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Synthesis and biological activity of nitrogen heterocycles from anthranilic acid derivative

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ABSTRACT

Reaction of 2-phenyl-6,8-dibromo-3,1-benzoxazine-4-one (1) with benzoylhydrazine, hydroxylamine, ammonia and sodium azide gave the corresponding 6,8-dibromo-3-substituted-4(3H)quinazolinones (2, 3 and 8), tetrazole derivative (6) and 1-benzoylbenzimidazole-2-one. Acetylation and alkylation of 3 with acetyl chloride and ethyl chloroactate yielded the corresponding 3-substituted-4(3H)-quinazolinones (4 and 5). Chlorination of 8 with $POCl_3$/ PCl_5 afforded the corresponding 4-chloro-6, 8-dibromoquinazoline (9). Treatment of 9 with mercapto compounds, aromatic amines, piperidine and active methylene compounds gave the corresponding 4-substituted quinazolines (10, 11, 12 and 14). Reaction of 9 with thiourea, sodium azide and hydrazine hydrate yielded the corresponding 4(3H)-quinazoline-4-thione (13), tetrazolo quinazoline (15) and 4-hydrazino-quinazoline (16). Triazoloquinazoline (18) was prepared via cyclocondensation of compound 16 with carbon disulphide in presence of alcoholic potassium hydroxide. Some synthesized compounds also exhibited antimicrobial activities.

Key words: Synthesis, biological activity, nitrogen heterocycles.

INTRODUCTION

The quinazolinone moiety is an important pharmacophore showing many types of pharmacological activities as showin in a recent exhaustive review on the chemistry of 2-heteroaryl and heteroalkyl-4(3H)-quinazolinones[1]. Like the benzodiazepines the quinazolines are considered to be a "privileged structure" for drug development[2]. Aromatic quinazolines have been shown to possess tyrosine kinase inhibiting effects, useful to inhibit tumour growth[3]. This has recently inspired the development of new ring synthesis methods[4, 5]. The general synthetic chemistry of quinazolines has also recently been reviewed[6].

In a previous work, El-Hashash, M. A. *et al*.[7-12], reported the synthesis of 2-substituted quinazolinones from anthranilic acid derivatives. This paper describes the synthesis of 2-phenyl quinazolinone from the reaction of benzoxazinone (1) with formamide, hydroxyl amine and acid hydrazide.

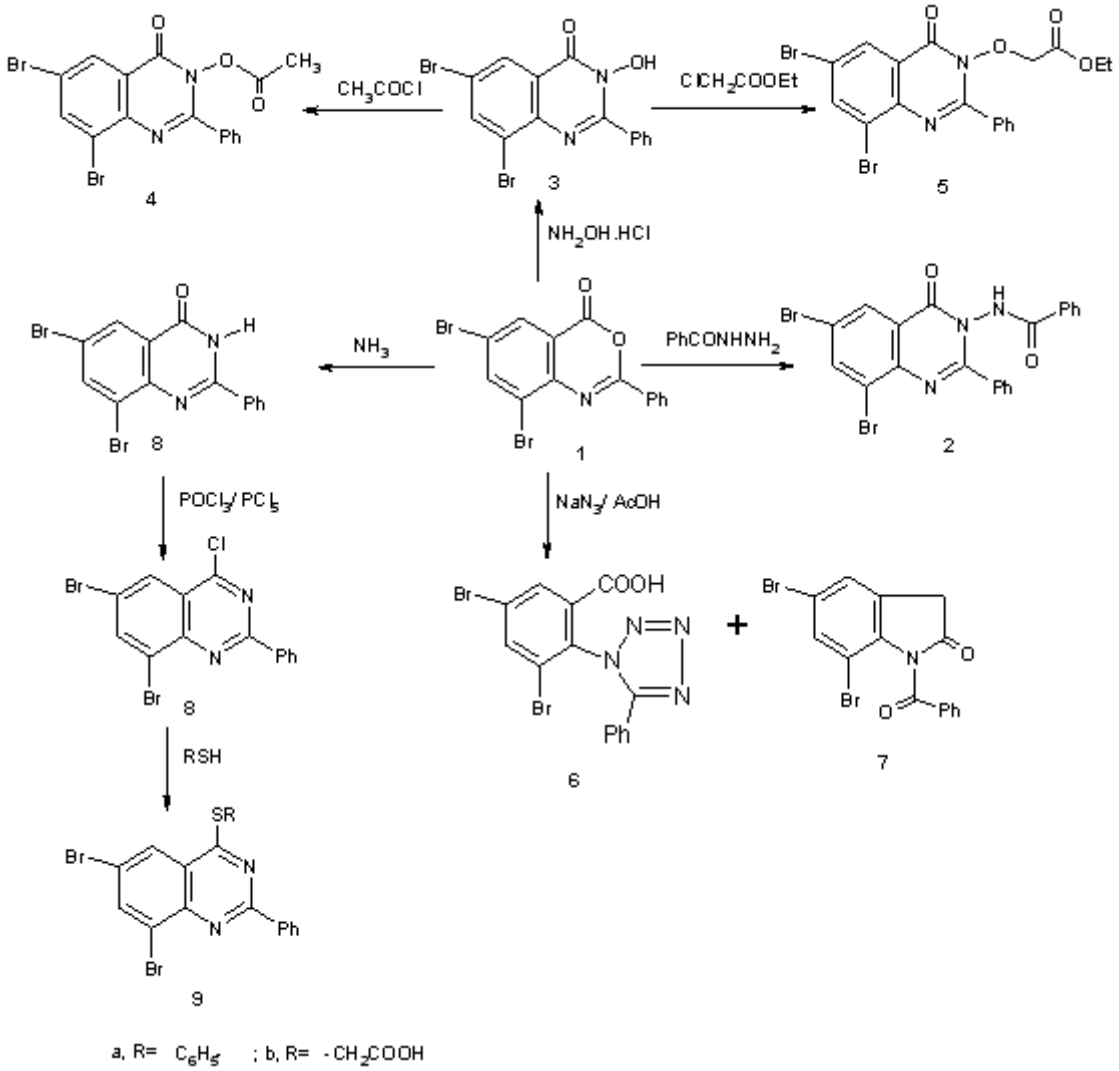
RESULTS AND DISCUSSION

2-phenyl-6, 8-dibromo-3, 1-benzoxazin4-one (1) was prepared from 3, 5-dibromo anthranilic acid with benzoyl chloride in pyridine under reflux. Condensation[13] of 6,8-dibromo-3,1-benzoxazine-4-one (1) with benzoyl hydrazine and hydroxyl amine hydrochloride under reflux gave the corresponding 2-phenyl-3-benzoylamino-6,8-dibromo-4(3H)-quinazolinone (2) and 2-phenyl-3-hydroxy-6,8-dibromo-4(3H)-quinazolinone (3), respectively.

2-phenyl-3-acetyloxy-6,8-dibromo-4(3H)-quinazolinone (4) and 2-phenyl-3-ethoxycarbonyl methoxy-6,8-dibromo-4(3H)-quinazolinone (5) were prepared via acelylation and / or alkylation of 2-phenyl-3-hydroxy-6,8-dibromo-4(3H)-quinazolinone (3) with acetyl chloride and ethyl chloroacetate.

When compound 1 was submitted to react with sodium azide in boiling acetic acid it afforded 1-(2-carboxy)-3,5-dibromophenyl-5-phenyl tetrazole (6) and 1-benzoyl-benzimidazol-2-one (7), together. Amonolysis[14] of 2-phenyl-3,1-benzoxazin-4-one derivative (1) with formamide and / or ammonium acetate under fusion in an oil-bath at 160 °C, yielded the corresponding 2-phenyl-6,8-dibromo-4(3H)-quinazolinone (8).

Treatment of the quinazolinone (8) with a mixture of phosphorous oxychloride and phosphorous pentachloride under reflux on a water bath affording 2-phenyl-4-chloro-6,8-dibromo-quanazoline (9). Reaction of chloroquinazoline (9) with mercapto compounds (such as thiophenol and thioglycolic acid) under reflux yielded the corresponding 2-phenyl-4-phenothioxy-6,8-dibromoquinazoline (10 a) and 2-phenyl-4-carboxymethylthioxo-6,8-dibromoquinazoline (10 b), respectively (Scheme 1).



Scheme 1

Condensation of chloroquinazoline (9) with aromatic amine such as O-aminophenol and sulphanilamide in boiling dimethyl formamaide, gave the corresponding 4-substituted quinazolines (11 a,b).

On the other hand, when 4-chloroquinazoline (9) was allowed to react with piperdine to give 2-phenyl-4-piperidino-6,8-dibromoquinazoline (12). Reaction of chloroquinazoline (9) was allowed to react with piperdine to give 2-phenyl-4-piperidino-6,8-dibromoquinazoline (12). Reaction of chloroquinazoline (9) with thiourea in ethanol under reflux yielded the corresponding 2-phenyl-6,8-dibromo-4-thioxo-quinazoline (31). The structure 13 was obtained from anthor pathway involving treatment of the 4-chloroquinazoline (9) with phosphorus penta sulphide in xylene under reflux. 2-phenyl-4-acetonyl-6,8-dibromoquinazoline (14) was prepared via the rea+ction of 4-chloroquinazoline (9) with active methylene compounds (namely, acetyl acetone and ethyl acetoacetate) in ethanol under reflux. Subsequently, 4-chloroquinazoline (9) reacted with sodium azide in glacial acetic acid afforded the corresponding 6,8-dibromo-1,2,3,4-tetrazolo [4,3-c] quinazoline (15). Hydrazonolysis of 4-chloroquinazoline (9) with hydrazine hydrate, gave the corresponding 2-phenyl-4-hydrazino-6,8-dibromoquinazoline (16). Condensation of compound 16 with benzaldehyde in butanol under reflux yielded the corresponding hydrazone derivative (17). 3-mercapto-4-phenyl-6,8-dibromo-1,2,4-triazolo [3,4-c] quinazoline (18), Scheme (2), was synthesized via the reaction of 4-hydrazinoquinazoline (16) with carbon disulphide in the presence of alcoholic potassium hydroxide.

Biological activity

Some compounds were screened against different strains microorganisms, including Gram positive bacteria (*Staphylococcus aureus* and *Pseudomonas aeruginosa*) and *Gram-negative* bacteria (*Bacillus subtilis* and *Escherichia coli*) using chloramphenicol as reference antimicrobial compounds[15]. The compounds were tested at different concentrations and the activity was determined by measuring the zone of inhibition the screening results are given in Table 1.

EXPERIMENTAL

All melting points are uncorrected. Elemental analyses were carried out in the micro analytical center, Cairo University, Giza, Egypt. IR spectra (KBr) were recorded on Pye Unicam SP 1200 spectrophotometer. Proton NMR spectra were obtained on a Varian EM 360 spectrometer using solution in hexadeuteriodim ethyl sulphoxide with tetramethyl silane as the internal standard. The mass spectra were determined with HP model MS-5988 at electron energy 70 eV. Homogeneity of all

Table 1: Antibacterial activity of some prepared componds 1, 2, 6 and 8-11

Comd. No	*Gram positive* bacteria						*Gram negative* bacteria					
	Staphylococcus aureus			*Pseudomonas aeruginosa*			*Bacillus subtilis*			*Escherichia coli*		
	5	22.5	1	5	22.5	1	5	22.5	1	5	22.5	1
1	++	++	++	+++	+++	++	++	+++	++	++	++	++
2	+	-	-	+	-	-	+	+	-	-	-	-
6	-	-	-	+	+	-	-	-	-	+	-	-
8	+	-	-	+	-	+	-	-	-	+	-	-
9	+	-	-	-	-	-	-	-	-	+	-	-
10a	++	++	+	++	+	+	-	-	-	+	-	-
10b	++	+	+	++	++	++	-	-	-	+	-	-
11b	+	-	-	+	+	+	-	-	-	+	-	-

(+) Inhibition Zone (0.1- 0.5 cm) (++) Inhibition Zone (0.6- 1 cm)
(+++) Inhibition Zone (1.1- 1.5 cm) (-) Not detected

compounds synthesized was checked by TLC. Characterization data of various synthesized compounds are given in Table 2.

2-Phenyl-3-(benzoyl) amino-6,8-dibromo-4(3H)-quinazolinone (2)

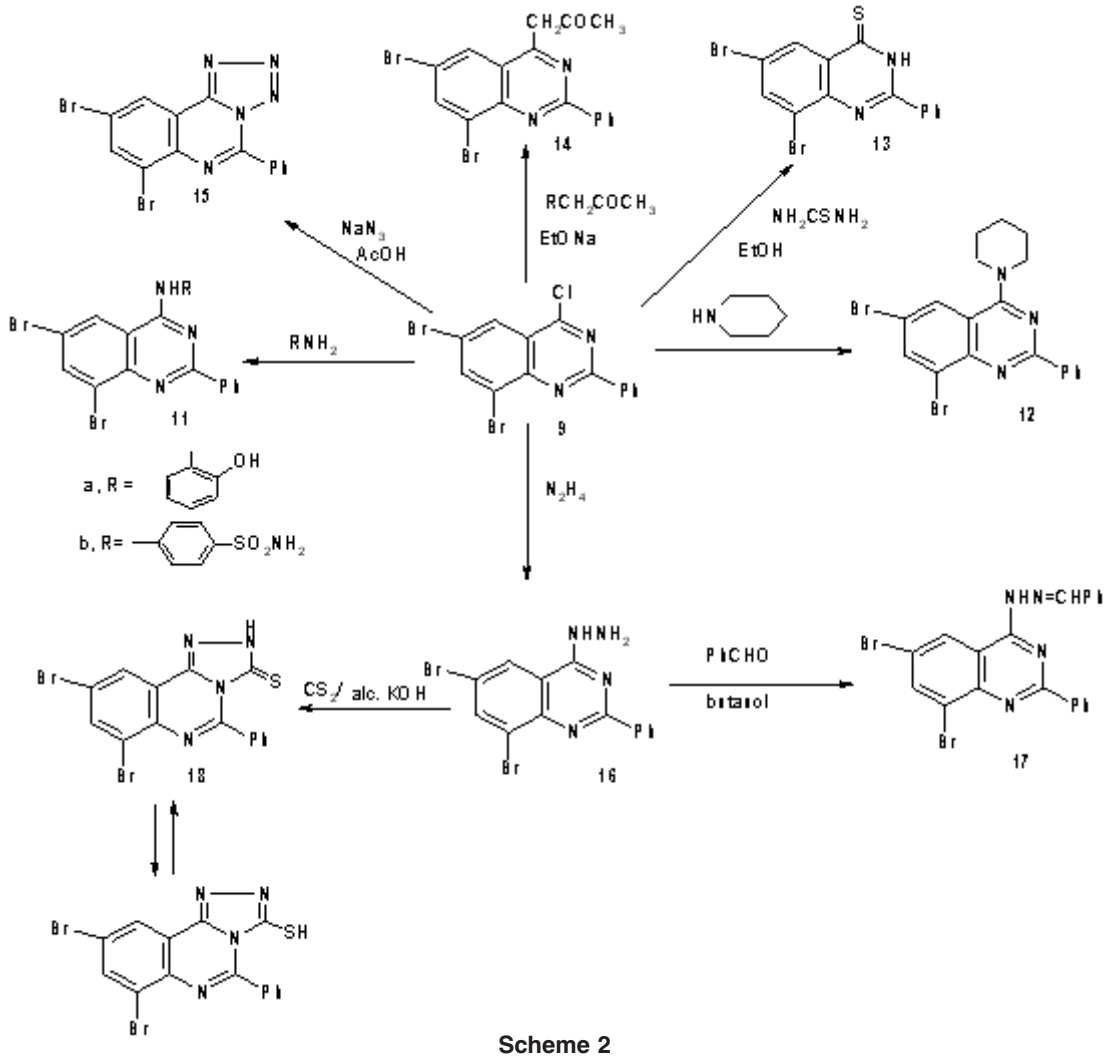
A mixture of 1 (0.01 mole, 3.81 gm) and benzoyl hydrazine (0.01 mole, 1.36 gm) in ethanol (30 ml) was heated under reflux for 48 hr. The reaction mixture was cooled and poured into water. The product formed was collected by filtration, washed with water, dried and purified by recrystallization with proper solvent to give 2. γ_{max} (KBr): 1675 (C=O), 1610, 1589 (C=C), 3250 (NH) cm^{-1}. Mass spectrum, m/z (%): 499 (M^+, 10.40), 454 (9.35), 105 (100), 77 (67.20).

2-Phenyl-3-hydroxy-6,8-dibromo-4(3H)-quinazolinone (3)

A mixture of 1 (0.01 mole, 3.8 gm) and hydroxyl amine hydrochloride (0.01 mole, 2.1 gm) in pyridine (30 ml) was heated under reflux for 5 hr. The reaction mixture was cooled and poured into ice/ HCl. The solid formed was filtered off, washed with water, dried and purified by recrystallization with proper solvent to give 3. g_{max} (KBr): 1673 (C=O), 1605, 1593 (C=C), 3320-2956 (br. OH) cm^{-1}.

2-Phenyl-3-acetyloxy-6,8-dibromo-4(3H)-quinazolinone (4)

A solution of 3 (0.01 mole, 3.9 gm) in acetyl chloride (20 ml) was heated under reflux for 2 hr. The solid formed after cooling was filtered off, dried



Scheme 2

and purified by recrystallization with proper solvent to give 4. γ_{max} (KBr): 1812, 1702 (C=O), 1625 (C=N), 1605, 1583 (C=C), 1205, 1030 (C-O) cm^{-1}. Mass spectrum, m/z (%): 438 (M^+, 18.30), 395 (100), 365 (23.20).

2-Phenyl-3-ethoxy carbonyl methoxy-6,8-dibromo-4(3H)-quinazolinone (5)

A mixture of 3 (0.01 mole, 3.9 gm), anhydrous potassium carbonate (0.03 mole, 4.14 gm) and ethyl chloroacetate (0.03 mole, 4.2 ml) in dry acetone (50 ml) was heated under reflux for 25 hr. The excess of solvent was removed and the reaction mixture was diluted with water. The solid obtained was filtered off, washed with water, dired and purified by recrystallization from the proper solvent to give 5. γ_{max} (KBr): 1752 (C=O), 1625 (C=N), 1603, 1588 (C=C), 1250, 1081, 1020 (C-O) cm^{-1}. d_H ($CDCl_3$): 1.10 (t, 3H, CH_3), 4.12 (q, 2H, CH_2), 5.10 (s, 2H, OCH_2CO), 7.30-8.91 (m, 7H, ArH).

1-(2-Carboxy)-3,5-dibromophenyl-5-phenyl tetrazole (6)

1-Benzoyl benzimidazole-2-one (7)

A mixture of 1 (0.01 mole, 3.81 gm) and sodium azid (0.01 mole, 1.80 gm) in acetic acid (30 ml) was heated under reflux for 5 hr. The reaction mixture was cooled and poured into water. The product obtained was filtered off, washed with water, dried and purified by frictionally crystallization with proper solvent to give 6 and 7. γ_{max} (KBr) of compound 6: 3341 (OH), 1714 (C=O), 1632 (C=N), 1205, 1030 (C-O) cm^{-1}. Mass spectrum, m/z (%): 442 (M^+, 11.30), 427 (15.30), 382 (19.30), 343 (16.30), 243 (17.60), 184 (18.30), 109 (26.30), 55 (100). γ_{max} (KBr) of compound 7: 3162 (NH), 1692, 1667 (C=O), 1605, 1582 (C=C) cm^{-1}. Mass spectrum, m/z (%): 396 (M^+, 12.20), 291 (26.30), 105 (100), 77 (62.10).

2-Phenyl-6,8-dibromo-4(3H)-quinazolinone (8)

A mixture of 1 (0.01 mole, 3.81 gm) and formamide (10 ml) was heated under reflux for 2 hr. The reaction mixture was cooled and poured into crushed ice. The crude product was filtered off, washed with water, dried and purified by recrystallization with proper solvent to give 8. γ_{max} (KBr): 3170 (NH), 1672 (C=O), 1625 (C=N), 1603, 1590 (C=C) cm^{-1}. Mass spectrum, m/z (%): 380 (M^+, 100), 277 (76.10), 153 (15.30), 77 (71.70).

2-Phenyl-4-chloro-6,8-dibromoquinazolinone (9)

A suspension of 8 (0.01 mole, 3.8 gm) in phosphorus oxychloride (0.05 mole, 7.5 ml) in presence of phosphorous pentachloride (0.03 mole, 6 gm) was heated on a water bath for 2 hr. The reaction mixture was cooled and poured slowly onto crushed ice. The solid formed was filtered off, washed with water, dried and purified by crystallization with proper solvent to give 9. γ_{max} (KBr): 1631 (C=N), 1605, 1583 (C=C) cm^{-1}. Mass spectrum, m/z (%): 398 (M^+, 69.50), 363 (100), 319 (21.20), 203 (13.30), 135 (25.51), 101 (31.20), 77 (76.20).

2-Phenyl-4-phenothioxy-6,8-dibromoquinazolinone (10 a)

2-Phenyl-4-(hydroxyl carbonyl) methylthioxo-6,8-dibromoquinazolinone (10 b)

A mixture of 9 (0.01 mole, 3.9 gm) and mercapto compounds (such as thiophenol and thioglycolic acid, 0.01 mole) in dry acetone (30 ml) in presence of anhydrous potassium carbonate (0.03 mole, 4.14 gm) was heated under reflux for 6 hr. The reaction mixture was cooled and poured into water. The solid formed was filtered off, washed with water, dried and purified by recrystallization with proper solvent to give 10. γ_{max} (KBr) of compound 10 a: 1632 (C=N), 1605, 1582 (C=C) cm^{-1}. Mass spectrum, m/z (%): 472 (M^+, 31.20), 363 (33.20), 109 (10.20), 77 (100). γ_{max} (KBr) of compound 10 b: 3410-2870 (br. OH), 1702 (C=O), 1631 (C=N), 1605, 1591 (C=C), 1210, 1035 (C-O) cm^{-1}. Mass spectrum, m/z (%): 453 (M^+, 10.30), 380 (100), 277 (75.30), 104 (21.20), 77 (46.20).

4-Substituted-6,8-dibromoquinazoline (11 a, b)

A mixture of 9 (0.01 mole, 3.9 gm) and aromatic amines (namely, O-aminophenol and sulphanilamide, 0.01 mole) in dimethyl formamide (30 ml) was heated under reflux for 6 hr. The reaction mixture was cooled and poured onto water. The solid formed was filtered off, washed with water, dried and purified by recrystallization with the proper solvent to give 11. γ_{max} (KBr) of compound 11 a: 3420 (br. OH), 3225 (NH), 1625 (C=N) and 1603, 1583 (C=C) cm^{-1}. γ_{max} (KBr) of compound 11 b: 3368, 3200, 3195 (NH_2, NH), 1629 (C=N) and 1608, 1592 (C=C) cm^{-1}. Mass spectrum, m/z (%): 534 (M^+,

77.20), 470 (73.20), 426 (11.20), 363 (18.20), 310 (16.31), 235 (9.80), 195 (10.50), 156 (16.30), 92 (100), 76 (61.20).

2-Phenyl-4-piperidino-6,8-dibromoquinazoline (12)

A mixture of 9 (0.01 mole, 3.9 gm) and pipridine (0.01 mole, 0.86 gm) was fused in an oil-bath at 150°C. The reaction mixture was cooled and purified by recrystallization with proper solvent to give 12. γ_{max} (KBr): 1632 (C=N) and 1605, 1583 (C=C) cm^{-1}. d_H ($CDCl_3$): 1.7 (s, 6H, 3 CH_3), 3.2 (s, 2H, CH_2), 3.4 (s, 2H, NCH_2), 7.20-8.60 (m, 7H, ArH).

2-Phenyl-4-thioxo-6,8-dibromoquinazoline (13)

A mixture of 9 (0.01 mole, 3.9 gm) and thiourea (0.01 mole, 0.76 gm) in ethanol (30 ml) in presence of sodium methoxide (0.02 mole) was heated under reflux for 4 hr. The excess of solvent was removed and the reaction mixture was acidified

Table 2: Characterization and Physical data for prepared compounds

Compd	m.p.(°C)	Solvent	M. Formula	Analyses % Calcd/ Found					
No.	/Colour		M. Wt	C	H	N	Br	Cl	S
1	187	ACOH	$C_{14}H_7NO_2Br_2$	44.13	1.85	3.67	41.94		
	Yellow	(381.011)	44.25	1.95	3.72	41.99			
2	200	Benzene	$C_{21}H_{13}N_3O_2Br_2$	50.53	2.62	8.41	32.01		
	Colorless	(499.15)	50.63	2.75	8.53	32.15			
3	165	EtOH	$C_{14}H_8N_2O_2Br_2$	42.46	2.04	7.07	40.35		
	Yellow	(396.02)	42.57	2.15	7.19	40.45			
4	230	EtOH	$C_{16}H_{10}N_2O_3Br_2$	43.87	2.30	6.39	36.48		
	Colorless	(438.05)	43.98	2.41	6.50	36.00			
5	170	EtOH	$C_{18}H_{14}N_2O_4Br_2$	44.84	2.93	5.81	33.15		
	Yellow	(482.10)	44.95	3.04	5.93	33.26			
6	>300	DMF	$C_{14}H_8N_4O_2Br_2$	39.65	1.90	13.21	37.69		
	Yellow	(424.028)	39.77	2.10	13.32	37.80			
7	150	Benzene	$C_{14}H_8N_2O_2Br_2$	42.46	2.40	7.07	40.35		
	Colorless	(396.016)	42.56	2.51	7.18	40.46			
8	>300	DMF	$C_{14}H_8N_2OBr_2$	44.24	2.11	7.37	42.05		
	Pale yellow	(380.025)	44.38	2.22	7.48	42.11			
9	180	Acetone	$C_{14}H_7N_2ClBr_2$	42.20	1.77	7.03	40.10	8.90	
		Yellow	(398.446)	42.35	1.82	7.13	40.25	9.00	
10a	165	Benzene	$C_{20}H_{12}N_2SBr_2$	50.87	2.56	5.43	33.84		7.06
		Deep yellow	(499.15)	50.98	2.66	6.05	33.95		7.17
10b	>300	Chloroform	$C_{16}H_{10}N_2O_2SBr_2$	42.32	2.22	6.17	35.19		
		Yellow	(454.126)	42.45	2.33	6.28	35.30		
11a	200	Benzene	$C_{20}H_{13}N_3OBr_2$	50.99	2.87	8.92	33.92		
		Yellow	(471.128)	51.10	2.89	9.01	34.03		
11b	>300	DMF	$C_{20}H_{14}N_4O_4SBr_2$	44.97	2.64	10.49	29.91		6.00
		Colorless	(534.21)	45.07	3.75	10.60	30.02		6.15
12	145	Acetone	$C_{19}H_{17}N_3Br_2$	51.03	3.83	9.40	35.74		
		Colorless	(447.146)	51.15	3.95	9.52	35.86		
13	150	Chloroform	$C_{14}H_8N_2SBr_2$	42.45	2.04	7.07	40.35		8.10
		Yellow	(396.088)	42.55	2.15	7.18	40.46		8.21
14	170	Acetone	$C_{17}H_{12}N_2OBr_2$	48.60	2.88	6.67	38.04		
		Colorless	(420.075)	48.71	2.99	6.78	38.15		

with diluted hydrochloric acid (1%). The crude product was filtered off, washed with water, dried and purified by recrystallization with proper solvent to give 13. g $_{max}$ (KBr): 1629 (C=N), 1605, 1588 (C=C), 1389 (C=S) cm^{-1}. Mass spectrum, m/z (%): 396 (M^{+}, 76.50), 363 (72.30), 318 (76.30), 283 (100), 199 (26.30), 158 (9.20), 118 (5.60), 77 (100), 51 (33.20).

2-Phenyl-4-acetonyl-6,8-dibromoquinazoline (14)

A mixture of 9 (0.01 mole, 3.9 gm) and active methylene compounds (namely, ethyl acetoacetate and acetylacetone (0.015 mole) in ethanol (30 ml) in presence of sodium ethoxide (0.02 mole) was heated under reflux for 6 hr. The reaction mixture was cooled and poured into dilute hydrochloric acid (2%). The solid formed was filtered off, washed with water, dried and purified by recrystallization with proper solvent to give 14. g $_{max}$ (KBr): 1710 (C=O), 1629 (C=N) and 1603, 1583 (C=C) cm^{-1}. d $_{H}$ (DMSO-d$_6$): 2.51 (s, 3H, $COCH_3$), 3.30 (s, 2H, CH_2CO), 7.5-8.30 (m, 7H, ArH).

6,8-Dibromo-1,2,3,4-tetrazolo[4,3-c]-quinazoline (15)

A mixture of 9 (0.01 mole, 3.9 gm) and sodium azide (0.01 mole, 1.8 gm) in acetic acid (30 ml) was heated under reflux for 5 hr. The solid obtained after cooling was filtered off, dried and purified by recrystallization with proper solvent to give 15. g $_{max}$ (KBr): 1630 (C=N) and 1607, 1598 (C=C) cm^{-1}.

2-Phenyl-4-hydrazino-6,8-dibromoquinazoline (16)

A mixture of 9 (0.01 mole) and hydrazine hydrate (0.01 mole, 0.75 ml) in butanol (30 ml) was heated under reflux for 6 hr. The reaction mixture was concentrated and cooled. The solid obtained was filtered off, dried and purified by recrystallizatrion with proper solvent to give 16. g $_{max}$ (KBr): 3410, 3310, 3190 (NH_2, NH), 1629 (C=N) and 1603, 1589 (C=C) cm^{-1}.

2-Phenyl-4-(benzylidene) amino-6,8-dibromoquinazoline (17)

A mixture of 16 (0.01 mole, 3.9 gm) and benzaldehyde (0.01 mole, 1.1 ml) in butanol (30 ml) was heated under reflux for 6 hr. The solid formed after cooling was filtered off, dried and purified by recrystallization with proper solvent to give 17. g $_{max}$ (KBr): 3225 (NH), 1635 (C=N), 1605, 1598 (C=C) cm^{-1}. d $_{H}$ ($CDCl_3$): 7.26-8.17 (m, 11, ArH), 8.54 (s, 1H, CH=N), 10.64 (s, 1H, NH).

3-Mercapto-4-phenyl-6,8-dibromo-1,2,4-tetrazolo[4,3-c] quinazoline (18)

A mixture of 16 (0.01 mole, 3.9 gm), carbon disulphide (10 ml) and potassium hydroxide (0.25 mole) in ethanol (30 ml) was heated under reflux in water-bath for 6 hr. The reaction mixture was cooled and poured into diluted hydrochloric acid (2%). The crude product was filtered off, washed with water, dried and purified by recrystallization with proper solvent to give 18. g$_{max}$ (KBr): 3220 (NH), 1635 (C=N), 1606, 1589 (C=C), 1398 (C=S) cm^{-1}. Mass spectrum, m/z (%): 436 (M^{+}, 53.20), 358 (86.30), 300 (33.20), 277 (23.50), 215 (15.30), 182 (13.30), 100 (48.40), 77 (100).

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