

## Synthesis and bronchodilatory activity of new 4-aryl-3,5-bis(2-chlorophenyl)-carbamoyl-2,6-dimethyl-1,4-dihydropyridines & their 1-substituted analogues<sup>#</sup>

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Thirty five different 4-aryl-1-substituted 2,6-dimethyl-3, 5-bis-N-[(substituted) carbamoyl] 1,4-dihydropyridines have been prepared from a three component condensation reaction of N-(2-chlorophenyl)-acetoacetamide; an aromatic aldehyde and a primary amine under four different experimental conditions. Except for conventional, all the experimental conditions are simple, eco-friendly, economical, and the reactions are rapid and high yielding. All the compounds have been purified and characterized by their spectral and elemental analysis data. The methods employed have been compared in terms of yields, cost and simplicity. All the compounds have been tested for their acute toxicity, gross behavioural studies and screened for their bronchodilatory activity by standard methods.

**Keywords:** N-(2-Chlorophenyl)acetoacetamide, 1,4-dihydropyridine, potassium *tert*-butoxide, trimethyl silyl iodide, 1-*n*-butyl-3-methylimidazolium tetrafluoroborate, bronchodilatory activity.

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The interest in 1,4-dihydropyridines is ever-growing due to their varied biological, pharmacological and medicinal applications. The DHP-frame-work is one among the most prolific chemo-types found in the computational analysis of the comprehensive medicinal chemistry database. The DHPs have established themselves as one of the most potent Ca<sup>+2</sup> channel blockers and have formed a distinct class of drugs for the treatment of several cardio-vascular diseases including angina pectoris and hypertension<sup>1</sup>. Interestingly, this heterocyclic system has been found to be the structural feature of several bio-active compounds known for vasodilatory, bronchodilatory, smooth muscle contraction inhibitors, antidiabetic, antitumor, genoprotective and hepato-protective properties<sup>2</sup>. Further studies have revealed them also to exhibit neuroprotectant, platelet antiaggregatory, cerebral antiischemic activities besides acting as a chemosensitizer in tumor therapy<sup>3</sup>. Thus 1,4-DHP derivatives demonstrate a remarkable potential as a source for novel drugs.

The classical methods involve the Hantzsch and modified Hantzsch procedure, which are long run reactions resulting finally in poor yields. But the interesting applications of DHPs lead to the development of novel synthetic strategies that have witnessed in a drastic reduction of reaction times and a phenomenal increase in percentage yield. Microwave irradiation technique has proved to be quite useful for the synthesis of DHPs<sup>4</sup>.

Recent literature reveals a few more simple, eco-friendly and cost-effective methods such as solvent-free solid supported microwave technique<sup>5</sup>, using the ionic-liquid<sup>6</sup> as catalyst and reaction medium, and the iodotrimethyl silane-mediated methods<sup>7</sup>. The microwave method has witnessed a further improvement with the use of an aqueous hydrotrope solution as a safer reaction medium<sup>8</sup>. A convenient Hantzsch synthesis of DHPs also been reported using tetraethyl orthosilicate<sup>9</sup>.

A close observation of DHPs' literature indicated clearly the extensive work reported on DHP esters, probably due to the proto-type Nifedipine. And one comes across only a couple of reports on N-substituted carbamoyl DHP derivatives<sup>10</sup>, inspite of the fact that they too exhibit interesting biological and

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pharmacological properties. Therefore, in continuation of the studies on N-substituted carbamoyl DHPs<sup>11,12</sup> it has been considered interesting to extend the recently developed synthetic techniques to DHP carbamoyl derivatives for their synthesis, in analogy and to evaluate them for possible biological and pharmacological properties. As a step in this direction, the synthesis of 4-aryl-1-substituted 3,5-bis-[N-(2-chlorophenyl)carbamoyl]-1,4-dihydropyridines has been chosen.

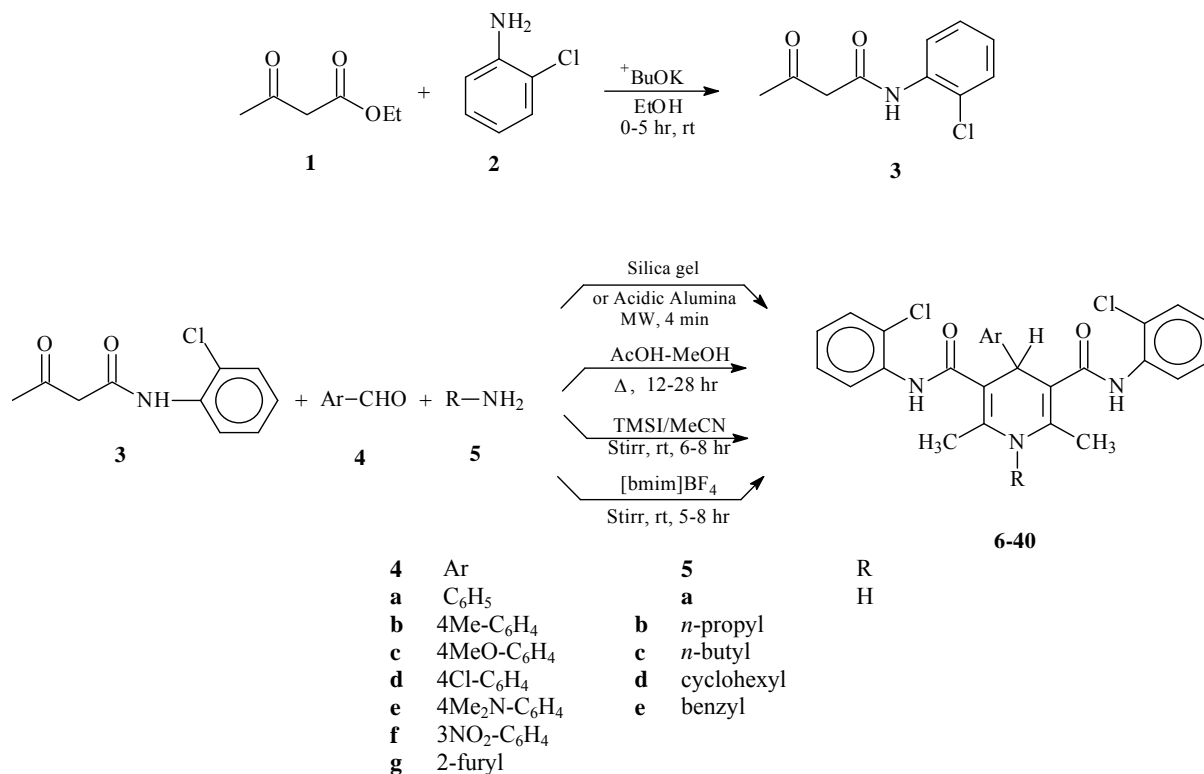
For this purpose, N-(2-chlorophenyl)acetoacetamide<sup>13</sup> **3** has been prepared from the reaction of 2-chloroaniline **2** with ethyl acetoacetate **1** in the presence of potassium tertiary butoxide, as a catalyst. This acetoacetamide **3** has been subjected to a three-component condensation with seven different arylaldehydes **4a-g** viz. benzaldehyde **4a**, 4-methylbenzaldehyde **4b**, 4-methoxybenzaldehyde **4c**, 4-chlorobenzaldehyde **4d**, 4-(N,N-dimethylamino)benzaldehyde **4e**, 3-nitrobenzaldehyde **4f**, and furfural **4g** and against ammonia and four different primary amines **5b-e**: *n*-propylamine, *n*-butyl amine, cyclohexylamine and benzyl amine. Four different experimental techniques, viz; conventional heating, solvent-free, solid supported microwave heating, TMSI-mediated, and using an ionic liquid 1-*n*-butyl-

3-methylimidazolium tetrafluoroborate[bmim]BF<sub>4</sub> (**Scheme I**). The product obtained in each case has been characterized as the respective 4-aryl-1-substituted-3,5-bis[N-(aryl substituted)carbamoyl]-1,4-dihydropyridine **6-40** by their spectral and analytical studies. The synthetic methods have been compared in terms of percentages yield, reaction times and ease of isolation of products.

All the thirty five compounds have been tested for their acute toxicity while observing for gross behavioural changes in experimental animals(mice) by standard method<sup>14</sup> upto an oral dose of 200 mg/kg (bw). Then, these compounds have been evaluated pharmacologically for the possible bronchodilatory or inhibition of bronchoconstriction by a standard method<sup>15,16</sup> using guinea pigs.

## Results and Discussion

**Chemistry.** The percentage yield of N-(2-chlorophenyl)-acetoacetamide **3** has been improved considerably by using the base, potassium *tert*-butoxide. Among the four sets of reaction conditions employed for the three-component cyclocondensation reaction to obtain dihydropyridines, the TMSI-mediated method and the ionic-liquid method have been found to be almost on a par with each other. Both



Scheme I

the methods are useful even for *ortho*-substituted aldehydes and aldehydes with acid sensitive groups with excellent yields in the range of 75-87%. The TMSI-method makes use of acetonitrile as a solvent for reaction where as ionic liquid requires diethyl ether as a solvent for washing and both the methods proceed at ambient temperature with almost the same duration of the reaction time. The other merit happens to be the microwave irradiation method on a solid support of silica gel or acidic alumina. Among these adsorbents, silica gel has been found to be marginally more advantageous than alumina and as expected, all these three alternative methods are many more times superior than the conventional method, in all respects.

**Pharmacology.** All the thirty five bis-N-substituted-1,4-dihydropyridines of the present investigations have been found to be safe even at an oral dose of 1200 mg/kg (bw) and devoid of any gross behavioral effects. Their assay for bronchodilatory activity as studied by the protection against histamine-induced bronchoconstriction on guinea pigs has revealed that at a concentration of 200 µg/mL, some of the compounds could exhibit a moderate to good inhibition in comparison with 100% inhibition of the reference drug chloropheniramine maleate at the same concentration. Compound **23** with a *n*-butyl group at 1-position and 4-chlorophenyl group at 4-position has been shown to be the most potent with 55% amongst the thirty five test compounds, the next being compound **4** with 1-cyclohexyl and 4-phenyl groups, causing 48% inhibition. The next one with closer percentage inhibition (46%) has been compound **34** with 1-cyclohexyl and 4-(3-nitrophenyl) substitution.

The present studies revealed another interesting fact that some of the test compounds are relatively more potent as agonists than antagonists, further a majority of compounds are agonists. Compound **19** with 1-cyclohexyl and 4-(4-methoxyphenyl) substituents has been found to be the most potent agonist with 72% potentiation and the next being the compound **35** with 1-benzyl and 4-(3-nitrophenyl) substituents causing 60% agonistic action. The next in order are compounds **18**, **13**, and **20**. It could be noted from the results that the compounds with and benzyl substituent at 1-position are good agonists.

### Experimental Section

Melting points were determined using the Toshniwal electrical melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FT IR-8700 spectrometer in KBr discs. <sup>1</sup>H NMR

spectra were recorded in CDCl<sub>3</sub> or CDCl<sub>3</sub>+DMSO-*d*<sub>6</sub> with TMS as an internal reference on a Bruker 80 MHz FT-NMR spectrometer. Mass spectra were recorded on a GC-MS QP-1100 Shimadzu instrument (70 eV). A domestic LG Little Chef microwave oven was used for the microwave activated reactions. The CHN-analyses were conducted using the Perkin-Elmer 240 B analyzer.

### Synthesis of N-(2-chlorophenyl)acetoacetamide, **3**

**(a) Conventional method.** A mixture of ethyl acetoacetate (**1**, 13 g, 0.1 mole) and 2-chloro aniline (**2**, 12.7 g, 0.1 mole) were taken into a RB flask (250 mL) and dissolved in alcohol (15 mL). The reaction mixture was heated under reflux for half an hour on a water bath. Alcohol was removed from the reaction mixture under reduced pressure to the extent possible and the residue was cooled. The residue was triturated with dry ether and the resultant product was filtered, washed with small portions of dry ether and dried. The resultant compound was purified by recrystallization from aqueous alcohol to obtain a colorless crystalline solid: 10.82 g (65%); m.p. 108°C (lit<sup>13</sup>, m.p. 107-08°C).

**(b) Improved method using catalyst.** The reaction mixture as specified above was taken into a conical flask (250 mL) and a catalytic amount of potassium *tert*-butoxide dissolved in alcohol (25 mL) was added. The reaction mixture was shaken vigorously for half an hour while cooling the flask now and then. Completion of the reaction was checked by TLC and alcohol was removed and the residue was cooled and triturated with crushed ice (~100 g). The compound was filtered, washed with cold water and dried. The product was purified by crystallization from aq. alcohol; yield recorded was 90%.

IR (KBr): 3286(NH), 3037-3056(C-H, arom.), 2839-2920(C-H, aliph.), 1708 (C=O, ketone), 1685(C=O, amide), 1602(C=C, aromatic) and 1120 (C-Cl) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.28(s, 3H, -CO-CH<sub>3</sub>), 2.86(s, 2H, -CO-CH<sub>2</sub>-CO), 6.78 (br, s, 1H, D<sub>2</sub>O exchangeable, -CO-NH-) and 6.96 – 7.80 (m, 4H, Ar-H); MS : m/z 211 [M<sup>+</sup>], 213 [M+2], 176, 43 (100%) [CH<sub>3</sub>-C≡O<sup>+</sup>], 92, 99.

### Synthesis of 1-alkyl/aralkyl-4-Aryl-3,5-bis-[N-(2-chlorophenyl)-carbamoyl] -2,6-dimethyl-1,4-dihydropyridines, **6-40**

**(a) Conventional method.** General Procedure: (2-Chlorophenyl)acetoacetamide (**3**, 4.18 g, 0.02 mole)

and an appropriate aromatic aldehyde (**4a-g**, 0.01 mole) were taken into a RB flask (250 mL) and dissolved in methanol (25 mL). Excess ammonia **5a** or an appropriate primary amine (**5b-e**, 0.01 mole) was added while shaking. The reaction mixture was heated under reflux, on hot water-bath for 12-18 h (monitoring by TLC). Methanol was removed to the extent possible and the residue was cooled. It was triturated with crushed ice (~150 g) and the product was filtered, washed with cold water and dried. It was placed in silica gel column and eluted with pet. ether-chloroform (3:1) mixture to get a pure compound. Yield: 23 to 52%.

**(b) The solvent-free micro-wave irradiation method.** General Procedure: N-(2-Chlorophenyl)-acetoacetamide (**3**, 0.02 mole) ammonium acetate (0.02 mole) or appropriate primary amine **5b-e** (0.01 mole) and appropriate aromatic aldehyde **4a-g** (0.01 mole) were mixed thoroughly with silica gel (~10 g) in a mortar. The reaction mixture was transferred to a Pyrex beaker (250 mL) and irradiated in a microwave oven for 4 min. The progress of reaction was monitored by TLC. On completion of the reaction, it was cooled and triturated with dichloromethane (3×50 mL). Silica gel was removed by filtration, washed with small portions of dichloromethane and the washings were added to the filtrate. The dichloromethane extracts were dried over anhydrous sodium sulphate, filtered and the solvent was removed by a rotary vacuum evaporator under reduced pressure to obtain the product **6-40**. Further purification was effected by recrystallization from pet. ether-chloroform (3:1) mixture. Yield: 62-76%.

**(c) The TMSI-mediated method.** An appropriate aldehyde (**4a-g**, 10 mmole), N-(2-chlorophenyl)-acetoacetamide (**3**, 20 mmole) and ammonium acetate (20 mmole) or appropriate primary amine (**5b-e**, 10 mmole) were suspended in acetonitrile (25 mL). Chlorotrimethyl silane (TMSCl, 10 mmole) was added to the suspension, drop wise while shaking, followed by the addition of sodium iodide (10 mmole) in one lot. The reaction mixture was stirred for 2.5-3 h while monitoring the progress of reaction by TLC. On completion of the reaction, the reaction mixture was triturated with crushed ice (~100 g) and extracted with ethyl acetate. The organic extracts were washed with a solution of sodium thiosulphate, then with water. The extracts were dried over anhydrous sodium sulphate and concentrated *in vacuo* to get the product **6-40**. It was purified by recrystallization from pet.

ether-chloroform (3:1) to obtain the compound in its pure form. Yield: 78-89%.

**(d) Ionic liquid mediated method.** To a mixture of N-(2-chlorophenyl) acetoacetamide (**3**, 10 mmole), appropriate aldehyde (**4a-g**, 5 mmole), and ammonium acetate (10 mmole) or appropriate primary amine (**5b-e**, 5 mmole), 1-butyl-3-methylimidazolium tetrafluoroborate, [bmim] BF<sub>4</sub> (5 mmole) was added and stirred at RT for 6-8.5 h while monitoring the progress of reaction by TLC. On completion of the reaction, the reaction mixture was washed with dry ether (3×25 mL). The combined ether extracts were concentrated *in vacuo* and the product was purified by recrystallization from pet. ether-chloroform (3:1) mixture. Yield: 76-87%. The viscous ionic liquid left as residue was washed further with dry ether and dried at 80°C for activation and reuse.

Characterization data and response against histamine-induced contraction of the compounds are presented in **Table I**.

#### Spectral characterization data of new 1,4-dihydropyridines.

**Compound 7:** IR (KBr): 3357 (amide NH), 3030 (C-H, aromatic) 2915 (C-H, aliphatic), 1690 (amide CO) 1605 (C=C, aromatic), 780 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.12 (t, 3H, *J* = 6.9 Hz, CH<sub>3</sub>-CH<sub>2</sub>), 1.24 (sextet, 2H, *J* = 7.0 Hz, H<sub>3</sub>C-CH<sub>2</sub>-CH<sub>2</sub>), 2.31 (s, 6H, C<sub>2</sub>-CH<sub>3</sub> and C<sub>6</sub>-CH<sub>3</sub>), 3.56 (t, 2H, *J* = 7.0 Hz, N-CH<sub>2</sub>), 5.63 (s, 1H, C<sub>4</sub>-H), 7.18-7.82 (m, 13H, Ar-H) and 8.42 (brs, 2H, D<sub>2</sub>O exchangeable, 2×CO-NH-); MS: M<sup>+</sup> at *m/z* 534; 536 (M<sup>+</sup>+2), 538 (M<sup>+</sup>+4), 423, 408, 380, 77.

**Compound 16:** IR (KBr): 3218 (NH, DHP), 3355 (NH, amide) 1685 cm<sup>-1</sup> (CO amide); <sup>1</sup>H NMR (CDCl<sub>3</sub> + DMSO-*d*<sub>6</sub>): δ 2.28 (s, 6H, C<sub>2</sub>-CH<sub>3</sub> and C<sub>6</sub>-CH<sub>3</sub>) 3.76 (s, 3H, O-CH<sub>3</sub>), 4.84 (s, 1H, C<sub>4</sub>-H), 5.68 (s, 1H, NH-DHP), 6.83-7.72 (m, 12H, Ar-H) and 8.20 (brs, 2H, D<sub>2</sub>O exchangeable, 2×CO-NH); MS: M<sup>+</sup> at *m/z* 522, 524 (M<sup>+</sup>+2), 526 (M<sup>+</sup>+4).

**Compound 29:** IR (KBr): 3360 (NH, amide), 3010 (C-H, aromatic), 2920 (C-H, aliphatic), 1692 cm<sup>-1</sup> (CO, amide); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.20-1.90 (m, 10H, 5×-CH<sub>2</sub>, cyclohexyl), 2.34 (s, 6H, C<sub>2</sub>-CH<sub>3</sub> and C<sub>6</sub>-CH<sub>3</sub>), 3.12 (m, 1H, NCH, cyclohexyl), 3.76 (s, 6H, ArNMe<sub>2</sub>), 5.02 (s, 1H, C<sub>4</sub>-H), 7.21-7.85 (m, 12H, Ar-H) and 8.28 (brs, 2H, D<sub>2</sub>O exchangeable, 2×CO-NH).

**Compound 40:** IR (KBr): 3368 (NH, amide), 2985-3015 (C-H, aromatic), 2865-2900 (C-H, aliphatic),

**Table I** — Characterization data and response against histamine induced contraction of new 1,4-dihydropyridines

Sl.No.	Nature of the substituents		Mol. formula	m.p. (°C)	Elemental Analyses Found (Calcd)			% Antagonism* / Agonist
	1-Subst. (R)	2-Subst. (Ar)			C	H	N	
6	hydrogen	phenyl	C <sub>27</sub> H <sub>23</sub> N <sub>3</sub> O <sub>2</sub> Cl <sub>2</sub>	201	65.97 (65.85)	4.72 4.67	8.61 8.53)	+20
7	<i>n</i> -propyl	phenyl	C <sub>30</sub> H <sub>29</sub> O <sub>2</sub> Cl <sub>2</sub> N <sub>3</sub>	206	67.50 (67.41)	5.39 5.43	7.92 7.86)	0
8	<i>n</i> -butyl	phenyl	C <sub>31</sub> H <sub>31</sub> N <sub>3</sub> O <sub>2</sub> Cl <sub>2</sub>	208	68.00 (67.88)	5.72 5.65	7.71 7.66)	+25
9	cyclohexyl	phenyl	C <sub>33</sub> H <sub>33</sub> N <sub>3</sub> O <sub>2</sub> Cl <sub>2</sub>	201	69.11 (68.98)	5.68 5.74	7.38 7.31)	+48
10	benzyl	phenyl	C <sub>34</sub> H <sub>29</sub> N <sub>3</sub> O <sub>2</sub> Cl <sub>2</sub>	207	70.22 (70.10)	4.92 4.98	7.29 7.21)	-30
11	hydrogen	4-methylphenyl	C <sub>28</sub> H <sub>25</sub> N <sub>3</sub> O <sub>2</sub> Cl <sub>2</sub>	192	66.57 (66.41)	4.95 4.98	8.25 8.30)	+30
12	<i>n</i> -propyl	4-methylphenyl	C <sub>31</sub> H <sub>31</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub>	170	67.95 (67.88)	5.76 5.70	7.54 7.66)	0
13	<i>n</i> -butyl	4-methylphenyl	C <sub>32</sub> H <sub>33</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub>	206	68.39 (68.32)	5.96 5.91	7.55 7.47)	-40
14	cyclohexyl	4-methylphenyl	C <sub>34</sub> H <sub>35</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub>	208	69.34 (69.38)	5.95 5.99	7.02 7.14)	0
15	benzyl	4-methylphenyl	C <sub>35</sub> H <sub>31</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub>	200	70.35 (70.47)	5.34 5.24	7.15 7.04)	+14
16	hydrogen	4-methoxyphenyl	C <sub>28</sub> H <sub>25</sub> N <sub>3</sub> O <sub>3</sub> Cl <sub>2</sub>	201	64.49 (64.36)	4.83 4.78	8.12 8.04)	+10
17	<i>n</i> -propyl	4-methoxyphenyl	C <sub>31</sub> H <sub>31</sub> N <sub>3</sub> O <sub>3</sub> Cl <sub>2</sub>	218	66.07 (65.95)	5.54 5.49	7.52 7.44)	0
18	<i>n</i> -butyl	4-methoxyphenyl	C <sub>32</sub> H <sub>33</sub> N <sub>3</sub> O <sub>3</sub> Cl <sub>2</sub>	206	66.54 (66.43)	5.62 5.70	7.39 7.26)	-48
19	cyclohexyl	4-methoxyphenyl	C <sub>34</sub> H <sub>35</sub> N <sub>3</sub> O <sub>3</sub> Cl <sub>2</sub>	214	67.68 (67.54)	5.86 5.79	7.11 6.95)	-72
20	benzyl	4-methoxyphenyl	C <sub>35</sub> H <sub>31</sub> N <sub>3</sub> O <sub>3</sub> Cl <sub>2</sub>	224	68.73 (68.62)	5.12 5.06	6.94 6.86)	-40
21	hydrogen	4-chlorophenyl	C <sub>27</sub> H <sub>22</sub> Cl <sub>3</sub> N <sub>3</sub> O <sub>2</sub>	221	61.51 (61.55)	4.18 4.21	7.93 7.98)	+10
22	<i>n</i> -propyl	4-chlorophenyl	C <sub>30</sub> H <sub>28</sub> Cl <sub>3</sub> N <sub>3</sub> O <sub>2</sub>	236	63.38 (63.33)	4.91 4.96	7.45 7.39)	0
23	<i>n</i> -butyl	4-chlorophenyl	C <sub>31</sub> H <sub>30</sub> Cl <sub>3</sub> N <sub>3</sub> O <sub>2</sub>	203	65.81 (65.08)	5.25 5.19	7.26 7.21)	+55
24	cyclohexyl	4-chlorophenyl	C <sub>33</sub> H <sub>32</sub> Cl <sub>3</sub> N <sub>3</sub> O <sub>2</sub>	247	65.18 (65.08)	5.27 5.30	6.80 6.90)	+12
25	benzyl	4-chlorophenyl	C <sub>34</sub> H <sub>28</sub> Cl <sub>3</sub> N <sub>3</sub> O <sub>2</sub>	246	66.12 (66.19)	4.62 4.57	6.88 6.81)	0
26	hydrogen	4(N,N-dimethyl amino)phenyl	C <sub>29</sub> H <sub>28</sub> N <sub>4</sub> O <sub>2</sub> Cl <sub>2</sub>	200	65.12 (65.04)	5.30 5.23	10.55 10.4)	-24
27	<i>n</i> -propyl	4(N,N-dimethyl amino)phenyl	C <sub>32</sub> H <sub>34</sub> N <sub>4</sub> O <sub>2</sub> Cl <sub>2</sub>	204	66.63 (66.55)	5.82 5.89	9.79 9.70)	-24
28	<i>n</i> -butyl	4(N,N-dimethyl amino)phenyl	C <sub>33</sub> H <sub>36</sub> N <sub>4</sub> O <sub>2</sub> Cl <sub>2</sub>	212	67.11 (67.00)	6.02 6.09	9.56 9.47)	-20
29	cyclohexyl	4(N,N-dimethyl amino)phenyl	C <sub>35</sub> H <sub>38</sub> N <sub>4</sub> O <sub>2</sub> Cl <sub>2</sub>	204	68.19 (68.07)	6.22 6.15	9.14 9.07)	-9

—Contd

**Table I** — Characterization data and response against histamine induced contraction of new 1,4-dihydropyridines—*Contd*

Sl.No.	Nature of the substituents		Mol. formula	m.p. (°C)	Elemental Analyses Found (Calcd)			% Antagonism* / Agonist
	1-Subst. (R)	2-Subst. (Ar)			C	H	N	
30	benzyl	4(N,N-dimethyl amino)phenyl	C <sub>36</sub> H <sub>34</sub> N <sub>4</sub> O <sub>2</sub> Cl <sub>2</sub>	254	69.21 (69.12)	5.38 5.44	9.04 8.96)	+28
31	hydrogen	3-nitrophenyl	C <sub>27</sub> H <sub>22</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>4</sub>	196	60.31 (60.34)	4.09 4.13	10.38 10.43)	-20
32	<i>n</i> -propyl	3-nitrophenyl	C <sub>30</sub> H <sub>28</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>4</sub>	198	62.01 (62.18)	4.75 4.87	9.51 9.67)	0
33	<i>n</i> -butyl	3-nitrophenyl	C <sub>31</sub> H <sub>30</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>4</sub>	192	62.68 (62.73)	5.01 5.09	9.55 9.44)	0
34	cyclohexyl	3-nitrophenyl	C <sub>33</sub> H <sub>32</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>4</sub>	200	63.85 (62.98)	5.15 5.21	9.15 9.04)	+46
35	benzyl	3-nitrophenyl	C <sub>34</sub> H <sub>28</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>4</sub>	180	65.01 (65.08)	4.64 4.50	8.86 8.93)	-60
36	hydrogen	2-furyl	C <sub>25</sub> H <sub>21</sub> N <sub>3</sub> O <sub>3</sub> Cl <sub>2</sub>	214	62.36 (62.24)	4.42 4.35	8.80 8.71)	-13
37	<i>n</i> -propyl	2-furyl	C <sub>28</sub> H <sub>27</sub> N <sub>3</sub> O <sub>3</sub> Cl <sub>2</sub>	220	64.25 (64.12)	5.10 5.15	8.09 8.01)	-15
38	<i>n</i> -butyl	2-furyl	C <sub>29</sub> H <sub>29</sub> O <sub>3</sub> N <sub>3</sub> Cl <sub>2</sub>	222	64.77 (64.68)	5.45 5.39	7.90 7.80)	-20
39	cyclohexyl	2-furyl	C <sub>31</sub> H <sub>31</sub> N <sub>3</sub> O <sub>3</sub> Cl <sub>2</sub>	218	66.06 (65.95)	5.42 5.49	7.53 7.44)	-19
40	benzyl	2-furyl	C <sub>32</sub> H <sub>27</sub> N <sub>3</sub> O <sub>3</sub> Cl <sub>2</sub>	223	67.01 (67.14)	4.83 4.75	12.34 12.39)	-27
chloropheniramine maleate								+100

\* (-) : Agonist; (+) : Antagonist

1695 (C=O, amide), 1607 cm<sup>-1</sup> (C=C, aromatic); <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.48 (s, 6H, C<sub>2</sub>-CH<sub>3</sub> and C<sub>6</sub>-CH<sub>3</sub>), 4.46 (s, 2H, -N-CH<sub>2</sub>-Ph), 4.92 (s, 1H, C<sub>4</sub>-H), 6.80-7.05 (m, 3H, 2-furyl), 7.17-7.68 (m, 8 H, Ar-H) and 8.26 (br s, 2H, D<sub>2</sub>O exchangeable, 2×CO-NH).

### Pharmacology

**Acute toxicity studies and gross behavioural changes.** Toxicity and gross behavioural studies were carried by standard methods<sup>14,15</sup>. Albino mice were employed as experimental animals and test compounds were administered orally in graded doses of 50, 100, 250, 500, 1000 and 1200 mg/kg (bw). The animals were observed for 72 h, for behavioural changes and mortality.

**Bronchodilatory activity/bronchoconstriction activity<sup>15</sup>.** This was evaluated by determining the percentage protection against histamine-induced broncho-constriction on guinea pig. Male guinea pigs weighing 375-400 g were placed in a plastic chamber and exposed to histamine aerosol (0.4% w/v)

produced by a Halpern column and a compressed air supply. The pre-convulsion times two days before the administration of test compounds were determined. The protective effect of the drug was evaluated in guinea pigs exposing them to the histamine aerosol for 45 min. (sometimes 24 or 48 h) after oral administration. Recovery of the preconvulsion time to the control value was verified at 48 and 96 h after treatment. The percentage of protection was assessed according to Armitage *et al.*<sup>16</sup>

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