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4-(3-Methoxyphenyl)-1-substituted-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-ones: new class of H_1-antihistaminic agents

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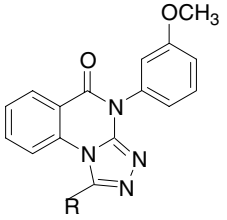
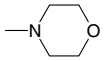
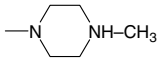
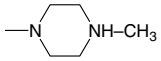
A series of 1-substituted-4-(3-methoxyphenyl)-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-ones were synthesized by the cyclization of 2-hydrazino-3-(3-methoxyphenyl)-3*H*-quinazolin-4-one with various electrophile. The starting material 2-hydrazino-3-(3-methoxyphenyl)-3*H*-quinazolin-4-one was synthesized from 3-methoxy aniline by an innovative route. Title compounds were tested for their *in vivo* H_1-antihistaminic activity on guinea pigs; all the tested compounds protected the animals from histamine induced bronchospasm significantly. Compound 1-methyl-4-(3-methoxyphenyl)-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (**II**) emerged as the most active compound of the series and was more potent (72.76%) than the reference standard chlorpheniramine maleate (71%). Compound **II** showed negligible sedation (10%) when compared to chlorpheniramine maleate (25%). Hence it could serve as prototype molecule for further development as a new class of H_1-antihistaminic agents.

1. Introduction

A common feature of first generation compounds includes two aryl or heteroaryl rings linked to an aliphatic tertiary amine via the side chain (e.g. diphenhydramine and pheniramine) (Estelle et al. 1991; Simons 1993; Simons and Simons 1999), the second-generation compounds (terfenadine and cetirizine) (Van der Goot et al. 1991; Simons and Simons 1994) also contain many of the 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 (Carr and Meyer 1982). 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 and mangostin (Hopp et al. 1985; Chairungsrilerd et al. 1996). A literature survey reveals excellent antihistaminic activity in quinazolines and condensed quinazolines (Rao and Reddy 1992; Buyuktimkin et al. 1989; Alagarsamy et al. 2002, 2004). In view of these facts and to continue our structure activity relationship (SAR) study efforts in the search of quinazoline derivatives as potent antihistamines with least sedation, we aimed to synthesis of a series of 1,2,4-triazolo-4*H*-[4,3-*a*]quinazolin-5-ones compounds containing 3-methoxyphenyl substitution at position 4 and alkyl/alicyclic amines substitution at position 1. The title compounds were synthesized by cyclization of 2-hydrazi-

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



Compd.	R	Mol. formula	Mp °C (% yield)
I	−H	$C_{16}H_{12}N_4O_2$	239–241 (78)
II	$-CH_3$	$C_{17}H_{14}N_4O_2$	287–288 (73)
III	$-CH_2CH_3$	$C_{18}H_{16}N_4O_2$	265–267 (80)
IV	$-(CH_2)_2CH_3$	$C_{19}H_{18}N_4O_2$	274–276 (74)
V	$-CH_2Cl$	$C_{17}H_{13}ClN_4O_2$	296–298 (81)
VI		$C_{21}H_{21}N_5O_2$	255–256 (74)
VII		$C_{22}H_{23}N_5O_2$	220–262 (76)
VIII		$C_{21}H_{21}N_5O_3$	219–221 (72)
IX		$C_{21}H_{22}N_6O_2$	260–262 (70)
X		$C_{22}H_{24}N_6O_2$	245–246 (78)

no-3-(3-methoxyphenyl)-3*H*-quinazolin-4-one (**6**) with various electrophiles. Compound **6** was synthesized from 3-methoxy aniline (**1**) by a novel innovative route. 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.

2. Investigations and results

The key intermediate 3-(3-methoxyphenyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one (**4**) was prepared by refluxing methyl anthranilate with 3-methoxyphenyl isothiocyanate in ethanol. However, this route is not attractive as the preparation of 3-methoxyphenyl isothiocyanate required for the reaction is a tedious and time consuming process; and the yield was also low. An alternate route was attempted to synthesize **4**. In this route, 3-methoxy aniline (**1**) was reacted with carbon disulphide and anhydrous potassium carbonate in acetone to give potassium dithiocarbamate, which was methylated with dimethyl sulphate to afford dithiocarbamic acid methyl ester (**2**). Compound **2** on reflux with methyl anthranilate (**3**) yielded **4**. This process of synthesizing **4** suffers from the following drawbacks; it is a multi step process, it requires prolonged reaction time (37 h) and the yield is also very low (27%). Hence, this method needed to be improved. Aqueous sodium hydroxide (20 mol solution) was used as a base instead of anhydrous K_2CO_3 and dimethyl sulphoxide (DMSO) was substituted for acetone as the reaction solvent (Scheme). 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 modification not only curtails the reaction time from 37 h to 26 h, also increased the yield from 27% to 85%. Thus 3-methoxy aniline (**1**) treated with carbon disulphide and sodium hydroxide in dimethyl sulphoxide 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-(3-methoxyphenyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one **(4)** via the thiourea intermediate in good yield (82%). The product obtained was cyclic and not an open chain thiourea **3a**. The 3-(3-methoxyphenyl)-2-methylsulfanyl-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. Nucleophilic displacement of methylthio group of **5** with hydrazine hydrate was carried out using ethanol as solvent to afford 2-hydrazino-3-(3-methoxyphenyl)-3*H*-quinazolin-4-one (**6**). The long duration of reaction (35 h) required might be due to the pre-

Scheme

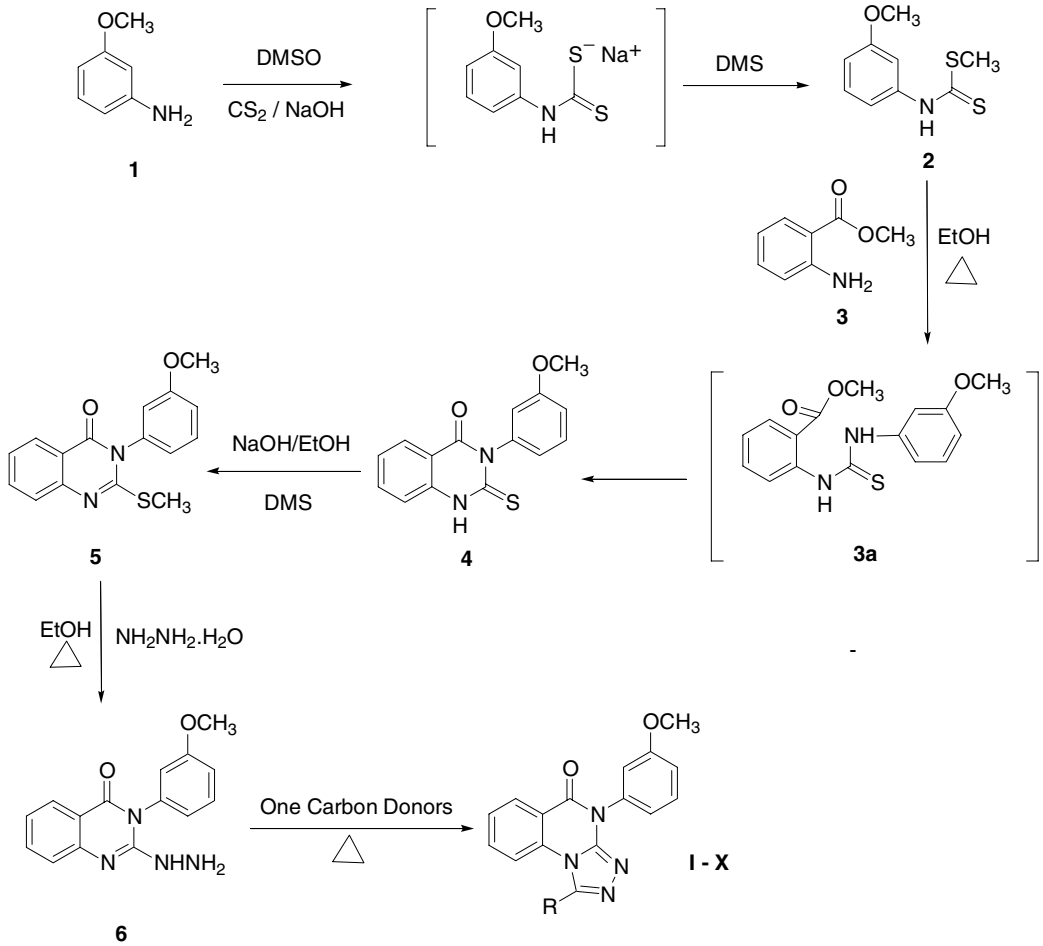


Table 2: Antihistaminic and sedative-hypnotic activity of compounds (I–X)

Compd.	Degree of bronchoconstriction (s)	% Protection	Percent CNS depression		
			1 h	2 h	3 h
I	$391 \pm 6.92^{*}$	$70.33 \pm 1.89^{*}$	$7 \pm 1.45^{*}$	$10 \pm 1.92^{*}$	6 ± 1.35^{Ns}
II	$426 \pm 8.63^{*}$	$72.76 \pm 1.36^{*}$	$10 \pm 1.61^{*}$	$12 \pm 1.49^{**}$	$8 \pm 1.82^{*}$
III	$393 \pm 9.71^{*}$	$70.48 \pm 1.02^{*}$	$12 \pm 1.38^{**}$	$13 \pm 1.87^{**}$	$8 \pm 1.45^{*}$
IV	$379 \pm 11.92^{*}$	$69.39 \pm 1.69^{*}$	$14 \pm 1.93^{***}$	$14 \pm 1.28^{***}$	$9 \pm 1.93^{*}$
V	$365 \pm 5.05^{*}$	$68.21 \pm 1.81^{*}$	6 ± 1.56^{Ns}	$10 \pm 1.54^{*}$	5 ± 1.30^{Ns}
VI	$374 \pm 7.81^{*}$	$68.98 \pm 1.01^{*}$	$9 \pm 1.29^{*}$	$13 \pm 1.93^{**}$	$8 \pm 1.27^{*}$
VII	$370 \pm 5.98^{*}$	$68.64 \pm 1.82^{*}$	$11 \pm 1.64^{*}$	$14 \pm 1.49^{***}$	$8 \pm 1.83^{*}$
VIII	$388 \pm 6.45^{*}$	$70.10 \pm 1.73^{*}$	$12 \pm 1.02^{**}$	$15 \pm 1.68^{***}$	$9 \pm 1.39^{*}$
IX	$398 \pm 7.60^{*}$	$70.85 \pm 1.83^{*}$	$12 \pm 1.48^{**}$	$15 \pm 1.03^{***}$	$9 \pm 1.67^{*}$
X	$409 \pm 8.11^{*}$	$71.63 \pm 1.49^{*}$	$13 \pm 1.02^{**}$	$16 \pm 1.46^{***}$	$10 \pm 1.83^{*}$
Control	116 ± 4.56	–	6 ± 0.49	4 ± 0.59	4 ± 0.91
Chlorpheniramine	$400 \pm 9.50^{*}$	$71.00 \pm 1.36^{*}$	$37 \pm 1.82^{***}$	$32.0 \pm 1.73^{***}$	$22 \pm 1.98^{***}$

Each value represents the mean ± SEM (n = 6). Significance levels $^{*}p < 0.5$, $^{**}p < 0.1$ and $^{***}p < 0.05$ and ^{NS} indicate not significant, as compared with respective control.

sence of the bulky aromatic ring at position **3**, which might have reduced the reactivity of quinazoline ring system at C-2 position. 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 ^{1}H NMR spectrum of **I–V** showed the 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. All the synthesized compounds were confirmed by spectral data (IR, NMR and mass spectra). Elemental (C, H, N) analysis satisfactorily confirmed elemental composition and purity of the synthesized compounds (**I–X**).

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 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 (Van Arman et al. 1961). The advantage of this method is that it is a non-invasive method and the animals are recovered after the experiment. As the test compounds could not be converted to water-soluble form, *in vitro* evaluation for antihistaminic activity could not be performed.

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 68–72%. Pharmacological studies indicated that different substituents over the first position of the triazoloquinazoline ring exerted various biological activity. The presence of a methyl group (compound **II**, Log P = 3.19) showed better activity than the unsubstituted compound (compound **I**, Log P = 2.51), with increased lipophilicity (i.e., ethyl compound **III**, Log P = 3.76) activity retained, further increase in lipophilicity (i.e., propyl compound **IV**, Log P = 4.18) leads to decrease in activity. Replacement of a proton of the methyl group by chloro (compound **V**, Log P = 3.68) showed further decrease in activity. Replacement of a proton of the methyl group by alicyclic amines (pyrrolidinyl and piperidinyl compound **VI**, Log P = 4.10 and **VII**, Log P = 4.51, respectively) showed increase in activity over the chloro substituent. Placement of alicyclic amines with additional hetero atom (morpholinyl compound **VIII**, Log P = 3.16 piperazinyl compound **IX**, Log P = 3.54 and 4-methyl piperazinyl compound **X**, Log P = 3.77) led to further increase in activity. A comparison of the percentage protection of compounds (**I–X**) with their corresponding, calculated log P values (Table 1) found no correlation, indicating that *in vivo* activity observed is not based on liphophilicity alone.

Sedative-hypnotic activity was determined by measuring the reduction in locomotor activity using an actophotometer (Dews 1953; Kuhn and Van Maanen 1961) on swiss albino mice. The results of sedative-hypnotic activity indicate that all the test compounds were found to exhibit only negligible sedation (8–13%), whereas the reference standard chlorpheniramine maleate showed 25% sedation.

3. Discussion

In summary the synthesis of a new series of 1-substituted-4-(3-methoxyphenyl)-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-ones has been described. In this study, the intermediate compound of 3-(3-methoxyphenyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one has been synthesized by a new innovative route with improved yield. These derivatives have exhibited promising antihistaminic activity against histamine-induced bronchospasm in conscious guinea pigs model. Among the test compounds 1-methyl-4-(3-methoxyphenyl)-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (**II**) was the most active antihistaminic agent, which was more potent than the reference standard chlorpheniramine maleate and could therefore serve as a lead molecule for further modification to obtain a clinically useful novel class of antihistaminic agents.

4. Experimental

4.1. Chemistry

Melting points (mp) were determined in open capillaries on a 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) 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 (±0.4%) 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 synthe-

sized compounds and the purity of these compounds was ascertained by microanalysis. 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. Synthesis of 3-(3-methoxyphenyl)-2-thioxo-2,3-dihydro-1H-quinazolin-4-one (***4***)

A solution of 3-methoxy aniline (**1**, 0.02 mol) in dimethyl sulphoxide (10 ml) was stirred vigorously. To this were added carbon disulphide (1.6 ml; 0.026 mol) and aqueous sodium hydroxide 1.2 ml (20 molar solution) drop wise during 30 min with stirring. Dimethyl sulphate (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*-(3-methoxyphenyl)-methyl dithiocarbamic acid (0.01 mol), were dissolved in ethanol (20 ml). To this anhydrous potassium carbonate (100 mg) was added and refluxed for 23 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 255–256 °C. IR: 3312 (NH), 1690 (C=O), 1210 (C=S) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.10 (s, 3 H, OCH_3), 7.31–7.92 (m, 8 H, ArH), 10.53 (br s, 1 H, NH); MS (m/z, %): 284 (M^+, 100), 254 (54), 178 (75), 148 (35).
$C_{15}H_{12}N_2O_2S$

4.1.2. Synthesis of 3-(3-methoxyphenyl)-2-methylsulfanyl-3H-quinazolin-4-one (***5***)

The 3-(3-methoxyphenyl)-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 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 filtered, washed with water, dried and recrystallized from an ethanol-chloroform (75 : 25) mixture. Yield = 86%, mp 155–156 °C. IR: 1690 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.85 (s, 3 H, SCH_3), 3.34 (s, 3 H, OCH_3), 7.23–7.72 (m, 8 H ArH); MS (m/z, %): 298 (M^+, 76), 300 (89), 270 (55), 194 (47), 148 (100), 136 (35).
$C_{16}H_{14}N_2O_2S$

4.1.3. Synthesis of 2-hydrazino-3-(3-methoxyphenyl)-3H-quinazolin-4-one (***6***)

The 3-(3-methoxyphenyl)-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) was added and refluxed for 35 h. The reaction mixture was cooled and poured into ice water. The solid obtained was filtered, washed with water, dried and recrystallized from a chloroform-benzene (25 : 75) mixture. Yield = 79%, mp 211–213 °C. IR: 3368, 3210 ($NHNH_2$), 1678 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.54 (s, 3 H, OCH_3), 5.33 (s, 2 H, NH_2), 7.32–7.81 (m, 8 H, ArH), 9.30 (s, 1 H, NH); ^{13}C NMR ($CDCl_3$): δ 53.9, 103.8, 108.7, 112.9, 120.2, 121.3, 126.5, 127.7, 128.3, 129.8, 131.9, 132.4, 146.9, 159.8, 162.7; MS (m/z, %): 282 (M^+, 89), 252 (76), 176 (45), 160 (56), 146 (34).
$C_{15}H_{14}N_4O_2$

4.1.4. Synthesis of 4-(3-methoxyphenyl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (***I***)

The 2-hydrazino-3-(3-methoxyphenyl)-3*H*-quinazolin-4-one (**6**) (0.01 mol) and formic acid (25 ml) were placed in a round bottomed flask and refluxed for 35 h, cooled and poured into ice water. The solid obtained was filtered, washed with water, dried and recrystallized from ethanol. IR: 1685 (C=O), 1612 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.90 (s, 3 H, OCH_3), 7.00–7.31 (m, 4 H, ArH), 7.82 (s, 1 H, ArH), 8.02–8.34 (m, 4 H, ArH); ^{13}C NMR ($CDCl_3$): δ 54.2, 102.7, 108.9, 112.7, 126.4, 127.8, 129.5, 129.9, 131.6, 132.3, 134.6, 136.4, 139.9, 148.9, 159.8, 160.9; MS (m/z, %): 292 (M^+, 100), 262 (75), 186 (50), 168 (70), 148 (25), 144 (50). Adopting this procedure compounds **II–V** were prepared.

4.1.5. Synthesis of 4-(3-methoxyphenyl)-1-methyl-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (***II***)

IR: 1680 (C=O), 1611 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.5 (s, 3 H, CH_3), 3.3 (s, 3 H, OCH_3), 7.3–7.8 (m, 8 H, ArH). MS (m/z, %): 306 (M^+, 75), 262 (75), 275 (60), 186 (50), 168 (70), 148 (25), 144 (50).

4.1.6. Synthesis of 1-ethyl-4-(3-methoxyphenyl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (***III***)

IR: 1690 (C=O), 1615 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.52–1.64 (t, 3 H, CH_2CH_3), 2.11–2.24 (q, 2H, CH_2CH_3), 3.64 (s, 3 H, OCH_3), 7.80–8.23 (m, 8 H, ArH); ^{13}C NMR ($CDCl_3$): δ 12.8, 18.9, 53.9, 102.9, 107.9, 111.9, 125.9, 126.9, 129.7, 129.9, 131.8, 132.7, 134.9, 135.9, 138.9, 147.8, 158.9, 160.5; MS (m/z, %): 320 (M^+, 80), 262 (60), 186 (56), 168 (71), 148 (29), 144 (44).

4.1.7. Synthesis of 4-(3-methoxyphenyl)-1-propyl-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (***IV***)

IR: 1678 (C=O), 1612 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.80–0.92 (t, 2 H, $CH_2CH_2CH_3$), 1.21–1.32 (sext, 2 H, $CH_2CH_2CH_3$), 1.63–1.72 (t, 3 H, $CH_2CH_2CH_3$), 3.11 (s, 3 H, OCH_3), 7.60–8.11 (m, 8 H, ArH). MS (m/z, %): 334 (M^+, 75), 320 (75), 306 (34), 262 (65), 186 (60), 168 (41), 148 (29), 144 (33).

4.1.8. Synthesis of 1-chloromethyl-4-(3-methoxyphenyl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (***V***)

IR: 1688 (C=O), 1609 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.22 (s, 3 H, OCH_3), 3.83 (s, 2 H, CH_2), 7.21–7.73 (m, 8 H, ArH); ^{13}C NMR ($CDCl_3$): δ 33.7, 54.9, 103.1, 106.9, 111.7, 126.2, 126.7, 128.9, 129.5, 131.2, 132.9, 135.3, 136.9, 139.8, 147.5, 159.5, 161.3; MS (m/z, %): 340 (M^+, 95), 342 (M + 2, 31), 262 (65), 186 (60), 168 (41), 148 (29), 144 (33).

4.1.9. Synthesis of 4-(3-methoxyphenyl)-1-(pyrrolidinyl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (***VI***)

A mixture of 1-chloromethyl-4-(3-methoxyphenyl)-4*H*-[1,2,4]triazolo[4,3-*a*] quinazolin-5-one (**V**) (0.01 mol) and pyrrolidine (0.05 mole) and anhydrous potassium carbonate (100 mg) in dioxan (25 ml) were taken in a round bottomed flask and refluxed for 29 h, cooled and poured into ice water. The solid obtained was filtered, washed with water, dried and recrystallized from ethanol-benzene (50 : 50). IR: 1695 (C=O), 1612 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.31–1.52 (m, 4 H, NCH_2CH_2), 1.84–2.02 (m, 4 H, NCH_2CH_2), 2.95 (s, 3 H, OCH_3), 3.45 (s, 2 H, CH_2), 7.04–7.63 (m, 8 H, ArH). MS (m/z, %): 375 (M^+, 100), 262 (55), 186 (50), 168 (41), 148 (44), 144 (33).
Adopting this procedure compounds **VII–X** were prepared.

4.1.10. Synthesis of 4-(3-methoxyphenyl)-1-(piperidinyl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (***VII***)

IR: 1693 (C=O), 1603 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.00–1.32 (m, 6 H, CH_2-piperidinyl), 1.90–2.11 (m, 4 H, CH_2-piperidinyl), 2.83 (s, 3 H, OCH_3), 3.21 (s, 2 H, CH_2), 7.62–8.14 (m, 8 H, ArH); ^{13}C NMR ($CDCl_3$) : δ 24.3, 24.9 (2C), 51.7 (2C), 53.7, 103.9, 107.5, 111.9, 126.9, 127.9, 129.5, 129.9, 130.8, 131.7, 134.9, 137.5, 138.9, 147.9, 155.9, 161.9; MS (m/z, %): 389 (M^+, 80), 262 (55), 186 (50), 168 (41), 148 (44), 144 (33).

4.1.11. Synthesis of 4-(3-methoxyphenyl)-1-(morpholinyl)-4H-[1,2,4] triazolo[4,3-a] quinazolin-5-one (***VIII***)

IR: 1691 (C=O), 1610 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.22–1.41 (m, 4 H, NCH_2CH_2O), 2.00–2.22 (m, 4 H, NCH_2CH_2O), 2.74 (s, 3 H, OCH_3), 3.34 (s, 2 H, CH_2), 7.23–7.74 (m, 8 H, ArH); MS (m/z, %): 391 (M^+, 100), 262 (50), 186 (45), 168 (40), 148 (34), 144 (23).

4.1.12. Synthesis of 4-(3-methoxyphenyl)-1-(piperazinyl)-4H-[1,2,4] triazolo[4,3-a] quinazolin-5-one (***IX***)

IR: 1685 (C=O), 1614 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.0–1.2 (m, 4 H, NCH_2CH_2NH), 1.60–1.83 (m, 4 H, NCH_2CH_2NH), 2.84 (s, 3 H, OCH_3), 3.33 (s, 2 H, CH_2), 7.63–8.14 (m, 8 H, ArH), 9.05 (s, 1 H, NH); ^{13}C NMR ($CDCl_3$): δ 44.7 (2C), 51.9 (2C), 53.7, 104.1, 107.5, 111.9, 126.7, 127.7, 129.8, 129.9, 131.9, 132.9, 133.9, 137.6, 139.8, 147.5, 157.9, 161.9; MS (m/z, %): 390 (M^+, 90), 262 (60), 186 (55), 168 (50), 148 (44), 144 (33).

4.1.13. Synthesis of 4-(3-methoxyphenyl)-1-(4-methylpiperazinyl)-4 H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (***X***)

IR: 1688 (C=O), 1608 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.0–1.2 (m, 4 H, NCH_2CH_2N), 1.74–1.90 (m, 4 H, NCH_2CH_2N), 2.02 (s, 3 H, CH_3), 2.95 (s, 2 H, OCH_3), 3.21 (s, 2 H, CH_2), 7.20–7.73 (m, 8 H, ArH); ^{13}C NMR ($CDCl_3$): δ 41.9, 46.8 (2C), 53.6 (2C), 54.9, 103.5, 106.9, 111.7, 125.7, 126.9, 128.9, 129.7, 131.9, 132.9, 133.9, 137.6, 139.8, 147.5, 157.9, 161.0; MS (m/z, %): 404 (M^+, 100), 262 (65), 186 (50), 168 (48), 148 (44), 144 (40).

4.2. Pharmacology screening

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.

4.2.1. Antihistaminic activity

A modification of the technique of Van Arman et al. (1961) 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 action 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).

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.

4.2.2. Sedative-hypnotic activity

Reduction in locomotor activity was determined using actophotometer (Dews 1953; Kuhn and Van Maanen 1961). 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. The percent reduction in locomotor activity was calculated by the following formula and shown in Table 2.

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

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

4.2.3. Statistical analysis

Statistical analysis of the biological activity of the synthesized compounds on animals was evaluated using a one-way analysis of variance (ANOVA). In all cases, *post-hoc* comparisons of the means of individual groups were performed using Tukey's test. A significance level of $P < 0.05$ denoted significance in all cases. All values are expressed as mean $\pm$ SD (standard deviations). For statistical analysis we have used GraphPad Prism 3.0 version. (GraphPad Prism 3.0 version, GraphPad Software, Inc.11452 El Camino Real, #215, San Diego, CA 92130 USA).

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References

Alagarsamy V, Venkatesaperumal R, Vijayakumar S, Angayarkanni T, Pounammal P, Senthilganesh S, Kandeeban S (2002) Synthesis and pharmacological investigation of some novel 2-phenyl-3-(substituted methyl amino) quinazolin-4(3*H*)-ones as H_1-receptor blockers. Pharmazie 57: 306–307.

Alagarsamy V (2004) Synthesis and pharmacological investigation of some novel 2-methyl-3-(substituted methylamino)-(3*H*)-quinazolin-4-ones as histamine H_1-receptor blockers. Pharmazie 59: 753–755.

Buyuktimkin S, Buyuktimkin N, Ozdemir O, Rollas S (1989) Synthesis of 3-[2-(2,3-dihydro-5-phenyl-4-substituted-3*H*-1,2,4-triazole-3-thione-2-yl)-acetylamino]-2-methyl-4(3*H*)-quinazolinones and their pharmacological activities. Arch Pharm 322: 49–51.

Carr AA, Meyer DR (1982) Synthesis of terfenadine. Arzneimittelforschung 32: 1157–1159.

Chairungsrilerd N, Furukawa K, Ohta T, Nozoe S, Ohizumi Y (1996) Pharmacological properties of alpha-mangostin, a novel histamine H_1 receptor antagonist. Eur J Pharmacol 314: 351–356.

Dews PB (1953) The measurement of the influence of drugs on voluntary activity in mice. Br J Pharmacol 8: 46–48.

Ellis EF, Adkinson, NF, Yungingen JW, Busso WW (1985) H_1-receptor antagonists. In: Musby-year book, Inc. (Eds), p. 856–891.

Estelle F, Simons R, Simons K (1991) Pharmacokinetic optimisation of histamine H_1-receptor antagonist therapy. Clin. Pharmacokinet 21: 372–393.

Hopp RJ, Bewtra A, Nair NM, Townley RG (1985) The effect of age on methacholine response. J Allergy Clin Immunol 76: 609–613.

Kuhn WL, Van Maanen EF (1961) Central nervous system effects of thalidomide. J Pharmacol Exp Ther 134: 60–68.

Misawa M, Omori S, Yanaura S (1986) Effects of the new antiallergic drug 11-oxo-11*H*-pyrido[2,1-*b*] quinazoline-2-carboxylic acid on bronchial and cutaneous allergic responses to ascaris in dogs. Arzneimittelforschung 36: 647–650.

Rao AR, Reddy VM (1992) Synthesis and H_1-antihistaminic activity of beta-alkoxyethyl and beta-(*N*,*N*-dialkylamino)ethyl-(3-aryl-3,4-dihydro-4-oxoquinazolin-2-yl) methyl ethers. Pharmazie 47: 794–796.

Simons FE. (1993) Evolution of H_1-receptor antagonist treatment. Ann Allergy 71: 282–287.

Simons FE, Simons KJ (1994) The pharmacology and use of H_1-receptor-antagonist drugs. N Engl J Med 330: 1663–70.

Van Arman CG, Miller LM, O'Malley MP (1961) SC-10049: a catecholamine bronchodilator and hyperglycemic agent. J Pharmacol Exp Ther 133: 90–97.

Van der Goot H, Bast A, Timmerman H (1991) Structural Requirements for Histamine H_2 Agonists and H_2 Antagonists. In Histamine and Histamine Antagonists; Uvniis, B., Ed.; Handbook of Experiment Pharmacology, Vol. 97; Springer: Berlin Heidelberg, pp 573–748.