Chemistry of Heterocyclic Compounds, Vol. 45, No. 12, 2009

SYNTHESIS OF SOME QUINAZOLINES DERIVED FROM 6,8-DIBROMO-2-(2-CARBOXY-PHENYL)-4H-3,1-BENZOXAZIN-4-ONE AS ANTIMICROBIAL AGENTS

I. F. Nassar[1]*

The reactivity of 6,8-dibromo-2-(2-carboxyphenyl)-4H-3,1-benzoxazin-4-one towards the action of electrophilic and nucleophilic reagents led to the direct formation of heterobicyclic nitrogen compounds. The antimicrobial activity of some synthesized compounds was investigated.

Keywords: quinazolin-4-one, antimicrobial agents, electrophilic and nucleophilic reagents.

Some quinazoline derivatives are used in large scale in medicine as antitumor and antimicrobial agents. This promted us to synthesize some new substituted quinazolines with potential biological activity. 4H-3,1-Benzoxazin-4-ones substituted in position 2 with aliphatic groups such as methyl [1], *n*-propyl [2], isopropyl [3], acetylmethyl [4], cyanomethyl [5], CH_2CH_2COOH [6], and benzyl [7] are among the more recently synthesized heterocyclic compounds. The electron-deficient character of benzoxazine rings hinders the synthesis of sufficiently stable derivatives. New organic substituents with special steric and electronic properties help to solve this problem. In the last two decades the solution of this problem includes the use of bulk substituents with strong conjugation power (the so-called static benzoxazinones) [8].

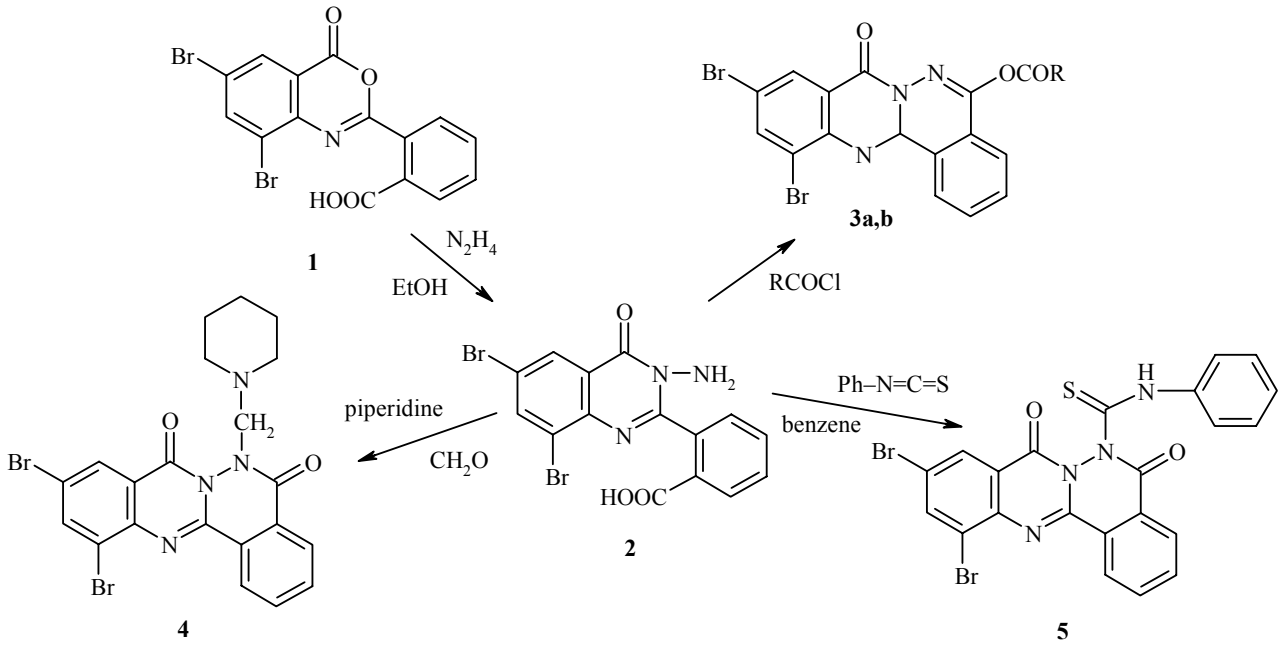
The required starting material **1** [9–11] was synthesized by the condensation of phthalic anhydride and 2-amino-3,5-dibromobenzoic acid in *n*-butanol under reflux for 20 h. The treatment of compound **1** with hydrazine hydrate in ethanol under reflux afforded 3-aminoquinazolinone derivative **2** [12–14], which was used as a key material for the synthesis of some interesting heterocyclic quinazolines. Thus, boiling compound **2** with either acetyl chloride and/or benzoyl chloride afforded 5-acetoxy/benzoyloxy-substituted phthalazino-[1,2-*b*]quinazoline derivatives **3a,b**. Refluxing compound **2** with piperidine in ethanol in the presence of formaldehyde gave the Mannich base **4**. The treatment of compound **2** with phenyl isothiocyanate in dry benzene produced 1-phenylthioureido-substituted phthalazinoquinazoline derivative **5**.

Recently the chemistry of quinazolinones received much attention principally due to the novel synthesis of some new oxazines with high potential biological activity. Thus, the treatment of compound **2** with benzaldehyde or 4-chlorobenzaldehyde in ethanol under reflux afforded Schiff's bases **6a,b** [15]. The reaction took place *via* an addition/elimination reaction mechanism. Refluxing the Schiff's base **6a** with *o*-amino-thiophenol in the presence of a few drops of piperidine as a catalyst yielded the corresponding 2-amino-

* To whom correspondence should be addressed, e-mail: tasneem_05nassar@yahoo.com.

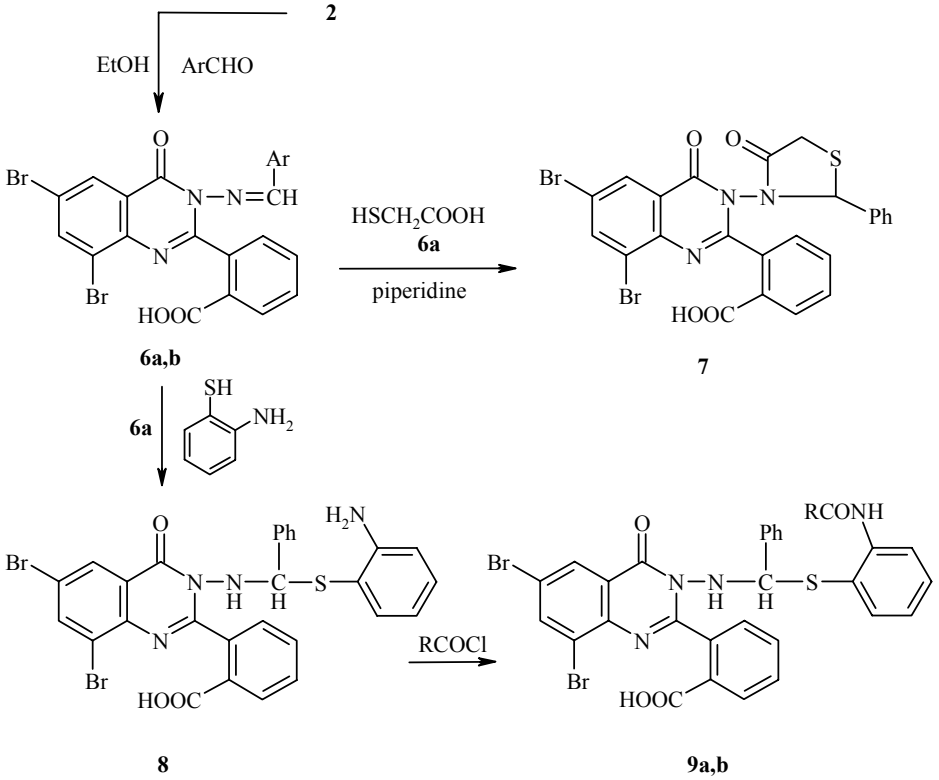
[1]Faculty of Specific Education, Ain Shams University, Abbassia, Cairo, Egypt.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, 1878-1887, December, 2009. Original article received June 19, 2008. Revised version received December 4, 2009.



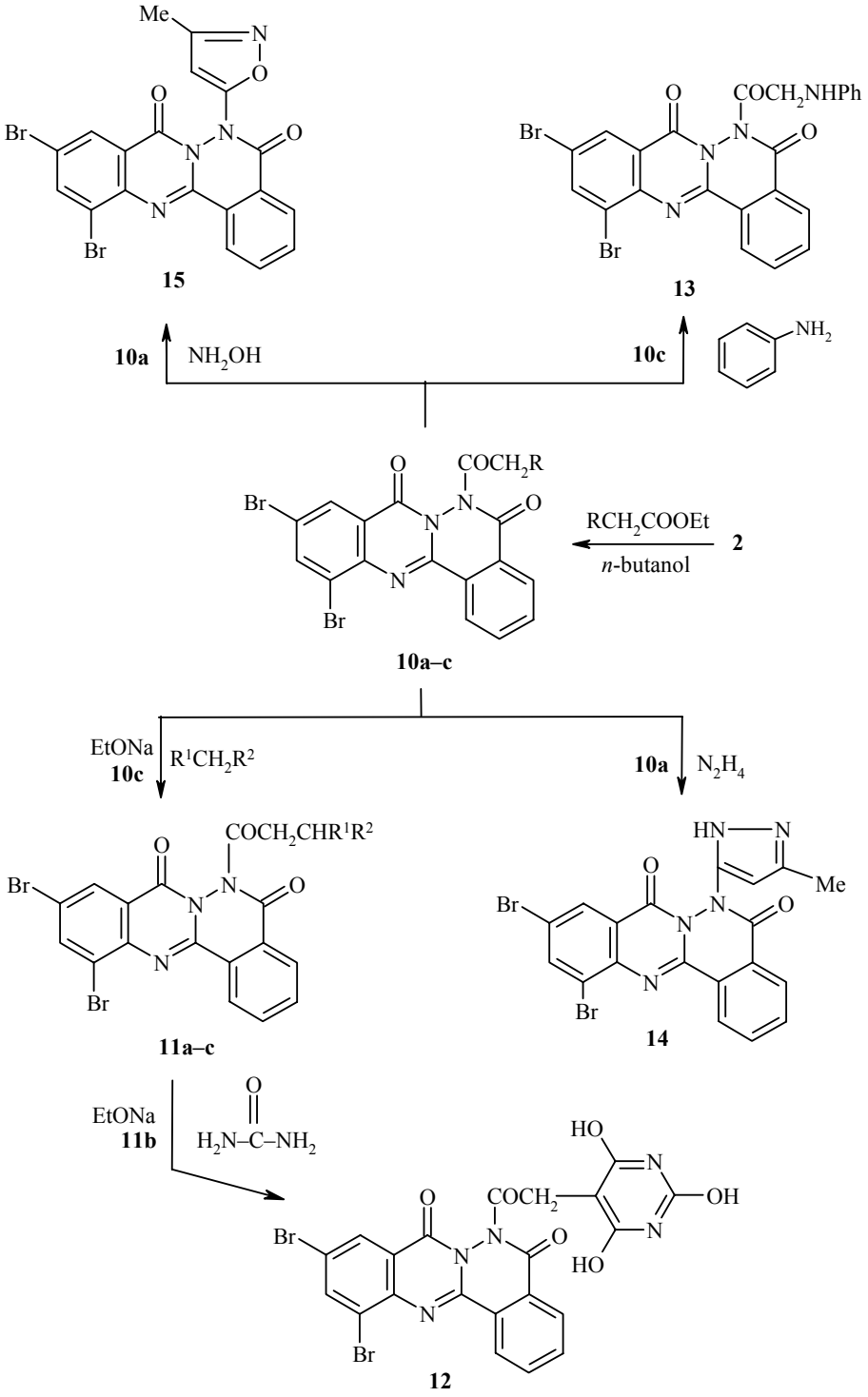
3 a R = Me, **b** R = Ph

phenylsulfanyl-substituted products **8**, which on reaction with acetyl chloride or benzoyl chloride afforded N-acyl-substituted quinazolines **9a,b**. On the other hand, when the Schiff's base **6a** was refluxed with thioglycolic acid in the presence of a few drops of piperidine, 1,3-dihydro-4-thiazolone derivative **7** was prepared. The reaction mechanism involves the addition of the thiolate anion derived from thioglycolic acid to the azomethyne moiety followed by cyclization.



6 a Ar = Ph, **b** Ar = 4-ClC_6H_4; **9 a** R = Me, **b** R = Ph

The reaction of compound **2** with carbon electrophiles such as ethyl acetoacetate, ethyl phenylacetate, or ethyl chloroacetate in *n*-butanol afforded N-(1-substituted acetyl)phthalazinoquinazoline derivative**s 10a-c** [16]. The reaction of compound **10c** with active methylene compounds (acetyl acetone, diethyl malonate or ethyl acetoacetate) in the presence of sodium ethoxide yielded the corresponding side-chain substituted



10 a R = COMe, **b** R = Ph, **c** R = Cl; **11 a** $R^1 = R^2$ = MeCO, **b** $R^1 = R^2$ = COOEt, **c** R^1 = MeCO, R^2 = COOEt

phthalazinoquinazoline derivatives **11a-c** [17]. The reaction took place *via* the S_N2 mechanism. The treatment of compound **11b** with urea in the presence of boiling sodium ethoxide and ethanol afforded (2,4,6-trihydroxy-pyrimidin-5-yl-acetyl)phthalazinoquinazoline **12**, and reaction of compound **10c** with aniline in an oil bath at 150°C afforded 1-phenylaminoacetylphthalazinoquinazoline (**13**). Refluxing compound **10a** in either hydrazine hydrate in ethanol or hydroxylamine hydrochloride in pyridine afforded 5-methyl-2H-pyrazolophthalazino-quinazoline **14** or 3-methylisoxazol-5-yl-substituted phthalazinoquinazoline **15**. The reaction took place *via* the tetrahedral mechanism.

Antimicrobial activity. The antimicrobial activity of some newly synthesized compounds was tested using the hole plate and filter paper disk method [18]. Some selected compounds were tested against a variety

TABLE 1. Characteristics and Physical Data for the Synthesized Compounds **2-15**

Compound	Empirical formula	Found, % / Calculated, %					mp, °C*
		C	H	Br	N	S (Cl)	
2	$C_{15}H_9Br_2N_3O_3$	41.00 / 41.03	2.10 / 2.07	36.40 / 36.39	9.58 / 9.57		166-167
3a	$C_{17}H_9Br_2N_3O_3$	44.10 / 44.09	2.00 / 1.96	34.53 / 34.51	9.00 / 9.07		185-186
3b	$C_{22}H_{11}Br_2N_3O_3$	50.33 / 50.32	2.11 / 2.11	30.42 / 30.43	8.00 / 8.00		125-126
4	$C_{21}H_{18}Br_2N_4O_2$	48.66 / 48.67	3.52 / 3.50	30.76 / 30.84	6.16 / 6.17		120-21
5	$C_{22}H_{12}Br_2N_4O_2S$	47.50 / 47.51	2.18 / 2.17	28.74 / 28.73	10.08 / 10.07	5.76 / 5.76	180-181
6a	$C_{22}H_{13}Br_2N_3O_3$	50.11 / 50.12	2.50 / 2.49	30.33 / 30.31	8.00 / 7.97		280-281
6b	$C_{22}H_{12}Br_2ClN_3O_3$	47.00 / 47.05	2.30 / 2.15	28.34 / 28.46	7.50 / 7.48	(6.43) / (6.31)	334-335
7	$C_{24}H_{15}Br_2N_3O_4S$	48.00 / 47.94	2.45 / 2.51	26.54 / 26.58	6.97 / 6.99	5.30 / 5.33	155-157
8	$C_{28}H_{20}Br_2N_4O_3S$	51.50 / 51.52	3.10 / 3.09	24.50 / 24.49	8.60 / 8.59	4.87 / 4.91	120-122
9a	$C_{30}H_{22}Br_2N_4O_4S$	51.90 / 51.90	3.09 / 3.19	22.04 / 23.01	7.99 / 8.07	4.65 / 4.62	122-124
9b	$C_{35}H_{24}Br_2N_4O_4S$	55.54 / 55.57	3.10 / 3.20	21.10 / 21.13	7.23 / 7. 41	4.20 / 4.24	146-147
10a	$C_{19}H_{11}Br_2N_3O_4$	45.23 / 45.18	2.09 / 2.19	31.66 / 31.64	8.34 / 8.32		199-200
10b	$C_{23}H_{13}Br_2N_3O_3$	51.34 / 51.24	2.44 / 2.43	29.55 / 29.64	7.67 / 7.79		195-196
10c	$C_{17}H_8Br_2ClN_3O_3$	41.45 / 41.46	1.67 / 1.64	32.45 / 32.45	8.67 / 8.53	(7.23) / (7.20)	205-206
11a	$C_{22}H_{15}Br_2N_3O_5$	47.12 / 47.09	2.89 / 2.70	28.56 / 28.48	7.56 / 7.49		204-205
11b	$C_{24}H_{19}Br_2N_3O_7$	46.45 / 46.40	3.24 / 3.08	25.72 / 25.72	6.45 / 6.76		205-206
11c	$C_{23}H_{17}Br_2N_3O_6$	46.35 / 46.73	2.56 / 2.89	27.00 / 27.03	7.35 / 7.11		201-202
12	$C_{21}H_{11}Br_2N_5O_6$	42.67 / 42.81	1.89 / 1.88	27.23 / 27.12	11.78 / 11.89		133-135
13	$C_{23}H_{14}Br_2N_4O_3$	49.90 / 49.85	2.54 / 2.55	28.82 / 28.84	10.11 / 10.11		219-220
14	$C_{19}H_{11}Br_2N_5O_2$	45.56 / 45.54	2.34 / 2.21	31.78 / 31.89	13.67 / 13.97		185-186
15	$C_{19}H_{10}Br_2N_4O_3$	45.50 / 45.42	2.01 / 2.01	31.83 / 31.83	11.15 / 11.16		180-182

* Solvent: benzene (compounds **2, 3a,b, 8,9a,b,10a,b**), ethanol (compounds **4, 6a,b, 7, 10c, 11a–c,12–15**), toluene (compound **5**).

of microorganisms, including Gram-positive bacteria (*Bacillus subtilis*, *Staphylococcus aureus*, and *Micrococcus autea*) (Table 2) and Gram-negative bacteria (*Escherichia coli*, *Salmonella typhosa*, and *Pseudomonas aeruginosa*) (Table 3) using acetone as reference antimicrobial compounds. The extent of activity was expressed in terms of the diameters of the inhibition zones.

The results showed that compounds **8,9** possess high activities against all tested bacteria (Gram-positive and Gram-negative), but compounds **6**, **10c**, and **11c** are inactive against all tested bacteria at all concentrations. On the other hand, compounds **5**, **12**, and **14** exhibited a high activity towards all Gram-positive bacteria and are inactive towards all Gram-negative bacteria at all concentrations, while compound **7** was found to be active only against Gram-negative bacteria at all concentrations tested.

Regarding the structure-activity relationships we showed that the higher activity of compounds **8**, **9** may be due to the presence of N=C=S and quinazolin-4-one moieties in their structures.

EXPERIMENTAL

The reported mp's were recorded on an Electrothermal instrument. TLC was performed on plastic plates Silica Gel 60 F254 (E. Merck, layer thickness 0.2 mm). IR spectra (KBr) were recorded on a Bruker Vector 22 FT spectrophotometer, and ^{1}H NMR spectra were recorded on a Varian Gemini 200MHz (Germany) and Varian-Mercury-300 UH2 Oxford using DMSO-d_6 as a solvent. The microanalyses were performed at the Microanalytical unit, Cairo University, Egypt. The physical data of the synthesized compounds are given in Table 1.

TABLE 2. Relative activity of some compounds against Gram-positive expressed as diameters of inhibition zone

Com-pound*	Inhibition zone, mm								
	Bacillus subtilis, Atcc 7972			*Micrococcus autea*, NCIB 196			*Staphylococcus aureus*, Atcc 6538		
	50 μ/disc.	100 μ/disc.	200 μ/disc.	50 μ/disc.	100 μ/disc.	200 μ/disc.	50 μ/disc.	100 μ/disc.	200 μ/disc.
5	10	11	12	10	11	11	10	12	13
8	12	12	13	10	11	12	11	12	14
9	11	12	13	12	14	15	14	15	17
12	15	17	20	11	11	13	12	12	15
14	12	13	14	10	11	12	11	11	12

* Compounds **6, 7, 10c**, and **11c** are inactive.

TABLE 3. Relative activity of some compounds against Gram-negative bacteria expressed as diameters of inhibition zone

Com-pound*	Inhibition zone, mm								
	Escherichia coli, NCIB 9132			*Salmonella typhosa*, NRRL.B.573			*Pseudomonas eruginosa*, Atcc 77853		
	50 μ/disc.	100 μ/disc.	200 μ/disc.	50 μ/disc.	100 μ/disc.	200 μ/disc.	50 μ/disc.	100 μ/disc.	200 μ/disc.
7	12	12	14	11	12	14	11	11	13
8	10	11	11	13	14	16	16	18	20
9	12	13	15	13	15	16	12	13	14

* Compounds **5, 6, 10c, 11c, 12**, and **14** are inactive.

3-Amino-6,8-dibromo-2-(2-carboxyphenyl)-4(3H)-quinazolin-4-one (**2**). A mixture of compound **1** (4.25 g, 0.01 mol) and hydrazine hydrate (0.75 g, 0.015 mol) in ethanol (40 ml) was heated under reflux for 3 h. The product separated on cooling was crystallized from benzene to give compound **2** (3.07 g, 70%). IR spectrum, ν, cm^{-1}: 3480 (OH), 3274–3183 (NH_2), 1705 (C=O), 1670 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.85 (3H, m, Ar); 7.95 (1H, m, Ar); 8.11 (2H, s, Ar-Br); 9.75 (2H, s, NH_2); 11.5 (1H, br. s, COOH).

Synthesis of 10,12-Dibromophthalazino[1,2-*b*]quinazolinones 3a,b (General Method). A solution of compound **2** (4.39 g, 0.01 mol) in 20 cm^3 acetyl chloride or benzoyl chloride was heated under reflux for 2 h. The product that separated on cooling was crystallized from the proper solvent to give compound **3a** (2.55 g, 55%) or **3b** (2.78 g, 60%).

5-Acetoxy-10,12-dibromophthalazino[1,2-*b*]quinazolin-8-one (**3a**). IR spectrum, ν, cm^{-1}: 1735 (C=O), 1670 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.83 (3H, s, CH_3); 7.85 (3H, m, Ar); 8.11 (3H, m, Ar).

5-Benzoyloxy-10,12-dibromophthalazino[1,2-*b*]quinazolin-8-one (**3b**). IR spectrum, ν, cm^{-1}: 1742 (C=O), 1672 (C=O).

10,12-Dibromo-6-(piperidinomethyl)phthalazino[1,2-*b*]quinazoline-5,8-dione (**4**). A mixture of compound **2** (4.39 g, 0.01 mol), formaldehyde (1 ml, 0.33 mol), piperidine (0.85 g, 0.01 mol), and morpholine (0.87 g, 0.01 mol) was heated under reflux for 1 h. The product that separated on cooling was crystallized from ethanol to give compound **4** (2.8 g, 54%). IR spectrum, ν, cm^{-1}: 1673 (C=O), 1625 (C=O).

10,12-Dibromo-6-(phenylthiocarbamoyl)phthalazino[1,2-*b*]quinazoline-5,8-dione (**5**). A solution of compound **2** (4.39 g, 0.01 mol) and phenyl isothiocyanate (0.14 g, 0.01 mol) in dry benzene (30 ml) was refluxed for 2 h. The product that separated on cooling was crystallized from the proper solvent to give compound **5** (3.17 g, 57%). IR spectrum, ν, cm^{-1}: 3200 (NH), 1668 (C=O), 1213 (C=S). ^{1}H NMR spectrum, δ, ppm: 7.20 (4H, m, Ar); 7.75 (2H, m, Ar); 8.18 (5H, s, Ar); 8.43 (1H, s, NH).

Synthesis of 3-Arylmethylideneamino-6,8-dibromoquinazolin-4-ones 6a,b (General Method). A solution of compound **2** (4.39 g, 0.01 mol) and benzaldehyde or 4-chlorobenzaldehyde (0.01 mol) in ethanol (30 ml) was refluxed for 3 h. The products that separated on cooling were crystallized from the suitable solvent to give compound **6a** (3.16 g, 60%) or **6b** (3.31 g, 59%).

3-Benzylideneamino-6,8-dibromo-2-(2-carboxyphenyl)quinazolin-4-one (**6a**). IR spectrum, ν, cm^{-1}: 3460 (OH), 1683 (C=O), 1675 (C=O), 1620 (C=N).

6,8-Dibromo-2-(2-carboxyphenyl)-3-(4-chlorobenzylidene)aminoquinazolin-4-one (6b). IR spectrum, ν, cm^{-1}: 3465 (OH), 1685 (C=O), 1670 (C=O), 1617 (C=N). ^{1}H NMR spectrum, δ, ppm: 6.32 (1H, s, CH); 7.20 (5H, m, Ar); 7.55 (3H, m, Ar); 8.18 (2H, s, Ar); 11.4–11.6 (1H, s, OH).

6,8-Dibromo-2-(2-carboxyphenyl)-3-(4-oxo-2-phenylthiazolidinyl)quinazolin-4-one (**7**). A mixture of compound **6a** (5.27 g, 0.01 mol) and thioglycolic acid (0.92 g, 0.01 mol) and 3 drops of piperidine in ethanol (30 ml) was refluxed for 3 h. The products that separated on cooling were crystallized from ethanol to give compound **7** (3.37 g, 56%). IR spectrum, ν, cm^{-1}: 3480 (OH), 1690 (C=O), 1670 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.27 (2H, s, CH_2); 4.30 (1H, s, CH); 6.80 (5H, m, Ar); 7.65 (3H, m, Ar); 8.12 (3H, m, 2H ArBr + 1H ArCOO); 11.24 (1H, s, OH).

3-[(2-Aminophenylsulfanyl)(phenyl)methylamino]-6,8-dibromo-2-(2-carboxyphenyl)quinazolin-4-one (**8**). A solution of compound **6a** (5.27 g, 0.01 mol), 2-aminothiophenol (1.25 g, 0.01 mol), and 3 drops of piperidine in benzene (30 ml) was refluxed for 3 h. The products that separated on cooling were crystallized from benzene to give compound **8** (2.48 g, 38%). IR spectrum, ν, cm^{-1}: 3381 (OH), 3300–3100 (NH_2), 1695 (C=O), 1680 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.51 (1H, s, CH); 4.29 (1H, s, NH); 5.40 (2H, s, NH_2); 6.90 (5H, m, C_6H_5); 7.15 (5H, m, 3H ArCOO + 2H ArS); 7.50 (3H, m, 1H ArCOO + 2H ArN, ArS); 8.12 (2H, m, ArBr); 11.3 (1H, s, OH).

Synthesis of 3-[(2-Acylaminophenylsulfanyl)(phenyl)methylamino]-6,8-dibromo-2-(2-carboxyphenyl)-quinazolin-4-ones 9a,b (General Method). Compound **8** (6.52 g, 0.01 mol) was refluxed for 1 h in 20 ml of acetyl chloride or benzoyl chloride. The products that separated after removing excess acid chloride were crystallized from benzene to give compound **9a** (3.33 g, 48%) or **9b** (3.25 g, 43%).

3-[(2-Acetylaminophenylsulfanyl)(phenyl)methylamino]-6,8-dibromo-2-(2-carboxyphenyl)quinazolin-4-one (**9a**). IR spectrum, ν, cm^{-1}: 3460 (OH), 3272 (NH), 3190 (NH), 1718 (C=O), 1677 (C=O), 1636 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.83 (3H, s, CH_3); 6.33 (1H, s, CH); 7.15 (5H, m, Ar); 7.20 (5H, m, 3H ArCOO + 2H ArS); 7.55 (3H, m, 1H ArCOO + 2H ArN, ArS); 7.90 (2H, m, ArBr); 8.01 (1H, s, NH); 8.18 (1H, s, NH); 10.70 (1H, s, OH).

3-[(2-Benzoylaminophenylsulfanyl)(phenyl)methylamino]-6,8-dibromo-2-(2-carboxyphenyl)quinazolin-4-one (**9b**). IR spectrum, ν, cm^{-1}: 3480 (OH), 3072 (NH), 1675 (C=O), 1665 (C=O).

Synthesis of 6-Acyl-substituted 10,12-Dibromophthalazino[1,2-*b*]quinazoline-5,8-diones 10a,b (General Method). A solution of compound **2** (4.39 g, 0.01 mol) and ethyl acetoacetate, ethyl phenylacetate, or ethyl chloroacetate (0.01 mol) in *n*-butanol (40 ml) was refluxed for 3 h. The products that separated on cooling were crystallized from the suitable solvent to give compound **10a** (2.27 g, 45%), **10b** (3.45 g, 64%), or **10c** (2.96 g, 60%).

6-Acetoacetyl-10,12-dibromophthalazino[1,2-*b*]quinazoline-5,8-dione (**10a**). IR spectrum, ν, cm^{-1}: 1690 (C=O), 1685 (C=O), 1680 (C=O), 1640 (C=O).

10,12-Dibromo-6-phenylacetylphthalazino[1,2-*b*]quinazoline-5,8-dione (**10b**). IR spectrum, ν, cm^{-1}: 1694 (C=O), 1685 (C=O), 1680 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.39 (2H, s, CH_2); 7.49 (5H, m, C_6H_5); 7.88 (4H, m, Ar); 8.11 (2H, m, ArBr).

10,12-Dibromo-6-chloroacetylphthalazino[1,2-*b*]quinazoline-5,8-dione (**10c**). IR spectrum, ν, cm^{-1}: 1690 (C=O), 1685 (C=O), 1675 (C=O). ^{1}H NMR spectrum, δ, ppm: 4.27 (2H, s, CH_2); 7.75 (4H, m, Ar); 8.00 (2H, m, ArBr).

Synthesis of 6-Acyl-substituted 10,12-Dibromophthalazino[1,2-*b*]quinazoline-5,8-diones 11a-c (General Method). A mixture of compound **10c** (4.93 g, 0.01 mol) and active methylene compounds, namely, acetyl acetone, diethyl malonate, or ethyl acetoacetate (0.01 mol) was treated with sodium ethoxide obtained from sodium metal (0.75 g, 0.033 mol) in 30 ml of ethanol under reflux for 3 h. The excess solvent was removed under reduced pressure. The reaction mixtures were treated with ice/HCl, and the products that separated were crystallized from the suitable solvent to give compound **11a** (3.93 g, 70%), **11b** (4.29 g, 69%), or **11c** (2.90 g, 49%).

6-(3-Acetyl-4-oxopentanoyl)-10,12-dibromophthalazino[1,2-*b*]quinazoline-5,8-dione (**11a**). IR spectrum, ν, cm^{-1}: 1715 (C=O), 1695 (C=O), 1685 (C=O), 1670 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.03 (6H, s, $COCH_3$); 2.62 (2H, s, CH_2); 6.32 (1H, s, CH); 7.85 (4H, m, Ar); 8.09 (2H, m, ArBr).

10,12-Dibromo-6-[3,3-di(ethoxycarbonyl)propionyl]phthalazino[1,2-*b*]quinazoline-5,8-dione (**11b**). IR spectrum, ν, cm^{-1}: 1745 (C=O), 1735 (C=O), 1680 (C=O), 1675 (C=O), 1670 (C=O).

10,12-Dibromo-6-(3-ethoxycarbonyl-4-oxopentanoyl)phthalazino[1,2-*b*]quinazoline-5,8-dione (**11c**). IR spectrum, ν, cm^{-1}: 1740 (C=O), 1683 (C=O), 1680 (C=O), 1670 (C=O), 1630 (C=O).

10,12-Dibromo-6-[(2,4,6-trihydroxypyrimidin-5-yl)acetyl]phthalazino[1,2-*b*]quinazoline-5,8-dione (**12**). A solution of compound **11b** (6.21 g, 0.01 mol) and urea (0.60 g, 0.01 mol) in sodium ethoxide solution obtained from sodium metal (0.75 g, 0.033 mol) in 40 ml of ethanol was refluxed for 3 h, and the excess solvent was removed under reduced pressure. The reaction mixture was treated with ice/HCl, and the products that separated were crystallized from ethanol to give compound **12** (2.81 g, 47%). IR spectrum, ν, cm^{-1}: 3444 (OH), 3350 (NH), 1681 (C=O), 1640 (C=N). ^{1}H NMR spectrum, δ, ppm: 3.23 (2H, s, CH_2C=O); 6.32 (1H, s, CH); 6.80 (3H, m, Ar); 7.99 (3H, m, Ar); 10.26 (1H, s, OH); 10.29 (1H, s, OH); 10.40 (1H, s, OH).

10,12-Dibromo-6-(phenylaminoacetyl)phthalazino[1,2-*b*]quinazoline-5,8-dione (**13**). A mixture of compound **10c** (4.93 g, 0.01 mol) and aniline (0.93 g, 0.01 mol) was fused in an oil bath at 150°C for 3 h and then cooled and poured on ice/HCl. The solid that separated was crystallized from ethanol to give compound **13** (2.77 g, 50%). IR spectrum, ν, cm^{-1}: 3150 (NH), 1695 (C=O), 1685 (C=O), 1675 (C=O).

10,12-Dibromo-6-(5-methylpyrazol-3-yl)phthalazino[1,2-*b*]quinazoline-5,8-dione (**14**). A solution of compound **10a** (5.05 g, 0.01 mol) and hydrazine hydrate (0.75 g, 0.015 mol) in ethanol (50 ml) was refluxed for 4 h. The product that separated on cooling was crystallized from ethanol to give compound **14** (2.26 g, 45%). IR spectrum, ν, cm^{-1}: 3244 (NH), 1697 (C=O), 1651 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.82 (3H, s, CH_3); 6.30 (1H, s, CH); 7.17 (3H, m, Ar); 8.01 (3H, m, Ar); 8.18 (1H, s, NH).

10,12-Dibromo-6-(3-methylisoxazol-5-yl)phthalazino[1,2-*b*]quinazoline-5,8-dione (**15**). A solution of compound **10a** (5.05 g, 0.01 mol) and hydroxylamine hydrochloride (0.33 g, 0.01 mol) in pyridine (20 ml) was heated under reflux for 3 h. The product that separated on cooling was crystallized from ethanol to give compound **15** (2.0 g, 40%). IR spectrum, ν, cm^{-1}: 1680 (C=O), 1670 (C=O), 1605 (C=N).

REFERENCES

1. M. F. Ismail, A. A. El-Khamry, H. A. Abdel Hamid, and S. A. Emara, *Acta Chim. Hung.*, **127**, 35 (1990).
2. M. M. Mahmoud, M. A. El-Hashash, A. Essawy, and M. E. Shabana, *Indian J. Chem.*, **20B**, 718 (1981).
3. A. Sammour, A. Rabie, M. A. El-Hashash, and M. A. Sayed, *J. Chem. UAR*, **19**, 571 (1976).
4. A. M. Fahmy, M. A. El-Hashash, M. A. Habishy, and S. J. Nassar, *Rev. Roum. Chim.*, **23**, 1567 (1978).
5. M. A. El-Hashash, M. A. Hassan, and M. A. Sayed, *Pakistan J. Sci. Ind. Res.*, **20**, 336 (1977).
6. A. Essawy, M. A. El-Hashash, A. M. El-Gendy, and M. M. Hamad, *Indian J. Chem.*, **21**B, 593 (1982).
7. M. A. El-Hashash and M. A. Sayed, *Egypt. J. Chem.*, **21**, 115 (1978).
8. A. F. El-Farargy, M. M. Hamad, S. A. Said, and A. Haikal, *Egypt. J. Chem.*, **33**, 283 (1990).
9. S. El-Nagdy, M. A. El-Hashash, A. A. Afify, and F. El-Shahed F, *Indian J. Chem.*, **28B**, 126 (1989).
10. M. A. El-Hashash, A. A. El-Afify, M. A. Sayed, A. Y. Soliman, and M. Y. Amer, *Oriental J. Chem.*, **4**,165 (1988).
11. M. A. El-Hashash, H. M. F. Madkour, and M. S. Amine, *Pakistan J. Sci. Ind. Res.*, **34**, 288 (1991).
12. M. I. Husain and S. Shukla, *Indian J. Chem.*, **25B**, 545 (1986).
13. M. M. Mohamed, A. A. El-Khamry, S. El-Nagdy, and S. W. Shoshaa, *Indian J. Chem.*, **25B**, 207 (1986).
14. M. S. Amine, M. A. El-Hashash, and I. A. Attia, *Indian J. Chem.*, **32B**, 577 (1993).
15. T. M. Abdel-Rahman, *J. Heterocycl. Chem.*, **43**, 1 (2006).
16. T. M. Abdel-Rahman, M. A. El-Hashash, and I. F. Nassar, *Egypt. J. Chem.*, **4**, 461 (2006).
17. C. Mitsos, A. Zografos, and O. Igglessi-Markopoulou, *Heterocycles*, **51**, 1543 (1999).
18. A. A. Abu-Zeid and Y. M. Shehata, *Indian J. Pharm.*, **31**, 72 (1969).