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Synthesis and antihypertensive activity of novel 3-benzyl-2-substituted-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-ones

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Abstract—A series of 3-benzyl-2-substituted-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-ones have been synthesized by the cyclocondensation of 3-amino-2-benzylamino-3*H*-quinazolin-4-one with a variety of one-carbon donors. The starting material 3-amino-2-benzylamino-3*H*-quinazolin-4-one was synthesized from methyl anthranilate by a novel innovative route. The title compounds were evaluated for their in vivo antihypertensive activity using spontaneously hypertensive rats (SHR). While all the test compounds exhibited significant antihypertensive activity, 3-benzyl-2-methyl-3*H*-[1,2,4]triazolo[5,1-*b*] quinazolin-9-one exhibited antihypertensive activity more than the reference standard prazocin.

1. Introduction

Diseases of the arterial tree cause more premature deaths than all other diseases such as cancer and infections combined. Among the major risk factors for arterial diseases, high blood pressure has been identified as the most powerful one.[1] Quinazolines and condensed quinazolines are reported to possess interesting pharmacological activities like antihypertensive,[2,3] antihistaminic,[4,5] analgesic and antiinflammatory,[6,7] anticancer,[8] and anti-HIV[9] activities. In spite of various triazolo quinazoline systems having been prepared and studied, the synthesis of 1,2,4-triazolo[5,1-*b*]quinazoline nucleus is relatively unexplored.[10,11] Quinazoline derived α_1 blockers like prazocin, terazocin and doxazocin are reputed class of antihypertensive agents. Potent antihypertensive activity has been observed in 1,2,4-triazolo quinazoline derivatives.[12] In view of these facts and to develop our earlier reported quinazolines[13] and its bioisostere thienopyrimidines[14] that showed significant antihypertensive activity, in the present study we aimed to synthesize some 3-benzyl-2-substituted-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-ones.

The title compounds were synthesized by the cyclocondensation of 3-amino-2-benzylamino-3*H*-quinazolin-4-one with a variety of one-carbon donors. The starting material 3-amino-2-benzylamino-3*H*-quinazolin-4-one was synthesized from methyl anthranilate by a novel innovative route (Scheme 3). The chemical structures of the synthesized compounds were confirmed on the basis of their spectral data (IR, NMR and mass spectra) and the purity was ascertained by microanalysis. The title compounds were investigated for their in vivo antihypertensive activity on spontaneously hypertensive rats (SHR) by tail cuff method.

2. Results and discussion

2.1. Chemistry

The key intermediate 3-amino-2-mercapto-3*H*-quinazolin-4-one **3** was prepared by the cyclization of 2-(methoxycarbonyl) phenyl isothiocyanate (**2**) with hydrazine hydrate (Scheme 1). The starting material 2-(methoxycarbonyl) phenyl isothiocyanate (**2**) was synthesized by the reaction between methyl anthranilate and phosgene. However, this route is not much attractive as it involves the use of highly toxic chemical, thiophosgene, making it less environment friendly. Moreover it also gives compound **3** in low yield (40%).

Hence an alternate route (Scheme 2) was attempted to synthesize **3**. In this route, methyl anthranilate (**1**) was reacted with carbon disulfide and potassium carbonate

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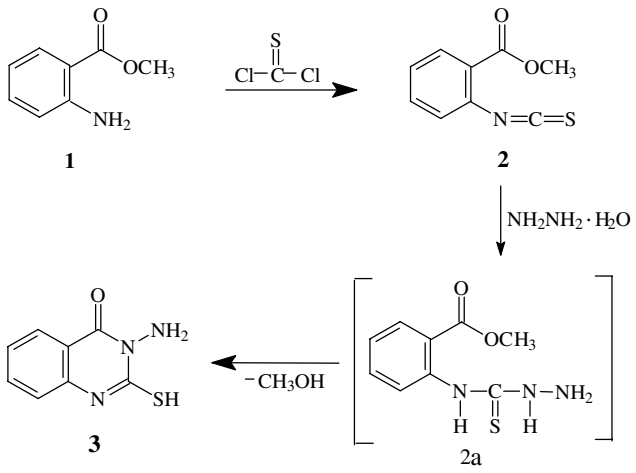
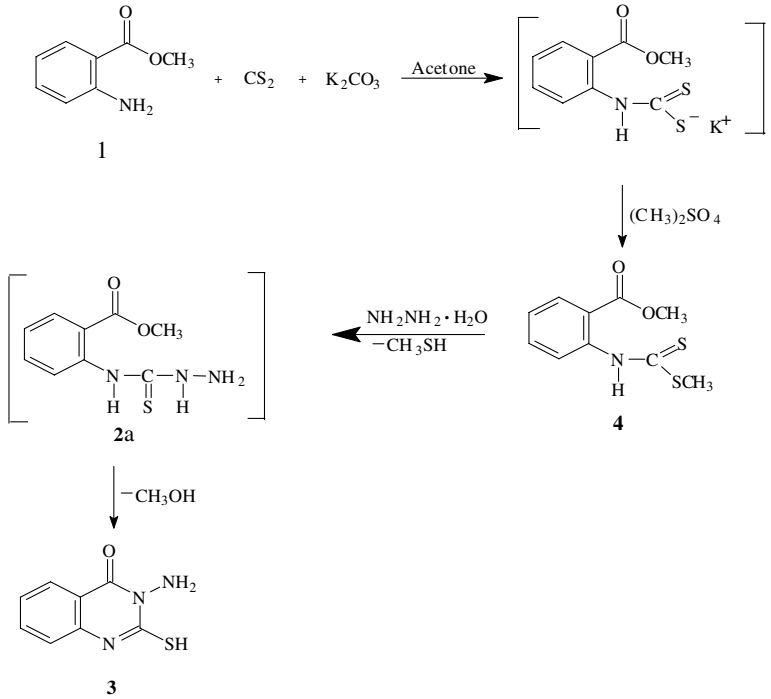


Scheme 1. Synthesis of 3-amino-2-mercapto-3*H*-quinazolin-4-one.

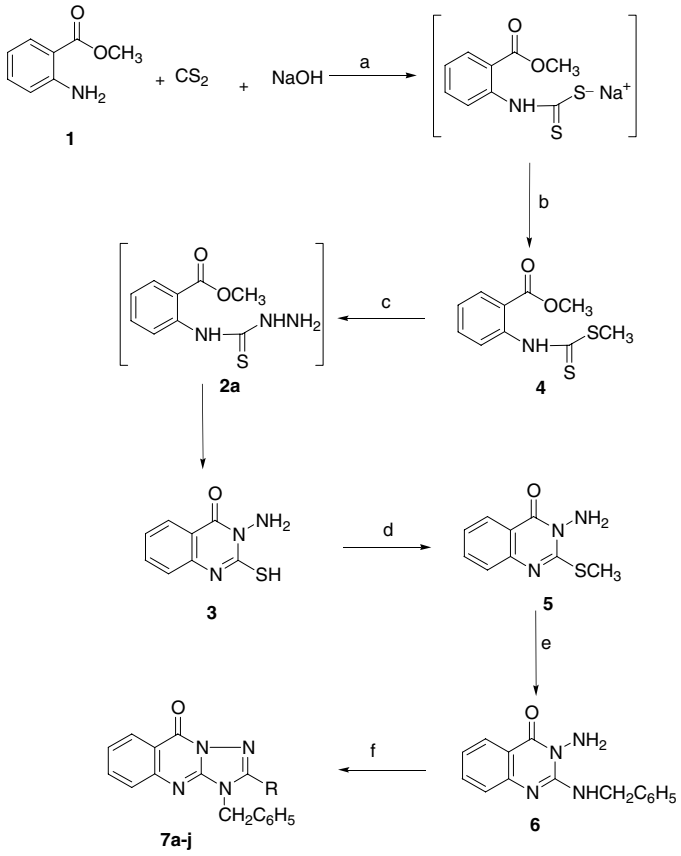
in acetone to give potassium dithiocarbamate, which was methylated with dimethyl sulfate to afford dithiocarbomic acid methyl ester (**4**). Compound **4** on treatment with hydrazine hydrate yielded **3**. The process of synthesizing **3**, by this scheme, suffers from the following drawbacks: it requires prolonged reaction time (36 h) and a multi-step process, also yield is low (43%). Hence, improvisation was carried out on this method, aqueous sodium hydroxide (20 mol solution) was used as a base instead of anhydrous K_2CO_3 and dimethylsulfoxide was substituted for acetone as the reaction solvent (Scheme 3). The use of DMSO as the reaction solvent enhanced the rate of reaction and the use of alkali in higher concentration helped in preventing the hydrolysis of the intermediate, probably, due to less solvation. These modifications not only curtail the reaction time from 37 to 5 h, but also increased the yield from 43% to 90%.

Thus, methyl anthranilate (**1**) was treated with carbon disulfide and sodium hydroxide in dimethylsulfoxide to give sodium dithiocarbamate, which was methylated with dimethyl sulfate to afford the dithiocarbomic acid methyl ester (**4**). Compound **4** on reaction with hydrazine hydrate afforded the desired 3-amino-2-mercapto-3*H*-quinazolin-4-one **3** via the thiosemicarbazide intermediate in good yield (90%). The product obtained was cyclic and not an open-chain thiosemicarbazide **2a**. IR spectra of compound **3** showed intense peaks at 3300 and 3220 cm^{-1} for amino (NH_2), 2560 $cm^{-1}$for SH and 1680 cm^{-1} for carbonyl (C=O). NMR spectrum of **3** showed singlet at δ 3.21 due to SH; a singlet at δ 5.12 due to NH_2 group and a multiplet at δ 7.14–7.32 for aromatic (4H) protons. Data from the elemental analyses have been found to be in conformity with the assigned structure. Further, the molecular ion peak recorded in the mass spectra is in agreement with the molecular weight of the compound.

The 3-amino-2-methylsulfanyl-3*H*-quinazolin-4-one **5** was obtained by dissolving **3** in 10% aqueous sodium hydroxide solution and methylating with dimethyl sulfate with stirring at room temperature. The IR spectra of **5** showed disappearance of mercapto (SH) signal of the starting material. It showed a peak for carbonyl (C=O) stretching at 1700 cm^{-1}. The NMR spectrum of compound **5** showed singlet at δ 2.51 and 6.6 due to $SCH_3$and NH_2, respectively, and a multiplet at δ 7.5–7.8 was observed for aromatic (4H) protons. Data from the elemental analyses and molecular ion peak recorded in the mass spectrum further confirmed the assigned structure.



Scheme 2. Synthesis of 3-amino-2-mercapto-3*H*-quinazolin-4-one.



Scheme 3. Synthesis of 3-benzyl-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-ones. Reagents and conditions: (a) DMSO, rt, 30 min; (b) $(CH_3)_2SO_4$, 5–10 °C, 3 h; (c) NH_2NH_2, ethanol reflux for 1.5 h; (d) NaOH, $(CH_3)_2SO_4$, DMF, rt, 12 h; (e) $C_6H_5CH_2NH_2$, 80 °C, 36 h; (f) one-carbon donor, reflux for 6 h.

Nucleophilic displacement of methylthio group of **5** with benzylamine was carried out by heating at 80 °C to afford 3-amino-2-benzylamino-3*H*-quinazolin-4-one **6**. The long duration of reaction (36 h) required might be due to the presence of amino group at position 3, which might have reduced the reactivity of quinazoline ring system at C-2 position towards the nucleophiles. The formation of **6** was confirmed by IR spectra of NH and NH_2 signals at 3400–3350 cm^{-1}. It also showed a peak for carbonyl (C=O) at 1680 cm^{-1}. The NMR spectrum of the compound **6** showed singlet at δ 4.3, 4.9 and 5.3 due to NH, CH_2 and NH_2, respectively, and a multiplet at δ 7.4–8.4 was observed for aromatic (9H) protons. Data from the elemental analyses have been found to be in conformity with the assigned structure. Further, the molecular ion peak recorded in the mass spectra is in agreement with the molecular weight of the compound.

The title compounds **7a**–**j** were obtained in fair to good yields through the cyclization of **6** with a variety of single-carbon donors such as carboxylic acids (formic acid, acetic acid, butyric acid and chloroacetyl chloride), isothiocyanates (phenyl isothiocyanate, 4-methylphenyl isothiocyanate, 4-methoxyphenyl isothiocyanate and 4-ethoxy phenyl isothiocyanate). Nucleophilic displacement of chloro compound **7d** with morpholine and pyrrolidine afforded the compounds **7e** and **7f**. The formation of cyclic product is indicated by the disappearance of peaks due to NH and NH_2 of the starting material in IR and NMR spectra of all the compounds **7a**–**j**. The mass spectrum of the title compounds are in conformity with the assigned structure. The mass spectrum of these compounds showed molecular ion peaks corresponding to their molecular formulae. In mass spectra of compounds **7a**–**j** the peak due to 1,2,4-triazolo [4,3-*a*] quinazoline cation appeared at *m*/*z* 168. In addition a common peak at *m*/*z* 144 corresponding to quinazolin-4-one moiety appeared in all mass spectra. The MS of compound **7d**showed M^++2 peak confirming the presence of a chlorine atom in the compound, the relative intensity of this M^++2 peak compared with M^+ peak was in the ratio of 1:3. Elemental (C, H, N) analysis satisfactorily confirmed elemental composition and purity of the synthesized compounds.

2.2. Antihypertensive activity

In vivo antihypertensive activity study of the title compounds was performed on SHR by tail cuff method using Harvard Blood Pressure Monitor. Advantage of this method is that it is non-invasive and the animals are recovered after the experiment. The results of antihypertensive activity study indicate that all the test compounds were found to reduce blood pressure (BP) significantly (Table 1), however there was no significant

Table 1. Antihypertensive activity of compounds **7a–j** [percent decrease in BP (mm Hg)]

Compound	1 h	2 h	3 h	4 h	5 h
7a	05.4 ± 1.14*	07.3 ± 1.32*	17.3 ± 1.39*	20.8 ± 2.37**	19.8 ± 2.29*
7b	15.3 ± 1.91*	31.5 ± 2.13***	33.5 ± 3.12***	38.8 ± 1.32**	15.3 ± 1.18*
7c	13.4 ± 1.55*	20.5 ± 1.32**	19.0 ± 1.18**	17.0 ± 1.35*	15.7 ± 1.33**
7d	03.7 ± 3.10*	11.9 ± 1.99*	15.0 ± 1.58*	17.2 ± 1.37*	06.7 ± 1.38**
7e	08.6 ± 3.33*	10.0 ± 1.36*	21.7 ± 1.31**	25.6 ± 2.32***	19.4 ± 2.35*
7f	03.6 ± 1.31**	05.1 ± 1.17*	09.1 ± 3.19*	16.1 ± 1.31**	13.1 ± 2.19*
7g	06.1 ± 1.71**	07.1 ± 3.32*	10.1 ± 1.17*	13.1 ± 7.12*	14.1 ± 4.32*
7h	04.7 ± 4.32*	05.6 ± 6.34**	9.1 ± 3.33*	11.6 ± 3.81*	16.2 ± 5.13**
7i	05.9 ± 7.65*	09.7 ± 4.63*	09.6 ± 4.51*	12.6 ± 7.44*	15.4 ± 6.53*
7j	06.5 ± 4.41*	07.6 ± 4.31**	9.52 ± 6.81*	13.6 ± 7.75*	16.5 ± 6.59*
Prazocin	30.2 ± 1.82**	24.6 ± 1.32**	18.0 ± 1.27*	19.6 ± 1.36**	12.9 ± 1.19*

Each value represents the mean ± SEM ($n = 6$).
Significance levels $^{*}p < 0.1$, $^{**}p < 0.05$ and $^{***}p < 0.01$ as compared with the respective control.

effect on heart rate. Biological activity studies indicated that different substituents over the second position of triazoloquinazoline ring exerted varied biological activity. The compound **7a** with no substitution at C-2 moderately reduced BP. When lipophilicity was increased by substituting with methyl group (**7b**) activity increased. Further increase of lipophilicity by placing propyl group (**7c**) leads to retaining the activity. Replacement of a methyl group of **7b** by lipophobic group (chloro) (**7d**) or by a secondary amine (**7e** and **7f**) results in decreased activity. Placement of aryl amines (**7g**–**7j**) at C-2 also showed decrease in activity.

3. Conclusion

In summary, the synthesis of new series of 3-benzyl-2-substituted-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-ones has been described. In this study, intermediate compound of 3-amino-2-mercapto-3*H*-quinazolin-4-one has been synthesized by novel innovative route with improved yield. These derivatives have exhibited promising antihypertensive activity against *in vivo* model. Among the series, 3-benzyl-2-methyl-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-one (**7b**) was found to be the most active antihypertensive agent which is more potent than the reference standard prazocin and could therefore serve as a lead molecule for further modification to obtain a clinically useful novel class of antihypertensive agents.

4. Experimental

4.1. General

Melting points (mp) were taken in open capillaries on Thomas Hoover melting point apparatus and are uncorrected. The IR spectra were recorded in film or in potassium bromide disks on a Perkin-Elmer 398 spectrometer. The ^{1}H NMR spectra were recorded on a DPX-300 MHz Bruker FT-NMR spectrometer. The chemical shifts were reported as parts per million (δ ppm) with tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained on a JEOL-SX-102 instrument using fast atom bombardment (FAB positive). Elemental analysis was performed on a Perkin-Elmer 2400 C, H, N analyzer and values were within the acceptable limits of the calculated values. The progress of the reaction was monitored on readymade silica gel plates (Merck) using chloroform/methanol (9:1) as a solvent system. Iodine was used as a developing agent. Spectral data (IR, NMR and mass spectra) confirmed the structures of the synthesized compounds and the purity of these compounds was ascertained by microanalysis. Elemental (C, H, N) analysis indicated that the calculated and observed values were within the acceptable limits (±0.4%). All chemicals and reagents were obtained from Aldrich (USA), Lancaster (UK) or Spectrochem Pvt. Ltd (India) and were used without further purification.

4.1.1. 3-Amino-2-mercapto-3*H*-quinazolin-4-one (3). To a vigorously stirred solution of methyl anthranilate (**1**) (0.02 mol) in dimethylsulfoxide (10 ml) at room temperature, carbon disulfide (1.6 ml, 0.026 mol) and aqueous sodium hydroxide (1.2 ml, 20 mol solution) were added dropwise simultaneously over 30 min, the mixture was then allowed to stir for 30 min more. CAUTION dimethyl sulfate (0.02 mol) was added dropwise under cooling with an ice bath. Stirring was continued for 3 h, the reaction mixture was poured into ice-water and then it was extracted with chloroform. The solvent was removed by distillation under reduced pressure. Thus, the obtained crude methyl *N*-(2-methoxycarbonyl phenyl) dithiocarbamate dissolved in ethanol 30 ml was treated with hydrazine hydrate (0.2 mol) added dropwise to this by keeping the reaction mixture at 5–10 °C. Stirring was continued for 1.5 h at 50 °C and then the reaction mixture was poured into ice-water. The solid obtained was filtered, washed with water, dried and recrystallized from dimethyl formamide and ethanol. Yield = 90%; mp 236–237 °C; ^{1}H NMR ($CDCl_3$): δ 3.21 (s, 1H, SH), 5.12 (s, 2H, NH_2, D_2O exchangeable), 7.14–7.32 (m, 4H, ArH); IR (KBr) cm^{-1}: 3300, 3220 (NH_2), 2560 (SH), 1680 (C=O); MS *m*/*z*: 193 (M^+); Anal. Calcd for $C_8H_7N_3OS$: C, 49.72; H, 03.64; N, 21.74. Found: C, 49.81; H, 03.61; N, 21.67.

4.1.2. 3-Amino-2-methylsulfanyl-3*H*-quinazolin-4-one (5). To a solution of 3-amino-2-mercapto-3*H*-quinazolin-4-one (**3**) (0.01 mol) in sodium hydroxide (10 ml, 10% solution), dimethyl sulfate (0.01 mol) was added drop-

wise under constant stirring. The solution was stirred further at room temperature for 12 h. The solid obtained was filtered, washed with cold water, dried and recrystallized from chloroform/ethanol (50:50), yield = 91%, mp 155–159 °C; ^{1}H NMR (DMSO-d_6): δ 2.51 (s, 3H, SCH_3), 6.6 (s, 2H, NH_2, D_2O exchangeable), 7.5–7.8 (m, 4H, ArH); IR (KBr) cm^{-1}: 3400, 3320 (NH_2), 1700 (C=O); MS *m*/*z*: 207 (M^+); Anal. Calcd for $C_8H_9N_3OS$: C, 52.15; H, 04.37; N, 20.27. Found: C, 52.10; H, 04.39; N, 20.31.

4.1.3. 3-Amino-2-benzylamino-3*H*-quinazolin-4-one (6). A mixture of benzylamine (0.05 mol) and 3-amino-2-methylsulfanyl-3*H*-quinazolin-4-one (**5**) (0.01 mol) was heated at 80 °C on an oil bath for 36 h. The reaction mixture was cooled and triturated with petroleum ether (60–80), the separated solid was filtered and recrystallized from ethanol. Yield = 72%, mp 168–170 °C; ^{1}H NMR ($CDCl_3$): δ 4.3 (t, 1H, NH, D_2O exchangeable), 4.9 (s, 2H, CH_2), 5.3 (s, 2H, NH_2), 7.4–8.4 (m, 9H, ArH); IR (KBr) cm^{-1}: 3400, 3350 (NH_2), 1680 (C=O); MS *m*/*z*: 266 (M^+); Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 05.29; N, 21.03. Found: C, 67.61; H, 5.36; N, 21.07.

4.1.4. 3-Benzyl-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-one (7a). A mixture of **6** (0.01 mol) and formic acid (15 ml) was refluxed on an oil bath for 6 h. The reaction mixture was then poured into crushed ice, the solid separated was filtered, washed with water, dried and recrystallized from ethanol. Yield = 94%, mp 224–225 °C; ^{1}H NMR ($CDCl_3$): δ 5.3 (s, 2H, CH_2), 5.5 (s, 1H, CH), 7.7-8.0 (m, 9H, ArH); IR (KBr) cm^{-1}: 1700 (C=O); MS *m*/*z*: 276 (M^+); Anal. Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 04.37; N, 20.27. Found: C, 69.51; H, 04.41; N, 20.29. The following compounds **7b** and **7c** were prepared using a similar procedure to that described for **7a**.

4.1.5. 3-Benzyl-2-methyl-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-one (7b). The title compound was prepared from **6** and acetic acid in 95% yield. Mp 221–223 °C; ^{1}H NMR ($CDCl_3$): δ 2.3 (s, 3H, CH_3), 4.9 (s, 2H, CH_2), 7.2–8.3 (m, 9H, ArH); IR (KBr) cm^{-1}: 1680 (C=O), MS *m*/*z*: 290 (M^+); Anal. Calcd for $C_{17}H_{14}N_4O$: C, 70.33; H, 04.86; N, 19.29. Found: C, 70.35; H, 04.83; N, 19.33.

4.1.6. 3-Benzyl-2-propyl-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-one (7c). The title compound was prepared from **6** and butyric acid in 88% yield. Mp 135–137 °C; ^{1}H NMR ($CDCl_3$) δ 1.1–1.2 (t, 3H, $CH_2CH_2CH_3$), 1.7–1.8 (sext, 2H, $CH_2CH_2CH_3$), 2.8–2.9 (t, 2H, $CH_2CH_2CH_3$), 3.7 (s, 2H, CH_2), 7.6–8.2 (m, 9H, ArH); IR (KBr) cm^{-1}: 1690 (C=O); MS *m*/*z*: 318 (M^+); Anal. Calcd for $C_{19}H_{18}N_4O$: C, 71.67; H, 05.69; N, 17.59 Found: C, 71.74; H, 5.72; N, 17.57.

4.1.7. 3-Benzyl-2-chloromethyl-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-one (7d). A mixture of **6** (0.01 mol) and chloroacetylchloride (0.01 mol) in glacial acetic acid (15 ml) was refluxed on an oil bath for 8 h, the reaction mixture was then poured into crushed ice and the solid separated was filtered, washed with water, dried and recrystallized from ethanol. Yield = 79%, mp 212–215 °C; ^{1}H NMR ($CDCl_3$): δ 5.5 (s, 2H, N–CH_2), 5.9 (s, 2H, CH_2-Cl), 7.4–8.3 (m, 9H, ArH); IR (KBr) cm^{-1}: 1685 (C=O); MS *m*/*z*: 324 (M^+); Anal. Calcd for $C_{17}H_{13}N_4OCl$: C, 62.87; H, 04.03; N, 17.25. Found: C, 62.91; H, 04.07; N, 17.29.

4.1.8. 3-Benzyl-2-(morphlinyl methyl)-3*H*-[1,2,4]triazolo-[5,1-*b*] quinazolin-9-one (7e). A mixture of **7d** (0.01 mol), morpholine (0.05 mol) and anhydrous potassium carbonate (100 mg) in dioxane (15 ml) was refluxed on an oil bath for 30 h. Then the reaction mixture was poured into crushed ice, the solid obtained was filtered, washed with water, dried and recrystallized from benzene/methanol (50:50). Yield = 80%, mp 200–203 °C; ^{1}H NMR ($CDCl_3$): δ 3.4 (m, 4H, –$N(CH_2CH_2)_2O$–), 3.9 (m, 4H, –$N(CH_2CH_2)_2O$–), 4.84 (s, 2H, N–CH_2), 5.4 (s, 2H, CH_2), 7.1–8.0 (m, 9H, ArH); IR (KBr) cm^{-1}: 1693 (C=O); MS *m*/*z*: 375 (M^+); Anal. Calcd for $C_{21}H_{21}N_5O_2$: C, 67.18; H, 05.63; N, 18.65. Found: C, 67.26; H, 5.65; N, 18.62. Adopting this procedure compound **7f** was prepared.

4.1.9. 3-Benzyl-2-(piperidyl methyl)-3*H*-[1,2,4]triazolo-[5,1-*b*] quinazolin-9-one (7f). The title compound was prepared from **7d** and piperidine in 50% yield. Mp 189–190 °C; ^{1}H NMR ($CDCl_3$): δ 1.6–1.9 (m, 6H, –$NCH_2CH_2CH_2$-piperidinyl), 2.0–2.2 (m, 4H, –NCH_2CH_2-piperidinyl), 4.3 (s, 2H, –N–CH_2-piperidinyl), 5.1 (s, 2H, CH_2), 7.8–8.4 (m, 9H, ArH); IR (KBr) cm^{-1}: 1690 (C=O); MS *m*/*z*: 373 (M^+); Anal. Calcd for $C_{22}H_{23}N_5O$: C, 70.75; H, 06.20; N, 18.75. Found: C, 70.81; H, 06.29; N, 18.74.

4.1.10. 3-Benzyl-2-phenyl-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-one (7g). A mixture of **6** (0.01 mol) and phenyl isothiocyanate (0.01 mol) in dimethylformamide (10 ml) was refluxed on an oil bath for 12 h. The reaction mixture was cooled, poured into ice water and the solid separated was filtered, dried and recrystallized from benzene/methanol (50:50). Yield = 38%, mp 216–218 °C; ^{1}H NMR ($CDCl_3$): δ 4.5 (s, 1H, NH), 5.4 (s, 2H, CH_2), 7.1–8.2 (m, 14H, ArH); IR (KBr) cm^{-1}: 3380 (NH), 1680 (C=O); MS *m*/*z*: 367 (M^+); Anal. Calcd for $C_{22}H_{17}N_5O$: C, 71.92; H, 04.66; N, 19.06. Found: C, 71.86; H, 04.71; N, 19.09. Using this procedure compounds **7h**–**7j** were prepared.

4.1.11. 3-Benzyl-2-(4-methylphenyl)-3*H*-[1,2,4]triazolo[5,1-*b*] quinazolin-9-one (7h). The title compound was prepared from **6** and 4-methylphenyl isothiocyanate in 40% yield. Mp 205–207 °C; ^{1}H NMR ($CDCl_3$): δ 2.7 (s, 3H, CH_3), 4.0 (s, 1H, NH), 4.9 (s, 2H, CH_2), 7.0–8.5 (m, 13H, ArH); IR (KBr) cm^{-1}: 3320 (NH), 1686 (C=O); MS *m*/*z*: 381 (M^+); Anal. Calcd for $C_{23}H_{19}N_5O$: C, 72.42; H, 05.02; N, 18.35. Found: C, 72.51; H, 05.09; N, 18.37.

4.1.12. 3-Benzyl-2-(4-methoxyphenyl)-3*H*-[1,2,4]triazolo-[5,1-*b*] quinazolin-9-one (7i). The title compound was prepared from **6** and 4-methoxyphenyl isothiocyanate in 38% yield. Mp 260–262 °C; ^{1}H NMR ($CDCl_3$): δ 2.8 (s, 3H, OCH_3), 4.2 (s, 1H, NH), 4.7 (s, 2H, CH_2), 7.7–8.9 (m, 13H, ArH); IR (KBr) cm^{-1}: 3290 (NH),

1692 (C=O); MS *m/z*: 397 (M^+); Anal. Calcd for $C_{23}H_{19}N_5O_2$: C, 69.50; H, 04.81; N, 17.62. Found: C, 69.41; H, 04.86; N, 17.66.

4.1.13. 3-Benzyl-2-(4-ethoxyphenyl)-3*H*-[1,2,4]triazolo[5,1-*b*] quinazolin-9-one (7j). The title compound was prepared from **6** and 4-ethoxyphenyl isothiocyanate in 40% yield. Mp 272–273 °C; ^{1}H NMR ($CDCl_3$): δ 2.1 (3H, t, CH_2CH_3), 3.8 (s, 1H, NH), 4.2 (q, 2H, CH_2CH_3), 4.7 (s, 2H, CH_2), 7.6–8.7 (m, 13H, ArH); IR (KBr) cm^{-1}: 3260 (NH), 1687 (C=O); MS *m/z*: 411 (M^+); Anal. Calcd for $C_{24}H_{21}N_5O_2$: C, 70.05; H, 05.14; N, 17.02. Found: C, 70.16; H, 05.17; N, 17.04.

4.2. Antihypertensive activity

In vivo antihypertensive activity study of the title compounds was performed on SHR by tail cuff method using Harvard Blood Pressure Monitor.[15] In each group six rats were taken. Test compounds and prazocin at a dose of 5 mg/kg were administered orally as suspension in 1% sodium carboxy methyl cellulose. Measurements (blood pressure and heart rate) were recorded before and after the treatment of test compounds and standard drug, at the interval of 1 h for 5 h. Student's *t*-test was performed to ascertain the significance of the exhibited activity. Percent decrease in BP was calculated by the following formula and is shown in Table 1.

$$\%\ \text{Reduction in BP} = [\text{BP of SHR before drug treatment} - \text{BP of SHR after drug treatment}] / [\text{BP of SHR before drug treatment}] \times 100$$

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2007.03.007.

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