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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Antitussive effects of azepino[2,1-b]quinazolones

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Abstract A series of azepino[2,1-b]quinazolones (**C-1**–**C-16**) have been synthesized and evaluated for their antitussive activity using citric acid-induced cough model in Guinea pigs. The compounds **C-1**–**C-16** caused notable decrease in cough frequency and increase in cough latency induced by citric acid. **C-3** [2,4-dibromo-7,8,9,10-tetrahydroazepino[2,1-b]quinazolin-12(6H)-one] showed notable antitussive effect as compared with codeine (10 mg/kg). Various substitutions were made at Rings A and B, and all substituents like methoxy, hydroxyl, nitro, amino (Ring A) and alkyl, acetyl, benzoyl (Ring B) other than bromine were found to reduce the potential of the unsubstituted 7,8,9,10-tetrahydroazepino[2,1-b]quinazolin-12(6H)-one as antitussive.

Keywords Antitussive · Azepinoquinazolone · Codeine · Cough

Introduction

Cough, a reflex defence mechanism, can be considered not only as idiopathic in nature but also as a common symptom of various airway inflammatory diseases (Higenbottam, 2002). Although cough is not life-threatening, it causes general liability, social embarrassment, and nuisance, thereby deteriorating the quality of life (French et al., 1998). The medication involves huge expenditure on prescription and over the counter (OTC) cough remedies (Dicpinigaitis, 2007). Currently used antitussives are attributed with side effects along with limited efficacy (Chung, 2005; Schroeder and Fahey, 2002; Eccles, 2002). Keeping this in view, development of an effective and safer antitussive agent is required.

Alkaloids having a long history of use as antitussives are codeine (Freestone and Eccles, 1997) and dextromethorphen (Wong et al., 1988). *Stemona* alkaloids croomine (A), stemoninine (B), neotuberostemonine (C), and tuberostemonine (D) have also been reported as antitussives (Fig. 1) (Chung et al., 2003; Xu et al., 2006).

The azepine ring with nitrogen at the bridgehead position appears to be an important structural feature among the structures in Fig. 1. Antitussive potential of quinazolones have earlier been proven (Dua et al., 1967). With this background, in this study, we have further explored 7,8,9,10-tetrahydroazepino[2,1-b]quinazolin-12(6H)-one(**C-1**) (Fig. 1), synthetic analog of alkaloid vasicine (E) (Fig. 1), first synthesized and reported as having a bronchodilatory effect 6–10 times more potent than aminophylline by Dhar et al. (Sharma et al., 1979; Malhotra et al., 1988; Malhotra et al., 1989; Zabeer et al., 2006) along with its several derivatives for their antitussive effects using citric acid-induced cough model in conscious guinea pigs.

Chemistry

Anthranilic acid was treated with thionyl chloride to yield corresponding sulfonamide anhydride which was further

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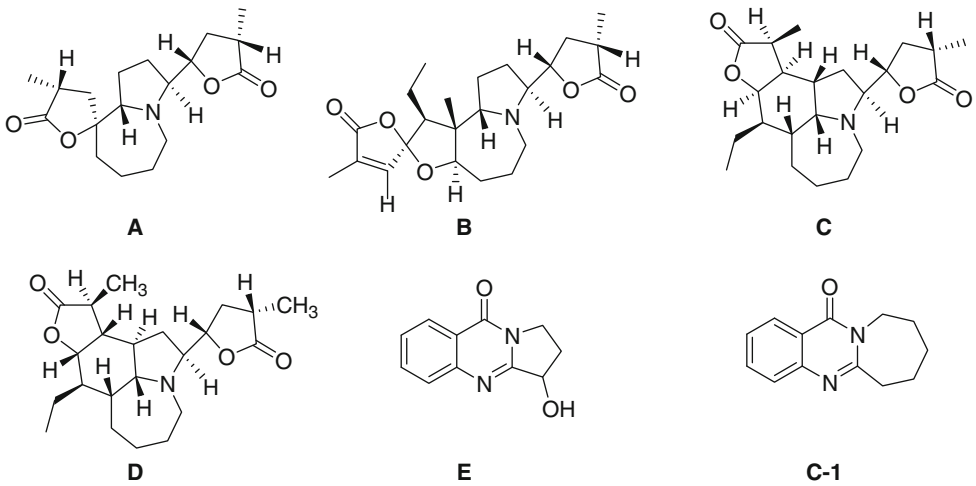

Fig. 1 Structures having azepine ring with nitrogen at the bridgehead position

condensed with caprolactam to yield the 7,8,9,10-tetrahydroazepino [2,1-b]quinazolin-12(6H)-one **(C-1)** (Fig. 2). Various substitutions on Rings A and B of **C-1** have been made to synthesize a series of azepinoquinazolones as shown in Figs. 3, 4, and 5. All products reported showed ^{1}H NMR spectra that are in agreement with the assigned structures. Reaction courses and product mixtures were routinely monitored by TLC on silica gel (precoated F254 Merck plates). Dragondorff reagent was used as a spraying reagent.

Results and discussion

Citric acid induction caused notable cough in Guinea pigs as evidenced by decreased cough latency time and increased cough frequencies. It has been demonstrated that the guinea pigs and humans respond to similar concentrations of citric acid and responses are well correlated with concentration–response relationship (Laude, 1993). Pretreatment with the compounds C1–C16 (*i.p*) and Codiene as standard showed notable increase in cough latency and decrease in cough frequencies/10 min in comparison to vehicle control (Figs. 6, 7). The compounds C-3 showed notable antitussive effect at 10, 20 mg/kg as compared to codeine (10 mg/kg). C-1 also showed notable antitussive effect in comparison with codeine, but the effect of C-3 at 20 mg/kg was more pronounced than that of C-1 (20 mg/kg). Among all the synthesized compounds, C-3 having dibromo substitution proved to be the most effective antitussive. Moreover, the unsubstituted C-1 was found to be better active than all the other derivatives except C-3. C-2 formed by the reduction of C=N bond at position 5 of C-1 resulted in drastic decline of the antitussive effect as C-2 was found to have only mild antitussive effect. Alkylation, acetylation, benzylation, and benzoylation at position 5 of C-2 further reduced the potential of the synthesized compounds as antitussives, and the decline in the antitussive effect was notably higher with the bulkier groups such as benzyl and benzoyl.

Conclusion

Antitussive potential of the synthesized compounds was evaluated. Decrease in cough frequency and increase in cough latency were observed in all the tested compounds as compared with the vehicle. The overall weight of evidence led us to conclude that the azepinoquinazolone skeleton represents an active moiety as far as antitussive activity is concerned, with the dibromo derivative (C-3) showing better activity than even codeine (10 mg/kg). All the other substituents except bromine were found to reduce the potential of C-1 as an antitussive. Our study can thus give new dimensions to the investigation of the molecules with azepinoquinazolone skeleton as antitussive agents.

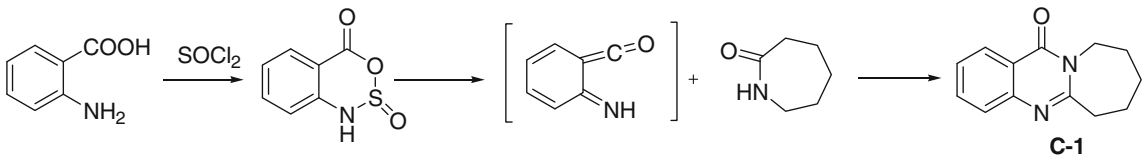

Fig. 2 Mechanism showing the formation of **C-1**

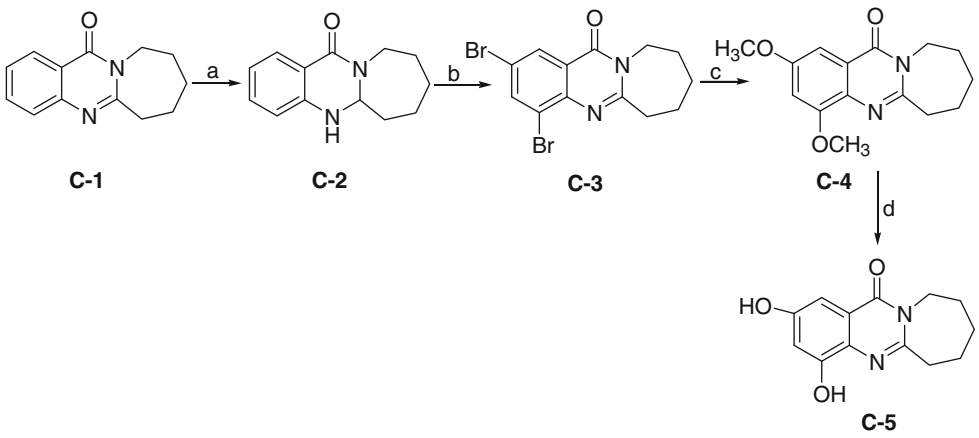

Fig. 3 **a** $NaBH_4$, Stirring, r.t., 2 h. **b** Br_2, CCl_4, stirring, r.t. **c** NaOMe, $CuCl_2$, methanol, N_2, reflux, 12 h. **d** 48%HBr, reflux, 12 h

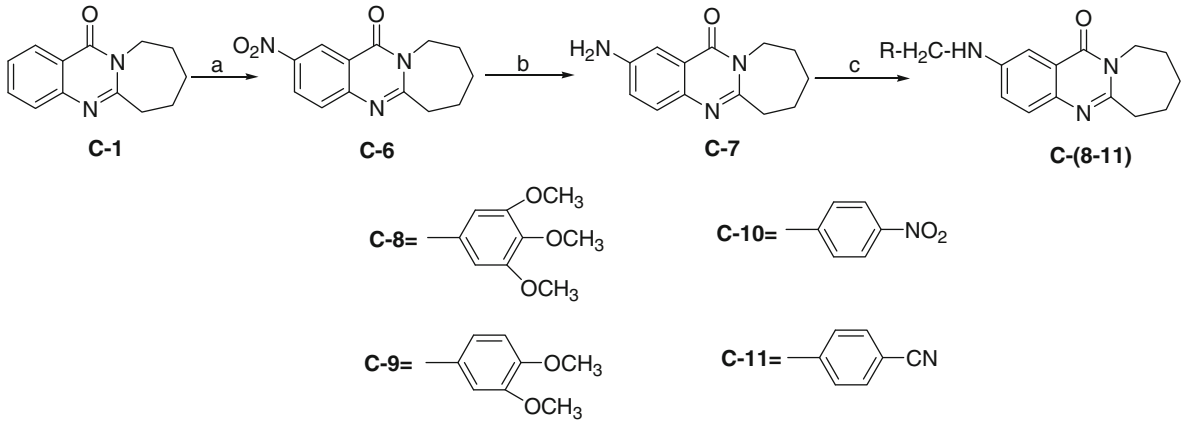

Fig. 4 **a** Concentrated HNO_3-H_2SO_4, stirring 0°C. **b** Sn-concentrated HCl, reflux, 2 h. **c** (i) R-CHO, methanol (ii) $NaBH_4$, 0°C

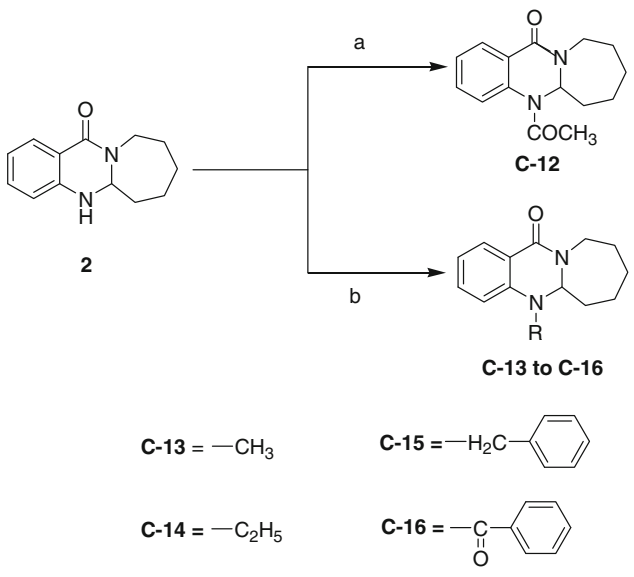

Fig. 5 **a** Acetic anhydride, pyridine, stirring, r.t., 2 h. **b** R–X, acetone, K_2CO_3, Reflux, 2 h

Experimental

Chemistry

All melting points (m.p.) were observed on a Veego melting point apparatus and were uncorrected. IR spectra were recorded as KBr pellets on Perkin-Elmer 882 spectrophotometer model. Proton (^1H) nuclear magnetic resonance spectroscopy was performed using Varian EM-360L and Bruker AC-300F, 200 and 500 MHz spectrometer with TMS as an internal standard. Plates for TLC were prepared using silica gel G.

Procedure for the synthesis of azepinoquinazolone derivatives

*7,8,9,10-Tetrahydroazepino[2,1-b]quinazolin-12(6H)-one (**C-1**)* 13.7 g (0.1 mol) of anthranilic acid was dissolved in dry benzene (200 ml) in a 500-ml round-bottomed flask, and 29.5 ml of thionyl chloride (0.25 mol) was added to it.

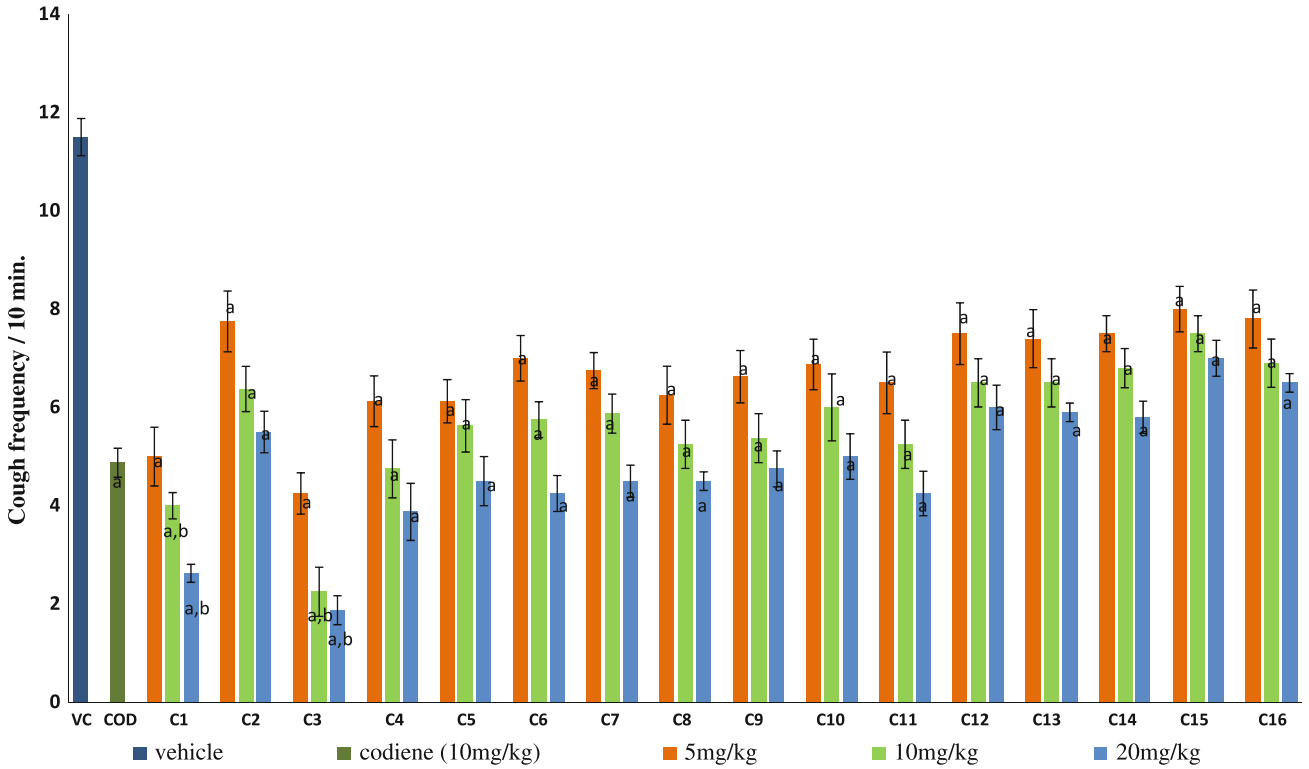

Fig. 6 The effect of synthesized compounds and codiene (*i.p.*) on cough frequency induced by citric acid. *Results*: Mean ± SEM. a = $P < 0.05$ vs VC; *b* = $P < 0.05$ vs. Codiene 10 mg/kg; *c* = $P < 0.05$ vs. C1—20 mg/kg; [VC: vehicle control; COD: codiene; and C1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C12, C13, C14, C15, and C16: synthesized compounds in series]

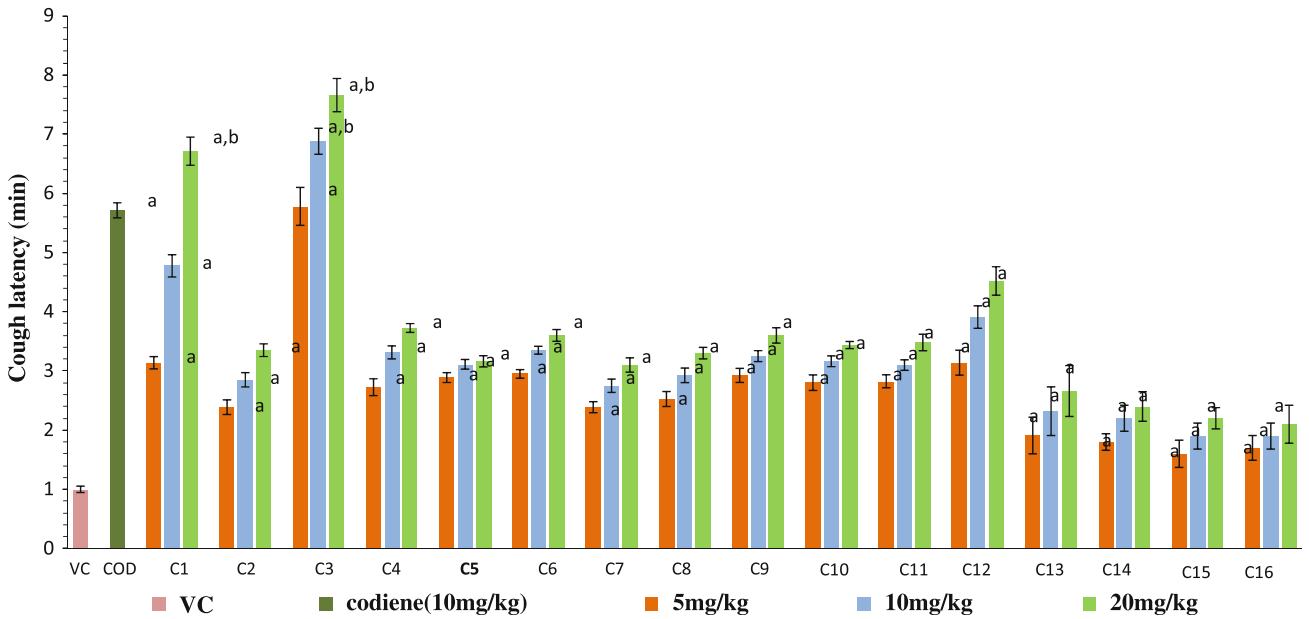

Fig. 7 The effect of synthesized compounds and codeine (*i.p.*) on cough latency induced by citric acid. *Results*: Mean ± SEM; *a* = $P < 0.05$ vs. VC; *b* = $P < 0.05$ vs. codiene 10 mg/kg; and *c* = $P < 0.05$ vs. C1—20 mg/kg; [VC: vehicle control, COD: Codiene and C1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C12, C13, C14, C15 & C16: synthesized compounds in series]

The reaction mixture was refluxed for 3 h on a water bath under anhydrous conditions. After completion of the reaction, excess of thionyl chloride and benzene were distilled off. Benzene (100 ml) was again added to remove residual thionyl chloride. 11.3 g (0.1 mol) of caprolactam was dissolved in benzene in a 100-ml round-bottomed

flask. The solution was added slowly to the sulfinylanthraniloyl chloride under cold conditions and kept overnight. Progress of the reaction was monitored on TLC. The reaction mixture was basified with aqueous ammonia and extracted with chloroform. The chloroform extract was dried and distilled under reduced pressure, which yielded crude product. The crude product was purified by column chromatography on neutral alumina with increasing percentage of ethyl acetate in hexane (hexane:ethyl acetate::90:10) to yield **C-1** (11.0 g, 51%). m.p. 97–99°C. ^{1}H NMR ($CDCl_3$): δ 8.25 (1H, d, $J = 8.12$ Hz), 7.10–7.90 (3H, m), 4.20 (2H, d, $J = 6.75$ Hz), 3.15 (2H, d, $J = 6.43$ Hz), 1.86 (6H, bs).

*5a,6,7,8,9,10-Hexahydroazepino[2,1-b]quinazoline-12(5H)-one (**C-2**)* 10 g (0.046 mol) of **C-1** was dissolved in ethanol (75 ml) in a 250-ml round-bottomed flask containing a magnetic stirring piece 20 g of sodium borohydride (0.054 mol) was added in small proportions and the reaction was monitored on TLC. After completion of the reaction, the reaction mixture was basified with ammonia solution and extracted with chloroform. The chloroform layer was dried, and the solid residue was subjected to column chromatography on neutral alumina with increasing percentage of ethyl acetate in hexane (hexane:ethyl acetate::85:15) to yield **C-2** (6.12 g, 60.71%). m.p. 168°C. ^{1}H NMR ($CDCl_3$): δ 7.89 (1H, dd, $J = 1.32$ and 7.76 Hz), 7.27 (1H, m) 6.82 (1H, m), 6.64 (1H, d, $J = 7.79$ Hz) 4.94 (2H, m), 4.42 (2H, m), 2.93 (2H, m), 1.25–2.14 (6H, m).

*2,4-Dibromo-7,8,9,10-tetrahydroazepino[2,1-b]quinazolin-12(6H)-one (**C-3**)* 2 g (0.009 mol) of **C-2** was dissolved in 20 ml of carbon tetrachloride, and the solution was kept in a 100-ml round-bottomed flask containing a magnetic stirring piece. Bromine (2.99 g, 0.018 mol) was dissolved in 10 ml of carbon tetrachloride, and the solution was added to the reaction mixture dropwise accompanied by constant stirring. Completion of the reaction was monitored on TLC. The precipitate thus obtained was filtered and washed with water. The residue obtained was crystallized from ethanol to yield **C-3** (1.74 g, 50.58%). m. p. 168°C. ^{1}H NMR ($CDCl_3$): δ 8.35 (1H, d, $J = 2.21$ Hz), 8.09 (1H, d, $J = 2.21$ Hz), 4.37 (2H, d, $J = 6.36$ Hz) 3.11 (2H, d, $J = 6.21$ Hz), 1.86 (6H, bs).

*2,4-Dimethoxy-7,8,9,10-tetrahydroazepino[2,1-b]quinazolin-12(6H)-one (**C-4**)* 1 g of **C-3** (0.0026 mol) was dissolved in 10 ml methanol in a 100-ml round-bottomed flask. Freshly prepared sodium methoxide (0.14 g, 0026 mol) and cupric chloride (25 mg) was added to it. The reaction mixture was refluxed for 12 h and the completion of the reaction was monitored on TLC. Solvent was removed by distillation. The solid residue obtained was washed with water to remove sodium methoxide and dried under reduced pressure. The residue obtained was crystallized from ethanol to yield **C-4** (0.55 g, 75.34%). m.p. 193°C. ^{1}H NMR ($CDCl_3$): δ 7.15 (1H, d, $J = 2.62$ Hz), 6.75 (1H, d, $J = 2.62$ Hz), 4.34 (2H, d, $J = 6.75$ Hz), 3.93 (3H, s), 3.85 (3H, s), 3.07 (2H, d, $J = 6.45$ Hz), 1.87 (6H, bs).

*2,4-Dihydroxy-7,8,9,10-tetrahydroazepino[2,1-b]quinazolin-12(6H)-one (**C-5**)* 300 mg of **C-4** (0.0010 mol) was taken in a 25-ml round-bottomed flask and 3 ml of 48% HBr was added to it. The reaction mixture was refluxed for 12 h and then dried under vacuum. 5 ml of distilled water was added to it and the solution was basified with ammonia solution. White precipitate were formed which were filtered and dried under vacuum to yield **C-5** (0.214 g, 79.55%). m.p. 259°C. ^{1}H NMR ($CDCl_3$): δ 6.82(1H, d, $J = 2.34$ Hz), 6.66 (1H, d, $J = 2.34$ Hz), 4.26(2H, d, $J = 6.75$ Hz), 2.98 (2H, d, $J = 6.43$ Hz), 1.69 (6H, s).

*2-Nitro-7,8,9,10-tetrahydroazepino[2,1-b]quinazolin-12(6H)-one (**C-6**)* 2 g of **C-1** was taken in a 100-ml round-bottomed flask which was kept in an ice bath, an ice cold solution of nitrating mixture (4 ml; 2 ml each of conc. HNO_3 and conc. H_2SO_4) with constant stirring. After 1 h, the reaction mixture was kept at room temperature for 10 h. It was then poured on to crushed ice and rendered alkaline with aq. Ammonia. The yellow solid thus obtained was filtered, washed with ice cold water, dried, and chromatographed over silica gel column. Elution with hexane–ethyl acetate (95:5) yielded the nitro compound which was recrystallized from ethanol m.p. 170°C. ^{1}H NMR ($CDCl_3$) δ 9.11 (1H, d, $J = 2.58$ Hz), 8.49 (1H, dd, $J = 2.58$ and 8.96 Hz), 7.71 (1H, d, $J = 8.97$ Hz), 4.43 (2H, d, $J = 5.51$ Hz), 3.12 (2H, bs) 1.89 (6H, bs).

*General procedure for the synthesis of benzylamines C (**8–11**)*

For the synthesis of benzylamines, **C-6** was reduced to 2-amino-7,8,9,10 -tetrahydroazepino-[2,1-*b*]quinazolin-12 (6H)-one (**C-7**). A solution of **C-7** (0.4 g, 1.75 mmol) in MeOH (8.0 ml) was added to a solution of aldehydes (4.0 mmol) in MeOH (8.0 ml) with constant stirring. The reaction mixture was allowed to stand overnight at room temperature. Sodium borohydride (0.8 g, 21.1 mmol) was added in small portions to the chilled and stirred reaction mixture over a period of 2 h. The reaction mixture was further stirred for 2 h. Crushed ice was added to the reaction mixture and the precipitate was filtered, washed with water, dried, and recrystallized to yield the required amines **C(8–11)**.

*2-(3,4,5-Trimethoxybenzylamino)-7,8,9,10-tetrahydroazepino [2,1-b]quinazolin-12(6H)-one (**C-8**)* Yield: 36%, m.p. 170–172°C. ^{1}H NMR ($CDCl_3$): δ 7.49 (1H, d, $J = 7.45$ Hz), 7.24 (1H, d, $J = 7.23$ Hz), 7.16 (1H, dd, $J = 2.03$ and 7.90 Hz), 6.69 (2H, s), 4.41 (1H, s), 4.31 (4H, m), 3.88 (9H, s), 3.12 (2H, t, $J = 6.79$ Hz), 1.84 (6H, m).

*2-(3,4-Dimethoxybenzylamino)-7,8,9,10-tetrahydroazepino [2,1-b]quinazolin-12(6H)-one (**C-9**)* Yield: 67.43%, m.p. 206–210°C. ^{1}H NMR ($CDCl_3$): δ 7.49 (1H, d, $J = 8.75$ Hz), 7.34 (1H, d, $J = 3$ Hz), 7.04 (1H, dd, $J = 2.73$ and 8.95 Hz), 6.81 (2H, m), 6.79 (1H, d, $J = 6.23$ Hz), 4.39 (5H, m), 3.79 (6H, s), 3.12 (2H, m), 1.85 (6H, m).

*2-(4-Nitrobenzylamino)-7,8,9,10-tetrahydroazepino[2,1-b] quinazolin-12(6H)-one (**C-10**)* Yield: 68.84%, m.p. 218–224°C. ^{1}H NMR ($CDCl_3$): δ 8.17 (2H, d, $J = 8.23$ Hz), 7.09–7.68(5H, m, aromatic), 5.53 (1H, s), 4.22–4.68 (4H, m), 3.07 (2H, s), 1.85 (6H, s).

*2-(4-Cyanobenzylamino)-7,8,9,10-tetrahydroazepino[2,1-b] quinazolin-12(6H)-one (**C-11**)* Yield: 77.33%, m.p. 188–194°C. ^{1}H NMR ($CDCl_3$): δ 7.10–7.93 (7H, m), 4.43 (5H, m), 3.02 (2H, s), 1.80 (6H, s).

*5-Acetyl-5a,6,7,8,9,10-hexahydroazepino[2,1-b]quinazoline-12(5H)-one (**C-12**)* 1 g of R-2(0.004 mol) was taken in a 100-ml round-bottomed flask and dissolved in 10 ml acetic anhydride. A few drops of pyridine were added to it. The reaction mixture was refluxed for 6 h. under anhydrous conditions. The completion of the reaction was monitored with the help of TLC. The reaction mixture was poured on to crushed ice. The precipitates were filtered and dried under vacuum to yield **C-12** 1.09 g (90.83%). m.p. −125°C. ^{1}H NMR ($CDCl_3$) δ 8.06 (1H, dd, $J = 1.55$ and 7.68 Hz), 7.26–7.63 (3H, m), 4.48 (1H, dd, $J = 6.31$ and 13.46 Hz), 2.95 (2H, m) 2.21 (3H, s) 1.25–2.04 (8H, m).

*General procedure for the synthesis of C- (**13–15**)*

2 g of C-2 (0.009 mol) was taken in a 250-ml round-bottomed flask and dissolved in 20 ml of acetone. Anhydrous potassium carbonate (2.5 g) and alkyl or aryl iodide (0.009 mol) was added to this reaction mixture. The reaction mixture was refluxed for 2 h. The completion of the reaction was monitored with the help of TLC. The work up of the reaction was done with water and ethyl acetate. The ethyl acetate portion was dried under reduced pressure and subjected to column chromatography. The required product **C-13** to **C-15** was eluted with increasing percentage of ethyl acetate in hexane.

*5-Methyl-5a,6,7,8,9,10-hexahydroazepino[2,1-b]quinazoline-12(5H)-one (**C-13**)* m.p. −102°C. ^{1}HNMR ($CDCl_3$) δ 7.95 (1H, m), 7.31 (1H, m), 6.86 (1H, t, $J = 7.46$ Hz), 6.63 (1H, t, $J = 8.55$ Hz), 4.98 (1H, dd, $J = 3.54$ and 5.27 Hz), 4.53 (2H, m), 2.94 (3H, s), 1.25–2.14 (8H, m).

*5-Ethyl-5a,6,7,8,9,10-hexahydroazepino[2,1-b]-quinazoline-12(5H)-one (**C-14**)* m.p. semisolid. ^{1}HNMR ($CDCl_3$) δ 7.93 (1H, m), 7.34 (1H, m), 6.83 (1H, t, $J = 7.53$ Hz), 6.66 (1H, t, $J = 8.23$ Hz), 4.93 (1H, dd, $J = 3.63$ and 5.34 Hz), 4.46 (2H, m), 3.40 (2H, q, $J = 7.33$ Hz), 1.25–2.14 (11H, m).

*5-Benzyl-5a,6,7,8,9,10-hexahydroazepino[2,1-b]quinazoline-12(5H)-one (**C-15**)* m.p. semisolid. ^{1}HNMR ($CDCl_3$) δ 7.98 (1H, dd, $J = 1.51$ and 7.72 Hz), 7.26–7.34 (6H, m), 6.86 (1H, t, $J = 7.23$ Hz), 6.65 (1H, d, $J = 8.22$ Hz), 4.77 (2H, s), 4.50 (2H, m), 2.71 (1H, m), 1.20–2.13 (8H, m). ^{13}CNMR ($CDCl_3$) δ 162.50, 146.27, 137.22, 133.24, 128.88, 128.79, 127.69, 127.31, 118.76, 118.22, 118.16, 114.03, 75.64, 53.47, 53.41, 44.80, 31.68, 27.59, 25.24, 25.03.

*5-Benzoyl-5a,6,7,8,9,10-hexahydroazepino[2,1-b]quinazoline-12(5H)-one (**C-16**)* 1 g of **C-2** (0.004 mol) was taken in a 250-ml flask, and 20 ml of acetone was added into the flask. Anhydrous potassium carbonate (2.5 g) and benzoyl chloride (0.504 g, 0.004 mol) were added to this reaction mixture. The reaction mixture was refluxed for 2 h. The completion of the reaction was monitored with the help of TLC. The work up of the reaction was done with water and ethyl acetate. The ethyl acetate portion was dried under reduced pressure and then subjected to column chromatography to yield the required product (**16**) which was eluted with hexane:ethyl acetate (95:5).

m.p. −189°C. ^{1}H NMR ($CDCl_3$) δ 8.08 (1H, dd, $J = 2.35$ and 9.46 Hz, H-1), 7.11–7.45 (7H, m), 6.50 (1H, d, $J = 7.60$ Hz), 5.97 (1H, d, $J = 3.92$ and 10.40 Hz), 4.61 (1H, m), 3.02 (1H, m), 1.46–1.82 (8H, m). ^{13}C ($CDCl_3$) δ 168.50, 161.41, 138.27, 134.08, 133.53, 131.57, 131.41, 130.19, 129.21, 128.47, 125.14, 124.26, 122.14, 70.14, 45.10, 32.81, 27.32, 25.31, 24.96.

Pharmacological assessment

Albino guinea pigs weighing 400–600 g of either sex were employed in different groups ($n = 6$) selected. Each group included six animals. Animals were maintained in the animal house and exposed to normal day–night cycles under standard conditions with the temperature at 25 ± 2°C and the relative humidity of 55–65%. The protocol of this study was approved by the Institutional Animal Ethics Committee (IAEC). All the compounds **C-1**–**C-16** were evaluated for their antitussive effect using

citric acid-induced cough model in guinea pig (Laude et al., 1994). Animals underwent a screening procedure before pretreatment with drugs. On the first day, after a 3 min acclimatization period, the animals were first exposed to normal saline and 5 min later to aerosolized 7.5% citric acid for a period of 10 min. Animal selection criterion was made either on the basis of number of coughs (<7 or >15) on exposure to aerosolized 7.5% citric acid or their tendency to cough on exposure to normal saline. Animal producing cough outside the stated limit of citric acid or on exposure to aerosolized saline was excluded as this was taken as an indication of infection or hyper-reactivity. Cough challenge was given at the same time of day for each animal and a minimum of 24-h interval was allowed between challenges to eliminate any short-term prophylaxis. Animals were allowed free access to food and water up to the time of testing. Each animal was placed in a Perspex chamber, dimensions 30 cm × 20 cm × 20 cm, and exposed to an aerosolized aqueous solution of 7.5% w/v citric acid for a period of 10 min. The output of the aerosolizer (INCO Laboratories, Ambala, India) was 0.25 ± 0.02 ml per minute, and same aerosolizer was used throughout the experiment. The animals were watched continuously by the trained observer, and number of coughs and latency time to initial cough response were noted. Coughs could easily be distinguished from sneeze since there is a clear difference in sound as well as in the behavior of the animals (fox, 1996). All the drugs were dissolved in 4% HCl and then diluted in saline. Their pH values were adjusted to 6.5–7.0 with 1% Na_2CO_3. The samples were intraperitoneally administered at 30 min. before the second challenge of aerosolized citric acid (7.5% w/v) solution for 10 min. The above protocol was performed 30 min after the intraperitoneal administration of following solutions for a period of 10 min. The synthesized compounds **C-1–C-16** were administered at doses 5, 10, and 15 mg/kg (dissolved in normal saline, *i.p.*). Codeine 10 mg/kg was administered as standard. The protocol of this study was approved by the Institutional Animal Ethics Committee (IAEC).

Statistical analysis

All the values were expressed as Mean ± SEM and were statistically analyzed using one way ANOVA followed by Tukey's multiple comparison test. The $p < 0.05$ was considered to be statistically significant.

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