cooled water gave a solid that was filtered off, washed with water, dried, and crystallized from ethanol to afford **2**. Yield 27%; m.p. 181–183 ºC. IR spectrum, *ν,* cm^{-1}: 1227 ($C=S_{cyclic}$), 1610 (C=N), 1748 (C=O, acetyl), 2925 (CH); ^1H NMR (DMSO-d_6), δ, ppm: 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), δC, ppm: 20.1 (CH_3, C´6), 20,3 (CH_3, C´4), 20.3 (CH_3, C´2), 20.3 (CH_3, C´3), 61.6, 67.9, 68.5, 73.0, 75.0, 81.9 (C´6, C´4, C´2, C´3, C´5, $C´1_{anomeric}$), 127.1, 128.8, 129.04, 129.8, 130.2 ($C_{ar.}$), 153.5 ($C=N_{cyclic}$), 169.0, 169.2, 169.7, 169.8 ($C=O_{,\ acetyl}$), 189.0 ($C=S_{cyclic}$). Found, %: C, 55.77; H, 4.80; N, 4.49. $C_{28}H_{28}N_2O_9S_2$. Calculated, %: C 55.99; H 4.70; N 4.66. *M* 600.

Deblocking of Compound 2. Two drops of sodium methoxide solution (0.001 N) were added to methanolic solution of (1.5 g, 0.01 ml), and the reaction mixture was stirred at r. t. for 4 h (tlc). Vacuum evaporation of the solvent gave a residual solid which was dissolved in water and then neutralized with dil HCl. Filteration of the formed solid, washing with water, drying, recrystallization from ethanol produced the starting material **1** in excellent yield 1.2 g (92%); m.p. 260–262 °C [30].

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

Compound **1** (0.81 g, 0.003 mol) was dissolved in MeOH (20 ml) and NaOH (0.5 g). Methyl iodide (0.13 ml, 0.003 mol) was added, and then stirring at r.t. for 5 h (tlc) gave a solid which was filtered off, recrystallized from methanol to afford **4a**.

Yield 75%, m.p.122–4 °C. IR spectrum, *ν,* cm^{-1}: 1188 ($C=S_{cyclic}$), 1665 (C=N), 2925 (CH); ^1H NMR (DMSO-d_6), δ, ppm: 2.75 (s, 3H, CH_3), 6.88–7.88 (m, 9H, $H_{ar.}$) ppm; ^{13}C NMR (DMSO-d_6), δC, ppm: 14,1 (CH_3), 122.0, 124.1, 126.1, 128.9, 136.8, 143.1 and 149.1 ($C_{ar.}$), 163.2 ($C=N_{cyclic}$), 179.1 (C=S). Found, %: C, 62.96; H 4.46; N 9.31. $C_{15}H_{12}N_2S_2$. Calculated, %: C 63.35; H 4.25; N 9.85. *M* 284.

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

To a solution of compound **96** (0.81 g, 0.003 mol) in EtOH (20 ml), NaOH (0.6 gm), and benzylchloride (0.38 ml, 0.003 mol) was added, and the solution was stirred at r.t. for 4 h (tlc). The precipitate was filtered off, recrystallized from petroleum ether to afford **99b.** Yield 86% m.p. 181–3 °C. IR spectrum, *ν,* cm^{-1}: 1200 ($C=S_{cyclic}$), 1690 (C=N), 2875 ($CH_{aliph.}$), 3037 ($CH_{ar.}$); ^1H NMR (DMSO-d_6), δ, ppm: 4.51 (s, 2H, CH_2), 7.25 – 8.57 (m, 14H, $H_{ar.}$) ppm; ^{13}C NMR (DMSO-d_6), δC, ppm: 39.2 (CH_2), 126.8, 127.3, 128.4, 129.0, 129.4, 129.8, 129.9 and 135.4 ($C_{ar.}$), 156.6 ($C=N_{cyclic}$), 188.9 (C=S). Found, %: C 69.63; H 4.42; N 7.73. $C_{21}H_{16}N_2S_2$. Calculated, %: C 69.97; H 4.47; N 7.77. *M* 360.

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

To a solution of compound **1** (0.81 g, 0.003 mol) in anhydrous pyridine (15 ml), was added anhydrous K_2CO_3 (0.8 g, 0.006 mol) followed by the addition of phenacyl chloride [47] (0.46 g, 0.003 mol). The reaction mixture was left stirring at r.t. for 5 h (tlc). Filtration of the precipitate then recrystallization from MeOH afforded **4c**. Yield 82%; m.p. 192–4 °C. IR spectrum, *ν,* cm^{-1}: 1193 (C=S), 1635 ($C=N_{cyclic}$), 1728 (C=O Ph), 2979 ($CH_{aliph.}$), 3088 ($CH_{ar.}$); ^1H NMR (DMSO-d_6), δ, ppm: 4.76 (s, 2H, CH_2), 7.20– 8.51(m, 14H, H_{ar}) ppm.; ^{13}C NMR (DMSO-d_6), δC, ppm: 43.7 (CH_2CO), 126,2, 128.2, 128.7, 128.9, 129.9, 130.0, 133.4 and 135.2 ($C_{ar.}$),186.1 ($C=S_{cyclic.}$), 193.5 ($C=OC_6H_5$). Found, %: C 67.92 H 3.93 N 7.05. $C_{22}H_{16}N_2OS_2$.Calculated, %: C 68.01; H 4.15 N 7.21. *M* 389.

2-Hydrazinyl-3-phenylquinazoline-4(3*H*)-thione (5)

A mixture of compound **4b** (2.16 g, 0.006 mol) and NH_2. NH_2 (2 ml, 0.006 mol) in EtOH (20 ml) was refluxed for 5 h (tlc) and then allowed to cool. The solid formed was collected and recrystallized from ethanol to afford **5.** Yield 73%; m.p. 185–187 ºC. IR spectrum, *ν,* cm^{-1}: 1190 (C=S), 3362 ($NH_{2\ asym}$), 3498 ($NH_{2\ sym}$). ^1H NMR (DMSO-d_6), δ, ppm: 4.41 (NH_2), 5.07 (NH), 7.26–8.64 (m, 9H, $H_{ar.}$) ppm; ^{13}C NMR (DMSO-d_6), δC, ppm: 125.9, 126.0, 127.2, 128.3, 128.4, 129.2, 129.3, 129.4, 137.2 and 147.1($C_{ar.}$), 156.8 (C=N), 160.6 (C-NH), 185.4 (C=S). Found, %: C 62.51; H 4.38; N 20.73. $C_{14}H_{12}N_4S$. Calculated, %: C, 62.66; H, 4.51; N, 20.88. *M* 268.

Reaction of compound 1 with ethyl chloroformate and/or ethyl chloroacetate

Compound **1** (0.81 g, 0.003 mol) was fused in ethyl chloroformate and / or ethyl chloroacetate (0.003 mol) at 85 °C for 4–5 h (tlc). The excess of the reagent was evaporated till dryness under vacuum. The residual solid was crystallized from petroleum ether (80–100 °C) to give compounds **6a** and/or **6b**, respectively.

Ethyl-2-(3-phenyl-4-thioxo-1,2,3,4-tetrahydroquinazolin-2-ylthio)formate (6a)

Yield 87%, m.p. 184–6 °C. IR spectrum, *v,* cm^{-1}: 1235 (C=S), 1690 (C=N), 1760 (C=O), 2945 ($CH_{aliph.}$); ^{1}H NMR (DMSO-d_6), δ, ppm: 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,9H, $H_{ar.}$) ppm.; ^{13}C NMR (DMSO-d_6), δC, ppm: 22.5 (CH_3), 58.1 (CH_2), 115.5, 115.9, 125.2, 127.90, 128.0, 128.5, 129.0, 129.2, 131.7, 131.7, 135.2, 125.3 and 135.7 ($C_{ar.}$), 144.1 (C=N), 172.8 (COO), 189.7 (C=S). Found, %: C 59.26; H 4.06; N 8.13. $C_{17}H_{14}N_2O_2S_2$. Calculated, %: C 59.63; H 4.12; N 8.18. *M* 342.

Ethyl-2-(3-phenyl-4-thioxo-1,2,3,4-tetrahydroquinazolin-2-ylthio)acetate (6b)

Yield 89%, m.p. 210–12 °C. IR spectrum, *v,* cm^{-1}: 1197 (C=S), 1610 (C=N), 1675 (C=O), 2930 ($CH_{aliph.}$); ^{1}H NMR (DMSO-d_6), δ, ppm: 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, 9H, $H_{ar.}$) ppm; ^{13}C NMR (DMSO-d_6), δC, ppm: 14.0 (CH_3), 33.4 (CH_2CO), 61.4 (CH_2), 110.1, 119.8, 129.8, 130.0, 136.0, 137.9, 139.3, 143.3, 151.0 and 154.3 ($C_{ar.}$), 173.0 (C=N), 179.2 (C=O), 203.9 (C=S). Found, %: C 60.29; H 4.46 N 7.81. $C_{18}H_{16}N_2O_2S_2$. Calculated, %: C 60.65; H 4.52; N 7.86. *M* 356.

Ethyl-3-oxo-2-(3-phenyl-4-thioxo-1,2,3,4-tetrahydroquinazolin-2-ylthio)butanoate (7)

To a solution of compound **1** (0.81 g, 0.003 mol) in methanol (15 ml) and KOH (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 h (tlc). The solid product that separated was filtered off and recrystallized from EtOH to give **7**. Yield 78%. m.p. 190–2 °C. IR spectrum, *v,* cm^{-1}: 1250 (C=S), 1610 (C=N), 1742,1665 (2C=O) 2940 ($CH_{aliph.}$); ^{1}H NMR (DMSO-d_6), δ, ppm: 1.64 (t, 3H, $J = 4.91$ Hz,CH_3CH_2), 2.55 (s, 3H, CH_3CO), 3.41 (q, 2H, $J = 2.53$ Hz, CH_2), 3.95 (s, 1H, CH), 7.00–7.9 (m, 9H, H-Ar). Found, %: C 59.95: H 4.49; N 6.99. $C_{20}H_{18}N_2O_3S_2$. Calculated, %: C 60.28; H 4.55; N 7.03. *M* 398.

2-(Benzhydrylthio)-3-phenylquinazoline-4(3H)-thione (8)

Compound **1** (0.8 g, 0.003 mol) was refluxed with diphenyl diazomethane [31] (0.5 ml, 0.004 mol) dissolved in anhydrous benzene (30 ml) for 6 h (tlc). The reaction mixture was cooled to r.t.. The formed solid was filtered off, recrystallized from methanol, filtered, and dried to afford **8**. Yield 85%, m.p. 196–8 °C; IR spectrum, *v,* cm^{-1}: 1240 (C=S), 1690 (C=N), 2927 ($CH_{aliph.}$), 3090 ($CH_{ar.}$). ^{1}H NMR (DMSO-d_6), δ, ppm: 3.51 (s, 1H, SCH), 6.32–8.51 (m, 19H, $H_{ar.}$) ppm; ^{13}C NMR (DMSO-d_6), δC, ppm: 55.2 (CH), 127.2, 128.2, 128.5, 128.6, 128.9, 129.5, 129.8 and 140.0 ($C_{ar.}$), 156.1 (C=N), 190.0 (C=S). Found, %: C 73.90; H 4.56; N 6.38. $C_{27}H_{20}N_2S_2$. Calculated, %: C 74.28; H 4.62; N 6.42. *M* 436.

Synthesis of 3-amino-6,8-dibromo-2-thioxo-2,3-dihydroquina-zolin-4(1*H*)-one (9)

A mixture of 2-amino-3,5-dibromobenzoic acid hydrazide (10 g, 0.03 mol), NaOH (1.2 g, 0.03 mol) and CS_2 (0.7 ml, 0.03 mol) in ethanol (120 ml) was refluxed for 15 h (tlc). Evaporation of the solvent gave a solid that was dissolved in water (100 ml.) and neutralized with dil. HCl (1:1). The precipitate that formed was filtered off, washed with H_2O (100 ml.) and recrystallized from ethanol to afford **9**, yield 50%, m. p. 260 °C, reported m.p. 260–262 [30].

Reaction of compound 9 with a mixture of triethyl- and/or triphenyl–phosphite and aromatic aldehydes

A mixture of **9** (0.98 g, 0.0028 mol), aromatic aldehydes namely: benzaldehyde and 4-chloro-benzaldehyde (0,003 mol) and triethyl- and/or triphenylphosphite (0.003 mol) in glacial AcOH (30 ml) was heated at 100 °C for 4–6 h (tlc). The reaction mixture was concentrated to 1/4 volume and poured onto ice. Filtration of the formed solid then washing with petroleum ether followed by recrystallization from MeOH gave the amino phosphonates (**10a-d**), respectively.

Diethyl(6,8-dibromo-4-oxo-2-thioxo-1,2-dihydroquinazolin-3(4*H*)-ylamino)(phenyl)-methylphosphonate (10a)

Yield 87%. m.p. 215–217 °C. IR spectrum, *v,* cm^{-1}: 680 (C–Br), 745 (C–Cl), 1050 (P-O-C), 1260 ($C=S_{cyclic}$), 1310 (P=O), 1687 (C=O), 2849 (CH), 3197, 3300 (2NH); ^{1}H NMR (DMSO-d_6), δ, ppm: 1.22 (t, 6H, $2CH_3$), 2.52 (s, 1H, $NH_{acyclic}$), 3.94 (s, 1H, CH), 4.15 (q, 4H, $2CH_2$), 7.42–8.05 (m, 6H, $H_{ar.}$), 8.55 (s, 1H, NH_{cyclic}) ppm. ^{13}C NMR (DMSO-d_6), δC, ppm: 14.1 ($2CH_3$), 39.2 (CH), 61.1 ($2CH_2$), 126.5, 127.4, 129.0, 129.9, 130.1, 135.50

and 139.9 ($C_{ar.}$), 168.2 (C=O), 188.8 (C=S). Found, %: C 37.05; H 3.08; N 6.82. $C_{19}H_{19}Br_2ClN_3O_4PS$.Calculated, %: C 37.31; H 6.87; N 3.13. *M* 611.

Diethyl(4-chlorophenyl)(5,7-dibromo-1-oxo-3-thioxo-3,4-di-hydroiso-quinolin-2(1*H*)-ylamino)methylphosphonate (10b)

Yield 89%, m.p. 195–17 °C. IR spectrum, *v,* cm^{-1}: (cm^{-1}) 695 (C–Br), 1172 (C=S), 1050–1030 (P-O-C), 1280 (P=O), 1663 (C=O), 2955 ($CH_{aliph.}$), 3065 ($CH_{ar.}$), 3231, 3410 (2NH); ^{1}H NMR (DMSO-d_6), δ, ppm: 1.20 (t, 6H, $2CH_3$), 2.51 (s, 1H, $NH_{acyclic}$), 3.94 (s, 1H, CH), 4.15 (q, 4H, $2CH_2$), 7.40–8.05 (m, 6H, $H_{ar.}$), 8.55 (s, 1H, NH_{cyclic}) ppm.; ^{13}C NMR (DMSO-d_6), δC, ppm: 14.6 ($2CH_3$), 39.4 (CH), 62.1 ($2CH_2$), 127.7, 127.8, 129.8, 129.9, 130.2, 131.6, 136.1 and 138.5 ($C_{ar.}$), 167.1 (C=O), 186.1 (C=S). Found, %: C 39.51; H 3.37; N 5.96. $C_{19}H_{20}Br_2N_3O_4PS$. Calculated, %: C 39.53; H 3.49; N 7.28. *M* 437.

Diphenyl(6,8-dibromo-4-oxo-2-thioxo-1,2-dihydroquinazolin-3(4*H*)ylamino)(phenyl)methylphosphonate (10c)

Yield 80%, m.p. 220–22 °C. IR spectrum, *v,* cm^{-1}: 680 (C–Br), 1120 (C=S), 1190 (P-O-C), 1260 (P=O), 1640 (C=O), 2849 (CH), 3321 (NH); ^{1}H NMR (DMSO-d_6), δ, ppm: 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), δC, ppm: 53.5 (CH), 125.5, 126.3, 128.2, 129.1, 131.7, 133.9, 134.5 and 140.7 (2Ph, $C_{ar.}$), 154.3 (P-O-C), 169.2 (C=O), 185.9 (C=S). Found, %: C 48.05 H 2.96 N 6.22. $C_{27}H_{20}Br_2N_3O_4PS$. Calculated, %: C 48.16; H 2.99; N 6.24. *M* 673.

Diphenyl(4-chlorophenyl)(5,7-dibromo-1-oxo-3-thioxo-3,4-dihydroiso-quinolin-2(1*H*)-ylamino)methylphosphonate (10d)

Yield 77%, m.p. 189–91 °C. IR spectrum, *v,* cm^{-1}: 603 (C–Br), 692 (C–Cl), 1185 (C=S), 1195 (P-O-C), 1265 (P=O), 1640 (C=O), 2845 (CH), 3321 (NH); ^{1}H NMR (DMSO-d_6), δ, ppm: 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), δC, ppm: 53.1 (CH), 127.0, 128.8, 129.3, 129.9, 130.3, 131.9, 136.2 and 138.8 ($C_{ar.}$), 152.1 (P-O-C), 169.4 (C=O), 189.0 (C=S). Found, %: C 45.72; H 2.68; N 5.92. $C_{27}H_{19}Br_2ClN_3O_4PS$. Calculated, %: C 45.82; H 2.71; N 5.94. *M* 707.

Ethyl N-6,8-dibromo-4-oxo-2-thioxo-1,2-dihydroquina-zolin-3(4*H*)-yl-formimidate (11)

A mixture of compound **9** (0.7 g, 0.002 mol) and triethylorthoformate (0.43 g, 0.003 mol) in glacial AcOH (25 ml) was refluxed for 3 h (tlc). The reaction mixture was cooled at r.t. The solid product that formed was filtered off, recrystallized from EtOH and dried to give **11**. Yield 76%, m. p. 192 °C. IR spectrum, *v,* cm^{-1}: 670 (C–Br),1180 ($C=S_{cyclic}$), 1630 (C=N), 1740 ($C=O_{cyclic}$), 2950 (CH), 3498 (NH); ^{1}H NMR (DMSO-d_6), δ, ppm: 1.61 (t, 3H, $J=4.11$ Hz, CH_3), 4.10 (q, 2H, $J=2.17$ Hz, CH_2), 7.41 (s, 1H, CH), 8.23 (d, 2H, C_6H_5), 8.91 (s, 1H, NH). ^{13}C NMR (DMSO-d_6), δC, ppm: 14.1 (CH_3), 61.5 (CH_2), 126.5, 127.4, 129.0, 130.1, 135.5 and 140.9 ($C_{ar.}$), 155.6 (C=N), 167.8 (C=O), 186,7 (C=S). Found, %: C, 32.31; H, 2.14; N,10.17. $C_{11}H_9Br_2N_3O_2S$. Calculated, %: C, 32.45; H, 2.23; N, 10.32. *M* 407.

Reaction of compound 9 with 4-chlorophenyl isocyanate and/or phenyl isothyocyanate

To a solution of compound **9** (0.35 g, 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 h (tlc). The solvent was evaporated and to dryness under vacuum, and the solid formed was recrystallized from MeOH to afford **13** and/or **15**, respectively.

1-(4-Chlorophenyl)-3-(6,8-dibromo-4-oxo-2-thioxo-1,2-dihydroquinazolin-3(4*H*)-yl)urea (13)

Yield 57%. m.p. 192–4 °C. IR spectrum, *v,* cm^{-1}: 1190 ($C=S_{cyclic}$), 1610 ($C=O_{cyclic}$), 1660 (O=C-NH), 2961 (CH), 3450 (NH); ^{1}H NMR (DMSO-d_6), δ, ppm: 7.30–8.21 (m, 6H, $H_{ar.}$), 8.81 (s, 1H, $NH_{cyclic.}$) 11.7 (s, 2H, $2NH_{acyclic}$) ppm.; ^{13}C NMR (DMSO-d_6), δC, ppm: 119.8, 128.6, 128.8, 129.4, 130.9, 137.7, 138.5 and 139.0 (C-Ar), 149.8 (C=O), 161.0 ($C=O_{cyclic}$), 179.0 (C=S). Found, %: C 35.60; H 1.78; N 11.07. $C_{15}H_9Br_2ClN_4O_2S$. Calculated, %: C 35.70; H 1.80; N 11.10. *M* 504.

7,9-Dibromo-2-(phenylimino)-2,3dihydro[1,3,4]thiadiazolo[2,3-b]quinazolin-5-one (15)

Yield 71%. m.p. 122–4 °C. IR spectrum, *v,* cm^{-1}: 678 (C–Br), 1610 (C=N), 1690 (C=O), 3450 (NH); ^{1}H NMR (DMSO-d_6), δ, ppm: 2.41 (s, 1H, NH), 7.45–8.25 (m, 7H, $H_{ar.}$)ppm. ^{13}C NMR (DMSO-d_6), δC, ppm: 125.9, 126.0, 127.2, 128.3, 129.2, 129.3 and 137.2 ($C_{ar.}$), 147.1 (C=N), 156.8 (C=O), 160.6 (C-S). Found, %: C 39.73; H 1.76; N 12.36. $C_{15}H_8Br_2N_4OS$. Calculated, %: C 39.85; H 1.78; N 12.39. *M* 452.

2-(3-Amino-6,8-dibromo-4-oxo-1,2,3,4-tetrahydroquinazolin-2-ylthio)-acetaldehyde (16)

A mixture of compound **9** (0.35 g, 0.001 mol) and chloroacetaldehyde (0.15 g, 0.002 mol) in EtOH (20 ml) was refluxed for 3 h (tlc). The reaction mixture was cooled at r.t., The solid product that formed was filtered off, recrystallized from ethanol and dried to give **16**. Yield 88%, m. p. 185 °C. IR spectrum, *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, ppm: 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). Found, %: 30.46; 1.77; 10.66. $C_{10}H_7Br_2N_3O_2S$. Calculated, %: C, 30.56; H, 1.80; N, 10.69. *M* 393.

6,8-Dibromo-2-thioxo-2,3-dihydroquinazolinoylpropane-1,3-sultam (19a)

A mixture of compounds **9** (0.35 g, 0.001 mol) and 1,3-propane- and/or 1,4-butane-sultone (0.002 mol) was fused in an oil bath at 180 °C for 4–6 h (tlc) and cooled to r.t. The residual solid was recrystallized from EtOH and afforded the corresponding sultams **19a** and **19b**, respectively.

Yield 61%. m.p. 192–4 °C. IR spectrum, *v,* cm^{-1}: 685 (C–Br), 1120 (C=S), 1151 and 1360 (SO_2), 1710 ($C{=}O_{cyclic}$), 3390 (NH); ^{1}H NMR (DMSO-d_6), δ, ppm: 1.20 (s, 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), δC, ppm: 14.1 (CH_2), 39.2 (CH_2N), 61.1 (CH_2SO_2), 126.5, 127.4, 129.0, 130.1, 139.9 ($C_{ar.}$), 168.2 (C=O), 188.8 (C=S). Found, %: C 28.94; H 1.97; N 9.20. $C_{11}H_9Br_2N_3O_3S_2$. Calculated, %: C 29.03 H 1.99; N 9.23. *M* 455.

6,8-Dibromo-2-thioxo-2,3-dihydroquinazolinoylbutane-1,4-sultam (19b)

Yield 89%. m.p. 122–4 °C. IR spectrum, *v,* cm^{-1}: 690 (C–Br), 1120 (C=S), 1156 and 1350 (SO_2), 1670 ($C{=}O_{cyclic}$), 3400 (NH); ^{1}H NMR (DMSO-d_6), δ, ppm: 1.21 (s, 2H, CH_2), 2.01 (s, 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), δC, ppm: 19.1 (CH_2), 21.2 (CH_2), 47.5 (CH_2N), 50.5 (CH_2SO_2), 126.6, 129.9, 130.1, 135.3, 139.9 (C-Ar), 160.2 (C=O), 186.4 (C=S). Found, %: C 30.63; H 2.34; N 8.93. $C_{12}H_{11}Br_2N_3O_3S_2$. Calculated, %: C 30.72; H 2.36; N 8.96%. *M* 469.

Antimicrobial activities

Strains of human pathogenic microorganisms used in this study were as follows: *Escherichia coli* (NCIM2065) as gram-negative bacteria, S. *aureus* MARS as gram-positive bacteria, and *Candida albicans* as fungal pathogenes. All these strains were collected from Botany Department, Faculty of science, Tanta university and maintained in temperature freezer at – 80 °C. The antimicrobial spectrum of the prepared quinazolinone derivatives were determined against the tested organisms on powdered samples on nutrient agar which contained per liter: 3 g peptone, 5 g NaCl, 5 g beef extract, and 20 g agar and Sabouraud's agar for *Candida albicans.*

Conclusion

Some new derivatives of 3*H*-quinazoline-4-ones were synthesized from their precursor 3-phenyl-quinazoline-2,4(1*H*,3*H*)-dithione. Characterization and elucidation of the structures of all new products were inferred based on the spectral as well as elemental analytical data. Some compounds were chosen for testing their biological activities as antibacterial, antifungal, and anticancer agents Compound **7** was subjected to cytotoxic evaluation against two cancer cell lines namely: **CACO** and **PC3** cell lines Compounds **9**, **6b** and **5** showed antibacterial activities and their *MICs* of these compounds were 1.0 µg/ml with different tested organisms. Moreover, compounds **9**, **6b**, **7**, **5** against another type of bacteria as *S.areous (MARSA)* gave high antimicrobial activity. The highest inhibition zone (25 mm) caused by compound **9**.

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