Scientific paper

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

**Yaser Abdel-Moemen El-Badry**

*Organic Chemistry Deptartment, Faculty of Pharmacy, Ain Shams University, 11566 Abbasseya, Cairo, Egypt*

** Corresponding author: E-mail: yaser75moemen@yahoo.com*

*Received: 12-03-2010*

## Abstract

Synthesis of 2-carboxyvinyl-4-chloro-6,8-dibromoquinazoline (**2**) has been achieved via chlorination of the corresponding 6,8-dibromoquinazoline analog. The simple replacement of the chlorine atom at the position 4 of quinazoline nucleus with different amines has produced derivatives of the 4-heteroarylquinazoline and the fused quinazolino[4,3-*c*]quinazoline. The reaction of the chloroquinazoline derivative **2** with hydrazine hydrate and subsequent condensation with different aromatic aldehydes furnished a series of fused 5-substituted-[1,2,4]triazoloquinazoline derivatives. Finally, its reaction with acyl hydrazide (acetyl hydrazide) furnished the heterocyclic system 7,9-dibromo-3-methyl-[1,2,4]triazolo[4,3-*c*]Quinazolin-5-yl-2-propenoic acid.

**Keywords:** 4-chloroquinazoline, 4-heteroarylquinazolines, triazolo-quinazolines.

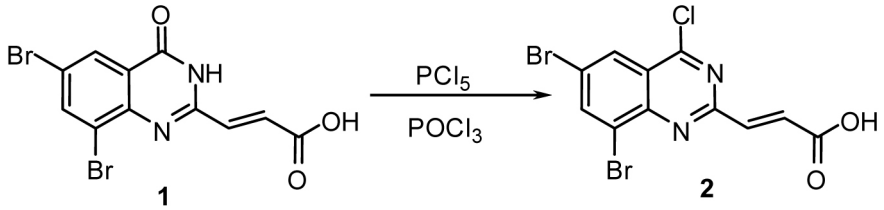
## 1. Introduction

Diverse biological activity is encountered in organic compounds containing the quinazoline system.[1–8] Moreover, many fused quinazoline derivatives are found to exhibit remarkable pharmacological properties[9] and can be adopted in a combinatorial synthesis of fused quinazolines for biological evaluation, like the synthesis of Asperlicin.[10,11] The present work is an extension of our ongoing efforts towards the development of a set of new substituted quinazoline derivatives as a source of functionalized molecules possessing many biological applications. Furthermore, many studies suggested this class of heterocyclic compounds to be pharmaceutically active. Their whole structure was required, but activity is further enhanced by introducing a halide substituent at the positions 6 and 8.[12–14] This information enforced us to construct the 6,8-dibromo-substituted quinazoline derivatives **2**.

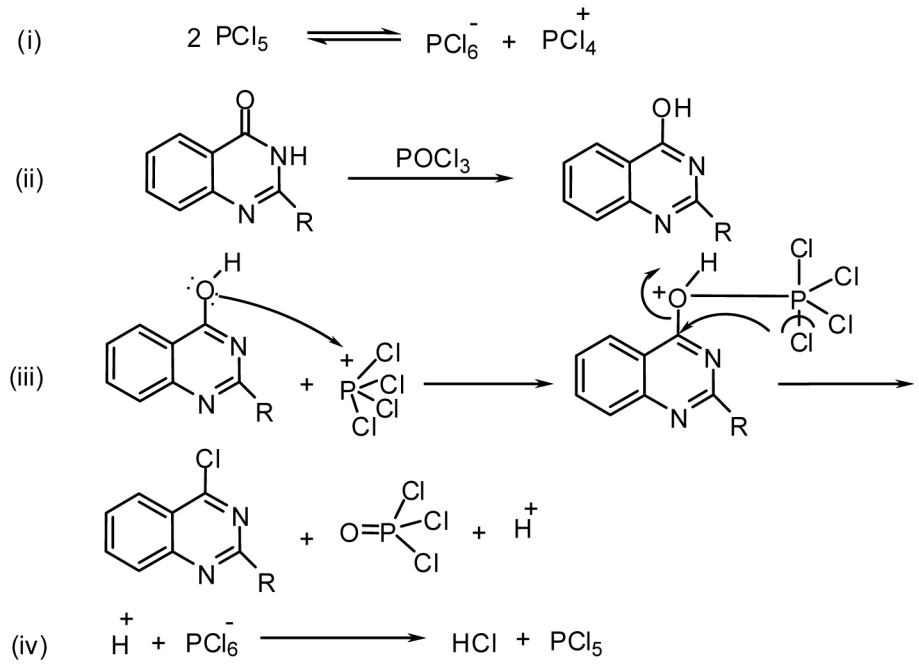
## 2. Results and Discussion

The synthesis of 4-chloroquinazoline **2** has been achieved via chlorination of the corresponding 4-oxoquinazoline analog **1** (prepared according to a reported method)[15] using a mixture of phosphorus oxychloride and phosphorus pentachloride in boiling water bath. (Scheme 1)

It was found that the iminol form of **1** is the favored tautomer for chlorination. The role of $POCl_3$ is to furnish the iminol species and the reaction proceeds further via the following suggested reaction mechanism (Scheme 2).

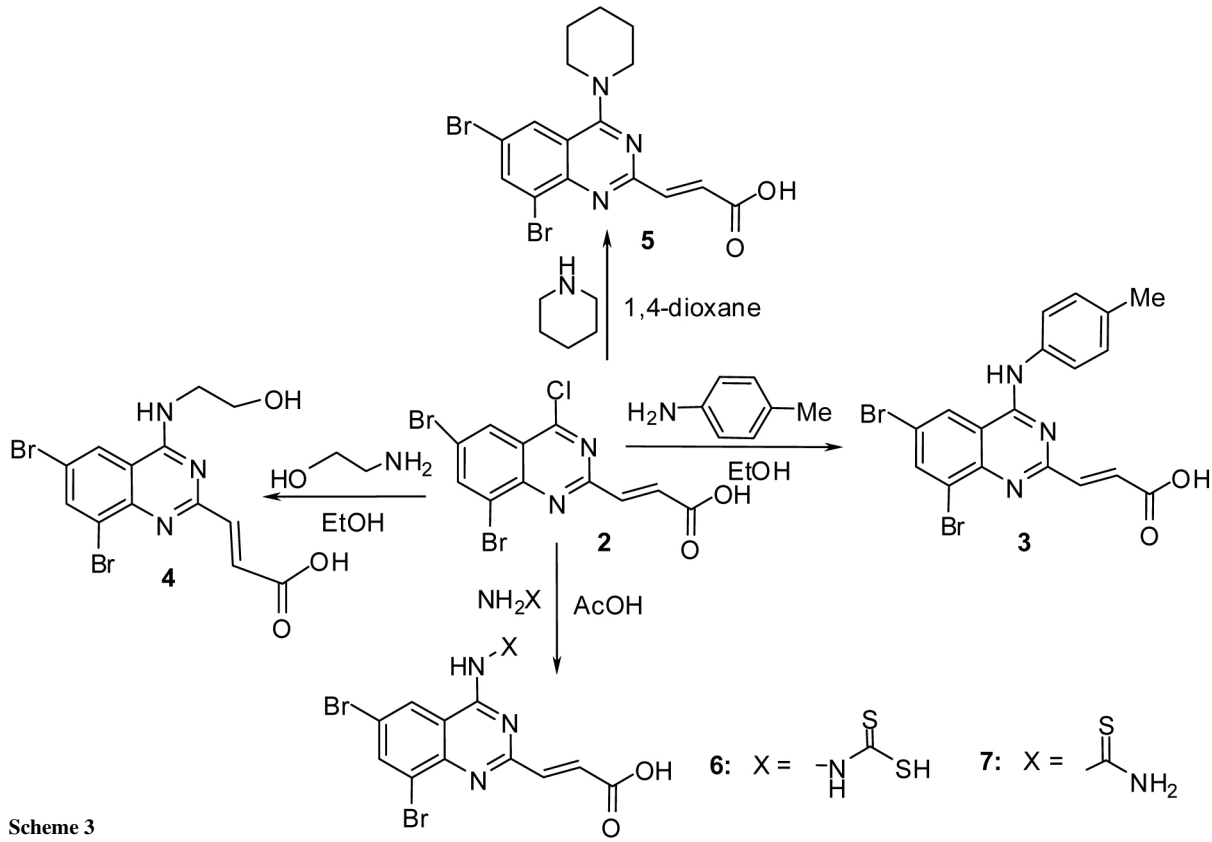



**Scheme 1**



**Scheme 2**

Recently, it was reported that 4-substituted-aminoquinazolines are exploited as a potent antitumor compounds (human breast carcinoma cell line in which EGFR is highly expressed).[16] Under this circumstance, condensation of chloroquinazoline derivative **2** with primary amines, namely 4-methylaniline and ethanol amine, affords the aryl/alkyl amino derivatives **3** and **4** in 68% and 72% yield, respectively. Whereas in the case of secondary amines like piperidine it affords the 4-piperidino-6,8-dibromo-2-carboxyvinylquinazoline (**5**) in 65%



**Scheme 3**

yield. Nucleophilic substitution of the chloroquinazoline derivative **2** with thiadicarbamyl hydrazine and thiourea in acidic media results in the corresponding amino derivatives **6** and **7** in 74% and 56% yield, respectively. (Scheme 3)

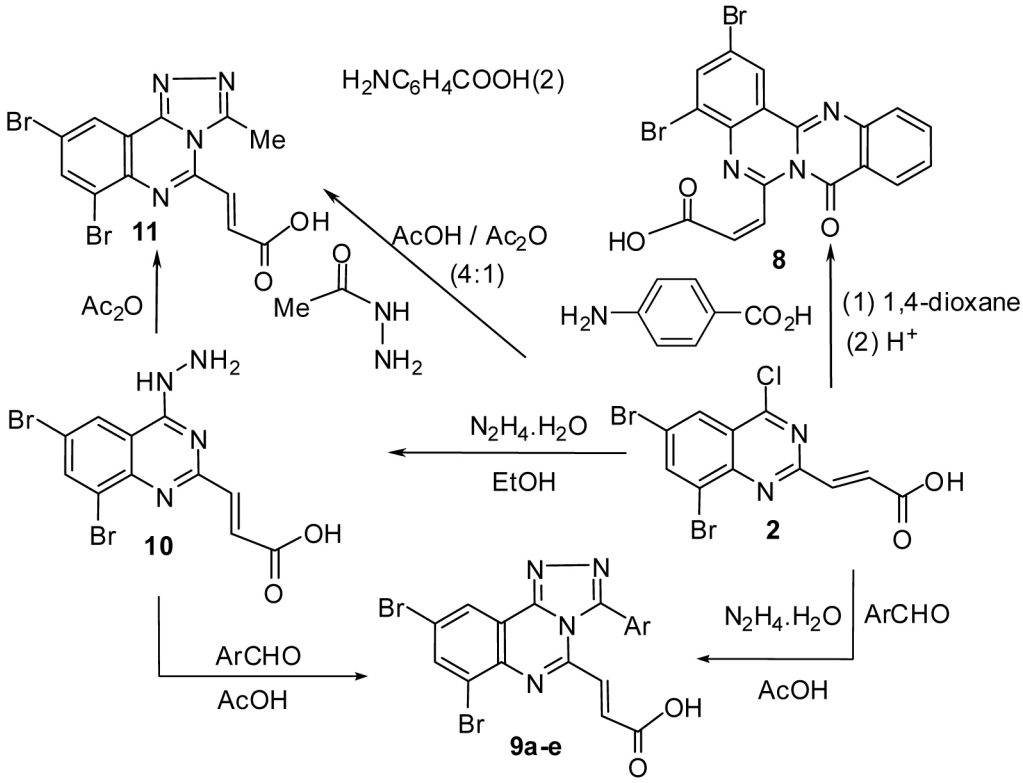
Interaction of 2-substituted chloroquinazoline with 2-aminobenzoic acid was reported[17] to proceed via fusion in an oil bath at 170 °C with poor to moderate yield. Herein we present a more convenient method which provides the target molecule with good yield. In this context, refluxing the chloroquinazoline **2** with 2-aminobenzoic acid in 1,4-dioxane followed by treatment with a few drops of concentrated sulphuric acid with continuous stirring at room temperature results in the fused 3-(2,4-dibromo-8-oxo-8*H*-quinazolino[4,3-*c*]quinazolin-6-yl)-2-propenoic acid (**8**) in 58% yield. (Scheme 4)

Additionally, some 1,2,4-triazole containing compounds have shown anticonvulsant and muscle relaxant activities.[18] Moreover, a series of triazolo-quinazoline derivatives are proved as a new class of $H_1$-antihistaminic.[19] A successful attempt for hydrazinolysis of the chloroquinazoline **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 has furnished a series of fused 5-substituted-triazoloquinazoline 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**, as well as their absence in $^1$H NMR of **9a–e**. Furthermore, the course of this reaction is chemically confirmed via constructing the 4-hydrazinoquinazoline system **10** in 73% yield as an isolated intermediate. Thereafter, the obtained hydrazinoquinazoline **10** is submitted to react with the above mentioned aromatic aldehydes and the 1,2,4-triazolo-quinazoline derivatives **9a–e** were formed in high yields. (Scheme 4)

Finally, the reaction of the chloroquinazoline **2** with acetyl hydrazide in a mixture of glacial acetic acid and freshly distilled acetanhydride (4:1) at 110 °C has furnished the non-mixed heterocyclic 7,9-dibromo-3-methyl-[1,2,4]triazolo[4,3-*c*]Quinazolin-5-yl-2-propenoic acid **11** in 84% yield. (Scheme 4)

## 3. Conclusion

We have established a novel convenient procedure for obtaining **2** in excellent yield based on the lactam-lactim dynamic equilibrium. Its behaviour towards nitrogen replacement reactions revealed that the presence of a hydrolysable chlorine atom at the position 4 exerted a significant reactivity for the formation of a series of fused-quinazoline derivatives **9**.




Ar = 4-Cl-$C_6H_4$ (**9a**), 4-$NO_2$-$C_6H_4$ (**9b**), 4-Me-$C_6H_4$ (**9c**), 2-Cl-$C_6H_4$ (**9d**), 4-MeO-$C_6H_4$ (**9e**)

**Scheme 4**

# 4. Experimental

## 4. 1. General Procedure

All melting points are uncorrected and were determined on a Stuart electric melting point apparatus. Elemental analyses 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). $^1$H 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 $^1$H 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. EIMS were recorded on a gas chromatographic GCMS – Qploopx Shimadzu (Japan, 1990).

**3-(6,8-Dibromo-4-chloroquinazolin-2-yl)-2-propenoic acid (2)** A solution of 4-oxoquinazolinone 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 °C 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%. Mp 246–248 °C. IR (KBr) 1626 (C=N), 1685 (CO), 3013 (CH-arom.), 3430 (OH) $cm^{-1}$. $^1$HNMR (DMSO-$d_6$) δ 6.42 (d, *J* = 15.3 Hz, 1H, vinyl-H), 7.06 (d, *J* = 15.3 Hz, 1H, vinyl-H), 8.12 (s, 1H, Ar-H), 8.72 (s, 1H, Ar-H). $^{13}$C NMR (DMSO-$d_6$) δ 113.8 (C-5), 117.1 (C-3), 121.1 (C-7), 135.0 (C-6, C-10), 138.2 (C-4, C-9), 146.3 (C-8), 152.6 (C-2), 154.8 (C-1), 168.4 (C-11). Anal. Calcd for $C_{11}H_5Br_2ClN_2O_2$ (Mwt 392.4): C, 33.67; H, 1.28; N, 7.14; Br, 40.72. Found: C, 33.92; H, 1.43; N, 7.31; Br, 41.12. MS: *m/z* 394 $[M+2]^+$, 392 $[M^+]$, 332, 236, 196, 57.

**3-{6,8-Dibromo-4-[(4-methylphenyl)amino]quinazolin-2-yl}-2-propenoic acid (3)** A mixture of 4-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 °C 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%. Mp 340–341 °C. IR (KBr) 1625 (C=N), 1687 (CO), 2939 (CH-aliph.), 3057 (CH-arom.), 3157 $cm^{-1}$ (NH). $^1$HNMR (DMSO-$d_6$) δ 2.17 (s, 3H, $CH_3$), 6.41 (d, *J* = 15.3 Hz, 1H, vinyl-H), 6.95 (m, 4H, Ar-H), 7.67 (d, *J* = 15.3 Hz, 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). $^{13}$C NMR (DMSO-$d_6$) δ 23.3 (C-16), 106.8 (C-13), 111.2 (C-3), 116.3 (C-5, C-7), 129.2 (C-15), 132.2 (C-14, C-9), 134.1 (C-6, C-10), 143.8 (C-4), 146.3 (C-8), 152.4 (C-1), 159.2 (C-2, C-12), 167.4 (C-11). Anal. Calcd for $C_{18}H_{13}Br_2N_3O_2$ (Mwt 463.1): C, 46.68; H, 2.83; N, 9.07; Br, 34.51. Found: C, 46.25; H, 2.96; N, 9.19; Br, 34.93. MS: *m/z* 465 $[M+2]^+$, 463 $[M^+]$, 419, 329, 236, 76.

**3-[6,8-Dibromo-4-(2-hydroxyethylamino)quinazolin-2-yl]-2-propenoic acid (4)** A solution of 4-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%. Mp 334 °C. IR (KBr) 1624 (C=N), 1683 (CO), 2941 (CH-aliph.), 3065 (CH-arom.), 3162 (NH), 3426 $cm^{-1}$(OH). $^1$HNMR (DMSO-$d_6$) δ 3.58 (m, 4H, 2 × $CH_2$), 4.53 (s, 1H, NH), 6.31 (brs, 1H, OH), 6.35 (d, *J* = 15.3 Hz, 1H, vinyl-H), 7.19 (d, *J* = 15.3 Hz, 1H, vinyl-H), 8.06 (d, *J* = 1.9 Hz, 2H, Ar-H), 11.87 (s, 1H, OH). $^{13}$C NMR (DMSO-$d_6$) δ 43.1 (C-12), 61.4 (C-13), 108.7 (C-3), 116.8 (C-5, C-7), 132.3 (C-9), 134.2 (C-6, C-10), 140.4 (C-4), 144.1 (C-8), 152.8 (C-1), 161.3 (C-2), 168.3 (C-11). Anal. Calcd for $C_{13}H_{11}Br_2N_3O_3$ (Mwt 417.1): C, 37.44; H, 2.66; N, 10.08; Br, 38.32. Found: C, 37.82; H, 2.51; N,10.26; Br, 38.10. MS: *m/z* 373 $[M^+–CO_2]$, 313, 236, 75, 60.

**3-[6,8-Dibromo-4-(piperidin-1-yl)quinazolin-2-yl]-2-propenoic acid (5)** A mixture of chloroquinazoline **2** (3.92 g, 0.01 mol) and piperidine (1.73 g, 0.02 mol) was heated at 140 °C 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%. Mp 287–289 °C. IR (KBr) 1625 (C=N), 1686 (CO), 2939 (CH-aliph.), 3054 $cm^{-1}$ (CH-arom.). $^1$HNMR (DMSO-$d_6$) δ 1.64 (m, 5H, piperdine-H), 3.42 (dd, $J_1$ = 3.7 Hz, $J_2$ = 4.5 Hz, 4H, 2 × $CH_2$), 6.41 (d, *J* = 15.2 Hz, 1H, vinyl-H), 6.84 (d, *J* = 15.2 Hz, 1H, vinyl-H), 7.94 (s, 1H, Ar-H), 8.20 (s, 1H, Ar-H), 11.32 (s, 1H, OH). $^{13}$C NMR (DMSO-$d_6$) δ 23.8 (C-14), 27.2 (C-13), 50.2 (C-12), 114.9 (C-3), 117.8 (C-5, C-7), 131.0 (C-6, C-9), 134.8 (C-10), 143.3 (C-4), 146.2 (C-8), 154.3 (C-1), 160.1 (C-2), 168.6 (C-11). Anal. Calcd for $C_{16}H_{15}Br_2N_3O_2$ (Mwt 441.1): C, 43.56; H, 3.43; N, 9.53; Br, 36.23. Found: C, 43.89; H, 3.52; N, 9.78; Br, 36.62. MS: *m/z* 443 $[M+2]^+$, 441 $[M^+]$, 397, 358, 288, 236, 55.

**Quinazolines 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 °C 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.

**3-[6,8-Dibromo-4-(2-dithiocarboxyhydrazinyl)quinazolin-2-yl]-2-propenoic acid (6):** Yield 74%. Mp 328 °C. IR (KBr) 158 (C-S), 1625 (C=N), 1683 (CO), 3064 (CH-arom.), 3162 $cm^{-1}$ (NH). $^1$HNMR (DMSO-$d_6$) δ 2.55 (s, 1H, SH), 6.48 (d, *J* = 15.3 Hz, 1H, vinyl-H), 7.12 (d, *J* = 15.3 Hz, 1H, vinyl-H), 8.07 (s, 1H, Ar-H), 8.38 (s, 1H, Ar-H), 9.19 (s, 2H, NH). $^{13}$C NMR (DMSO-$d_6$) δ 106.2 (C-

8), 108.0 (C-7, C-5), 130.9 (C-9), 133.2 (C-6, C-10), 142.2 (C-4), 147.8 (C-8), 156.1 (C-1), 161.3 (C-2), 167.3 (C-11), 200.9 (C-12). Anal. Calcd for $C_{12}H_8Br_2N_4O_2S_2$ (Mwt 464.1): C, 31.05; H, 1.74; N, 12.07; Br, 34.43. Found: C, 31.46; H, 1.52; N, 12.24; Br, 34.67. MS: *m/z* 419 [$M^+$–$CO_2$], 343, 313, 234, 108, 76.

**3-(6,8-Dibromo-4-thioureidoquinazolin-2-yl)-2-propenoic acid (7):** Yield 56%. Mp 312 °C. IR (KBr) 1258 (C-S), 1624 (C=N), 1685 (CO), 3063 (CH-arom.), 3160, 3276 (NH), 3477cm$^{-1}$ (OH). $^1$HNMR (DMSO-$d_6$) δ 6.37 (d, *J* = 15.3 Hz, 1H, vinyl-H), 7.06 (d, *J* = 15,3 Hz, 1H, vinyl-H), 8.22 (d, *J* = 1.8 Hz, 2H, Ar-H), 8.62 (s, 3H, NH). $^{13}$C NMR (DMSO-$d_6$) δ 108.7 (C-3), 120.1 (C-5, C-7), 132.0 (C-9), 134.3 (C-6, C-10), 140.8 (C-4), 147.1 (C-8), 154.1 (C-1), 160.2 (C-2), 167.4 (C-12), 168.1 (C-11). Anal. Calcd for $C_{12}H_8Br_2N_4O_2S$ (Mwt 432.1): C, 33.36; H, 1.87; N, 12.97; Br, 36.98. Found: C, 33.71; H, 1.95; N,13.25; Br, 37.19. MS: *m/z* 388 [M–$CO_2$]$^+$, 372, 313, 234, 75.

**3-(2,4-Dibromo-8-oxo-8*H*-quinazolino[4,3-*c*]quinazolin-6-yl)-2-propenoic acid (8)** An equimolar amounts of chloroquinazoline **2** and 2-aminobenzoic acid (0.01 mol) in *N*,*N*-dimethylformamide (30 mL) was heated under reflux at 100 °C for 2 h. The reaction mixture was cooled down and a 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%. Mp 345–347 °C. IR (KBr) 1626 (C=N), 1667, 1687 (CO), 3478 cm$^{-1}$ (OH). $^1$HNMR (DMSO-$d_6$) δ 6.82 (d, *J* = 15.2 Hz, 1H, vinyl-H), 7.47 (t, *J* = 8.4 Hz, 1H, Ar-H), 7.73 (d, *J* = 15.2 Hz, 1H, vinyl-H), 8.01 (m, 4H, Ar-H), 8.17 (s, 1H, Ar-H), 10.94 (brs, 1H, OH). $^{13}$C NMR (DMSO-$d_6$) δ 114.7 (C-13), 116.4 (C-7), 121.1 (C-15), 128.0 (C-5, C-14), 129.7 (C-3), 132.2 (C-4, C-10), 138.2 (C-9), 139.1 (C-6), 139.8 (C-16), 144.0 (C-17), 150.2 (C-8), 158.1 (C-2), 160.0 (C-12), 162.1 (C-11), 165.3 (C-1). Anal. Calcd for $C_{18}H_9Br_2N_3O_3$ (Mwt 475.1): C, 45.51; H, 1.91; N, 8.84; Br, 33.64. Found: C, 45.74; H, 2.13; N, 9.16; Br, 33.90. MS: *m/z* 477 [M+2]$^+$, 475 [$M^+$], 431, 234, 105.

**Triazoloquinazolines 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-hydrazinylquinazoline **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**.

**3-(7,9-Dibromo-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-*c*]quinazolin-5-yl)-2-propenoic acid (9a):** Yield 61%. Mp 280 °C. IR (KBr) 1628 (C=N), 1687 (CO), 3057 cm$^{-1}$ (CH-arom.). $^1$HNMR ($CDCl_3$) δ 6.54 (d, *J* = 15.3 Hz, 1H, vinyl-H), 7.48 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.84 (m, 3H, Ar-H, vinyl-H), 8.32 (s, 1H, Ar-H), 8.61 (s, 1H, Ar-H), 11.70 (s, 1H, OH). Anal. Calcd for $C_{18}H_9Br_2ClN_4O_2$ (Mwt 508.6): C, 42.51; H, 1.78; N, 11.02; Br, 31.42. Found: C, 42.32; H, 1.94; N, 10.84; Br, 31.68.

**3-(7,9-Dibromo-3-(4-nitrophenyl)-[1,2,4]triazolo[4,3-*c*]quinazolin-5-yl)-2-propenoic acid (9b):** Yield 69%. Mp 213–215 °C. IR (KBr) 1623 (C=N), 1682 (CO), 3057 cm$^{-1}$ (CH-arom.). $^1$HNMR ($CDCl_3$) δ 6.47 (d, *J* = 15.2 Hz, 1H, vinyl-H), 8.05 (m, 5H, Ar-H, vinyl-H), 8.90 (d, *J* = 1.8 Hz, 2H, Ar-H), 11.92 (s, 1H, OH). $^{13}$C NMR (DMSO-$d_6$) δ 108.7 (C-7), 124.9 (C-3), 128.1 (C-5), 128.8 (C-9, C-4), 132.0 (C-14), 135.9 (C-13), 137.1 (C-6, C-10), 139.2 (C-12, C-15), 141.2 (C-16), 147.7 (C-8), 154.3 (C-2), 157.0 (C-1), 168.8 (C-11). Anal. Calcd for $C_{18}H_9Br_2N_5O_4$ (Mwt 519.1): C, 41.65; H, 1.75; N, 13.49; Br, 30.79. Found: C, 41.86; H, 1.89; N, 13.76; Br, 30.48.

**3-(7,9-Dibromo-3-(4-methylphenyl)-[1,2,4]triazolo[4,3-*c*]quinazolin-5-yl)-2-propenoic acid (9c):** Yield 57%. Mp 288–289 °C. IR (KBr) 1625 (C=N), 1684 (CO), 2941 (CH-aliph.), 3055 cm$^{-1}$ (CH-arom.). $^1$HNMR (DMSO-$d_6$) δ 2.19 (s, 3H, $CH_3$), 6.51 (d, *J* = 15.3 Hz, 1H, vinyl-H), 7.17 (d, *J* = 1.7 Hz, 2H, Ar-H), 7.39 (d, *J* = 2.2 Hz, 2H, Ar-H), 7.98 (m, 3H, Ar-H, vinyl-H), 11.80 (s, 1H, OH). Anal. Calcd for $C_{19}H_{12}Br_2N_4O_2$ (Mwt 488.1): C, 46.75; H, 2.48; N, 11.48; Br, 32.74. Found: C, 46.97; H, 2.73; N, 11.31; Br, 32.89. MS: *m/z* 445 [$M^+$–$CO_2$], 417, 355, 234, 91, 75.

**3-(7,9-Dibromo-3-(2-chlorophenyl)-[1,2,4]triazolo[4,3-*c*]quinazolin-5-yl)-2-propenoic acid (9d):** Yield 49%. Mp 261–263 °C. IR (KBr) 1626 (C=N), 1688 (CO), 3057 cm$^{-1}$ (CH-arom.). $^1$HNMR (DMSO-$d_6$) δ 6.38 (d, *J* = 15.2 Hz, 1H, vinyl-H), 7.44 (m, 4H, Ar-H), 7.89 (d, *J* = 15.2 Hz, 1H, vinyl-H), 8.24 (s, 1H, Ar-H), 8.59 (s, 1H, Ar-H). Anal. Calcd for $C_{18}H_9Br_2ClN_4O_2$ (Mwt 508.6): C, 42.51; H, 1.78, N, 11.02; Br, 31.42. Found: C, 42.82; H, 2.07; N, 11.33; Br, 31.25.

**3-(7,9-Dibromo-3-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-*c*]quinazolin-5-yl)-2-propenoic acid (9e):** Yield 72%. Mp 319 °C. $^1$HNMR (DMSO-$d_6$) δ 3.92 (s, 3H, $OCH_3$), 6.44 (d, *J* = 15.2 Hz, 1H, vinyl-H), 6.78 (d, *J* = 1.9 Hz, 2H, Ar-H), 8.06 (m, 5H, Ar-H, vinyl-H), 11.86 (s, 1H, OH). Anal. Calcd for $C_{19}H_{12}Br_2N_4O_3$ (Mwt 504.1): C, 45.27; H, 2.40; N, 11.11; Br, 31.70. Found: C, 45.44; H, 2.53; N, 11.39; Br, 32.08. MS: *m/z* 506 [M+2]$^+$, 504 [$M^+$], 460, 433, 236, 196, 57.

**3-(6,8-Dibromo-4-hydrazinylquinazolin-2-yl)-2-propenoic acid (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 a few drops of piperidine was heated under reflux at 70 °C 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%. Mp 352 °C. IR (KBr) 1627 (C=N), 1686 (CO), 3060 (CH-arom.), 3160, 3308 $cm^{-1}$ (NH). $^1$HNMR (DMSO-$d_6$) δ 4.95 (s, 3H, NH), 6.32 (d, *J* = 15.3 Hz, 1H, vinyl-H), 6.87 (d, *J* = 15.3 Hz, 1H, vinyl-H), 8.06 (d, *J* = 1.8 Hz, 2H, Ar-H), 11.74 (s, 1H, OH). $^{13}$C NMR (DMSO-$d_6$) δ 108.2 (C-3), 109.8 (C-7), 113.2 (C-5), 127.4 (C-9, C-10), 132.9 (C-6), 135.1 (C-4), 147.0 (C-8), 157.3 (C-1), 161.1 (C-1), 168.3 (C-11). Anal. Calcd for $C_{11}H_8Br_2N_4O_2$ (Mwt 388.0): C, 34.05; H, 2.08; N, 14.44; Br, 41.19. Found: C, 33.86; H, 2.19; N, 14.93; Br, 41.46. MS: *m/z* 344 [$M^+$–$CO_2$], 317, 314, 302, 287.

**3-(7,9-Dibromo-3-methyl-[1,2,4]triazolo[4,3-*c*]quinazolin-5-yl)-2-propenoic acid (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 acetanhydride was heated at 110 °C for 5 h. The excess solvent was distilled off and the solid that separated after cooling was filtered off, washed with light pet. ether (b.p. 60–80 °C), 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 acetanhydride (10 mL) was heated in water bath at 70 °C for 3 h. The reaction mixture was cooled and the solid that formed was collected washed with light pet. ether (b.p. 60–80°) and crystallized from *n*-butanol to give **11**.

Yield 76%. Mp 307–308 °C. IR (KBr) 1626 (C=N), 1679 (CO), 2939 (CH-aliph.), 3057 $cm^{-1}$ (CH-arom.). $^1$HNMR (DMSO-$d_6$) δ 3.16 (s, 3H, $CH_3$), 6.49 (d, *J* = 15.3 Hz, 1H, vinyl-H), 7.94 (d, *J* = 15.3 Hz, 1H, vinyl-H), 8.32 (s, 1H, Ar-H), 8.53 (s, 1H, Ar-H), 11.84 (s, 1H, OH). $^{13}$C NMR (DMSO-$d_6$) δ 16.4 (C-13), 115.6 (C-3), 122.1 (C-3), 126.2 (C-5), 128.8 (C-4, C-9), 131.0 (C-10), 132.1 (C-12), 136.4 (C-6), 148.1 (C-8), 157.3 (C-2), 159.3 (C-1), 172.0 (C-11). Anal. Calcd for $C_{13}H_8Br_2N_4O_2$ (Mwt 412.1): C, 37.89; H, 1.96; N, 13.60; Br, 38.78. Found: C, 38.21; H, 1.83; N, 13.93; Br, 38.46. MS: *m/z* 414 $[M+2]^+$, 412 $[M^+]$, 368, 236, 57.

## 5. References


1. V. Alagarsamy, D. Shankar, S. Murugesan, *Biomed. Pharmacother.* **2008**, *62*, 173–178.
2. A. R. Genady, *Eur. J. Med. Chem.* **2009**, *44*, 409–416.
3. A. M. F. Eissa, A. M. El-Metwally, M. A. El-Hashash, A. M. F. El-Gohary, *J. Korean Chem. Soc.* **2008**, *52*, 328–337.
4. G. A. El-Hiti, M. F. Abdel-Megeed, *Heterocycles* **2005**, *65*, 3007–3041.
5. H. Wamhoff, G. Hendrikx, *Chem. Ber.* **1985**, *118*, 863–872.
6. V. Alagarsamy, *Pharmazie* **2004**, *59*, 753–755.
7. J. J. Wade, U.S. Patent No. 4, 528288, *Chem. Abstr*. **1986**, *104*, 5889.
8. N. Chairungsrilerd, K.-I. Furukawa, T. Ohta, S. Nozoe, Y. Ohizumi, *Eur. J. Pharmacol.* **1996**, *314*, 351–356.
9. S. S. Ibrahim, A. M. Abdel-Halim, Y. Gabr, S. El-Edfawy, R. M. Abdel-Rahman, *Ind. J. Chem.* **1998**, *37B*, 62–67.
10. N. H. Al-Said, Z. N. Ishtaiwi, *Acta Chim. Slov.* **2005**, *52*, 328–331.
11. N. H. Al-Said, L. S. Al-Qaisi, *Acta Chim. Slov.* **2006**, *53*, 204–209.
12. J. B. Jiang, D. P. Hesson, B. A. Dusak, D. L. Dexter, G. J. Kang, E. Hamel, *J. Med. Chem.* **1990**, *33*, 1721–1728.
13. M. Patel, R. J. McHugh, Jr., B. C. Cordova, R. M. Klabe, S. Erickson-Viitanen, G. L. Trainor, S. S. Ko, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3221–3224.
14. F. Clémence, O. Le Martret, J. Collard, *J. Heterocycl. Chem.* **1984**, *21*, 1345–1353.
15. M. A. El-Hashash, T. M. Abdel-Rahman, Y. A. El-Badry, *Ind. J. Chem.* **2006**, *45B*, 1470–1477.
16. K. Abouzid, S. Shouman, *Bioorg. Med. Chem.* **2008**, *16*, 7543–7551.
17. M. S. Amin, *Ind. J. Chem. Sec. B* **1998**, *37*, 303–305.
18. A. Almasirad, N. Vousooghi, S. A. Tabatabai, A. Kebriaeezadeh, A. Shafiee, *Acta Chim. Slov.* **2007**, *54*, 317–324.
19. V. Alagarsamy, V. R. Solomon, M. Murugan, *Bioorg. Med. Chem.* **2007**, *15*, 4009–4015.


## Povzetek


S pomočjo kloriranja ustreznih 6,8-dibromokinazolinskih analogov smo uspeli pripraviti 2-karboksivinil-4-kloro-6,8-dibromokinazolin (**2**). Enostavna zamenjava atoma klora na položaju 4 kinazolinskega sistema z različnimi amini je omogočila pripravo 4-heteroarilkinazolinskih derivatov in pripojenih kinazolino[4,3-*c*]kinazolinov. Pri reakciji klorokinazolinskega derivata **2** s hidrazin hidratom in po sledeči kondenzaciji z različnimi aromatskimi aldehidi je nastala serija pripojenih 5-substituiranih-[1,2,4]triazolokinazolinskih derivatov. Pri reakciji z acil hidrazidom (acetil hidrazidom) pa je nastal heterociklični sistem 7,9-dibromo-3-metil-[1,2,4]triazolo[4,3-*c*]kinazolin-5-il.