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Short communication

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

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A series of novel 4-(3-ethylphenyl)-1-substituted-4*H*-[1,2,4] triazolo[4,3-*a*]quinazolin-5-ones (**4a-j**) were synthesized by the cyclization of 3-(3-ethylphenyl)-2-hydrazino-3*H*--quinazolin-4-one (**3**) with various one-carbon donors. The starting material, compound **3**, was synthesized from 3-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 test compounds protected the animals from histamine induced bronchospasm significantly. Compound 4-(3-ethylphenyl)-1-methyl-4*H* --[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (**4b**) emerged as the most active compound of the series and it is more potent (74.6 % protection) compared to the reference standard chlorpheniramine maleate (71 % protection). Compound **4b** shows negligible sedation (10 %) compared to chlorpheniramine maleate (30 %). Therefore compound **4b** can serve as the leading compound for further development of a new class of H_1-antihistamines.

Keywords: quinazolin-5-ones, sedation, H_1-antihistaminic agents

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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 the first generation compounds includes two aryl or heteroaryl rings linked to an ali-

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phatic tertiary amine *via* the side chain (diphenhydramine and pheniramine) (2). The second generation compounds (terfenadine and cetirizine) contain many of the structural features of the first generation compounds. The real breakthrough of non-sedative antihistamines came in the early eighties of the twentieth century when modern antihistamines were found to exhibit potent antihistaminic activity without sedative effect (3). Condensed heterocycles containing the new generation of H_1-antihistamines (loratadine, azelastine and flazelastine) that do not possess the above mentioned pharmacophore for H_1-antihistamines paved the way for the discovery of many novel antihistamines, temelastine (4) and mangostin (5). Quinazolines and condensed quinazolines show excellent antihistaminic activity (6, 7). In continuation, we demonstrated (8, 9) the quinazoline derivatives as potent antihistamines with the least sedation. The present work is an extension of our ongoing efforts towards development and identification of new molecules. Therefore we undertook to synthesize a series of 1,2,4-triazolo-4*H*-[4,3-*a*]quinazolin-5-ones containing 3-ethylphenyl substituted at position 4 and alkyl/alicyclic amines substituted at position 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 an actophotometer.

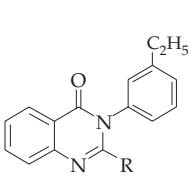
EXPERIMENTAL

Melting points were taken in open capillaries on a Thomas Hoover melting point apparatus (Thomas Hoover, USA) and are uncorrected. IR spectra were recorded in film or in potassium bromide disks on a Perkin-Elmer 398 spectrometer (Perkin-Elmer, USA). ^{1}H spectra were recorded on a DPX-300 MHz Bruker FT-NMR spectrometer (Bruker, USA). Chemical shifts were reported as parts per million (δ ppm) using tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained on a Jeol-SX-102 instrument (Jeol, Japan) using fast atom bombardment (FAB positive). Elemental analysis was performed on a Perkin-Elmer 2400 CHN analyzer (Perkin-Elmer, USA); the values were found within the acceptable limits of the calculated values (± 0.4 %). Spectral data (IR, NMR and mass spectra) and elemental analysis data are presented in Tables I and II. The progress of the reaction was monitored on ready-made silica gel plates (Merck, Norway) using chloroform/methanol (9:1) as a solvent system. Iodine was used as a developing agent. All chemicals and reagents used in the syntheses were obtained from Aldrich (USA), Lancaster (USA) or Spectrochem (India). They were used without further purification.

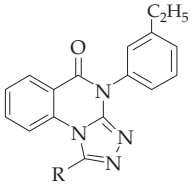
Syntheses

*3-(3-Ethylphenyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one* (***1***). – A solution of 3-ethyl aniline (0.02 mol) in dimethyl sulfoxide (10 mL) was stirred vigorously. To this, carbondisulphide (1.6 mL) and aqueous sodium hydroxide 1.2 mL (2 mol L^{-1}) were added dropwise during 30 min under stirring. Dimethyl sulfate (0.02 mol) was added gradually keeping the reaction mixture stirred for 2 h. The reaction mixture was then poured into ice water. The solid obtained was filtered, washed with water, dried and recrystallized from

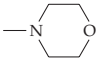
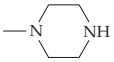
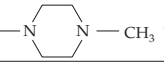
Table I. Physical and analytical data of newly synthesized compounds



1–3



4a–j

Compd.	R	Molecular formula	Molecular mass[a]	M.p. (°C) Yield (%)	Elemental analysis calcd./found (%)		
					C	H	N
1	–SH	$C_{16}H_{14}N_2OS$	282	273–274	68.06	5.00	9.92
				80	68.12	5.07	9.93
2	$-SCH_3$	$C_{17}H_{16}N_2OS$	296	162–163	68.89	5.44	9.45
				89	68.83	5.40	9.47
3	$-NHNH_2$	$C_{16}H_{16}N_4O$	280	213–215	68.55	5.75	19.99
				81	68.62	5.78	19.98
4a	–H	$C_{17}H_{14}N_4O$	290	245–247	70.33	4.86	19.30
				81	70.30	4.88	19.34
4b	$-CH_3$	$C_{18}H_{16}N_4O$	304	263–265	71.04	5.30	18.41
				70	71.07	5.23	18.40
4c	$-CH_2CH_3$	$C_{19}H_{18}N_4O$	318	212–214	71.68	5.70	17.60
				77	71.62	5.74	17.57
4d	$-(CH_2)_2CH_3$	$C_{20}H_{20}N_4O$	332	221–222	72.27	6.06	16.86
				76	72.24	6.07	16.84
4e	$-CH_2Cl$	$C_{18}H_{15}ClN_4O$	338	274–276	63.81	4.46	16.54
				71	63.80	4.45	16.57
4f		$C_{22}H_{23}N_5O$	373	212–213	70.76	6.21	18.75
				78	70.72	6.27	18.70
4g		$C_{23}H_{25}N_5O$	387	251–253	71.29	6.50	18.07
				73	71.36	6.54	18.09
4h		$C_{22}H_{23}N_5O_2$	389	198–199	67.85	5.95	17.98
				77	67.86	5.91	17.93
4i		$C_{22}H_{24}N_6O$	388	231–233	68.02	6.23	21.63
				78	68.09	6.26	21.65
4j		$C_{23}H_{26}N_6O$	402	271–273	68.63	6.51	20.88
				79	68.68	6.50	20.83

ethanol. Methyl anthranilate (0.01 mol) and the prepared *N*-(3-ethylphenyl)-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 reprecipitated by treating with dilute hydrochloric

Table II. IR and NMR spectral data of intermediate and newly synthesized compounds

Compd.	IR (KBr) (cm^{-1})		1H NMR ($CDCl_3$), δ (ppm)
	C=O	C=N	
1	1692	–[a]	1.52–1.64 (t, 3H, $CH_2C\mathbf{H}_3$), 2.43–2.56 (q, 2H, $C\mathbf{H}_2CH_3$), 7.15–7.79 (m, 8H, ArH), 10.45 (br s, 1H, NH, D_2O exchangeable)
2	1692	–[a]	1.25–1.38 (t, 3H, $CH_2C\mathbf{H}_3$), 2.05–2.17 (q, 2H, $C\mathbf{H}_2CH_3$), 2.46 (s, 3H, SCH_3), 7.33–8.05 (m, 8H ArH)
3	1680	–[a]	1.33–1.45 (t, 3H, $CH_2C\mathbf{H}_3$), 2.75–2.89 (q, 2H, $C\mathbf{H}_2CH_3$) 5.02 (br s, 2H, NH_2 D_2O exchangeable), 7.11–7.79 (m, 8H, ArH), 9.53 (br s, 1H, NH D_2O exchangeable)
4a			1.01–1.15 (t, 3H, $CH_2C\mathbf{H}_3$), 2.13–2.26 (q, 2H, $C\mathbf{H}_2CH_3$), 7.01–7.35 (m, 4H, ArH), 7.54 (s, 1H, ArH), 7.73–8.05 (m, 4H, ArH)
4b	1680	1610	1.23 (s, 3H, CH_3), 1.42–1.51 (t, 3H, $CH_2C\mathbf{H}_3$), 2.85–2.97 (q, 2H, $C\mathbf{H}_2CH_3$), 7.14–7.63 (m, 8H, ArH)
4c	1678	1604	1.13–1.24 (t, 3H, $CH_2C\mathbf{H}_3$), 1.44–1.54 (t, 3H, $CH_2C\mathbf{H}_3$), 2.21–2.33 (q, 3H, $C\mathbf{H}_2CH_3$), 2.62–2.75 (q, 2H, $C\mathbf{H}_2CH_3$), 7.05–7.65 (m, 8H, ArH)
4d	1681	1612	0.65–0.73 (t, 2H, $C\mathbf{H}_2CH_2CH_3$), 1.08–1.15 (sext, 2H, $CH_2C\mathbf{H}_2CH_3$), 1.34–1.45 (q, 2H, $C\mathbf{H}_2CH_3$), 2.42–2.55 (t, 3H, $CH_2C\mathbf{H}_3$), 2.83–2.94 (t, 3H, $CH_2CH_2C\mathbf{H}_3$), 7.21–7.95 (m, 8H, ArH)
4e	1684	1616	1.04–1.15 (t, 3H, $CH_2C\mathbf{H}_3$), 2.25–2.36 (q, 2H, $C\mathbf{H}_2CH_3$), 3.15 (s, 2H, CH_2), 7.05–7.66 (m, 8H, ArH)
4f	1680	1610	1.01–1.25 (m, 4H, CH_2-pyrrolidinyl), 1.43–1.64 (m, 4H, CH_2-pyrrolidinyl), 2.43–2.51 (t, 3H, $CH_2C\mathbf{H}_3$), 2.72–2.83 (q, 3H, $C\mathbf{H}_2CH_3$), 3.65 (s, 2H, CH_2), 7.22–7.84 (m, 8H, ArH)
4g	1690	1615	0.89–1.09 (m, 6H, CH_2-piperidyl), 1.42–1.65 (m, 4H, CH_2-piperidyl), 2.33–2.45 (t, 3H, $CH_2C\mathbf{H}_3$), 2.63–2.78 (q, 2H, $C\mathbf{H}_2CH_3$), 3.45 (s, 2H, CH_2), 7.35–7.76 (m, 8H, ArH)
4h	1670	1612	1.21–1.42 (m, 4H, CH_2-morpholinyl), 1.75–1.85 (m, 4H, CH_2-morpholinyl), 2.13–2.25 (t, 3H, $CH_2C\mathbf{H}_3$), 2.51–2.64 (q, 2H, $C\mathbf{H}_2CH_3$), 3.35 (s, 2H, CH_2), 7.11–7.75 (m, 8H, ArH)
4i	1691	1610	0.95–1.13 (m, 4H, CH_2-piperazinyl), 1.45–1.66 (m, 4H, CH_2-piperazinyl), 2.03–2.15 (t, 3H, $CH_2C\mathbf{H}_3$), 2.63–2.75 (q, 2H, $C\mathbf{H}_2CH_3$), 3.75 (s, 2H, CH_2), 7.35–7.89 (m, 8H, ArH), 9.57 (s, 1H, NH, D_2O exchangeable)
4j	1686	1602	1.01–1.25 (m, 4H, CH_2-piperazinyl), 1.44–1.65 (m, 4H, CH_2-piperazinyl), 2.11–2.36 (t, 3H, $CH_2C\mathbf{H}_3$), 2.52–2.66 (q, 2H, $C\mathbf{H}_2CH_3$), 3.05 (s, 3H, CH_3), 3.26 (s, 2H, CH_2), 7.34–7.87 (m, 8H, ArH)

[a] Not applicable

acid. The solid obtained was filtered, washed with water, dried and recrystallized from ethanol.

*3-(3-Ethylphenyl)-2-methylsulfanyl-3*H*-quinazolin-4-one (**2**).* – Compound **1** (0.01 mol) was dissolved in 40 mL of 2 % alcoholic sodium hydroxide solution. To this, dimethyl sulfate (0.01 mol) was added dropwise under 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 the ethanol/chloroform (75:25) mixture.

*3-(3-Ethylphenyl)-2-hydrazino-3*H*-quinazolin-4-one (**3**).* – Compound **2** (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 38 h. The reaction mixture was cooled and poured into ice water. The solid so obtained was filtered, washed with water, dried and recrystallized from the chloroform/benzene (25:75) mixture.

*4-(3-Ethylphenyl)-1-subtituted-4*H*-[1,2,4]triazolo[4,3-a]quinazolin-5-ones (**4a-e**).* – 3-(4-Ethylphenyl)-2-hydrazino-3*H*-quinazolin-4-one (**3**) (0.01 mol) and formic acid (25 mL) were print in a round-bottomed flask and refluxed for 36 h, cooled and poured into ice water. The solid obtained **4a** was filtered, washed with water, dried and recrystallized from ethanol. Adopting this procedure, compounds **4b-e** were also prepared.

*4-(3-Ethylphenyl)-1-subtituted-4*H*-[1,2,4]triazolo[4,3-a]quinazolin-5-one (**4f-j**).* – A mixture of 1-chloromethyl-4-(3-ethylphenyl)-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (**4e**) (0.01 mol) pyrrolidine (0.05 mol) and anhydrous potassium carbonate (100 mg) in dioxane (25 mL) was put in a round bottomed flask and refluxed for 39 h, cooled and poured into ice water. The solid obtained **4f** was filtered, washed with water, dried and recrystallized from ethanol/benzene (50:50). Implementing this protocol, compounds **4g-j** were also prepared.

Pharmacology

Animals. – Antihistaminic activity was evaluated on male Dunkin Hartley guinea pigs (250–300 g), while sedative-hypnotic activity was tested on albino Swiss mice. 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 animals were acclimatized for a week before the experiment. The Institutional Animal Ethics Committee approved the protocol adopted for the experimentation on animals.

Antihistaminic activity. – A modification of the method of Van Arman (10) was adopted to determine the antihistaminic potential of the synthesized compounds. Six animals were alloted to each group and were fasted for 12 h. The test compounds and reference standard (chlorpheniramine maleate) were administered orally at a dose of 10 mg kg^{-1} in 1 % CMC (carboxymethylcelluose) and challenged with histamine aerosol (3 mL of 0.2 % aqueous solution of histamine hydrochloride) 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 the 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, India) at a dose of 25 mg kg^{-1} was given for the recovery of test animals.

Sedative-hypnotic activity. – Sedative-hypnotic activity was determined by measuring the reduction in locomotor activity using an actophotometer (11, 12). Six albino Swiss mice were allotted to each group. Basal activity score was taken and then compounds **4a-j** and standard chlorpheniramine maleate were administered orally at a dose of 5 mg kg^{-1} in 1 % CMC. Scores were recorded 1, 2 and 3 h after the drug administration.

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, *posthoc* comparisons of the means of individual groups were performed using Tukey's test. All values are expressed as mean ± SD (standard deviation). For statistical analysis, the GraphPad Prism 3.0 version was used.

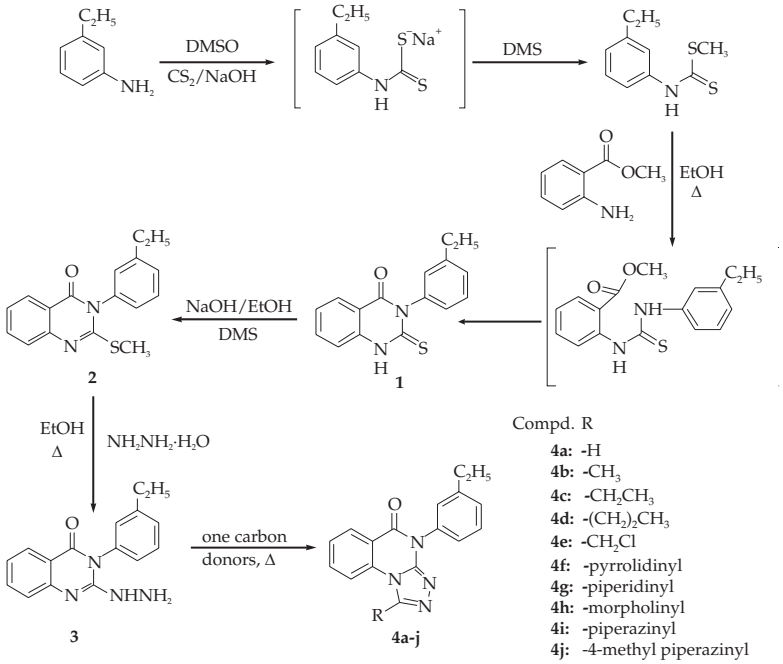
RESULTS AND DISCUSSION

Chemistry

The key intermediate 3-(3-ethylphenyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one (**1**) was prepared by refluxing methyl anthranilate with 3-ethylphenyl isothiocyanate in ethanol. However, the preparation of 3-ethylphenyl isothiocyanate required for the reaction was a tedious, time consuming process and the yield was also low (60 %). An alternate route was attempted to synthesize compound **1**. In this route, 3-ethyl aniline was reacted with carbon disulphide and anhydrous potassium carbonate in acetone to give potassium dithiocarbamate, which was methylated with dimethyl sulfate to afford the dithiocarbamic acid methyl ester, which was refluxed with methyl anthranilate to yield **1**. This way of synthesizing **1** suffers from the drawbacks such as the multi-step process, prolonged reaction time (37 h) and low yield (30 %). Hence, improvisation was carried out in this method by using aqueous sodium hydroxide (2 mol L^{-1}) instead of anhydrous K_2CO_3, and dimethyl sulphoxide (DMSO) (Scheme 1) as a solvent instead of acetone. The use of DMSO as the reaction solvent enhanced the rate of reaction and the use of alkali in higher concentration helped prevent hydrolysis of the intermediate, probably due to less solvation. These modifications not only curtailed the reaction time from 37 to 25 h, but also increased the yield from 30 to 80 %. The product obtained was cyclic and not open-chain thiourea. The structure was confirmed by the IR spectrum, which showed intense peaks at 3216 cm^{-1} for cyclic thiourea (NH), 1692 cm^{-1} for carbonyl (C=O) and 1210 cm^{-1} for thioxo (C=S) stretching. ^{1}H NMR spectrum of **1** showed a triplet at δ 1.52–1.64 ppm due to the CH_3 group, a quartet at δ 2.43–2.56 ppm due to CH_2 and a multiplet at δ 7.15–7.79 ppm for aromatic (8H) protons and a singlet at δ 10.45 ppm indicating the presence of NH. Data from the elemental analyses were found to be in conformity with the assigned structure. Further, the molecular ions recorded in the mass spectrum are also in agreement with the molecular mass of compound **1**.

3-(3-Ethylphenyl)-2-methysulfanyl-3*H*-quinazolin-4-one (**2**) was obtained by dissolving product **1** in a 2 % alcoholic sodium hydroxide solution and methylating with dimethyl sulfate while stirring at room temperature. The IR spectrum of **2** showed disappearance of NH and C=S stretching signals of cyclic thiourea. It showed a peak for carbonyl (C=O) stretching at 1692 cm^{-1}. The ^{1}H NMR spectrum of compound **2** showed a triplet at δ 1.25–1.38 ppm due to CH_3, a quartet at δ 2.05–2.17 ppm due to CH_2, a singlet at δ 2.46 ppm due to SCH_3 and a multiplet at δ 7.33–8.05 ppm due to aromatic (8H) protons. Data from the elemental analyses and the molecular ion recorded in the mass spectrum further confirmed the assigned structure of **2**.

Nucleophilic displacement of methylthio group of compound **2** with hydrazine hydrate was carried out using ethanol as solvent to afford 3-(3-ethylphenyl)-2-hydrazino-



Scheme 1

-3*H*-quinazolin-4-one (**3**). The required long duration of the reaction (38 h) might be due to the presence of the bulky aromatic ring at position 3, which might have reduced the reactivity of the quinazoline ring system at C-2 position. The formation of **3** was confirmed by the presence of NH and NH_2 signals at 3390–3225 cm^{-1} in the IR spectrum. It also showed a peak for carbonyl (C=O) at 1680 cm^{-1}. The ^1H NMR spectrum of compound **3** showed singlets at δ 2.46 ppm due to SCH_3, a triplet at δ 1.33–1.45 ppm due to CH_3 group, a quartet at δ 2.75–2.89 due to CH_2, singlets at δ 5.02 ppm and 9.53 ppm due to NH_2 and NH respectively, a multiplet at δ 7.11–7.77 ppm for aromatic (8H) protons. Data from the elemental analyses were found to be in conformity with the assigned structure of **3**. Further, the molecular ion recorded in the mass spectrum is also in agreement with the molecular mass of compound **3**.

The title compounds were synthesized by cyclization of 3-(3-ethylphenyl)-2-hydrazino-3*H*-quinazolin-4-one (**3**) with various one-carbon donors. The 3-(3-ethylphenyl)-2-hydrazino-3*H*-quinazolin-4-one was synthesized from 3-ethyl aniline by a new innovative route (Scheme 1). The title compounds **4a-j** were obtained in fair to good yields through cyclization of **3** with a variety of one-carbon donors such as formic acid, acetic acid, propionic acid, butyric acid and chloroacetyl chloride at reflux. The cyclic product formation is indicated by the disappearance of peaks due to NH and NH_2 of the starting compound at 3390–3225 cm^{-1} in IR spectra of all compounds **4a-e**. The ^1H NMR spectra of **4f-j** showed the absence of NH and NH_2 signals. Compounds **4f-j** were obtained by the displacement of chlorine of compound **4e** with various alicyclic amines such as pyrro-

lidine, piperidine, morpholine, piperazine and 4-methylpiperazine. The IR spectra of compounds **4a-j** showed a peak for carbonyl (C=O) around 1680 cm^{-1}. The ^1H NMR spectra of compounds **4a-j** showed multiplets around δ 7.01–8.09 ppm integrating for aromatic protons. Mass spectra of the title compounds are in conformity with the assigned structure and showed molecular ion peaks corresponding to their molecular formula. The M^++2 peak was observed in the spectrum of compound **4e**, confirming the presence of the chlorine atom in the compound. The relative intensity of this M^++2 peak compared to M^+ peak is in a ratio of 1:3. The M^++2 peak observed in the spectrum of compound **4e** disappeared in compounds **4f-j**, confirming the displacement of chlorine. In mass spectra of compounds **4a-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. Elemental analyses confirmed the elemental composition and purity of the synthesized compounds.

Pharmacology

Compounds containing the 1,4-disubstituted [1,2,4]triazoloquinazoline ring system (**4a-j**) were evaluated for their *in vivo* antihistaminic activity. All the tested compounds were found to exhibit good antihistaminic activity (Table III). Protection data showed that all compounds of the series show significant protection in the range of 70–74 %. Biological studies indicated that different substituents over the first position of the triazoloquinazoline ring exerted varying biological activity. The presence of the methyl group (compound **4b,** 74.6 % protection) showed better activity than the unsubstituted com-

*Table III. Antihistaminic and sedative-hypnotic activity of compounds **4a-j***

Compd.	Time of onset of convulsion (s)	Protection (%)[a]	CNS depression (%)[b]		
			1 h	2 h	3 h
Control[c]	116 ± 2[d]	–	6 ± 1[d]	4 ± 1[d]	4 ± 1[d]
Chlorpheniramine	400 ± 10	71 ± 1	37 ± 2	32 ± 2	22 ± 2[d]
4a	415 ± 2[f]	72 ± 2	8 ± 1[d]	12 ± 1[d]	6 ± 2[d]
4b	456 ± 3[d]	75 ± 2[e]	9 ± 2[d]	13 ± 2[d]	9 ± 1[d]
4c	445 ± 9[e]	74 ± 1[e]	11 ± 2[d]	15 ± 2[d]	7 ± 2[d]
4d	398 ± 7	71 ± 2	14 ± 2[d]	17 ± 2[d]	9 ± 2[d]
4e	390 ± 7[f]	70 ± 1[f]	6 ± 2[d]	12 ± 2[d]	6 ± 2[d]
4f	395 ± 7	71 ± 1[f]	8 ± 2[d]	10 ± 1[d]	8 ± 2[d]
4g	403 ± 8	71 ± 2	10 ± 2[d]	11 ± 2[d]	7 ± 2[d]
4h	409 ± 7	72 ± 2	11 ± 2[d]	13 ± 1[d]	9 ± 1[d]
4i	426 ± 6[e]	73 ± 2[f]	10 ± 1[d]	14 ± 2[d]	8 ± 1[d]
4j	438 ± 5[d]	74 ± 2[f]	13 ± 2[d]	12 ± 2[d]	8 ± 1[d]

[a] Control: oral dose of 10 mg kg^{-1} in 1 % CMC.
[b] Control: oral dose of 5 mg kg^{-1} in 1 % CMC.
[c] Control: animals were administered 1 % CMC orally.
Significant different relative to chlorpheniramine: [d] $p < 0.0001$, [e] $p < 0.001$, [f] $p < 0.01$.

pound (compound **4a**, 72.0 % protection). With increased lipophilicity (*i.e.*, ethyl compound **4c**, 73.9 % protection) the activity remained but further increase in lipophilicity (*i.e.*, propyl compound **4d**, 70.8 % protection) led to a decrease in activity. Replacement of a proton of the methyl group by chlorine (compound **4e**, 70.2 % protection) showed a further decrease in activity. Replacement of a proton of the methyl group by alicyclic amines (pyrrolidinyl and piperidinyl compound **4f** 70.6 % protection and **4g** 71.2 % protection, respectively) showed an increase in activity compared to the chloro substituent. Placement of alicyclic amines with additional hetero atom (morpholinyl compound **4h** 71.6 % protection; piperazinyl compound **4i** 72.8 % protection and 4-methyl piperazinyl compound **4j** 73.5 % protection) led to further increase in activity. As the test compounds could not be converted to 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 exhibited negligible sedation (8–13 %) whereas the reference standard chlorpheniramine maleate showed 30 % sedation.

CONCLUSIONS

The present study describes the synthesis of a new series of 4-(3-ethylphenyl)-1-substituted-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-ones (**4a-j**). The title compounds have exhibited promising antihistaminic activity against histamine-induced bronchospasm on conscious guinea pigs in the *in vivo* model. Among the series, 4-(3-ethylphenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (**4b**) was found to be the most active compound. It was more potent than the reference standard chlorpheniramine maleate. Interestingly, compound **4b** also showed negligible sedation and could therefore serve as a lead molecule for further modifications to obtain a clinically useful novel class of non-sedating antihistamines.

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S A Ž E T A K

Sinteza i farmakološko ispitivanje novih 4-(3-etilfenil)-1-supstituiranih 4*H*-[1,2,4]triazolo [4,3-*a*]kinazolin-5-ona kao nove klase H_1-antihistaminika

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Ciklizacijom 3-(3-etilfenil)-2-hidrazino-3*H*-kinazolin-4-ona (**3**) s različitim donorima jednog C atoma sintetizirana je serija novih 4-(3-etilfenil)-1-supstituiranih 4*H*-[1,2,4]triazolo[4,3-*a*]kinazolin-5-ona (**4a-j**). Početni spoj **3** pripravljen je iz 3-etil anilina na novi, inovativni način, s poboljšanim iskorištenjem. U testovima *in vivo* na zamorcima, svi testirani spojevi pokazali su značajno zaštitno djelovanje protiv bronhospazma induciranog histaminom. Spoj 4-(3-etilfenil)-1-metil-4*H*-[1,2,4]triazolo[4,3-*a*]kinazolin-5-on (**4b**) najaktivniji je među testiranim spojevima (zaštita 74.6 %) i jači od referentnog standarda klorfeniramin maleata (zaštita 71 %). Spoj **4b** pokazuje zanemarivu sedaciju (10 %) u usporedbi s klorfeniramin maleatom (30 %). Stoga spoj **4b** može biti vodeći spoj za daljnji razvoj nove klase H_1-antihistaminika.

Ključne riječi: kinazolin-5-oni, sedacija, H_1-antihistaminici

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