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RESEARCH ARTICLE

Design and synthesis of novel 2-(3-substituted propyl)-3-(2-methyl phenyl) quinazolin-4-(3*H*)-ones as a new class of H_1-antihistaminic agents

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Abstract

A series of novel 2-(3-substituted propyl)-3-(2-methyl phenyl) quinazolin-4-(3*H*)-ones were synthesized by the reaction of 2-(3-bromopropyl thio)-3-(2-methyl phenyl) quinazolin-4-(3*H*)-one with various amines. The starting material, 2-(3-bromopropyl thio)-3-(2-methyl phenyl) quinazolin-4-(3*H*)-one was synthesized from 2-methyl aniline. 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. Compound 2-(3-(4-methylpiperazin-1-yl) propylthio)-3-(2-methyl phenyl) quinazolin-4(3*H*)-one (**OT5**) emerged as the most active compound (71.70% protection) of the series when compared to the reference standard chlorpheniramine maleate (70.09% protection). Compound **OT5** shows negligible sedation (7%) compared to chlorpheniramine maleate (33%). Therefore, compound **OT5** can serve as the leading molecule for further development into a new class of H_1-antihistaminic agents.

Keywords: Quinazolin-4-ones, sedation, H_1-antihistaminic agents

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Introduction

Histamine is one of the most important chemical mediators and through its interaction with H_1 receptors, present in most tissues, is involved in the pathophysiology of allergic rhinoconjuntivitis, urticaria and asthma[1]. The first-generation antihistamines are effective and relatively inexpensive against these symptoms; however, they also cause sedation and dry mouth at therapeutic doses, due to their blood-brain barrier penetration and lack of receptor specificity[2]. A common feature of the first-generation compounds includes two aryl or heteroaryl rings linked to an aliphatic tertiary amine via the side chain (Figure 1 diphenhydramine and pheniramine[3]). In contrast, most of the second generation H_1-antagonists such as terfenadine, cetirizine and astemizole[4], have a greatly improved benefit-to-risk ratio compared to their predecessors. These drugs are lesser perspective to cross the blood-brain barrier and possess the higher receptor specificity[4] they are labeled as "non sedative antihistamines". The second-generation compounds (Figure 1 terfenadine and cetirizine) also contain many of the structural features of first-generation compounds. Condensed heterocycles containing new generation of H_1-antihistamines (loratadine, azelastine and flazelastine) that do not possess the above mentioned pharmacophore for H_1-antihistamines gave way for the discovery of many novel H_1-antihistaminic drugs temelastine[4] and mangostin[5]. Quinazolines and condensed quinazolines showed excellent antihistaminic activity[6–8]. In this continuation, we demonstrated[9–11] the quinazoline derivatives (Figure 2) as potent antihistamines with least sedation. The present work is an extension of our ongoing efforts toward development and identification of new molecules. Therefore we undertook to synthesize a series of 2-(3-substituted propyl)-3-(2-methyl phenyl) quinazolin-4-(3*H*)-ones, in which heterocyclic quinazoline ring linked to an aliphatic tertiary amine via the side chain. The synthesized compounds were tested for their *in vivo* H_1-antihistaminic activity on conscious guinea pigs. As sedation is one of

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Abbreviations

δ ppm, part per million;
DMSO, dimethyl sulfoxide;
GI_{50}, 50% growth inhibition;
IR, Infrared; mp, melting point;
NMR, nuclear magnetic resonance;
SAR, Structure-activity relationship;
CMC, carboxymethylcellulose;
ANOVA, one-way analysis of variance

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 section

General

Melting points (mp) were taken in open capillaries on Thomas Hoover melting point apparatus and are uncorrected. The IR spectra were recorded in film or in potassium bromide disks on a Perkin-Elmer 398 spectrometer. The ^{1}H spectra were recorded on a DPX-500 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.

Synthesis of 3-(2-methyl phenyl)-2-thioxo quinazolin-4(3*H*)-one (4)

A solution of 2-methyl aniline (1.82 g; 0.02 mol) in dimethyl sulfoxide (10 mL) was stirred vigorously. To this was added carbon disulphide (1.6 mL) and aqueous sodium hydroxide (1.2 mL; 20 molar) dropwise during 30 min with stirring. Dimethyl sulphate (2.5 g; 0.02 mol) was then added gradually keeping the reaction mixture in freezing mixture with stirring and the stirring was continued for further 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 (1.5 g; 0.01 mol) and the above prepared *N*-(2-methyl 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 18 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 hydrocholoric acid. The solid obtained was filtered, washed with water, and dried. It was recrystallized from ethanol to afford (**4**). Yield = 85%; mp 241–242°C; IR (KBr) cm^{-1}: 3211 (NH), 1686 (C=O), 1213 (C=S); ^{1}H NMR ($CDCl_3$): δ 2.4 (s, 3H, CH_3), 7.1–7.4 (m, 4H, Ar-*H*), 7.5–7.8 (m, 4H, Ar-H), 10.3 (br s, 1H, NH); MS (m/z) 268 (M^+); Anal. Calcd for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44; Found: C, 67.19; H, 4.57; N, 10.38.

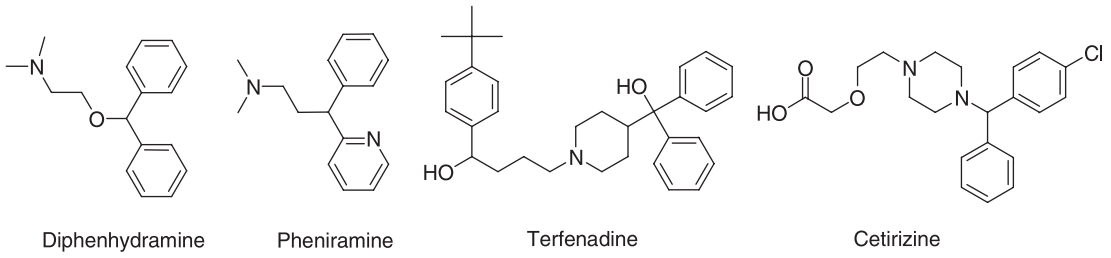

Figure 1. Structure of some clinically available H_1-antihistaminic agent.

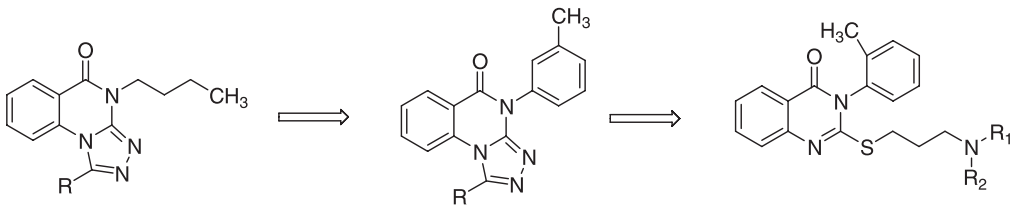

Figure 2. Quinazolin-4-(3*H*)-one lead optimization from this laboratory.

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Synthesis of 2-(3-bromopropyl thio)-3-(2-methyl phenyl) quinazolin-4-(3*H*)-one (6)

A solution of 3-(2-methyl phenyl)-2-thixo quinazolin-4(3*H*) one **(4)** (2.53 g; 0.01 mol), 1,3-dibromopropane (0.02 mol) and K_2CO_3 (4.14 g; 0.03 mol) in acetone (20 mL) was heated to reflux temperature for 1 h. The reaction mixture was cooled to room temperature and filtered off to remove the inorganic materials. The solvent was removed under reduced pressure to afford 2-(3-bromo propylthio)-3-(2-methyl phenyl) quinazolin-4-(3*H*)-one **(6)**, it was then recrystallized from ethanol. Yield = 85%; mp 200–203°C; IR (KBr) cm^{-1}: 1716 (C=O), 1610 (C=N), 1275 (C-N), 590 (C-Br); ^1H NMR ($CDCl_3$): δ 2.16–2.18 (m, 2H,CH_2), 2.36–2.40 (m, 2H, CH_2), 2.67 (s, 3H, CH_3), 3.27–3.30 (m, 2H, CH_2), 7.21–7.22 (d, 1H, Ar-*H*), 7.37–7.44 (m, 3H, Ar-H), 7.47–7.51 (m, 2H, Ar-H), 7.70–7.74 (d, 1H, Ar-H), 8.25–8.27 (dd, 1H, Ar-*H*); MS (m/z) 389 (M^+); Anal. Calcd for $C_{18}H_{17}BrN_2OS$: C, 55.53; H, 4.40; Br, 20.52; N, 7.20; O, 4.11; S, 8.24. Found: C, 55.58; H, 4.41; N, 07.18.

General procedure for synthesis of 2-(3-substitutedpropyl)-3-(2-methyl phenyl) quinazolin-4-(3*H*)-one (OT1–OT10)

A mixture of 2-(3-bromo propyl thio)-3-(2-methyl phenyl) quinazolin-4-(3*H*)-one **(6)** (3.75 g; 0.01 mol), alkyl/aryl amine (0.015 mol), Potassium iodide (1.66 g; 0.015 mol) and sodium carbonate (2.12 g; 0.02 mol) in 1-butanol (25 mL) was heated at reflux temperature (for 3 h by conventional refluxing or 15 min by microwave oven). The reaction mixture was cooled, filtered and the filtrate was then concentrated in vacuum and kept in refrigerator overnight. The product obtained was filtered, dried and recrystallized using chloroform-ethanol (50:50) mixture to yield the title compounds.

2-(3-(Diethylamino)propylthio)-3-(2-methyl phenyl) quinazolin-4(3H)-one (OT1)

Yield = 81%; mp 182–184°C; IR (KBr) cm^{-1}: 1666 (C=O), 1606 (C=N), 1299 (C-N); ^1H NMR ($CDCl_3$): δ 0.97–1.15 (m, *J* = 7.5 Hz, 6H, 2-CH_3), 2.16–2.22 (m, 4H, CH_2), 2.81–2.85 (m, 4H, CH_2), 2.90 (s, 3H, CH_3), 2.97–3.01 (m, 2H, CH_2), 7.21–7.22 (d, 1H, Ar-*H*), 7.28–7.39 (m, 4H, Ar-*H*), 7.40–7.42 (d, 1H, Ar-*H*), 7.73–7.74 (d, 1H, Ar-*H*), 8.25–8.31 (dd, 1H, Ar-*H*); MS (m/z) 381 (M^+); *Anal.* Calcd for $C_{22}H_{27}N_3OS$: C, 69.26; H, 7.13; N, 11.01; O, 4.19; S, 8.40. Found: C, 69.25; H, 7.17; N, 11.03.

3-(2-Methyl phenyl)-2-(3-(pyrrolidin-1-yl) propylthio) quinazolin-4(3H)-one (OT2)

Yield = 78%; mp 186–187°C; IR (KBr) cm^{-1}: 1668 (C=O), 1649 (C=N), 1258 (C-N); ^1H NMR ($CDCl_3$): δ 1.53–1.61 (m, 4H, CH_2), 2.08–2.25 (m, 6H, CH_2), 2.36 (s, 3H, CH_3), 2.81–2.84 (m, 2H, CH_2), 3.27–3.29 (m, 2H, CH_2), 7.18–7.19 (d, 1H, Ar-*H*), 7.30–7.38 (m, 4H, Ar-*H*), 7.48–7.51 (d, 1H, Ar-*H*), 7.72–7.73 (d, 1H, Ar-*H*), 8.26–8.31 (dd, 1H, Ar-*H*); MS (m/z) 379 (M^+); Anal. Calcd for $C_{22}H_{25}N_3OS$: C, 69.62; H, 6.64; N, 11.07; O, 4.22; S, 8.45. Found: C, 69.66; H, 6.66; N, 11.05.

3-(2-Methyl phenyl)-2-(3-(piperidin-1-yl)propylthio) quinazolin-4(3H)-one (OT3)

Yield = 80%; mp 212–213°C; IR (KBr) cm^{-1}: 1666 (C=O), 1606 (C=N), 1250 (C-N); ^1H NMR ($CDCl_3$): δ 1.54–1.60 (m, 4H, CH_2), 1.67–1.71 (m, 2H, CH_2), 2.16–2.22 (m, 4H, CH_2), 2.36 (s, 3H, CH_3), 2.80–2.83 (m, 4H, CH_2), 3.29–3.31 (m, 2H, CH_2), 7.18–7.19 (d, 1H, Ar-*H*), 7.30–7.43 (m, 4H, Ar-*H*), 7.48–7.51 (d, 1H, Ar-*H*), 7.72–7.73 (d, 1H, Ar-*H*), 8.26–8.31 (dd, 1H, Ar-*H*); MS (m/z) 393 (M^+); *Anal.* Calcd for $C_{23}H_{27}N_3OS$: C, 70.19; H, 6.92; N, 10.68; O, 4.07; S, 8.15 Found: C, 70.17; H, 6.90; N, 10.69.

3-(2-Methyl phenyl)-2-(3-(piperazin-1-yl) propylthio) quinazolin-4(3H)-one (OT4)

Yield = 81%; mp 171–173°C; IR (KBr) cm^{-1}: 3292 (N-H), 1666 (C=O), 1606 (C=N), 1240 (C-N); ^1H NMR ($CDCl_3$): δ 1.79–1.85 (m, 4H, CH_2), 2.17–2.22 (m, 6H, CH_2), 2.30 (s, 3H, CH_3), 2.81–2.84 (m, 2H, CH_2), 3.29–3.31 (m, 2H, CH_2), 7.18–7.19 (d, 1H, Ar-*H*), 7.30–7.43 (m, 4H, Ar-*H*), 7.48–7.51 (d, 1H, Ar-*H*), 7.72–7.73 (d, 1H, Ar-*H*), 8.26–8.31 (dd, 1H, Ar-*H*), 8.63 (br s, 1H, NH); MS (m/z) 394 (M^+); Anal. Calcd for $C_{22}H_{26}N_4OS$: C, 66.97; H, 6.64; N, 14.20; O, 4.06; S, 8.13. Found: C, 66.99; H, 6.65; N, 14.23.

2-(3-(4-Methylpiperazin-1-yl) propylthio)-3-(2-methyl phenyl) quinazolin-4(3H)-one (OT5)

Yield = 78%; mp 214–215°C; IR (KBr) cm^{-1}: 1666 (C=O), 1606 (C=N), 1300 (C-N); ^1H NMR ($CDCl_3$): δ 1.58 (s, 3H, CH_3), 2.16–2.17 (m, 8H, CH_2), 2.43 (s, 3H, CH_3), 2.81–2.84 (m, 2H, CH_2), 2.90–2.97 (m, 2H, CH_2), 3.28–3.29 (m, 2H, CH_2), 7.21–7.22 (d, 1H, Ar-*H*), 7.30–7.43 (m, 4H, Ar-*H*), 7.48–7.50 (d, 1H, Ar-*H*), 7.73–7.74 (d, 1H, Ar-*H*), 8.25–8.31 (dd, 1H, Ar-*H*); ^{13}C NMR ($CDCl_3$): 18.41, 29.37, 34.19, 44.24, 45.79, 54.25 (4C), 118.74, 120.19, 121.45, 125.64, 127.15, 128.15, 128.54, 129.14, 132.47, 133.47, 133.65, 145.64, 160.15, 162.18; MS (m/z) 409 (M^+); Anal. Calcd for $C_{23}H_{28}N_4OS$: C, 67.61; H, 6.91; N, 13.71; O, 3.92; S, 7.85, Found: C, 67.76; H, 6.90; N, 13.69.

3-(2-Methyl phenyl)-2-(3-morpholinopropylthio) quinazolin-4(3H)-one (OT6)

Yield = 82%; mp 175–176°C; IR (KBr) cm^{-1}: 1666 (C=O), 1606 (C=N), 1299 (C-N); ^1H NMR ($CDCl_3$): δ 1.58–1.65 (m, 2H, CH_2), 2.17–2.24 (m, 6H, CH_2), 2.34 (s, 3H, CH_3), 2.81–2.83 (m, 2H, CH_2), 3.29–3.30 (m, 4H, CH_2), 7.21–7.22 (d, 1H, Ar-*H*), 7.30–7.43 (m, 4H, Ar-*H*), 7.48–7.50 (d, 1H, Ar-*H*), 7.73–7.74 (d, 1H, Ar-*H*), 8.25–8.28 (dd, 1H, Ar-*H*; MS (m/z) 395 (M^+); *Anal.* Calcd for $C_{22}H_{25}N_3O_2S$: C, 66.81; H, 6.37; N, 10.62; O, 8.09; S, 8.11. Found: C, 66.80; H, 6.34; N, 10.65.

3-(2-Methyl phenyl)-2-(3-phenylpropylthio) quinazolin-4(3H)-one (OT7)

Yield = 79%; mp 221–222°C; IR (KBr) cm^{-1}: 3280 (N-H), 1666 (C=O), 1606 (C=N), 1300 (C-N); ^1H NMR ($CDCl_3$): δ 1.76–1.79 (m, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.81–2.84 (m, 2H, CH_2), 3.29–3.30 (m, 2H, CH_2), 7.17–7.95 (m, 11H, Ar-*H*), 8.19–8.21 (m, 1H, Ar-*H*), 8.25–8.31 (m, 1H, Ar-*H*),

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8.74 (br s, 1H, NH); MS (m/z) 401 (M^+); Anal. Calcd for $C_{24}H_{23}N_3OS$: C, 71.79; H, 5.77; N, 10.47; O, 3.98; S, 7.99. Found: C, 71.78; H, 5.74; N, 10.44.

2-(3-(4-Chlorophenyl propylthio)-3-(2-methyl phenyl) quinazolin-4(3H)-one (OT8)

Yield = 77%; mp 188–189°C; IR (KBr) cm^{-1}: 3280 (N-H), 1660 (C=O), 1609 (C=N), 1300 (C-N); ^1H NMR ($CDCl_3$): δ 2.17–2.20 (m, 2H, CH_2), 2.36 (s, 3H, CH_3), 2.81–2.84 (m, 2H, CH_2), 3.28–3.29 (m, 2H, CH_2), 7.29–7.77 (m, 10H, Ar-*H*), 7.94–7.95 (m, 1H, Ar-*H*), 8.11–8.14 (m, 1H, Ar-*H*), 8.64 (br s, 1H, NH); MS (m/z) 436 (M^+); Anal. Calcd for $C_{24}H_{22}ClN_3OS$: C, 66.12; H, 5.09; Cl, 8.13; N, 9.64; O, 3.67; S, 7.35. Found: C, 66.15; H, 5.07; N, 09.65.

2-(3-(4-Methylphenylpropylthio)-3-(2-methylphenyl) quinazolin-4(3H)-one (OT9)

Yield = 81%; mp 179–181°C; IR (KBr) cm^{-1}: 3278 (N-H), 1666 (C=O), 1606 (C=N), 1300 (C-N); ^1H NMR ($CDCl_3$): δ 2.16–2.18 (m, 2H, CH_2), 2.76–2.79 (m, 2H, CH_2), 2.91 (s, 3H, CH_3), 2.98 (s, 3H, CH_3), 3.28–3.29 (m, 2H, CH_2), 7.18–7.85 (m, 11H, Ar-*H*), 8.05 (br s, 1H, NH), 8.25–8.32 (m, 1H, Ar-*H*); MS (m/z) 415 (M^+); Anal. Calcd for $C_{25}H_{25}N_3OS$: C, 72.26; H, 6.06; N, 10.11; O, 3.85; S, 7.72, Found: C, 72.25; H, 6.04; N, 10.14.

2-(3-(Benzylpropylthio)-3-(2-methylphenyl) quinazolin-4(3H)-one (OT10)

Yield = 80%; mp 211–213°C; IR (KBr) cm^{-1}: 3279 (N-H), 1666 (C=O), 1606 (C=N), 1300 (C-N); ^1H NMR ($CDCl_3$): δ 1.72 (ms, 2H, CH_2), 2.19–2.23 (m, 2H,CH_2), 2.82–2.84 (m, 2H, CH_2), 2.97 (s, 3H, CH_3), 3.28–3.29 (m, 2H, CH_2), 7.17–7.76 (m, 12H, Ar-*H*), 8.04 (brs 1H, NH), 8.25–8.31 (m, 1H, Ar-*H*); MS (m/z) 415 (M^+); Anal. Calcd for $C_{25}H_{25}N_3OS$: C, 72.26; H, 6.06; N, 10.11; O, 3.85; S, 7.72, Found: C, 72.25; H, 6.08; N, 10.13.

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 the experiment. The Institutional Animal Ethics committee approved the protocol adopted for the experimentation of animals.

Antihistaminic activity

A modification of the technique of Van Arman was adopted to determine the antihistaminic potential of the synthesized compounds[12]. Male Dunkin Hartley Guinea pigs (250–300 g) were fasted for 12 h. Six animals were taken in each group. The test compounds and reference compound chlorpheniramine maleate (Avil; Hoechst, Mumbai, India), was administered orally at a dose of 10 mg/kg in 1% W/V carboxymethylcellulose (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 Pheniramine 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 1).

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

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

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

Sedative-hypnotic activity

Sedative-hypnotic activity was determined by measuring the reduction in locomotor activity using actophotometer[13,14]. Six albino Swiss mice were allotted to each group. Basal activity score was taken and then compounds **OT1–OT10** and standard chlorpheniramine

Table 1. Antihistaminic and sedative-hypnotic activity of compounds **OT1–OT10.**

Compound Code	Time of onset of convulsion (in sec)	% Protection	Percent CNS depression			
			0.5 h	1 h	2 h	3 h
OT1	355 ± 1.85*	66.83 ± 0.17*	13.77 ± 1.06**	13.70 ± 1.05**	14.95 ± 0.99**	11.40 ± 0.76**
OT2	370 ± 3.06*	67.61 ± 0.37*	10.53 ± 1.06**	11.03 ± 0.92**	11.96 ± 1.04**	8.14 ± 0.80**
OT3	362 ± 2.24*	67.42 ± 0.20*	11.68 ± 1.56**	12.96 ± 1.30**	13.29 ± 0.77**	9.26 ± 0.78**
OT4	396 ± 1.53*	70.21 ± 0.11*	8.62 ± 0.68**	8.79 ± 0.64**	9.21 ± 0.68**	6.31 ± 0.67**
OT5	417 ± 2.50*	71.70 ± 0.17*	8.19 ± 0.73**	9.48 ± 0.88**	9.25 ± 0.73**	7.51 ± 0.71**
OT6	390 ± 2.27*	69.75 ± 0.17*	7.56 ± 0.82**	9.20 ± 1.06**	9.96 ± 0.80**	7.44 ± 0.83**
OT7	351 ± 2.28*	66.39 ± 0.21*	8.97 ± 1.00*	8.79 ± 0.99**	10.34 ± 0.84**	6.12 ± 0.75**
OT8	352 ± 2.41*	66.54 ± 0.22*	8.33 ± 0.61**	9.20 ± 0.65**	9.49 ± 0.55**	6.13 ± 0.97**
OT9	335 ± 2.90*	64.78 ± 0.30*	8.78 ± 1.22**	10.30 ± 0.81**	11.54 ± 0.73**	8.92 ± 1.14**
OT10	346 ± 1.64*	65.90 ± 0.16*	9.23 ± 1.35**	9.37 ± 1.35**	12.39 ± 0.84**	7.56 ± 0.69**
Chlorpheniramine	394 ± 4.43*	70.09 ± 0.33*	32.04 ± 0.50**	38.80 ± 1.32**	34.80 ± 0.72**	29.58 ± 0.72**

Each value represents the mean ± SEM ($n = 6$).
Significance levels *$p < 0.001$, **$p < 0.05$.

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maleate were administered orally at the dose of 5 mg/kg in 1% CMC. Scores were recorded at 0.5, 1, 2 and 3 h after the drug administration. The percent reduction in loco motor activity was calculated by the following formula and shown in Table 1.

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

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

Statistical analysis

Statistical analysis of the biological activity of the synthesized compounds on animals was evaluated using an 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 ± SD (standard deviations). For statistical analysis GraphPad Prism 3.0 version was used. (GraphPad Software, Inc.San Diego, CA).

Results and discussion

Chemistry

The key intermediate 3-(2-methyl phenyl)-2-thioxo-2-,3-dihydro-1*H*-quinazolin-4-one **4** was synthesized by straightforward method. In this synthetic scheme, 3-methyl aniline (**1**) treated with carbon disulphide and sodium hydroxide in dimethyl sulphoxide 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-(2-methyl phenyl)-2-thioxo-2,3-dihydro-1*H*- quinazolin-4-one **(4)** via the thiourea intermediate in good yield (85%). The use of DMSO as the reaction solvent enhanced the rate of reaction and the use of alkali in higher concentration helped prevent the hydrolysis of the intermediate, probably due to less solvation. The product obtained was cyclic and not an open chain thiourea **3a**. The IR spectrum of **4** show intense peaks at 3211 cm^{-1} for cyclic thio urea (NH), 1686 cm^{-1} for carbonyl (C=O) and 1213 cm^{-1} for thioxo (C=S) stretching. ^{1}H NMR spectrum of **4** showed singlet at δ 2.42 due to methyl group; for aromatic (8H) protons a multiplet at δ 7.14–7.45 and 7.53–7.81 ppm and a singlet at δ 10.31 ppm indicating the presence of NH. Data from the elemental analyses have been found to be in conformity with the assigned structure. Further the molecular ion recorded in the mass spectrum is also in agreement with the molecular weight of the compound.

The 2-(3-bromo propyl thio)-3-(2-methyl phenyl) quinazolin-4-(3*H*)-one **(6)** was prepared by heating at reflux temperature, a solution of 2-thioxo-3-(2-methylphenyl) quinazolin-4(3*H*)one **(4)**, and 1,3-Dibromopropane in acetone in the presence of K_2CO_3 for 1h. The IR spectrum of **6** showed disappearance of NH and C=S stretching signals of cyclic thiourea. It showed a peak for carbonyl (C=O) stretching at 1716 cm^{-1}. The ^{1}H NMR spectrum of compound **6** showed multiplet at δ 2.16–3.30 for S-$CH_2CH_2CH_2$ group; a singlet at δ 2.67 for–CH_3 group and multiplet for aromatic (8H) protons observed at δ 7.21–8.27. Data from the elemental analyses and molecular ion recorded in the mass spectrum further confirmed the assigned structure.

The title compounds **OT1–OT10** were obtained in fair to good yields through the nucleophilic displacement of–Br group of 2-(3-bromo propyl thio)-3-(2-methyl phenyl) quinazolin-4-(3*H*)-one (**6**) with a variety of amines, using ethanol as solvent to afford 2-(3-substituted propyl)-3-(2-methylphenyl) quinazolin-4-(3*H*)-one **(OT1–OT10)**. The formation of the title compounds is indicated by the disappearance of peaks due to Br of the starting material and the appearance of NH signal at 3320 cm^{-1} in the IR spectra of the compounds **OT4**, **OT7**, **OT8**, **OT9** and **OT10**. It also showed a peak for carbonyl (C=O) around 1680 cm^{-1}. The ^{1}H NMR spectra of the title compounds **OT1–OT10** showed peaks for substituents at C-2 and singlet around δ 8.04 ppm due to NH, a multiplet at δ 7.10–8.31 ppm was observed for aromatic protons. In mass spectra of compounds **OT1–OT10** the common peak appeared due quinazolin-4-one moiety cation at m/z 168. Elemental (C, H, N) analysis satisfactorily confirmed elemental composition and purity of the synthesized compounds.

Pharmacology

The compounds containing 2-(substituted propyl)-3-(2-methyl phenyl) quinazolin-4-(3*H*)-ones, (**OT1–OT10**) 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[12]. The advantage of this method is that it is one of the non-invasive method and the animals are recovered after the experiment.

All the test compounds were found to exhibit good antihistaminic activity (Table 1). Percentage protection data showed that all test compounds of the series showed significant protection in the range of 64–71%. Biological studies indicated that different substituents over the second position of quinazoline ring exerted varied biological activity. The presence of diethyl group (compound **OT1**) showed significant activity, when the cyclic amines with the similar lipophilicity are substituted (pyrrolidinyl compound **OT2** and piperidinyl Compound **OT3**) the activity is retained. Placement of additional heteroatoms like nitrogen (piperazinyl compound **OT4** and *N*-methyl piperazinyl compound **OT5**) and oxygen (morpholinyl compound **OT6**) leads to increase in activity. Placement of aryl substitutions (phenyl compound **OT7**; *p*-chlorophenyl compound **OT8**; *p*-methyl phenyl compound **OT9**) results in decreased activity). Placement of arylalkyl (benzyl compound **OT10**) further decreased the activity. Compound 2-(3-(4-methylpiperazin-1-yl)propylthio)-3--(2-methyl phenyl) quinazolin-4(3*H*)-one (**OT5**) exhibited the most potent activity of the series.

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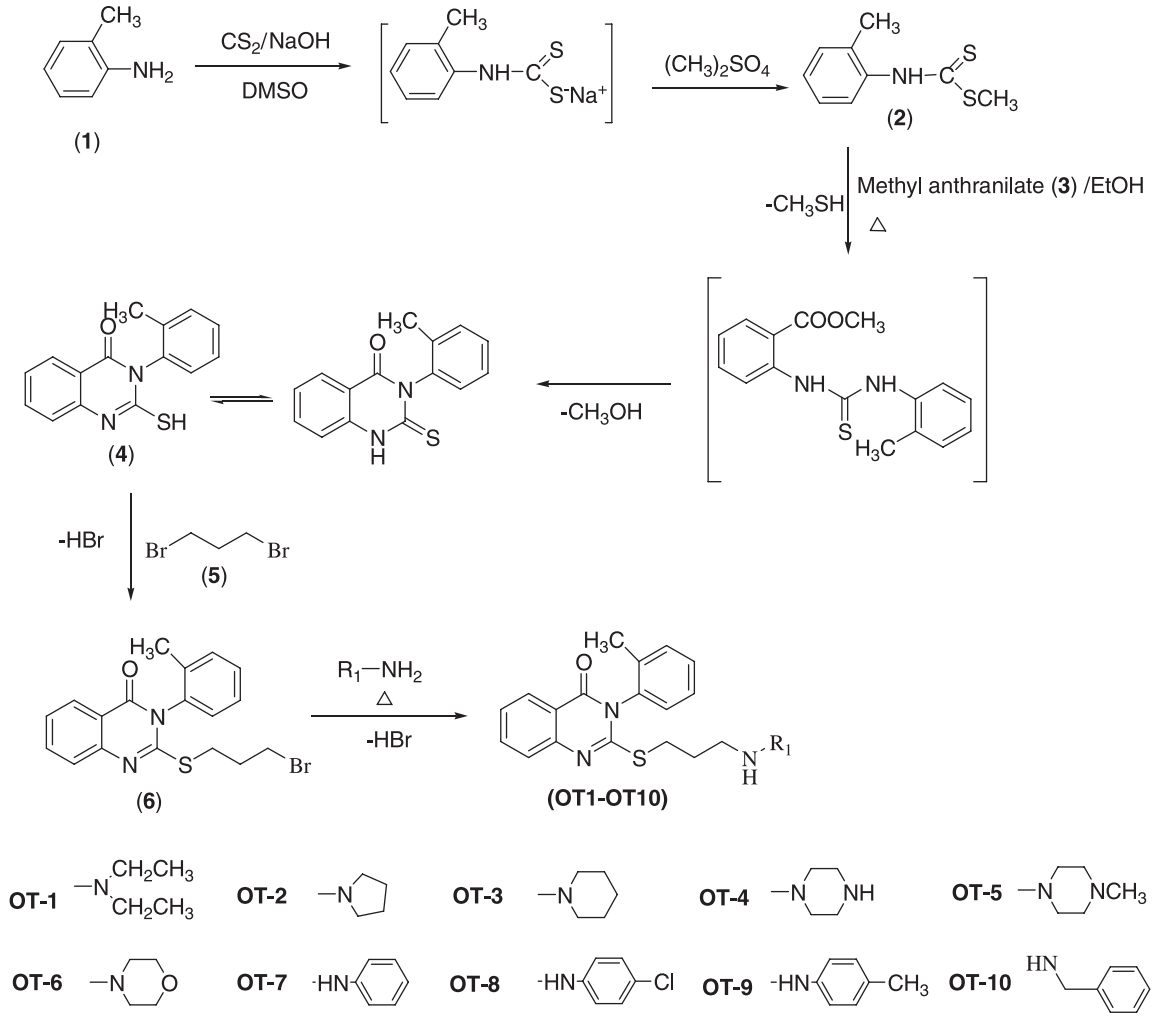

Scheme 1. Synthesis of 2-(3-substituted propyl)-3-(2-methyl phenyl) quinazolin-4-(3*H*)-one (**OT1**–**OT10**).

Sedative-hypnotic activity was determined by measuring the reduction in locomotor activity using actophotometer[13,14] on Albino Swiss mice. The results of sedative-hypnotic activity indicate that all the test compounds were found to exhibit only negligible sedation (6–11%), whereas the reference standard chlorpheniramine maleate showed 33% sedation.

Conclusion

In summary, synthesis of new series of 2-(3-substitutedpropyl)-3-(2-methyl phenyl) quinazolin-4-(3*H*)-one (**OT1–OT10**) have been described. The title compounds have exhibited promising antihistaminic activity against histamine-induced bronchospasm on conscious guinea pigs *in vivo* model. Among the series, 2-(3-(4-methylpiperazin-1-yl)propylthio)-3-(2-methyl phenyl) quinazolin-4(3*H*)-one (**OT5**) was found to be the most active compound (71.70%), which is more potent when compared to reference standard chlorpheniramine maleate (70.09%). Interestingly compound **OT5** also showed negligible sedation (10%) compared to chlorpheniramine maleate (33%) and 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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Declaration of interest

The authors report no conflicts of interest.

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