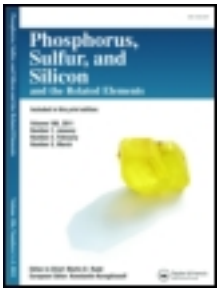

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis and Antibacterial Activity of Some New 4(3H)Quinazolin-4-one Derivatives

M. E. Azab [a] , E. A. Kassab [b] , M. A. El-Hashash [a] & R. S. Ali [b]

[a] Organic Synthetic Laboratory, Chemistry Department, Faculty of Science, Ain Shams University, Cairo, Egypt

[b] Helwan University, Industrial Education College, Ammeria, Cairo, Egypt

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Synthesis and Antibacterial Activity of Some New 4(3H)Quinazolin-4-one Derivatives

M. E. Azab,[1] E. A. Kassab,[2] M. A. El-Hashash,[1] and R. S. Ali[2]

[1]Organic Synthetic Laboratory, Chemistry Department, Faculty of Science, Ain Shams University, Cairo, Egypt
[2]Helwan University, Industrial Education College, Ammeria, Cairo, Egypt

2-Phenylamino-6,8-dibromo-4H-3,1-benzoxazinone has been reacted with nitrogen nucleophiles, such as hydrazine hydrate, amines, and formamide, yielding 4(3H)quinazolinone derivatives; and with sulfur nucleophiles producing the corresponding thioesters. The behavior of aminoquinazolinone and 4(3H)quinazolinone towards some carbon electrophiles under different conditions has been studied.

Keywords Antibacterial; nitrogen nucleophiles; quinazoline

INTRODUCTION

Potent benzoxazinones are inhibitors for human leukocyte elastase (HLE),[1] human Cathepsin G, and bovine chymotrypsin.[2] Also, the inhibition of chymotrypsin-like and elastase-like serine proteases by 4H-3,1-benzoxazinones has been investigated.[3]

In addition, many fused pyrimidines such as quinazolines and quinazolinones have been reported to exhibit anti-inflammatory,[4] antimicrobial,[5] anticancer,[6] and antimalarial[7] activities. 3H-Quinazoline-4-one is a frequently encountered unit in natural products such as L-vasicinone[8] and chrysogine.[9]

For the above-mentioned findings and in continuation of our program[10–14] on the synthesis of novel heterocyclic systems exhibiting biological activity, we synthesize a varieties of quinazolinone derivatives via the interaction of the benzaxazinone derivative **1** with different nitrogen nucleophiles, with the aim of obtaining more precise

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Address correspondence to M. E. Azab, Organic Synthetic Laboratory, Chemistry Department, Faculty of Science, Ain Shams University, Cairo, Egypt. E-mail: meazab_ali@yahoo.com

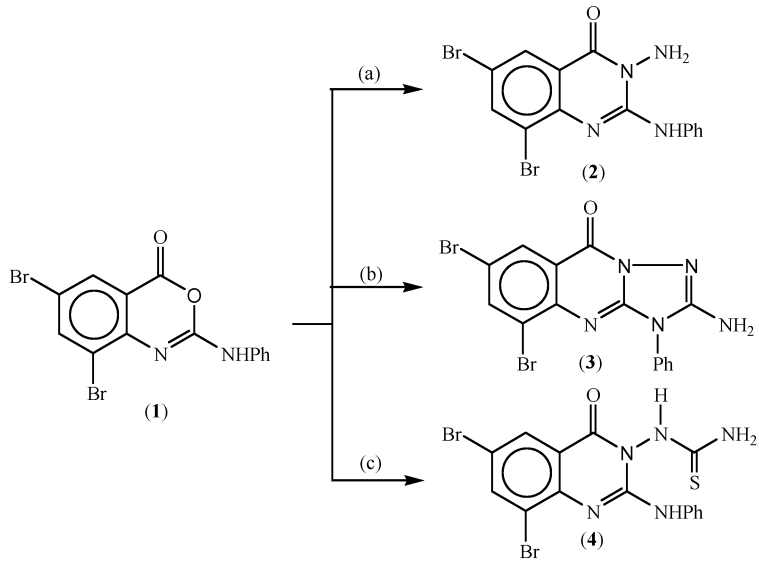
information about the course of the reaction and some interesting pharmaceutical compounds.

RESULTS AND DISCUSSION

The interaction of 3,5-dibromoanthranilic acid with phenyl isocyanate in boiling toluene afforded 6,8-dibromo-2-(phenylamino)-4H-benzo[d][1,3]oxazin-4-one (**1**). The structure of compound **1** was inferred from its IR spectrum, which reveals strong absorption bands at 1646, 1749, and 3286 cm^{-1} attributable to $\nu_{C=N}$, $\nu_{C=O}$, and ν_{NH} respectively. ^{1}H-NMR ($CDCl_3$) displayed the following peaks at δ: 7.28–8.31 (m, 7H, Ar-H) and 8.97 (br. s, 1H, NH, D_2O exchangeable). Electron impact fragmentation of compound **1** exhibits the molecular ion peak m/e, M^+ (394, 43.5%), M+2 (396, 78.2%), and M+4 (398, 41.8%).

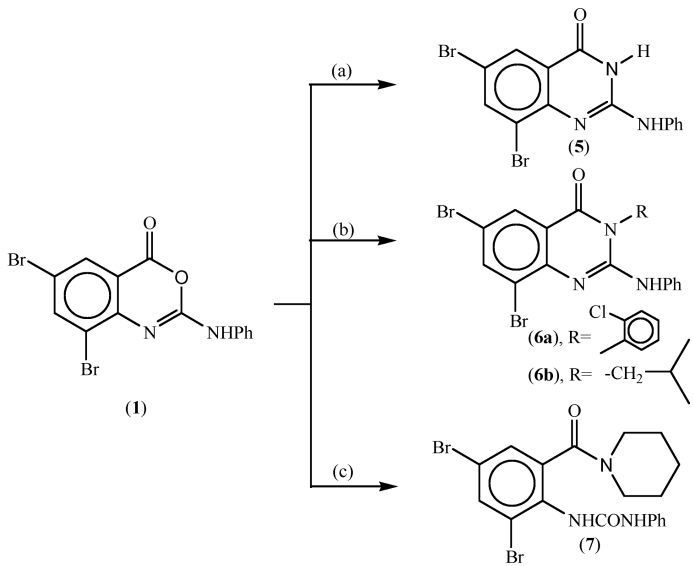
When compound **1** was allowed to react with hydrazine hydrate (in boiling EtOH), semicarbazide, and/or thiosemicarbazide (in boiling pyridine), it yielded 3-amino-quinazolinone **2**, 1,2,4-triazolo[5,1-b]quinazolinone **3**, and thiourea derivative **4**, respectively (Scheme 1).

Alternatively, reaction of **1** with formamide and/or primary amines, namely, 2-chloroaniline and isobutylamine, produced the quinazolinone derivatives **5** and**6a**,**b**, respectively (Scheme 2). Formation of **6a**,**b** takes



Reagents and conditions:a) N_2H_4/EtOH/Δ, b)$NH_2NHCONH_2$/pyridine/Δ, c)$NH_2NHCSNH_2$/pyridine/Δ.

SCHEME 1



Reagents and conditions:a) $HCONH_2$ /Δ, b)2-chloroaninline and/or isobutylamine/EtOH/Δ, c)piperidine/EtOH/Δ.

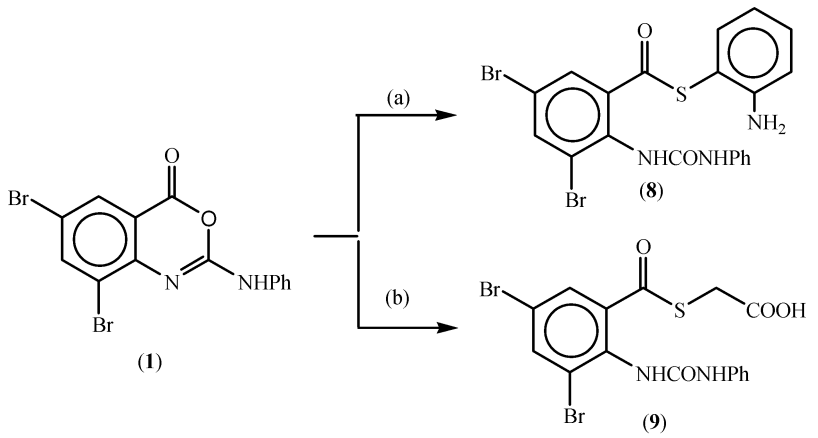
SCHEME 2

place via hetero-ring opening followed by cyclization, while the benzoxazinone **1** undergoes hetero-ring opening upon treatment with piperidine (secondary amine) in boiling ethanol to give the aniline derivative **7** (Scheme 2).

The behavior of the benzoxazinone **1** with aliphatic and aromatic mercaptans was also investigated. Thus, when compound **1** was allowed to react with 2-aminothiophenol and/or thioglycolic acid in dry toluene, it underwent hetero-ring opening producing thiobenzoate derivatives **8** and **9**, respectively (Scheme 3).

Also, in this investigation, we used 3-aminoquinazolinone derivative **2** as a key starting material for synthesis of 3-substituted quinazolinone derivatives and annulated fused quinazolinone compounds. Thus, reactions of **2** with active methyl and methylene compounds were studied, which afforded different compounds according to the pathway of the reaction, wherein reaction with diethyl malonate gave the 2-substituted quinazolinone derivative **10** as a result of losing ethanol molecule.

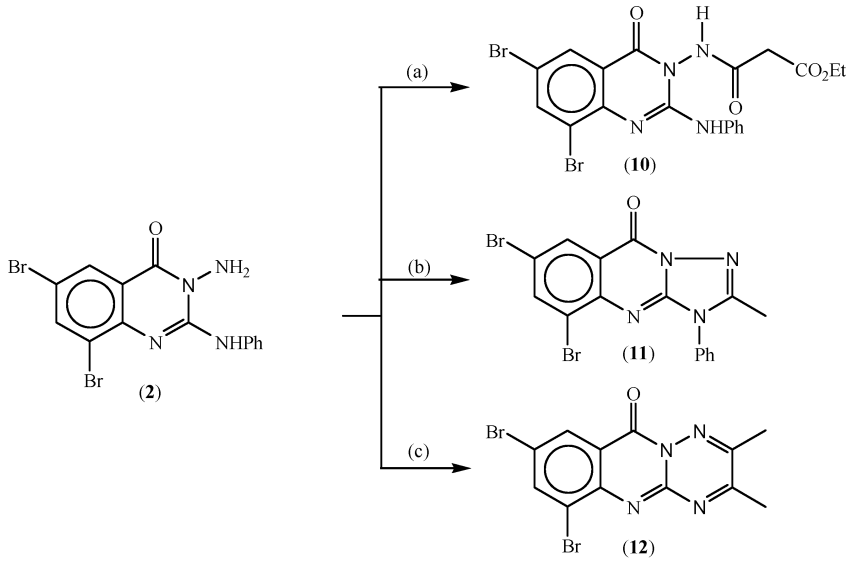
Alternatively, refluxing **2** with acetylacetone furnished the bridgehead nitrogen compound **11**. Formation of the triazoloquinazolinone **11** takes place via condensation of acetylacetone with the amino group followed by ring closure and deacetonylation, while treatment of the



Reagents and conditions:a)2-aminothiophenol/toluene/Δ, b)thioglycolic acid/toluene/Δ.

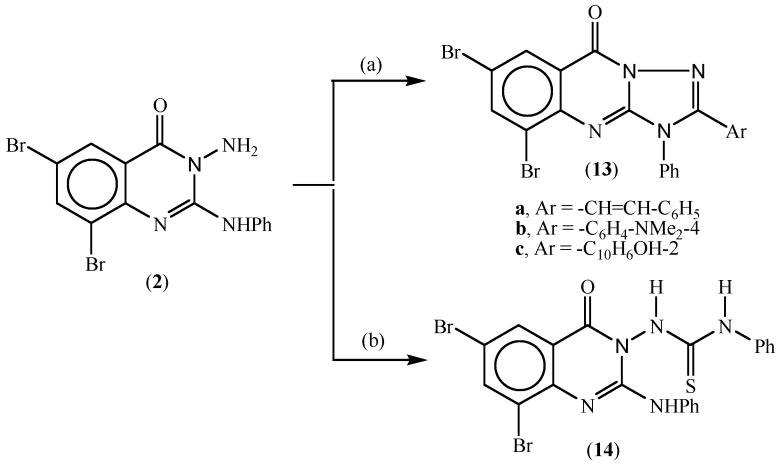
SCHEME 3

quinazolinone **2** with diacetyl in boiling ethanol yielded the triazinoquinazolinone **12**. Formation of **12** takes place via condensation followed by elimination of the phenol molecule yielding the more thermodynamically stable compound (Scheme 4).



Reagents and conditions:a) $CH_2(CO_2Et)_2/\Delta$, b)$CH_2(COCH_3)_2/\Delta$, c)$(CH_3CO)_2$/EtOH/Δ.

SCHEME 4



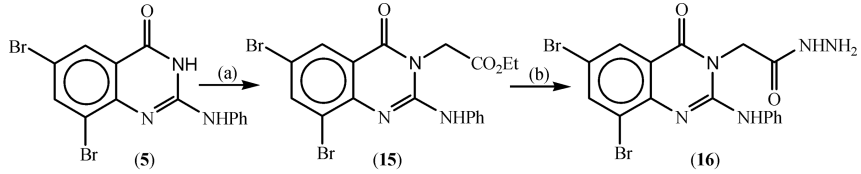
Reagents and conditions:a) Aromatic aldehyde/piperidine/EtOH/Δ, b)Ph-N=C=S/EtOH/Δ.

SCHEME 5

Treatment of the quinazolinone **2** with aromatic aldehydes, namely cinnamaldehyde, 4-N,N-dimethylaminobenzaldehyde and/or 2-hydroxy-1-naphthaldehyde, afforded 5-aryl-triazoloquinazolinone derivatives **13a–c**. The reaction possibly takes place through non-isolated intermediate arylidene amino derivative followed by cyclization, and dehydrogenation yielded the more thermodynamically stable annulated quinazolinone.

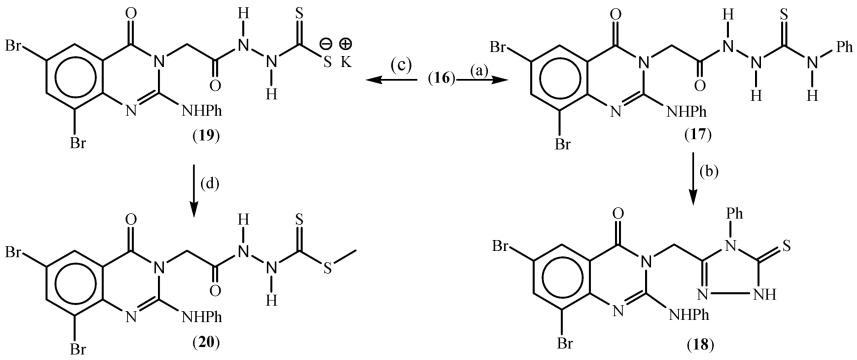
Interaction of aminoquinazolinone derivative **2** with phenylisothiocyanate in boiling ethanol provided 3-substitutedquinazolinone **14** (Scheme 5).

As an extension of this investigation, when quinazolinone **5** was submitted to react with ethyl chloroacetate in refluxing dioxin, in the presence of potassium carbonate, yielded the ester **15**. Isolation of compound **15** as a sole product suggests that the lactam form (ketoform) is the predominant one[15] (ketoform is more stable than the enol form by about 10 kcal/mol). Hydrazinolysis of compound **15** in boiling ethanol produced the hydrazide derivative **16** (Scheme 6).



Reagents and conditions:a)$ClCH_2CO_2Et/K_2CO_3$/Dioxane/Δ, b)N_2H_4/EtOH/Δ.

SCHEME 6



Reagents and conditions:a) Ph-N=C=S/dioxane /Δ, b)NaOH solution/Δ, c)CS_2/alc.KOH/Δ, d) MeI/stirring.

SCHEME 7

The hydrazide **16** was used as versatile starting material for preparing different quinazolinone derivatives. Thus, reaction of compound **16** with phenyl-isothiocyanate gives the thiourea derivative **17**. Treatment of compound **17** with sodium hydroxide yielded 1,2,4-triazole-4(3H)-quinazolinone derivative **18** (Scheme 7).

On the other hand, reaction of the hydrazide**16** with carbon disulfide in the presence of potassium hydroxide yielded the potassium salt of dithioic acid **19**, which reacts with methyl iodide to furnish the dithioester **20** (Scheme 7).

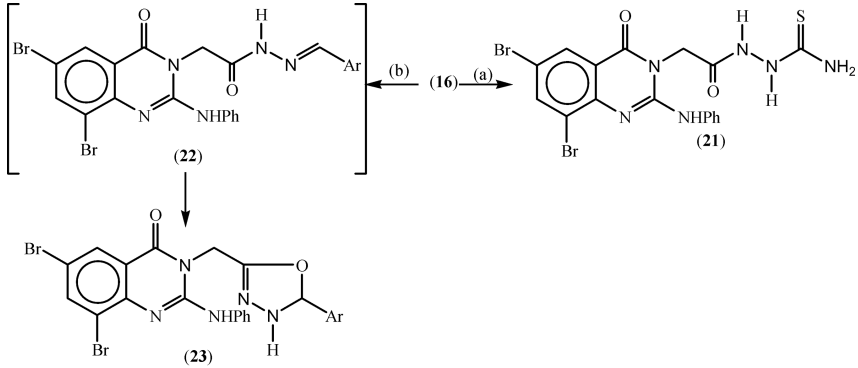
Furthermore, when compound **16** was refluxed with potassium thiocyanate in the presence of hydrochloric acid, it afforded the thioamide derivative **21**.

Finally, reacting **16** with 4-methoxy-benzaldehyde and 2-hydroxy-1-naphthaldehyde in boiling ethanol afforded 1,3,4-oxadiazole-4(3H)quinazolinone derivatives **23a**,**b** respectively. The reaction takes place through the formation of the fleeting intermediate **22** followed by cyclization via addition of enolic hydroxyl group to azaolefinic double bond (Scheme 8).

ANTIBACTERIAL ACTIVITY

The behavior of the newly synthesized compounds as antibacterial has been investigated at the Medical Mycology Lab, The Regional Center for Mycology and Biotechnology, Alazhar University.

The new synthesized compounds were screened in vitro for their antibacterial activities against four strains of bacteria *Staphylococcus aureus* (NCTC-7447), *Bacillus subtillis* (NCTC 10400), *Proteus mirabilis* (NCTC-289), and *Escherichia coli* (NCTC 10416) by the agar



Reagents and conditions:a) KSCN/conc.HCl/H_2O /Δ, b)ArCHO/piperidine/EtOH/Δ.

SCHEME 8

diffusion technique.[16] 1, 2.5, and 5 mg/mL solutions in dimethylformamide (DMF) were used. The bacteria were maintained on nutrient agar media. DMF showed no inhibition zones. The agar media was incubated with different microorganisms and culture tested. After 24 h of incubation at 30°C, the diameter of the inhibition zone was measured. Chloramphenicol was used as a reference of antibacterial activity. The minimal inhibitory concentration (MIC) of some of the tested compounds was measured by a twofold serial dilution method.[17] Most of synthesized compounds exhibited antibacterial activity towards all the microorganisms used. The results are presented in Table I.

EXPERIMENTAL

All melting points reported are uncorrected and were determined on a Stuart electric melting point apparatus. The microanalyses were within ±0.4% of theoretical values and were measured at the Microanalytical Unit of the Faculty of Science, Cairo University. The IR spectra were measured on a Shimadzu FT-IR 8101 PC using the KBr wafer technique. The mass spectra were recorded on Shimadzu GCMS-QP-1000EX mass spectrometer at 70 eV. The ^{1}H-NMR spectra were recorded on a Varian 300 MHz instrument in ($CDCl_3$) or (DMSO-d_6) as solvents, using TMS as internal standard with chemical shifts (δ) expressed in ppm. TLC was performed on ready-to-use silica gel plates (Merck 60) to monitor the reactions and test the purity of the new synthesized compounds. Physical data for the synthesized compounds are given in (Table II).

TABLE I Relative Activity of the Compounds Against Gram-Positive and Gram-Negative Bacteria

Organisms / Sample No.	Gram-positive bacteria						Gram-negative bacteria					
	Staphylococcus aureus			*Bacillus subtillis*			*Proteus mirabilis*			*Escherichia coli*		
	5	2.5	1	5	2.5	1	5	2.5	1	5	2.5	1
1	++	++	++	++	++	++	++	++	++	++	++	++
2	+++	++	++	+++	++	+	++	++	+	+++	++	++
3	++	++	+	++	++	+	+++	++	+	++	++	+
4	++	++	+	++	+	+	++	+	+	+	+	+
5	++	+	+	++	+	+	++	++	+	+	+	+
6a	++	++	+	++	++	++	+	+	+	++	+	+
6b	++	++	+	++	++	+	++	+	+	++	++	+
7	+	+	−	+	−	−	+	+	−	−	−	−
8	+	+	+	+	+	+	+	+	+	+	+	+
9	+	−	−	+	−	−	+	+	−	+	−	−
10	++	++	++	++	++	++	++	++	++	++	++	++
11	++	++	+	++	++	+	++	++	+	++	++	+
12	++	++	++	++	++	++	++	++	++	++	++	++
13a	++	+	+	++	++	+	++	+	+	++	+	+
13b	++	++	+	++	++	+	++	++	+	++	++	+
13c	++	++	++	++	++	++	++	++	++	++	++	++
14	++	++	+	++	++	+	++	++	++	++	++	++
15	++	+	+	++	+	+	++	++	+	++	++	+
16	+++	++	++	+++	++	++	+++	+++	++	+++	+++	++
17	++	++	++	++	++	++	++	++	++	++	++	++
18	+	+	+	+	+	+	+	+	+	+	+	+
20	++	+	+	++	+	+	++	+	+	++	+	+
21	++	++	++	++	++	++	++	++	++	++	++	++
23a	++	+	+	++	+	+	++	+	+	+	+	+
23b	++	++	+	++	++	+	++	++	+	+	+	+
Chloramphenicol	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++

Inhibition values + = Less active (0.2 – 0.5 cm), ++ = Moderately active (0.6 – 1.4 cm), +++ = Highly active (1.5–3 cm), ++++ = Very highly active (over 3 cm).

TABLE II Physical Data for the Synthesized Compounds

Compd. No.	Mp °C	*Solvent/ color	Formula M. Wt.	Analysis % Calc./Found C	H	N	Br/Cl/S
1	276	Toluene	$C_{14}H_8N_2O_2Br_2$	42.42	2.02	7.07	40.40
		Yellow	(396)	42.13	1.83	6.81	40.12
2	252	Butanol	$C_{14}H_{10}N_4OBr_2$	40.98	2.44	13.66	39.02
		White	(410)	41.26	2.61	13.41	38.78
3	222	Toluene	$C_{15}H_9N_5OBr_2$	41.38	2.07	16.09	36.78
		Brown	(435)	41.66	2.30	15.79	36.41
4	196	Ethanol	$C_{15}H_{11}N_5OSBr_2$	38.38	2.35	14.93	34.12/—/6.82
		White	(469)	38.04	2.56	15.21	33.74/—/6.55
5	Over	Dioxan	$C_{14}H_9N_3OBr_2$	42.53	2.28	10.63	40.51
	300	Pale brown	(395)	42.31	2.09	10.25	40.17
6a	224	Toluene	$C_{20}H_{12}N_3OBr_2Cl$	47.48	2.37	8.31	31.65/7.02
		White	(505.5)	47.12	2.51	8.60	31.41/6.79
6b	218	Toluene	$C_{18}H_{17}N_3OBr_2$	47.89	3.77	9.31	35.47
		White	(451)	48.17	3.59	9.52	35.70
7	172	Toluene	$C_{19}H_{19}N_3O_2Br_2$	47.40	3.95	8.73	33.26
		White	(481)	47.64	4.17	8.50	32.97
8	160	Pet. 8-100	$C_{20}H_{15}N_3O_2SBr_2$	46.07	2.88	8.06	30.71/—/6.14
		White	(521)	45.78	2.61	7.81	30.34/—/6.31
9	216	Dioxan	$C_{16}H_{12}N_2O_4SBr_2$	39.34	2.46	5.74	32.79/—/6.56
		White	(488)	39.05	2.60	5.99	33.00/—/6.72
10	230	Butanol	$C_{19}H_{16}N_4O_4Br_2$	43.51	3.05	10.68	30.53
		White	(524)	43.12	2.87	10.44	30.22
11	162	Toluene	$C_{16}H_{10}N_4OBr_2$	44.24	2.30	12.90	36.87
		Brown	(434)	44.45	2.52	13.16	37.15
12	216	Toluene	$C_{12}H_8N_4OBr_2$	37.50	2.08	14.58	41.67
		Brown	(384)	37.24	1.92	14.75	41.92
13a	244	Toluene	$C_{23}H_{14}N_4OBr_2$	52.87	2.68	10.73	30.75
		Brick red	(522)	53.13	2.55	10.92	31.04
13b	266	Butanol	$C_{23}H_{17}N_5OBr_2$	51.21	3.15	12.99	29.68
		Deep yellow	(539)	50.89	3.34	13.26	29.42
13c	Over	Dioxan	$C_{25}H_{14}N_4O_2Br_2$	53.38	2.49	9.96	28.47
	300	Yellow	(562)	53.56	2.63	10.11	28.18
14	260	D.M.F	$C_{21}H_{15}N_5OBr_2S$	46.24	2.75	12.84	29.36
		White	(545)	45.95	2.56	13.14	29.09
15	176	Benzen	$C_{18}H_{15}N_3O_3Br_2$	44.91	3.12	8.73	33.26
		White	(481)	45.18	2.99	9.01	33.52
16	Over	Dioxan	$C_{16}H_{13}N_5O_2Br_2$	41.11	2.78	14.99	34.26
	300	White	(467)	40.84	2.94	15.21	34.54
17	Over	Ethanol	$C_{23}H_{18}N_6O_2SBr_2$	45.85	2.99	13.95	26.58/—/5.32
	300	Pale yellow	(602)	46.09	3.13	13.69	26.91/—/5.55
18	224	Ethanol	$C_{23}H_{18}N_6OSBr_2$	47.26	3.08	14.38	27.40/—/5.48

(Continued on next page)

TABLE II Physical Data for the Synthesized Compounds *(Continued)*

Compd. No.	Mp °C	*Solvent/ color	Formula M. Wt.	Analysis % Calc./Found C	H	N	Br/Cl/S
		White	(584)	47.47	3.21	14.12	27.67/—/5.72
19	—	Salt	$C_{17}H_{12}N_5O_2S_2KBr_2$	35.11	2.07	12.05	27.54/—/11.02
		Pale yellow	(581)	34.80	1.91	11.87	27.75/—/10.79
20	238	Toluene	$C_{18}H_{15}N_5O_2S_2Br_2$	38.78	2.69	12.57	28.73/—/11.49
		White	(557)	39.09	2.51	12.88	28.40/—/11.21
21	Over	Methanol	$C_{17}H_{14}N_6O_2SBr_2$	38.78	2.66	15.97	30.42/–/6.08
	300	White	(526)	38.41	2.52	16.18	30.72/–/5.77
23a	Over	Dioxan	$C_{24}H_{19}N_5O_3Br_2$	49.23	3.25	11.97	27.35
	300	Pink	(585)	49.59	3.41	11.72	27.70
23b	Over	D.M.F.	$C_{27}H_{19}N_5O_3Br_2$	52.17	3.06	1127	25.76
	300	Deep yellow	(621)	52.51	3.21	10.93	25.41

6,8-Dibromo-2-(phenylamino)-4H-benzo[d][1,3]oxazin-4-one (1)

A mixture of 3,5-dibromoanthranilic acid (2.95 g, 0.01 mol) and phenyl isocyanate (1.19 g, 0.01 mol) in dry toluene (30 mL) was refluxed for 2 h. The solid that separated after cooling was filtered off, dried, and crystallized to afford the benzoxazine **1** (Table II).

3-Amino-6,8-dibromo-2-(phenylamino)quinazolin-4(3H)-one (2)

A mixture of benzoxazinone (3.96 g, 0.01 mol) and hydrazine hydrate (1 g, 0.02 mol) was heated under reflux in absolute ethanol (30 mL) for 3 h. The reaction mixture was concentrated. The solid that separated out was filtered off, dried, and then recrystallized to afford the quinazolinone **2** (Table II). IR (ν/cm^{-1}): 3436, 3305, 3203, 3170 (NH_2, NH), 1666 (C=O), 1617 (C=N). ^{1}H-NMR: 5.66 (s, 2H, NH_2, D_2O exchangeable), 7.33–8.33 (m, 7H, Ar-H), 8.87 (s, 1H, NH, D_2O exchangeable). MS: (m/z, %): molecular ion peak at M^+ (408, 32.4%), M+2 (410, 63.6%) and M+4 (412, 31.2%).

2-Amino-5,7-dibromo-3-phenyl-[1,2,4]triazolo[5,1-b]quinazolin-9(3H)-one (3) and 1-(6,8-Dibromo-4-oxo-2-(phenylamino)quinazolin-3(4H)-yl)thiourea (4)

A mixture of benzoxazinone **1** (3.96 g, 0.01 mol), semicarbazide (0.75 g, 0.01 mol), and/or thiosemicarbazide (0.91 g, 0.01 mol) was boiled in

pyridine (20 mL) for 4–6 h. After cooling, the reaction mixture was poured into crushed ice/HCl. The solid that was deposited was filtered off, dried, and crystallized to give **3** and **4**, respectively (Table II).
3: IR (ν/cm^{-1}): 3423, 3301, 3211, (NH_2), 1670 (C=O), 1620 (C=N). The ^{1}H-NMR: 5.78 (s, 2H, NH_2, D_2O exchangeable) and 7.35–8.29 (m, 7H, ArH). MS, (m/z, %), M^+ (435, 58.2%), M+2 (437, 100%), and M+4 (439, 58.7%).
4: IR (ν/cm^{-1}): 3429, 3338, 3277, 3172 (NH_2, NH), 1668 (C=O), 1370 (C=S). The ^{1}H-NMR: and 7.41–8.39 (m, 7H, ArH), 8.82, 9.64, 10.73 (s, 4H, 2NH, NH_2, D_2O exchangeable).

6,8-Dibromo-2-(phenylamino)quinazolin-4(3H)-one (5)

A solution of benzoxazinone 1 (3.96 g, 0.01 mol) in formamide (15 mL) was refluxed for 2 h. The reaction mixture after cooling was poured onto ice/H_2O. The solid that separated out was filtered, dried, and recrystallized to give compound **5** (Table II). IR (ν/cm^{-1}): 3274, 3169 (NH), 1681 (C=O). The ^{1}H-NMR: and 7.22-8.31 (m, 7H, ArH), 8.85, 10.69 (s, 2H, 2NH, D_2O exchangeable).

6,8-Dibromo-3-(2-chlorophenyl)-2-(phenylamino)quinazolin-4(3H)-one (6a) and 6,8-Dibromo-3-isobutyl-2-(phenylamino) quinazolin-4(3H)-one (6b)

A mixture of benzoxazinone **1** (3.96 g, 0.01 mol) and amines, namely 2-chloroaniline (1.28, 0.01 mol) and/or isobutylamine (0.73 g, 0.01 mol), was refluxed in ethanol (30 mL) for 6–8 h. The reaction mixture was concentrated. The solid that separated out was filtered off, dried, and then recrystallized to afford the quinazolinone **6a,b** (Table II).
6a: IR (ν/cm^{-1}): 3274, 3211 (NH), 1678 (C=O). The ^{1}H-NMR: 7.35–8.29 (m, 7H, ArH) and 8.78 (s, 2H, NH_2, D_2O exchangeable). MS, (m/z, %), M^+ (503, 1.9%), M+2 (505, 4.2%), and M+4 (507, 1.7%).
6b: IR (ν/cm^{-1}): 3277, 3207 (NH), 1676 (C=O). MS, (m/z, %), M^+ (449, 12.5%), M+2 (451, 23.2%), and M+4 (453, 11.7%).

1-(2,4-Dibromo-6-(piperidine-1-carbonyl)phenyl)-3-phenylurea (7)

A solution of benzoxazinone **1** (3.96 g, 0.01 mol) and piperidine (0.85 g, 0.01 mol) in ethanol (30 mL) was heated under reflux for 4 h. The solid separated on cooling was crystallized to provide **7** (Table II). IR (ν/cm^{-1}): 3246, 3199 (NH), 1675 (C=O). The ^{1}H-NMR: 1.61 (m, 6H, piperidine),

3.88 (m, 4H, CH_2-N-CH_2), 7.24–8.32 (m, 7H, ArH) and 8.89, 9.12 (s, 2H, NH, D_2O exchangeable).

2-Aminophenyl-3,5-dibromo-2-(3-phenylureido)benzothioate (8) and 2-(3,5-Dibromo-2-(3-phenylureido)benzoylthio)acetic acid (9)

A solution of benzoxazinone **1** (3.96, 0.01 mol), 2-aminothiophenol (1.88 g, 0.015 mol), and/or thioglicolic acid (1.38 g, 0.015 mol) in dry toluene was stirred for 3–4 h. The solid separated was filtered off, washed by dry toluene, dried, and crystallized to give **8** and**9** (Table II).

8: IR (ν/cm^{-1}): 3432, 3341, 3264, 3179 (NH_2, NH), 1654, 1676 (C=O). The ^{1}H-NMR: 5.77 (br., 2H, NH_2, D_2O exchangeable), 7.22–8.41 (m, 11H, ArH) and 8.81, 9.08 (s, 2H, 2NH, D_2O exchangeable). MS, (m/z, %), M^+ (519, 23.3%), M+2 (521, 41.2%), and M+4 (523, 21.7%).
9: IR (ν/cm^{-1}): 2567–3488 (NH, OH acid) 1658, 1671 (C=O). The ^{1}H-NMR: 4.12 (s, 2H, S-CH_2-), 7.26–8.39 (m, 7H, ArH) and 8.91, 9.13 (s, 2H, NH, D_2O exchangeable) and 12.34 (br.s, 1H, OH, D_2O exchangeable).

Ethyl 3-(6,8-dibromo-4-oxo-2-(phenylamino)quinazolin-3(4H)-ylamino)-3-oxopropanoate (10)

A mixture of quinazolinone **2** (4.1 g, 0.01 mol) and diethylmalonate (10 mL) was refluxed for 4 hr. After cooling, the solid was filtered off, washed with methanol, dried, and crystallized to give **10** (Table II). IR (ν/cm^{-1}): 3256, 3187 (NH), 1671, 1692, 1731 (C=O). The ^{1}H-NMR: 1.32 (d, 3H, $OCH_2\underline{CH_3}$, $J = 6.1$ Hz), 3.78 (s, 2H, CO-CH_2-), 4.25 (t, 2H, $O\underline{CH_2}CH_3$, J = 8.3 Hz), 7.24–8.37 (m, 7H, ArH) and 8.86, 10.57 (s, 2H, NH, D_2O exchangeable).

5,7-Dibromo-2-methyl-3-phenyl-[1,2,4]triazolo[5,1-b]quinazolin-9(3H)-one (11) and 6,8-Dibromo-2,3-dimethyl-10H-[1,2,4] triazino[3,2-b]quinazolin-10-one (12)

A mixture of quinazolinone **2** (4.1 g, 0.01 mol), acetyl acetone (5 mL), and/or diacetyl (0.86 g, 0.01 mol) in ethanol (30 mL) was refluxed for 2–3 h. After cooling, the precipitate was filtered off, washed with cold ethanol, dried, and crystallized to produce **11** and **12** (Table II).
11: IR (ν/cm^{-1}): 1688 (C=O), 1621 (N=N). The ^{1}H-NMR: 2.33 (s, 3H, CH_3), 7.26–8.34 (m, 7H, ArH).

12: IR (ν/cm^{-1}): 1682 (C=O), 1619 (N=N). The ^{1}H-NMR: 2.29 (s, 6H, 2CH$_3$), 8.21, 8.39 (s, 2H, ArH). MS, (m/z, %), M$^+$ (382, 34.2%), M+2 (384, 63.8%), and M+4 (386, 31.7%).

5,7-Dibromo-3-phenyl-2-styryl-[1,2,4]triazolo[5,1-b]quinazolin-9(3H)-one (13a), 5,7-Dibromo-2-(4-(dimethylamino)phenyl)-3-phenyl-[1,2,4]triazolo[5,1-b]quinazolin-9(3H)-one (13b), and 5,7-Dibromo-2-(2-hydroxynaphthalen-1-yl)-3-phenyl-[1,2,4]triazolo[5,1-b]-quinazolin-9(3H)-one (13c).

A mixture of the quinazolinone **2** (4.1 g, 0.01 mol) and aromatic aldehydes, namely cinnimaldehyde (1.6 g, 0.012 mol), 4-N,N-dimethylaminobenzaldehyde (1.7 g, 0.012 mol), and/or 2-hydroxy-1-naphthaldehyde (2.07 g, 0.012 mol) was placed in absolute ethanol (50 mL) containing (1 mL) pipridine and refluxed for 4–6 h. The crystalline solid that was obtained after cooling was collected by filtration, dried, and recrystallized to afford **13a–c**, respectively (Table II).
13a: IR (ν/cm^{-1}): 1671 (C=O), 1612 (N=N).
13b: IR (ν/cm^{-1}): 1676 (C=O), 1610 (N=N). The ^{1}H-NMR: 3.59 (s, 6H, 2CH$_3$), 7.34–8.45 (s, 11H, ArH).
13c: IR (ν/cm^{-1}): 1676 (C=O), 1610 (N=N). The ^{1}H-NMR: 7.26–8.39 (s, 13H, ArH) and 10.84 (s, 1 H, OH, D$_2$O exchangeable). MS, (m/z, %), M$^+$ (560, 51.3%), M+2 (562, 100%), and M+4 (564, 46.7%).

1-(6,8-Dibromo-4-oxo-2-(phenylamino)quinazolin-3(4H)-yl)-3-phenylthiourea (14)

A mixture of quinazolinone **2** (4.1 g, 0.01 mol) and phenyl isothiocyanate (1.35 g, 0.01 mol) in ethanol (30 mL) was refluxed for 2–3 h. After cooling, the precipitate was filtered off, washed with cold ethanol, dried, and crystallized to produce **14** (Table II). IR (ν/cm^{-1}): 3288, 3245, 3191 (NH), 1676 (C=O), 1614 (N=N). The ^{1}H-NMR: 7.28–8.32 (s, 12H, ArH) and 8.87, 9.54, 10.61 (s, 3H, 3 NH, D$_2$O exchangeable).

Ethyl 2-(6,8-dibromo-4-oxo-2-(phenylamino)quinazolin-3(4H)-yl)acetate (15)

A mixture of quinazolinone **5** (3.95 g, 0.01 mol), ethyl chloroacetate (4.9 g, 0.04 mol), and anhydrous potassium carbonate (5.5 g, 0.04 mol) in dioxin (50 mL) was heated under reflux for 24 h. The reaction mixture was concentrated, filtered off, dried, and recrystallized to afford quinazolinone **15** (Table II). IR (ν/cm^{-1}): 3263, 3199 (NH), 1687, 1730(C=O).

The ^{1}H-NMR: 1.31 (d, 3H, $OCH_2\underline{CH}_3$, $J = 6.3$ Hz), 4.06 (s, 2H, N-CH_2-CO), 4.28 (t, 2H, $O\underline{CH}_2CH_3$, J = 8.2 Hz), 7.28–8.34 (m, 7H, ArH) and 8.91, (s, H, NH, D_2O exchangeable).

2-(6,8-Dibromo-4-oxo-2-(phenylamino)quinazolin-3(4H)-yl)acetohydrazide (16)

A mixture of quinazolinone **15** (4.81 g, 0.01 mol) and hydrazine hydrate (1.0 g, 0.02 mol) in absolute ethanol (30 mL) was heated under reflux for 3 h. The reaction mixture was concentrated, filtered off, dried, and crystallized to give **16** (Table II). IR (ν/cm^{-1}): 3432, 3343, 3253, 3177 (NH_2, NH), 1654, 1677 (C=O). The ^{1}H-NMR: 4.12 (s, 2H, N-CH_2-CO), 5.31 (br., 2H, NH_2, D_2O exchangeable), 7.28–8.31 (m, 7H, ArH) and 8.89, 9.37 (s, 2H, 2NH, D_2O exchangeable). MS, (m/z, %), M^+ (465, 2.7%), M+2 (467, 4.5%), and M+4 (523, 2.1%).

2-(2-(6,8-Dibromo-4-oxo-2-(phenylamino)quinazolin-3(4H)-yl)acetyl)-N-phenylhydrazine-carbothioamide (17)

An equimolecular quantity of the acetohydrazide **16** (4.67, 0.01 mol) and phenyl isothiocyanate (1.35 g, 0.01 mol) in dioxin (40 mL) was refluxed for 6 h. The reaction mixture was cooled at room temperature, and the fine crystals that was separated out were filtered off and recrystallized to furnish **17** (Table II). IR (ν/cm^{-1}): 3307, 3283, 3242, 3189 (NH), 1666, 1679 (C=O). The ^{1}H-NMR: 4.08 (s, 2H, N-CH_2-CO), 7.27–8.32 (m, 12H, ArH) and 8.86, 9.59, 10.77, 11.89 (s, 4H, 4NH, D_2O exchangeable).

6,8-Dibromo-3-((4-phenyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl)-2-(phenyl-amino)quinazolin-4(3H)-one (18)

Carbothioamide **17** (6.02 g, 0.01 mol) was refluxed in sodium hydroxide solution (4%, 25 mL) for 3 h. The resulting solution was treated with charcoal, filtered, and cooled. The filtrate was acidified with hydrochloric acid to pH 5–6. The solid deposited was filtered, dried, and recrystallized to give **18** (Table II). IR (ν/cm^{-1}): 3238, 3178 (NH), 1676 (C=O). The ^{1}H-NMR: 3.77 (s, 2H, N-CH_2-), 7.30–8.35 (m, 12H, ArH) and 8.91, 12.93 (s, 2H, 2NH, D_2O exchangeable). MS, (m/z, %), M^+ (582, 7.3%), M+2 (584, 12.7%), and M+4 (586, 6.5%).

Potassium 2-(2-(6,8-Dibromo-4-oxo-2-(phenylamino) quinazolin-3(4H)-yl)acetyl)hydrazine-carbodithioate (19)

Carbon disulfide (11.4 g, 0.15 mol) was added dropwise to an ice-cold solution of **16** (4.67 g, 0.01 mol) in alc. KOH (5.6 g, 0.1 mol in 5 mL C_2H_5OH). The whole mixture was stirred at room temperature for 2 h. Dry ether (50 mL) was added, and the separated solid was filtered off to give **19** (Table II).

Methyl 2-(2-(6,8-Dibromo-4-oxo-2-(phenylamino)quinazolin-3(4H)-yl)acetyl)hydrazine-carbodithioate (20)

Methyl iodide (1.42 g, 0.01 mol) was added to a stirred solution of the potassium salt **19** (5.81 g, 0.01 mol) in (50 mL) of water. After 1 h, the white solid was filtered, washed with water, and recrystallized to give **20** (Table II). IR (ν/cm^{-1}): 3332, 3247, 3184 (NH), 1655, 1679 (C=O). The ^{1}H-NMR: 2.87 (s, 3H, S-CH_3), 4.16 (s, 2H, N-CH_2-CO), 7.30–8.31 (m, 7H, ArH) and 8.89, 9.37, 11.01 (s, 3H, 3NH, D_2O exchangeable). MS, (m/z, %), M^+ (555, 16.6%), M+2 (557, 30.5%), and M+4 (559, 15.1%).

2-(2-(6,8-Dibromo-4-oxo-2-(phenylamino)quinazolin-3(4H)-yl)acetyl)hydrazinecarbothio-amide (21)

A suspension of **16** (4.67 g, 0.01 mol), potassium thiocyanate (1.94 g, 0.02 mol), hydrochloric acid (10 mL), and water (200 mL) was refluxed for 3 h. The white solid that appeared upon cooling was filtered, dried, and recrystallized to produce **21** (Table II). IR (ν/cm^{-1}): 3443, 3337, 3261, 3191 (NH_2, NH), 1667, 1684 (C=O). The ^{1}H-NMR: 4.11 (s, 2H, N-CH_2-CO), 7.30–8.36 (m, 12H, ArH) and 8.88, 9.62, 10.84, 11.47 (s, 5H, 3NH, NH_2, D_2O exchangeable).

6,8-Dibromo-3-((5-(4-methoxyphenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)-2-(phenyl-amino)quinazolin-4(3H)-one (23a) and 6,8-Dibromo-3-((5-(2-hydroxynaphthalen-1-yl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)-2-(phenylamino)quinazolin-4(3H)-one (23b)

A mixture of quinazolinone **16** (4.67 g, 0.01 mol), p-anisaldehyde (1.63 g, 0.012 mol), and/or 2-hydroxy-1-naphthaldehyde (2.1 g, 0.012 mol) in absolute ethanol (50 mL) containing (1 mL) piperidine was refluxed for 3–4 hr. The solid formed was filtered off and recrystallized to provide **23a**,**b**, respectively (Table II).

23a: IR (ν/cm^{-1}): 3247, 3184 (NH), 1678 (C=O). The ^{1}H-NMR: 3.71 (s, 2H, N-CH_2-), 3.97 (s, 3H, O-CH_3), 5.83 (s, 1H, oxadiazole), 7.27–8.33 (m, 11H, ArH) and 8.85, 9.42, 12.01 (s, 3H, 2NH, OH, D_2O exchangeable). **23b:** IR (ν/cm^{-1}): 3453 (OH), 3252, 3196 (NH), 1681 (C=O). MS, (m/z, %), M^+ (619, 33.2%), M+2 (621, 60.4%), and M+4 (623, 30.5%).

REFERENCES

[1] A. Krantz, R. Spencer, T. Tam, T. Liak, L. Copp, E. Thomas, and S. Rafferty, *J. Med. Chem.*, **33,** 464 (1990).

[2] M. Gütschow and U. Neumann, *Bioorg. Med. Chem.*, **5,** 1935 (1997).

[3] U. Neumann, N. Schechter, and M. Gütschow, *Bioorg. Med. Chem.*, **9,** 947 (2001).

[4] M. M. Gineinah, M. A. El-Sherbeny, M. N. Nasr, and A. R. Maarouf, *Arch. Pharm. Med. Chem.*, **335,** 556 (2002).

[5] S. El-Meligie, A. El-Ansary, M. M. Said, and M. M. M. Hussein, *Indian J. Chem.*, **40B,** 62 (2001).

[6] J. V. Partin, I. E. Anglin, and N. Kyprianou, *J. Cancer*, **88**(10), 1615 (2003).

[7] H. Kikuchi, H. Tasaka, S. Hirai, Y. Takaya, Y. Lwabuchi, H. Ooi, S. Hatakeyama, H.S. Kim, Y. Wataya, and Y. Oshima, *J. Med. Chem.*, **45**(12), 2563 (2002).

[8] S. Eguchi, T. Suzuzi, T. Okawa, Y. Matsushita, E. Yashima, and Y. Okamoto, *J. Org. Chem.*, **61,** 7316 (1996).

[9] (a) J. Bergman and A. Brynolf, *Tetrahedron*, **46,** 1295 (1990); (b) J. Bergman, *J. Chem. Res*., 224 (S) (1997).

[10] M. R. Mahmoud, E. A. El-Bordany, M. E. Azab, and E. A. Soliman, *Phosphorus, Sulfur, and Silicon*, **182,** 1275 (2007).

[11] M. E. Azab, G. A. M. El-Hag Ali, and A. F. Abdel-Wahab, *Acta Chemica Pharmaceutica*, **53,** 213 (2003).

[12] M. E. Azab, M. E. A. Ibraheem, and H. M. F. Madkour, *Phosphorus, Sulfur, and Silicon*, **181,** 1299 (2006).

[13] M. A. I. Salem, E. A. Soliman, M. B. Smith, M. R. Mahmoud, and M. E. Azab, *Phosphorus, Sulfur, and Silicon*, **179,** 61 (2004).

[14] A. S. Hamad and M E. Azab, *Phosphorus, Sulfur, and Silicon*, **173,** 105 (2001).

[15] S. Eddy, B. C. Nuria, R. Jordi, and R. Enrique, *Tetrahedron*, **58,** 2389 (2002).

[16] L. P. Carrod and F. D. Grady, *Antibiotic and Chemotherapy*, 3rd ed. (Churchill Livingstone, Edinburgh, UK, 1972), p. 477.

[17] P. Courvalin, *Am. Soc. Microbial News*, **85,** 368 (1992).