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Synthesis and pharmacology of new 1,4-dihydropyridines. 2,6-Dimethyl-4-(substituted phenyl) or (2-furyl)-, (2-thienyl)- or (3-pyridyl)-3,5-di[(*N*-methyl) or (*N*-diethyl)]carbamoyl-1,4-dihydropyridines as potent calcium-channel blockers*

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3,5-di-*N*-methyl / *N*-diethylcarbamoyl-1,4-dihydropyridine / calcium-channel blocker / antiinflammatory activity / analgesic activity

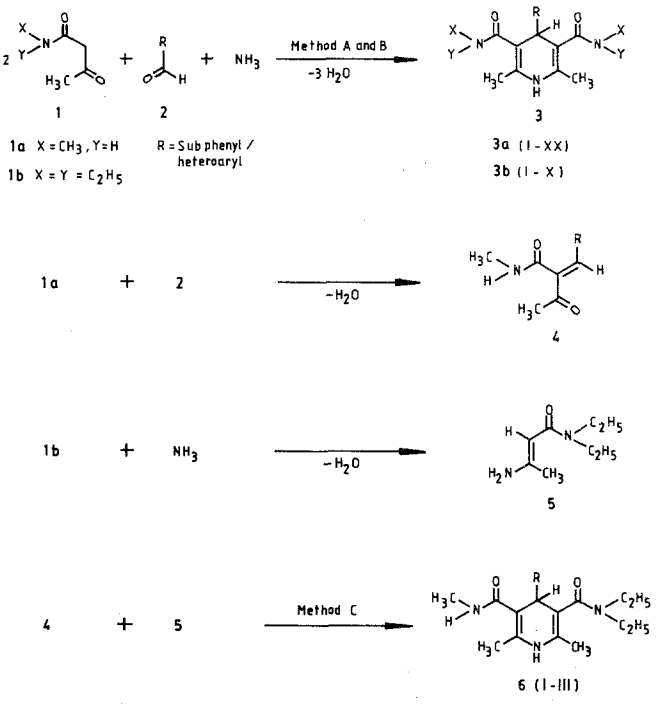
Introduction

The 1,4-dihydropyridines first prepared by Hantzsch [1] almost 100 years ago have recently been found to be highly effective calcium-channel blockers or calcium antagonists with suitable pharmacological profiles [2].

As part of our research work on the design of biologically active molecules [3–6], we have now synthesised some new substituted 1,4-dihydropyridines with certain structural modifications incorporating *N*-methyl and *N*-diethylcarbamoyl moieties at the 3 and 5 positions of 1,4-dihydropyridine so as to obtain **3a**, **3b** and **6** with a view to studying the pharmacological behaviour of such compounds on the cardiovascular system.

Chemistry

In the present investigation a number of new 1,4-dihydropyridines of the general structures **3** and **6** were synthesised by a one-pot condensation of 2 mol *N*-methylacetoacetamide **1a** or *N*-diethylacetoacetamide **1b** with an aromatic or heteroaromatic aldehyde **2** and aqueous ammonia in methanol, *Methods A* and *B* (scheme 1). The 1,4-dihydropyridines with non-identical amide groups **6** were synthesised by the condensation of substituted *N*-methyl-α-acetyl cinnamamides **4** and β-amino-*N*-diethyl crotonamide **5** in methanol, *Method C* (scheme 1). All the compounds in table I were characterised on the basis of their elemental analysis and spectroscopic data.



Scheme 1.

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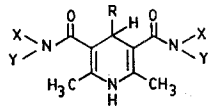
Table I. Physicochemical data of 2,6-dimethyl-4-(substituted phenyl/heteroaryl)-3,5-di[(*N*-methyl) or (*N*-diethyl)]carbamoyl-1,4-dihydropyridines (**3a I–XX**, **3b I–X** and **6 I–III**).



Compound	*R*	*X*	*Y*	*Mp (°C)*	*Yield (%)*	*Method*	*Crystallisation solvent*[a]
3a–I	C_6H_5	H	CH_3	225–226	37	A	b
3a–II	2-$CH_3C_6H_4$	H	CH_3	224–226	63	A	e
3a–III	2-OH-C_6H_4	H	CH_3	310–311	60	A	b
3a–IV	2-OCH_3-C_6H_4	H	CH_3	176–178	62	A	a
3a–V	4-Br, 2-OCH_3-C_6H_3	H	CH_3	168–170	51	A	a
3a–VI	4-OCH_3-C_6H_4	H	CH_3	220–221	80	A	b
3a–VII	3,4-di-OCH_3-C_6H_3	H	CH_3	231–232	58	A	c
3a–VIII	3,4,5-tri-OCH_3-C_6H_2	H	CH_3	278–280	62	A	b
3a–IX	3,4-O-CH_2-O-C_6H_3	H	CH_3	251–252	60	A	c
3a–X	2-NO_2-C_6H_4	H	CH_3	110–112	37	A	b
3a–XI	3-NO_2-C_6H_4	H	CH_3	310–312	64	A	b
3a–XII	4-NO_2-C_6H_4	H	CH_3	328–330	45	A	c
3a–XIII	2-Cl-C_6H_4	H	CH_3	140–141	47	A	b
3a–XIV	4-Cl-C_6H_4	H	CH_3	249–250	40	A	b
3a–XV	2,4-di-Cl-C_6H_3	H	CH_3	243–245	52	A	d
3a–XVI	3,4-di-Cl-C_6H_3	H	CH_3	232–233	44	A	b
3a–XVII	2-CF_3-C_6H_4	H	CH_3	166–168	48	A	a
3a–XVIII	2-Furyl	H	CH_3	226–228	75	A	b
3a–XIX	2-Thienyl	H	CH_3	242–244	47	A	b
3a–XX	3-Pyridyl	H	CH_3	298–300	52	A	a
3b–I	C_6H_5	C_2H_5	C_2H_5	130–132	45	A	e
3b–II	4-CH_3-C_6H_4	C_2H_5	C_2H_5	118–120	50	A	b
3b–III	4-OCH_3-C_6H_4	C_2H_5	C_2H_5	101–102	42	A	b
3b–IV	3,4-di-OCH_3-C_6H_3	C_2H_5	C_2H_5	132–134	51	A	e
3b–V	3,4-O-CH_2-O-C_6H_3	C_2H_5	C_2H_5	108–110	48	A	e
3b–VI	3-NO_2-C_6H_4	C_2H_5	C_2H_5	98–100	47	A	b
3b–VII	4-NO_2-C_6H_4	C_2H_5	C_2H_5	126–128	42	A	c
3b–VIII	4-Cl-C_6H_4	C_2H_5	C_2H_5	96–98	52	A	b
3b–IX	2,4-di-Cl-C_6H_3	C_2H_5	C_2H_5	164–165	55	B	d
3b–X	3,4-di-Cl-C_6H_3	C_2H_5	C_2H_5	122–124	52	B	d
6–I	2-NO_2-C_6H_4	H	CH_3	102–104	52	C	z
		C_2H_5	C_2H_5				
6–II	4-NO_2-C_6H_4	H	CH_3	209–211	55	C	z
		C_2H_5	C_2H_5				
6–III	2,4-di-Cl-C_6H_3	H	CH_3	118–120	64	C	z
		C_2H_5	C_2H_5				

[a]All compounds were analysed for C, H and N and the results obtained were within ± 0.4% of the theoretical values; a: methanol; b: ethanol; c: diethylether/methanol; d: diethylether/isopropanol; e: diethylether/ethanol; z: column chromatography chloroform/methanol.

Pharmacology

The compounds obtained (**3a VIII–XV** and **3b IX**) were screened for their acute toxicity, and cardiovascular, calcium-channel blocker, antiinflammatory and analgesic activities. The pharmacological results are presented in tables II and III.

Acute toxicity

Acute toxicity was studied according to the method described by Ghosh [7]. The animals were observed for gross behavioural and other central nervous system effects.

Cardiovascular activity

This was studied by the following methods: i) conventional dog blood pressure with respiration; and ii) dog blood pressure with ventriculogram. The procedures were described previously by Turner and Brown *et al* [8, 9]. After injecting adrenaline, noradrenaline, acetylcholine and the test compound, the changes in the blood pressure and cardiac activity were recorded. The doses of test compound used were 20–40 mg.

Cardiovascular activity was also investigated using isolated vascular bed preparations and isolated rabbit auricle preparations. These experiments were carried out according to the method described by Burns [10]. The effect of acetylcholine and adrenaline were studied before and after administration of the test compounds. The doses of test compound used in this study were 0.4–2 mg/ml solutions.

Antiinflammatory (antioedematous) activity

The antiinflammatory activity of the test compounds was studied by using carrageenin-induced rat paw oedema as described by Winter *et al* [11]. The percentage inhibition of the oedema of the treated rats with respect to controls was calculated and compared with phenylbutazone (table III).

Table II. Cardiovascular activity of 2,6-dimethyl-4-(substituted phenyl)-3,5-di-[(*N*-methyl) or (*N*-diethyl)]carbamoyl-1,4-dihydropyridines.

Compound	*Dose (mg/kg)*	*Cardiovascular activity in dog*					*Isolated rabbit auricle (dose 10–50 g/ml)*				*Vascular bed (dose 200–800 g)*		
		BP	*HR*	*V*	*AR*	*CO*	*HR*	*AC*	*AR*	*CA*	*Rabbit ear*	*Rat limb*	*Frog vessels*
Control dog		160	120				120						
Nifedipine	10	180	96	↓	↓	↓							
3a VIII	40												
	80	NE	NE	NE	NE	NE	NC	NE	NE	NE	NE	NE	NE
3a X	40	100	80										
	80	100	80	NE	NE	NE	NC	NE	NE	NE	NE	NE	NE
3a XI	40	100	80										
	80	100	80	NE	NE	↓	NC	NE	NE	NE	NE	NE	NE
3a XIII	40												
	80	NE	NE	NE	NE	NE	NC	NE	NE	NE	NE	NE	NE
3a XV	40												
	80	NE	NE	NE	NE	NE	NC	NE	NE	NE	NE	NE	NE
3b IX	20	140	96	↓	↓	↓	100	↓	↓	Yes,	NE	NE	NE
	30	120	60				40			potent			
	40	60	40										

BP blood pressure in mmHg; AR adrenaline response; CO carotid occlusion; HR heart rate per minute; AC amplitude concentration; V ventriculogram (amplitude); CA calcium antagonism; ↓ decrease; NE no effect; NC no change; LD_{50} (ip) in rats > 800.

Table III. Antiinflammatory and analgesic activities of 2,6-dimethyl-4-(substituted phenyl)-3,5-di[(*N*-methyl) or (*N*-diethyl)]-carbamoyl-1,4-dihydropyridines.

Compound	*Antiinflammatory action*[a] *% inhibition of inflammation (Carrageenin)*	*Analgesic action*[b] *% protection from pain (writhing)*
3b I	30.34	4.52
3a VIII	25.75	7.85
3a IX	30.66	7.20
3a X	39.39	11.36
3a XI	5.60	20.31
3a XIII	53.03	8.00
3a XV	87.87	12.77
3b IX	1.51	30.51
Phenylbutazone	39.5	–
Aspirin	–	57.3

[a]Albino rats both sexes 140–200 g were used. The test compound 100 mg/kg was given *po* in gum acacia. [b]Albino mice weighing 18–25 g were used. The test compound 100 mg/kg was given *po*.

Analgesic activity. Writhing (chemical) method

The acetic-acid writhing test, a method modified from that of Koster *et al* [12], was used. The average number of writhes for each group of animals and the percentage change compared with the control group were calculated (table III).

Results and discussion

Some broad generalisations regarding the structure–activity relationships of the compounds tested could be drawn. From the results summarised in tables II and III, it is apparent that the cardiovascular and calcium-channel-blocking activities of compounds **3a VIII, X, XI, XIII** and **XV** were much less than that of nefidipine.

The compounds **3a X** and **3a XI** with nitro substituents in the 2 and 3 positions of the phenyl ring showed no calcium-channel-blocking activity. The compound **3a VIII** carrying 3,4,5-trimethoxyphenyl moiety was chosen to explore the influence of methoxyl group, but no calcium-channel-blocking activity was observed. Increasing the alkyl side chain length from *N*-dimethylcarbamoyl **3a XV** to *N*-diethylcarbamoyl **3b IX** increases the calcium-channel-blocking activity. The influence of substituents in the 4-phenyl ring, as in compound **3b IX** with 2,4-dichloro substituents in the phenyl ring, appears to increase the calcium-channel-blocking activity and showed marked blood pressure lowering at very small doses ranging from 20 to 40 mg. Compound **3b IX** resembles nifedipine in its effects on cardiac and blood pressure and was found to be 5 times less potent than nifedipine. Compound **3a XV** also exhibited strong antiinflammatory activity as measured by inhibition of edema compared to phenylbutazone (table III).

Experimental protocols

Melting points were taken using Edmund Bühler melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 283B spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian 80A and Varian Gemini 200. The chemical shifts are in ppm relative to tetramethylsilane. Mass spectra were determined on a VG micromass 7070H mass spectrometer operating at 70 eV. The purity of all compounds was checked on silica gel 'G' TLC plates using iodine as a visualising agent. Elemental analyses were within the acceptable limits of ± 0.4% of the theoretical values.

General procedure for the synthesis of 1,4-dihydropyridines

Method A. A mixture of *N*-methylacetoacetamide **1a** or **1b** (0.1 mol), substituted benzaldehyde or hetero aromatic aldehyde **2** (0.05 mol) and concentrated ammonia or aqueous ammonia (25%) (0.15 mol) and methanol (50 ml) was refluxed for 6–9 h on a steam bath. After cooling the separated solid was filtered and recrystallised from a suitable solvent.

*2,6-Dimethyl-4-(2-furyl)-3,5-di-N-methylcarbamoyl-1,4-dihydropyridine **3a XV III***. Yield 75%; mp 226–228°C, IR (KBr) (cm^{-1}): 3300 (NH), 2960 (CH_3), 1680 (C=O), 1610 (C=C); ^{1}H-NMR (DMSO-d_6): δ 2.18 (s, 6H, $2CH_3$), 2.70 (d, 6H, 2N-CH_3), 4.75 (s, 1H, CH), 5.90–5.93 (m, 1H, furyl-4H), 6.13–6.25 (m, 1H, furyl-3H), 6.90 (br, 2H, CONH), 7.20–7.25 (m, 1H, furyl-5H), 7.68 (s, 1H, NH); MS m/e: 230 (100%), 289 (30), 258 (40), 231 (95), 200 (80), 144 (40). ^{13}C-NMR (DMSO-d_6): δ 17.50 ($2CH_3$), 26.96 (2N-CH_3), 34.86 (C-4), 101.53 (C-3,5), 104.39 (C-4'), 110.07 (C-3'), 139.48 (C-2,6), 141.22 (C-5'), 158.39 (C-2'), 168.59 (CO-3',5').

Method B. An autoclave of 100 ml capacity was successively charged with *N*-methyl or *N*-diethyl acetoacetamide **1a** or **1b** (0.1 mol), substituted benzaldehyde **2** (0.5 mol), methanol (50 ml) and aqueous ammonia 25% (0.6 mol) and heated at 100–110°C for 15–18 h. After cooling, the solvent was removed and the product was recrystallised from a suitable solvent.

*2,6-Dimethyl-4-(2,4-dichlorophenyl)-3,5-(di-N-ethyl)-carbamoyl-1,4-dihydropyridine **3b IX***. Yield 55%; mp 164–165°C, IR (KBr) (cm^{-1}): 3380 (NH), 1630 (C=O), 1585 (C=C), 1040 (C-Cl); ^{1}H-NMR (DMSO-d_6): δ 1.16–1.50 (t, 12H, $4CH_3$), 2.27 (s, 6H, $2NCH_3$), 3.70–3.86 (8H, $4CH_2$), 5.55 (s, 1H, CH), 7.69–7.74 (m, 3H, Ar-H), 8.37 (s, 1H, NH); MS m/e: 306 (100%), 452 (25).

Method C. A mixture of substituted *N*-methyl-α-acetylcinnamamide **4** (0.1 mol), β-amino-*N*-diethylcrotonamide **5** (0.1 mol) and methanol (200 ml) was refluxed for 9 h on a steam bath. The product was cooled and then the solvent was removed completely on a rotary evaporator. The product **6** was either recrystallised from suitable solvents or purified by column chromatography. The compounds listed in table I were prepared by general *Methods A, B* or *C* as illustrated in scheme 1.

*2,6-Dimethyl-4-(4-nitrophenyl)-3-(N-methyl)-5-(N-diethyl)-carbamoyl-1,4-dihydropyridine **6 II***. Yield 55%; mp 209–211°C, IR ($CHCl_3$) (cm^{-1}): 3290 (NH), 1670 (C=O), 1590 (C=C), 1470, 1340 (NO_2), ^{1}H-NMR ($CDCl_3$): δ 0.97 (m, 6H, $2CH_3$), 1.78 (s, 3H, CH_3-6), 2.28 (s, 3H, CH_3-2), 2.66 (d, 3H, N-CH_3), 3.18 (m, 4H, $2CH_2$), 4.75 (s, 1H, CH), 5.40 (br, 2H, CONH), 7.31 (d, 2H, Ar-H), 8.06 (d, 2H, Ar-H); MS m/e: 264 (100%), 386 (10), 371 (60), 355 (30), 312 (30), 255 (40).

*General procedure for the synthesis of N-methyl-α-acetyl cinnamamides **4***
A mixture of *N*-methylacetoacetamide **1a** (0.1 mol), substituted benzaldehyde **2** (0.1 mol), pyridine (1 ml) , glacial acetic acid (3.5 ml) and dry toluene (150 ml) was heated under reflux for 2–3 h. The solvent was removed and the crystals separated were collected by filtration, washed with toluene and used in the next reaction. The following compounds were prepared by the above procedure.

N-Methyl-α-acetyl-2,4-dichlorocinnamamide. Yield 65%; mp 121–123°C, ^{1}H-NMR ($CDCl_3$) δ: 2.50 (s, 3H, CH_3), 2.83 (d, 3H, N-CH_3), 6.03 (br, 1H, NH), vinyl proton merged with aromatic protons, 7.12–7.25 (m, 3H, Ar-H).

*β-Amino-N-diethylcrotonamide **5***
N-Diethylacetoacetamide **1b** (0.1 mol) and dry chloroform (20 ml) were mixed and cooled to 10°C and then saturated with gaseous NH_3. The reaction mixture was diluted with 50 ml chloroform and dried over anhydrous Na_2SO_4. The chloroform was removed and the residue was distilled under reduced pressure to give the pure product. Yield 93%; bp 122–124°C/1.5 mmHg; ^{1}H-NMR ($CDCl_3$): δ 1.06 (t, 6H, CH_3), 1.77 (s, 3H, CH_3), 3.18 (q, 4H, CH_2), 4.43 (s, 1H, CH), 6.43 (br, 2H, NH_2).

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