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Synthesis and pharmacological investigation of novel 4-benzyl-1-substituted-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-ones as new class of H_1-antihistaminic agents

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Abstract—A series of novel 1-substituted-4-benzyl-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-ones were synthesized by the cyclization of 2-hydrazino-3-benzyl-3*H*-quinazolin-4-one with various one-carbon donors. The starting material 2-hydrazino-3-benzyl-3*H*-quinazolin-4-one was synthesized from benzylamine by a new innovative route. When tested for their in vivo H_1-antihistaminic activity on guinea pigs, all the test compounds protected the animals from histamine induced bronchospasm significantly. The compound 1-methyl-4-benzyl-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (**II**) emerged as the most active compound of the series and it is more potent (percent protection 76%) when compared to the reference standard chlorpheniramine maleate (percent protection 71%). Compound **II** showed negligible sedation (7%) when compared to chlorpheniramine maleate (30%). Hence it could serve as prototype molecule for further development as a new class of H_1-antihistamines.

1. Introduction

The first generation antihistamines penetrate the blood–brain barrier and also possess anticholinergic properties and this has led to the development of a second generation[1] of H_1-antagonists such as terfenadine, cetirizine, and astemizole. A common feature of first generation compounds includes two aryl or heteroaryl rings linked to an aliphatic tertiary amine via the side chain[2] (e.g., Diphenhydramine and Pheniramine), the second-generation compounds (Terfenadine and Cetirizine) also contain many of the common structural features of first generation compounds. The real breakthrough of non-sedative antihistamines came in the early eighties of twentieth century when the discovery of modern antihistamines was found to exhibit potent antihistaminic activity without sleep-inducing effect.[3] Condensed heterocycles containing new generation of H_1-antihistamines (e.g., Loratadine, Azelastine, and Flazelastine) that do not possess the above-mentioned pharmacophore for H_1-antihistamines gave way for the discovery of many novel antihistamines temelastine[4] and mangostin.[5] A literature survey reveals excellent antihistaminic activity in quinazolines and condensed quinazolines.[6,7] In view of these facts and to continue our efforts[8,9] in the search of quinazoline derivatives as potent antihistamines with least sedation, we aimed at preparing a series of 1,2,4-triazolo-4*H*-[4,3-*a*]quinazolin-5-ones containing benzyl substitution at position 4 and alkyl/alicyclic amine substitution at position 1. The title compounds were synthesized by the cyclization of 3-benzyl-2-hydrazino-3*H*-quinazolin-4-one **6** with various one-carbon donors. The 3-benzyl-2-hydrazino-3*H*-quinazolin-4-one **6** was synthesized from benzylamine **1** by a new innovative route (Scheme 3). Spectral data (IR, NMR, and mass spectra) confirmed the structures of the synthesized compounds; the purity of these compounds was ascertained by microanalysis (Table 1). The synthesized compounds were tested for their in vivo H_1-antihistaminic activity on conscious guinea pigs. As sedation is one of the major side effects associated with antihistamines, the test compounds were also evaluated for their sedative potentials, by measuring the reduction in locomotor activity using actophotometer.

Keywords: Quinazoline; Pyrimidine; Antihistamine.
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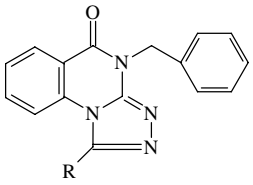
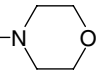
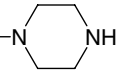
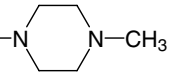
Table 1. Characterization data of 4-benzyl-substituted-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-ones



Compound	R	Mol. formula	Mp °C (% yield)	Elemental analysis calculated/found		
				%C	%H	%N
I	–H	$C_{16}H_{12}N_4O$	249–251 (73)	69.55 69.59	04.38 04.49	20.08 20.03
II	$-CH_3$	$C_{17}H_{14}N_4O$	258–259 (79)	70.33 70.38	04.86 04.84	19.30 19.33
III	$-CH_2CH_3$	$C_{18}H_{16}N_4O$	234–236 (78)	71.04 71.02	05.30 05.31	18.41 18.48
IV	$-(CH_2)_2CH_3$	$C_{19}H_{18}N_4O$	241–243 (79)	71.68 71.66	05.70 05.73	17.60 17.69
V	$-CH_2Cl$	$C_{17}H_{13}ClN_4O$	280–281 (81)	62.87 62.93	04.03 04.04	17.25 17.28
VI		$C_{21}H_{21}N_5O$	241–243 (78)	70.17 70.13	05.89 05.90	19.48 19.45
VII		$C_{22}H_{23}N_5O$	225–226 (77)	70.76 70.73	06.21 06.20	18.75 18.72
VIII		$C_{21}H_{21}N_5O_2$	273–274 (78)	67.18 67.15	05.64 05.69	18.65 18.64
IX		$C_{21}H_{22}N_6O$	291–293 (74)	67.36 67.40	05.92 05.90	22.44 22.49
X		$C_{22}H_{24}N_6O$	286–288 (79)	68.02 68.09	06.23 06.28	21.63 21.62

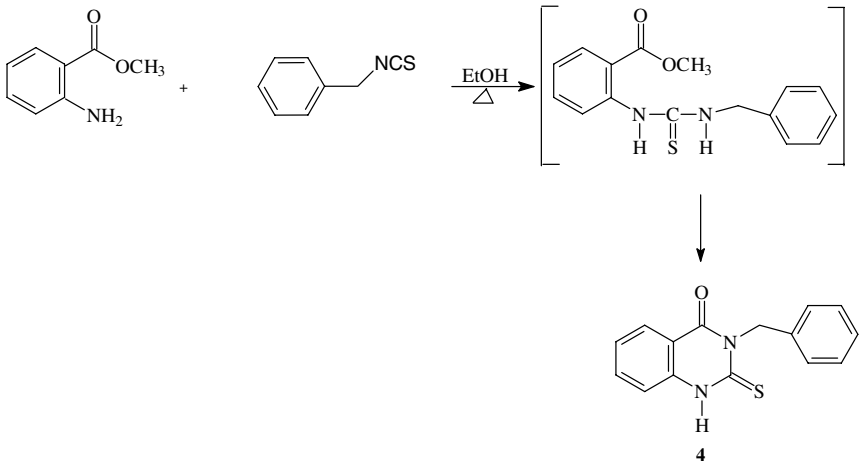
2. Chemistry

The key intermediate 3-benzyl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one **4** was prepared by refluxing methyl anthranilate with benzyl isothiocyanate in ethanol (Scheme 1). However, this route is not much attractive as the preparation of benzyl isothiocyanate required for the reaction is a tedious and time consuming process; and the yield was also low (60%).

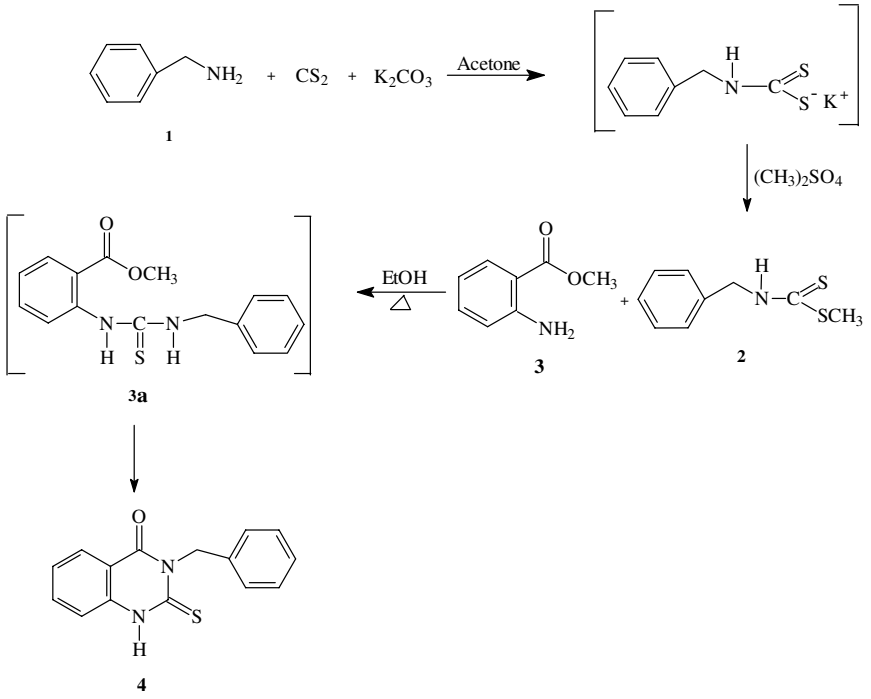
An alternate route (Scheme 2) was attempted to synthesize **4**. In this route, benzyl amine (**1**) was reacted with carbon disulfide and anhydrous potassium carbonate in acetone to give potassium dithiocarbamate, which was methylated with dimethyl sulfate to afford dithiocarbamic acid methyl ester (**2**). Compound **2** on reflux with methyl anthranilate (**3**) yielded **4**. This process of synthesizing **4** by this scheme suffers from the following drawbacks such as multistep process, it requires prolonged reaction time (37 h), and the yield is also very low (30%).

Hence, improvisation was carried out on this method, by using aqueous sodium hydroxide (20 mol) as a base instead of anhydrous K_2CO_3 and substituting dimethylsulfoxide (DMSO) 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 curtailed the reaction time from 37 to 24 h, also increased the yield from 30% to 80%.

Thus benzylamine (**1**) was treated with carbon disulfide and sodium hydroxide in dimethylsulfoxide to give sodium dithiocarbamate, which was methylated with dimethyl sulfate to afford the dithiocarbamic acid methyl ester (**2**). Compound **2** on reflux with methyl anthranilate (**3**) in ethanol yielded the desired 3-benzyl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one (**4**) via the thiourea intermediate in good yield (80%). The product obtained was cyclic and not an open-chain thiourea **3a**. It was confirmed by IR spectra of compound **4** showing intense peaks at 3200 cm^{-1} for cyclic thiourea (NH), 1680 cm^{-1} for carbonyl (C=O), and 1208 cm^{-1} for thioxo (C=S) stretching. ^1H NMR spectra of **4** showed singlet at δ 5.7 due to CH_2 group, a multiplet at δ 7–7.9 for aromatic (9H) protons, and a singlet at δ 10.1 indicating the presence of NH. Data



Scheme 1. Synthesis of 3-benzyl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one from benzyl isothiocyanate.

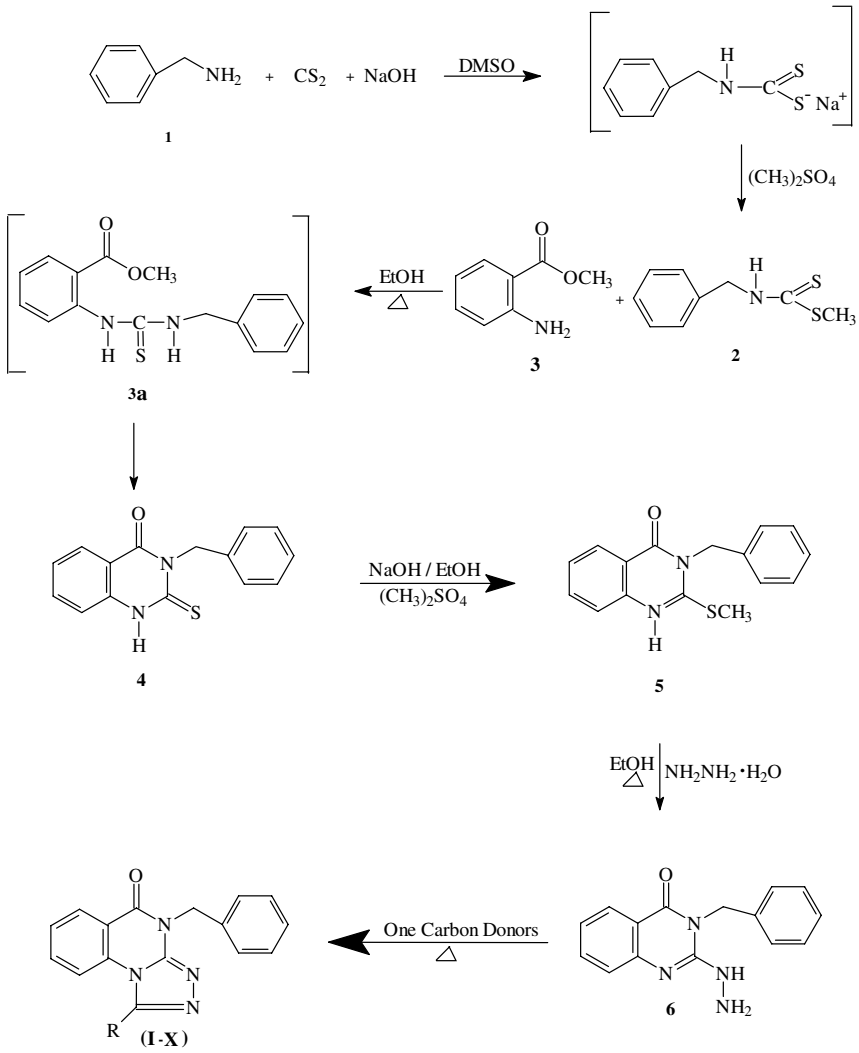


Scheme 2. Synthesis of 3-benzyl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one from benzyl amine.

from the elemental analyses have been found to be in conformity with the assigned structure. Further the molecular ion recorded in the mass spectrum is also in agreement with the molecular weight of the compound.

The 3-benzyl-2-methylsulfanyl-3*H*-quinazolin-4-one **5** was obtained by dissolving **4** in 2% alcoholic sodium hydroxide solution and methylating with dimethyl sulfate with stirring at room temperature. The IR spectra of compound **5** showed disappearance of NH and C=S stretching signals of cyclic thiourea. It showed a peak for carbonyl (C=O) stretching at 1681 cm^{-1}. The ^1H NMR spectra of compound **5** showed singlets at δ 2.6 and 5.3 due to SCH_3 and CH_2, respectively, a multiplet at δ 7.2–8.2 was observed for aromatic (9H) protons. Data from the elemental analyses and molecular ion recorded in the mass spectrum further confirmed the assigned structure.

Nucleophilic displacement of methylthio group of **5** with hydrazine hydrate was carried out using ethanol as solvent to afford 3-benzyl-2-hydrazino-3*H*-quinazolin-4-one **6**. The long duration of reaction (33 h) required might be due to the presence of bulky aromatic ring at position **3**, which might have reduced the reactivity of quinazoline ring system at C-2 position. The formation of **6** was confirmed by the presence of NH and NH_2 signals at 3383–3295 cm^{-1} in the IR spectra. It also showed a peak for carbonyl (C=O) at 1677 cm^{-1}. The ^1H NMR spectra of the compound **6** showed singlets at δ 5.2, 4.5, and 9.9 due to CH_2, NH_2, and NH, respectively, a multiplet at δ 7.1–8.0 was observed for aromatic (9H) protons. Data from the elemental analyses have been



Scheme 3. Synthesis of 4-benzyl-1-substituted-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-ones.

found to be in conformity with the assigned structure. Further the molecular ion recorded in the mass spectrum is also in agreement with the molecular weight of the compound.

The title compounds **I**–**V** were obtained in fair to good yields through the cyclization of **6** with a variety of one-carbon donors such as formic acid, acetic acid, propionic acid, butyric acid, and chloroacetyl chloride at reflux. The formation of cyclic product is indicated by the disappearance of peaks due to NH and NH_2 of the starting material at 3383–3295 cm^{-1} in IR spectrum of all the compounds **I**–**V**. The ^1H NMR spectrum of **I**–**V** showed the absence of NH and NH_2 signals. Compounds **VI**–**X** were obtained by the replacement of chloro group of compound **V** with various alicyclic amines like pyrrolidine, piperidine, morpholine, piperazine, and 4-methylpiperazine. In the IR spectra compounds **I**–**X** showed a peak for carbonyl (C=O) around 1680 cm^{-1}. The ^1H NMR spectra of the compounds **I**–**X** showed multiplet at δ 7.0–8.5 integrating for aromatic protons. The mass spectra of the title compounds is in conformity with the assigned structure. The mass spectrum of these compounds showed molecular ion peaks corresponding to their molecular formula. The M+2 peak was observed in the spectrum of compound **V** confirming the presence of chlorine atom in the compound. The relative intensity of this M+2 peak in comparison to M^+ peak is in the ratio of 1:3. The M+2 peak observed in the spectrum of compound **V** disappeared in the compounds **VI**–**X** confirming the displacement of chloro group. In mass spectra of compounds **I**–**X** 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 of the compounds. Elemental (C, H, N) analysis satisfactorily confirmed elemental composition and purity of the synthesized compounds. Physical data of all the synthesized compounds are represented in Table 1.

3. Results and discussion

The compounds containing 1,4-disubstituted [1,2,4]-triazolo quinazoline ring system (**I**–**X**) have been evaluated for their in vivo antihistaminic activity. Histamine causes bronchospasm and the guinea pigs are most susceptible animals for histamine, hence

Table 2. Antihistaminic and sedative-hypnotic activity of compounds **I–X**

Compound	Time of onset of convulsion (in s)	% Protection	Percent CNS depression		
			1 h	2 h	3 h
I	446 ± 9.03*	73.99 ± 1.39*	6 ± 1.56*	9 ± 1.41*	4 ± 1.74^{Ns}
II	485 ± 11.03*	76.08 ± 1.26*	6 ± 1.42*	11 ± 1.59**	6 ± 1.38*
III	453 ± 7.14*	74.39 ± 1.41*	7 ± 1.83*	12 ± 1.62**	9 ± 1.70*
IV	444 ± 8.23*	73.87 ± 1.48*	9 ± 1.47*	15 ± 1.61***	11 ± 1.71**
V	429 ± 7.64*	72.96 ± 1.27*	5 ± 1.48*	7 ± 1.86*	4 ± 1.23^{Ns}
VI	441 ± 3.97*	73.69 ± 1.46*	8 ± 1.53*	12 ± 1.83**	8 ± 1.57*
VII	445 ± 7.13*	73.93 ± 1.24*	9 ± 1.58*	15 ± 1.67***	8 ± 1.73*
VIII	448 ± 2.42*	74.10 ± 1.29*	7 ± 1.66*	13 ± 1.72**	6 ± 1.28*
IX	454 ± 4.33*	74.44 ± 1.43*	6 ± 1.41*	14 ± 1.73**	8 ± 1.32*
X	461 ± 3.70*	74.83 ± 1.39*	8 ± 1.59*	17 ± 1.72***	7 ± 1.39*
Chlorphe-niramine	400 ± 29.50*	71.00 ± 1.36*	37 ± 1.82***	32.0 ± 1.73***	22 ± 1.98***

Each value represents the mean ± SEM ($n = 6$). Significance levels $^{*}p < 0.5$, $^{**}p < 0.1$, and $^{***}p < 0.05$; ^{Ns}indicates not significant.

protection against histamine-induced bronchospasm on conscious guinea pigs method was adopted to determine the antihistaminic potential of the test compounds. The advantage of this method is it is one of the non-invasive methods and the animals are recovered after the experiment.

All the test compounds were found to exhibit good antihistaminic activity (Table 2). Percentage protection data showed that all compounds of the series show significant protection in the range of 72–76%. The pharmacological studies indicated that different substituents over the first position of triazoloquinazoline ring exert varied biological activity. The presence of methyl group (compound **II**) showed better activity over the unsubstituted compound (compound **I**), with increased lipophilicity (i.e., ethyl compound **III**) activity retained, further increase in lipophilicity (i.e., propyl compound **IV**) leading to decrease in activity. Replacement of a proton of the methyl group by chloro (compound **V**) showed further decrease in activity. Replacement of a proton of the methyl group by alicyclic amines such as pyrrolidyl and piperidyl (compounds **VI** and **VII**, respectively) showed increase in activity over the chloro substituent. Placement of alicyclic amines with additional heteroatom such as morpholinyl, piperazinyl, and 4-methylpiperazinyl (compounds **VIII**, **IX**, and **X**, respectively) led to further increase in activity. The results of sedative-hypnotic activity indicate that all the test compounds were found to exhibit only negligible sedation (6–12%), whereas the reference standard chlorpheniramine maleate showed 30% sedation.

4. Conclusion

In summary, synthesis of new series of 4-benzyl-1-substituted-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-ones has been described. In this study, intermediate compound 3-benzyl-2-thioxo-3*H*-quinazolin-4-one has been synthesized by new innovative route with improved yield. The title compounds have exhibited promising antihistaminic activity against histamine-induced bronchospasm on conscious guinea pigs in vivo model. Among the series, 4-benzyl-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (**II**) was found to be the most active compound (76.08%), which is more potent than the reference standard chlorpheniramine maleate (71%). Interestingly compound **II** also showed negligible sedation (7%) compared to chlorpheniramine maleate (30%) and could therefore serve as a lead molecule for further modification to obtain a clinically useful novel class of non-sedative antihistamines.

5. Experimental

5.1. 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 are 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.

5.1.1. 3-Benzyl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one (4). A solution of benzylamine **1** (0.02 mol) in dimethylsulfoxide (10 ml) was stirred vigorously. To this were added carbon disulfide (1.6 ml) and aqueous sodium hydroxide 1.2 ml (20 M solution) dropwise during

30 min with stirring. Dimethyl sulfate (0.02 mol) was added gradually keeping the reaction mixture stirring in freezing mixture for 2 h. The reaction mixture was then poured into ice water. The solid obtained was filtered, washed with water, dried, and recrystallized from ethanol. Methyl anthranilate (0.01 mol) and the above prepared *N*-(benzyl)-methyl dithiocarbamic acid (0.01 mol) were dissolved in ethanol (20 ml). To this anhydrous potassium carbonate (100 mg) was added and refluxed for 22 h. The reaction mixture was cooled in ice and the solid separated was filtered and purified by dissolving in 10% alcoholic sodium hydroxide solution and re-precipitated by treating with dilute hydrochloric acid. The solid obtained was filtered, washed with water, dried, and recrystallized from ethanol. Yield = 85%, mp 230–231 °C; IR (KBr) cm^{-1}: 3200 (NH), 1680 (C=O), 1208 (C=S); ^1H NMR ($CDCl_3$): δ 5.7 (s, 2H, CH_2), 7.1–7.9 (m, 9H, ArH), 10.1 (br s, 1H, NH); MS (*m*/*z*): 268 [M^+]. Anal. Calcd for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44. Found: C, 67.19; H, 4.49; N, 10.46.

5.1.2. 3-Benzyl-2-methylsulfanyl-3*H*-quinazolin-4-one (5). The 3-benzyl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one **4** (0.01 mol) was dissolved in 40 ml of 2% alcoholic sodium hydroxide solution. To this dimethyl sulfate (0.01 mol) was added dropwise with stirring. The stirring was continued for 1 h, the reaction mixture was then poured into ice water. The solid obtained was filtered, washed with water, dried, and recrystallized from ethanol/chloroform (75:25) mixture. Yield = 78%, mp 150–152 °C; IR (KBr) cm^{-1}: 1681 (C=O), 1616 (C=C); ^1H NMR ($CDCl_3$): δ 2.6 (s, 3H, SCH_3), 5.3 (s, 2H, CH_2), 7.2–8.2 (m, 9H ArH); MS (*m*/*z*): 282 [M^+]; Anal. Calcd for $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.00; N, 9.92. Found: C, 68.03; H, 5.01; N, 9.96.

5.1.3. 3-Benzyl-2-hydrazino-3*H*-quinazolin-4-one (6). The 3-benzyl-2-methylsulfanyl-3*H*-quinazolin-4-one **5** (0.01 mol) was dissolved in ethanol (25 ml). To this hydrazine hydrate (99%) (0.1 mol) and anhydrous potassium carbonate (100 mg) were added and refluxed for 33 h. The reaction mixture was cooled and poured into ice-water. The solid so obtained was filtered, washed with water, dried, and recrystallized from chloroform/benzene (25:75) mixture. Yield = 81%, mp 242–245 °C; IR (KBr) cm^{-1}: 3383, 3295 ($NHNH_2$), 1677 (C=O); ^1H NMR ($CDCl_3$): δ 5.2 (s, 2H, CH_2), 4.5 (s, 2H, NH_2), 7.1–8.0 (m, 9H, ArH), 9.9 (s, 1H, NH); MS (*m*/*z*): 266 [M^+]; Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.69; H, 5.32; N, 21.09.

5.1.4. 4-Benzyl-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (I). The 3-benzyl-2-hydrazino-3*H*-quinazolin-4-one (**6**) (0.01 mol) and formic acid (25 ml) were taken in a round-bottomed flask and refluxed for 36 h, cooled, and poured into ice water. The solid obtained was filtered, washed with water, dried, and recrystallized from ethanol. IR (KBr) cm^{-1}: 1680 (C=O), 1601 (C=N); ^1H NMR ($CDCl_3$): δ 4.6 (s, 2H, CH_2), 7.3–8.1 (m, 9H, ArH), 8.3 (s, 1H, ArH); MS (*m*/*z*): 276 [M^+]. Adopting this procedure compounds **II**–**V** were prepared.

5.1.5. 4-Benzyl-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (II). IR (KBr) cm^{-1}: 1713 (C=O), 1610 (C=N); ^1H NMR ($CDCl_3$): δ 2.1 (s, 3H, CH_3), 4.9 (s, 2H, CH_2), 7.4–8.2 (m, 9H, ArH); MS (*m*/*z*): 290 [M^+].

5.1.6. 4-Benzyl-1-ethyl-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (III). IR (KBr) cm^{-1}: 1671 (C=O), 1609 (C=N); ^1H NMR ($CDCl_3$): δ 1.1–1.2 (t, 3H, CH_2CH_3), 2.3–2.4 (q, 2H, CH_2CH_3), 4.7 (s, 2H, CH_2), 7.6–8.2 (m, 9H, ArH); MS (*m*/*z*): 304 [M^+].

5.1.7. 4-Benzyl-1-propyl-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (IV). IR (KBr) cm^{-1}: 1688 (C=O), 1608 (C=N); ^1H NMR ($CDCl_3$): δ 0.4–0.5 (t, 2H, $CH_2CH_2CH_3$), 1.0–1.1 (sext, 2H, $CH_2CH_2CH_3$), 2.3–2.4 (t, 3H, $CH_2CH_2CH_3$), 4.6 (s, 2H, CH_2), 7.3–8.1 (m, 9H, ArH); MS (*m*/*z*): 318 [M^+].

5.1.8. 4-Benzyl-1-chloromethyl-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (V). IR (KBr) cm^{-1}: 1710 (C=O), 1608 (C=N); ^1H NMR ($CDCl_3$): δ 4.1 (s, 2H, CH_2), 4.6 (s, 2H, CH_2), 7.1–7.9 (m, 9H, ArH); MS (*m*/*z*): 324 [M^+], 326 [M+2].

5.1.9. 4-Benzyl-1-(pyrrolidyl methyl)-4*H*-[1,2,4]triazolo-[4,3-*a*]quinazolin-5-one (VI). A mixture of 4-benzyl-1-chloromethyl-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (**V**) (0.01 mol) and pyrrolidine (0.05 mol) and anhydrous potassium carbonate (100 mg) in dioxane (25 ml) were taken in a round-bottomed flask and refluxed for 33 h, cooled, and poured into ice water. The solid obtained was filtered, washed with water, dried, and recrystallized from ethanol/benzene (50:50). Adopting this procedure compounds **VII**–**X** were prepared. IR (KBr) cm^{-1}: 1692 (C=O), 1602 (C=N); ^1H NMR ($CDCl_3$): δ 1.3–1.5 (m, 4H, CH_2-pyrrolidyl), 1.7–1.9 (m, 4H, CH_2-pyrrolidyl), 4.6 (s, 2H, CH_2), 7.3–8.1 (m, 9H, ArH); MS (*m*/*z*): 359 [M^+].

5.1.10. 4-Benzyl-1-(piperidyl methyl)-4*H*-[1,2,4]triazolo-[4,3-*a*]quinazolin-5-one (VII). IR (KBr) cm^{-1}: 1696 (C=O), 1610 (C=N); ^1H NMR ($CDCl_3$): δ 1.5–1.8 (m, 6H, CH_2-piperidyl), 1.9–2.2 (m, 4H, CH_2-piperidyl), 4.9 (s, 2H, CH_2), 7.0–7.9 (m, 9H, ArH); MS (*m*/*z*): 373 [M^+].

5.1.11. 4-Benzyl-1-(morpholinyl methyl)-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (VIII). IR (KBr) cm^{-1}: 1688 (C=O), 1615 (C=N); ^1H NMR ($CDCl_3$): δ 2.1–2.3 (m, 4H, –N–CH_2CH_2–O), 2.6–2.8 (m, 4H, N–CH_2CH_2–O), 4.9 (s, 2H, CH_2), 7.4–8.2 (m, 9H, ArH); MS (*m*/*z*): 375 [M^+].

5.1.12. 4-Benzyl-1-(piperazinyl methyl)-4*H*-[1,2,4]triazolo-[4,3-*a*]quinazolin-5-one (IX). IR (KBr) cm^{-1}: 1690 (C=O), 1611 (C=N); ^1H NMR ($CDCl_3$): δ 1.8–2.0 (m, 4H, N–CH_2CH_2–NH), 2.3–2.5 (m, 4H, N–CH_2CH_2–NH), 4.5 (s, 2H, CH_2), 7.1–7.9 (m, 9H, ArH); 9.8 (br s, 1H, NH); MS (*m*/*z*): 374 [M^+].

5.1.13. 4-Benzyl-1-((4-methylpiperazinyl) methyl)-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (X). IR (KBr) cm^{-1}: 1686 (C=O), 1606 (C=N); ^1H NMR ($CDCl_3$): δ 1.5–1.7 (m, 4H, N–CH_2CH_2–N), 1.9–2.1 (m, 4H,

N–CH_2CH_2–N), 2.3 (s, 3H, CH_3), 4.9 (s, 2H, CH_2), 7.5–8.3 (m, 9H, ArH); MS (*m*/*z*): 388 [M^+].

5.2. Pharmacology

The synthesized compounds were evaluated for antihistaminic and sedative-hypnotic activities. The animals were maintained in colony cages at 25 ± 2 °C, relative humidity of 45–55%, under 12 h light and dark cycle; they were fed standard animal feed. All the animals were acclimatized for a week before use. The Institutional Animal Ethics Committee approved the protocol adopted for the experimentation of animals.

5.2.1. Antihistaminic activity. A modification of the technique of Van Arman[10] was adopted to determine the antihistaminic potential of the synthesized compounds. Male Dunkin Hartley Guinea pigs (250–300 g) were fasted for 12 h. Six animals were taken in each group. The test compounds were administered orally at a dose of 10 mg/kg in 1% CMC and challenged with histamine aerosol (0.2% aqueous solution of histamine acid chloride 3 ml) in a vaponephrin pocket nebulizer sprayed into a closed transparent cage. The respiratory status reflecting the increasing degree of bronchoconstriction was recorded. The time for onset of convulsions (preconvulsion) was recorded. Animals remaining stable for more than 6 min were considered protected against histamine-induced bronchospasm. An intraperitoneal injection of chlorpheniramine maleate (Avil; Hoechst, Mumbai, India) at a dose of 25 mg/kg was given for the recovery of the test animals. The mean preconvulsion time of animals, treated with the test compounds, was compared to control and is expressed in terms of percentage protection (Table 2).

$$\text{Percent protection} = [1 - (T_1/T_2)] \times 100$$

T_2, preconvulsive time of test compound; T_1, preconvulsive time of control.

The activity of the test compounds was compared with the standard antihistamine chlorpheniramine maleate.

5.2.2. Sedative-hypnotic activity. It was determined by measuring the reduction in locomotor activity using actophotometer.[11,12] Swiss albino mice were chosen as test animals in a group of six. Basal activity score was taken and then compounds **I**–**X** and standard chlorpheniramine maleate were administered orally at the dose of 5 mg/kg in 1% CMC. Scores were recorded at 1, 2, and 3 h after the drug administration. Student's *t* test was performed to ascertain the significance of the exhibited activity. The percent reduction in locomotor activity was calculated by the following formula and is shown in Table 2

$$\%\text{Reduction in motor activity} = [(A - B)/A] \times 100$$

where *A*-basal score, *B*-score after drug treatment.

5.2.3. Statistical analysis. Statistical analysis of the biological activity of the test compounds on various animals was performed by two-tailed Student's '*t*' test (manually). In all cases significance level of the means of individual groups was determined and compared with control. A significance level of $p < 0.5$ denoted significance in all cases.

References and notes

1. Simons, F. E.; Simons, K. *J. N. Engl. J. Med.* **1994**, *330*, 1663–1670.
2. Ellis, E. F.; Adkinson, N. F.; Yungingen, J. W.; Busso, W. W. H_1-receptor antagonists. In Musby-year book, Inc. Eds.; 1985, pp 856–891.
3. Carr, A. A.; Meyer, D. R. *Arzneim.Forsch.* **1982**, *32*, 1157–1159.
4. Hopp, R. J.; Bewtra, A.; Nair, N. M.; Townley, R. G. *J. Allergy Clin. Immunol.* **1985**, *76*, 609–613.
5. Chairungsrilerd, N.; Furukawa, K.; Ohta, T.; Nozoe, S.; Ohizumi, Y. *Eur. J. Pharmacol.* **1996**, *314*, 351–356.
6. Wade, J. J. U.S. Patent No. 4, 528288; *Chem. Abstr*. **1986**, *104*, 5889.
7. West, W. R.; July, W. R. Eur. Patent No. 34, 529; . *Chem. Abstr.* **1982**, *96*, 20114.
8. Alagarsamy, V.; Venkatesaperumal, R.; Vijayakumar, S.; Angayarkanni, T.; Pounammal, P.; Senthilganesh, S.; Kandeeban, S. *Pharmazie* **2002**, *57*, 306–307.
9. Alagarsamy, V. *Pharmazie* **2004**, *59*, 753–755.
10. Van Arman, C. G.; Miller, L. M.; O'Malley, M. P. *J. Pharmacol. Exp. Ther.* **1961**, *133*, 90–97.
11. Dews, P. B. *Br. J. Pharmacol.* **1953**, *8*, 46–48.
12. Kuhn, W. L.; Van Maanen, E. F. *J. Pharmacol. Exp. Ther.* **1961**, *134*, 60–68.