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Behaviour of dynamic 6,8-dibromo-2-methyl-4-(H)-3, 1-benzoxazin-4-one towards some nitrogen nucleophiles: Synthesis of new quinazolinones with anticipated biological activity

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ABSTRACT

4(H)-3,1-Benzoxazin-4-one derivative 1 reacted with ammonium acetate and/or formamide, hydrazine hydrate and ethanolamine to give pyrimidine derivatives 2-4. Treatment of 2 with P_2S_5 and ethyl chloroacetate produced thazine 5 and ester 7 which upon reaction with hydrazine furnished the hydrazide 8. The hydrazide 8 reacted with CS_2/KOH at room temperature and/or reflux, benzoyl chloride, 2-chlorobenzoic acid/$POCl_3$, and p-chlorobenzaldehyde to afford pyrimidine derivatives 9, 11-14, respectively. On the other hand, when the aminopyrimidine derivative 3 reacted with p-chlorobenzaldehyde, phthalimide and ethyl acetoacetate, it produces the quinazolinones 18-20, respectively. Furthermore, refluxing the 1,3-diketone 20 with hydrazine and benzylamine gave the pyrazole derivative 21, and the condensation product 22, respectively. All new synthesized compounds were structurally confirmed by elemental analyses and spectroscopic data (IR, ^{1}H-NMR and MS spectroscopy).

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KEYWORDS

4(H)-3;
1-Benzoxazin-4-one;
3-Aminoquinazoloinone;
Ethanolamine;
4-Ethoxycarbonyl methoxyquinazoline.

INTRODUCTION

Quinazolin-4(3H)-one are a class of fused heterocycles that are of considerable interest on account of the diverse range of their biological properties, e.g. antifungal, antibacterial, anticancer, antiinflammatory, anticonvulasant, immunotropic, hypolipidemic, antitumor, antiulcer analgesic, antiproliferative, antihypertensive, diuretic, anti-HIV, antihestaminic activities as well as inhibitory effects for thymidylate synthase and poly-(ADP-ribose) polymerase (PARP)[1-21].

In view of the biological activity and importance of quinazolinones and their derivatives, and within the framework of our systematic studies on the synthesis of new heterocyclic compounds[22-30] we have decided to synthesize a series of novel 3-substituted-2-methylquinazolin-4(3H)one, with two bromine atoms in the benzene using 6,8-dibromo-2-methyl-4-(H)-3,1-benzoxazin-4-one (1) as a versatile starting material, which was obtained via the interaction of 2-amino-3,5-dibromobenzoic acid with acetic anhydride.

RESULTS AND DISCUSSIONS

Ammonolysis of compound 1 with formamide and or ammonium acetate yielded 6,8-dibromo-2-methyl quinazolin-4(3H)-one 2. The reaction involved hetero-ring opening of benzoxazinone 1 followed by cyclization to give the quinazolinone 2.

When compound 1 was allowed to react with hydrazine hydrate in boiling ethanol, it afforded 3-amino-6,8-dibromo-2-methylquinazolin-4(3H)-one 3.

The amination of compound 1 using ethanolamine[31] led to the formation of 6,8-dibromo-3-(2-hydroxyethyl)-2-methylquinazolin-4(3H)-one 4(SCHEME 1). The reaction could proceed via the nucleophilic attack by the amino group rather than by the hydroxyl group (NH_2 is stronger nucleophile than OH group) followed by ring closure to furnish compound 4.

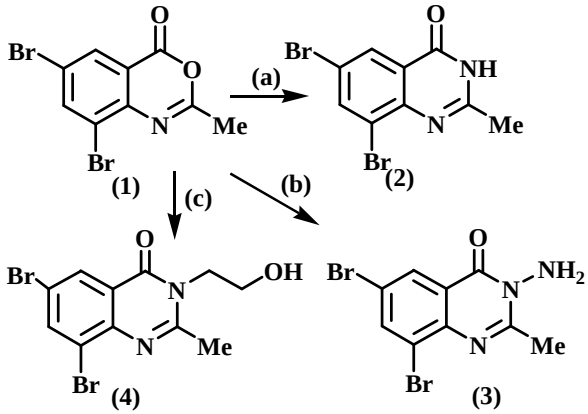
In the present work the hitherto unknown reaction of the quinazoline 2 with phosphorous pentasulfide in boiling dioxane has been investigated. Thus when compound 2 was allowed to react with P_2S_5, it afforded the unexpected 6,8-dibromo-2-methyl-benzothiazinone 5.

The quinazolinone derivative 2 reacted with ethyl chloroacetate in dry acetone in the presence of anhydrous potassium carbonate as a catalyst[32] to give 6,8-dibromo-4-ethoxycarbonylmethoxyquinazoline 7. In acetone the lactim form is more predominant[33] and consequently the reaction takes place via nucleophilic substitution of the lone pair of oxygen on the primary alkyl halide moiety SN^2 as a regiospecific reaction.

When compound 7 was allowed to react with hydrazine hydrate[34] in boiling ethanol it afforded 4-aminocarbamoylmethoxy-6,8-dibromo-2-methylquinazoline 8. The reaction possibly proceeded via tetrahedral mechanism in which N-C bond was formed before C-OEt which started to break and consequently a lot of energy is released in the reaction medium which decreases the activation energy of the reaction and a facile conversion occurred.

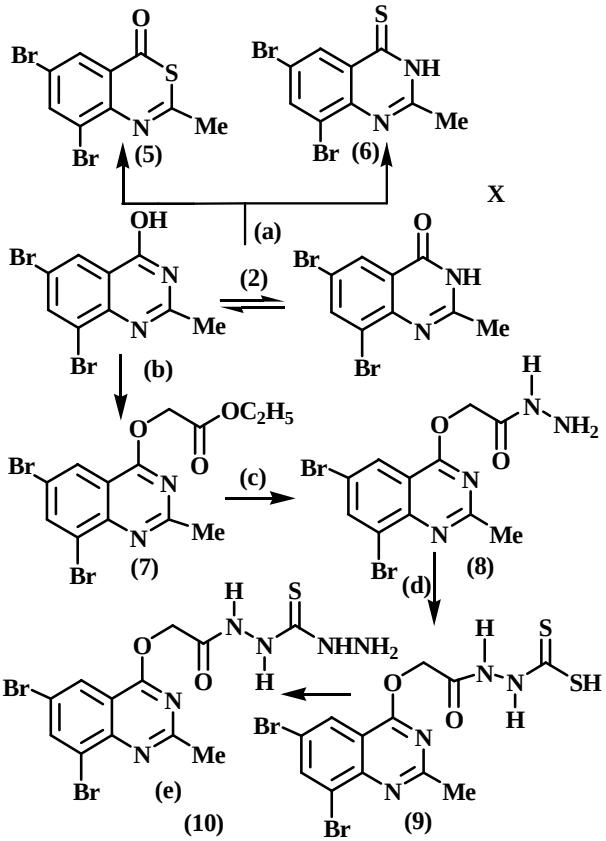
Treatment of hydrazide 8 with carbon disulphide in the presence of aqueous KOH at room temperature yielded 4-dithiocarboxyaminocarbamoylmethoxy-6,8-dibromo-2-methyl-quinazoline 9 which upon refluxing with hydrazine hydrate afforded the thiohydrazide derivative 10 (SCHEME 2).

On the other hand, when compound 8 reacted with carbon disulphide in the presence of aqueous KOH on boiling water bath, 6,8-dibromo-2-methyl-4-[3-thioxopyrazol-5-one-4-yloxy]quinazoline 11 was obtained and not the mercapto-1,3,4-oxadiaole[35]. The reaction could proceed via ring closure followed by dehydrogenation.



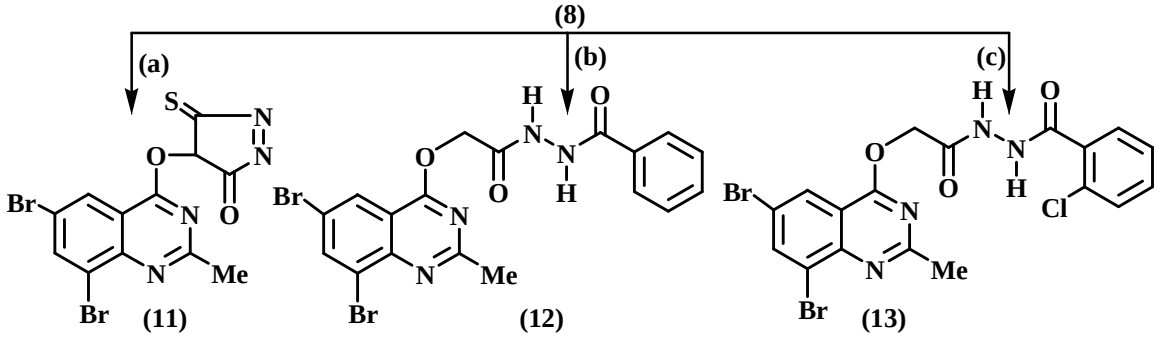
Reagents and reaction coditions:
(a) Amm.acetatate /fusion, or formamide/reflux;
(b) Hydrazine/reflux; (c) Ethanolamine/reflux.

SCHEME 1



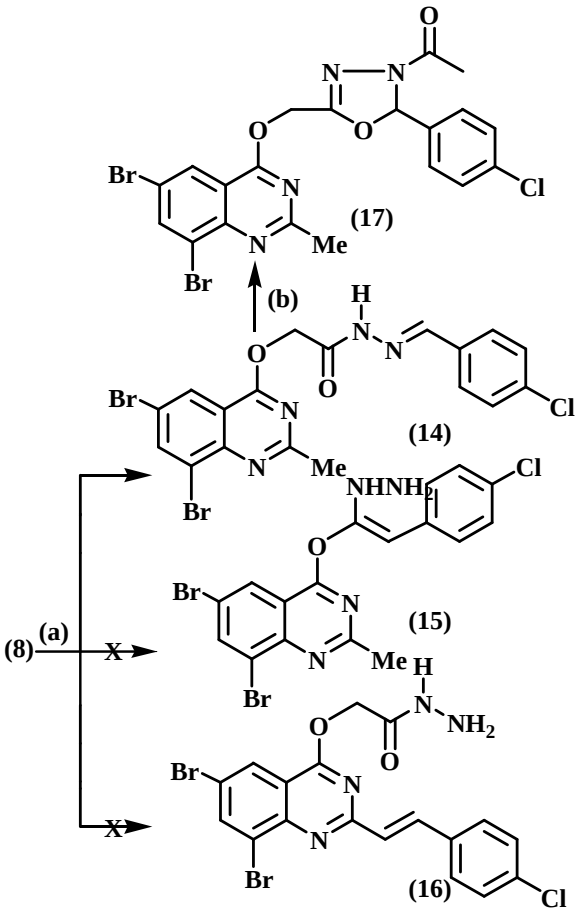
Reagents and Reaction coditions:
(a) P_2S_5/xylene; (b) $ClCH_2COOEt/K_2CO_3$;
(c) N_2H_4/reflux;d) CS_2 / KOH/RT; (e) N_2H_4/reflux.

SCHEME 2



Reagents and Reaction conditions: (a) CS_2/KOH/reflux; (b) PhCOCl/pyridine/reflux; (c) 2-$ClC_6H_4COOH/POCl_3$.

SCHEME 3



Reagents and Reaction conditions:
(a) 4-ClC_6H_4CHO/butanol; (b) Ac_2O/reflux

SCHEME 4

Reaction of 8 with benzoyl chloride, in the presence of pyridine, led to benzoylation at the more nucleophilic nitrogen of the aminocarbamoyl moiety, and afforded compound 12.

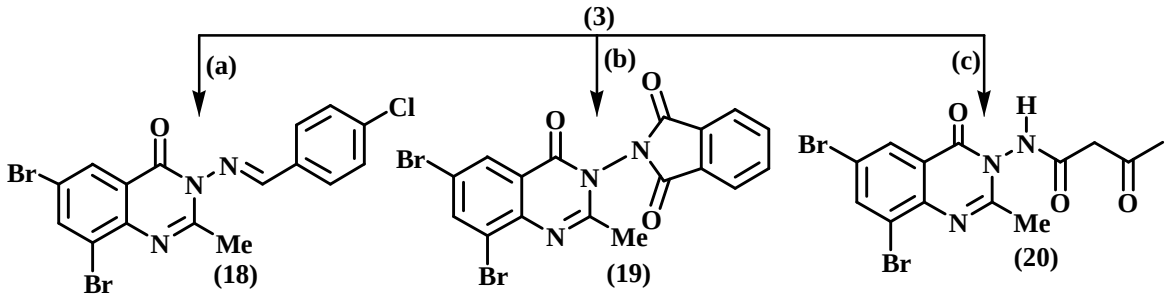
When hydrazide 8 was allowed to react with o-chlorobenzoic acid in the presence of phosphorous oxy chloride it yielded 2-methyl-4-[2-chlorobenzoyl aminocarbamoyl]-methoxy-quinazoline 13(SCHEME 3). The reaction possibly takes place via formation of the corresponding acid chloride in situ firstly followed by reaction with the hydrazide 8 via nucleophilic displacement through a tetrahedral mechanism.

In this investigation the author sought the behaviour of the compound 8 towards the aromatic aldehydes. Thus, when compound 8 reacted with 4-chlorobenzal dehyde, it produced the corresponding hydrazone[36] 14. The reaction possibly takes place via nucleophilic attack by the lone pair of nitrogen on the electronically deficient carbon of the carbonyl group followed by dehydration. No benzylidene derivative 15 or stilbazole derivative 16 were obtained. This is due to condensation with active methylene or methyl needs strong catalyst like sodium ethoxide for methylene group or anhydrous zinc chloride for active methyl group.

Herein, the author aimed to report a new methodology for the synthesis of functionalized biaryl-1,3,4-oxadiazole. Thus treatment of compound 14 with acetic anhydride afforded 2-(4-chlorophenyl)-5-[(6,8-bromo-2-methyl-quinazolin-4yl)oxymethyl]–1,2-dihydro-1,3,4-oxadiazole followed by acetylation at position 3 to give the corresponding 3-acetyl derivative 17 (SCHEME 4).

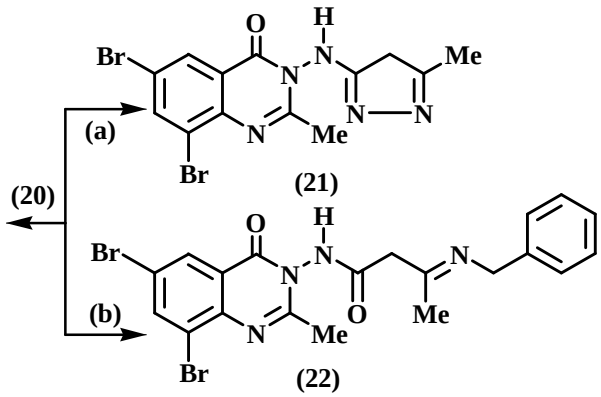
When 3-aminoquinazolinone 3 was allowed to react with 4-chlorobenzaldehyde and/or phthalic anhydride, it afforded 3-(4-chlorobenzylideneamino–6,8-dibromo-2-methylquinazolinone 18 and 6,8–dibromo-2–methyl–3–phthalimidoquinazolinone 19.

The quinazolinone 3 reacted with ethyl acetoacetate in boiling ethanol to give 3-actoacetylamino-6,8-dibromo-2–methyl–quinazolinone 20(SCHEME 5).



Reagents and Reaction conditions: (a) 4-ClC_6H_4CHO/fusion; (b) Phthalic anhydride/fusion; (c) $H_3COCH_2CO_2Et$/reflux

SCHEME 5



Reagents and Reaction conditions:
(a) N_2H_4/reflux;(b) $PhCH_2NH_2$/reflux

SCHEME 6

The reaction takes place *via* nucleophilic displacement on the carbonyl group of ethoxycarbonyl moiety through a tetrahedral mechanism.

In the present investigation, the behaviour of the 1,3-diketone 20 towards nitrogen nucleophiles has been studied. Thus, the interaction of compound 20 with hydrazine hydrate afforded 6,8–dibromo-2-methyl-3-[(3-methylpyrazol-5-yl)]aminoquinazolinone 21. The reaction possibly takes place *via* the fleeting intermediate hydrazone followed by cyclization.

On the other hand, when the quinazolinone 20 was allowed to react with benzylamine in refluxing ethanol, it afforded the condensation product 22 (SCHEME 6).

EXPERIMENTAL

Melting Points reported are uncorrected. IR spectra were recorded on Mattson infinity series FT-IR using KBr Wafer technique. ^{1}H-NMR spectra were determined on AC-250(200MHz.) Bruker. In all NMR experiments the internal standard was TMS. All chemical shifts are in ppm downfield from TMS. The mass spectra were determined using MS-TSQ 70 Finnegan MAT and GCMS-QP1000 EX Shimadza, Japan, EI = 70ev. The microanalytical data were measured in microanalytical unit of Faculty of Science, Cairo University. Elemental analyses gave satisfactory resultes. TLC were preformed on ready-to-use silica gel plates Merck 60 to moniterate the reactions and ascertain the purity of the new synthesized compounds. Compound 1 was prepared by a previously reported method[37].

6,8-Dibromo-2-methylquinazolin-4(3H)-one (2)

Method 1

A mixture of benzoxazinone 1 (3.19g; 0.01mol) and ammonium acetate (2.68g; 0.01mol) was fused in an oil bath at 160-170°C for 2 h. The reaction mixture was left to cool, washed with water several times, filtered off, dried and recrystallized from acetic acid to produce 2 [TABLE 1]; IR, ν(cm^{-1}): 3159, 3066 (NH), 1689(C=O), 1625 (C=N); ^{1}H-NMR(DMSO-d_6): δ 2.67(s, 3H, CH_3), 8.00, 8.20(2s, 2H, Ar-H), 8.76(s, 1H, NH, D_2O exchangeable).

Method 2

A solution of benzoxazinone 1(3.19g; 0.01mol) in formamide(50mL) was heated to reflux for 3h. The solid which separated out was cooled, filtered, dried and then recrystallized to give quinazolinone 2.

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

A mixture of benzoxazinone 1(3.19g; 0.01mole) and hydrazine hydrate(1.0g; 0.02mole) was heated under reflux in ethanol (30ml) for 6h. The reaction mixture was concentrated and then poured over ice/water. The solid that separated out, filtered off, washed with wa-

ter, dried and then recrystallized from butanol to afford quinazolinone 3[TABLE 1]; IR, ν(cm^{-1}): 3306, 3202 (NH), 1665(C=O), 1620(C=N); ^{1}H-NMR (DMSO-d_6): δ 2.70(s, 3H, CH_3), 8.02, 8.17 (2s, 2H, Ar-H), 4.55 (s, 2H, NH_2, D_2O exchangeable).

6,8-Dibromo-3(2-hydroxyethyl)-2-methylquinazolin -4(3H)-one (4)

An ethanolic solution of benzoxazinone 1(3.19g; 0.01mol) and ethanolamine (0.45g; 0.01 mol) was heated under reflux in ethanol (30ml) for 6h. Excess solvent was distilled off then poured onto ice/water. The solid that separated out, was filtered off, washed with water, dried and recrystallized from toluene to yield quinazolinone 4 [TABLE 1]. IR, ν (cm^{-1}): 3450 (OH), 1670(C=O), 1620(C=N); ^{1}H-NMR (DMSO-d_6): δ 2.71 (s, 3H, CH_3), 3.73(t, 2H, N-CH_2), 4.31 (t,2H, O-CH_2), 4.82 (s, 1H, OH, D_2O exchangeable), 8.00 and 8.20 (two s, 2H, ArH).

6,8-Dibromo-2-methyl-4H-benzo[d][1,3]thiazin-4-one (5)

A mixture of quinazolinone 2(3.17g; 0.01mol) and phosphorous pentasulfide in dioxane(30ml) was refluxed for 3h. The reaction mixture was left to cool then poured over ice/water. The solid that was separated out, filtered off, washed with water, dried and then crystallized from benzene yielding 5[TABLE 1]. IR, ν(cm^{-1}): 1695(C=O), 1614(C=N); ^{1}H-NMR(DMSO-d_6): δ2.68 (s, 3H, CH_3), 8.05, 8.20(2s, 2H, Ar-H); MS: m/e (%) 335(13.0), 334(96.6), 332 (51.0)320 (39.5), 302(19.2), 301(100), 260(10.1), 154(7.6) and 76 (43.0).

6,8-Dibromo-4-ethoxycarbonylmethoxy quinazoline (7)

To a mixture of quinazolinone 2(3.17g; 0.01mol) and ethyl chloroacetate (5.0g; 0.04mol) in dry acetone (50ml) was added anhydrous potassium carbonate (4.9g; 0.05mol) and the reaction mixture was refluxed on water bath for 24h. The excess solvent was removed by distillation and the residue poured into water with vigorous stirring. The solid that precipitated was filtered off, dried and then recrystallized from Light Petrol (80-100°C) to give the desired product 7[TABLE 1]. IR, ν(cm^{-1}): 1735(C=O ester), 1594(C=N), 1225(C-O); ^{1}H-NMR ($CDCl_3$): δ 1.20(t ,3H, CH_3 of ester), 2.67(s, 3H, CH_3 attached to the ring), 4.15(q, 2H, CH_2 of ester), 4.91(s, 2H, OCH_2 attached to the ring), and 8.05, and 8.22 (two s, 2H, Ar-H).

4-Aminocarbamoylethoxy-6,8-dibromo-2-methylquinazoline (8)

A mixture of quinazoline 7 (4.04 g; 0.01 mol) and hydrazine hydrate(1.0g; 0.02mol) in 50mL ethanol was heated under reflux for 6 h. The reaction mixture was concentrated, filtered off and then dried. The solid that separated out, was recrystallized from butanol to afford the product 8[TABLE 1]. IR, ν(cm^{-1}): 3342, 3260 (NH_2, NH), 1675(C=O), 1646(C=N); ^{1}H-NMR ($CDCl_3$): δ 2.66(s, 3H, CH_3 attached to the ring), 4.55 (br. s, 2H, NH_2, D_2O exchangeable), 4.91 (s, 2H, OCH_2 attached to the ring), and 8.00, and 8.20(two s, 2H, Ar-H), 8.9(br. s, 1 H, NH, D_2O exchangeable); MS: m/e(%), 491(0), 359(15.0), 345(50.7), 317 (39.1), 288(29.0), 261(17.9), 234(11.9), 155(33.2) and 76(10.8).

6,8–dibromo-4-dithiocarboxyaminocarbamoyl methoxy-2-methylquinazolin (9)

A mixture of quinazoline 8(3.9g; 0.01mol), potassium hydroxide(0.56g; 0.01mole) and carbon disulphide (1.52g; 0.02mol) in butanol (50 ml) was stirred at room temperature for 12 h. The residue that separated out after evaporation of solvent was poured into ice/HCl, the solid that deposited was filtered off, washed with water, dried and then recrystallized from benzene to yield the quinazoline 9[TABLE 1]. IR, ν(cm^{-1}): 3244, 3193(2NH), 2365(SH), 1675(C=O), 1316(C=S).

2Methyl-4-thiosemicarbazinocarbamoylmethoxy-6,8-dibromoquinazoline (10)

Hydrazine hydrate (1.0g; 0.02mol) was added to 9 (4.38g; 0.01mol) and fused at 240-250°C for 2h. The reaction mixture was triturated with ice/HCl. The solid that deposited was filtered off, washed with water, dried and recrystallized from ethanol to give the product 10 [TABLE 1]. IR, ν(cm^{-1}): 3440, 3307, 3252, 3212 (NH_2, NH), 2361 (SH), 1698 (C=O), 1616 (C=N); ^{1}H-NMR ($CDCl_3$): δ2.67(s, 3H, CH_3), 3.61(s, 3H, CH_2 and SH protons), 5.94 (s, NH, D_2O exchangeable) and 8.11, 8.28 (two s, 2H, Ar-H).

4-[3-thiopyrazole-5-one-4-yloxy]-4-methyl-6,8–dibromoquinazolin (11).

A mixture of quinazoline 8(3.9g; 0.01mol), potas-

sium hydroxide (0.56g; 0.01mol) and carbon disulfide (1.52g; 0.02mol) in butanol (50ml) was heated under reflux on water bath for 8h. The residue that remained out after evaporation of the solvent was poured into ice/HCl, the solid that precipitated was filtered off, washed with water, dried and then recrystallized from benzene to yield compound 11[TABLE 1]; IR, ν(cm^{-1}): 1681(C=O), 1620(C=N); ^{1}H-NMR (DMSO-d_6): δ 2.69(s, 3H, CH_3), 4.92(s, 1H, methine proton), 8.13 and 8.31 (two s, 2H, Ar-H).

Benzoaminocarbamoylmethoxy-6,8–dibromo-2-methylquinazolin (12)

Benzoyl chloride(1.40g; 0.02mole) was added to a solution of quinazoline 8(3.9g; 0.01mole) in dry pyridine (30ml) and the reaction mixture was refluxed for 8 h, left to cool then poured into ice/HCl. The solid that separated out, was filtered off, washed with water, dried and then recrystallized from toluene to afford the corresponding quinazoline 12 [TABLE 1]. IR, ν(cm^{-1}): 3264(NH), 1685(C=O); δ2.70(s, 3H ,CH_3), 5.32(s, 2H, CH_2), 7.43-7.63 (m, 5H, Ar-H, phenyl moiety) 8.21, 8.42(two s, 2H, Ar-H, quinazoline moiety), 10.11(s, 1H, NH, benzamide moiety, D_2O exchangeable), 10.85(s, 1H, acetamide moiety, D_2O exchangeable).

6,8–Dibromo-4-[2-chlorobenzoylaminocarbamoyl]-2-methylquinazolin (13).

A mixture of quinazoline 8 (3.9g; 0.01mol) and 2-chlorobenzoic acid (1.56g; 0.01mol) in phosphorous oxychloride(10ml) was heated under reflux for 8h. The reaction mixture was left to cool then poured onto ice/HCl. A pale brown precipitate was filtered off, washed with water several times, dried and then recrystallized from methanol yielding compound 13 [TABLE 1]; IR, ν(cm^{-1}): 3169(NH), 1691(C=O); ^{1}H-NMR(DMSO-d_6): δ 2.64(s, 3H ,CH_3), 5.23(s, 2H, CH_2), 7.39-7.60(m, 4H, Ar-H, phenyl moiety) 8.17, 8.32(two s, 2H, Ar-H, quinazoline moiety), 10.04(s, 1H, NH, benzamide moiety), 10.81(s, 1H, acetamide moiety).

N'-(4-Chlorobenzylidene)-2-(6,8-dibromo-2-methylquinazolin-4-yloxy)acetohydrazide (14).

To a solution of quinazoline 8(3.9g; 0.01mol) in butanol (50ml), p-chlorobenzaldehyde (1.47 g; 0.01 mol) was added. The reaction mixture was refluxed for 8 h, cooled then poured over ice /HCl. The solid that was separated out, filtered off, washed with water, dried and then recrystallized from ethanol to afford the adduct 14 [TABLE 1]; IR, ν (cm^{-1}): 3187 (NH), 1670 (C=O), 1605 (C=N); ^{1}H-NMR (DMSO-d_6): δ 2.69 (s, 3H,CH_3), 4.95 (d, 2H, OCH_2), 5.32 (s, 1H, N=CH), 7.53 and 7.81 (two d, 4H, Ar-H of phenyl moiety) 8.22 and 8.53 (two s, 2H, Ar-H of quinazoline moiety), and 11.92 (s, 1H, NH, D_2O exchangeable).

3-Acetyl-2(4-chlorophenyl)-5-[6,8-dibromo-2-methylquinazolin-4-yl]oxymethyl]dihydro-1,3,4-oxadiazole (17)

A solution of quinazoline 14(5.5g; 0.01mol) in acetic anhydride (15ml) was heated under reflux on water bath for 2 h. The reaction mixture was cooled then poured over ice/water. The solid that so formed was filtered off, washed with water, dried and crystallized from methanol forming the product 17[TABLE 1]. IR, ν(cm^{-1}): 1667(C=O), 1612(C=N); ^{1}H-NMR(DMSO-d_6): δ 2.11(s, 3H, acetyl proton), 2.73(s, 3H, CH_3 picolinic), 5.29(s, 2H, OCH_2), 7.48 and 7.89 (two doublets 4H, ArH of phenyl moiety), 8.12 and 8.73 (two s, 2H, Ar-H of quinazoline moiety).

3-(4-Chlorobenzylideneamino)-6,8-dibromo-2-methylquinazolin-4(3H)-one (18) and 2-(6,8-dibromo-2-methyl-4-oxoquinazolin-3(4H)-yl)isoindoline-1,3-dione (19)

A mixture of hydrazide 3(3.3g; 0.01mol) and p-chlorobenzaldehyde and/or phthalic anhydride (0.01 mol) with few drops of piperidine was fused in sand bath at 170-180^{0}C for 2h. The reaction mixture was triturated with ice/HCl. The crude solid product was filtered off, washed with water, dried and then recrystallized from benzene affording compounds 18 and 19, respectively [TABLE 1]. 18; IR, ν(cm^{-1}): 1673(C=O), 1633 (C=N); ^{1}H-NMR (DMSO-d_6): δ 2.67 (s, 3H,CH_3), 4.92 (d, 2H, OCH_2), 5.36(s, 1H, N=CH), 7.51 and 7.78(two d, 4H, Ar-H of phenyl moiety) 8.18 and 8.39(two s, 2H, Ar-H of quinazoline moiety); MS: m/e (%) 455 (0) 441 (100), 440(75.5), 361 (10.2), 281(3.0), 137(96.3), 143(4.2), 111(11.6), 102 (49.7) and 76 (14.1). 19; IR, ν(cm^{-1}): 1796, 1748, 1709 (C=O and mechanical coupling of two C=O of imide moiety), 1613(C=N); ^{1}H-NMR(DMSO-d_6): δ 2.66(s, 3H, CH_3), 7.48-7.70(m, 4H, Ar-H, phthalimde moiety), 8.10, 8.29(2s, 2H, Ar-H of quinazoline moiety); MS: m/e(%) 463 (100), 421 (26.5), 302(31.9), 275(24.3),

TABLE 1 : Physical data of products

Compound	M.P. (Colour)	Solvent of crystallization (yield%)	M.F. (M.wt.)	Analysis calc./found C%	H%	N%
2	310-312	Acetic acid	$C_9H_6N_2OBr_2$	33.96	91.8	8.81
	grey	70	318	033.8	1.84	8.78
3	238-240	Butanol	$C_9H_7N_3OBr_2$	32.43	2.10	12.61
	white	65	333	32.22	2.05	12.56
4	160	Toluene	$C_{11}H_{10}N_2O_2Br_2$	36.46	2.76	7.73
	grey	69	362	36.50	2.68	7.65
5	262 –265	Benzene	$C_9H_5NOSBr_2$	432.2	1.49	4.18
	white	60	335	31.59	1.48	4.05
7	160–162	L.Petrol (80-100^{0}C)	$C_{13}H_{12}N_2O_3Br_2$	38.61	2.97	6.93
	white	74	404	38.49	3.00	6.85
8	300	Butanol	$C_{11}H_{10}N_4O_2Br_2$	533.8	2.56	14.36
	white	64	390	33.70	2.52	14.28
9	264-267	Benzene	$C_{12}H_{10}N_4O_2S_2Br_2$	30.90	2.15	12.02
	green	55	466	29.80	1.99	12.30
10	220-222	Ethanol	$C_{12}H_{12}N_6O_2SBr_2$	31.03	92.5	18.10
	white	60	464	30.12	2.60	17.80
11	190-191	Benzene	$C_{12}H_6N_4O_2SBr_2$	33.49	1.40	13.02
	yellow	50	430	33.20	1.35	12.80
12	260-262	Toluene	$C_{18}H_{14}N_4O_3Br_2$	43.72	2.83	411.3
	white	69	494	43.80	2.81	11.20
13	274–276	Methanol	$C_{18}H_{13}N_4O_3Br_2Cl$	40.87	62.4	6010.
	white	48	528.5	40.77	2.43	10.52
14	228-230	Ethanol	$C_{18}H_{13}N_4O_2Br_2Cl$	42.15	2.54	10.93
	white	55	512.5	41.97	2.51	10.89
17	222–224	Methanol	$C_{20}H_{15}N_4O_3Br_2Cl$	43.28	12.7	1010.
	white	72	554.5	43.19	2.73	10.2
18	252-254	Benzene	$C_{16}H_{10}N_3OBr_2Cl$	42.15	2.20	9.22
	yellow	63	455.5	41.80	2.17	9.01
19	230-232	Benzene	$C_{17}H_9N_3O_3Br_2$	44.06	1.94	9.07
	white	60	463	44.21	1.91	9.12
20	150-152	L.P/ Benzene.	$C_{13}H_{11}N_3O_3Br_2$	37.41	2.64	10.07
	white	75	417	37.21	2.61	10.01
21	234–236	Ethanol	$C_{13}H_{11}N_5OBr_2$	37.77	2.66	516.9
	white	88	413	36.90	2.54	17.10
22	210	Benz./Ethanol	$C_{20}H_{18}N_4O_2Br_2$	347.4	63.5	.0711
	white	72	506	48.59	3.39	10.98

160(7.3), 104(63.0), 90(35.7) and 76 (69.1).

3-Acetoacetylamino-6,8-dibromo-2-methylquinazolinone (20)

A mixture of hydrazide 3(3.3g; 0.01mol) and ethyl acetoacetate(1.28g; 0.01mol) was fused in sand bath at 190-200^{0}C for 2h. The reaction mixture was triturated with ice/HCl. The crude solid product was filtered off, washed with water several times, dried and then recrystallized from L.P/ benzene to afford the product 20[TABLE 1]. IR, ν(cm^{-1}): 3173(NH), 1663(C=O acetyl), 1651(C=O amide), 1628(C=N); ^{1}H-NMR (DMSO-d$_6$): δ 2.14(s, 3H, $COCH_3$), 2.65(s, 3H, CH_3), 3.67(s, 2H, CH_2), 8.11, 8.33(2s, 2H, Ar-H of quinazoline moiety), 9.21 (s, 1H, NH, D_2O exchangeable).

3-(5-Methyl-4H-pyrazol-3-ylamino)-6,8-dibromo-2-methylquinazolin-4(3H)-one (21)

A mixture of 20 (4.17g; 0.01mol) and hydrazine hydrate(1.0g; 0.02mol) in ethanol (30ml) was heated under reflux for 6h. The reaction mixture was concentrated and left to cool. The solid so formed was filtered off, washed with ethyl alcohol, dried and then recrystallized from ethanol to yield the product 21[TABLE 1]. IR, ν(cm^{-1}): 3249, 3200(NH bonded and non bonded), 1668(C=O), 1603(C=N); ^{1}H-NMR (DMSO -d$_6$): δ 2.42 and 2.51 (two s, 8H, 2CH_3 and methylene protons), 5.83(s, 1H, NH), 8.15, 8.33(two s, 2H, Ar-H).

3-(Benzylimino)-N-(6,8-dibromo-2-methyl-4-oxoquinazolin-3(4H)-yl)butanamide (22)

A solution of 20 (4.17g; 0.01mol) and benzyl amine (2.1g; 0.01mol) in ethanol (30ml) was refluxed for 6h. The reaction mixture was concentrated and left to cool. The solid that separated out was filtered off, washed with ethyl alcohol, dried and then recrystallized from benzene /ethanol to give compound 22[TABLE 1]. IR, ν (cm^{-1}): 3305, 3202 (NH bonded and non bonded), 3075, 3002(CHar.), 2970(CHal.), 1696 (C=O quinazolinone), 1668 (C=O amide), 1603(C=N); ^{1}H-NMR ($CDCl_3$): δ1.96 (s, 2H, CH_2Ph), 2.62 (s, 3H, N=C-CH_3), 2.75 (s, 3H, CH_3 of quinazolinone ring), 4.94 (s, 2H, -CO-CH_2-C=N) 7.10-7.25 & 8.05-8.20 (two m, 7H, ArH) 4.63 and 9.49(two s, -NH-CO- and -N=C-OH, D_2O exchangeable).

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