

## Synthesis of some novel triazolo-quinazolinone derivatives and investigation of their antihypertensive agents

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### ABSTRACT

Quinazolinone is fused heterocyclic that have been reported to possess versatile type of biological activities such as anticancer, anticonvulsant, anti-inflammatory, antihelminthic, antimicrobial activities. A series of mannich based triazolo-quinazolinone derivatives were synthesized and all synthesized compound's structures were confirmed by IR, <sup>1</sup>H-NMR and Mass spectroscopic analysis. Our seven synthesized compounds K 1, K 3, K 8, K 9, K 10, K 17 and K 18 have shown antihypertensive activity. However compound K 1, K 3, K 8, K 9 and K18 has shown significant antihypertensive activity comparable to standard drug Prazocin (20 mg/kg body mass).

**Key Words:** Mannich base, Antihypertensive activity, Tail- cuff method.

### INTRODUCTION

Quinazolinone is fused heterocyclic ring system and a building block for around 120 naturally occurring alkaloids.

Quinazolinone constitute an important class of medicinally important small molecules which have been reported to possess anticonvulsant [1-3], antimicrobial [4-8], anti-inflammatory [9-11], antitumor [12], anticancer [13-14], sedative-hypnotic [15], diuretic [16-17], antiviral [18], antihypertensive [19] and antitubercular [20-21] activities. Several triazolo-quinazolinone derivatives were synthesized and tested for different biological activities. These reports showed that aryl substitution at 2<sup>nd</sup> and 3<sup>rd</sup> position enhances biological activities.

Efforts towards the development and identification of new molecules for antihypertensive activities with minimal side effects have gained significance in the recent past during which the quinazolinones came into the scenario.

With the revelation of exploring the diverse pharmacological nature of triazolo-quinazolinone derivatives, it was contemplated to synthesize some substituted quinazolinone derivatives by mannich reaction having general structure of figure 1 as potential anti-hypertensive agents.

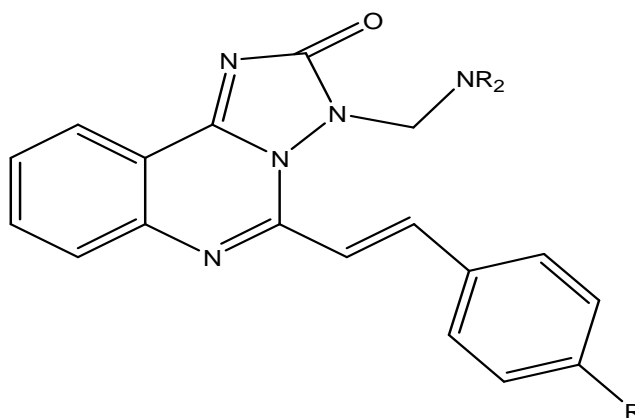


Figure 1

### MATERIALS AND METHODS

**Chemistry:** All the solvents were LR grades and were obtained from Merck and S D Fine Chemicals. Melting points were recorded in open capillaries with electric melting point apparatus and were uncorrected. IR spectra (KBr disks) were recorded using Shimadzu 8400S FTIR spectrophotometer.  $^1\text{H-NMR}$  were recorded in Bruker Avance II(400 MHz) spectrophotometer in  $\text{CDCl}_3$  solution and chemical shift values were reported in ppm relative to TMS( $\delta = 0$ ) as internal standard. Mass spectra were recorded on a Shimadzu LC-MS (2010A) spectrophotometer. TLC was performed on silica gel coated plates for monitoring the reactions. Adults Albino rats of either sex (200 g each) were used as experimental animals. The all synthesized compounds were suspended in 1% CMC.

The synthesis of 2-methylbenzoxazin-4-one (**I**) was achieved by reported methods [22]. The 2-methyl-4-oxo-4H-quinazolin-3-yl- thiourea (**II**) was obtained by the fusion of thiosemicarbazide with 2-methylbenzoxazin-4-one (**I**). The product (**II**) was heated above its melting point to get 5-methyl-[1,2,4]triazolo[1,5-c]quinazolin-2-thione (**III**). The one pot reaction of (**III**) with appropriate aldehydes, namely benzaldehyde, p-bromobenzaldehyde, p-nitrobenzaldehyde, 2,4-dihydroxybenzaldehyde and salisaldehyde in presence of NaOH afforded the corresponding derivatives, namely, 5-[2-(substituted-phenyl)-vinyl]-[1,2,4]triazolo[1,5-c]quinazolin-2-thione (**IVa-f**), respectively. Compounds (**IVa-f**) were allowed to condense with appropriate secondary amines in presence of formamide followed the mannich reaction to give titled compounds (**K 1-10**), respectively (scheme 1).

On the other hand, the 2-methyl-4-oxo-4H-quinazolin-3-yl- urea (**V**) was obtained by the fusion of semicarbazide with 2-methylbenzoxazin-4-one (**I**). This product (**V**) was heated above its melting point to get 5-methyl-[1,2,4]triazolo[1,5-c]quinazolin-2-one (**VI**). The one pot reaction of (**VI**) with appropriate aldehydes, in presence of NaOH afforded the corresponding derivatives, namely, 5-[2-(substituted-phenyl)-vinyl]-[1,2,4]triazolo[1,5-c]quinazolin-2-one (**VII a-e**), respectively. Compounds (**VII a-e**) followed the mannich reaction to give titled compounds (**K 11-19**), respectively (scheme 2).

#### 2-methyl-benzoxazin-4-one (**I**)

Compound was prepared according to reported method, m.p. 168°C.

#### Substituted (2-Methyl-4-oxo-4H-quinazolin-3-yl)-urea (**II, V**)

An equi-molar quantity (8.5 g, 0.05 mol) of 2-methyl-benzoxazin-4-one and Thiosemicarbazide/ Semicarbazide were dissolved in ethanol separately. Then, mixture was refluxed for 1 hour with glacial acetic acid. After the completion of reaction, contents were cooled to room temperature. Solid mass was collected and recrystallized with methanol.

#### 2-Methyl-4-oxo-4H-quinazolin-3-yl-thiourea (**II**)

Yield: 80%; m. p: 178°C, Rf: 0.78 (chloroform : Ethanol, 1 :9 v/v).

IR ( $\text{cm}^{-1}$ ): 3367 (NH Str), 2625 ( $\text{CH}_3$  Str), 1646 (CO Str), 1485 ( $\text{CH}_2$  bending), 1646 (NH bending), 700 (disubst. aromatic ring).

<sup>1</sup>H-NMR (δ ppm): 8.1-7.0 (m, 4H, Ar-H), 2.0 (s, 2H, amine), 1.9 (s, 3H, CH<sub>3</sub>).

**2-Methyl-4-oxo-4H-quinazolin-3-yl-urea (V)**

Yield: 78%; m. p: 180°C, Rf: 0.78 (chloroform: Ethanol, 1:9 v/v).

IR (cm<sup>-1</sup>): 3479 (NH Str), 2925 (CH<sub>3</sub> Str), 1646 (CO Str), 1485 (CH<sub>2</sub> bending), 1656 (NH bending), 1377 (deform. of alkene).

<sup>1</sup>H-NMR (δ ppm): 8.6-7.05(m, 4H, Ar-H), 6.8 (s, 3H, CH<sub>2</sub>), 6.6 (s, 3H, amine).

**Substituted 5-methyl-[1,2,4]triazolo[1,5-c]quinazolin-2-one (III, VI)**

The product obtained from step 2 was heated above its melting point to get 5-methyl-[1,2,4]triazolo[1,5-c]quinazolin-2-one. Product was recrystallized with methanol.

**5-methyl-[1,2,4]triazolo[1,5-c]quinazolin-2-thione (III)**

Yield: 73%; m. p: 158°C, Rf: 0.78 (chloroform: Ethanol, 3:7 v/v).

IR (cm<sup>-1</sup>): 3321 (NH Str), 3169 (CONH), 1466 (CH=CH bending), 1008 (C=S), 1641 (NH bending), 766 (monosubs. benzene).

<sup>1</sup>H-NMR (δ ppm): 8.1-7.3 (m, 4H, Ar-H), 2.0 (s, 1H, NH), 0.86 (s, 3H, methyl).

**5-methyl-[1,2,4]triazolo[1,5-c]quinazolin-2-one (VI)**

Yield: 73%; m. p: 160°C, Rf: 0.91 (chloroform: Ethanol, 3:7 v/v).

IR (cm<sup>-1</sup>): 3375 (NH Str), 2902 (CH<sub>3</sub> Str), 3186 (CONH), 1485 (CH<sub>2</sub> bending), 1694 (NH bending), 698 (monosubs. benzene).

<sup>1</sup>H-NMR (δ ppm): 8.6-8.1 (s, 1H, NH), 7.8-7.5 (m, 4H, Ar-H), 2.7-2.0 (s, 3H, methyl).

**5-[2-(substituted-phenyl)-vinyl]-[1,2,4]triazolo[1,5-c]quinazolin-2-one derivatives (IV a-f)**

An equimolar mixture (0.01 mol) of (III, VI) and appropriate benzaldehyde was fitted with mechanical stirrer, and solution was immersed into cold water bath. To this, 10% of NaOH solution was added slowly until the mixture become just acidic to litmus. The reaction mixture was poured into ice cold water. The solid so obtained was filtered, dried and recrystallized with methanol.

**5-[2-(4-bromo-phenyl)-vinyl]-[1,2,4]triazolo[1,5c]quinazolin-2-thione (IV a)**

Yield: 60%; m. p: 175°C, Rf: 0.85 (dichloromethane: Ethanol, 3:7 v/v).

**5-[2-(4-nitro-phenyl)-vinyl]-[1,2,4]triazolo[1,5c]quinazolin-2-thione (IV b)**

Yield: 64%; m. p: 80°C, Rf: 0.89 (dichloromethane: Ethanol, 2:8 v/v).

IR (cm<sup>-1</sup>): 3382 (NH Str), 2850 (CH<sub>3</sub> Str), 3080 (C=C), 1485 (CH<sub>2</sub> bending), 1198 (C=S), 1521 (NH bending), 766 (benzene).

<sup>1</sup>H-NMR (δ ppm): 9.3 (s, 1H, NH amine), 8.4-7.9 (m, 8H, Ar-H).

**5-[2-(2,4-dihydroxy-phenyl)-vinyl]-[1,2,4]triazolo[1,5c]quinazolin-2-thione (IV c)**

Yield: 62%; m. p: 225°C, Rf: 0.81 (dichloromethane: Ethanol, 5: 5 v/v).

IR (cm<sup>-1</sup>): 3434 (OH str), 3382 (NH Str), 2850 (CH<sub>3</sub> Str), 3080 (C=C), 1485 (CH<sub>2</sub> bending), 1581 (NH bending), 766 (benzene).

<sup>1</sup>H-NMR (δ ppm): 8.3-8.0 (s, 1H, NH amine), 7.9-6.3(m, 7H, Ar-H), 5.7(s, 1H, OH).

**5-[2-(2-hydroxy-phenyl)-vinyl]-[1,2,4]triazolo[1,5c]quinazolin-2-thione (IV d)**

Yield: 65%; m. p: 192°C, Rf: 0.90 (dichloromethane: Ethanol, 5: 5 v/v).

IR (cm<sup>-1</sup>): 3498 (OH str), 3367 (CONH Str), 2850 (CH<sub>3</sub> Str), 3080 (C=C), 1332 (OH bending), 1507 (NH bending), 1154 (C=S).

<sup>1</sup>H-NMR (δ ppm): 8.6-8.0 (s, 1H, NH amine), 7.9-7.0(m, 9H, Ar-H), 3.6(d, 2H, -C=CH<sub>2</sub>).

**5-styryl-[1,2,4]triazolo[1,5c]quinazolin-2-thione (IV e)**

Yield: 62%; m. p: 182°C, Rf: 0.79 (dichloromethane: Ethanol, 5: 5 v/v).

IR (cm<sup>-1</sup>): 3154 (NH str), 2986 (CH<sub>3</sub> Str), 3080 (C=C), 1372 (CH bending), 1594 (NH bending), 1154 (C=S), 856 (m-disubs. Benzene).

<sup>1</sup>H-NMR (δ ppm): 8.0-7.6 (benzyl idenin), 7.4-7.3 (d, 2H, -C=CH<sub>2</sub>), 2.1-2.0 (s, 1H, NH), 1.2-0.87 (d, 2H, CH<sub>3</sub>).

**5-[2-(4-chloro-phenyl)-vinyl]-[1,2,4]triazolo[1,5c]quinazolin-2-thione (IV f)**

Yield: 62%; m. p: 194°C, Rf: 0.75 (dichloromethane: Ethanol, 7: 3 v/v).

IR (cm<sup>-1</sup>): 3434 (NH Str), 2853 (CH<sub>3</sub> Str), 1372 (CH bending), 1682 (NH bending), 1086 (C=S), 700 (m-disubs. Benzene).

<sup>1</sup>H-NMR (δ ppm): 8.0-7.6 (benzylimidine), 2.5-2.1(s, 1H, NH), 1.3 (d, 2H, CH<sub>3</sub>).

**5-[2-(substituted-phenyl)-vinyl]-[1,2,4]triazolo[1,5-c]quinazolin-2-one derivatives (VII a-e)**

An equimolar mixture (0.01 mol) of (VI) and appropriate benzaldehyde was fitted with mechanical stirrer, and solution was immersed into cold water bath. To this, 10% of NaOH solution was added slowly until the mixture become just acidic to litmus. The reaction mixture was poured into ice cold water. The solid so obtained was filtered, dried and recrystallized with methanol.

**5-[2-(4-bromo-phenyl)-vinyl]-[1,2,4]triazolo[1,5c]quinazolin-2-one (VII a)**

Yield: 60%; m. p: 185°C, Rf: 0.78 (dichloromethane: Ethanol, 2: 8 v/v).

IR (cm<sup>-1</sup>): 3463 (NH Str), 2994 (CH<sub>3</sub> Str), 3060 (C=C), 1399 (CO), 1669 (NH bending), 954 (Benzene).

<sup>1</sup>H-NMR (δ ppm): 8.0 (s, 1H, NH), 7.8-7.5(m, 4H, Ar-H), 6.3 (s, 3H, CH<sub>3</sub>).

**5-[2-(4-nitro-phenyl)-vinyl]-[1,2,4]triazolo[1,5c]quinazolin-2-one (VII b)**

Yield: 60%; m. p: 95°C, Rf: 0.79 (dichloromethane: Ethanol, 5: 5 v/v).

IR (cm<sup>-1</sup>): 3382 (NH Str), 2850 (CH<sub>3</sub> Str), 3080 (C=C str), 1399 (CO), 1521 (NH bending), 866 (m subs. benzene).

<sup>1</sup>H-NMR (δ ppm): 9.3 (s, 1H, NH), 8.4-7.9 (m, 4H, Ar-H).

**5-[2-(2,4-dihydroxy-phenyl)-vinyl]-[1,2,4]triazolo[1,5c]quinazolin-2-one (VII c)**

Yield: 50%; m. p: 184°C, Rf: 0.95 (dichloromethane: Ethanol, 2: 8 v/v).

IR (cm<sup>-1</sup>): 3428 (OH Str), 3479 (CONH str), 3060 (C=C), 1390 (CO), 1592 (NH bending), 856 (m- subs. benzene).

<sup>1</sup>H-NMR (δ ppm): 8.6-8.0 (s, 1H, NH), 7.9-6.3(m, 7H, Ar-H), 5.7 (s, 1H, Ar-OH).

**5-styryl-[1,2,4]triazolo[1,5c]quinazolin-2-one (VII d)**

Yield: 56%; m. p: 193°C, Rf: 0.89 (dichloromethane: Ethanol, 5: 5 v/v).

IR (cm<sup>-1</sup>): 3463 (NH Str), 2994 (CH<sub>3</sub> Str), 3060 (C=C), 1399 (CO), 1669 (NH bending), 954 (Benzene).

<sup>1</sup>H-NMR (δ ppm): 8.0 (s, 1H, NH), 7.8-7.5(m, 4H, Ar-H), 6.3 (s, 3H, CH<sub>3</sub>).

**5-[2-(2-hydroxy-phenyl)-vinyl]-[1,2,4]triazolo[1,5c]quinazolin-2-one (VII e)**

Yield: 60%; m. p: 182°C, Rf: 0.80 (dichloromethane: Ethanol, 5: 5 v/v).

IR (cm<sup>-1</sup>): 3434 (OH Str), 2927 (CH<sub>3</sub> Str), 1942 (C=C bending), 1383 (CO), 1588 (NH bending), 731 (monosubs, benzene).

<sup>1</sup>H-NMR (δ ppm): 8.6-8.0 (s, 1H, NH), 7.7-6.9 (m, 8H, Ar-H), 6.7 (d, 2H, -C=CH), 5.4 (s, 1H, Ar-OH).

**Substituted-[1,2,4]triazolo[1,5-c]quinazolin-2-thione derivatives (K 1- K 10)**

A slurry consisting of (IV a-f), ethanol (5 ml) and 37% formamide (1 ml) was made. To this added appropriate secondary amine (0.01 mol) drop wise with cooling and shaking. The reaction mixture was allowed to stand at room temperature for 1 hour with occasional shaking, after which it was warmed on steam bath for 15 minutes. At the end of the period the contents were cooled and recrystallized from chloroform and petroleum ether.

**5-[2-(4-bromo-phenyl)-vinyl]-3-piperazin-1-ylmethyl-[1,2,4]triazolo[1,5-c]quinazolin-2-thione:(K 1)**

Yield: 43%; m. p: 260°C, Rf: 0.81 (dichloromethane: Ethanol, 7: 3 v/v).

IR (cm<sup>-1</sup>): 3383 (NH Str), 2853 (C=C Str), 1494.9 (CH<sub>3</sub> def), 1086 (C-S Str), 1593 (NH bending), 505 (Br).

<sup>1</sup>H-NMR (δ ppm): 8.3-7.5 (m, 12H, Ar-H), 4.9-4.0 (9d, 2H, -C=CH<sub>2</sub>), 2.1-1.0 (m, 2H, -N-C).

TOF MS *m/z*: 480 (M<sup>+</sup>), 111.1, 370, 453.

**5-[2-(4-Nitro-phenyl)-vinyl]-3-piperazin-1-ylmethyl-[1,2,4]triazolo[1,5-c]quinazolin-2-thione: (K 3)**

Yield: 40%; m. p: 270°C, Rf: 0.94 (dichloromethane: Ethanol, 5: 5 v/v).

IR (cm<sup>-1</sup>): 3459.86 (NH Str), 2359 (CN Str), 1494.9 (CH<sub>3</sub> def), 848.65 (CH<sub>2</sub> bending), 1590 (NH bending), 590.4 (Br).

<sup>1</sup>H-NMR (δ ppm): 5.2 (m, 12H, Ar-H), 3.3 (s, 2H, -C=CH<sub>2</sub>), 2.5 (m, 2H, -N-C).

TOF MS *m/z*: 446.3( M<sup>+</sup>), 220, 170, 269, 435.

**5-[2-(2,4-dihydroxy-phenyl)-vinyl]-3-piperazin-1-ylmethyl-[1,2,4]triazolo[1,5-c]quinazolin-2-thione: (K 5)**

Yield: 42%; m. p: 225°C, Rf: 0.88 (chloroform: Ethanol, 2: 8 v/v).

IR (cm<sup>-1</sup>): 3454.013 (NH Str), 2959.5 (CH<sub>3</sub> Str), 2358.9 (CN Str), 1412.9 (CH<sub>3</sub> def), 1593.79 (NH bending).

<sup>1</sup>H-NMR (δ ppm): 7.3 (s, 3H, Ar-H), 6.15 (s, 1H, Ar-OH), 5.4(s, 1H, =C-Ar), 5.0 (s, 2H, Ar-OH), 2.6 (s, 4H, N-CH<sub>2</sub>).

TOF MS *m/z*: 433( M<sup>+</sup>), 269, 187, 346, 105.

**3-[(Diphenylamino)-methyl]-5-[2-(2-hydroxy-phenyl)-vinyl]-[1,2,4]triazolo[1,5-c]quinazolin-2-thione (K 6)**

Yield: 52%; m. p: 202°C, Rf: 0.65 (chloroform: Ethanol, 2: 8 v/v).

IR (cm<sup>-1</sup>): 3406 (NH Str), 3041.39 (CH<sub>3</sub> Str), 1706 (CN Str), 1932.9 (CH<sub>2</sub> bending), 1596.7 (NH bending).

<sup>1</sup>H-NMR (δ ppm): 8.1-6.8 (m, 17H, Ar-H), 6.7 (d, 2H, -C=CH), 3.4(m, 2H, CH<sub>2</sub>).

TOF MS *m/z*: 500( M<sup>+</sup>), 260, 187, 182, 105, 346.

**3-Piperazin-1-yl-5-styryl-[1,2,4]triazolo[1,5-c]quinazolin-2-thione: (K 8)**

Yield: 43%; m. p: 210°C, Rf: 0.80 (ethyl acetate: ethanol, 3: 7 v/v).

IR (cm<sup>-1</sup>): 3384.6 (NH Str), 2959.78 (CH<sub>3</sub> Str), 2345.04 (CN Str), 1932.5 (CH<sub>2</sub> bending), 1451.99 (NH bending), 1254.43 (CS Str).

<sup>1</sup>H-NMR (δ ppm): 8.1-7.2 (m, 12H, Ar-H), 3.3 (s, 2H, -CH<sub>2</sub>), 2.5-1.2 (m, 2H, -N-C).

TOF MS *m/z*: 422( M<sup>+</sup>), 182, 105, 187, 269, 346.

**5-[2-(4-chloro-phenyl)-vinyl]-3-piperazin-1-ylmethyl-[1,2,4]triazolo[1,5-c]quinazolin-2-thione: (K 9)**

Yield: 50%; m. p: 330°C, Rf: 0.80 (ethyl acetate: ethanol, 2: 8 v/v).

IR (cm<sup>-1</sup>): 3361.08 (NH Str), 2935.05 (CH<sub>3</sub> Str), 2345.04 (CN Str), 1932.5 (CH<sub>2</sub> bending), 1595.73 (NH bending), 1087.8 (CS Str), 831.66 (Cl).

<sup>1</sup>H-NMR (δ ppm): 7.3(s, 3H, Ar-H), 7.2(m, 4H, Ar-Cl), 5.6(s, 1H, =CH), 2.5 (t, 2H, N-CH<sub>2</sub>), 2.3(t, 2H, N-CH<sub>2</sub>), 2.0 (s, H, NH).

TOF MS *m/z*: 405( M<sup>+</sup>), 268, 269, 105, 187, 238, 204.

**5-[2-(4-chloro-phenyl)-vinyl]-3-diethylaminoethyl-[1,2,4]triazolo[1,5-c]quinazolin-2-thione: (K 10)**

Yield: 45%; m. p: 290°C, Rf: 0.85 (ethyl acetate: ethanol, 1: 9 v/v).

IR (cm<sup>-1</sup>): 3361.08 (NH Str), 2953.05 (CH<sub>3</sub> Str), 2325.04 (CN Str), 1912.5 (CH<sub>2</sub> bending), 1560.27 (NH bending), 1087.8 (CS Str), 659.83 (Cl).

<sup>1</sup>H-NMR (δ ppm): 7.3(s, 3H, Ar-H), 7.2(m, 4H, Ar-Cl), 5.6(s, 1H, =CH), 1.4(q, 4H, CH<sub>2</sub>-CH<sub>3</sub>), 1.3 (t, 6H, CH<sub>3</sub>).

TOF MS *m/z*: 401(M<sup>+</sup>), 105, 269, 187, 182, 322.

**Substituted-[1,2,4]triazolo[1,5-c]quinazolin-2-one derivatives (K 11- K 19)**

A slurry consisting of (VII a-e), ethanol (5 ml) and 37% formamide (1 ml) was made. To this added appropriate secondary amine (0.01 mol) drop wise with cooling and shaking. The reaction mixture was allowed to stand at room temperature for 1 hour with occasional shaking, after which it was warmed on steam bath for 15 minutes. At the end of the period the contents were cooled and recrystallized from chloroform and petroleum ether.

**5-[2-(4-bromo-phenyl)-vinyl]-3-diethylaminomethyl-[1,2,4]triazolo[1,5-c]quinazolin-2-one (K 11)**

Yield: 43%; m. p: 180°C, Rf: 0.78 (dichloromethane: ethanol, 7: 3 v/v).

IR (cm<sup>-1</sup>): 3383.86 (NH Str), 3041.10 (CH<sub>3</sub> Str), 1383.69 (CO Str), 1942.95 (CH<sub>2</sub> bending), 1593 (NH bending), 500 (Br group).

<sup>1</sup>H-NMR (δ ppm): 7.9-6.7 (m, 18H Ar-H), 5.4-5.0 (2H, d, =C=CH), 3.4-3.3 (s, 2H, CH<sub>2</sub>).

TOF MS *m/z*: 461( M<sup>+</sup>), 269, 187, 105, 335.

**5-[2-(4-bromo-phenyl)-vinyl]-3-piperazin-1-yl-[1,2,4]triazolo[1,5-c]quinazolin-2-one (K 13)**

Yield: 53%; m. p: 173°C, Rf: 0.71 (dichloromethane: ethanol, 2: 8 v/v).

IR (cm<sup>-1</sup>): 3454.01 (NH Str), 2340.82 (CN Str), 2959.5 (CH<sub>3</sub> Str), 1347.8 (CO Str), 1412.61 (CH<sub>2</sub> bending), 1593.79 (NH bending).

<sup>1</sup>H-NMR (δ ppm): 7.9-6.7 (m, 18H Ar-H), 5.4-5.0 (d, 2H, -C=CH<sub>2</sub>), 3.4-3.3 (s, 2H, CH<sub>2</sub>).

TOF MS *m/z*: 463( M<sup>+</sup>), 105, 269, 346, 187.

**3-[(diphenylamino)-methyl]-5-[2-(4-nitro-phenyl)-vinyl]-[1,2,4]triazolo[1,5-c]quinazolin-2-one (K 14)**

Yield: 50%; m. p: 186°C, Rf: 0.68 (dichloromethane: ethanol, 2: 8 v/v).

IR (cm<sup>-1</sup>): 3406 (NH Str), 3041.6 (CH<sub>3</sub> Str), 1706 (CN bending), 1347.8 (CO Str), 1465.61 (CH<sub>2</sub> bending), 1596.79 (NH bending), 1343 (NO<sub>2</sub> group).

<sup>1</sup>H-NMR (δ ppm): 8.2-6.7 (m, 18H Ar-H), 5.6-4.9 (d, 2H, -C=CH<sub>2</sub>), 2.64-2.0 (s, 2H, CH<sub>2</sub>).

TOF MS *m/z*: 513(M<sup>+</sup>), 269, 105, 335, 187.

**5-[2-(2,4-dihydroxy-phenyl)-vinyl]-3-piperazin-1-yl-[1,2,4]triazolo[1,5-c]quinazolin-2-one (K 17)**

Yield: 40%; m. p: 175°C, Rf: 0.78 (dichloromethane: ethanol, 3: 7 v/v).

IR (cm<sup>-1</sup>): (3789.47 (OH Str), 2935.51 (CH<sub>3</sub> Str), 2341.71 (CN Str), 1097.59 (CO Str), 1412.44 (OH bending).

<sup>1</sup>H-NMR (δ ppm): 8.0 (m, 7H Ar-H), 3.3 (s, 2H, CH<sub>2</sub>), 2.5-2.1 (m, 4H, -N-C).

TOF MS *m/z*: 346(M<sup>+</sup>), 269, 187.

**3-[(diethylamino)-methyl]-5-styryl-[1,2,4]triazolo[1,5-c]quinazolin-2-one (K 18)**

Yield: 45%; m. p: 165°C, Rf: 0.80 (dichloromethane: ethanol, 3: 7 v/v).

IR (cm<sup>-1</sup>): 2935.51 (CH<sub>3</sub> Str), 2341.71 (CN Str), 1097.59 (CO Str).

<sup>1</sup>H-NMR (δ ppm): 8.6-8.0 (s, 1H, NH), 7.9-7.0 (m, 9H, Ar-H), 3.6(2H, d, -C=CH<sub>2</sub>).

TOF MS *m/z*: 372(M<sup>+</sup>), 170, 182, 187.

**5-[2-(4-hydroxy-phenyl)-vinyl]-3-piperazin-1-ylmethyl-[1,2,4]triazolo[1,5-c]quinazolin-2-one (K 19)**

Yield: 40%; m. p: 215°C, Rf: 0.90 (dichloromethane: ethanol, 1: 9 v/v).

IR (cm<sup>-1</sup>): (3776.09 (OH Str), 3423.88 (NH Str), 2935.51 (CH<sub>3</sub> Str), 2365.30 (CN Str), 1412.69 (OH bending).

<sup>1</sup>H-NMR (δ ppm): 8.6-7.2 (m, 8H Ar-H), 6.9-6.8 (d, 2H, -C=CH<sub>2</sub>), 2.7-2.3 (m, 4H,NC), 2.38-2.0 (s, 1H, NH), 2.0-1.9 (s, 2H, CH<sub>2</sub>).

TOF MS *m/z*: 401 (M<sup>+</sup>), 281, 161, 229, 263.

**Biological evaluation****Acute Toxicity Studies**

The acute oral toxicity study was carried out as per OECD-423 guidelines. The synthesized compound was found to be non-toxic up to 2000 mg/kg body weight and did not cause any death and therefore 100 mg/kg dose level was selected. The animal experimental protocol has met the approval of Institutional Animal Ethics Committee (IAEC).

**ANTIHYPERTENSIVE ACTIVITY:****Procurement of animals:**

For conducting the BP measurement studies, the animals were kept in a restrainer for 10 min every day for one week. This exercise was done to avoid the fluctuation in blood pressure due to aggressive behavior of animal while keeping into the restrainer for measuring the activity.

**Induction of hypertension in normotensive rats**

After recording the initial BP of rats, the animals were divided into groups of 5 animals each. One group was taken as control. Hypertension was induced in the remaining groups by subcutaneous injection of Deoxycorticosterone acetate (20 mg/kg/wk) for twice a week for 45 days as per method reported by Krakoff et al. The drinking water was replaced by 2% NaCl solution.

**Measurement of mean blood pressure of rats**

Mean arterial blood pressure was measured in conscious rats using CODA Non Invasive Blood Pressure Recorder by Tail-Cuff method (Kent Scientific Corporation, USA). The restrainer carrying the rat was placed in the BP instrument with tail protruding out. The tail was gently placed in contact with a transducer membrane, which was connected to the digital BP display panel. The instrument was then turned on and allowed to stabilize until steady pulse rate was observed. Once the "pulse level ready" signal appeared, the BP recording button was pressed and the mean arterial BP was recorded. Albino rats (body weight 150-200 g) were used in present study. Rats were assigned to groups of four animals in each. Each compound (100 mg/kg body weight) was injected intraperitoneally after suspending in 1% carboxymethyl cellulose (CMC) solution. The mean arterial blood pressure was recorded after 1 h.



**Statistical analysis:** All values were expressed as mean  $\pm$  SEM. The values obtained from the above parameters in case of synthesized compounds were compared with standard drug and controlled group by using one way ANOVA followed  $p < 0.001$ , was considered significant.

## RESULTS AND DISCUSSION

The structures of synthesized compounds were confirmed by IR,  $^1\text{H}$ NMR and mass spectral analysis. Our seven synthesized compounds K 1, K 3, K 8, K 9, K 10, K 17 and K 18 have shown antihypertensive activity. However compound K 1, K 3, K 8, K 9 and K18 has shown significant antihypertensive activity comparable to standard drug prazosin (20 mg/kg, i.p.). This effect might be due to vasodilatation. So, further research is required to determine the specific mode of its antihypertensive activity. Results are shown in figure 2 and Table 1.

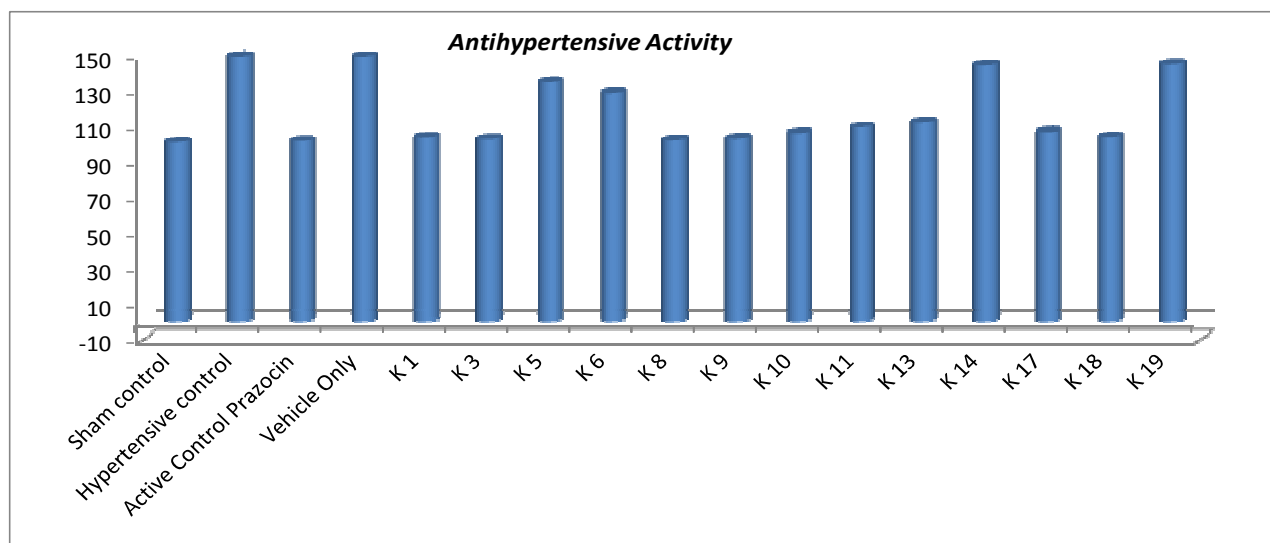
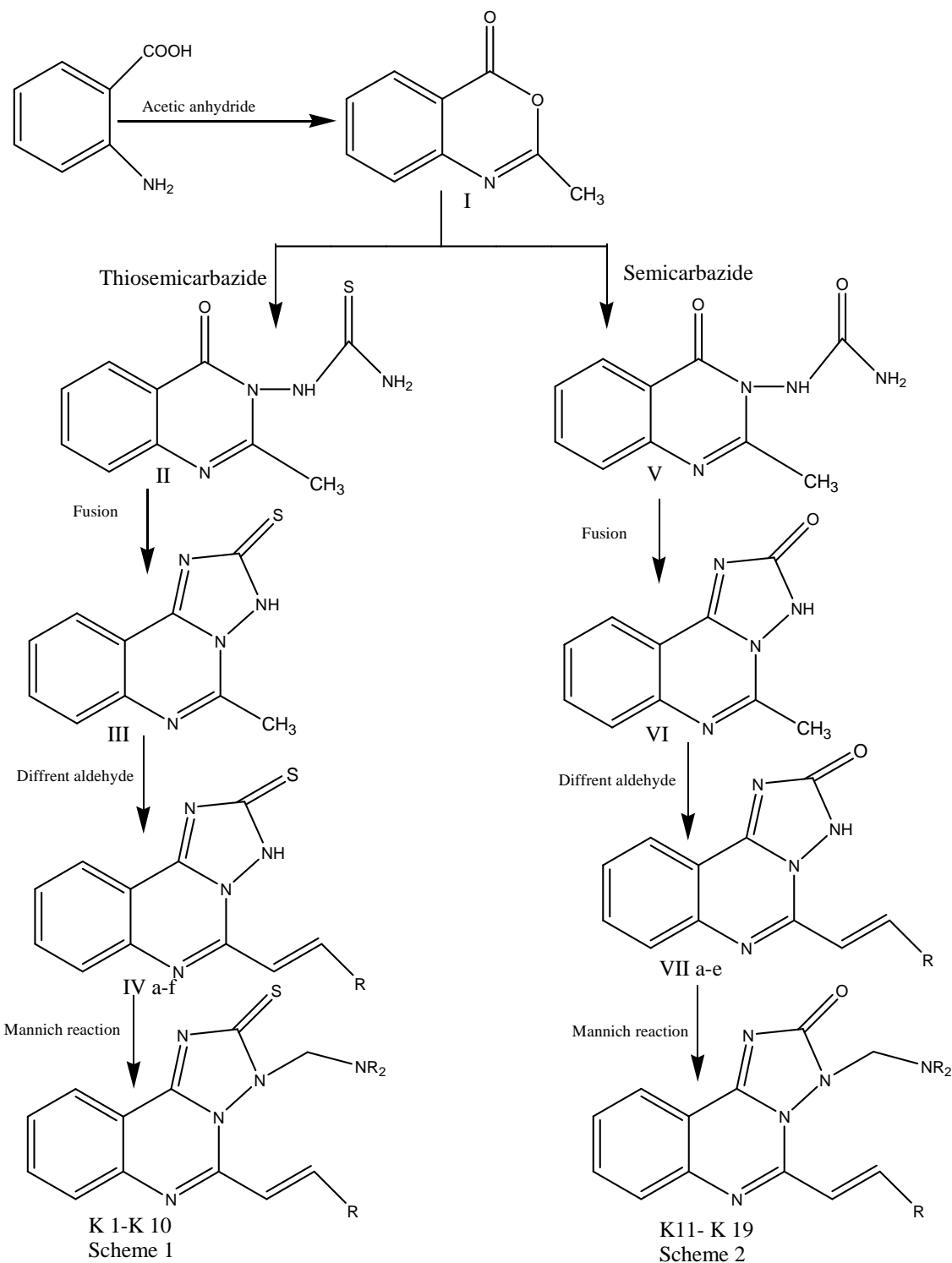


Figure 2: Change in MABP Vs synthesized triazolo-quinazolinone compounds

Table 1: Antihypertensive activity of synthesized compounds

Group	Compound	Dose mg/kg i.p	MABP (Mean $\pm$ Sem)	% Reduction of MABP
1.	Sham control	5 ml/kg.	101.50 $\pm$ 0.56	--
2.	Hypertensive control (Deoxy cortico sterone acetate)	20	166.50 $\pm$ 0.76	--
3.	Active Control (Standard drug Prazocin)	20	102.30 $\pm$ 0.38	38.55
4.	Negative control (Vehicle Only)	5 ml/kg	169.20 $\pm$ 0.65	---
5.	K 1	100	104.25 $\pm$ 0.75	37.38
6.	K 3	100	103.30 $\pm$ 0.70	37.48
7.	K 5	100	135.40 $\pm$ 0.45	18.70
8.	K 6	100	129.25 $\pm$ 0.65	22.30
9.	K 8	100	102.75 $\pm$ 0.80	38.50
10.	K 9	100	103.50 $\pm$ 0.38	37.80
11.	K 10	100	106.50 $\pm$ 0.65	36.16
12.	K 11	100	109.70 $\pm$ 0.78	33.50
13.	K 13	100	112.50 $\pm$ 0.50	32.50
14.	K 14	100	144.90 $\pm$ 0.35	13.02
15.	K 17	100	107.25 $\pm$ 0.54	35.80
16.	K 18	100	104.50 $\pm$ 0.78	37.65
17.	K 19	100	145.50 $\pm$ 0.68	12.15



Scheme



## CONCLUSION

All synthesized compounds (K 1-19) resulted in good yields with 50-60%. The anti-hypertensive activity of synthesized compounds was performed on albino rats using Prazocin 20 mg/kg as standard drug. Seven synthesized compounds have shown good antihypertensive activity as compared to standard drug Prazocin. Compounds K 1, K 3, K 8, K 9 and K18 have shown significant antihypertensive activity. This result reveals that the compounds containing piperazine and diethylamine substitution at 3<sup>rd</sup> position of triazolo-quinazolinone nucleus enhances their anti-hypertensive activities. So, further research is required to determine the specific mode of antihypertensive activity of triazolo-quinazolinone derivatives.

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