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Short communication

Synthesis and bronchodilatory activity of some nitrogen bridgehead compounds

Dharam Paul Jindal *, Ravinder Singh Bhatti, Seema Ahlawat, Ranju Gupta

University Institute of Pharmaceutical Sciences (formerly Department of Pharmaceutical Sciences), Panjab University, Chandigarh 160 014, India

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Abstract

A series of tricyclic nitrogen bridgehead compounds **7**–**22** have been synthesised and evaluated for their in vitro bronchodilatory activity using isolated guinea pig tracheal chain, precontracted with acetylcholine. The relaxant effect of 2,3,4,5-tetrahydroazepino[2,1-*b*]-8,9-dimethoxyquinazolin-11(1*H*)-one (**7**) (DPJ-386) was greater than that of theophylline, aminophylline and quinazoline derivative **3**, which lacks methoxy groups at positions 8 and 9. Various nitrogen containing functionalities such as benzylamino, acetamido, benzamido and phthalimido were also introduced at 9 position of **3**. This resulted in loss of relaxation activity in precontracted guinea pig tracheal chain. These results show that the better relaxation property possessed by compound **7** hydrochloride is due to methoxy groups at 8 and 9 positions. © 2002 Published by Éditions scientifiques et médicales Elsevier SAS.

Keywords: Quinazoline; Bronchodilators; Vasaka alkaloids; Nitrogen bridgehead compounds; Guinea pig tracheal chains; Theophylline

1. Introduction

There are various factors such as exercise, allergen exposure, viral infections, irritants, environmental chemicals, etc. which are responsible for inducing symptoms of asthma. It is a complex and chronic disease characterised by reversible airway obstruction, airways inflammation and bronchial hyperresponsiveness. The first and the second reports of the national asthma education and prevention programme expert panel in US [1,2] and similar reports from other countries [3,4] have been beneficial in the management of asthma. Many classes of drugs namely bronchodilators such as β_2-adrenoceptor agonists [5,6], methylxanthines [7,8], anticholinergics [6], antihistaminics [9] and anti-inflammatory agents such as glucocorticoids [10], leukotriene receptor antagonists [6], adenosine antagonists [11], 5-lipoxygenase inhibitors [10] cromolyn sodium [12], phosphodiesetrase inhibitors [13,14] have resulted in substantial improvement in survival and quality of life of asthmatic patients. The treatment of asthma is complex and necessitates aggressive newer medical therapies and also involvement of asthmatic patients [12]. Our aim with this study was to search a new chemical entity possessing better bronchodilatory effects. The findings are reported in this communication.

Vasicine (**1**) and its oxidised product vasicinone (**2**) [15–17] (Fig. 1) are the alkaloids obtained from the leaves of plant *Adhatoda vasica* Nees family Acanthaceae. Both possess in vitro and in vivo bronchodilatory activity [16,18]. Vasicinone (**2**) has been reported to possess antiasthmatic activity comparable to sodium chromoglycate. Several modifications on vasicine (**1**) and vasicinone (**2**) have been made to get better uterotonic or bronchodilatory effects [16]. This resulted in the development of a compound 2,3,4,5-tetrahydroazepino[2,1-*b*]quinazolin-11(1*H*)-one (**3**), RLX (Fig. 1) which has been reported to be six to 10 times more potent than aminophylline [19,20]. On the basis of these observations, SAR studies have also been reported [21].

Hermecz et al. [21] have reported the synthesis and bronchodilator activity of bis- and tricyclic nitrogen bridgehead derivatives with a pyrimidine-4(3*H*)-one ring against serotonin-, histamine- and acetylcholine-induced spasms in guinea pig Konzett–Rössler test.

* Correspondence and reprints.
E-mail address: dharampjindal@yahoo.co.in (D.P. Jindal).

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Among the various synthesised compounds, 2,3,4,5-tetrahydroazepino[2,1 - *b*] - 7,8,9,10 - tetrahydroquinazolin-11(1*H*)-one (**4**) and cyclopenta[*d*]tetrahydroazepino[1,2-*a*]pyrimidine (**5**) (Fig. 1) were found to be 28 and 10 times more potent than theophylline anisate in carbachol-induced contractions of isolated human bronchus.

Papaverine (**6**) (Fig. 1) also has a direct relaxant effect on smooth muscles (a non-selective PDE inhibitor). It possesses a dimethoxy group in heteroaromatic nucleus [22].

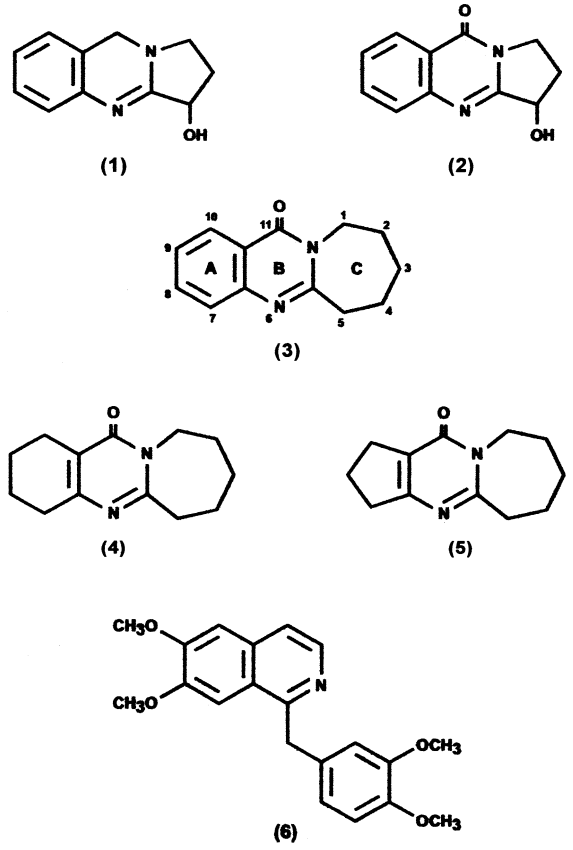

Fig. 1. Structures of vasicine (**1**), vasicinone (**2**), RLX (**3**), tricyclic nitrogen bridgehead compounds (**4**, **5**) and papaverine (**6**).

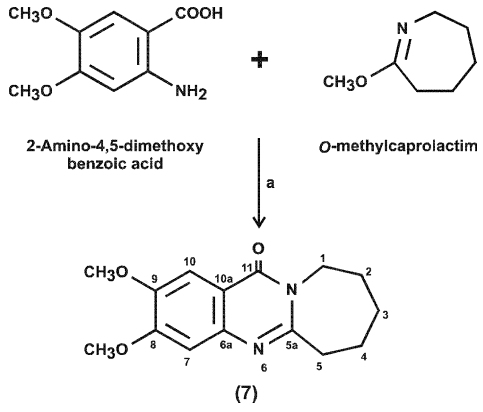

Fig. 2. Synthesis of 8,9-dimethoxy derivative (**7**). Reagents and conditions: (a) benzene/reflux.

Taking into account all these considerations, we introduced dimethoxy functions in tricyclic nitrogen bridgehead compound through the synthesis of 2,3,4,5-tetrahydroazepino[2,1 - *b*] - 8,9 - dimethoxyquinazolin-11(1*H*)-one (**7**) (Fig. 2). In addition, a number of nitrogenous functions were introduced at position 9 of compound **3**. The synthesised compounds were studied for their bronchodilatory activity using isolated guinea pig tracheal chain.

2. Chemistry

Compounds have been synthesised according to Figs. 2–5. The target compound **7** was prepared by condensing 2-amino-4,5-dimethoxy benzoic acid with 1-aza-2-methoxy-1-cycloheptene(*O*-methylcaprolactim), which, in turn, was prepared by treating ε-caprolactam with dimethyl sulphate at 80 °C (Fig. 2).

As a part of the programme, number of functionalities were introduced at position 9 of compound **3**. For this purpose structure **3** was subjected to nitration using a concentrated nitric acid–sulphuric acid mixture at 80 °C to obtain 9-nitro derivative **8** [19], which, after reduction with tin–concentrated hydrochloric acid afforded the 9-amino congener **9** [19]. Various functionalities were introduced by treating **9** with trimethoxybenzaldehyde, veratraldehyde, *p*-anisaldehyde, *p*-nitrobenzaldehyde, *p*-cyanobenzaldehyde, pyridine-2-carboxaldehyde, pyridine-4-carboxaldehyde, *p*-isopropylbenzaldehyde, indole-2-carboxaldehyde at room temperature. Subsequent reduction with sodium borohydride under chilled conditions gave amino derivatives **10**–**18** (Fig. 3); among these products 9-(4′-isopropylbenzylamino) derivative **15** was characterised as a hydrochloride salt.

Amide derivatives **19** and **20** were prepared by treating 9-amino congener **9** with isobutyryl chloride and trimethoxybenzoylchloride at room temperature (Fig. 4).

It was thought worthwhile to introduce imide functionality to observe its effect on biological activity. Fusion of phthalic anhydride and dimethoxyphathlic anhydride with 9-amino derivative **9** at 160–180 °C for 2 h resulted in the formation of 9-phthalimido derivatives **21** and **22** (Fig. 5).

Structures of the synthesised compounds were established with the help of the spectral and elemental analyses.

3. Pharmacology

Hydrochlorides of the compounds **7**–**22** were evaluated for their in vitro bronchodilator activity using

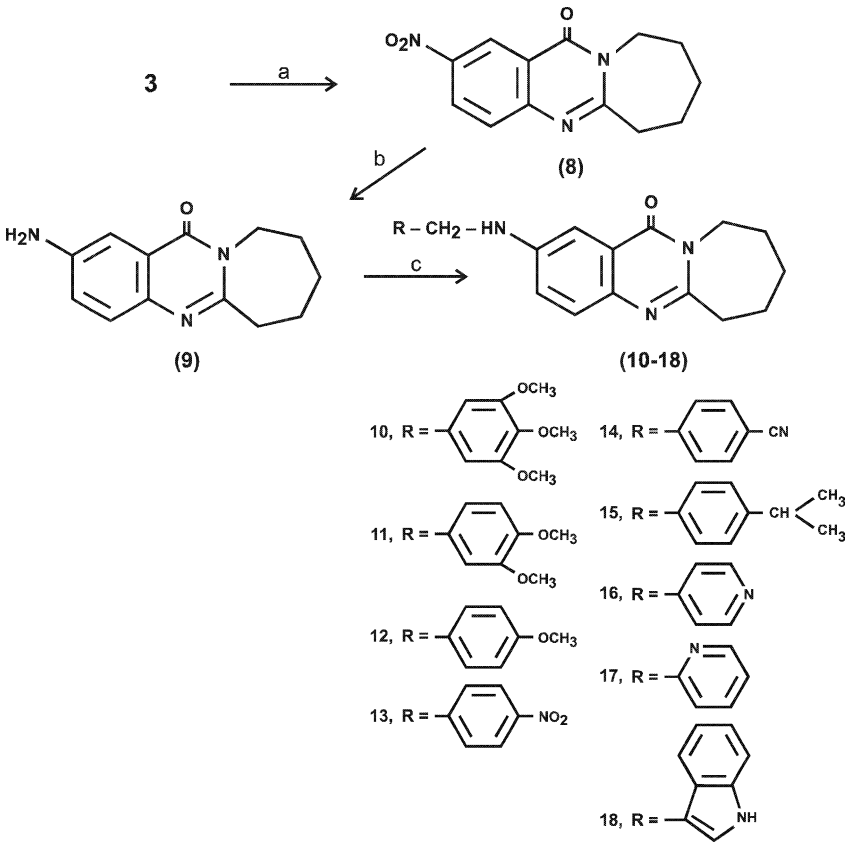

Fig. 3. Synthetic procedure to **8**–**18**. Reagents and conditions: (a) concentrated HNO_3–H_2SO_4; (b) Sn–concentrated HCl; (c) (i) R–CHO–MeOH; and (ii) $NaBH_4$/ice cold.

isolated guinea pig tracheal chain precontracted with acetylcholine (1 μg ml^{-1}). Aminophylline and theophylline were used as the standard drugs.

4. Results and discussion

The results of bronchodilatory activity for compounds **7**–**22** are reported in Tables 1 and 2.

The compound **7**, having structural resemblance to papaverine, has been found more potent than **3**, theophylline and aminophylline (Table 1). The introduction of dimethoxy functionality at positions 8 and 9 of tricyclic nitrogen bridgehead compound looks responsible for increased potency.

A dose dependent relaxation of acetylcholine induced contractions in guinea pig tracheal chain were also observed with dimethoxy derivative **7** and it showed much more potential towards bronchodilation than **3** (Table 2).

9-Substituted derivatives did not show significant bronchodilatory effects. These results suggest that dimethoxy group at 8- and 9-positions of heteroaromatic nucleus is significant for activity whereas substitution at 9 position by amino functionalities results in loss of bronchodilatory activity (Table 1).

5. Experimental

5.1. Chemistry

All m.p.s were obtained 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, 60 MHz and Brucker AC-300F, 300 MHz spectrometers using Me_4Si as an internal standard. Plates for TLC were prepared using silica gel G

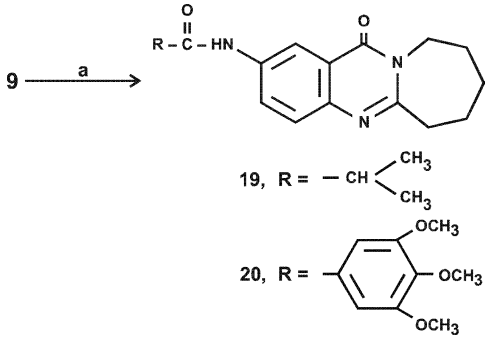

Fig. 4. Synthetic procedure to **19** and **20**. Reagents and conditions: (a) CH_2Cl_2–RCOCl.

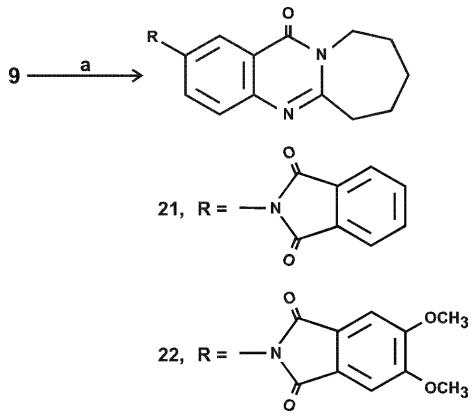

Fig. 5. Synthetic procedure to **21** and **22**. Reagents and conditions: (a) fusion/160–180 °C/phthalic anhydride–dimethoxy phthalic anhydride.

Table 1
In vitro bronchodilatory activity of compounds **7**–**22**

Compound	Concentration (μg ml^{-1})	In vitro guinea pig tracheal % relaxation
7	20	82.14
8	30	0.00
9	30	0.00
10	30	2.13
11	30	10.19
12	30	5.16
13	30	4.28
14	30	0.00
15	30	3.21
16	30	1.10
17	30	0.00
18	30	0.00
19	30	3.20
20	30	6.50
21	30	0.00
22	30	2.24
3	30	67.14
Theophylline	30	40.00
Aminophylline	30	50.00

Table 2
Comparative % relaxation produced by (**3**) HCl and (**7**) HCl in acetylcholine-induced bronchoconstriction

Concentration (μg ml^{-1})	% relaxation produced in μg ml^{-1} acetylchloine-induced bronchoconstriction	
	(**3**) HCl	(**7**) HCl (DPJ-386)
3	–	20.00
10	21.74	43.40
20	58.33	82.14
30	67.14	not accessed

according to Stahl (E. Merck) using EtOAc as solvent and activated at 110 °C for 30 min.

5.1.1. 2,3,4,5-Tetrahydroazepino[2,1-b]-8,9-dimethoxyquinazolin-11(1H)-one (7)

Dimethyl sulfate (0.3 mL) was added to 2-oxo-hexamethyleneamine (ε-caprolactam) (1.0 g, 8.8 mmol) in a two necked flask to get clear solution at room temperature (r.t.) and then heated at 80 °C. Additional quantity of dimethyl sulfate (0.6 mL) was added dropwise while maintaining the temperature at 80 °C. The mixture was then stirred for 3 h at 80–90 °C, cooled to r.t., diluted with thiophene-free-C_6H_6 and washed with 40% NaOH (10 mL) to remove the excess of dimethyl sulfate. The NaOH solution was then extracted with C_6H_6. The combined C_6H_6 layer was dried. 2-Amino-4,5-dimethoxybenzoic acid (1.0 g, 5.1 mmol) was added in small portions to the solution of 1-aza-2-methoxy-1-caprolactim(*O*-methylcaprolactim) at r.t. with constant stirring. The reaction mixture was refluxed for 5 h and solvent removed. The residue so obtained was picked up in $CHCl_3$ and washed with 5% NaOH (2 × 20 mL) and then with distilled water and dried. Chloroform was removed under reduced pressure and residue obtained was crystallised from MeOH to give **7** (0.7 g, 28.86%): m.p. 186–190 °C. IR (KBr, cm^{-1}): ν_{max} 1701, 1645, 1377, 1328, 1253, 1026. ^{1}H-NMR ($CDCl_3$): δ 1.85 (m, 6H, 2,3, and 4-CH_2), 3.05 (t, 2H, 5-CH_2), 3.99 (s, 6H, 8 and 9-OCH_3), 4.39 (t, 2H, 1-CH_2), 7.01 (s, 1H, 7-C*H*), 7.57 (s, 1H, 10-C*H*) ppm; ^{13}C-NMR ($CDCl_3$): δ 25.5 (C-3), 28.1 (C-4), 29.6 (C-2), 37.7 (C-1), 42.8 (C-5), 56.2 (–OCH_3), 56.3 (–OCH_3), 106.0 (C-7), 107.2 (C-10), 113.5 (C-10a), 143.7 (C-9), 148.8 (C-8), 154.9 (C-6a), 158.5 (C-5a), 161.3 (C-11) ppm. MS: *m*/*z* 274 [M$^+$]. Anal. Calc. for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.21. Found: C, 66.08; H, 6.34; N, 10.60%.

*5.1.2. General procedure for the synthesis of benzylamines **10**–**18***

To a solution of 9-amino-2,3,4,5-tetrahydroazepino-[2,1-*b*]quinazolin-1(1*H*)-one (**9**) [19] (0.4 g, 1.75 mmol) in MeOH (8.0 mL) was added a solution of aldehyde (4.0 mmol) in MeOH (8.0 mL) with constant stirring. The reaction mixture was allowed to stand overnight at r.t. 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 precipitate was filtered, washed with water, dried and recrystallised to give the desired amines **10**–**18**.

*5.1.2.1. 9-(3′,4′,5′-Trimethoxybenzylamino)-2,3,4,5-tetrahydroazepino[2,1-b]quinazolin-11(1H)-one (**10**).* Yield: 36%, m.p. 170–172 °C. IR (KBr, cm^{-1}): ν_{max} 3367, 1662, 1226, 1035, 842, 789. ^{1}H-NMR ($CDCl_3$): δ 1.82 (m, 6H, 2,3,4-CH_2), 3.02 (t, 2H, 5-CH_2), 3.83 (s, 9H, 3′,4′,5′-OCH_3), 4.33 (m, 4H, 1-CH_2, NH–CH_2), 4.37 (b, 1H, –N*H*), 6.59 (s, 2H, 2′ and 5′-C*H*), 7.06 (dd,

1H, 7-C*H*), 7.34 (d, 1H, 8-C*H*), 7.45 (d, 1H, 10-C*H*) ppm. MS: *m*/*z* 409 [M^+]. Anal. Calc. for $C_{23}H_{27}N_3O_4$: C, 67.46; H, 6.29; N, 10.26. Found: C, 67.09; H, 6.29; N, 10.60%.

5.1.2.2. 9-(3′,4′-Dimethoxybenzylamino)-2,3,4,5-tetrahydroazepino[2,1-b]quinazolin-11(1H)-one ***(11)****.* Yield: 67.43%, m.p. 206–210 °C. IR (KBr, cm^{-1}): ν_{max} 3380, 3010, 1658, 1620, 1580, 1260. ^{1}H-NMR ($CDCl_3$): δ 1.82 (m, 6H, 2,3, and 4-CH_2), 3.08 (m, 2H, 5-CH_2), 3.87 (s, 6H, 3′ and 4′-OCH_3), 4.33 (m, 5H, 1-CH_2, NH–CH_2, disappeared on deuterium exchange, –N*H*), 6.83 (d, 1H, $J = 6.0$ Hz, 7-C*H*, aromatic), 6.91 (m, 2H, 8-C*H* and 6′-C*H*, aromatic), 7.04 (dd, 1H, $J = 3.0$ and 9.0 Hz, 5′-C*H*, aromatic), 7.36 (d, 1H, $J = 3$ Hz, 2′-C*H*, aromatic), 7.45 (d, 1H, $J = 9.0$ Hz, 10-C*H*, aromatic) ppm. Anal. Calc. for $C_{22}H_{25}N_3O_3$: C, 69.63; H, 6.64; N, 11.07. Found: C, 69.33; H, 6.36; N, 11.37%.

5.1.2.3. 9-(4′-Methoxybenzylamino)-2,3,4,5-tetrahydroazepino[2,1-b]quinazolin-11(1H)-one ***(12)****.* Yield: 74.67%, m.p. 160–164 °C. IR (KBr, cm^{-1}): ν_{max} 3375, 3060, 2830, 1650, 1390, 1250, 1020. ^{1}H-NMR ($CDCl_3$): δ 1.80 (s, 6H, 2,3, and 4-CH_2), 3.0 (s, 2H, 5-CH_2), 3.76 (s, 3H, 4′-OCH_3), 4.26 (m, 5H, 1-CH_2, NH–CH_2, disappeared on deuterium exchange, –N*H*), 6.70–7.50 (m, 7H, aromatic protons) ppm. Anal. Calc. for $C_{21}H_{23}N_3O_2$: C, 72.18; H, 6.68; N, 12.03. Found: C, 72.54; H, 6.73; N, 12.14%.

5.1.2.4. 9-(4′-Nitrobenzylamino)-2,3,4,5-tetrahydroazepino[2,1-b]quinazolin-11(1H)-one ***(13)****.* Yield: 68.84%, m.p. 218–224 °C. IR (KBr, cm^{-1}): ν_{max} 3400, 3115, 3080, 2920, 2850, 1650, 1620, 1585, 1505, 1375, 1330, 840. ^{1}H-NMR ($CDCl_3$–DMSO-d_6): δ 1.80 (s, 6H, 2,3, and 4-CH_2), 3.00 (s, 2H, 5-CH_2), 4.20–4.66 (m, 4H, N-CH_2, NH–CH_2), 5.46 (br, disappeared on deuterium exchange, –N*H*), 7.00–7.70 (m, 5H, aromatic), 8.13 (d, 2H, $J = 9.0$ Hz, aromatic) ppm. Anal. Calc. for $C_{20}H_{20}N_4O_3$: C, 65.55; H, 5.50; N, 15.83. Found: C, 65.78; H, 5.55; N, 15.61%.

5.1.2.5. 9-(4′-Cyanobenzylamino)-2,3,4,5-tetrahydroazepino[2,1-b]quinazolin-11(1H)-one ***(14)****.* Yield: 77.33%, m.p. 188–194 °C. IR (KBr, cm^{-1}): ν_{max} 3220, 3060, 2910, 2200, 1640, 1590, 1510. ^{1}H-NMR ($CDCl_3$–DMSO-d_6): δ 1.80 (s, 6H, 2,3, and 4-CH_2), 3.00 (br, 2H, 5-CH_2), 4.33 (m, 5H, 1-CH_2, NH–CH_2, disappeared on deuterium exchange, –N*H*), 7.00–7.90 (m, 7H, aromatic) ppm. Anal. Calc. for $C_{21}H_{20}N_4O$: C, 72.81; H, 5.82; N, 16.75. Found: C, 72.44; H, 5.51; N, 16.84%.

5.1.2.6. 9-(4′-Isopropylbenzylamino)-2,3,4,5-tetrahydroazepino[2,1-b]quinazolin-11(1H)-one ***(15)*** *hydrochloride.* Yield: 77.57%, m.p. 212–218 °C. IR (KBr, cm^{-1}): ν_{max} 3300, 3010, 2900, 1695, 1615, 1525, 1380, 1350. ^{1}H-NMR ($CDCl_3$–DMSO-d_6): δ 1.22 (d, 6H, $J = 6.6$ Hz, –CH(CH_3)$_2$), 1.86 (m, 6H, 2,3 and 4-CH_2), 2.89 (sept, 1H, $J = 6$ Hz, –CH(CH_3)$_2$), 3.50 (m, 2H, 5-CH_2), 4.35 (s, 2H, –NH–CH_2), 4.46 (m, 2H, 1-CH_2), 7.17 (m, 3H, 2′-C*H*, 6′-C*H* and 7-C*H*, aromatic), 7.30 (m, 3H, 3′,5′- and 8-C*H*, aromatic), 7.89 (d, 1H, $J = 9.0$ Hz, 10-C*H*, aromatic) ppm. Anal. Calc. for $C_{23}H_{28}ClN_3O$: C, 69.41; H, 7.09; N, 10.56. Found: C, 69.75; H, 6.79; N, 10.24%.

5.1.2.7. 9-(4-Picolylamino)-2,3,4,5-tetrahydroazepino[2,1-b]quinazolin-11(1H)-one ***(16)****.* Yield: 71.51%, m.p. 144–148 °C. IR (KBr, cm^{-1}): ν_{max} 3240, 2930, 1650, 1585, 1350, 840. ^{1}H-NMR ($CDCl_3$): δ 1.82 (s, 6H, 2,3, and 4-CH_2), 3.02 (m, 2H, 5-CH_2), 4.36 (m, 2H, 1-CH_2), 4.46 (s, 2H, NH–CH_2), 4.58 (m, 1H, disappeared on deuterium exchange, –N*H*), 7.05 (dd, 1H, $J = 3.0$ and 9.0 Hz, 7-C*H*, aromatic), 7.26–7.31 (m, 3H, pyridino protons and 8-C*H*, aromatic), 7.46 (d, 1H, $J = 9.0$ Hz, 10-C*H*, aromatic), 8.54 (d, 2H, $J = 5.8$ Hz, pyridino protons adjacent to nitrogen) ppm. Anal. Calc. for $C_{19}H_{20}N_4O$: C, 70.78; H, 6.25; N, 18.00. Found: C, 70.37; H, 6.50; N, 17.71%.

5.1.2.8. 9-(2-Picolylamino)-2,3,4,5-tetrahydroazepino[2,1-b]quinazolin-11(1H)-one ***(17)****.* Yield: 74.90%, m.p. 90–94 °C. IR (KBr, cm^{-1}): ν_{max} 3300, 3090, 2850, 1650, 1630, 1590, 1500. ^{1}H-NMR ($CDCl_3$): δ 1.82 (s, 6H, 2,3, and 4-CH_2), 3.02 (m, 2H, 5-CH_2), 4.38 (m, 2H, 1-CH_2), 4.54 (d, 2H, $J = 3.6$ Hz, NH–CH_2), 5.26 (s, 1H, disappeared on deuterium exchange, –N*H*), 7.12–7.66 (m, 6H, aromatic and pyridino protons), 8.59 (d, 1H, $J = 4.8$ Hz, pyridino protons adjacent to nitrogen) ppm. Anal. Calc. for $C_{19}H_{20}N_4O$: C, 70.78; H, 6.25; N, 18.00. Found: C, 70.69; H, 6.09; N, 18.32%.

5.1.2.9. 9-(3-Indolylmethylamino)-2,3,4,5-tetrahydroazepino[2,1-b]quinazolin-11(1H)-one ***(18)****.* Yield: 70.52%, m.p. 148–154 °C. IR (KBr, cm^{-1}): ν_{max} 3400, 3120, 3080, 1660, 1595, 1500. ^{1}H-NMR ($CDCl_3$): δ 1.77 (s, 6H, 2,3, and 4-CH_2), 2.98 (m, 2H, 5-CH_2), 4.33 (m, 2H, 1-CH_2), 4.48 (s, 2H, NH–CH_2), 6.0 (br, 1H, N*H*, disappeared on deuterium exchange), 6.97–7.64 (m, 8H, aromatic protons and indolic-C*H*), 10.69 (s, 1H, disappeared on deuterium exchange, N*H*) ppm. Anal. Calc. for $C_{22}H_{22}N_4O$: C, 73.31; H, 6.15; N, 16.10. Found: C, 73.03; H, 6.27; N, 16.38%.

5.1.3. General procedure for the synthesis of amides ***19*** *and* ***20***

To a stirred solution of 9-amino-2,3,4,5-tetrahydroazepino[2,1-*b*]quinazolin-11(1*H*)-one (**9**) (0.4 g, 1.75 mmol) in CH_2Cl_2 (10 mL) was added respective acid chlorides (5 mL) dropwise under anhydrous conditions. The stirring was continued for 2 h at r.t. Solvent was removed under vacuo and sticky residue so obtained

was neutralised with Na_2CO_3 solution. The precipitate obtained was filtered, washed, dried and crystallised to afford the amides **19** and **20**.

*5.1.3.1. 9-(Dimethylacetamido)-2,3,4,5-tetrahydroazepino[2,1-b]quinazolin-11(1H)-one (**19**).* Yield: 75.43%, m.p. 190–194 °C. IR (KBr, cm^{-1}): ν_{max} 3325, 3100, 3060, 1698, 1650, 1530, 850. ^{1}H-NMR ($CDCl_3$–DMSO-d_6): δ 1.24 (d, 6H, $J = 6.7$ Hz, –CH(CH_3)$_2$), 1.80 (m, 6H, 2,3, and 4-CH_2), 2.61 [septet, 1H, $J = 6.7$ Hz, –CH(CH$_2$)$_3$], 3.06 (m, 2H, 5-CH_2), 4.36 (m, 2H, 1-CH_2), 7.53 (d, 1H, $J = 8.8$ Hz, 7-CH, aromatic), 8.13 (d, 1H, $J = 2.4$ Hz, 8-CH, aromatic); 8.38 (dd, 1H, $J = 2.4$ and 8.8 Hz, 10-CH, aromatic), 8.74 (br, 1H, disappeared on deuterium exchange, –NH) ppm. Anal. Calc. for $C_{17}H_{21}N_3O_2$: C, 68.20; H, 7.07; N, 14.04. Found: C, 68.08; H, 7.17; N, 14.24.

*5.1.3.2. 9-(3′,4′,5′-Trimethoxybenzamido)-2,3,4,5-tetrahydroazepino[2,1-b]quinazolin-11(1H)-one (**20**).* Yield: 65.70%, m.p. 148–152 °C. IR (KBr, cm^{-1}): ν_{max} 3350, 3100, 3060, 1680, 1650, 1585, 1500. ^{1}H-NMR ($CDCl_3$–DMSO-d_6): δ 1.83 (m, 6H, 2,3 and 4-CH_2), 3.06 (m, 2H, 5-CH_2), 3.92 (s, 9H, 3′,4′, and 5′-OCH_3), 4.32 (m, 2H, 1-CH_2), 7.16 (s, 2H, 2′ and 6′-CH, aromatic), 7.63 (d, 1H, $J = 8.7$ Hz, 7-CH aromatic), 8.19 (d, 1H, J = 2.2 Hz, 8-CH, aromatic), 8.43 (dd, 1H, $J = 2.2$ and 8.7 Hz, 10-CH, aromatic), 8.58 (s, 1H, disappeared on deuterium exchange, –NH) ppm. Anal. Calc. for $C_{23}H_{25}N_3O_5$: C, 65.23; H, 5.95; N, 9.92. Found: C, 65.57; H, 5.87; N, 9.80%.

*5.1.4. General procedure for the synthesis of phthalimido derivatives **21** and **22***

9-Amino-2,3,4,5-tetrahydroazepino[2,1-*b*]quinazolin-11(1*H*)-one (**9**) (0.5 g, 2.2 mmol) and phthalic anhydride (3.3 mmol) were fused together at 160–180 °C for 2 h. The fused mixture was refluxed in distilled water for 1 h to remove the unreacted material and filtered. The residue obtained was dried and crystallised to afford 9-phthalimido derivatives **21** and **22**.

*5.1.4.1. 9-Phthalimido-2,3,4,5-tetrahydroazepino[2,1-b]quinazolin-11 (1H)-one (**21**).* Yield: 68.24%, m.p. >310 °C. IR (KBr, cm^{-1}): ν_{max} 3100, 3080, 1770, 1720, 1660, 1580, 1490. ^{1}H-NMR ($CDCl_3$): δ 1.87 (m, 6H, 2,3, and 4-CH_2), 3.10 (m, 2H, 5-CH_2), 4.40 (m, 2H, 1-CH_2), 7.80 (m, 4H, aromatic), 7.96 (m, 2H, aromatic), 8.33 (d, 1H, $J = 2.2$ Hz, 10-CH, aromatic) ppm. Anal. Calc. for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.77; N, 11.69. Found: C, 69.88; H, 5.03; N, 11.46%.

*5.1.4.2. 9-(5′-6′-Dimethoxyphthalimido)-2,3,4,5-tetrahydroazepino[2,1-b]quinazolin-11(1H)-one (**22**).* Yield: 57.17%, m.p. >310 °C. IR (KBr, cm^{-1}): ν_{max} 3085, 2865, 1770, 1710, 1675, 1592, 1225, 1090. ^{1}H-NMR ($CDCl_3$): δ 2.05 (m, 6H, 2,3 and 4-CH_2), 3.38 (m, 2H, 5-CH_2), 4.08 (s, 6H, 5′ and 6′-OCH_3), 4.59 (m, 2H, 1-CH_2), 7.54 (s, 2H, 4′ and 7′-CH, phthalimido protons), 7.88 (d, 1H, $J = 8.7$ Hz, 7-CH, aromatic), 8.13 (dd, 1H, $J = 2.2$ and 8.7 Hz, 8-CH, aromatic), 8.50 (d, 1H, $J = 2.2$ Hz, 10-CH, aromatic) ppm. Anal. Calc. for $C_{23}H_{21}N_3O_5$: C, 65.85; H, 5.05; N, 10.02. Found: C, 65.66; H, 4.87; N, 10.30%.

5.2. Pharmacology

Tracheal chain of the guinea pig was exposed by giving a longitudinal incision in the neck then removed from the body and transferred in the beaker containing Kreb's–Hanslet solution. Tracheal chain was prepared according to the method of Akcasu [23]. A 2 g tension was provided to the trachea by sticking plasticin on the lever. The tissue was provided a rest for half an hour. Dose dependent relaxant effect of the compound were recorded on the kymograph tracings in the concentrations of 1, 3, 10, 20 and 30 μg ml^{-1} on tracheal chain precontracted with 1 μg ml^{-1} acetylcholine.

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