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

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Abstract—A series of novel 1-substituted-4-phenyl-1,2,4-triazolo[4,3-*a*]quinazolin-5(4*H*)-ones **7** were synthesized by the cyclization of 2-hydrazino-3-phenylquinazolin-4(3*H*)-one **6** with various one carbon donors. The starting material 2-hydrazino-3-phenylquinazolin-4(3*H*)-one **6**, was synthesized from aniline **1** by a novel innovative route. When tested for their in vivo H_1-antihistaminic activity on conscious guinea pigs all the test compounds protected the animals from histamine induced bronchospasm significantly, whereas the compound 1-methyl-4-phenyl-1,2,4-triazolo[4,3-*a*]quinazolin-5(4*H*)-one **7b** (percentage protection 70.7%) was found to be equipotent with the reference standard chlorpheniramine maleate (percentage protection 71%). These compounds show negligible sedation (~5%) when compared to the reference standard (26%). Hence they could serve as prototype molecules for future development.

The prevalence of asthma and other allergic diseases is increasing[1–3] providing a rapidly expanding market for antiallergic drugs. 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[4] 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[5] (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 80s of 20th century with the discovery of modern antihistamines which were found to exhibit potent antihistaminic activity without a sleep-inducing effect.[6] 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[7] and mangostin[8]). A literature survey reveals excellent antihistaminic activity in quinazolines and condensed quinazolines.[9,10] In view of these facts and to continue our efforts[11,12] in the search of quinazoline-derived potent antihistamines with least sedation, in the present study we aimed to synthesize a series of 1,2,4-triazolo-[4,3-*a*]quinazolin-5(4*H*)-ones containing phenyl substitution at position 4 and alkyl substitution at position 1. In spite of a few reported methods available for the synthesis of 1,2,4-triazolo[4,3-*a*] quinazolines,[13,14] the title compounds, we aimed to synthesize these compounds by a novel innovative route (Scheme 1).

Melting points were determined in open capillary tubes on a Thomas Hoover apparatus and are uncorrected. IR spectra were recorded in KBr on a Shimadzu FT-IR, 8300 spectrometer (cm^{-1}), mass spectra on a MASPEC msw 9629 mass spectrometer at 70 eV and NMR spectra on a Varian 300 MHz spectrometer, using tetramethylsilane as internal standard. Elemental analyses were performed on Carlo Erba 1108.

The key intermediate 2-thioxo-3-phenylquinazolin-4(3*H*)-one was prepared by adding carbondisulfide and sodium

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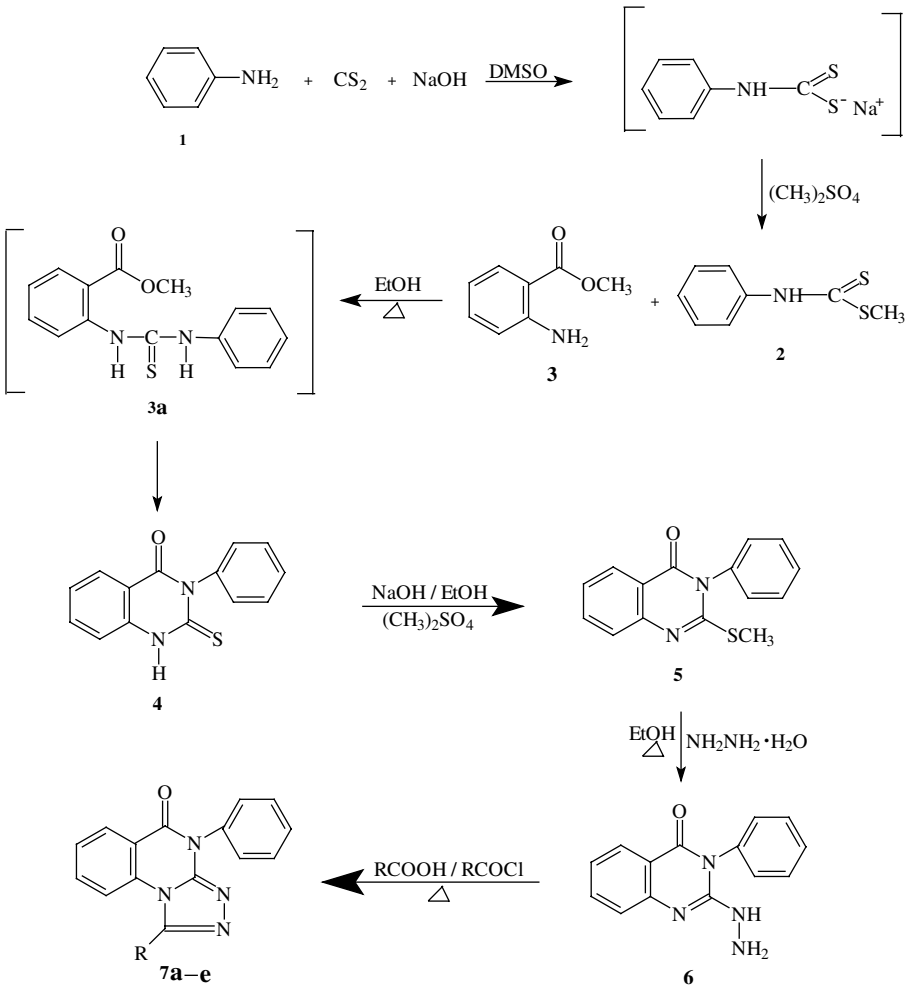

Scheme 1. Synthetic protocol of the compounds **7a**–**e**.

hydroxide solution simultaneously to a vigorously stirred solution of aniline **1** in dimethylsulfoxide over 30 min, stirring was continued for an additional 30 min. Dimethyl sulfate was added to the reaction mixture whilst stirring at 5–10 °C, it was further stirred for 2 h and poured into ice water to get a solid dithiocarbamic acid methyl ester **2**. The compound **2** and methyl anthranilate **3** when refluxed in ethanol for 18 h yielded the desired 2-thioxo-3-substituted quinazolin-4(3*H*)-one **4** (yield 86%; mp 305–306 °C). The product obtained was cyclic and not an open chain thiourea **3a**. It was confirmed by its low R_f value, high melting point and its solubility in sodium hydroxide solution. The IR spectra of these compounds show intense peaks at 3220 cm^{-1} for amino (NH), 1660 cm^{-1} for carbonyl (C=O) and 1200 cm^{-1} for thioxo (C=S) stretching. NMR spectrum of **4** showed signals at δ 7–9 (m, 9H, ArH) and 10.5 (s, 1H, NH). Data from the elemental analyses have been found to be in conformity with the assigned structure. Furthermore the molecular ion recorded in the mass spectrum is also in agreement with the molecular weight of the compound.

The 2-methylthio-3-substituted quinazolin-4(3*H*)-one **5** was obtained by dissolving **4** in 2% alcoholic sodium hydroxide solution and methylating with dimethyl sulfate whilst stirring at room temperature (yield 88%; mp 124–126 °C). The IR spectrum of **5** showed disappearance of amino (NH) and thioxo (C=S) stretching signals of the starting material. It showed a peak for carbonyl (C=O) stretching at 1680 cm^{-1}. The NMR spectrum of compound **5** showed signals at δ 2.5 (s, 3H, SCH_3) and 7.0–8.6 (m, 9H, ArH). 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 2-hydrazino-3-substituted quinazolin-4(3*H*)-one **6** (yield 81%; mp 158–160 °C). The long duration of reaction (22 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 around 3334–3280 cm^{-1} in the IR spectrum. It also showed a peak for carbonyl (C=O) at 1680 cm^{-1}. The NMR spectrum of the compound **6** showed signals at δ 5.0 (s, 2H, NHNH_2), 7.0–8.1 (m, 9H, ArH) and 8.7 (s, 1H, N*H*NH_2). Data from the elemental analyses have been

Table 1. Physical and pharmacological data of compounds **7a–e**

Compd no.	R	Yield, %	Mp, °C (recryst solv.[a])	Mol. formula[b]	Mol. wt.[c]	% Protection[d]	% CNS depression[d]
7a	–H	89	262–265 (C–E)	$C_{15}H_{10}N_4O$	262	69.9	4.2
7b	$-CH_3$	87	276–279 (C–E)	$C_{16}H_{12}N_4O$	276	70.7	4.8
7c	$-CH_2CH_3$	80	190–193 (E)	$C_{17}H_{14}N_4O$	290	70.0	5.3
7d	$-(CH_2)_2CH_3$	76	190–194 (C–E)	$C_{18}H_{16}N_4O$	304	69.2	7.3
7e	$-CH_2Cl$	78	258–260 (C–E)	$C_{16}H_{11}N_4OCl$	310	68.7	3.7
Chlorpheniramine maleate		—	—	—	—	71.0	26
Cetirizine						78.9	8.5

[a] Abbreviations for the solvents used are as follows: C = chloroform, E = ethanol.
[b] Elemental (C, H, N) analysis indicated that the calculated and observed values were within the acceptable limits (±0.4%).
[c] Molecular weight determination by mass spectral analysis.
[d] Values are the means from six separate experiments. SE was less than 10% of the mean. Dose of test compounds, chlorpheniramine maleate and cetirizine are 10 mg/kg for antihistaminic activity; and 5 mg/kg for sedative-hypnotic activity.

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

The title compounds **7a–e** 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 3400–3200 cm^{-1} in IR spectrum of all the compounds **7a–e**. The NMR spectrum of **7a–e** showed the absence of NH and NH_2 signals. A multiplet at 7.0–8.0 integrating for aromatic protons was observed. The molecular ion recorded in the mass spectrum is in agreement with the molecular weight of the compounds. Elemental (C, H, N) analysis indicated that the calculated and observed values were within the acceptable limits (±0.4%). Physical data of the title compounds is represented in Table 1.

The MS University of Baroda, India, Institutional Animal Ethics committee approved the protocol adopted for the experimentation of animals. A modification of the technique of Van Arman et al.[15] was adopted to determine the antihistaminic potential of the synthesized compounds. The test compounds and the reference standards (chlorpheniramine maleate and cetirizine) were administered orally at a dose of 10 mg/kg in 1% CMC. The mean preconvulsion time of test group animals was compared with control and is expressed in terms of percentage protection (Table 1). Student *t* test was performed to ascertain the significance of the exhibited activity.

The in vivo antihistaminic activity results indicate that all test compounds protected the animals from histamine induced bronchospasm significantly. Structural activity relationship (SAR) studies, indicated that different alkyl substituents on the first position of triazoloquinazoline ring exerted varied biological activity. Compound **7a** with no substitution, showed good activity (percentage protection 69.9%); with increased lipophilicity (methyl compound **7b**) activity increased (percentage protection 70.7%). Further increases in lipophilicity (i.e., ethyl compound **7c** and propyl compound **7d**) lead to decrease in activity (percentage protection 70% and 69.2%, respectively). Replacement of a proton of the methyl group by a lipophobic group (chloro) (compound **7e**) resulted in a further decrease in activity (percentage protection 68.7%). The order of activity of substituents at first position was methyl > ethyl > unsubstituted > propyl > chloromethyl. Compounds with a small substituent at C-1 seems to provide optimum activity. As the test compounds could not be converted to water soluble form, in vitro evaluation for antihistaminic activity could not be performed.

As sedation is one of the major side effects associated with antihistamines, the test compounds were also evaluated for their sedative potentials. It was determined by measuring the reduction in locomotor activity using actophotometer.[16,17] The test compounds and the reference standards (chlorpheniramine maleate and cetirizine) were administered orally at a dose of 5 mg/kg in 1% CMC. The percent reduction in locomotor activity was calculated and shown in Table 1. Student *t* test was performed to ascertain the significance of the exhibited activity. The results indicate that all the test compounds were found to exhibit only negligible sedation (4–7%), whereas the reference standard chlorpheniramine maleate showed 26% sedation and cetirizine showed 8.5%.

Among the series, 1-methyl-4-phenyl-1,2,4-triazoloquinazolin-5(4*H*)-one **7b** was the most potent with the percentage protection of 70.7, which is equipotent with that of standard chlorpheniramine maleate (percentage protection 71%) and less potent than cetirizine (percentage protection 78.9%). Compound **7b** showed negligible sedation (4.8%) compared to chlorpheniramine maleate (26%) and cetirizine (8.5%), hence it could therefore serve as a lead molecule for further modification to obtain a clinically useful novel class of non-sedative antihistamines.

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