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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of novel 2-phenyl-3-[2-(substituted amino) ethylamino] quinazolin-4(3*H*)-ones as a new class of H_1-antihistaminic agents

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Abstract A series of novel 2-phenyl-3-[2-(substituted amino) ethylamino] quinazolin-4(3*H*)-ones was synthesized by the nucleophilic substitution of 3-(2-bromo ethylamino)-2-phenyl quinazolin-4(3*H*)-one with various amines. The starting material, 3-(2-bromo ethylamino)-2-phenyl quinazolin-4(3*H*)-one, was synthesized from anthranilic acid by a multistep synthesis. All the title compounds were tested for their in vivo H_1-antihistaminic activity on conscious guinea pigs at the dose level of 10 mg/kg using chlorpheniramine as the standard drug. The results of the biologic activity revealed that all the test compounds protected the animals from histamine-induced bronchospasm significantly. Compound 2-phenyl-3-[2-(piperazinyl) ethylamino] quinazolin-4(3*H*)-one (**S3**) emerged as the most active compound of the series (73.67 % protection) when compared to the standard chlorpheniramine (70.09 % protection). Interestingly, compound **S3** shows negligible sedation (8.21 %) compared to chlorpheniramine maleate (29.58 %). Therefore, compound **S3** can serve as the lead molecule for further development into a new class of H_1-antihistaminic agents.

Keywords Quinazolin-4-ones · H_1-Antihistaminic agents · Sedation

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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 (Simons and Simons, 1994). 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 (Ellis *et al.* 1985). A common feature of the first-generation compounds includes two aryl or heteroaryl rings linked to an aliphatic tertiary amine via the side chain [Fig. 1, diphenhydramine and pheniramine] (Carr and Meyer, 1982). In contrast, most of the second generation H_1-antagonists, such as terfenadine, cetirizine and astemizole, have a greatly improved benefit-to-risk ratio compared to their predecessors. These drugs have lesser perspective to cross the blood–brain barrier and possess the higher receptor specificity (Hopp *et al.*, 1985; Chairungsrilerd *et al.*, 1996); they are labeled as "non-sedative antihistamines." The second-generation compounds [Fig. 1, terfenadine and cetirizine] also contain many of the structural features of the 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 and mangostin (Hopp *et al.*, 1985; Chairungsrilerd *et al.*, 1996). Quinazolines and condensed quinazolines showed excellent antihistaminic activity (Raghuramrao *et al.*, 1986; Devsingh *et al.*, 2001; Raju *et al.*, 1999). In this continuation, we demonstrated (Alagarsamy *et al.*, 2002; Alagarsamy, 2004; Alagarsamy *et al.*, 2002 Alagarsamy

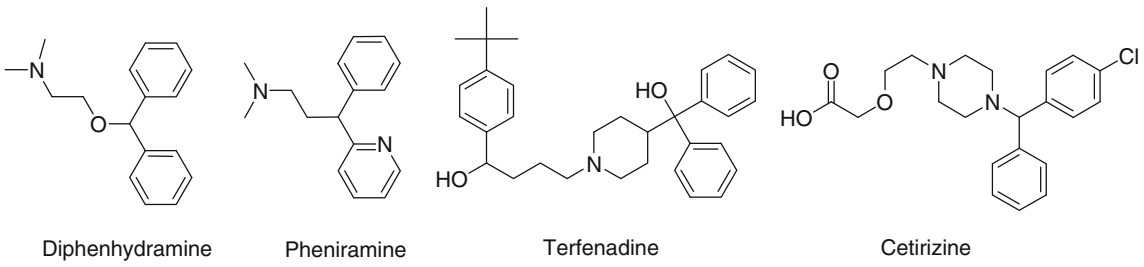


Fig. 1 Structure of some clinically available H_1 antihistaminic agent

et al., 2007) the quinazoline derivatives as potent antihistamines with least sedation. The present work is an extension of our ongoing efforts toward the development and identification of new molecules. Therefore, we undertook to synthesize a series of 2-phenyl-3-[2-(substituted amino) ethylamino] quinazolin-4(3*H*)-ones, in which heterocyclic quinazoline ring is 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 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 NMR 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 by 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 2-phenyl-3,1-benzoxazin-4-one (3)

To a solution of anthranilic acid (13.7 g, 0.1 mol) dissolved in pyridine (60 mL), benzoyl chloride (0.1 mol) was added. The mixture was stirred for 0.5 h followed by treatment with 5 % sodium bicarbonate (50 mL). The separated solid was recrystallized from ethanol. Yield: 80 %, m.p. 122–124 °C, IR (KBr) cm^{-1}: 1675 (C=O); ^{1}H NMR ($CDCl_3$) δ ppm: 7.22 (d, $J = 7.5$ Hz, 2H, Ar–*H*), 7.29–7.31 (m, 1H, Ar–*H*), 7.48–7.50 (m, 2H, Ar–*H*), 7.56 (s, 1H, Ar–*H*), 7.58 (d, $J = 8.0$ Hz, 2H, Ar–*H*), 8.08 (s, 1H, Ar–*H*); MS (m/z, %): 223 (M^+, 100), 153 (45).

Synthesis of 3-amino-2-phenyl quinazolin-4(3*H*)-one (5)

A mixture of 2-phenyl-3,1-benzoxazin-4-one (0.05 mol) and hydrazine hydrate (**4**) (0.5 mol) in ethanol was refluxed for 5 h and cooled. The separated solid was recrystallized from ethanol. Yield : 81 %, m.p. 196 °C, IR (KBr) cm^{-1}: 3300, 3252 (NH_2), 1680 (C=O), 1620 (C=N); ^{1}H NMR ($CDCl_3$) δ ppm : 4.51 (s, 2H, NH_2), 7.24 (d, $J = 7.5$ Hz, 2H, Ar–*H*), 7.31–7.33 (m, 1H, Ar–*H*), 7.49–7.51 (m, 2H, Ar–*H*), 7.58 (s, 1H, Ar–*H*), 7.60 (d, $J = 8.0$ Hz, 2H, Ar–*H*), 8.09 (s, 1H, Ar–*H*); MS (*m/z*, %): 237 (M^+, 100), 222 (65), 146 (45).

Synthesis of 3-(2-bromo ethylamino)-2-phenyl quinazolin-4(3*H*)-one (7)

A solution of 3-amino-2-phenyl quinazolin-4(3*H*)-one (**5**) (0.1 mol) in dry ethanol (25 mL), potassium carbonate (0.1 mol), and 1,2-dibromoethane (0.1 mol) was added, and the reaction mixture was heated with stirring for 6 h. The reaction mixture was then poured into ice water and extracted with ether and dried over anhydrous sodium sulfate, which upon evaporation afford compound **7**. Yield: 86 %, m.p. 240–242 °C, IR (KBr) cm^{-1} : 3249 (NH), 1669 (C=O), 1610 (C=N), 595 (C–Br); ^{1}H NMR ($CDCl_3$) δ ppm : 2.55–2.58 (m, 2H, CH_2), 3.22–3.25 (m, 2H, CH_2), 7.39–7.46 (m, 4H, Ar–*H*), 7.52–7.59 (m, 3H, Ar–*H*), 7.77–7.79 (d,

$J = 8.0$ Hz, 1H, Ar–H), 8.05–8.06 (d, $J = 7.5$ Hz, 1H, Ar–*H*), 8.49 (s, 1H, NH). MS (*m/z*, %): 346 (M+2, 55), 344 (M^+, 100), 265 (46), 236 (43), 146 (35).

General procedure for synthesis of 2-phenyl-3-[2-(substituted amino) ethylamino] quinazolin-4(3*H*)-ones (S1-S10)

A mixture of 3-(2-bromo ethylamino)-2-phenyl quinazolin-4(3*H*)-one (**7**) (0.005 mol), anhydrous potassium carbonate (100 mg), and the desired amine (0.005 mol) in 1, 4-dioxan (25 mL) was refluxed for 14–15 h. The reaction mixture was then poured into crushed ice. The solid obtained was filtered, washed with water, dried, and recrystallized from ethanol.

2-Phenyl-3-[2-(phenylamino) ethylamino] quinazolin-4(3*H*)-one (S1)

Yield : 81 %, m.p. 196–198 °C, IR (KBr) cm^{-1}: 3428 (NH), 1680 (C=O), 1630 (C=N); ^1H NMR ($CDCl_3$) δ ppm : 2.49–2.50 (m, 2H, CH_2), 3.22–3.24 (m, 2H, CH_2), 6.43 (d, $J = 7.5$ Hz, 2H, Ar–*H*), 6.58 (d, $J = 8.0$ Hz, 2H, Ar–*H*), 7.04 (m, 1H, Ar–*H*), 7.22 (d, $J = 7.5$ Hz, 2H, Ar–*H*), 7.29–7.31 (m, 1H, Ar–*H*), 7.48–7.50 (m, 2H, Ar–*H*), 7.56 (s, 1H, Ar–*H*), 7.58 (d, $J = 8.0$ Hz, 2H, Ar–*H*), 8.08 (s, 1H, Ar–*H*), 8.50 (br s, 1H, NH), 8.75 (br s, 1H, NH); MS (*m/z*, %): 371 (M^+, 88), 265 (66), 236 (53), 146 (36). Anal. Calcd for $C_{22}H_{20}N_4O$: C, 74.13; H, 5.65; N, 15.71. Found: C, 55.58; H, 4.41; N, 07.18.

3-[2-(4-Chloro phenyl amino) ethylamino]-2-phenyl-quinazolin-4(3*H*)-one (S2)

Yield : 79 %, m.p. 220–221 °C, IR (KBr) cm^{-1}: 3317 (NH), 1669 (C=O), 1630 (C = N); ^1H NMR ($CDCl_3$) δ ppm : 2.03–2.09 (m, 2H, CH_2), 3.22–3.25 (m, 2H, CH_2), 6.35 (d, $J = 7.5$ Hz, 2H, Ar–*H*), 7.03 (d, $J = 8.0$ Hz, 2H, Ar–*H*), 7.22 (d, $J = 7.5$ Hz, 2H, Ar–*H*), 7.31–7.33 (m, 1H, Ar–*H*), 7.46–7.48 (m, 2H, Ar–*H*), 7.54 (s, 1H, Ar–*H*), 7.60 (d, $J = 8.0$ Hz, 2H, Ar–*H*), 8.25 (s, 1H, Ar–*H*), 8.53 (br s, 1H, NH), 9.49 (br s, 1H, NH); MS (*m/z*, %): 392 (M+2, 66) 390 (M^+, 100), 265 (76), 236 (43), 146 (32). Anal. Calcd for $C_{22}H_{19}ClN_4O$: C, 67.60; H, 4.89; N, 14.33. Found: C, 55.58; H, 4.41; N, 07.18.

2-Phenyl-3-[2-(piperazinyl) ethylamino] quinazolin-4(3*H*)-one (S3)

Yield : 88 %, m.p. 225–227 °C, IR (KBr) cm^{-1}: 3387 (NH), 1736 (C=O), 1615 (C=N); ^1H NMR ($CDCl_3$) δ ppm: 2.44–2.48 (m, 4H, CH_2), 2.60–2.66 (m, 6H, CH_2), 3.81–3.83 (m, 2H, CH_2), 7.22 (d, $J = 7.5$ Hz, 2H, Ar–*H*), 7.29-7.31 (m, 1H, Ar–*H*), 7.52–7.54 (m, 2H, Ar–*H*), 7.58 (s, 1H, Ar–*H*), 7.62 (d, $J = 8.0$ Hz, 2H, Ar–*H*), 8.12 (s, 1H, Ar–*H*), 8.29 (br s, 1H, NH); MS (*m/z*, %): 349 (M^+, 100), 265 (62), 236 (52), 146 (42). Anal. Calcd for $C_{20}H_{23}N_5O$: C, 68.74; H, 6.63; N, 20.04. Found: C, 55.58; H, 4.41; N, 07.18.

3-[2-(Benzyl amino) ethylamino]-2-phenyl-quinazolin-4(3*H*)-one (S4)

Yield : 85 %, m.p. 260–261 °C, IR (KBr) cm^{-1}: 3251 (NH), 1664 (C=O), 1605 (C=N); ^1H NMR ($CDCl_3$) δ ppm : 2.73–2.78 (m, 2H, CH_2), 2.88–2.92 (m, 2H, CH_2), 3.78 (s, 2H, CH_2), 6.38 (d, $J = 7.5$ Hz, 2H, Ar–*H*), 6.48 (d, $J = 8.0$ Hz, 2H, Ar–*H*), 6.98–7.01 (m, 1H, Ar–*H*), 7.18 (d, $J = 7.5$ Hz, 2H, Ar–*H*), 7.20–7.22 (m, 1H, Ar–*H*), 7.38–7.40 (m, 2H, Ar–*H*), 7.46 (s, 1H, Ar–*H*), 7.62 (d, $J = 8.0$ Hz, 2H, Ar–*H*), 8.21 (s, 1H, Ar–*H*), 8.45 (br s, 1H, NH), 8.55 (br s, 1H, NH); MS (*m/z*, %): 370 (M^+, 100), 265 (66), 236 (53), 146 (36). Anal. Calcd for $C_{23}H_{22}N_4O$: C, 74.57; H, 5.98; N, 15.12. Found: C, 55.58; H, 4.41; N, 07.18.

3-(2-Morpholinoethylamino)-2-phenylquinazolin-4(3*H*)-one (S5)

Yield: 82 %, m.p. 245–247 °C, IR (KBr) cm^{-1}: 3364 (NH), 1733 (C=O), 1603 (C=N); ^1H NMR ($CDCl_3$) δ ppm: 2.35–2.39 (m, 4H, CH_2), 2.74–2.78 (m, 6H, CH_2), 3.74–3.82 (m, 2H, CH_2), 7.12 (d, $J = 8.0$ Hz, 2H, Ar–*H*), 7.25–7.28 (m, 1H, Ar–*H*), 7.42–7.48 (m, 2H, Ar–*H*), 7.58 (s, 1H, Ar–*H*), 7.72 (d, $J = 7.5$ Hz, 2H, Ar–*H*), 8.09 (s, 1H, Ar–*H*), 8.25 (br s, 1H, NH); MS (*m/z*, %): 350 (M^+, 100), 265 (66), 236 (53), 146 (36). Anal. Calcd for $C_{20}H_{22}N_4O$: C, 68.55; H, 6.32; N, 15.98. Found: C, 55.58; H, 4.41; N, 07.18.

3-[2-(4-Methoxy phenylamino) ethylamino]-2-phenyl-quinazolin-4(3*H*)-one (S6)

Yield: 86 %, m.p. 185–186 °C, IR (KBr) cm^{-1}: 3260 (NH), 1661 (C=O), 1609 (C=N); ^1H NMR ($CDCl_3$) δ ppm: 2.49–2.54 (m, 2H, CH_2), 3.28–3.32 (m, 2H, CH_2), 3.75 (s, 3H, OCH_3), 6.32 (d, $J = 8.0$ Hz, 2H, Ar–*H*), 6.54 (d, $J = 7.5$ Hz, 2H, Ar–*H*), 7.28 (d, $J = 7.5$ Hz, 2H, Ar–*H*), 7.27–7.29 (m, 1H, Ar–*H*), 7.38–7.42 (m, 2H, Ar–*H*), 7.58 (s, 1H, Ar–*H*), 7.61 (d, $J = 8.0$ Hz, 2H, Ar–*H*), 8.18 (s, 1H, Ar–*H*), 8.25 (br s, 1H, NH), 8.55 (br s, 1H, NH); MS (*m/z*, %): 386 (M^+, 100) 265 (62), 236 (48), 146 (34). Anal. Calcd for $C_{23}H_{22}N_4O_2$: C, 71.48; H, 5.73; N, 14.49. Found: C, 55.58; H, 4.41; N, 07.18.

2-Phenyl-3-(2-(thiazol-2-ylamino) ethylamino)quinazolin-4(3H)-one (S7)

Yield: 91 %, m.p. 235–236 °C, IR (KBr) cm^{-1}: 3261 (NH), 1668 (C=O), 1608 (C=N); ^1H NMR ($CDCl_3$) δ ppm : 2.34–2.38 (m, 2H, CH_2), 3.22–3.29 (m, 2H, CH_2), 6.56 (s, 1H, Ar–*H*), 7.04 (m, 1H, Ar–*H*), 7.22 (d, $J = 7.5$ Hz, 2H, Ar–*H*), 7.29–7.31 (m, 1H, Ar–*H*), 7.48–7.50 (m, 2H, Ar–*H*), 7.53 (s, 1H, Ar–*H*), 7.58 (d, $J = 8.0$ Hz, 2H, Ar–*H*), 8.18 (s, 1H, Ar–*H*), 8.25 (br s, 1H, NH), 8.55 (br s, 1H, NH); MS (*m/z*, %): 363 (M^+, 100) 265 (56), 236 (48), 146 (24). Anal. Calcd for $C_{19}H_{17}N_5OS$: C, 62.79; H, 4.71; N, 19.26. Found: C, 55.58; H, 4.41; N, 07.18.

3-(2-(*o*-Toluidino)ethylamino)-2-phenylquinazolin-4(3H)-one (S8)

Yield: 88 %, m.p. 223–225 °C, IR (KBr) cm^{-1}: 3261 (NH), 1668 (C=O), 1609 (C=N); ^1H NMR ($CDCl_3$) δ ppm : 2.30 (s, 3H, CH_3), 2.52–2.56 (m, 2H, CH_2), 3.38–3.42 (m, 2H, CH_2), 6.32 (d, $J = 8.0$ Hz, 2H, Ar–*H*), 6.54 (d, $J = 7.5$ Hz, 2H, Ar–*H*), 7.28 (d, $J = 7.5$ Hz, 2H, Ar–*H*), 7.27–7.29 (m, 1H, Ar–*H*), 7.38–7.42 (m, 2H, Ar–*H*), 7.58 (s, 1H, Ar–*H*), 7.61 (d, $J = 8.0$ Hz, 2H, Ar–*H*), 8.08 (s, 1H, Ar–*H*), 8.15 (br s, 1H, NH), 8.35 (br s, 1H, NH); MS (*m/z*, %): 370 [M^+]. Anal. Calcd for $C_{23}H_{22}N_4O$: C, 74.57; H, 5.98; N, 15.12. Found: C, 55.58; H, 4.41; N, 07.18.

3-[2-(3-Methoxy phenylamino) ethylamino]-2-phenyl- quinazolin-4(3*H*)-one (S9)

Yield: 87 %, m.p. 255–256 °C, IR (KBr) cm^{-1}: 3258 (NH), 1670 (C=O), 1605 (C=N); ^1H NMR ($CDCl_3$) δ ppm: 2.42–2.47 (m, 2H, CH_2), 3.32–3.36 (m, 2H, CH_2), 3.76 (s, 3H, OCH_3), 6.34 (d, $J = 7.5$ Hz, 2H, Ar–*H*), 6.57 (d, $J = 8.0$ Hz, 2H, Ar–*H*), 7.26 (d, $J = 8.0$ Hz, 2H, Ar–*H*), 7.29–7.31 (m, 1H, Ar–*H*), 7.42–7.44 (m, 2H, Ar–*H*), 7.56 (s, 1H, Ar–*H*), 7.63 (d, $J = 8.0$ Hz, 2H, Ar–*H*), 8.20 (s, 1H, Ar–*H*), 8.23 (br s, 1H, NH), 8.35 (br s, 1H, NH); MS (*m/z*, %): 386 (M^+, 100), 265 (75), 236 (62), 146 (42). Anal. Calcd for $C_{23}H_{22}N_4O_2$: C, 71.48; H, 5.73; N, 14.49. Found: C, 55.58; H, 4.41; N, 07.18.

3-[2-(4-Nitrophenylamino) ethylamino]-2-phenyl quinazolin-4(3*H*)-one (S10)

Yield: 87 %, m.p. 266–268 °C, IR (KBr) cm^{-1}: 3261 (NH), 1632 (C=O), 1607 (C=N); ^1H NMR ($CDCl_3$) δ ppm : 2.61–2.66 (m, 2H, CH_2), 2.91–2.95 (m, 2H, CH_2), 6.45 (d, $J = 7.5$ Hz, 2H, Ar–*H*), 6.99 (d, $J = 8.0$ Hz, 2H, Ar–*H*), 7.20 (d, $J = 7.5$ Hz, 2H, Ar–*H*), 7.33–7.35 (m, 1H, Ar–*H*), 7.47–7.49 (m, 2H, Ar–*H*), 7.57 (s, 1H, Ar–*H*), 7.62 (d, $J = 8.0$ Hz, 2H, Ar–*H*), 8.27 (s, 1H, Ar–*H*), 8.33 (br s, 1H, NH), 8.49 (br s, 1H, NH); MS (*m/z*, %): 401 (M^+, 100), 265 (72), 236 (65), 146 (42). Anal. Calcd for $C_{22}H_{19}N_5O_3$: C, 65.82; H, 4.77; N, 17.44. Found: C, 55.58; H, 4.41; N, 07.18.

Pharmacology

The synthesized compounds were evaluated for antihistaminic and sedative-hypnotic activities. The animals were maintained in colony cages at a temperature of 25 ± 2 °C, relative humidity of 45–55 %, and 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 (Van Arman *et al*., 1961). 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) were 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 chlorpheniramine maleate 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 is the preconvulsive time of test compound and T_1 is the 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

(Dews, 1953; Kuhn and Van Maanen, 1961). Six albino Swiss mice were allotted to each group. Basal activity score was taken and then compounds **S1**–**S10** and standard chlorpheniramine 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 locomotor activity was calculated by the following formula and shown in Table 1

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

where A is the basal score and B is the score after drug treatment.

Statistical analysis

Statistical analysis of the biologic 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 by 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.11452 El Camino Real, #215, San Diego, CA 92130 USA).

Results and discussion

Chemistry

The key intermediate 3-(2-bromo ethylamino)-2-phenyl quinazolin-4(3*H*)-one **(7)** was prepared by stirring at hot condition a solution of 3-amino-2-phenyl quinazolin-4(3*H*)-one and 1,2-dibromoethane in potassium carbonate for 6 h. The formation of compound **5** is confirmed by the disappearance of peak due to $-NH_2$ of the starting material in the IR and NMR spectrum. The IR spectrum of 3-(2-bromo ethylamino)-2-phenyl quinazolin-4(3*H*)-one (**7**) showed a peak for NH group at 3,249 cm^{-1} and peak for carbonyl (C=O) stretching at 1,669 cm^{-1}. The ^1H NMR spectrum of compound **(7)** showed multiplet at δ 2.55–3.25 ppm for $-CH_2CH_2-$ group and multiplet for aromatic (9H) protons observed at δ 7.39–8.06 ppm. Compound **5**, in turn, was prepared from anthranilic acid via 2-phenyl-3,1-benzoxazin-4-one **(3)** as shown in Scheme 1. 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 title compounds were obtained in fair- to good yield through the nucleophilic displacement of –Br group of 3-(2-

Table 1 Antihistaminic and sedative-hypnotic activity of compounds **S1–S10**

Compound code	Time of onset of convulsion (in s)	% Protection	Percent CNS depression			
			0.5 h	1 h	2 h	3 h
S1	402 + 5.81*	71.64 + 1.32*	11.32 ± 1.41**	11.55 ± 1.02**	12.32 ± 0.99**	10.11 ± 0.84**
S2	416 + 5.29*	72.12 + 1.61*	8.28 ± 1.21**	9.42 ± 1.42**	10.73 ± 1.31**	6.48 ± 0.91**
S3	433 + 5.03*	73.67 + 1.40*	9.35 ± 1.46**	10.42 ± 1.21**	10.79 ± 1.40**	8.21 ± 0.81**
S4	366 + 6.86*	68.85 + 1.62*	10.42 ± 1.83**	11.52 ± 1.62**	12.31 ± 1.32**	8.90 ± 093**
S5	428 + 5.42*	73.36 + 1.31*	8.43 ± 1.42**	9.32 ± 0.74**	10.41 ± 1.41**	7.32 ± 0.94**
S6	398 + 6.02*	71.35 + 1.43*	9.03 ± 0.92**	10.43 ± 1.52**	10.94 ± 1.43**	8.53 ± 0.93**
S7	409 + 5.47*	72.12 + 1.30*	8.21 ± 1.09*	9.52 ± 1.06**	9.85 ± 1.53**	7.43 ± 0.95**
S8	375 + 5.52*	69.60 + 1.21*	9.42 ± 1.76**	9.88 ± 0.85**	10.38 ± 1.43**	7.13 ± 1.42**
S9	382 + 4.48*	70.15 + 1.65*	10.35 ± 0.95**	10.89 ± 1.62**	11.63 ± 1.63**	9.32 ± 1.04**
S10	394 + 6.39*	71.06 + 1.42*	9.51 ± 1.43**	9.98 ± 1.23**	11.04 ± 1.93**	8.32 ± 0.89**
Chlorphe-niramine	394 + 4.43*	70.09 + 0.33*	32.04 + 0.50**	38.80 + 1.32**	34.80 + 0.72**	29.58 + 0.72**

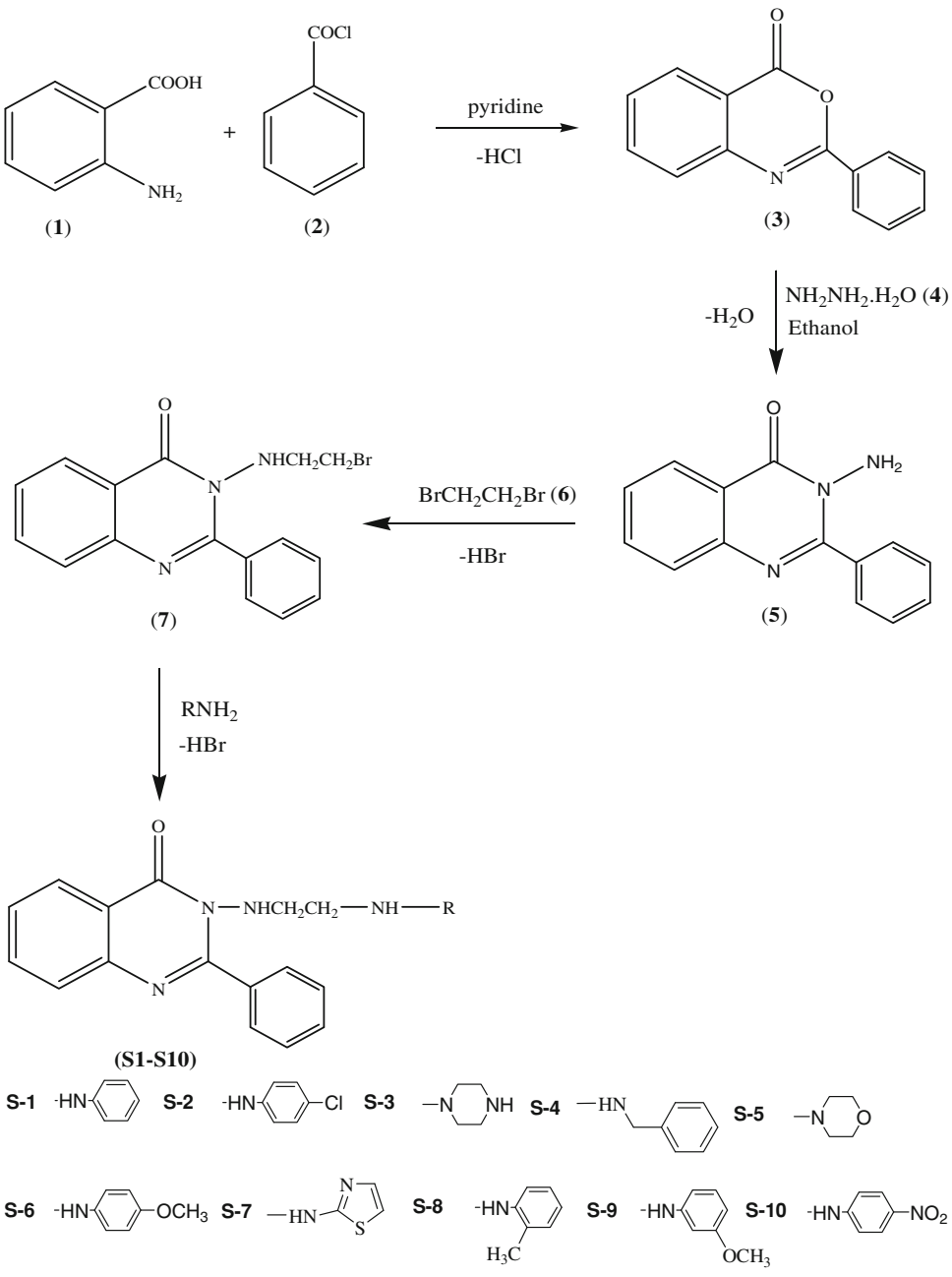
Each value represents the mean ± SEM ($n = 6$)

* $p < 0.001$; ** $p < 0.05$

bromo ethylamino)-2-phenyl quinazolin-4(3*H*)-one **(7)** with a variety of amines using 1,4-dioxan as solvent to afford 2-phenyl-3-[2-(substituted amino) ethylamino] quinazolin-4(3*H*)-ones (**S1**–**S10**). The formation of title compounds is indicated by the disappearance of peaks due to –Br of the starting material and the appearance of –NH signal at 3,350–3,200 cm^{-1} in the IR spectra of the compounds **S1**–**S10.** It also showed a peak for carbonyl (C=O) around 1,720–1,650 cm^{-1}. The ^1H NMR spectra of title compounds **S1**–**S10** showed peaks for substituent around N-3 of quinazolinones and singlet around δ 8.25–9.45 ppm; due to NH, a multiplet around δ 7.00–8.15 ppm was observed for aromatic protons. Data from the elemental analyses and molecular ion recorded in the mass spectrum further confirmed the assigned structure. In mass spectra of compounds **S1**–**S10,** 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-phenyl-3-[2-(substituted amino) ethylamino] quinazolin-4(3*H*)-one (**S1–S10**) were



Scheme 1 Synthesis of 2-phenyl-3-[2-(substituted amino) ethylamino] quinazolin-4(3*H*)-ones (**S1**–**S10**)

evaluated for their in vivo antihistaminic activity. Histamine causes bronchospasm and the guinea pigs are the most susceptible animals for histamine; hence, the 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 68–73 %. Biologic studies indicated that different substituents over the third position of quinazoline ring exerted varied biologic activity. The presence of piperazinyl group (compound **S3**) showed significant activity. When the additional heteroatoms like oxygen is introduced (morpholinyl substitution compound **S5**), the activity is retained. Placement of aryl group (phenyl substitution (compound **S1**)) and aryl ring with electron-donating substituents (2-methyl phenyl substitution (compound **S8**)) showed decrease in activity; whereas, placement of aryl ring with electron-withdrawing group (*p*-chloro aniline substitution (compound **S2**)) and heteroaryl group (2-amino thiazole substitution compound (**S7**)) results in retaining of activity. Placement of aralkyl group (benzyl substitution compound (**S4**)) further decreased the activity. Compound 2-phenyl-3-[2-(piperazinyl) ethylamino] quinazolin-4(3*H*)-one (**S3**) emerged as the most potent compound of the series.

Sedative-hypnotic activity was determined by measuring the reduction in locomotor activity using actophotometer (Dews, 1953; Kuhn and Van Maanen, 1961) on Albino Swiss mice. The results of sedative-hypnotic activity indicate that all the test compounds were found to exhibit only negligible sedation (8-12 %), whereas the reference standard chlorpheniramine maleate showed 33 % sedation.

Conclusion

In summary, the synthesis of new series of 2-phenyl-3-[2-(substituted amino) ethylamino] quinazolin-4(3*H*)-one (**S1**–**S10**) 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, compound 2-phenyl-3-[2-(piperazinyl) ethylamino] quinazolin-4(3*H*)-one (**S3**) emerged as the most potent compound of the series compound (73.67 %), which is more potent when compared to reference standard chlorpheniramine maleate (70.09 %). Interestingly, compound **S3** also showed negligible sedation (8.21 %) compared to chlorpheniramine maleate (29.58 %) 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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