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Design, synthesis and pharmacological screening of a series of N^1-(substituted)aryl-5,7-dimethyl-2-(substituted)pyrido(2,3-*d*)-pyrimidin-4(3H)-ones as potential histamine H_1-receptor antagonists

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Abstract

A series of N_1-(substituted)aryl-5,7-dimethyl-2-(substituted)pyrido(2,3-*d*)pyrimidin-4(3H)-one was designed on the basis of the triangular pharmacophoric requirement of histamine H_1-receptor antagonists. The designed series was synthesized by cyclo-condensation of monoaryl thiourea with ethyl cyanoacetate in the presence of dry HCl gas to give N_1-(substituted aryl)-2-mercaptopyrimidine-4(3H)-one, which on cyclo-condensation with acetylacetone gave the pyridopyrimidinone. Further methylation of the mercapto group at C-2 with methyl iodide followed by nucleophilic displacement of the methylmercapto group by various amines gave the targeted compounds. All the synthesized compounds were screened for histamine H_1-receptor antagonistic activity by the *in vitro* method of inhibition of the isotonic contraction induced by histamine on isolated guinea pig ileum using cetirizine as a standard drug. All the compounds exhibited potent histamine H_1-receptor antagonistic activity with pA_2 values from 7.30– 9.75 (cetirizine, pA_2 value 9.40). The potent compounds were screened for their *in vivo* antihistaminic activity by protection of animal from asphyxic shock. The sedative potential of potent compounds was checked on albino mice by photoactometer and they had comparative sedative potential to the standard drug cetirizine. None of the compound exhibited anticholinergic activity in the *in vitro* rat ileum model.

Keywords: *Histamine, H_1-receptor antagonist, allergy, pyrido (2,3-*d*)pyrimidin-4(3H)-ones*

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 rhinoconjuctivitis, urticaria and atopic dermatitis [1].

The first generation antihistamines like chlorpheniramine, diphenhydramine, promethazine and hydroxyzine have considerable sedative effects caused by their ability to cross the blood-brain barrier [2–6]. The second generation antihistamines were found to be devoid of these sedative effects but some of them have exhibited serious cardiac side effects. The third generation antihistamines have demonstrated no cardiac side effects [7–10].

Pyridopyrimidines are known to have a variety of biological activities [11–15]. Pyrido(2,3-*d)*pyrimidine is a bioisostere of quinazoline and pteridine.

The classical pharmacophoric model of H_1 receptor antagonists suggest that the presence of a ring heteroatom adjacent to the aminoalkyl side-chain, a nitrogen with at least one proton and the site for heteroatom capable of hydrogen bonding are the basic structural requirements for H_1 antagonists. Although the classical structures explain the pharmacophoric requirements, it has been observed that even structures falling outside the classical general formula can exhibit potent activity (e.g. temelastine, levocarbastine, epinastine etc.). Borea et al. further refined this model to a triangular pharmacophoric model [16]. On the basis of triangular pharmacophoric requirements, we have designed and synthesised a novel series of N_1-(substituted)aryl-5,7-dimethyl-2-(substituted)pyrido(2,3-*d)*pyrimidin-4(3H)-one as potential histamine H_1-receptor antagonist (see Figures 1, 2 and 3). The distances between centroids of aryl rings and the tertiary nitrogen were found close

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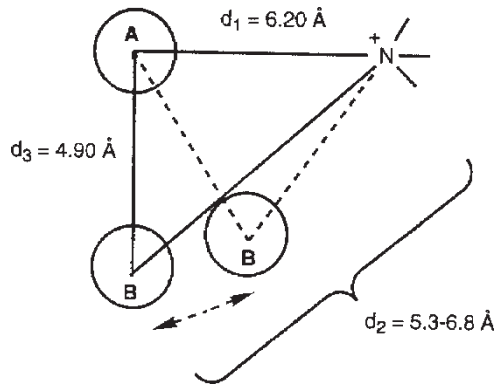


Figure 1. Triangular pharmacophoric measurement.

to the specified distance (the distances found were $d_1 = 5.71$ A°, $d_2 = 4.86$ A°, $d_3 = 7.08$ A°, using PC based software CS Chemoffice and chem.. 3D Pro See Table I. Moreover, the designed molecules has a protonatable nitrogen and carbonyl group at C-4, which will impart polarity to the molecules and reduce penetration through the blood brain barrier.

Materials and methods

Chemistry

All melting points were determined in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded on a DPX Spectrophotometer at 200 MHz using TMS as internal standard. Chemical shifts are reported in ppm downfield on a δ scale. IR spectra were recorded on a Perkin-Elmer 841 grating spectrophotometer in KBr pellets. Mass spectra were recorded on a Perkin-Elmer LC-MS PE SCIEX API 165 instrument. TLC was performed on microscopic slides, 2 × 7.5 cm, coated with silica gel G as stationary phase and the spots were visualized by exposure to iodine vapors and UV light.

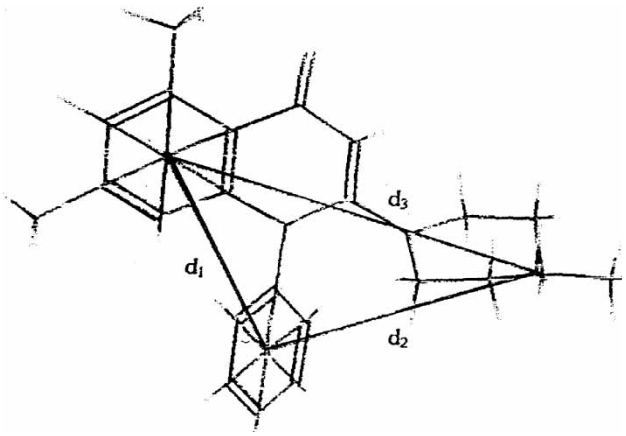
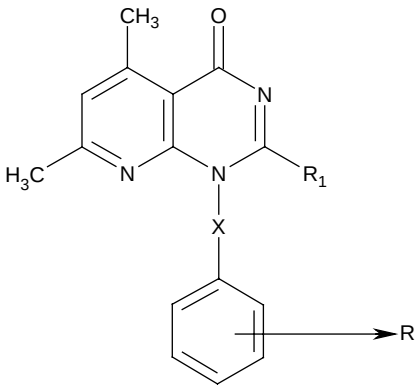


Figure 2. The distances between centroids of aryl ring and tertiary nitrogen in design series.



(**1**-**48**)

R = H, *m*-CH_3, *p*-CH_3, *m*-OCH_3, *p*-OCH_3, *p*-F, *m*-Cl, *p*-Cl, *p*-Br, 2,3-dimethyl, 2,4-dimethyl, X = - CH_2 -
R_1 = N, N,-dimethylamino, N, N-diethylamino, N,N-diethylethylenediamino, N, N-diethylpropylenediamino,

Figure 3. Structure of design series.

Synthetic grade chemicals were used. The starting materials monoarylthioureas [17], 6-amino-N_1-(substituted)aryl-2-mercaptopyrimidin-4(3H)-one [18] and 5,7-dimethyl-1-(substituted)-pyrido(2,3-*d)*pyrimidin-4-ones [18] were synthesized according to literature procedures. The designed series was synthesized in three steps. Cyclo-condensation of the monoaryl thiourea with ethyl cyanoacetate to N_1-(substituted aryl)-2-mercaptopyrimidine-4(3H)-one (b) was carried out in presence of dry HCl gas. Further, cyclo-condensation of the compound with acetylacetone gave pyridopyrimidinone (c). Methylation of the mercapto group at C-2 with methyl iodide followed by nucleophilic displacement of the methylmercapto group by various amines yielded the targeted compound (**1–48**) (See Figure 4). The structure of all the synthesized compounds was characterized by IR, ^{1}HNMR, MASS spectra and elemental analysis (See Tables III, IV).

*General method for synthesis of N_1-(substituted)aryl-2-methylmercapto-5,7-dimethyl-pyrido(2,3-*d)*pyrimidine-4(3H)-one (d).* The N_1-(substituted)aryl-5,7-dimethyl-2-mercaptopyrido(2,3-*d)*pyrimidin-4(3H)-one (c)(0.01 mole, 2.69 g) was suspended in aqaeous. sodium hydroxide (20% w/v, 25mL) and warmed on a water-bath. The clear solution formed was allowed to cool to room temperature. Methyl iodide (0.01 mole, 1.4 g) was added drop-wise with continuous stirring

Table I. The distances between centroids of aryl ring and tertiary nitrogen.

Distance	d_1(A°)	d_2(A°)	d_3(A°)
Required	6.20 ± 0.15	5.3–6.8	4.9 ± 0.24
Found	5.71	7.08	4.86

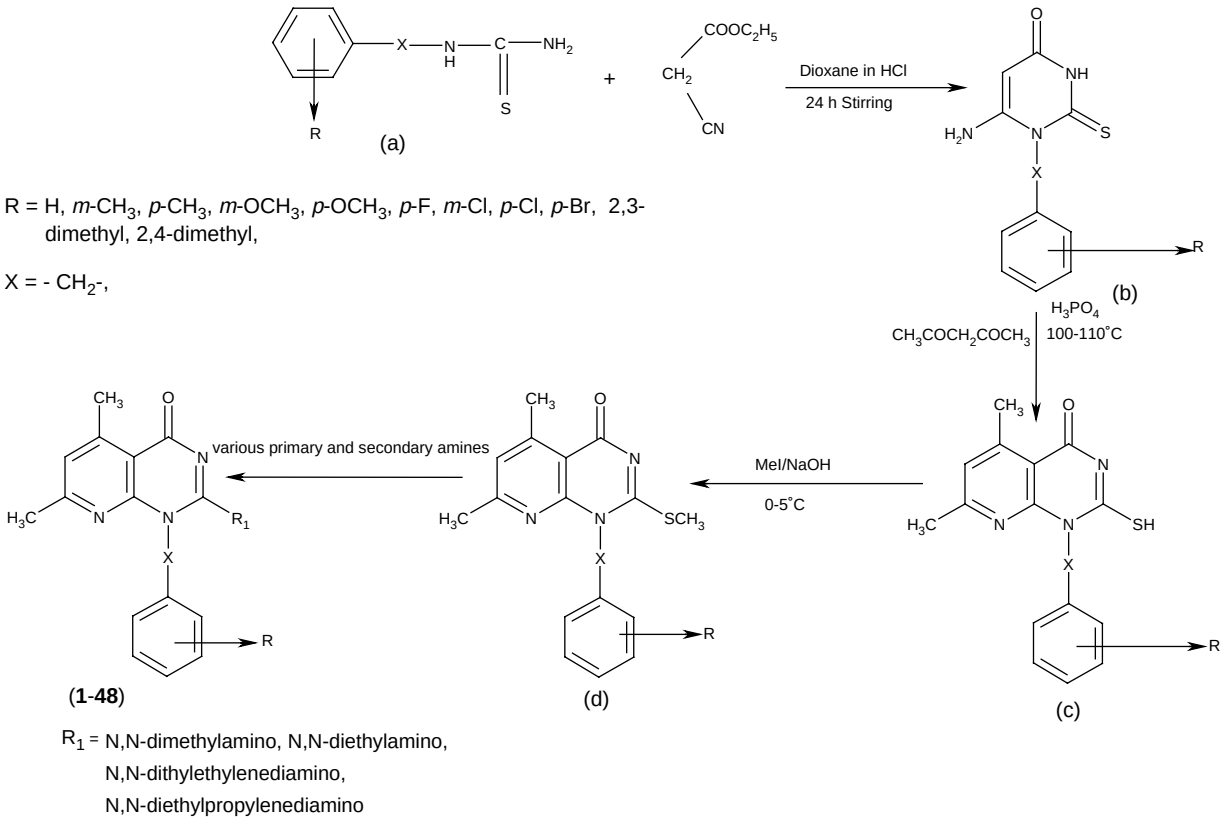


Figure 4. Scheme I for synthesis of design series.

over a period of 1 h. The reaction mixture was then allowed to stand overnight at room temperature, neutralized with dil. HCl (20% v/v, 12 mL) and the solid separated filtered, washed with water, dried and recrystallized.

*General method for synthesis of N_1-(substituted)aryl-5,7-dimethyl-2-(substituted)pyrido(2,3-*d*)pyrimidine-4(3H)-one* ***(1–48)***. A mixture of the N_1-(phenyl)-5,7-dimethyl-2-methylmercaptopyrido(2,3-*d*)pyrimidin-4(3H)one (d)(0.01 mole) with the appropriate amine (0.01 mole) was refluxed for 6 h. The progress of the reaction was monitored by TLC and the evolution of mercaptan gas. When all the starting material was consumed and there was no evolution of mercaptan gas, the reaction mixture was allowed to cool at room temperature and then poured into excess of ice-cold water. The solid separated was washed with water, dried and recrystallized from ethanol (See Table II).

Pharmacological screening

Animals. The experiments were carried out using English short hair strain guinea pigs and Albino wistar mice obtained from the animal house of Cadia Laboratories, Ahmedabad, India (mice and guinea pigs have been in-bred in the animal house of Cadila Laboratories for last 20 years). Colonies were maintained at the Animal House of L. M. College of Pharmacy, Ahmedabad, India and these animals were housed at a temperature of 24 ± 1°C and 50–70% humidity with 14 h light and 10 h dark cycles. These animals were given food and water *ad libitum*, unless otherwise specified. For all the studies, animals of either sex were selected at random.

In vitro *H_1-receptor antagonistic activity*. The *in vitro* antihistaminic activity was determined by using the inhibition of the isotonic contraction induced by histamine on isolated guinea pig ileum. As the compounds were not soluble in water and physiological salt solution, test compounds were dissolved in dimethyl sulphoxide with a little warming and further dilutions were made using physiological salt solution. Standard histamine solution was prepared in physiological salt solution. Cetrizine was used as a standard drug. The animal was fasted for 24 h, prior to sacrifice. Responses were taken on a 2 cm long piece of ileum stimulated by physiological salt solution at 37°C. The method involves the blocking of the histamine induced contraction by the antagonists at different logarithmically increasing dose levels. Each response was repeated 2–3 times.

Table II. Physical data, *In vivo* and *in vitro* antihistaminic activity and sedative potential of N_1-(substituted)aryl-5,7-dimethyl-2-(substituted) pyrido (2,3-*d*) pyrimidin-4(3H)-ones.

Comp.	R	R_1	X	Melting Point (°C)	% Yield*	Molecular formula	H_1-receptor antagonistic activity† $pA_2 \pm$ SEM	Sedative potentia after 120 min**	*In vivo* asphysic shock, time in min Control (Test)
1	H	$H-N(CH_3)_2$	–	135–137	56	$C_{17}H_{18}N_4O$	7.36 ± 0.15	64.58	
2	H	$H-N(CH_3)_2$	$-CH_2-$	98–101	45	$C_{18}H_{20}N_4O$	8.06 ± 0.21	55.32	
3	*m*-CH_3	$-N(CH_3)_2$	–	110–112	78	$C_{18}H_{20}N_4O$	8.08 ± 0.26	78.00	
4	*p*-CH_3	$-N(H_3)_2$	–	137–140	67	$C_{18}H_{20}N_4O$	7.53 ± 0.16	61.55	
5	*m*-OCH_3	$-N(CH_3)_2$	–	140–142	86	$C_{18}H_{20}N_4O_2$	8.44 ± 0.15	73.49	
6	*p*-OCH_3	$-N(CH_3)_2$	–	122–124	87	$C_{18}H_{20}N_4O_2$	8.42 ± 0.15	79.80	
7	*p*-F	$-N(CH_3)_2$	–	154–157	47	$C_{17}H_{17}FN_4O$	8.95 ± 0.48	65.32	
8	*m*-Cl	$-N(CH_3)_2$	–	102–105	64	$C_{17}H_{17}ClN_4O$	7.28 ± 0.37	78.75	
9	*p*-Cl	$-N(CH_3)_2$	–	130–132	65	$C_{17}H_{17}ClN_4O$	8.36 ± 0.13	62.13	
10	*p*-Br	$-N(CH_3)_2$	–	178–181	54	$C_{17}H_{17}BrN_4O$	9.04 ± 0.15	61.41	**2.5(9.3)**
11	2,3-$(CH_3)_2$	$-N(CH_3)_2$	–	105–107	54	$C_{19}H_{22}N_4O$	8.70 ± 0.14	75.11	
12	2,4-$(CH_3)_2$	$-N(CH_3)_2$	–	170–173	65	$C_{19}H_{22}N_4O$	8.49 ± 0.15	77.35	
13	H	$-N(C_2H_5)_2$	–	136–138	56	$C_{19}H_{22}N_4O$	7.38 ± 0.15	40.33	
14	H	$-N(C_2H_5)_2$	$-CH_2-$	101–103	68	$C_{20}H_{24}N_4O$	8.09 ± 0.21	31.70	
15	*m*- CH_3	$-N(C_2H_5)_2$	–	178–180	82	$C_{20}H_{24}N_4O$	8.19 ± 0.26	64.42	
16	*p*-CH_3	$-N(C_2H_5)_2$	–	135–137	78	$C_{20}H_{24}N_4O$	8.69 ± 0.14	35.90	
17	*m*-OCH_3	$-N(C_2H_5)_2$	–	105–107	64	$C_{20}H_{24}N_4O_2$	8.83 ± 0.16	61.27	
18	*p*-OCH_3	$-N(C_2H_5)_2$	–	143–146	54	$C_{20}H_{24}N_4O_2$	8.48 ± 0.15	36.83	
19	*p*-F	$-N(C_2H_5)_2$	–	154–156	78	$C_{19}H_{21}FN_4O$	8.93 ± 0.48	53.33	
20	*m*-Cl	$-N(C_2H_5)_2$	–	117–120	87	$C_{19}H_{21}ClN_4O$	9.04 ± 0.16	45.02	**2.6(10.1)**
21	*p*-Cl	$-N(C_2H_5)_2$	–	121–123	73	$C_{19}H_{21}ClN_4O$	8.22 ± 0.18	48.42	
22	*p*-Br	$-N(C_2H_5)_2$	–	140–142	80	$C_{19}H_{21}BrN_4O$	9.30 ± 0.16	74.58	**2.5(9.4)**
23	2,3-$(CH_3)_2$	$-N(C_2H_5)_2$	–	133–135	56	$C_{21}H_{26}N_4O$	8.71 ± 0.14	32.27	
24	2,4-$(CH_3)_2$	$-N(C_2H_5)_2$	–	102–105	67	$C_{21}H_{26}N_4O$	8.70 ± 0.15	59.54	
25	H	$-NH(CH_2)_2-N(C_2H_2)_2$	–	132–133	56	$C_{21}H_{27}N_5O$	9.34 ± 0.20	44.27	**2.3(11.7)**
26	H	$-NH(CH_2)_2-N(C_2H_5)_2$	$-CH_2-$	109–111	80	$C_{22}H_{29}N_5O$	9.73 ± 0.22	34.30	**2.6(12.4)**
27	*m*-CH_3	$-NH(CH_2)_2-N(C_2H_5)_2$	–	142–145	69	$C_{22}H_{29}N_5O$	8.59 ± 0.25	71.84	
28	*p*-CH_3	$-NH(CH_2)_2-N(C_2H_5)_2$	–	133–135	67	$C_{22}H_{29}N_5O$	8.05 ± 0.10	43.33	
29	*m*-OCH_3	$-NH(CH_2)_2-N(C_2H_5)_2$	–	119–120	45	$C_{22}H_{29}N_5O_2$	8.49 ± 0.11	49.50	
30	*p*-OCH_3	$-NH(CH_2)_2-N(C_2H_5)_2$	–	145–147	56	$C_{22}H_{29}N_5O_2$	9.04 ± 0.16	46.63	**(2.8)(10.5)**
31	*p*-F	$-NH(CH_2)_2-N(C_2H_5)_2$	–	118–121	76	$C_{22}H_{26}FN_5O$	9.67 ± 0.45	50.39	**2.5(11.5)**
32	*m*-Cl	$-NH(CH_2)_2-N(C_2H_5)_2$	–	112–115	65	$C_{21}H_{26}ClN_5O$	8.71 ± 0.25	41.39	
33	*p*-Cl	$-NH(CH_2)_2-N(C_2H_5)_2$	–	122–125	54	$C_{21}H_{26}ClN_5O$	9.41 ± 0.26	50.39	**2.6(12.1)**
34	*p*-Br	$-NH(CH_2)_2-N(C_2H_5)_2$	–	169–170	50	$C_{21}H_{26}BrN_5O$	9.74 ± 0.39	49.05	**2.3(11.8)**

Table II – *continued*

Comp.	R	R_1	X	Melting Point (°C)	% Yield⋆	Molecular formula	H_1-receptor antagonistic activity† $pA_2 \pm$ SEM	Sedative potentia after 120 min⋆⋆	*In vivo* asphysic shock, time in min Control (Test)
35	2,3-$(CH_3)_2$	$-NH(CH_2)_2-N(C_2H_5)_2$	–	111–112	87	$C_{23}H_{31}N_5O$	8.72 ± 0.34	47.50	
36	2,4-$(CH_3)_2$	$-NH(CH_2)_2-N(C_2H_5)_2$	–	124–126	78	$C_{23}H_{31}N_5O$	8.74 ± 0.21	56.39	
37	H	$-NH(CH_2)_3-N(C_2H_5)_2$	–	103–105	67	$C_{22}H_{29}N_5O$	7.69 ± 0.32	42.04	
38	H	$-NH(CH_2)_3-N(C_2H_5)_2$	$-CH_2-$	138–140	54	$C_{23}H_{31}N_5O$	8.25 ± 0.27	37.50	
39	*m*- CH_3	$-NH(CH_2)_3-N(C_2H_5)_2$	–	167–169	68	$C_{23}H_{31}N_5O$	9.44 ± 0.16	36.87	**2.6(11.4)**
40	*p*-CH_3	$-NH(CH_2)_3-N(C_2H_5)_2$	–	136–138	45	$C_{23}H_{31}N_5O$	8.49 ± 0.19	46.26	
41	*m*-OCH_3	$-NH(CH_2)_3-N(C_2H_5)_2$	–	163–165	80	$C_{23}H_{31}N_5O_2$	8.78 ± 0.21	72.76	
42	*p*-OCH_3	$-NH(CH_2)_3-N(C_2H_5)_2$	–	145–147	79	$C_{23}H_{31}N_5O_2$	8.46 ± 0.14	42.51	
43	*p*-F	$-NH(CH_2)_3-N(C_2H_5)_2$	–	142–145	65	$C_{22}H_{28}FN_5O$	9.52 ± 0.27	68.40	**2.4(9.1)**
44	*m*-Cl	$-NH(CH_2)_3-N(C_2H_5)_2$	–	86–89	56	$C_{22}H_{28}ClN_5O$	8.93 ± 0.25	72.79	
45	*p*-Cl	$-NH(CH_2)_3-N(C_2H_5)_2$	–	120–122	49	$C_{22}H_{28}ClN_5O$	9.30 ± 0.16	35.16	**2.6(12.3)**
46	*p*-Br	$-NH(CH_2)_3-N(C_2H_5)_2$	–	145–147	76	$C_{22}H_{28}BrN_5O$	9.75 ± 0.23	37.18	**2.5(12.7)**
47	2,3-$(CH_3)_2$	$-NH(CH_2)_3-N(C_2H_5)_2$	–	133–135	65	$C_{24}H_{33}N_5O$	9.02 ± 0.22	38.14	
48	2,4-$(CH_3)_2$	$-NH(CH_2)_3-N(C_2H_5)_2$	–	149–151	45	$C_{24}H_{33}N_5O$	8.67 ± 0.23	43.01	
Cetirizine#			–				9.40 ± 0.20	34.73	2.6(12.4)

⋆Recrystalization solvent - Ethanol. †H_1 receptor antagonistic activity on isolated guinea pig ileum; n = 3. ⋆⋆Sedative potential – by photoactometer on mice; n = 3. #Under experimental conditions.

Table III. ^{1}H NMR, Mass and IR spectral data of N_1-(substituted)aryl-5,7-dimethyl-2-(substituted) pyrido (2,3-*d*) pyrimidin-4(3H)-ones.

Com. No	R	R_1	X	^{1}HNMR shifts (δ ppm)	Mass(M^+) (m/z)	IR peaks (cm^{-1})
1	H	$-N(CH_3)_2$	–	δ 2.2 (s, 3H, C*H*$_3$ at C-5), δ 3.4 (s, 3H, C*H*$_3$ at C-7), δ 3.9 (s, 6H at N(C*H*$_3$)$_2$), δ 7.3–7.5 (m, 6H; 5H at Ar-*H* & C–*H* at C-6).	295(M + 1), 294(M +), 279, 264	1640(C═O)
2	H	$-N(CH_3)_2$	$-CH_2-$	δ 2.3 (s, 3H, C*H*$_3$ at C-5), δ 2.9 (s, 2H at –C*H*$_2$- Ar), δ 3.2 (s, 3H, C*H*$_3$ at C-7), δ 3.7 (s, 6H at N(C*H*$_3$)$_2$), δ 7.5–7.7 (m, 6H; 5H at Ar-*H* & C–*H* at C-6).	308 (M +), 293, 280	1650 (C═O)
3	*m*-CH_3	$-N(CH_3)_2$	–	δ 2.3 (s, 3H, C*H*$_3$ at C-5), δ 3.1 (s, 3H, C*H*$_3$ at C-7), δ 3.3 (s, 3H at Ar-C*H*$_3$), δ 3.9 (s, 6H at N(C*H*$_3$)$_2$), δ 7.5–7.7(m, 5H; 4H at Ar-*H* &C–*H* at C-6).	308(M +), 293, 264	1650(C═O)
4	*p*-CH_3	$-N(CH_3)_2$	–	δ 2.4 (s, 3H, C*H*$_3$ at C-5), δ 2.5 (s, 3H at Ar-C*H*$_3$), δ 3.3 (s, 3H, C*H*$_3$ at C-7), δ 3.6 (s, 6H at N(C*H*$_3$)$_2$), δ 7.2–7.4 (m, 5H; 4H at Ar-*H* & C–*H* at C-6).	309(M + 1), 308(M +), 293, 280	1640(C═O)
5	*m*-OCH_3	$-N(CH_3)_2$	–	δ 2.4 (s, 3H, C*H*$_3$ at C-5), δ 3.3 (s, 3H, C*H*$_3$ at C-7), δ 3.8 (s, 6H at N(C*H*$_3$)$_2$, δ 3.9 (s, 3H at Ar-OC*H*$_3$), δ 7.1–7.7(m, 5H; 4H at Ar-*H* & C–*H* at C-6).	325(M + 1), 324(M +) 309, 296	1640(C═O)
6	*p*-OCH_3	$-N(CH_3)_2$	–	δ 2.3 (s, 3H, C*H*$_3$ at C-5), δ 3.2 (s, 3H, C*H*$_3$ at C-7), δ 3.5 (s, 6H at N(C*H*$_3$)$_2$), δ 3.7 (s, 3H at Ar-OC*H*$_3$), δ 7.3–7.7 (m, 5H; 4H at Ar-*H* & C–*H* at C-6).	325(M + 1), 324(M +), 309, 280	1660(C═O)
7	*p*-F	$-N(CH_3)_2$	–	δ 2.3 (s, 3H, C*H*$_3$ at C-5), δ 2.8 (s, 3H, C*H*$_3$ at C-7), δ 3.7 (s, 6H at N(C*H*$_3$)$_2$), δ 7.2–7.5 (m, 5H; 4H at Ar-*H* & C–*H* at C-6).	313(M + 1), 312 (M +), 297, 284	1640(C═O)
8	*m*-Cl	$-N(CH_3)_2$	–	δ 2.0 (s, 3H, C*H*$_3$ at C-5), δ 3.1 (s, 3H, C*H*$_3$ at C-7), δ 3.7 (s, 6H at N(C*H*$_3$)$_2$), δ 7.2–7.5 (m, 5H; 4H at Ar-*H* & C–*H* at C-6).	330(M + 2), 328(M +), 313, 300	1660(C═O)
9	*p*-Cl	$-N(CH_3)_2$	–	δ 2.3 (s, 3H, C*H*$_3$ at C-5), δ 3.4 (s, 3H, C*H*$_3$ at C-7), δ 3.6 (s, 6H at N(C*H*$_3$)$_2$), δ 7.1–7.5 (m, 5H; 4H at Ar-*H* & C–*H* at C-6).	330 (M + 2), 328(M +), 313, 284	1640(C═0)
10	*p*-Br	$-N(CH_3)_2$	–	δ 2.3 (s, 3H, C*H*$_3$ at C-5), δ 3.2 (s, 3H, C*H*$_3$ at C-7), δ 3.6 (s, 6H at N(C*H*$_3$)$_2$), δ 7.1–7.5 (m, 5H; 4H at Ar-*H* & C–*H* at C-6).	375(M + 2), 373(M +), 358, 345	1640(C═O)
11	2,3-$(CH_3)_2$	$-N(CH_3)_2$	–	δ 2.3 (s, 3H, C*H*$_3$ at C-5), δ 2.5 (s, 6H at Ar-(C*H*$_3$)$_2$), δ 2.9 (s, 3H, C*H*$_3$ at C-7), δ 3.9 (s, 6H at N(C*H*$_3$)$_2$), δ 7.5–7.7 (m, 4H; 3H at Ar-*H* & C–*H* at C-6).	323(M + 1), 322(M +), 307, 294	1640(C═O)
12	2,3-$(CH_3)_2$	$-N(CH_3)_2$	–	δ 2.3 (s, 3H, C*H*$_3$ at C-5), δ 2.7 (s, 6H at Ar-(C*H*$_3$)$_2$), δ 3.0 (s, 3H, C*H*$_3$ at C-7), δ 3.9 (s, 6H at N(C*H*$_3$)$_2$), δ 7.3 – 7.7 (m, 4H; 3H at Ar-*H* & C–*H* at C-6).	323(M + 1), 322(M +), 307, 278	1640(C═O)
13	H	$-N(C_2H_5)_2$	–	δ 1.9–2.2 (t, 6H, of N-(CH$_2$C*H*$_3$)$_2$, δ 2.4–2.8 (q, 4H, of N-(C*H*$_2$CH$_3$)$_2$, δ 2.9 (s, 3H, C*H*$_3$ at C-5), δ 3.1 (s, 3H, C*H*$_3$ at C-7), δ 7.3–7.5 (m, 6H; 5H at Ar-*H* & C-*H* at C-6).	323 (M + 1), 322(M +), 307, 292	1640 (C═O)
14	H	$-N(C_2H_5)_2$	$-CH_2-$	δ 1.9–2.2 (t, 6H, of N-(CH$_2$C*H*$_3$)$_2$, δ 2.4–2.8 (q, 4H, of N-(C*H*$_2$CH$_3$)$_2$, δ 2.9 (s, 2H, at –C*H*$_2$- Ar), δ 3.1 (s, 3H, C*H*$_3$ at C-5), δ 3.4 (s, 3H, C*H*$_3$ at C-7), δ 7.3–7.5 (m, 6H; 5H at Ar-*H* & C–*H* at C-6).	337(M + 1), 336(M +), 321, 308	1640 (C═0)
15	*m*-CH_3	$-N(C_2H_5)_2$	–	δ 1.8–2.1 (t, 6H, of N-(CH$_2$C*H*$_3$)$_2$, δ 2.3–2.6 (q, 4H, of N–(C*H*$_2$CH$_3$)$_2$, δ 2.8 (s, 3H, C*H*$_3$ at C-5), δ 3.0 (s, 3H at Ar-C*H*$_3$), δ 3.3 (s, 3H, C*H*$_3$ at C-7), δ 7.1–7.4 (m, 5H; 4H at Ar-*H* & C–*H* at C-6).	337(M + 1), 336(M +), 308, 306	1640(C═O)
16	*p*-CH_3	$-N(C_2H_5)_2$	–	δ 1.7–1.9 (t, 6H, of N-(CH$_2$C*H*$_3$)$_2$, δ 2.2–2.5 (q, 4H, of N-(C*H*$_2$CH$_3$)$_2$, δ 2.6 (s, 3H, C*H*$_3$ at C-5), δ 2.9 (s, 3H at Ar-C*H*$_3$), δ 3.3 (s, 3H, C*H*$_3$ at C-7), δ 7.2–7.5 (m, 5H; 4H at Ar-*H* & C–*H* at C-6).	337(M + 1), 336(M +), 321, 308	1640(C═O)
17	*m*-OCH_3	$-N(C_2H_5)_2$	–	δ 1.6–1.9 (t, 6H, of N-(CH$_2$C*H*$_3$)$_2$, δ 2.2–2.5 (q, 4H, of N-(C*H*$_2$CH$_3$)$_2$, δ 2.7 (s, 3H at C*H*$_3$ at C-5), δ 3.1 (s, 3H, C*H*$_3$ at C-7), δ 3.9 (s, 3H at Ar-OC*H*$_3$), δ 7.3–7.5 (m, 5H; 4H at Ar-*H* & C–*H* at C-6).	353(M + 1), 352(M +), 337, 324	1650(C═O)
18	*p*-OCH_3	$-N(C_2H_5)_2$	–	δ 1.7–1.9 (t, 6H, of N-(CH$_2$C*H*$_3$)$_2$, δ 2.1–2.4 (q, 4H, of N-(C*H*$_2$CH$_3$)$_2$, δ 2.6 (s, 3H, C*H*$_3$ at C-5), δ 2.9 (s, 3H, C*H*$_3$ at C-7), δ 3.8 (s, 3H at Ar-OC*H*$_3$), δ 7.2–7.5 (m, 5H; 4H at Ar-*H* & C–*H* at C-6).	353 (M + 1), 352(M +), 337, 324	1640(C═0)
19	*p*-F	$-N(C_2H_5)_2$	–	δ 1.6–1.9 (t, 6H, of N-(CH$_2$C*H*$_3$)$_2$, δ 2.2–2.6 (q, 4H, of N-(C*H*$_2$CH$_3$)$_2$, δ 2.7 (s, 3H, C*H*$_3$ at C-5), δ 3.1 (s, 3H, C*H*$_3$ at C-7), δ 7.1–7.5 (m, 5H; 4H at Ar-*H* & C–*H* at C-6).	341(M + 1), 340(M +), 325, 312	1640 (C═0)

Table III – *continued*

Com. No	R	R_1	X	^{1}HNMR shifts (δ ppm)	Mass(M^+) (m/z)	IR peaks (cm^{-1})
20	*m*-Cl	$-N(C_2H_5)_2$	–	δ 1.6–1.9 (t, 6H, of N-(CH_2CH_3)$_2$, δ 2.2–2.6 (q, 4H, of N-(CH_2CH_3)$_2$, δ 2.8 (s, 3H, CH_3 at C-5), δ 3.2 (s, 3H, CH_3 at C-7), δ 7.3–7.5 (m, 5H; 4H at Ar-*H* & C–*H* at C-6).	358(M + 2), 356(M +), 341, 328	1640 (C=0)
21	*p*-Cl	$-N(C_2H_5)_2$	–	δ 1.6–1.9 (t, 6H, of N-(CH_2CH_3)$_2$, δ 2.1–2.4 (q, 4H, of N-(CH_2CH_3)$_2$, δ 2.6 (s, 3H, CH_3 at C-5), δ 3.2 (s, 3H, CH_3 at C-7), δ 7.2–7.6 (m, 5H; 4H at Ar-*H* & C–*H* at C-6).	358(M + 2), 356(M +), 341, 328	1660 (C=0)
22	*p*-Br	$-N(C_2H_5)_2$	–	δ 1.6–1.9 (t, 6H, of N-(CH_2CH_3)$_2$, δ 2.1–2.5 (q, 4H, of N-(CH_2CH_3)$_2$, δ 2.7 (s, 3H, CH_3 at C-5), δ 3.2 (s, 3H, CH_3 at C-7), δ 7.2–7.6 (m, 5H; 4H at Ar-*H* & C–*H* at C-6).	403(M + 2), 401(M +), 386, 373	1650(C=O)
23	2,3-$(CH_3)_2$	$-N(C_2H_5)_2$	–	δ 1.6–1.9 (t, 6H, of N-(CH_2CH_3)$_2$, δ 2.1–2.5 (q, 4H, of N-(CH_2CH_3)$_2$, δ 2.6 (s, 3H, CH_3 at C-5), δ 2.8 (s, 6H at Ar-(CH_3)$_2$), δ 3.1 (s, 3H, CH_3 at C-7), δ 7.3–7.5 (m, 4H; 3H at Ar-*H* & C–*H* at C-6).	351(M + 1), 350(M +), 335, 322	1640(C=O)
24	2,4-$(CH_3)_2$	$-N(C_2H_5)_2$	–	δ 1.5–1.9 (t, 6H, of N-(CH_2CH_3)$_2$, δ 2.1–2.4 (q, 4H, of N-(CH_2CH_3)$_2$, δ 2.7 (s, 3H, CH_3 at C-5), δ 2.9 (s, 6H at Ar-(CH_3)$_2$), δ 3.1 (s, 3H, CH_3 at C-7), δ 7.2–7.4 (m, 4H; 3H at Ar-*H* & C–*H* at C-6).	351(M + 1), 350(M +), 335, 322	1660(C=O)
25	H	$-NH(CH_2)_2$ $-N(C_2H_5)_2$	–	δ 1.5–2.1 (m, 4H, –(CH_2)$_2$), δ 2.4–2.66 (m, 10H, of N-(C_2H_5)$_2$ & 3H, CH_3 at C-5), δ 3.5 (s, 3H, CH_3 at C-7), δ 5.4 (s, 1H at –N*H*, D_2O exchangeable), δ 7.3–7.7 (m, 6H; 5H at Ar-*H* & C–*H* at C-6)	366(M + 1), 365(M +), 350, 337, 293, 250	3400(–NH) 1640(C=O)
26	H	$-NH(CH_2)_2$ $-N(C_2H_5)_2$	$-CH_2-$	δ 1.6–2.1 (m, 4H, –(CH_2)$_2$), δ 2.2–2.3 (m, 10H, of N-(C_2H_5)$_2$, δ 2.4 (s, 3H, CH_3 at C-5), δ 2.9 (s, 2H - at –CH_2-Ar), δ 3.5 (s, 3H, CH_3 at C-7), δ 5.3 (s, 1H at –N*H*, D_2O exchangeable), δ 7.3–7.5 (m, 6H; 5H at Ar-*H* & C–*H* at C-6).	380(M + 1), 379(M +), 364, 349	3452(–NH), 1650(C=O)
27	*m*-CH_3	$-NH(CH_2)_2$ $-N(C_2H_5)_2$	–	δ 1.7–2.0 (m, 4H, –(CH_2)$_2$), δ 2.2–2.5 (m, 10H, of N-(C_2H_5)$_2$ & 3H, CH_3 at C-5), δ 2.6 (s, 3H at Ar-CH_3), δ 3.5 (s, 3H, CH_3 at C-7), δ 5.3 (s, 1H at –N*H*, D_2O exchangeable), δ 7.3–7.6 (m, 6H; 5H at Ar-*H* & C–*H* at C-6).	380(M + 1), 379(M +), 364, 294	3456(–NH), 1650(C=O)
28	*p*-CH_3	$-NH(CH_2)_2$ $-N(C_2H_5)_2$	–	δ 1.5–1.9 (m, 4H, –(CH_2)$_2$), δ 2.1–2.3 (m, 10H, of N-(C_2H_5)$_2$, δ 2.4 (s,3H, CH_3 at C-5), δ 2.7 (s, 3H at Ar-CH_3), δ 3.1 (s, 3H, CH_3 at C-7), δ 5.6 (s, 1H at –N*H*, D_2O exchangeable), δ 7.3–7.7 (m, 6H; 5H at Ar-*H* & C–*H* at C-6).	379(M +), 364, 351	3452(NH), 1640(C=O)
29	*m*-OCH_3	$-NH(CH_2)_2$ $-N(C_2H_5)_2$	–	δ 1.6–2.0 (m, 4H, –(CH_2)$_2$), δ 2.1–2.4 (m, 10H, of N-(C_2H_5)$_2$, δ 2.5 (s, 3H, CH_3 at C-5), δ 3.0 (s, 3H, CH_3 at C-7), δ 3.8 (s, 3H at Ar-OCH_3), δ 5.5 (s, 1H at –N*H*, D_2O exchangeable), δ 7.3–7.7 (m, 6H; 5H at Ar-*H* & C–*H* at C-6).	396(M + 1), 395(M +), 360, 367	3452(NH), 1660(C=O)
30	*p*-OCH_3	$-NH(CH_2)_2$ – $N(C_2H_5)_2$	–	δ 1.5–1.9 (m, 4H, –(CH_2)$_2$), δ 2.0–2.3 (m, 10H, of N-(C_2H_5)$_2$, δ 2.5 (s, 3H, CH_3 at C-5), δ 3.0 (s, 3H, CH_3 at C-7), δ 3.9 (s, 3H at Ar-OCH_3), δ 5.4 (s, 1H at –N*H*, D_2O exchangeable), δ 7.3–7.7 (m, 6H; 5H at Ar-*H* & C–*H* at C-6).	396(M + 1), 395(M +), 380, 367	3460(–NH), 1650(C=O)
31	*p*-F	$-NH(CH_2)_2$ $-N(C_2H_5)_2$	–	δ 1.5–1.9 (m, 4H, –(CH_2)$_2$), δ 2.2–2.4 (m, 10H, of N-(C_2H_5)$_2$ & 3H, CH_3 at C-5), δ 3.5 (s, 3H, CH_3 at C–7), δ 5.3 (s, 1H at –N*H*, D_2O exchangeable), δ 7.3–7.6 (m, 6H; 5H at Ar-*H* & C–*H* at C-6).	384(M + 1), 383(M +), 368, 355	3300(–NH), 1650(C=O)
32	*m*-Cl	$-NH(CH_2)_2$ $-N(C_2H_5)_2$	–	δ 1.5–2.1 (m, 4H, –(CH_2)$_2$), δ 2.4–2.6 (m, 10H, of N-(C_2H_5)$_2$ & 3H, CH_3 at C-5), δ 3.5 (s, 3H, CH_3 at C-7), δ 5.4 (s, 1H at –N*H*, D_2O exchangeable), δ 7.3–7.7 (m, 6H; 5H at Ar-*H* & C–*H* at C-6).	401(M + 2), 399(M +), 384, 369	3300(–NH), 1640(C=O)
33	*p*-Cl	$-NH(CH_2)_2$ $-N(C_2H_5)_2$	–	δ 1.5–1.9 (m, 4H, –(CH_2)$_2$), δ 2.3–2.7 (m, 10H, of N-(C_2H_5)$_2$ & 3H, CH_3 at C-5), δ 3.6 (s, 3H, CH_3 at C-7), δ 5.5 (s, 1H at –N*H*, D_2O exchangeable), δ 7.3–7.8 (m, 6H; 5H at Ar-*H* & C–*H* at C-6).	401(M + 2), 399(M +), 384, 369	3452(–NH), 1640(C=O)
34	*p*-Br	$-NH(CH_2)_2$ $-N(C_2H_5)_2$	–	δ 1.6–1.9 (m, 4H, –(CH_2)$_2$), δ 2.1–2.3 (m, 10H, of N-(C_2H_5)$_2$, δ 2.5 (s, 3H, CH_3 at C-5), δ 3.3 (s, 3H, CH_3 at C-7), δ 5.4 (s, 1H at –N*H*, D_2O exchangeable), δ 7.3–7.7 (m, 6H; 5H at Ar-*H* & C–*H* at C-6).	446(M + 2), 444(M +), 429, 416, 414	3460(–NH), 1640(C=O)

Table III – *continued*

Com. No	R	R_1	X	^{1}HNMR shifts (δ ppm)	Mass(M^+) (m/z)	IR peaks (cm^{-1})
35	2,3-$(CH_3)_2$	$-NH(CH_2)_2$ $-N(C_2H_5)_2$	–	δ 1.5–1.9 (m, 4H, $-(CH_2)_2$), δ 2.1–2.3 (m, 10H, of N-$(C_2H_5)_2$, δ 2.4 (s, 3H, CH_3 at C-5), δ 3.2 (s, 6H at Ar-$(CH_3)_2$), δ 3.6 (s, 3H, CH_3 at C-7), δ 5.6 (s, 1H at –NH, D_2O exchangeable), δ 7.3–7.6 (m, 6H; 5H at Ar-H & C–H at C-6).	394(M + 1), 393(M +), 378, 365	3400(–NH), 1660(C═O)
36	2,4-$(CH_3)_2$	$-NH(CH_2)_2$ $-N(C_2H_5)_2$	–	δ 1.5–2.0 (m, 4H, $-(CH_2)_2$), δ 2.2–2.5 (m, 10H, of N-$(C_2H_5)_2$ & 3H, CH_3 at C-5), δ 3.2 (s, 6H at Ar-$(CH_3)_2$), δ 3.4 (s, 3H, CH_3 at C-7), δ 5.3 (s, 1H at –NH, D_2O exchangeable), δ 7.3–7.7 (m, 6H; 5H at Ar-H & C–H at C-6).	394(M + 1), 393(M +), 365, 298	3400(–NH), 1640(C═O)
37	H	$-NH(CH_2)_3$ $-N(C_2H_5)_2$	–	δ 1.5–2.1 (m, 6H at $-(CH_2)_3$), δ 2.3–2.6 (m, 10H, of N-$(C_2H_5)_2$, δ 2.9 (s, 3H,CH_3 at C-5), δ 3.4 (s, 3H, CH_3 at C-7), δ 5.73 (t, 1H, –NH, D_2O exchangeable), δ 7.1–7.5 (m, 6H; 5H at Ar-H & C–H at C-6).	379(M +), 364, 351	3452(–NH) 1640(C═O)
38	H	$-NH(CH_2)_3$ $-N(C_2H_5)_2$	$-CH_2-$	δ 1.5–1.9 (m, 6H at $-(CH_2)_3$), δ 2.0–2.3 (m, 10H, of N-$(C_2H_5)_2$, δ 2.5 (s, 3H, CH_3 at C-5), δ 2.7 (s, 3H at $-CH_2$-Ar), δ 3.3 (s, 3H, CH_3 at C-7), δ 5.73 (s, 1H, –NH, D_2O exchangeable), δ 7.1–7.4 (m, 6H; 5H at Ar-H & C–H at C-6).	394(M + 1), 393(M +), 378, 365	3300(–NH), 1640(C═O)
39	*m*-CH_3	$-NH(CH_2)_3$ $-N(C_2H_5)_2$	–	δ 1.7–2.2 (m, 6H at -$(CH_2)_3$), δ 2.3–2.6 (m, 10H, of N-$(C_2H_5)_2$, δ 2.7 (s, 3H,CH_3 at C-5), δ 3.1(s, 3H at Ar—CH_3), δ 3.4 (s, 3H, CH_3 at C-7), δ 5.3 (s, 1H, –NH, D_2O exchangeable), δ 7.3–7.7 (m, 5H; 4H at Ar-H & C–H at C-6).	394(M + 1), 393(M +), 378, 294	3300(–NH), 1640(C═O)
40	*p*-CH_3	$-NH(CH_2)_3$ $-N(C_2H_5)_2$	–	δ 1.5–2.0 (m, 6H at -$(CH_2)_3$), δ 2.2–2.5 (m, 10H, of N-$(C_2H_5)_2$, δ 2.6 (s, 3H, CH_3 at C-5), δ 3.2 (s, 3H at Ar—CH_3), δ 3.5 (s, 3H, CH_3 at C-7), δ 5.4 (s, 1H, –NH, D_2O exchangeable), δ 7.1–7.6 (m, 5H; 4H at Ar-H & C–H at C-6).	394(M + 1), 393(M +), 363, 294	3460(–NH), 1650(C═O)
41	*m*-OCH_3	$-NH(CH_2)_3$ $N(C_2H_5)_2$	–	δ 1.5–2.2 (m, 6H at -$(CH_2)_3$), δ 2.3–2.5 (m, 10H, of N-$(C_2H_5)_2$, δ 2.7 (s, 3H, CH_3 at C-5), δ 3.2 (s, 3H, CH_3 at C-7), δ 3.9 (s, 3H at Ar—OCH_3), δ 5.73 (s, 1H, –NH, D_2O exchangeable), δ 7.3–7.5 (m, 5H; 4H at Ar-H & C–H at C-6).	410(M + 1), 409(M +), 394, 381	3400(–NH), 1660(C═O)
42	*p*-OCH_3	$-NH(CH_2)_3$ $-N(C_2H_5)_2$	–	δ 1.6–2.0 (m, 6H at -$(CH_2)_3$), δ 2.2–2.5 (m, 10H, of N-$(C_2H_5)_2$, δ 2.7 (s, 3H, CH_3 at C-5), δ 3.1 (s, 3H, CH_3 at C-7), δ 3.7 (s, 3H at Ar—OCH_3), δ 5.5 (s, 1H, –NH, D_2O exchangeable), δ 7.2–7.5 (m, 5H; 4H at Ar-H & C–H at C-6).	410(M + 1), 409(M +), 394, 381	3460(–NH), 1650(C═O)
43	*p*-F	$-NH(CH_2)_3$ $-N(C_2H_5)_2$	–	δ 1.7–2.0 (m, 6H at -$(CH_2)_3$), δ 2.2–2.6 (m, 10H, of N-$(C_2H_5)_2$, δ 2.7 (s, 3H, CH_3 at C-5), δ 3.1 (s, 3H, CH_3 at C-7), δ 5.7 (s, 1H, –NH, D_2O exchangeable), δ 7.2–7.6 (m, 5H; 4H at Ar-H & C–H at C-6).	398(M + 1), 397(M +), 382,369	3452(–NH), 1650(C═0)
44	*m*-Cl	$-NH(CH_2)_3$ $-N(C_2H_5)_2$	–	δ 1.5–1.9 (m, 6H at -$(CH_2)_3$), δ 2.1–2.4 (m, 10H, of N-$(C_2H_5)_2$, δ 2.6 (s, 3H, CH_3 at C-5), δ 3.1 (s, 3H, CH_3 at C-7), δ 5.73 (s, 1H, –NH, D_2O exchangeable), δ 7.1–7.5 (m, 5H; 4H at Ar-H & C–H at C-6).	415(M + 2), 413(M +), 398, 385	3400(–NH) 1640(C═O)
45	*p*-Cl	$-NH(CH_2)_3$ $-N(C_2H_5)_2$	–	δ 1.5–1.8 (m, 6H at -$(CH_2)_3$), δ 2.0–2.4 (m, 10H, of N-$(C_2H_5)_2$, δ 2.6 (s, 3H, CH_3 at C-5), δ 3.3 (s, 3H, CH_3 at C-7), δ 5.5 (s, 1H, –NH, D_2O exchangeable), δ 7.4–7.7 (m, 5H; 4H at Ar-H & C–H at C-6).	415(M + 2), 413(M +), 385, 314	3400(–NH), 1640(C═O)
46	*p*-Br	$-NH(CH_2)_3$ $-N(C_2H_5)_2$	–	δ 1.5–2.0 (m, 6H at -$(CH_2)_3$), δ 2.1–2.3 (m, 10H, of N-$(C_2H_5)_2$, δ 2.5 (s, 3H, CH_3 at C-5), δ 3.1 (s, 3H, CH_3 at C-7), δ 5.6 (s, 1H, –NH, D_2O exchangeable), δ 7.3–7.5 (m, 5H; 4H at Ar-H & C–H at C-6).	460(M + 1), 458(M +), 445, 432	3300(–NH), 1640(C═O)
47	2,3-di(CH_3)	$-NH(CH_2)_3$ $-N(C_2H_5)_2$	–	δ 1.5–1.9 (m, 6H at -$(CH_2)_3$), δ 2.1–2.4 (m, 10H, of N-$(C_2H_5)_2$, δ 2.6 (s, 3H, CH_3 at C-5), δ 3.1(s, 6H at Ar—di (CH_3)), δ 3.5 (s, 3H, CH_3 at C-7), δ 5.73 (s, 1H, –NH, D_2O exchangeable), δ 7.3–7.6 (m, 4H; 3H at Ar-H & C–H at C-6).	408(M + 1), 407(M +), 392, 379	3452(–NH), 1660(C═O)
48	2,4-di(CH_3)	$-NH(CH_2)_3$ $-N(C_2H_5)_2$	–	δ 1.5–2.0 (m, 6H at -$(CH_2)_3$), δ 2.2–2.4 (m, 10H, of N-$(C_2H_5)_2$, δ 2.5 (s, 3H, CH_3 at C-5), δ 3.2 (s, 6H , at Ar—di(CH_3)), δ 3.4 (s, 3H, CH_3 at C-7), δ 5.6 (s, 1H, –NH, D_2O exchangeable), δ 7.2–7.5 (m, 4H; 3H at Ar-H & C–H at C-6).	408(M + 1), 407(M +), 379, 308	3300(–NH), 1640(C═O)

Graphs of log dose of the antagonist *vs* percent inhibition were plotted and EC_{50} values were calculated and pA_2 values were determined [19]. The results are shown in Table II.

In vivo *antihistaminic activity: Protection of animal from asphyxic shock*. *In vivo* antihistaminic activity of test compounds was screened by protection of animal from asphyxic shock. Guinea pigs of either sex were divided into groups of 5 and were fasted for 24 h before the experiment. Animals were subjected to a nebula spray of histamine solution (0.5% aqueous solution of histamine hydrochloride). The time required for the induction of an observable asphyxic shock was recorded as the blank reading. Each individual groups of animals was treated orally with various doses of the lead compounds on the next day of the experiment and subjected to the histamine nebula spray in the same way. The time required to induce the observable asphyxia was noted and the percentage increase in the time required to induce asphyxia was calculated and is reported as % protection [20] (Table II).

Sedative potential. Sedation is considered to be main side effect of by H_1-receptor antagonists, so, the sedative potential of the most potent compounds was evaluated. Mice (wt, 20–25 g) were divided into 5 groups of 3 each. The first group was kept as a control group, a second group received vehicle, and the third, fourth and fifth group received the test compound (i.p.) at a dose of 1 mg/kg. Each group of animals were separately placed in the photoactometer and the number of cut offs were recorded for 10 min, at an interval of 30 min, until the maximum effect of the drug was recorded [20] (Table II).

Anticholinergic activity. First generation antihistamines are reported to have an anticholinergic activity, so the anticholinergic activity of the compounds was tested *in vitro* by inhibition of the contraction of an isolated rat ileum induced by acetylcholine [18].

Results and discussion

Chemistry

The syntheses of the title N_1-(substituted)aryl-5,7-dimethyl-2-(substituted)pyrido(2,3-*d*)pyrimidine-4(3H)-ones (**1–48**) derivatives were accomplished in accordance with the scheme in Figure 4.

^{1}HNMR spectra of all the compounds were studied in $CDCl_3$ or DMSO-D_6. Some of the common characteristic peaks were observed in all the spectras; singlets in the region of δ 2.1–2.9 and δ 3.2–3.6 (three protons each) were observed due to the methyl groups at C-5 and C-7 respectively, methylene protons of various amines at the C-2 position were observed as multiplets, multiplets corresponding to five aryl protons and one proton at C-6 were observed in the region δ 7.0–7.6. The N*H* proton of N,N-diethylethlenediamine and diethylpropylenediamine series was found to be D_2O exchangeable and was observed at δ 5.40–5.73.

The N_1-(substituted)aryl-5,7-dimethyl-2-(substituted)pyrido(2,3-*d)*pyrimidin-4(3H)-ones exhibited certain well distinguished characteristic bands in the IR spectra; a sharp peak in the range of 1680–1640 cm^{-1} indicating the presence of the C-4 carbonyl group, multiple peaks of –CH stretching for CH_2 of the diethylethylenediamine and diethylpropylenediamine between 2900–2800 cm^{-1}, and Compounds of these two series exhibited one sharp peak in the range of 3200–3500 cm^{-1} (N–H stretching). An intense molecular ion peak was observed in the mass spectra of the compounds and compounds with aryl halides (Cl and Br) showed prominent M + 2 peaks.

^{1}H NMR, Mass, IR spectral data and elemental analysis data for individual compounds is given in Tables III, IV.

Pharmacological screening

In vitro *H_1-receptor antagonistic activity*. All the compounds were screened for histamine H_1-receptor antagonistic activity *in vitro* by inhibition of the histamine induced contraction of isolated guinea pig ileum. Cetirizine was used as a standard drug. All the test compounds exhibited significant and reversible H_1-receptor antagonistic activity with pA_2 value ranging from 7.30–9.75 (Table II). Compounds **34** and **46** were found to be the most potent, with pA_2 values of 9.74 and 9.75 respectively, which were higher than that for the standard drug cetirizine (pA_2 = 9.40).

In vivo *antihistaminic activity: Protection of animal from asphyxic shock*. The compounds that exhibited potent antihistaminic activity *in vitro* showed the most potent activity *in vivo* (Table II).

Sedative potential. All the compounds were screened for sedative potential on mice using a photoactometer at a dose level of 1 mg/kg i.p. and exhibited comparable sedation to that of the standard drug cetirizine. The most potent compound, **46,** had a sedative potential (37%) which was found comparable to that of cetirizine (34%) (Table II).

Anticholinergic activity. Anticholinergic activity of all the compounds was tested *in vitro* by their inhibition of acetylcholine-induced contraction. All were devoid of anticholinergic activity.

Table IV. Elemental analysis of N_1-(substituted) aryl-5,7-dimethyl-2-(substituted) pyrido (2,3-*d*) pyrimidin-4(3H)-ones.

Comp No.	R	R_1	X	%C		%H		%N	
				Calc.	Found	Calc.	Found	Calc.	Found
1	H	$-N(CH_3)_2$	–	69.37	69.51	6.15	6.23	19.03	19.23
2	H	$-N(CH_3)_2$	$-CH_2-$	70.11	70.20	6.53	6.66	18.16	18.46
3	*m*-CH_3	$-N(CH_3)_2$	–	70.11	70.19	6.53	6.58	18.16	18.36
4	*p*-CH_3	$-N(CH_3)_2$	–	70.11	70.25	6.53	6.67	18.16	18.40
5	*m*-OCH_3	$-N(CH_3)_2$	–	66.65	66.50	6.20	6.44	17.27	17.59
6	*p*-OCH_3	$-N(CH_3)_2$	–	66.65	66.71	6.20	6.29	17.27	17.31
7	*p*-F	$-N(CH_3)_2$	–	65.37	65.49	5.48	5.41	17.93	17.79
8	*m*-Cl	$-N(CH_3)_2$	–	62.10	62.34	5.20	5.33	17.04	17.15
9	*p*-Cl	$-N(CH_3)_2$	–	62.10	62.21	5.20	5.28	17.04	17.19
10	*p*-Br	$-N(CH_3)_2$	–	54.70	54.66	4.58	4.34	15.01	15.10
11	2,3-$(CH_3)_2$	$-N(CH_3)_2$	–	70.78	70.59	6.87	6.79	17.37	17.51
12	2,4-$(CH_3)_2$	$-N(CH_3)_2$	–	70.78	70.87	6.87	6.73	17.37	17.40
13	H	$-N(C_2H_5)_2$	–	70.78	70.80	6.87	6.75	19.16	19.36
14	H	$-N(C_2H_5)_2$	$-CH_2-$	71.40	71.63	7.18	7.38	16.65	16.50
15	*m*-CH_3	$-N(C_2H_5)_2$	–	71.40	71.56	7.18	7.40	16.65	16.70
16	*p*-CH_3	$-N(C_2H_5)_2$	–	71.40	71.50	7.18	7.37	16.65	16.73
17	*m*-OCH_3	$-N(C_2H_5)_2$	–	68.16	68.22	6.85	6.81	15.89	15.90
18	*p*-OCH_3	$-N(C_2H_5)_2$	–	68.16	68.19	6.85	6.87	15.89	15.93
19	*p*-F	$-N(C_2H_5)_2$	–	67.04	67.21	6.21	6.23	16.46	16.61
20	*m*-Cl	$-N(C_2H_5)_2$	–	63.95	63.79	5.92	5.85	15.77	15.54
21	*p*-Cl	$-N(C_2H_5)_2$	–	63.95	63.56	5.92	5.88	15.77	15.59
22	*p*-Br	$-N(C_2H_5)_2$	–	56.86	56.75	5.26	5.30	13.96	13.84
23	2,3-$(CH_3)_2$	$-N(C_2H_5)_2$	–	71.97	71.98	7.47	7.47	15.98	15.97
24	2,4-$(CH_3)_2$	$-N(C_2H_5)_2$	–	71.97	71.49	7.47	7.47	15.98	15.95
25	H	$-NH(CH_2)_2-N(C_2H_5)_2$	–	69.01	69.25	7.43	7.52	19.16	19.31
26	H	$-NH(CH_2)_2-N(C_2H_5)_2$	$-CH_2-$	69.63	69.59	7.69	7.45	18.45	18.59
27	*m*-CH_3	$-NH(CH_2)_2-N(C_2H_5)_2$	–	69.63	69.73	7.69	7.49	18.45	18.59
28	*p*-CH_3	$-NH(CH_2)_2-N(C_2H_5)_2$	–	69.63	69.78	7.69	7.51	18.45	18.42
29	*m*-OCH_3	$-NH(CH_2)_2-N(C_2H_5)_2$	–	66.81	66.88	7.38	7.36	17.70	17.73
30	*p*-OCH_3	$-NH(CH_2)_2-N(C_2H_5)_2$	–	66.81	66.71	7.38	7.61	17.70	17.62
31	*p*-F	$-NH(CH_2)_2-N(C_2H_5)_2$	–	65.78	65.85	6.82	6.87	18.26	18.37
32	*m*-Cl	$-NH(CH_2)_2-N(C_2H_5)_2$	–	63.07	63.25	6.54	6.60	17.51	17.47
33	*p*-Cl	$-NH(CH_2)_2-N(C_2H_5)_2$	–	63.07	63.17	6.54	6.52	17.51	17.53
34	*p*-Br	$-NH(CH_2)_2-N(C_2H_5)_2$	–	56.76	56.83	5.89	5.93	15.76	15.82
35	2,3-$(CH_3)_2$	$-NH(CH_2)_2-N(C_2H_5)_2$	–	70.20	70.34	7.93	7.90	17.79	17.56
36	2,4-$(CH_3)_2$	$-NH(CH_2)_2-N(C_2H_5)_2$	–	70.20	70.59	7.93	7.60	17.79	17.59
37	H	$-NH(CH_2)_3-N(C_2H_5)_2$	–	69.63	69.78	7.69	7.56	18.45	18.50
38	H	$-NH(CH_2)_3-N(C_2H_5)_2$	$-CH_2-$	70.20	70.34	7.93	7.61	17.79	17.59
39	*m*-CH_3	$-NH(CH_2)_3-N(C_2H_5)_2$	–	70.20	70.44	7.93	7.68	17.79	17.39
40	*p*-CH_3	$-NH(CH_2)_3-N(C_2H_5)_2$	–	70.20	70.35	7.93	7.67	17.79	17.42
41	*m*-OCH_3	$-NH(CH_2)_3-N(C_2H_5)_2$	–	67.46	67.56	7.62	7.59	17.10	17.12
42	*p*-OCH_3	$-NH(CH_2)_3-N(C_2H_5)_2$	–	67.46	67.54	7.62	7.67	17.10	17.20
43	*p*-F	$-NH(CH_2)_3-N(C_2H_5)_2$	–	66.48	66.53	7.09	7.20	17.62	17.61
44	*m*-Cl	$-NH(CH_2)_3-N(C_2H_5)_2$	–	63.83	63.85	6.81	6.61	16.91	16.60
45	*p*-Cl	$-NH(CH_2)_3-N(C_2H_5)_2$	–	63.83	63.85	6.81	6.71	16.91	16.60
46	*p*-Br	$-NH(CH_2)_3-N(C_2H_5)_2$	–	57.64	57.46	6.15	6.35	15.27	15.10
47	2,3-$(CH_3)_2$	$-NH(CH_2)_3-N(C_2H_5)_2$	–	70.73	70.81	8.15	8.18	17.18	17.24
48	2,4-$(CH_3)_2$	$-NH(CH_2)_3-N(C_2H_5)_2$	–	70.73	70.84	8.15	8.32	17.18	17.24

Discussion

Of all the compounds screened for H_1-receptor antagonist activity, **26**, **31**, **33**, **34**, **39**, **43**, **46** were found more potent than the standard drug cetirizine (see Table II).

Most of the classical antihistamines show an anticholinergic effect, while the relatively chemically diverse second generation of antihistamines are devoid of it. Anticholinergic properties of antihistamines are mainly due to the pharmacophoric similarity between these two receptor ligands - both require a lipophilic tail and a protonable nitrogen at a distance of 5–7Å. It has been suggested that the quaternization of the ubiquitous alkylamino group generally increases the anticholinergic property because the structure bears more resemblance to acetylcholine and the acetylcholine antagonist benzilylcholine [21]. Our designed molecule (compounds **1–48**) was devoid of a quaternizable nitrogen and structural resemblance to the acetylcholine antagonist benzilylcholine so were found to be devoid of anticholinergic activity.

The N,N-diethylenediamino and N,N-diethylpropylenediamino substituted compounds was found less sedative than the N,N-dimethylamino and N,N-diethylamino substituted compounds (Table II).

The SAR study shows that the compounds in the series that exhibit potent antihistaminic activity *in vitro* shows the most potent activity *in vivo* (Table II). High potency was achieved when substituents at aryl ring were bromo, chloro (halogen) atoms, and the methoxyl analogue was moderately active than methyl substituent, indicating that halogen and a bulky liphophilic group was an optimal substituent. Groups at the para- or meta-position of the N-1 aryl ring had enhanced potency, especially for compounds with polar substituents or terminal moieties capable of protonation at physiological pH at the C-2 position unsubstituted N-1 aryl ring compounds were found less potent and more sedative. Insertion of an additional methylene spacer at the N-1 position did not influence antihistaminic potency or sedative potential. N,N-diethylenediamino and N,N-diethylpropylenediamino substituted compounds was found more potent than the N,N-dimethylamino and N,N-diethylamino substituted compounds.

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