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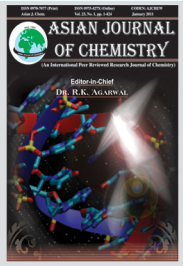

Synthesis and Reactions of 2-Carboxyvinyl-4-chloro-6,8-dibromoquinazoline and Some New Fused Triazolo-quinazoline Derivatives

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Synthesis of the 2-carboxyvinyl-4-chloro-6,8-dibromoquinazoline (**2**) has been established based on chlorination of the corresponding 6,8-dibromoquinazoline analogue. The simple replacement of the chlorine atom at 4-position of quinazoline nucleus with different amines has produced compounds of the type 4-heteroaryl-quinazoline derivatives and the fused [2-carboxyvinyl-6,8-dibromo quinazoline]-[quinazolin-4-one]. The reaction of the titled chloro-quinazoline derivative (**2**) with hydrazine hydrate and subsequent condensation with different aromatic aldehydes is furnished a series of fused 5-substituted-1,2,4-triazolo-quinazoline derivatives. Finally, its reaction with acyl hydrazide mainly, acetyl hydrazide is furnished the non-mixed heterocyclic system called 5-methyl-1,2,4-triazolo[4,3-c](6,8-dibromo-2-carboxyvinyl)quinazoline.

Key Words: 4-Chloroquinazoline, 4-Heteroarylquinazolines, Triazolo-quinazolines.

INTRODUCTION

Divers biological activity are encountered in organic compounds containing the quinazoline system[1-8]. Moreover, many fused quinazoline derivatives are found to exhibited remarkable pharmacological agents[9]. The present work is an extension of our engoing efforts towards the development of a series of new substituted quinazoline derivatives as a source of functionalized molecules interested in many biological applications. Furthermore, many studies suggested this class of compounds are pharmaceutically active heterocyclic compounds. The entire structure of them was required, but activity is further enhanced by introducing halide substituent at position-6 and 8[10-12]. This information prompted us to construct the 6,8-dibromo-substituted quinazoline derivative (**2**).

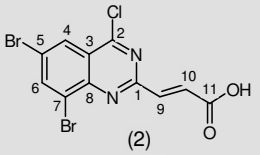
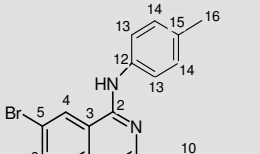
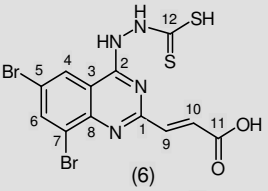
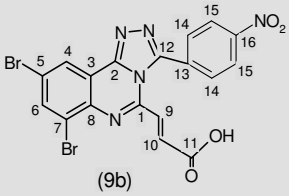
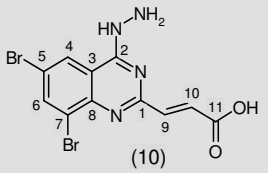
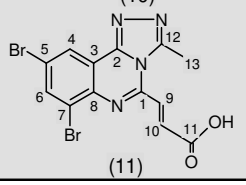
EXPERIMENTAL

General procedure: All melting points reported are uncorrected and were determined on a Stuart electric melting point apparatus. Elemental analysis were carried out in the Micro Analytical Center, Cairo University, Giza, Egypt. IR spectra (in KBr, cm^{-1}) were recorded on λ FTIR 8201PC Shimadzu (Japan, 1995). ^1H NMR spectra recorded in $CDCl_3$ or DMSO-d_6 on a Varian 300 MHz (Germany, 1999). TMS was used as an internal standard with chemical shifts δ in ppm from downfield to upfield. Disappearance of carboxylic proton in ^1H NMR of some compounds may be due to polymeric association or dimeric association involving hydrogen bonding results deshielding which causes resonance to move downfield (δ ≈ 13.5 out of our scale). ^{13}C NMR spectra were recorded on the same spectrometer for some synthesized compounds are given in Table-1. EIMS were recorded on a gas chromatographic GCMS-Qploopx Shimadzu (Japan, 1990).

2-Carboxyvinyl-4-chloro-6,8-dibromoquinazoline (2): A solution of quinazolinone derivative **1** (3.73 g, 0.01 mol) and 1 g of phosphorus pentachloride in phosphorus oxychloride (20 mL) was heated in water bath at 70 ºC for 2 h. The reaction mixture was cooled and diluted with ice water and the resulted precipitate was collected by filtration and crystallized from chloroform to give **2**. Yield 67 %. m.p. 246-248 ºC. IR (KBr, ν_{max}, cm^{-1}) 1626 (C=N), 1685 (CO), 3013 (CH-arom.) and 3430 (OH). ^1H NMR (DMSO-d_6) δ 6.42 (d, 1H, vinyl-H), 7.06 (d, 1H, vinyl-H), 8.12 (s, 1H, Ar-H), 8.72 (s, 1H, Ar-H). Anal. calcd. (%) for $C_{11}H_5N_2O_2Br_2Cl$ (m.w. 392.4): C, 33.67; H, 1.28. Found (%): C, 33.92; H, 1.43. MS: m/z 394 $[M + 2]^+$, 392 $[M^+]$, 332, 236, 196, 57.

2-Carboxyvinyl-6,8-dibromo-4-(*p*-tolylamino)quinazoline (3): A mixture of chloroquinazoline **2** (3.92 g, 0.01 mol) and 4-methylaniline (1.07 g, 0.01 mol) in ethanol (30 mL) and few drops of piperidine was heated under reflux at 70 ºC for 6 h. The reaction mixture was concentrated, cooled and the solid obtained was filtered off and recrystallized from *n*-butanol to give **3**. Yield 68 %. m.p. 340-341 ºC. IR (KBr, ν_{max}, cm^{-1}) 1625 (C=N), 1687 (CO), 2939 (CH-aliph.), 3057

TABLE-1
^{13}C NMR OF SOME SYNTHESIZED COMPOUNDS

δ (ppm) carbon atom number	Structure formula and compound number
δ 114 (C-5), 117 (C-3), 121 (C-7), 135 (C-6 and C-10), 138 (C-4 and C-9), 146 (C-8), 152 (C-2), 155 (C-1), 168 (C-11)	 (2)
δ 23 (C-16), 107 (C-13), 111 (C-3), 116 (C-5 and C-7), 129 (C-15), 132 (C-14 and C-9), 134 (C-6 and C-10), 144 (C-4), 146 (C-8), 152 (C-1), 159 (C-2 and C-12), 167 (C-11).	 (3)
δ 106 (C-8), 108 (C-7 and C-5), 131 (C-9), 133 (C-6 and C-10), 142 (C-4), 148 (C-8), 156 (C-1), 161 (C-2), 167 (C-11), 201 (C-12).	 (6)
δ 109 (C-7), 125 (C-3), 128 (C-5), 129 (C-9 and C-4), 132 (C-14), 136 (C-13), 137 (C-6 and C-10), 139 (C-12 and C-15), 141 (C-16), 148 (C-8), 154 (C-2), 157 (C-1), 169 (C-11).	 (9b)
δ 108 (C-3), 110 (C-7), 113 (C-5), 127 (C-9 and C-10), 133 (C-6), 135 (C-4), 147 (C-8), 157 (C-1), 161 (C-1), 168 (C-11).	 (10)
δ 16 (C-13), 116 (C-3), 122 (C-3), 126 (C-5), 129 (C-4 and C-9), 131 (C-10), 132 (C-12), 136 (C-6), 148 (C-8), 157 (C-2), 159 (C-1), 172 (C-11).	 (11)

(CH-arom.) and 3157 (NH). ^{1}H NMR (DMSO-d_6) δ 2.17 (s, 3H, CH_3), 6.41 (d, 1H, vinyl-H), 6.95 (m, 4H, Ar-H), 7.67 (d, 1H, vinyl-H), 8.05 (s, 1H, Ar-H), 8.42 (s, 1H, Ar-H), 9.13 (brs, 1H, NH), 11.70 (s, 1H, OH). Anal. calcd. for $C_{18}H_{13}N_3O_2Br_2$ (m.w. 463.1): C, 46.68; H, 2.83. Found (%): C, 46.25; H, 2.96.

2-Carboxyvinyl-6,8-dibromo-4-(2-hydroxyethylamino)-quinazoline (4): A solution of chloroquinazoline **2** (3.92 g, 0.01 mol) and ethanolamine (0.92 g, 0.015 mol) in DMF (20 mL) was heated under reflux for 4 h. The reaction mixture after cooling was poured on cold water and the solid that separated was collected and recrystallized from ethanol to give **4**. Yield 72 %. m.p. 334 ºC. IR (KBr, ν_{max}, cm^{-1}) 1624 (C=N), 1683 (CO), 2941 (CH-aliph.), 3065 (CH-arom.), 3162 (NH) and 3426 (OH). ^{1}H NMR (DMSO-*d*6) δ 3.58 (m, 4H, $2CH_2$), 4.53 (s, 1H, NH), 6.31 (brs, 1H, OH), 6.35 (d, 1H, vinyl-H), 7.19 (d, 1H, vinyl-H), 8.06 (d, 2H, Ar-H), 11.87 (s, 1H, OH). Anal. calcd. (%) for $C_{13}H_{11}N_3O_3Br_2$ (m.w. 417.1): C, 37.44; H, 2.66. Found (%): C, 37.82; H, 2.51.

2-Carboxyvinyl-6,8-dibromo-4-piperidinoquinazoline (5): A mixture of chloroquinazoline **2** (3.92 g, 0.01 mol) and piperidine (1.73 g, 0.02 mol) was heated at 140 ºC for 5 min. then 20 mL of ethanol was added and the reaction mixture was refluxed for 2 h. The excess solvent was distilled off and the solid that separated after cooling was collected and recrystallized from ethanol to give **5**. Yield 65 %. m.p. 287-289 ºC. IR (KBr, n_{max}, cm^{-1}) 1625 (C=N), 1686 (CO), 2939 (CH-aliph.) and 3054 (CH-arom.). ^{1}H NMR (DMSO-d_6) δ 1.64 (m, 5H, piperdine-H), 3.42 (dd, 4H, $2CH_2$), 6.41 (d, 1H, vinyl-H), 6.84 (d, 1H, vinyl-H), 7.94 (s, 1H, Ar-H), 8.20 (s, 1H, Ar-H), 11.32 (s, 1H, OH). Anal. calcd. (%) for $C_{16}H_{15}N_3Br_2O_2$ (m.w. 441.1): C, 43.56; H, 3.43. Found (%): C, 43.89; H, 3.52. MS: m/z 443 $[M + 2]^+$, 441 $[M^+]$, 397, 358, 288, 236, 55.

2-Carboxyvinyl-6,8-dibromo-4-(N-dithiocarboxy-hydrazino and/or thioureido)quinazoline (6 and 7): An equimolar mixture of compound **2** (3.92 g, 0.01 mol) and thiodicarbamyl hydrazine and/or thiourea (0.01 mol) in N,N-dimethylformamide (30 mL) was heated under reflux at 100 ºC for 4 h. The reaction mixture after cooling was poured over cold water and the precipitate that separated was filtered off and crystallized from DMF and touluene to give **6** and **7**, respectively.

Compound 6: Yield 74 %. m.p. 328 ºC. IR (KBr, ν_{max}, cm^{-1}) 158 (C-S), 1625 (C=N), 1683 (CO), 3064 (CH-arom.) and 3162 (NH). ^{1}H NMR (DMSO-d_6) δ 2.55 (s, 1H, SH), 6.48 (d, 1H, vinyl-H), 7.12 (d, 1H, vinyl-H), 8.07 (s, 1H, Ar-H), 8.38 (s, 1H, Ar-H), 9.19 (s, 2H, NH). Anal. calcd. (%) for $C_{12}H_8N_4O_2S_2Br_2$ (m.w. 464.1): C, 31.05; H, 1.74. Found (%): C, 31.46; H, 1.52.

Copound 7: Yield 56 %. m.p. 312 ºC. IR (KBr, ν_{max}, cm^{-1}) 1258 (C-S), 1624 (C=N), 1685 (CO), 3063 (CH-arom.), 3160, 3276 (NH) and 3477 (OH). ^{1}H NMR (DMSO-d_6) δ 6.37 (d, 1H, vinyl-H), 7.06 (d, 1H, vinyl-H), 8.22 (d, 2H, Ar-H), 8.62 (s, 3H, NH). Anal. calcd. (%) for $C_{12}H_8N_4O_2SBr_2$ (m.w. 432.1): C, 33.36; H, 1.87. Found (%): C, 33.71; H, 1.95. MS: m/z 388 $[M\text{-}CO_2]^+$, 372, 313, 234, 75.

6-Carboxyvinyl-2,4-dibromo-8-oxo-8*H*-quinazolino-[4,3-b]quinazoline (8): An equimolar amounts of chloro compound **2** and 2-aminobenzoic acid (0.01 mol) in N,N-dimethylformamide (30 mL) was heated under reflux at 100 ºC for 2 h. The reaction mixture was cooled down and few drops of concentrated H_2SO_4 was added with stirring at room temperature and stirring was continued for 2 h. Then the reaction mixture was poured over ice water and the solid that formed was collected and recrystallized from *n*-butanol to give **8**. Yield 47 %. m.p. 345-347 ºC. IR (KBr, ν_{max}, cm^{-1}) 1626 (C=N), 1667, 1687 (CO) and 3478 (OH). ^{1}H NMR (DMSO-d_6) δ 6.82 (d, 1H, vinyl-H), 7.47 (t, 1H, Ar-H), 7.73 (d, 1H, vinyl-H), 8.01 (m, 4H, Ar-H), 8.17 (s, 1H, Ar-H), 10.94 (brs, 1H, OH). Anal. calcd. (%) for $C_{18}H_9N_3O_3Br_2$ (m.w. 475.1): C, 45.51; H, 1.91. Found (%): C, 45.74; H, 2.13.

5-Carboxyvinyl-7,9-dibromo-3-(substituted-phenyl)[1,2,4]-triazolo[4,3-c]quinazoline (9a-e)

Procedure (a): A mixture of compound **2** (3.92 g, 0.01 mol), hydrazine hydrate (0.75 g, 0.015 mol) and aromatic aldehydes namely, 4-chlorobenzaldehyde, 4-nitrobenzaldehyde,

4-methylbenzaldehyde, 2-chlorobenzaldehyde and/or 4-methoxybenzaldehyde in 20 mL of N,N-dimethylformamide was refluxed for 4 h. The reaction mixture was concentrated, cooled and the residue was poured over cold water. The solid that formed was filtered off and crystallized from the suitable solvent to afford **9a-e**.

Procedure (b): A mixture of 4-hydrazinoquinazoline **10** (3.88 g, 0.01 mol) and aromatic aldehydes namely, 4-chlorobenzaldehyde, 4-nitrobenzaldehyde, 4-methylbenzaldehyde, 2-chlorobenzaldehyde and/or 4-methoxybenzaldehyde in glacial acetic acid (30 mL) was heated under reflux for 6 h. The excess solvent was distilled off and residue was leaved overnight, then the solid that separated was collected, dried and crystallized from the proper solvent to give **9a-e**.

Compound 9a: Yield 61 %. m.p. 280 ºC. IR (KBr, ν_{max}, cm^{-1}) 1628 (C=N), 1687 (CO), 3057 (CH-arom.). ^1H NMR ($CDCl_3$) δ 6.54 (d, 1H, vinyl-H), 7.48 (d, 2H, Ar-H), 7.84 (m, 3H, Ar-H and vinyl-H), 8.32 (s, 1H, Ar-H), 8.61 (s, 1H, Ar-H), 11.70 (s, 1H, OH). Anal. calcd. (%) for $C_{18}H_9N_4O_2Br_2Cl$ (m.w. 508.6): C, 42.51; H, 1.78. Found (%): C, 42.32; H, 1.94.

Compound 9b: Yield 69 %. m.p. 213-215 ºC. IR (KBr, ν_{max}, cm^{-1}) 1623 (C=N), 1682 (CO) and 3057 (CH-arom.). ^1H NMR ($CDCl_3$) δ 6.47 (d, 1H, vinyl-H), 8.05 (m, 5H, Ar-H and vinyl-H), 8.90 (d, 2H, Ar-H), 11.92 (s, 1H, OH). Anal. calcd. (%) for $C_{18}H_9N_5O_4Br_2$ (m.w. 519.1): C, 41.65; H, 1.75. Found (%): C, 41.86; H, 1.89.

Compound 9c: Yield 57 %. m.p. 288-289 ºC. IR (KBr, ν_{max}, cm^{-1}) 1625 (C=N), 1684 (CO), 2941 (CH-aliph.) and 3055 (CH-arom.). ^1H NMR (DMSO-d_6) δ 2.19 (s, 3H, CH_3), 6.51 (d, 1H, vinyl-H), 7.17 (d, 2H, Ar-H), 7.39 (d, 2H, Ar-H), 7.98 (m, 3H, Ar-H and vinyl-H), 11.80 (s, 1H, OH). Anal. calcd. (%) for $C_{19}H_{12}N_4O_2Br_2$ (mw. 488.1): C, 46.75; H, 2.48. Found (%): C, 46.97; H, 2.73.

Compound 9d: Yield 49 %. m.p. 261-263 ºC. IR (KBr, ν_{max}, cm^{-1}) 1626 (C=N), 1688 (CO) and 3057 (CH-arom.). ^1H NMR (DMSO-d_6) δ 6.38 (d, 1H, vinyl-H), 7.44 (m, 4H, Ar-H), 7.89 (d, 1H, vinyl-H), 8.24 (s, 1H, Ar-H), 8.59 (s, 1H, Ar-H). Anal. calcd. (%) for $C_{18}H_9N_4O_2Br_2Cl$ (m.w. 508.6): C, 42.51; H, 1.78. Found (%): C, 42.82; H, 2.07.

Compound 9e: Yield 72 %. m.p. 319 ºC. ^1H NMR (DMSO-d_6) δ 3.92 (s, 3H, OCH_3), 6.44 (d, 1H, vinyl-H), 6.78 (d, 2H, Ar-H), 8.06 (m, 5H, Ar-H and vinyl-H), 11.86 (s, 1H, OH). Anal. calcd. (%) for $C_{19}H_{12}N_4O_3Br_2$ (m.w. 504.1): C, 45.27; H, 2.40. Found (%): C, 45.44; H, 2.53.

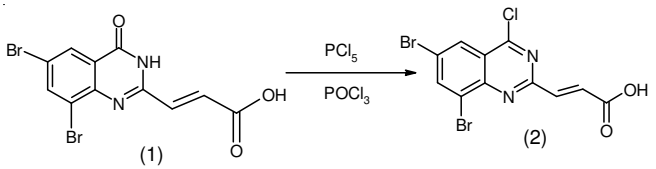
2-Carboxyvinyl-6,8-dibromo-4-hydrazinoquinazoline (10): A solution of compound **2** (3.92 g, 0.01 mol) and hydrazine hydrate (0.75 g, 0.015 mol) in absolute ethanol (30 mL) in presence of few drops of piperidine was heated under reflux at 70 ºC for 6 h. The excess solvent was distilled off under reduced pressure and the solid that obtained after cooling was collected and crystallized from *n*-butanol to afford **10**. Yield 81 %. m.p. 352 ºC. IR (KBr, ν_{max}, cm^{-1}) 1627 (C=N), 1686 (CO), 3060 (CH-arom.) and 3160, 3308 (NH). ^1H NMR (DMSO-d_6) δ 4.95 (s, 3H, NH), 6.32 (d, 1H, vinyl-H), 6.87 (d, 1H, vinyl-H), 8.06 (d, 2H, Ar-H), 11.74 (s, 1H, OH). Anal. calcd. (%) for $C_{11}H_8N_4O_2Br_2$ (m.w. 388.0): C, 34.05; H, 2.08. Found (%): C, 33.86; H, 2.19.

5-Carboxyvinyl-7,9-dibromo-3-methyl-[1,2,4]triazolo-[4,3-c]quinazoline (11): A solution of chloro compound **2** (3.92 g, 0.01 mol) and acetyl hydrazide (1.01 g, 0.015 mol) in glacial acetic acid (20 mL) and 5 mL of freshly distilled acetic acid anhydride was heated at 110 ºC for 5 h. The excess solvent was distilled off and the solid that separated after cooling was filtered off, washed with light pet. ether (60-80º) and recrystallized from *n*-butanol to afford **11** in 84 % yield.

Another procedure: A solution of 4-hydrazinoquinazoline **10** (3.88 g, 0.01 mol) in freshly distilled acetic acid anhydride (10 mL) was heated in water bath at 70 ºC for 3 h. The reaction mixture was cooled and the solid that formed was collected washed with light pet. ether (60-80º) and crystallized from *n*-butanol to give **11**. Yield 76 %. m.p. 307-308 ºC. IR (KBr, ν_{max}, cm^{-1}) 1626 (C=N), 1679 (CO), 2939 (CH-aliph.) and 3057 (CH-arom.). ^1H NMR (DMSO-d_6) δ 3.16 (s, 3H, CH_3), 6.49 (d, 1H, vinyl-H), 7.94 (d, 1H, vinyl-H), 8.32 (s, 1H, Ar-H), 8.53 (s, 1H, Ar-H), 11.84 (s, 1H, OH). Anal. calcd. (%) for $C_{13}H_8Br_2N_4O_2$ (m.w.): C; H. Found (%): C, H.

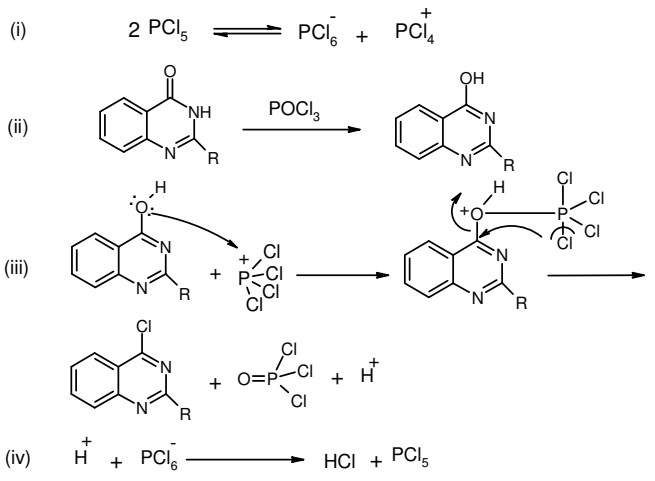
RESULTS AND DISCUSSION

The synthesis of 2-carboxyvinyl-4-chloro-6,8-dibromoquinazoline (**2**) has been established based on chlorination of the corresponding 6,8-dibromoquinazoline analogue (1) [quinazolinone (**1**) was prepared according to reported method[13]] using a mixture of phosphorus oxychloride and phosphorus pentachloride in boiling water bath (**Scheme-I**).



Scheme-I

It was found that, the iminol form is the favoured conformer for chlorination and $POCl_3$ has the role to furnish this species and the reaction is proceeding *via* the following suggested reaction mechanism (**Scheme-II**).



Scheme-II

Recently, it was reported that 4-substituted-aminoquinazolines are exploited as a potent antitumor (human breast carcinoma cell line in which EGFR is highly expressed)[14]. In this circumstance, condensation of chloroquinazoline derivative (**2**) with primary amines namely, 4-methylaniline and ethanol amine is afforded the aryl/alkyl amino derivatives **3** and **4** in 68 and 72 % yield, respectively. While in case of secondary amines like piperidine it affords the 4-piperidino-6,8-dibromo-2-carboxyvinylquinazoline (**5**) in 65 % yield. Nucleophilic substitution of the chloroquinazoline derivative (**2**) with thiadicar-bamyl hydrazine and thiourea in acidic media results the corresponding amino derivatives **6** and **7** in 74 and 56 % yield, respectively (**Scheme-III**).

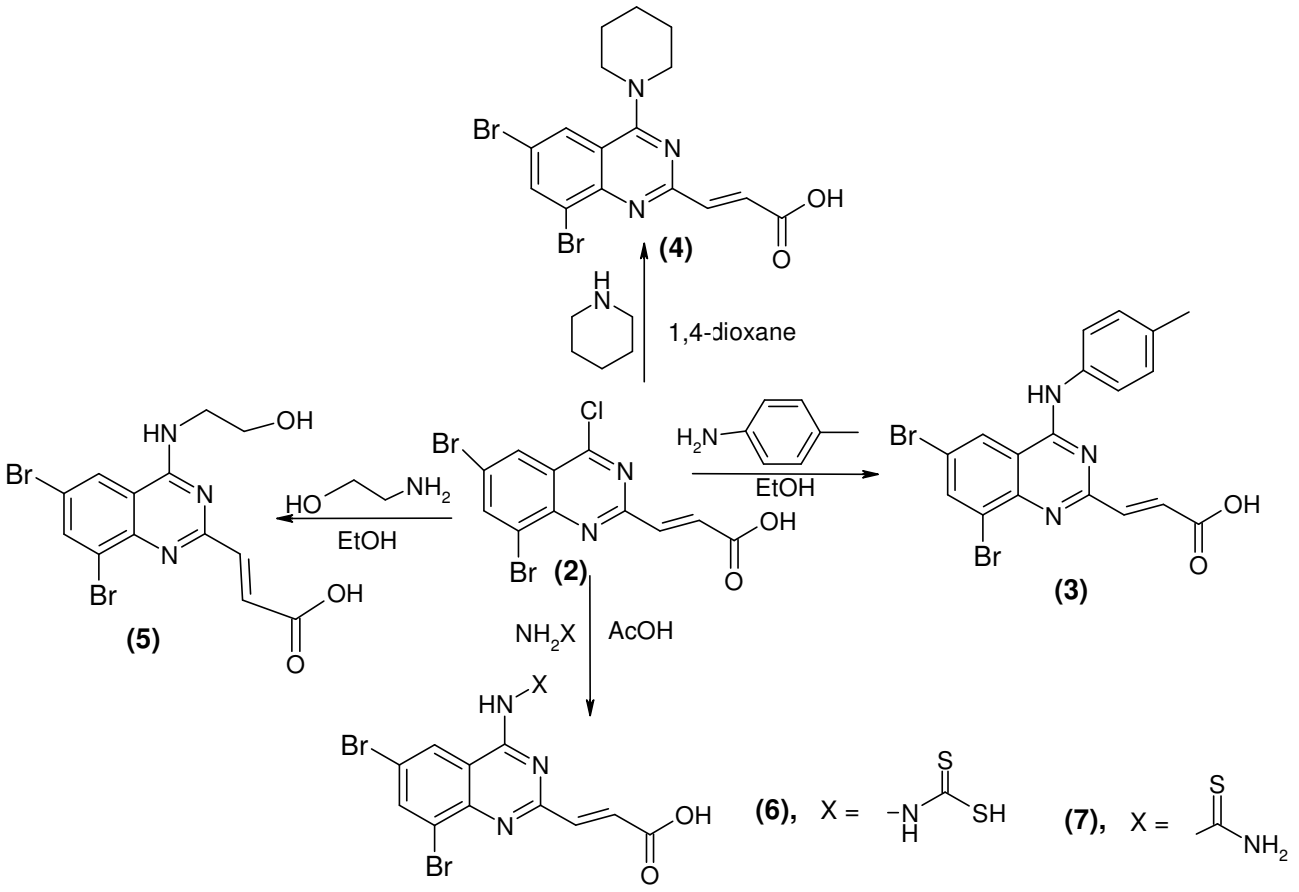
Interaction of 2-substituted chloroquinazoline with 2-amino benzoic acid was reported[15] to proceed *via* fusion in an oil bath at 170 ºC with poor to moderate yield. Herein we establish a more convenient method which provide the target molecule with good yield per cent. In this context, refluxing the titled chloroquinazoline (**2**) with 2-amino benzoic acid in 1,4-dioxane followed by treatment with few drops of concentrated sulphuric acid with continuous stirring at room temperature resulted in the fused [2-carboxyvinyl-6,8-dibromoquinazoline]-[quinazolin-4-one] (8) in 58 % yield (**Scheme-IV**).

A series of triazolo-quinazoline derivatives are proved as a new class of H_1-antihistaminic[16]. A successful attempt for hydrazinolysis of the titled chloro compound **2** was achieved, where its reaction with hydrazine hydrate and subsequent condensation with different aromatic aldehydes namely, 4-chlorobenzaldehyde, 4-nitrobenzaldehyde, 4-methylbenzaldehyde, 2-chlorobenzaldehyde and 4-methoxybenzaldehyde is furnished a series of fused 5-substituted-1,2,4-triazolo-quinazoline derivatives **9a-e** in good yield. Formation of the cyclic product is indicated by the absence of peaks due to NH and NH_2 in FT-IR spectra of **9a-e** compounds, as well as the ^{1}H NMR of **9a-e** showed also the absence of NH and NH_2 signals. Furthermore, the course of this reaction is chemically confirmed *via* constructing the 4-hydrazinoquinazoline system **10** in 73 % yield as an isolated intermediate. Therefore, the obtained hydrazinoquinazoline **10** is submitted to react with the above mentioned aromatic aldehydes and resulted in the 1,2,4-triazolo-quinazoline derivatives **9a-e** in higher yields (**Scheme-IV**).

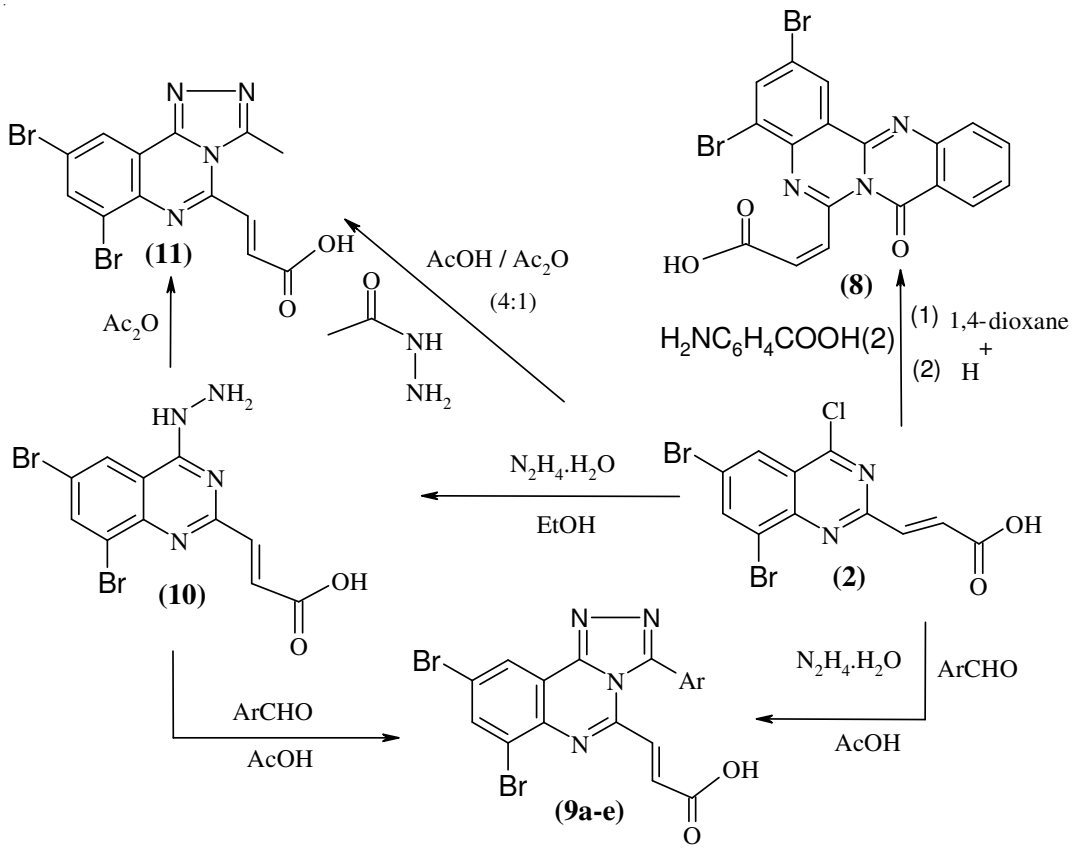
Finally, the reaction of the titled chloroquinazoline **2** with acyl hydrazide mainly, acetyl hydrazide in a mixture of glacial acetic acid and freshly distilled acetic acid anhydride (4:1) at 110 ºC is furnished the non-mixed heterocyclic system called 5-methyl-1,2,4-triazolo[4,3-c](6,8-dibromo-2-carboxyvinyl)-quinazoline **11** in 84 % yield (**Scheme-IV**).

Conclusion

We have established a novel convenient procedure for obtaining **2** in excellent yield based on lactam-lactim dynamic equilibrium. Its behaviour towards nitrogen replacement reactions revealed that, the presence of hydrolyzable chlorine atom at 4-position exerted a functionalized series of fused-quinazoline derivatives with significant reactivity.



Scheme-III



Ar = -C_6H_4.Cl(4) , -C_6H_4.NO_2(4) , -C_6H_4.Cl(4) ,
-C_6H_4.CH_3(4), -C_6H_4.OMe(4) , -C_6H_4.Cl(2)

Scheme-IV

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