Synthesis and Pharmacological Investigation of Novel 4-(4-Ethyl phenyl)-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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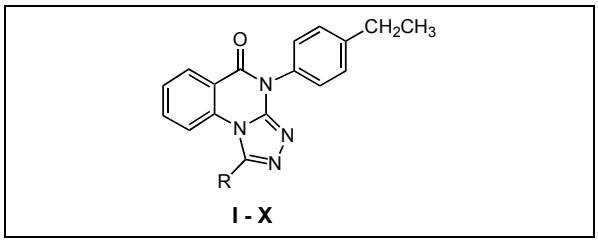

I - X

A series of novel 4-(4-ethylphenyl)-1-substituted-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-ones were synthesized by the cyclization of 2-hydrazino intermediate with various electrophile. The starting material 2-hydrazino compound was synthesized from 2-ethyl aniline by a new innovative route with improved yield. When tested for their *in vivo* H_1-antihistaminic activity on conscious guinea pigs, all the test compounds significantly protected the animals from histamine induced bronchospasm. The compound **II** emerged as the most active compound of the series and it is more potent (73.93% protection) when compared to the reference standard, chlorpheniramine maleate (71% protection), it showed negligible sedation (10%) when compared to chlorpheniramine maleate (30%). Therefore compound **II** will serve as prototype molecule for further development as a new class of H_1-antihistamines

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INTRODUCTION

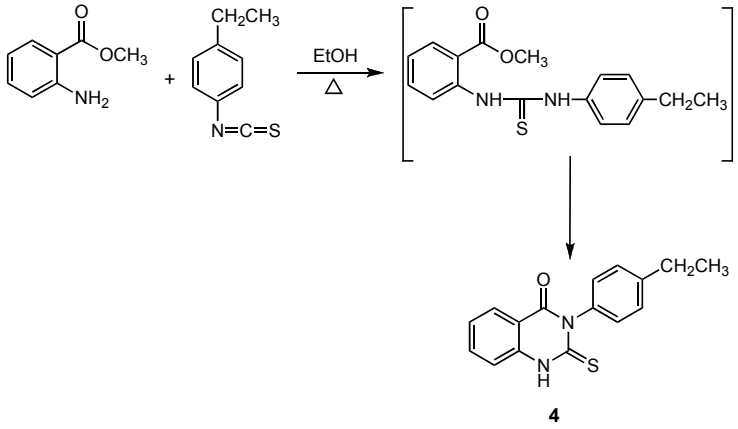
The first generation antihistamines penetrate the blood brain barrier and also possess anticholinergic properties; this has led to the development of a second generation of H_1-antagonists such as terfenadine, cetirizine and astemizole [1]. A common feature of first generation compounds includes two 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 structural features of first generation compounds. The real breakthrough of non-sedative antihistamines came in the early eighties of the twentieth century when the discovery of modern antihistamines, was found to exhibit potent antihistaminic activity without sedative effect [3]. Condensed heterocycles containing new generation of H_1-antihistamines (*e.g.* loratadine, azelastine and flazelastine) that does not possess the above mentioned pharmacophore for H_1-antihistamines gave way for the discovery of many novel antihistamines temelastine [4] and mangostin [5]. Quinazolines and condensed quinazolines show excellent antihistaminic activity [6,7]. In this continuation we demonstrated that [8,9] the quinazoline derivatives as potent antihistamines with least sedation. The present work is an extension of our ongoing efforts towards for the development and identification of new molecules therefore; we aimed to synthesize a series of 1,2,4-triazolo-4*H*-[4,3-*a*]quinazolin-5-ones containing 4-ethyl phenyl substitution at position 4 and alkyl/alicyclic amines substitution at position 1. The title compounds were synthesized by the cyclization of 3-(4-ethylphenyl)-2-hydrazino-3*H*-quinazolin-4-one **(6)** with various electrophiles. The compound **6** was synthesized from 4-ethyl aniline 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 products 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 triazoloquinazolinones were also evaluated for their sedative potentials, by measuring the reduction in locomotor activity using actophotometer.

Chemistry. The key intermediate 3-(4-ethylphenyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one **4** was prepared by refluxing methyl anthranilate with 4-ethylphenyl isothiocyanate in ethanol (Scheme 1). However, the preparation of 4-ethyl phenyl isothiocyanate required for

the reaction was a tedious, time consuming process and the yield was also low (60%) [10].

Thus, 4-ethyl aniline **(1)** treated with carbon disulphide and sodium hydroxide in DMSO to give sodium dithiocarbamate, which was methylated with dimethyl sulphate to afford the dithiocarbamic acid methyl ester **(2)**. Compound **2** on reflux with methyl anthranilate **(3)** in ethanol yielded the desired 3-(4-ethyl phenyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one **(4)** *via* the thiourea intermediate in good yield (81%).

Scheme 1. Synthesis of 3-(4-ethylphenyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one from 4-ethylphenylisothiocyanate.

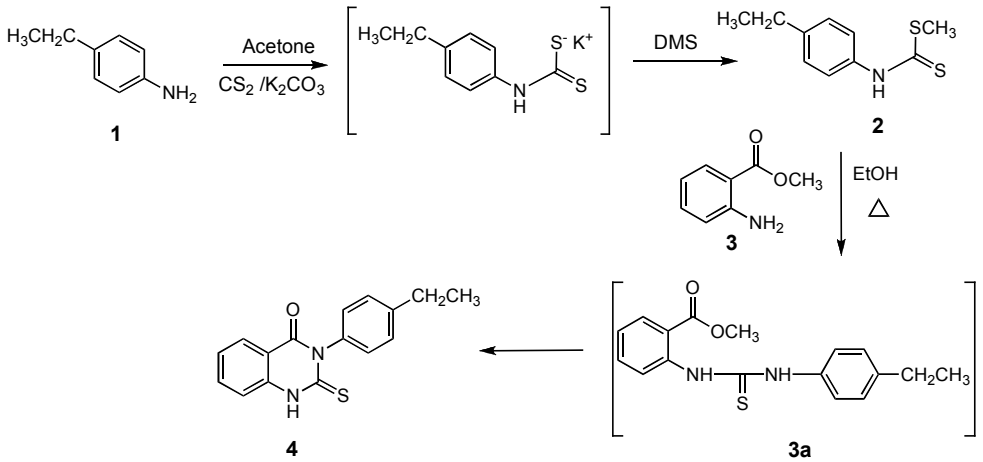


An alternate route to synthesize **4** was attempted (Scheme 2). In this route, 4-ethyl aniline **(1)** was reacted with carbon disulphide and anhydrous K_2CO_3 in acetone to give potassium dithiocarbamate, which was methylated with dimethyl sulphate to afford dithiocarbamic acid methyl ester **(2)** [11]. Compound **2** on reflux with methyl anthranilate **(3)** yielded **4**. This process of synthesizing **4** suffers from the following drawbacks: it is a multistep process, it requires prolonged reaction time (37 h) and the yield is also very low (30%).

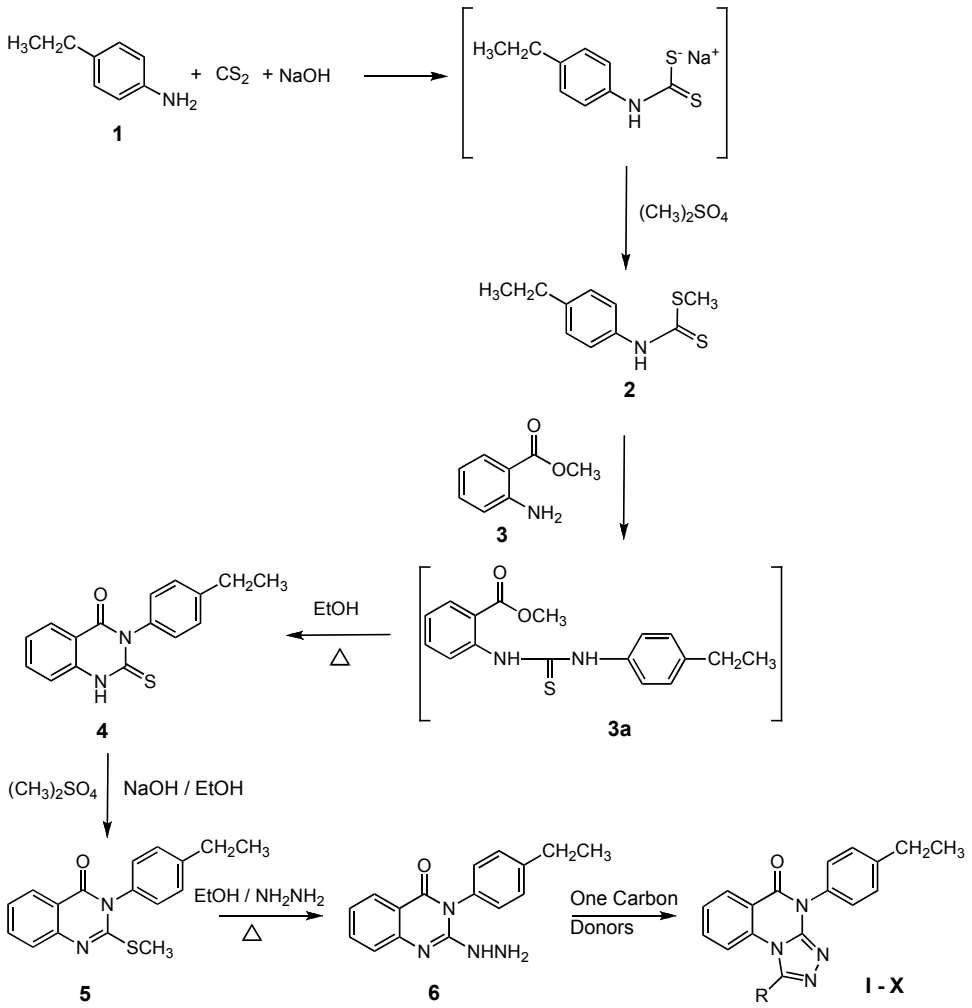
Hence, improvisation was carried out on this method, by using aqueous sodium hydroxide instead of anhydrous K_2CO_3, and dimethyl sulphoxide for acetone (Scheme 3). The use of DMSO as the reaction solvent enhanced the rate of reaction and the use of alkali in higher concentration helped in preventing the hydrolysis of the intermediate probably, due to less solvation. These modifications not only curtailed the reaction time from 37 h to 25 h, also increased the yield from 30% to 81%.

The product obtained was cyclic and not an open chain thiourea **3a**. It was confirmed by IR spectra of **4**, which showed intense peaks at 3210 cm^{-1} for cyclic thiourea (NH), 1690 cm^{-1} for carbonyl (C=O) and 1218 cm^{-1} for thioxo (C=S) stretching. ^1H NMR spectra of **4** showed a triplet at δ 1.3-1.4 ppm due to CH_3 group; a quartet at δ 2.1-2.2 due to CH_2 and a multiplet at δ 7.3-8.0 ppm for aromatic (8H) protons and a singlet at δ 10.1 ppm indicating the presence of NH. Data from the elemental analyses were found to be in conformity with the assigned structure. Further the molecular ion recorded in the mass spectra is also in agreement with the molecular weight of the compound.

Scheme 2. Synthesis of 3-(4-ethylphenyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one from 4-ethyl aniline.



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



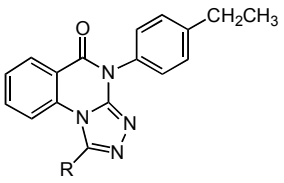
The 3-(4-ethylphenyl)-2-methysulfanyl-3*H*-quinazolin-4-one **5** was obtained by dissolving **4** in 2% alcoholic sodium hydroxide solution and methylating with dimethyl sulphate with stirring at room temperature. The IR spectra of **5** showed disappearance of NH and C=S stretching signals of cyclic thiourea. It showed a peak for carbonyl (C=O) stretching at 1681 cm^{-1}. The ^1H NMR spectra of compound **5** showed triplet at δ 1.5-1.6 ppm due to CH_3; a quartet at δ 2.3-2.4 due to CH_2; a singlet at δ 2.7 ppm SCH_3 and multiplet at δ 7.2-7.8 ppm was observed for aromatic (8H) protons. Data from the elemental analyses and molecular ion recorded in the mass spectra 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-(4-ethylphenyl)-2-hydrazino-3*H*-quinazolin-4-one **6** [12]. The long duration of reaction (39 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 3362–3281 cm^{-1} in the IR spectra. It also showed a peak for carbonyl (C=O) at 1686 cm^{-1}. The ^1H NMR spectra of the compound **6** showed triplet at δ 1.6-1.7 ppm due to CH_3 group; a quartet at δ 2.2-2.3 due to CH_2; singlet at δ 5.3 ppm and 9.8 ppm due to NH_2 and NH respectively, a multiplet at δ 7.4-8.1 ppm was observed for aromatic (8H) protons. Data from the elemental analyses were found to be in conformity with the assigned structure. Further the molecular ion recorded in the mass spectra 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 electrophiles such as formic acid, acetic acid, propionic acid, butyric acid and chloroacetyl chloride at reflux [13]. The formation of cyclic product is indicated by the disappearance of peaks due to NH and NH_2 of the starting material at 3362–3281 cm^{-1} in IR spectrum of all the compounds **I-V**. The ^1H NMR spectra of **I-V** showed the

Table 1

Characterization data of 4-(4-ethylphenyl)-1-substituted-substituted-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-ones.



I - X

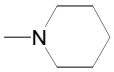
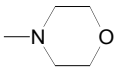
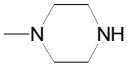
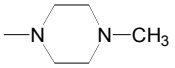
Compd. Code	R	Mol. Formula	Mp °C (% Yield)	Elemental analysis Calculated/Found		
				%C	%H	%N
I	-H	$C_{17}H_{14}N_4O$	269-271	70.33	4.86	19.30
			(79)	70.36	4.83	19.32
II	$-CH_3$	$C_{18}H_{16}N_4O$	228-229	71.04	5.30	18.41
			(78)	71.01	5.31	18.45
III	$-CH_2CH_3$	$C_{19}H_{18}N_4O$	267-268	71.68	5.70	17.60
			(73)	71.69	5.73	17.63
IV	$-(CH_2)_2CH_3$	$C_{20}H_{20}N_4O$	221-222	72.27	6.06	16.86
			(76)	72.29	6.08	16.84
V	$-CH_2Cl$	$C_{18}H_{15}ClN_4O$	256-257	63.81	4.46	16.54
			(77)	63.85	4.48	16.51
VI		$C_{22}H_{23}N_5O$	278-279 (76)	70.76 70.79	6.21 6.25	18.75 18.79
VII		$C_{23}H_{25}N_5O$	264-265 (77)	71.29 71.33	6.50 6.51	18.07 18.04
VIII		$C_{22}H_{23}N_5O_2$	219-221 (74)	67.85 67.80	5.95 5.96	17.98 17.96
IX		$C_{22}H_{24}N_6O$	247-248 (73)	68.02 68.05	6.23 6.20	21.63 21.60
X		$C_{23}H_{26}N_6O$	231-233 (74)	68.63 68.61	6.51 6.55	20.88 20.92

Table 2

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

Compound Code	Time of onset of convulsion (in sec)	% Protection	Percent CNS Depression		
			1 h	2 h	3 h
I	398 ± 6.11*	70.85 ± 1.53*	9 ± 1.36 *	13 ± 1.42**	6 ± 1.41*
II	445 ± 7.32*	73.93 ± 1.69*	8 ± 1.31*	14 ± 1.71**	8 ± 1.73*
III	416 ± 9.65*	72.11 ± 1.32*	12 ± 1.62**	14 ± 1.46**	9 ±1.57*
IV	393 ± 6.39*	70.48 ± 1.81*	13 ± 1.73**	16 ± 1.41**	10 ± 1.82*
V	381 ± 7.31*	69.55 ± 1.46*	7 ± 1.41*	11 ± 1.62 *	5 ± 1.64 ^{Ns}
VI	389 ± 4.74*	70.17 ± 1.71*	9 ± 1.84*	12 ± 1.33**	7 ± 1.72*
VII	396 ± 9.54*	70.70 ± 1.58*	11 ± 1.33*	12 ± 1.83**	8 ± 1.56*
VIII	401 ± 8.21*	71.07 ± 1.24*	10 ± 1.71*	12 ± 1.60**	8 ± 1.63*
IX	423 ± 5.93*	72.57 ± 1.19*	11 ± 1.83*	13 ± 1.57**	9 ± 1.45*
X	436 ± 8.63*	73.39 ± 1.53*	12 ± 1.36*	14 ± 1.62**	9 ± 1.51*
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} indicate not significant.

absence of NH and NH_2 signals. Compounds **VI**-**X** were obtained by the displacement of chloro of compound **V** with various alicyclic amines like pyrrolidine, piperidine, morpholine, piperazine and 4-methylpiperazine. The IR spectrum of compounds **I-X** showed a peak for carbonyl (C=O) around 1680 cm^{-1}. The ^1H NMR spectrum of the compounds **I-X** showed multiplet around δ 7.0–8.0 ppm integrating for aromatic protons. The mass spectra 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 formula. The M^++2 peak was observed in the spectra 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 spectra of compound **V** is not observed in that of compounds **VI**-**X**, which confirms the displacement. In the mass spectrum of compounds **I**-**X** the peak due to 1,2,4-triazolo[4,3-*a*]quinazoline cation was observed at m/z 168. In addition a common peak at m/z 144 corresponding to the quinazolin-4-one moiety appeared in all mass spectra. Elemental (C, H, N) analysis satisfactorily confirmed elemental composition and purity of the synthesized compounds. Physical data of the title compounds is represented in Table 1.

RESULTS AND DISCUSSION

The compounds containing the 1,4-disubstituted[1,2,4]-triazoloquinazoline ring system (**I-X**) were evaluated for their *in vivo* antihistaminic activity. Histamine causes bronchospasm and the guinea pigs are the most susceptible animals for histamine, hence 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 a non-invasive method 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 69-73 %. Biological studies indicated that different substituents over the first position of triazoloquinazoline ring exerted 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**) leads 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 (pyrrolidinyl and piperidinyl compound **VI** and **VII** respectively) showed increase in activity over the chloro substituent. Placement of alicyclic amines with additional heteroatom (morpholinyl compound **VIII**, piperazinyl compound **IX** and 4-methyl piperazinyl compound **X**) led to further increase in activity. As the test compounds could not be converted to a water-soluble form, *in vitro* evaluation for antihistaminic activity could not be performed. The results of sedative-hypnotic activity indicate that all the test compounds were found to exhibit only negligible sedation (10-13%), whereas the reference standard chlorpheniramine maleate showed 30% sedation.

In the present study, synthesis of new series of 4-(4-ethylphenyl)-1-substituted-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-ones have been described. The key intermediate compound of 3-(4-ethylphenyl)-2-thioxo-3*H*-quinazolin-4-one has been synthesized by new innovative route with improved the yield. The title compounds have exhibited promising antihistaminic activity against histamine-induced bronchospasm on conscious guinea pigs *in vivo* model. Among the series, 4-(4-ethylphenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one **(II)** was found to be the most active compound (73.93%), which is more potent than the reference standard chlorpheniramine maleate (71%). Interestingly compound **II** also showed negligible sedation (10%) 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.

EXPERIMENTAL

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 ^1H spectra were recorded on a DPX-300 MHz Bruker FT-NMR spectrometer. The chemical shifts were reported as parts per million (δ ppm) 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.

3-(4-Ethyl phenyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one (4). A solution compound **1** (0.02 mol) in dimethyl sulfoxide (10 mL) was stirred vigorously. To this was added carbon disulphide (1.6 mL) (CAUTION: Toxic and easily flammable substance and must be handled in high performance fume hood) and aqueous sodium hydroxide 1.2 mL (20 molar solution) drop wise during 30 min with stirring. Dimethyl

sulphate (0.02 mol) (CAUTION: Highly toxic compound and must be handled in high performance fume hood) 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 collected by filtration, washed with water, dried and recrystallized from ethanol. Methyl anthranilate (0.01 mol) and the above prepared *N*-(4-ethyl phenyl)-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 that separated was collected by filtration and purified by dissolving in 10% alcoholic sodium hydroxide solution and re-precipitated by treating with dilute hydrochloric acid. The solid obtained was collected by filtration, washed with water, dried and re-crystallized from ethanol. Yield = 81%, mp 265-266 °C; IR (KBr) cm^{-1}: 3210 (NH), 1690 (C=O), 1218 (C=S); ^{1}H NMR ($CDCl_3$) δ: 1.3-1.4 (t, 3H, CH_2CH_3), 2.1-2.2 (q, 3H, CH_2CH_3), 7.3-8.0 (m, 8H, ArH), 10.1 (br s, 1H, NH, D_2O exchangeable); 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, 68.09; H, 5.02; N, 9.86.

3-(4-Ethyl phenyl)-2-methylsulfanyl-3*H*-quinazolin-4-one (5). The compound **4** (0.01 mol) was dissolved in 40 mL of 2% alcoholic sodium hydroxide solution. To this dimethyl sulphate (0.01 mol) was added drop wise with stirring. The stirring was continued for 1 h, the reaction mixture was then poured into ice water. The solid obtained was collected by filtration, washed with water, dried and recrystallized from ethanol-chloroform (75:25) mixture. Yield = 85%, mp 151-153 °C; IR (KBr) cm^{-1}: 1681 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.5-1.6 (t, 3H, CH_2CH_3), 2.3-2.4 (q, 3H, CH_2CH_3), 2.7 (s, 3H, SCH_3), 7.2-7.8 (m, 8H ArH); MS (m/z) 296 (M^+). *Anal.* Calcd for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45. Found: C, 68.86; H, 5.47; N, 9.41.

3-(4-Ethyl phenyl)-2-hydrazino-3*H*-quinazolin-4-one (6). Compound **5** (0.01 mol) was dissolved in ethanol (25 mL). To this hydrazine hydrate (99%) (0.1 mol) and anhydrous potassium carbonate (100 mg) was added and refluxed for 39 h. The reaction mixture was cooled and poured into ice water. The solid so obtained was collected by filtration, washed with water, dried and recrystallized from chloroform-benzene (25:75) mixture. Yield = 85%, mp 187-189 °C; IR (KBr) cm^{-1}: 3362, 3281 ($NHNH_2$), 1686 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.6-1.7 (t, 3H, CH_2CH_3), 2.2-2.3 (q, 3H, CH_2CH_3) 5.3 (br s, 2H, NH_2 D_2O exchangeable), 7.4-8.1 (m, 8H, ArH), 9.8 (br s, 1H, NH D_2O exchangeable); MS (m/z) 280 (M^+). *Anal*. Calcd for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99. Found: C, 68.59; H, 5.74; N, 19.95.

(4-Ethyl phenyl)-4*H*-[1,2,4] triazolo [4,3-*a*] quinazolin-5-one (I). Compound **6** (0.01 mol) and formic acid (25 mL) was taken in a round bottomed flask and refluxed for 38 h, cooled and poured into ice water. The solid obtained was collected by filtration, washed with water, dried and recrystallized from ethanol. IR (KBr) cm^{-1}: 1683 (C=O), 1605 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.2-1.3 (t, 3H, CH_2CH_3), 2.3-2.4 (q, 3H, CH_2CH_3), 7.2-7.5 (m, 4H, ArH), 7.6 (s, 1H, ArH), 7.8-8.1 (m, 4H, ArH); MS (m/z): 290 [M^+].

4-(4-Ethylphenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (II). IR (KBr) cm^{-1}: 1670 (C=O), 1608 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.5 (s, 3H, CH_3), 1.9-2.0 (t, 3H, CH_2CH_3), 2.6-2.7 (q, 3H, CH_2CH_3), 7.2-7.8 (m, 8H, ArH); MS (m/z): 304 [M^+].

1-Ethyl-4-(4-ethylphenyl)-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (III). IR (KBr) cm^{-1}: 1689 (C=O), 1612 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.1-1.2 (t, 3H, CH_2CH_3), 1.5-1.6 (t, 3H, CH_2CH_3), 2.6-2.7 (q, 3H, CH_2CH_3), 2.8-2.9 (q, 2H, CH_2CH_3), 7.2-7.8 (m, 8H, ArH); MS (m/z): 318 [M^+].

4-(4-Ethylphenyl)-1-propyl-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (IV). IR (KBr) cm^{-1}: 1682 (C=O), 1606 (C=N); ^{1}H NMR ($CDCl_3$): δ 0.8-0.9 (t, 2H, $CH_2CH_2CH_3$), 1.1-1.3 (sext, 2H, $CH_2CH_2CH_3$), 1.6-1.7 (t, 3H, CH_2CH_3), 2.1-2.2 (q, 3H, CH_2CH_3), 2.6-2.7 (t, 3H, $CH_2CH_2CH_3$), 7.3-8.0 (m, 8H, ArH); MS (m/z): 332 [M^+].

1-Chloromethyl-4-(4-ethylphenyl)-4*H*-[1,2,4]triazolo[4,3-*a*]-quinazolin-5-one (V). IR (KBr) cm^{-1}: 1686 (C=O), 1603 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.3-1.4 (t, 3H, CH_2CH_3), 2.5.2.6 (q, 3H, CH_2CH_3), 3.5 (s, 2H, CH_2), 7.2-7.9 (m, 8H, ArH); MS (m/z): 338 [M^+], 340 [M^++2].

4-(4-Ethyl phenyl)-1-(pyrrolidinyl)-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (VI). A mixture of 1-chloromethyl-4-(4-ethylphenyl)-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (**V**) (0.01 mol), pyrrolidine (0.05 mole) and anhydrous potassium carbonate (100 mg) in dioxan (25 mL) were taken in a round bottomed flask and refluxed for 37 h, cooled and poured into ice water. The solid obtained was collected by filtration, washed with water, dried and recrystallized from ethanol-benzene (50:50). Adopting this procedure compounds **VII-X** were prepared. IR (KBr) cm^{-1}: 1681 (C=O), 1606 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.2-1.4 (m, 4H, CH_2-Pyrrolidinyl), 1.7-1.9 (m, 4H, CH_2-Pyrrolidinyl), 2.0-2.1 (t, 3H, CH_2CH_3), 2.3-2.4 (q, 3H, CH_2CH_3), 7.1-7.7 (m, 8H, ArH); MS (m/z): 373 [M^+].

4-(4-Ethylphenyl)-1-(piperidinyl)-4*H*-[1,2,4]triazolo[4,3-*a*]-quinazolin-5-one (VII). IR (KBr) cm^{-1}: 1687 (C=O), 1610 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.1-1.4 (m, 6H, CH_2-Piperidyl), 1.7-1.9 (m, 4H, CH_2-Piperidyl), 2.0-2.1 (t, 3H, CH_2CH_3), 2.3-2.4 (q, 3H, CH_2CH_3), 7.4-8.0 (m, 8H, ArH); MS (m/z): 387 [M^+].

4-(4-Ethylphenyl)-1-(morpholinyl)-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (VIII). IR (KBr) cm^{-1}: 1678 (C=O), 1608 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.3-1.5 (m, 4H, CH_2-Morpholinyl), 1.9-2.1 (m, 4H, CH_2-Morpholinyl), 2.3-2.4 (t, 3H, CH_2CH_3), 2.6-2.7 (q, 3H, CH_2CH_3), 7.2-7.8 (m, 8H, ArH); MS (m/z): 389 [M^+].

4-(4-Ethylphenyl)-1-(piperazinyl)-4*H*-[1,2,4]triazolo[4,3-*a*]-quinazolin-5-one (IX). IR (KBr) cm^{-1}: 1688 (C=O), 1612 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.0-1.2 (m, 4H, CH_2-Piperazinyl), 1.5-1.7 (m, 4H, CH_2-Piperazinyl), 1.8-1.9 (t, 3H, CH_2CH_3), 2.4-2.5 (q, 3H, CH_2CH_3), 7.0-7.7 (m, 8H, ArH); 9.9 (s, 1H, NH, D_2O Exchangeable); MS (m/z): 388 [M^+].

4-(4-Ethylphenyl)-1-(4-methylpiperazinyl)-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (X). IR (KBr) cm^{-1}: 1678 (C=O), 1609 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.3-1.5 (m, 4H, CH_2-Piperazinyl), 1.6-1.8 (m, 4H, CH_2-Piperazinyl), 2.0-2.1 (t, 3H, CH_2CH_3), 2.5-2.6 (q, 3H, CH_2CH_3), 2.8 (s, 2H, CH_3), 7.2-7.9 (m, 8H, ArH); MS (m/z): 402 [M^+].

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 a 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.

Antihistaminic activity. A modification of the technique of Van Arman [14] 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, was 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).

$$\text{Percent protection} = [1- (T1 / T2)] \times 100$$

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.

Sedative-hypnotic activity. It was determined by measuring the reduction in locomotor activity using actophotometer [15,16]. Swiss albino mice were chosen as test animals in a group of 6. 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-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 shown in Table 2.

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

Where A-basal score, B-score after drug treatment.

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

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