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Asymmetric *N*-(3,3-diphenylpropyl)aminoalkyl esters of 4-aryl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acids with antihypertensive activity

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Abstract – A series of asymmetric 4-aryl-1,4-dihydropyridine-3,5-dicarboxylates characterized by the presence of a 3,3-diphenylpropylamino moiety in one of the ester groups were synthesized. They exhibited remarkable antihypertensive activity in spontaneously hypertensive rats as well as affinity for the 1,4-dihydropyridines binding site labelled by ^{3}H-nitrendipine in the calcium channel. Introduction of this bulky and lipophilic amine confers to the whole series an elevated level of antihypertensive activity and a long duration of action, a structure-dependent modulation of the activity being found only in the subset characterized by the presence of a branched propylene bridge between the ester and the amino groups. The presence of the amino group is essential for oral activity. Out of this series, compound **9u** (Rec 15/2375-lercanidipine) was selected for clinical development and obtained marketing authorization as an antihypertensive in several countries. © Elsevier, Paris

1,4-dihydropyridine / antihypertensive / calcium antagonist / Rec 15 / 2375 / lercanidipine / calcium entry blocker

1. Introduction

The presently available drugs classified as calcium antagonists (calcium entry blockers) are largely employed in a number of cardiovascular diseases, in particular hypertension and angina [1, 2]. The possibility of extending their use to other therapeutical indications, such as cerebral insufficiency and vasospasm, migraine, hypertrophic cardiomyopathy, ventricular and supraventricular tachyarrhytmia, atherosclerosis and others contributes to maintain an elevated interest for these agents [3–7].

With regard to their structure, calcium antagonists can be roughly divided into two main groups: (a) the 4-aryl-1,4-dihydropyridine-3,5-dicarboxylic acid esters, and related derivatives, and (b) compounds containing one, or more, aryl moieties bearing a basic side chain as the essential active structure, such as verapamil, diltiazem, bepridil, cinnarizine and prenylamine [8–10].

The dihydropyridines attracted the interest of many medicinal chemists, because of their high potency and selectivity of action, and many modifications of the original structure of nifedipine have been carried out, leading to new active compounds [11, 12].

Among the performed modifications, the introduction of bulky, lipophilic aralkylaminoalkyl chains as one of the two esterifying groups at position 3 or 5, led to the discovery of new, very potent calcium antagonists. The first compound of this type, nicardipine [13] is widely used as antianginal and antihypertensive. Other analogues, namely barnidipine [14], benidipine [15] and manidipine [16], recently entered the market or are in advanced clinical trials, such as NKY-722 [17] and palonidipine [18] (see *figure 1*).

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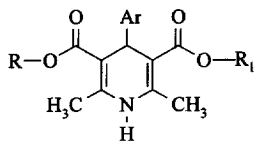
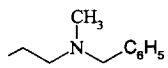
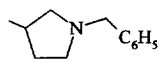
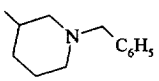
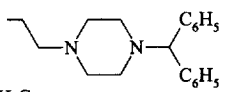
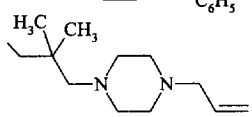
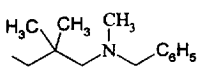
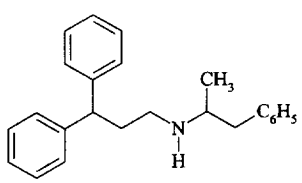
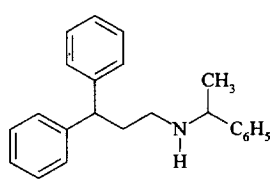


Compd	R	Ar	R_1
Nicardipine	CH_3	3-$NO_2C_6H_4$	
Barnidipine (Mepirodipine)	CH_3	3-$NO_2C_6H_4$	
Benidipine (Nacadipine)	CH_3	3-$NO_2C_6H_4$	
Manidipine (Franidipine)	CH_3	3-$NO_2C_6H_4$	
NKY-722	CH_3	3-$NO_2C_6H_4$	
Palonidipine	CH_3	2-F,5-$NO_2C_6H_3$	



Prenylamine



Fendiline

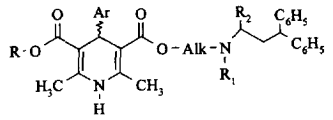
Figure 1. Selected basic and lipophilic calcium-antagonists.

Following this approach, our group investigated new esters of 2,6-dimethyl-4-aryl-1,4-dihydropyridine-3,5-dicarboxylic acid in which one estereal group represents a *N*-(3,3-diphenylpropyl)aminoalkyl moiety, which are reported here (*table I*).

The 3,3-diphenylpropylamino chain was chosen as a bulky, lipophilic group with the aim of improving the duration of action and also because it is present in other calcium antagonists such as prenylamine [19] and fendiline [20] (see *figure 1*).

Other structural variations were carried out, namely modification of the aryl group, of the non-basic ester chain and of the alkyl bridge between the carboxy and the amino functions, with the aim of possibly optimizing the pharmaco-toxicological properties of this series of compounds.

Table I. Alkyl *N*-[diphenylalkyl]aminoalkyl 4-aryl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates **9**[a].



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Compound	R	Ar	Alk	R_1	R_2	Method	Yield (%)	Eluents for base purification
9a	CH_3	2-NO_2–C_6H_4	$(CH_2)_2$	CH_3	H	A	34[b]	$CHCl_3$–EtOAc (100:0 to 97:3)
9b	CH_3	3-NO_2–C_6H_4	$(CH_2)_2$	CH_3	H	A	40	$CHCl_3$–EtOAc (85:15 to 1:1)
9c	CH_3	2,3-Cl_2–C_6H_3	$(CH_2)_2$	CH_3	H	A	40[c]	$CHCl_3$–EtOAc (4:1 to 3:2)
9d	CH_3	4-benzofurazanyl	$(CH_2)_2$	CH_3	H	A	32	$CHCl_3$–EtOAc (100:0 to 97:3)
9e	CH_3	3-NO_2–C_6H_4	$(CH_2)_2$	H	H	A	38	$CHCl_3$–EtOAc (4:1 to 1:1)
9f[d]	CH_3	3-NO_2–C_6H_4	$(CH_2)_2$	CH_3	CH_3	A	47	$CHCl_3$–EtOAc (100:0 to 85:15 to 0:100)
9g	C_2H_5	3-NO_2–C_6H_4	$(CH_2)_2$	CH_3	H	A	55	$CHCl_3$–EtOAc (100:0 to 7:3)
9h	$(CH_3)_2CH$	3-NO_2–C_6H_4	$(CH_2)_2$	CH_3	H	A	85	tol–EtOAc (4:1 to 3:2)
9i	$(CH_3)_2CHCH_2$	3-NO_2–C_6H_4	$(CH_2)_2$	CH_3	H	A	50	tol–EtOAc (3:1)
9j	$CH_3(CH_2)_2O(CH_2)_2$	3-NO_2–C_6H_4	$(CH_2)_2$	CH_3	H	A	59	tol–EtOAc (9:1 to 7:3)
9k	CH_3	3-NO_2–C_6H_4	$(CH_2)_3$	CH_3	H	A	35	$CHCl_3$–EtOAc (100:0 to 2:3)
9l[d]	CH_3	3-NO_2–C_6H_4	$(CH_2)_3$	CH_3	CH_3	A	48	$CHCl_3$–EtOAc (9:1 to 3:1)
9m	CH_3	3-NO2-C6H4	$(CH_2)_4$	CH_3	H	A	53[e]	$CHCl_3$–Me_2CO (95:5 to 7:3)
9n	CH_3	3-NO_2–C_6H_4	$CH(CH_3)CH_2$	CH_3	H	A	35	$CHCl_3$–EtOAc (95:5 to 7:3)
9n$_1$[f]						B_1	23[b]	$CHCl_3$–EtOAC (10:0 to 1:1)
9n$_2$[g]						B_1	29[e]	$CHCl_3$–EtOAc (10:0 to 1:1)
9o	$(CH_3)_2CH$	3-NO_2–C_6H_4	$CH(CH_3)CH_2$	CH_3	H	C	34	tol–EtOAc (9:1 to 0:10)
9p	$CH_3(CH_2)_2O(CH_2)_2$	3-NO_2–C_6H_4	$CH(CH_3)CH_2$	CH_3	H	C	30[e]	tol–EtOAc (4:1 to 1:1)
9q	$CH_3(CH_2)_2OCH_2C(CH_3)_2$	3-NO_2–C_6H_4	$CH(CH_3)CH_2$	CH_3	H	C	25[e]	tol–EtOAc (9:1 to 1:1)
9r	$(CH_3)_2CHCH_2$	2,3-Cl_2–C_6H_3	$CH(CH_3)CH_2$	CH_3	H	A	5	$CHCl_3$–EtOAc (4:1 to 3:2)
9s	$CH_3(CH_2)_2O(CH_2)_2$	2,3-Cl_2–C_6H_3	$CH(CH_3)CH_2$	CH_3	H	C	25	tol–EtOAc (4:1 to 1:1)
9t	CH_3	3-NO_2–C_6H_4	$C(CH_3)_2CH_2$	H	H	B_2	54	CH_2Cl_2–EtOAc (7:3)
9u	CH_3	3-NO_2–C_6H_4	$C(CH_3)_2CH_2$	CH_3	H	B_2	44	CH_2Cl_2–EtOAc (100:0 to 70:30)
9u$_1$						C	36[e]	petroleum ether–Me_2CO (90:10 to 85:15)
9v	CH_3	4-NO_2–C_6H_4	$C(CH_3)_2CH_2$	CH_3	H	B_2	57	$CHCl_3$–Me_2CO (100:0 to 97:3)
9w	C_2H_5	3-NO_2–C_6H_4	$C(CH_3)_2CH_2$	CH_3	H	C	35	petroleum ether–EtOAc (4:1 to 3:2)
9x	$(CH_3)_2CH$	3-NO_2–C_6H_4	$C(CH_3)_2CH_2$	CH_3	H	C	11[e]	$CHCl_3$–Me_2CO (100:0 to 95:5)
9y	$CH_3(CH_2)_2O(CH_2)_2$	3-NO_2–C_6H_4	$C(CH_3)_2CH_2$	CH_3	H	C	35[e]	$CHCl_3$–Me_2CO (100:0 to 94:6)
9z	$CH_3(CH_2)_2OCH_2C(CH_3)_2$	3-NO_2–C_6H_4	$C(CH_3)_2CH_2$	CH_3	H	C	40[e]	$CHCl_3$–Me_2CO (100:0 to 92:8)
9aa	CH_3	2,3-Cl_2–C_6H_3	$C(CH_3)_2CH_2$	CH_3	H	C	17[h]	$CHCl_3$–Me_2CO (100:0 to 95:5)
9ab	CH_3	3-NO_2–C_6H_4	$CH(CH_3)(CH_2)_2$	CH_3	H	B_1	51[b]	$CHCl_3$–EtOAc (10:0 to 0:10)
9ac	CH_3	3-NO_2–C_6H_4	$C(CH_3)_2(CH_2)_2$	CH_3	H	B_2	73	petroleum ether–Me_2CO (7:3 to 6:4)
9ad	CH_3	3-NO_2–C_6H_4	$CH_2C(CH_3)_2CH_2$	CH_3	H	B_2	60[e]	petroleum ether–EtOAc (7:3)
9ae	CH_3	2,3-Cl_2–C_6H_3	$CH_2C(CH_3)_2CH_2$	CH_3	H	B_2	34	petroleum ether–EtOAc (9:1 to 3:1)
9af	CH_3	3-NO_2–C_6H_4	$(CH_2)_2C(CH_3)_2$	CH_3	H	B_2	61[e]	petroleum ether–EtOAc (4:1 to 3:1)
9ag	CH_3	3-NO_2–C_6H_4	$C(CH_3)_2CH_2$	CH_3	=O	B_2	64	petroleum ether–EtOAc (3:2)

[a]Compounds **9a–f** were isolated as HCl salts; [b]•H_2O; [c]•0.6H_2O; [d]1,*N*-dimethyl-3,3-diphenylpropylamine used for the synthesis of these compounds was prepared according to the literature [21]; [e]•0.5H_2O; [f]diastereomer at lower R_F; [g]diastereomer at higher R_F; [h]•0.75H_2O.

2. Chemistry

The asymmetric monobasic diesters of 4-aryl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylic acids, listed in *table I*, were synthesized by three different routes depicted in *figure 2*.

The haloalkyl acetoacetates **2**, prepared starting from the corresponding haloalkyl alcohols **1**, were reacted with the suitable aldehydes **3** to give the haloalkyl 2-arylideneacetoacetates **4** as mixtures of the *E/Z* isomers. The suitable commercially available or synthesized aminocrotonates **5** were condensed with **4** to give the alkyl haloalkyl 4-aryl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates **6**. For the preparation of intermediate **6e** it was more convenient to carry out the esterification of 1,4-dihydro-2,6-dimethyl-3-methoxycarbonyl-4-(3-nitrophenyl)pyridine-5-carboxylic acid with 1,4-dibromobutane in anhydrous DMF and in the presence of K_2CO_3. The halogenderivatives **6** were then used to perform the alkylation of the diphenylalkylamines **8** by the general *method A* to give the desired compounds **9a–n,r**.

The 3-alkoxycarbonyl-4-aryl-1,4-dihydro-2,6-dimethylpyridine-5-carboxylic acids **7** were used to esterify the *N*-(hydroxyalkyl)-diphenylalkylamines **10** by *method B*, alternatively using a condensation agent (DCC in the presence of DMAP) to give the final compounds **9n,ab** (method B_1) or via acyl chloride formation to give **9t–v,ac–ag** (method B_2).

Following the third pathway, some aminoalkyl-alcohols **10** were reacted with diketene to give the corresponding *N*-(diphenylalkyl)aminoalkyl aceto-acetates **11** which were condensed with **3** to give the corresponding arylidene derivatives **12**. Subsequent cyclization with the suitable aminocrotonates **5** by *method C* gave the desired compounds **9o–q,s,u,w–aa**.

In steps i and vi diketene can be successfully replaced by its acetone adduct (2,2,6-trimethyl-1,3-dioxin-4-one) by operating at higher temperatures. In the reaction between intermediates **7** and **10** (method B_1), the formation of dicyclohexylcarbodiimide adduct occurred readily, but a long reaction time was needed in order to obtain the esters **9** in acceptable yields.

For the preparation of 2,3-dichlorobenzylidene-acetoacetates **4** and **12**, longer reaction times with respect to the other arylidene derivatives or heating with $CF_3COOH/CHCl_3$ was needed in order to accomplish the elimination reaction. Attempts to synthesize intermediates **12** in refluxing C_6H_6 in the presence of piperidinium acetate as catalyst resulted less satisfactory than using excess HCl in $CHCl_3$. This might be due to basic-assisted hydrolysis of the aminobenzylidene derivatives formed. Sometimes, the re-formation of small amounts of the corresponding **10** and **3** (5 to 10%) was noticed, after prolonged contact with water or silica gel of these compounds in the base form.

In some cases, the HCl-catalyzed condensation to **12** afforded also minor amounts of the addition compound of HCl to the benzylidene double bond. The aminoalcohols **10b,e,g** were synthesized by specific routes, as depicted in *figures 3* and *4*.

Addition of *N*-(3,3-diphenylpropyl)methylamine to 3-buten-2-one gave the 3-aminoketone **13** that was C-alkylated via methylmagnesium iodide, yielding the desired aminoalcohol **10e**. Intermediate **13** was also reduced with $NaBH_4$ to give the corresponding aminoalcohol **10d**.

In *figure 4*, esterification of 3-methylcrotonic acid with ethanol gave the corresponding ester **14**; the addition reaction of the commercially available 3,3-diphenylpropylamine to this ester gave the 3-amino-butyrate **15**. Alkylation of this secondary amine with methyl iodide gave the tert-aminoester **16** that was finally reduced with $LiAlH_4$ yielding **10g**.

Some of the 1,4-dihydropyridines **9** were isolated as hydrochloride salt in form of amorphous solids, because of difficulties in obtaining crystals. When the NMR spectrum of compound **9u** and some other **9** derivatives having only the C_4 chiral center, in the ·HCl form were recorded in $CDCl_3$ solution at high field (200–300 MHz) complex spectra were obtained, suggesting the presence of two different species, probably due to intramolecular interactions. This will be the subject of a separate publication.

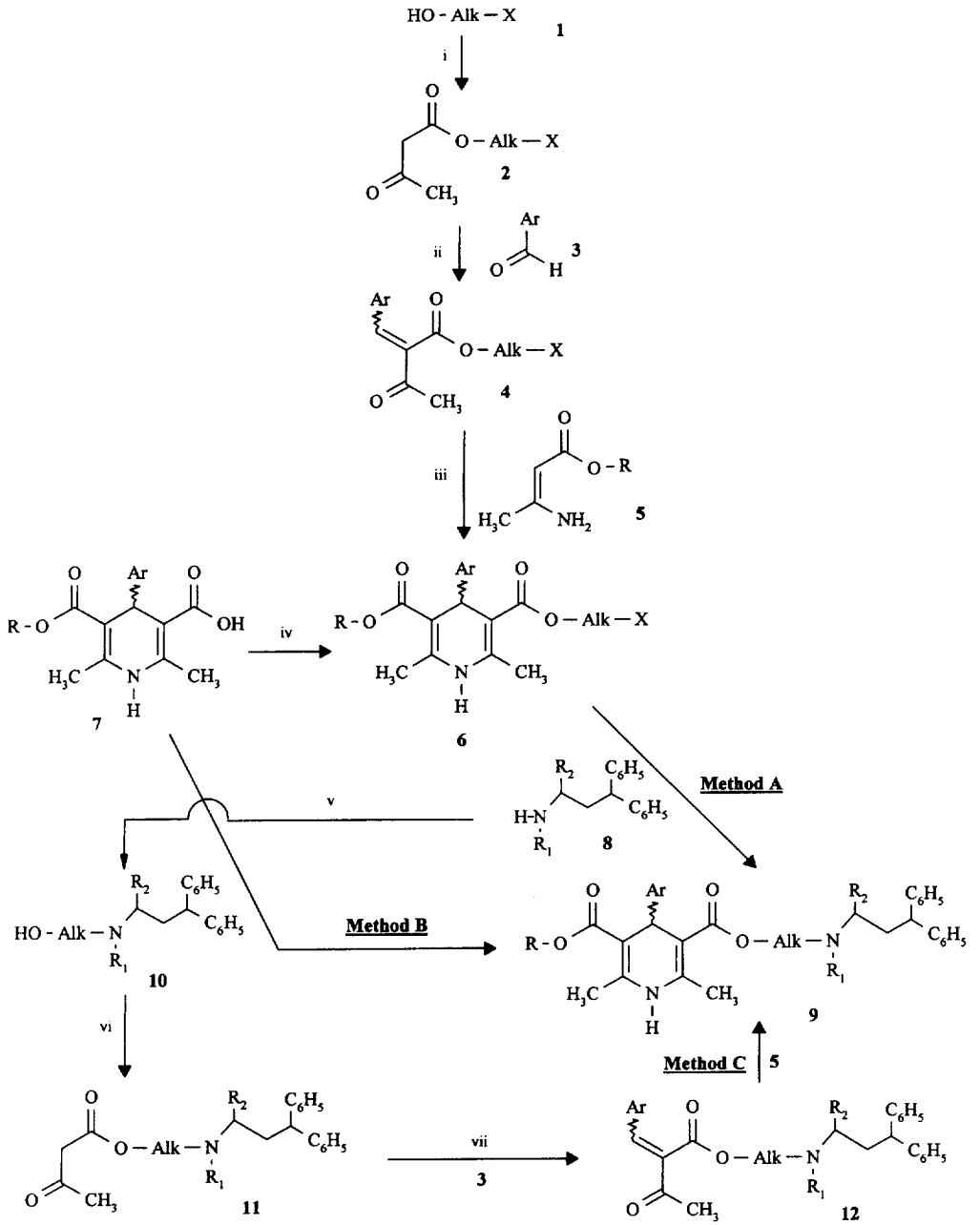
The structure and main characteristics of the intermediates utilized are shown in *tables II–VIII*. The 'final' compounds are listed in *table I*.

3. Pharmacology

Radioreceptor binding studies were performed with ^{3}H-nitrendipine on rat brain membrane, according to the method previously reported [27]. Test compounds were assayed as solutions in ethanol and the affinity for the channel is reported as IC_{50} (concentration inhibiting by 50% the binding of ^{3}H-nitrendipine). In *table IX*.

The antihypertensive activity of new and known compounds was tested in 12–16 weeks old SHR/Crl/BR rats (4 animals per dose). Test compounds were administered by gavage as suspensions in 0.5% methocel in saline. Conscious animals were pre-warmed at 37 °C for 15 min before tail-cuff recording of systolic blood pressure [28]. The antihypertensive effects at peak time were expressed as ED_{25} (dose lowering by 25% the systolic blood pressure). The time of peak effect was generally about 3 h, with few exceptions reported in table IX.

Indicative acute toxicity was determined after intraperitoneal and oral administration of test



i) diketene / 70-120°C
ii) **3**, HCl gas / toluene 0/+5°C
iii) **5** / *i*-PrOH or EtOH, reflux
iv) 1,4-dibromobutane, K_2CO_3 / DMF, 50°C
v) alkylene oxide / MeOH, r.t. or haloalkanol / xylene, reflux
vi) diketene / toluene, 85-100°C
vii) **3**, HCl gas / $CHCl_3$, 0°C-r.t.

Figure 2. Synthesis of final 1,4-dihydropyridines **9**.

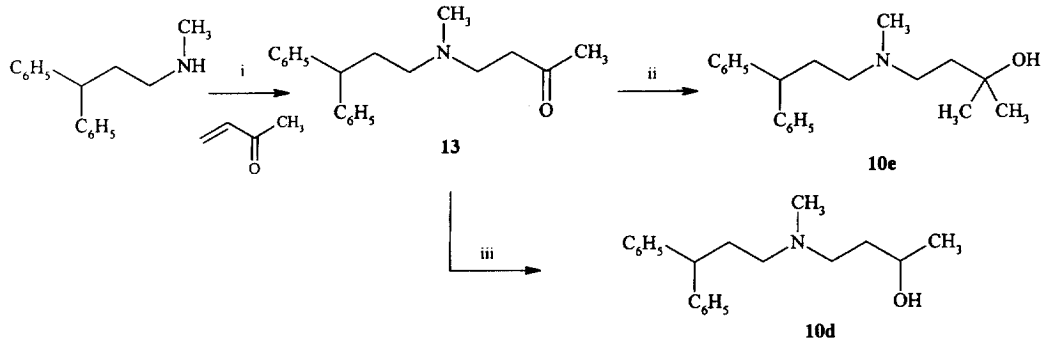


Figure 3. Synthetic pathway for aminoalcohol **10d** and **10e**.

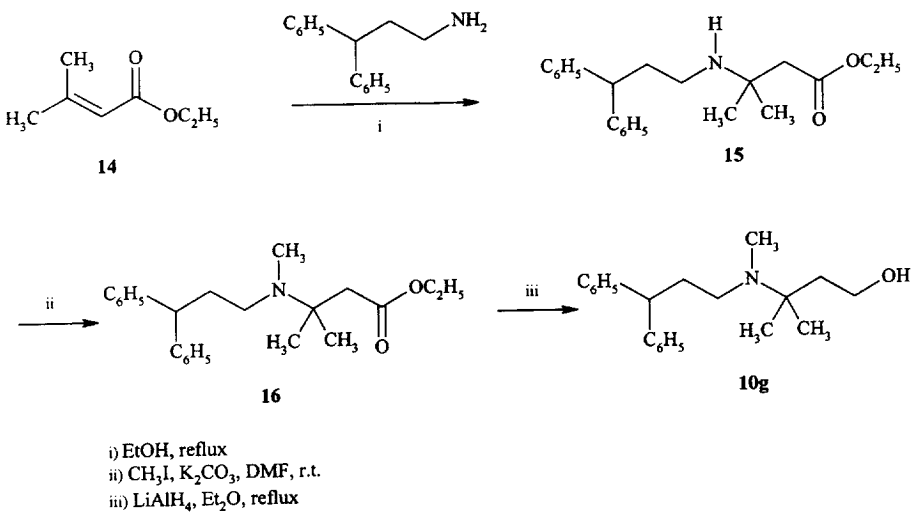


Figure 4. Synthetic pathway for aminoalcohol **10g**.

compounds, as suspension in 0.5% methocel in saline, to Crl/CD–I–(ICR)BR mice (4 animals per dose). For the interesting molecules, indicative acute toxicity was also determined in Sprague Dawley rats by intravenous administration of solutions in aqueous propylene glycol (4 animals per dose). The mortality rate was recorded over a 14-day period.

4. Results and discussion

As shown in *table IX*, most compounds exhibited antihypertensive activity and affinity for the calcium channel labelled by ^{3}H-nitrendipine comparable or better than the reference 1,4-DHPs. A trend to correlate was found between the in vitro and in vivo results (see *figure 5*), taking into account that the oral administration route was used for testing the antihypertensive activity ($Y = 5.49 - 0.53X$; $r = 0.723$; $n = 31$).

With regard to the structural modifications performed, the following comments can be made. With regard to the aromatic group at position 4 of the 1,4-DHP ring, Ar, the 3-nitrophenyl group showed the most desirable profile for pharmacological and toxicological properties.

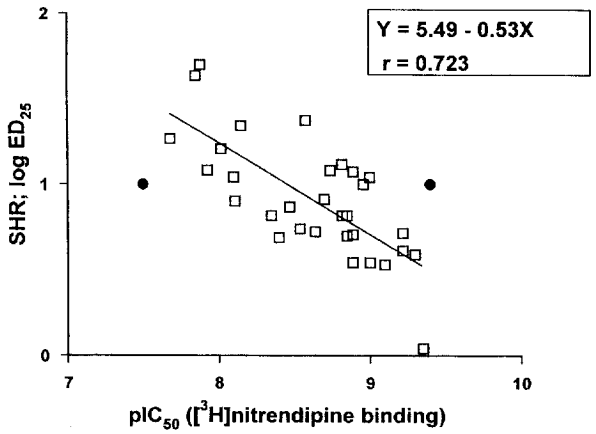


Figure 5. Correlation between affinity for the calcium channel binding site (pIC_{50}) and the antihypertensive activity in SHR (log ED_{25}). Points shown as closed circles were excluded from computation.

In agreement with the known SAR studies on this class of compounds [8, 29–31], the introduction of the 4-nitrophenyl group (compound **9v**) caused loss of activity. A tendency to a longer duration of the antihypertensive effect was noticed for compounds bearing the 2,3-dichlorophenyl group, in particular for **9c**.

As far as the non-basic ester group R is concerned, in the subset where Alk is an ethylene bridge (compounds **9b,g–j**) ethyl, *i*-propyl and *i*-butyl showed the best antihypertensive potency, whereas methyl group proved in general more potent when the ethylene bridge was branched (compounds **9n–s,u–z**).

Derivatives with R = propoxyalkyl resulted, on an average, less toxic in mouse. Since this loss of toxicity upon oral administration was not paralleled by a decrease in toxic effects after i.v. administration in rat, it is possible that lower toxicity in mouse is actually due to lower bioavailability in this species. Changing a hydrogen atom for a methyl group at R_1 or R_2 did not substantially affect the pharmaco-toxicological activity.

With regard to the alkylene spacer Alk, the propylene bridge of **9k** proved the best among linear chains. Branching with one or two methyl groups at the oxygen-bonded carbon in the ethylene subset enhanced potency and, in some cases, reduced toxicity in the rat.

The diastereoselectivity found with the 2-propylene derivatives $\mathbf{9n_1}$ and $\mathbf{9n_2}$ confirms the ability of this structural element in modulating, directly or indirectly, the affinity for the 1,4-DHP site in the calcium channel. This modulating role was more evident in the 1,3-propylene derivatives **9ac,ad,af**, where formal double methylation at position 2 of the chain afforded the most potent derivative in the series (**9ad**). Quite surprisingly, **9ac**, combining the desirable features of **9k** (linear propylene bridge) and of **9u** ($C(CH_3)_2CH_2$ in the bridge), proved significantly less potent than **9ad** and said analogues.

The absence of antihypertensive activity and toxic effects in the mouse seen with the 3,3-diphenylpropanamide derivative **9ag**, in presence of a strong affinity for the calcium channel, prompted us to evaluate its antihypertensive effect upon intravenous administration in catheterized SHR following the protocol described in [32]. In this case a strong antihypertensive effect was noticed (ED_{25} = 44 μg/kg, versus 16 μg/kg for **9u**), pointing out a very low systemic absorption for this compound upon oral administration and suggesting that the presence of the amino group in the whole series influences more the bioavailability of these compounds than their affinity for the calcium channel.

Inspection of data obtained for the new 4-(3-nitrophenyl)-1,4-DHPs suggests that the introduction of the 3,3-diphenylpropylamino moiety confers to the whole series an elevated and fairly constant level of antihypertensive activity irrespective of the structural variations of the groups R and Alk, the only feature which generates real differences in in vivo and in vitro pharmacological activity being the position of the gem-dimethyl group when the alkylene bridge is a propyl chain (compounds **9ac,ad,af**). In addition, the presence of this bulky and lipophilic moiety confers the new molecules a delayed peak of the antihypertensive effect, associated to a longer duration, with regard to the less lipophilic nifedipine.

5. Conclusions

Compound **9u** (Rec 15/2375-lercanidipine) was selected for development and obtained marketing authorization in several countries as an antihypertensive. The main characteristics of this drug are the slow onset and long duration of its action, although in the presence of low plasma levels and short plasma half life [33]. This behaviour is explained with the high partition coefficient, measured both in *n*-octanol/acidic buffer (log P = 6.0, pK_a' = 6.83, see experimental protocols) and in artificial cardiac phospholipids membranes (log $K_{p[mem]}$ = 6.1 at pH = 7.4) [34], which confers an elevated affinity for the lipidic bilayer of cells in the cardiovascular system.

Lercanidipine is also characterized by high vascular selectivity and absence of negative inotropic effects [35]. In agreement with the results obtained with most

chiral 1,4-dihydropyridines [36], (*S*)-lercanidipine proved to be the eutomer. The synthesis of lercanidipine enantiomers will be the subject of a separate publication. Full accounts on the pharmacological and clinical studies performed with lercanidipine are reported in references [37, 38].

6. Experimental protocols

6.1. Chemistry

Reagents, starting materials and solvents were purchased from commercial suppliers. Flash chromatography was performed on silica gel (Merck 70–230 mesh). Melting points were determined on a Buchi 535 apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Perkin-Elmer 297 infrared spectrophotometer and were consistent with the structures. ^{1}H-NMR spectra were recorded on a Hitachi-Perkin Elmer R24A or on a Brucker AC 200. The chemical shifts (δ) are in ppm relative to tetramethylsilane. The purity of the compounds was checked by TLC (Merck silica gel 60, F254 0.25 mm). Analyses indicated by the symbols of the elements were within ±0.4% of the theoretical values.

6.2. Preparation of intermediates ***1***

6.2.1. 2-Methyl-1-propoxy-2-propanol ***1a***

0.1 g-atom (2.3 g) of sodium was added in small portions to 0.53 mol (32 g) of 1-propanol and the mixture was stirred until sodium dissolution (1.5 h). The temperature was lowered to 80 °C and 0.1 mol (10.76 g) of 1-chloro-2-methyl-2-propanol was added dropwise in 30 min. The mixture was stirred at reflux temperature for 10 h then cooled to room temperature, filtered and the filtrate distilled at normal pressure; the fraction collected at 145–148 °C gave 27.7 g (52%) of pure compound. Anal. $C_7H_{16}O_2$ (C, H). ^{1}H-NMR ($CDCl_3$): 3.5 (t, 2H, C–C–CH_2–O–C), 3.3 (s, 2H, O–CH_2–C–O), 2.65 (s, 1H, OH), 1.55 (m, 2H, C–CH_2–C–O), 1.25 (s, 6H, gem-CH_3s), 0.95 (t, 3H, CH_3–C–C–O).

6.3. Preparation of intermediates ***2*** *(table II)*

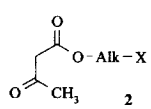
6.3.1. 2-Chloro-1-methylethyl acetoacetate ***2c***

0.42 mol (35.4 g) of diketene was added in 45 min to 0.40 mol (41.4 g) of 1-chloro-2-propanol stirred at 80 °C. The mixture was heated at 100 °C and after 45 min the temperature spontaneously rose to 120 °C for 20 min. Heating was continued at 100 °C for additional 3 h then the mixture was cooled to room temperature and distilled in vacuo. The fraction collected at 113–115 °C/16 mmHg gave 61.6 g (86%) of the pure compound. Anal. $C_7H_{11}ClO_3$ (C, H, Cl). ^{1}H-NMR ($CDCl_3$): 4.85–5.35 (m, 1H, CH), 3.4–3.7 (m, 4H, CH_2COO and CH_2Cl), 2.25 (s, 3H, CH_3–CO–C), 1.35 (d, 3H, COO–C–CH_3). The product contained about 8% of its enolic form whose main visible peaks are as follows: 12.2 (s, OH), 1.95 (s, CH_3–C=).

6.3.2. 3-Chloropropyl acetoacetate ***2d***

0.315 mol (26.5 g) of diketene was added in 45 min to 0.3 mol (28.35 g) of 3-chloropropanol stirred at 70 °C. During the addition the temperature was gradually raised to 120 °C and then was kept at 100 °C for 3 h. After cooling to room

Table II. Alkyl and haloalkyl acetoacetates **2**. Acetoacetates **2e–h** were reacted with ammonia to give the corresponding 3-aminocrotonates **5a–d** (*table IV*).



2

Compound	Alk-X	Yield (%)	B.p. (°C)/mmHg	Anal.
2a	$(CH_2)_2Cl$	89	115–117/19[a]	–
2b	$(CH_2)_2Br$	61	83–88/0.4[b]	–
2c	$CH(CH_3)CH_2Cl$	86	113–115/16	C, H, Cl
2d	$(CH_2)_3Cl$	82	125–131/15	C, H, Cl
2e	$CH(CH_3)_2$	84	73–75/15[c]	–
2f	$CH_2CH(CH_3)_2$	83	93–95/15[d]	–
2g	$(CH_2)_2O(CH_2)_2CH_3$	92	125–128/16[e]	–
2h	$C(CH_3)_2CH_2O(CH_2)_2CH_3$	88	123–125/16	C, H

[a]100–102 °C/10 mmHg [13]; [b]124–127 °C/20 mmHg [22]; [c]66–69 °C/10 mmHg [23]; [d]100 °C/22 mmHg [24]; [e]130–137 °C/20 mmHg [13].

temperature the mixture was distilled in vacuo and the fraction collected at 125–131 °C/15 mmHg gave 43.9 g (82%) of the pure compound. Anal. $C_7H_{11}ClO_3$ (C, H, Cl). ^{1}H-NMR ($CDCl_3$): 4.2 (t, 2H, OCH_2–C–C), 3.65 (t, 2H, O–C–C–CH_2Cl), 3.5 (s, 2H, $COCH_2COO$), 2.2 (s, 3H, CH_3CO), 2.05 (m, 2H, O–C–CH_2–C–Cl). A peak at 12.3 (OH) and a peak at 5.0 (C=CHCOO) were present, attributed to about 5% of the enolic form.

6.3.3. 2-Methyl-1-propoxy-2-propyl acetoacetate ***2h***

0.347 mol (29.2 g) of diketene was dropped in 40 min into a stirred mixture of 0.316 mol (41.9 g) of 2-methyl-1-propoxy-2-propanol (**1a**) and 1 mmol (0.1 g) of triethylamine, preheated at 100 °C. Further heating lasted 4 h, without exceeding the temperature of 105 °C. After cooling to room temperature, the mixture was distilled in vacuo and the fraction collected at 123–125 °C/16 mmHg gave 60.6 (88%) of the pure compound. Anal. $C_{11}H_{20}O_4$ (C, H). ^{1}H-NMR ($CDCl_3$): 3.5 (s, 2H, $COCH_2$), 3.4 (t, 2H, O–CH_2–C–C), 3.35 (s, 2H, O–C–CH_2–O), 2.25 (s, 3H, CH_3–CO), 1.5 (m, 2H, O–C–CH_2–C), 1.45 (s, 6H, gem-CH_3s), 0.9 (t, 3H, O–C–C–CH_3).

6.4. Preparation of intermediates ***3***

6.4.1. Benzofurazan-4-carbaldehyde

A mixture of 0.01 mol (1.34 g) of 4-methylbenzofurazan [39] and 0.011 mol (1.21 g) of selenium dioxide was stirred at 160 °C for 8 h. After cooling to room temperature the mixture was crushed with EtOAc, the insoluble was removed by filtration and the filtrate evaporated to dryness in vacuo. The crude was purified by flash chromatography eluting with a $CHCl_3$–petroleum ether 9:1 mixture. Yield 82% (1.21 g), m.p. 108–109 °C after crystallization from cyclohexane. Anal. $C_7H_4N_2O_2$ (C, H, N). ^{1}H-NMR ($CDCl_3$): 10.1 (s, 1H, CHO), 8.4–7.5 (m, 3H, aromatics). This compound was also obtained in lower yield starting from 4-bromomethylbenzofurazan through a Sommelet reaction [39].

6.5. Preparation of intermediates ***4*** *(table III)*

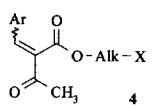
6.5.1. 2-Chloro-1-methylethyl 2-(3-nitrobenzylidene)acetoacetate ***4c***

A mixture of 0.08 mol (12.2 g) of 3-nitrobenzaldehyde and 0.08 mol (14.3 g) of 2-chloro-1-methylethyl acetoacetate **2c** in 80 mL of toluene was saturated with HCl at 0/5 °C. The solution was kept two days at room temperature and after this period a stream of N_2 was bubbled to eliminate excess HCl. The solvent was evaporated in vacuo and the oil was dissolved into CH_2Cl_2, washed with H_2O until neutrality, dried over Na_2SO_4, filtered, and evaporated in vacuo to dryness. Crystallization from *i*-propanol gave 20.7 g (83%) of the pure compound (*E/Z* mixture). M.p. 95–96 °C. Anal. $C_{14}H_{14}ClNO_5$ (C, H, N, Cl). ^{1}H-NMR ($CDCl_3$): 8.3–7.5 (m, 4H, aromatics), 7.55 (s, 1H, CH=C), 5.25 (m, 1H, COOCH), 3.55 (d, 2H, C–CH_2Cl), 2.45 (s, 3H, CH_3–CO–C), 1.36 (d, 3H, COO–C–CH_3).

6.5.2. 3-Chloropropyl 2-(3-nitrobenzylidene)acetoacetate ***4d***

A mixture of 0.17 mol (30.34 g) of 3-chloropropyl acetoacetate **2d** and 0.17 mol (25.7 g) of 3-nitrobenzaldehyde in 170 mL of toluene was treated as described for **4c**. The crude was purified by flash chromatography eluting with toluene. Yield 50.9 g (95%), m.p. 63–65 °C. Anal. $C_{14}H_{14}ClNO_5$ (C, H, N, Cl). ^{1}H-NMR ($CDCl_3$): 8.50–7.50 (m, 5H, aromatics and CH=C), 4.45 (t, 2H, $COOCH_2$), 3.65 and 3.50 (2t, 2H, CH_2Cl of *E/Z* isomers), 2.50 (s, 3H, CH_3CO), 2.10 (m, 2H, COO–C–CH_2).

Table III. Haloalkyl 2-benzylideneacetoacetates **4** (*E/Z* mixtures).



4

Compound	Ar	Alk-X	Yield	M.p. (°C)	Anal.
4a	2-NO_2–C_6H_4	$(CH_2)_2Cl$	58	Oil[a]	–
4b	3-NO_2–C_6H_4	$(CH_2)_2Cl$	86	92–95[b]	–
4c	3-NO_2–C_6H_4	$CH(CH_3)CH_2Cl$	83	95–96	C, H, N, Cl
4d	3-NO_2–C_6H_4	$(CH_2)_3Cl$	95	63–65	C, H, N, Cl
4e	3-NO_2–C_6H_4	$(CH_2)_2Br$	69	83–91	C, H, N, Br
4f	2,3-Cl_2–C_6H_3	$(CH_2)_2Cl$	87	Oil	C, H, N, Cl
4g	2,3-Cl_2–C_6H_3	$CH(CH_3)CH_2Cl$	100	Oil	C, H, Cl
4h	4-benzofurazanyl	$(CH_2)_2Cl$	95	Oil	C, H, N, Cl

[a]Sample enriched in the isomer with higher R_F, m.p. 74–75 °C (*i*-PrOH) [25]; [b]sample crystallized from CCl_4, m.p. 94–97 °C (*i*-PrOH) [25].

*6.5.3. 2-Bromoethyl 2-(3-nitrobenzylidene)acetoacetate **4e***

A mixture of 0.055 mol (8.3 g) of 3-nitrobenzaldehyde, 0.055 mol (11.5 g) of 2-bromoethyl acetoacetate **2b** and 55 mL of toluene was saturated with anhydrous HBr at 0/5 °C. The solution was kept at room temperature for 7 days, bubbled with a N_2 stream and evaporated to dryness. The solution was diluted with Et_2O and washed with with H_2O until neutrality; the organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was dissolved into $CHCl_3$ (100 mL), added with trifluoroacetic acid (20 mL) and the solution refluxed for 20 h. After cooling to room temperature the solution was washed with H_2O until neutrality, dried over anhydrous Na_2SO_4 and evaporated to dryness in vacuo to give a crude (15.75 g) that was treated with boiling CCl_4 (300 mL). The insoluble was removed by filtration, the filtrate was evaporated to dryness and the residue washed with Et_2O (60 mL) to give 12.9 g (69%) of the pure compound. M.p. 83–91 °C. Anal. $C_{13}H_{12}BrNO_5$ (C, H, N, Br). ^{1}H-NMR ($CDCl_3$): 8.5–8.2 (m, 2H, 3-nitrophenyl–H_2–H_4), 8.05–7.6 (m, 3H, 3-nitrophenyl–H_5–H_6 and CH=C), 4.65 (t, 2H, $COOCH_2$), 3.65 and 3.55 (2t, 2H, CH_2Br of *E/Z* isomers), 2.5 (s, 3H, CH_3CO).

*6.5.4. 2-Chloroethyl 2-(2,3-dichlorobenzylidene)acetoacetate **4f***

A mixture of 0.1 mol (17.5 g) of 2,3-dichlorobenzaldehyde, 0.1 mol (16.45 g) of 2-chloroethyl acetoacetate **2a** and 100 mL of toluene was saturated with HCl at 0/3 °C and the solution was kept at room temperature for 7 days. After this period a stream of N_2 was bubbled to eliminate HCl, the solution was diluted with Et_2O and washed with H_2O until neutrality. The organic phase was dried over anhydrous Na_2SO_4 and evaporated in vacuo to give an oily residue (35 g) that was dissolved into $CHCl_3$ (230 mL), added with trifluoroacetic acid (35 mL) and the solution refluxed for 20 min. After cooling to room temperature the solution was washed with H_2O until neutrality, dried over anhydrous Na_2SO_4 and evaporated to dryness in vacuo to give 28.5 g (87%) of the pure compound as a thick oil. Anal. $C_{13}H_{11}Cl_3O_3$ (C, H, Cl). ^{1}H-NMR ($CDCl_3$): 7.9 and 7.8 (2s, 1H, CH=C of *E/Z* isomers), 7.6–7.1 (m, 3H, aromatics), 4.5–4.2 (m, 2H, $COOCH_2$), 3.8–3.4 (m, 2H, CH_2Cl), 2.45 and 2.2 (2s, 3H, CH_3CO of *E/Z* isomers).

*6.5.5. 2-Chloro-1-methylethyl 2-(2,3-dichlorobenzylidene)-acetoacetate **4g***

A solution of 0.1 mol (17.5 g) of 2,3-dichlorobenzaldehyde in 70 mL of toluene was added at 20 °C to a solution of 0.1 mol (17.8 g) of 2-chloro-1-methylethyl acetoacetate **2c** in 30 mL of toluene. The mixture was saturated with HCl at 0/3 °C and the solution was kept at room temperature for 7 days. After this period a stream of N_2 was bubbled to eliminate HCl, the solution was diluted with Et_2O and washed with H_2O until neutrality. The organic phase was dried over anhydrous Na_2SO_4 and evaporated in vacuo to give an oily residue that was dissolved in $CHCl_3$ (300 mL) and added with trifluoroacetic acid (35 mL), and the solution refluxed for 20 h. After cooling to room temperature the solution was washed with H_2O until neutrality, dried over anhydrous Na_2SO_4 and evaporated to dryness in vacuo to give 33.5 g (100%) of the pure compound as a *E/Z* isomers mixture in form of a thick oil. A sample of this mixture was flash chromatographed eluting with toluene and the residue crystallized from cyclohexane to give the pure isomer melting at 63–65 °C. Anal. $C_{14}H_{13}Cl_3O_3$ (C, H, Cl). ^{1}H-NMR ($CDCl_3$): 7.9 (s, 1H, CH=C–CO), 7.7–7.1 (m, 3H, aromatics), 5.5–4.9 (m, 1H, COOCH), 3.5 (d, 2H, CH_2Cl), 2.5 (s, 3H, CH_3CO), 1.25 (d, 3H, COO–C–CH_3).

*6.5.6. 2-Chloroethyl 2-(4-benzofurazanylmethylidene)acetoacetate **4h***

A mixture of 0.1 mol (16.2 g) of 2-chloroethyl acetoacetate, 0.1 mol (14.8 g) of benzofurazan-4-carbaldehyde and 200 mL of $CHCl_3$ was saturated with anhydrous HCl at 0 °C. The solution was kept at room temperature for 7 days, bubbled with a N_2 stream and evaporated to dryness. The residue was dissolved in EtOAc and the solution was washed with diluted aqueous $NaHCO_3$ solution followed by H_2O; the organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to dryness to give the oily pure compound, (TLC $CHCl_3$–EtOAc, 95:5). Yield 28 g (95%). This compound was directly used for the synthesis of the corresponding dihydropyridine **6g**. Anal. $C_{13}H_{11}ClN_2O_4$ (C, H, N, Cl). ^{1}H-NMR ($CDCl_3$): 8.2–7.35 (m, 4H, $H_{5,6,7}$ of benzofurazanyl ring and CH=C), 3.0–2.7 and 2.7–2.35 (2m, 2H, CH_2Cl of *E/Z* isomers), 2.8–2.45 and 2.4–2.05 (2m, 2H, $COOCH_2$ of *E/Z* isomers), 2.55 and 2.2 (2s, 3H, CH_3 of *E/Z* isomers).

*6.6. Preparation of intermediates **5** (table IV)*

*6.6.1. 2-Methyl-1-propoxy-2-propyl 3-aminocrotonate **5d***

A stream of anhydrous NH_3 (150 g) was bubbled in about 50 h into a solution of 0.05 mol (10.81 g) of 2-methyl-1-propoxy-2-propyl acetoacetate **2h** in 40 mL of CH_2Cl_2. During this time the temperature was not allowed to exceed 15 °C and at the end the mixture was diluted with 50 mL of CH_2Cl_2, dried over anhydrous Na_2SO_4 and evaporated to dryness in vacuo at room temperature to give 10.1 g (94%) of the oily compound, which in some preparations contained from 5 to 10% of the starting material. This product was used without further purification for the synthesis of final compound **9aa**. Anal. $C_{11}H_{21}NO_3$ (C, H, N). ^{1}H-NMR ($CDCl_3$): 7.0–5.0 (bs, 2H, NH_2), 4.4 (s, 1H, CHCOO), 3.5 (s, 2H, COO–C–CH_2O), 3.4 (t, 2H, O–CH_2–C–C), 1.8 (s, 3H, CH_3–C=C), 1.8–1.1 (m, 2H, O–C–CH_2–C), 1.45 (s, 6H, gem-CH_3s), 0.9 (t, 3H, O–C–C–CH_3).

*6.7. Preparation of intermediates **6** (table V)*

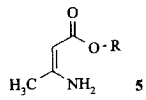
*6.7.1. 2-Chloroethyl methyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate **6a***

A mixture of 0.075 mol (22.33 g) of 2-chloroethyl 2-(2-nitrobenzylidene)acetoacetate **4a**, 0.075 mol (8.90 g) of methyl 3-aminocrotonate and 60 mL of 2-propanol was stirred at reflux temperature for 3 h. After cooling to room temperature, the solvent was evaporated in vacuo and the residue was purified by flash chromatography eluting with $CHCl_3$. The collected pure fractions (TLC $CHCl_3$–EtOAc, 9:1) were pooled and the solid residue obtained after solvent evaporation was washed with *i*-Pr_2O to give 11.2 g (38%) of pure **6a**. M.p. 118–120 °C (*i*-Pr_2O). Anal. $C_{18}H_{19}ClN_2O_6$ (C, H, N, Cl). ^{1}H-NMR ($CDCl_3$): 7.8–7.0 (m, 4H, aromatics), 6.1 (bs, 1H, NH), 5.75 (s, 1H, CH), 4.25 (t, 2H, $COOCH_2$), 3.55 (t, 2H, CH_2Cl), 3.55 (s, 3H, CH_3O), 2.35 and 2.25 (2s, 6H, 2,6 CH_3s).

*6.7.2. 2-Chloro-1-methylethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate **6c***

Same procedure as for **6a**.Yield 64% (after column chromatography, eluting with $CHCl_3$ and washing with H_2O); m.p. 115–119 °C. Anal. $C_{19}H_{21}ClN_2O_6$ (C, H, N, Cl). ^{1}H-NMR ($CDCl_3$): 8.1–7.2 (m, 4H, aromatics), 6.05 (bs, 1H, NH), 5.05 and 5.1 (2s, 1H, pyridine–CH), 4.2–3.8 (m, 1H, COOCH), 3.65 (s, 3H, CH_3O), 3.5 (dd, 2H, CH_2Cl), 2.35 (s, 6H, 2.6 CH_3s), 1.25 (dd, 3H, COO–C–CH_3).

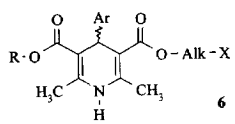
Table IV. Alkyl 3-aminocrotonates **5**.



Compound	R	Yield (%)	M.p. or b.p. (°C)/mmHg	Anal.
5a	$CH(CH_3)_2$	95	106–107/20[a]	–
5b	$CH_2CH(CH_3)_2$	85	131/22[b]	–
5c	$(CH_2)_2O(CH_2)_2CH_3$	97	Oil[c,d]	–
5d	$C(CH_3)_2CH_2O(CH_2)_2CH_3$	94	Oil[d]	C, H, N

[a]102–103 °C/12 mmHg [23]; [b]116–118 °C/17 mmHg [26]; [c]120 °C/0.7 mmHg [13]; [d]not distilled by us since the crude showed acceptable purity (tlc).

Table V. Alkyl haloalkyl 4-aryl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates **6**.



Compound	R	Ar	Alk-X	Yield (%)	M.p. (°C)	Anal.
6a	CH_3	2-NO_2–C_6H_4	$(CH_2)_2Cl$	38	118–120	C, H, N, Cl
6b	CH_3	3-NO_2–C_6H_4	$(CH_2)_2Cl$	62	136–138[a]	–
6c	CH_3	3-NO_2–C_6H_4	$CH(CH_3)CH_2Cl$	64	115–119	C, H, N, Cl
6d	CH_3	3-NO_2–C_6H_4	$(CH_2)_3Cl$	81	144–147	C, H, N, Cl
6e	CH_3	3-NO_2–C_6H_4	$(CH_2)_4Br$	84	124–125	C, H, N, Br
6f	CH_3	2,3-Cl_2–C_6H_3	$(CH_2)_2Cl$	44	167–169	C, H, N, Cl
6g	CH_3	4-benzofurazanyl	$(CH_2)_2Cl$	36	117–118	C, H, N, Cl
6h	CH_3CH_2	3-NO_2–C_6H_4	$(CH_2)_2Cl$	67	160–162	C, H, N, Cl
6i	$(CH_3)_2CH$	3-NO_2–C_6H_4	$(CH_2)_2Cl$	71	141–146[b]	–
6j	$(CH_3)_2CHCH_2$	3-NO_2–C_6H_4	$(CH_2)_2Cl$	69	155–157	C, H, N, Cl
6k[c]	$(CH_3)_2CHCH_2$	2,3-Cl_2–C_6H_3	$CH(CH_3)CH_2Cl$	48	Oil	C, H, N, Cl
6l	$CH_3(CH_2)_2O(CH_2)_2$	3-NO_2–C_6H_4	$(CH_2)_2Cl$	70	104–106	C, H, N, Cl

[a]130–131 °C [23]; [b]143–145 °C [23]; [c]unstable to heating and silicagel.

6.7.3. 3-Chloropropyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate ***6d***

The reaction was carried out as for **6a** but using ethanol, as reaction solvent, at reflux temperature for 6 h. The product crystallized from the reaction mixture. Yield 81%; m.p. 144–147 °C (EtOH). Anal. $C_{19}H_{21}ClN_2O_6$ (C, H, N, Cl). ^{1}H-NMR ($CDCl_3$): 8.2–7.2 (m, 4H, aromatics), 6.5 (s, 1H, NH), 5.1 (s, 1H, CH), 4.2 (t, 2H, $COOCH_2$), 3.7 (s, 3H, CH_3O), 3.45 (t, 2H, CH_2Cl), 2.4 (s, 6H, 2,6 CH_3s), 2.05 (t, 2H, COO–C–CH_2–C).

6.7.4. 4-Bromobutyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate ***6e***

A suspension of 0.03 mol (9.96 g) of 1,4-dihydro-2,6-dimethyl-5-methoxycarbonyl-4-(3-nitrophenyl)pyridin-3-carboxylic acid [40], 0.09 mol (19.43 g) of 1,4-dibromobutane, 0.015 mol (2.07 g) of anhydrous K_2CO_3 and 60 mL of anhydrous DMF was stirred at 50 °C for 2.5 h. After cooling to room temperature, the mixture was poured into 400 mL of H_2O, extracted with Et_2O, the organic layer washed with H_2O, dried over anhydrous Na_2SO_4 and evaporated to dryness in vacuo. The oily residue was purified by flash chromatography eluting with $CHCl_3$–EtOAc (100:0 to 97:3) gradient mixture, to give 11.75 g (84%) of the pure compound. M.p. 124–125 °C (*i*-PrOH or CCl_4). Anal. $C_{20}H_{23}BrN_2O_6$ (C, H, N, Br). ^{1}H-NMR ($CDCl_3$): 8.3–7.4 (m, 4H, aromatics), 6.45 (s, 1H, NH), 5.2 (s, 1H, CH), 4.3–4.0 (m, 2H, $COOCH_2$), 3.75 (s, 3H, OCH_3), 3.6–3.3 (m, 2H, CH_2Br), 2.4 (s, 6H, 2,6 CH_3s), 2.0–1.6 (m, 4H, O–C–CH_2CH_2–C).

6.7.5. 2-Chloroethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate ***6f***

Same procedure as for **6a**. The reaction mixture was refluxed for 8 h. The crude crystallized from the reaction mixture and was purified by flash chromatography eluting with $CHCl_3$–EtOAc (100:0 to 95:5) gradient mixture. Yield 44%; m.p. 167–169 °C (*i*-PrOH). Anal. $C_{18}H_{18}Cl_3NO_4$ (C, H, N, Cl). ^{1}H-NMR ($CDCl_3$): 7.5–6.8 (m, 3H, aromatics), 6.05 (s, 1H, NH), 5.45 (s, 1H, CH), 4.25 (t, 2H, $COOCH_2$), 3.6 (s + t, 5H, CH_3O and CH_2Cl), 2.3 (s, 6H, 2,6 CH_3s).

6.7.6. 2-Chloroethyl methyl 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate ***6g***

Same procedure as for **6a**.The reaction mixture was refluxed for 13 h and the crude was purified by flash chromatography eluting with $CHCl_3$–EtOAc (100:0 to 95:5) gradient mixture. The residue was washed with *i*-Pr_2O and dried in vacuo at 40 °C for 2 h. Yield 36%; m.p. 117–118 °C. Anal. $C_{18}H_{18}ClN_3O_5$ (C, H, N, Cl). ^{1}H-NMR ($CDCl_3$): 8.0–7.1 (m, 3H, aromatics), 6.8 (s, 1H, NH), 5.6 (s, 1H, CH), 4.3 (t, 2H, $COOCH_2$), 3.7 (s, 3H, CH_3O), 3.65 (t, 2H, CH_2Cl), 2.3 (s, 6H, 2,6 CH_3s).

6.7.7. 2-Chloroethyl ethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate ***6h***

Same procedure as for **6a**. The reaction was carried out in ethanol at reflux temperature for 7 h. Yield 67% (after column chromatography, eluent $CHCl_3$); m.p. 160–162 °C (*i*-PrOH). Anal. $C_{19}H_{21}ClN_2O_6$ (C, H, N, Cl). ^{1}H-NMR ($CDCl_3$): 8.2–7.2 (m, 4H, aromatics), 6.35 (bs, 1H, NH), 5.1 (s, 1H, CH), 4.3 (t, 2H, $COOCH_2$–C–Cl), 4.08 (q, 2H, $COOCH_2$–C), 3.6 (t, 2H, CH_2Cl), 2.35 (s, 6H, 2,6 CH_3s), 1.2 (t, 3H, COO–C–CH_3).

6.7.8. 2-Chloroethyl 2-methylpropyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate ***6j***

Same procedure as for **6a**. Yield 69% (after column chromatography, eluent $CHCl_3$); m.p. 155–157 °C (*i*-PrOH). Anal. $C_{21}H_{25}ClN_2O_6$ (C, H, N, Cl). ^{1}H-NMR ($CDCl_3$): 8.1–7.2 (m, 4H, aromatics), 6.2 (s, 1H, NH), 5.05 (s, 1H, pyridine–CH), 4.25 (t, 2H, $COOCH_2$–C–Cl), 3.8 (d, 2H, $COOCH_2$–C–C), 3.6 (t, 2H, CH_2Cl), 2.3 (s, 6H, 2,6 CH_3s), 2.0–1.5 (m, 1H, *i*-butyl–CH), 0.95–0.85 (dd, 6H, gem-CH_3s).

6.7.9. 2-Chloro-1-methylethyl 2-methylpropyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate ***6k***

Same procedure as for **6a**. Yield 48% (after column chromatography, eluting with $CHCl_3$–EtOAc, 98:2). Anal. $C_{22}H_{26}Cl_3NO_4$ (C, H, N, Cl). ^{1}H-NMR ($CDCl_3$): 7.7–7.1 (m, 3H, aromatics), 6.4 (m, 1H, NH), 5.5 (s, 1H, pyridine–CH), 5.3–4.8 (m, 1H, COOCH), 3.9 (d, 2H, $COOCH_2$), 3.65–3.45 (2d, 2H, CH_2Cl), 2.3 (s, 6H, 2,6 CH_3s), 2.3–1.7 (m, 1H, COO–C–CH), 1.3–1.1 (2d, 3H, COO–C–CH_3), 0.85–0.8 (2d, 6H, gem-CH_3s).

6.7.10. 2-Chloroethyl 2-propoxyethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate ***6l***

Same procedure as for **6a**. Yield 70% (after column chromatography, eluting with $CHCl_3$–EtOAc gradient, 100:0 to 97:3) m.p. 104–106 °C (*i*-PrOH or CCl_4). Anal. $C_{22}H_{27}ClN_2O_7$ (C, H, N, Cl). ^{1}H-NMR ($CDCl_3$): 8.4–7.3 (m, 4H, aromatics), 6.3 (s, 1H, NH), 5.2 (s, 1H, CH), 4.5–4.1 (m, 4H, 2 $COOCH_2$), 3.9–3.5 (m, 4H, CH_2OCH_2), 3.45 (t, 2H, CH_2Cl), 2.4 (s, 6H, 2,6 CH_3s), 2.0–1.3 (m, 2H, O–C–CH_2–C), 0.95 (t, 3H, O–C–C–CH_3).

6.8. Preparation of intermediates ***10*** *(table VI, figures 3 and 4)*

6.8.1. 1-[N-(3,3-Diphenylpropyl)-N-methylamino]-2-propanol ***10a***

0.011 mol (0.63 g) of propylene oxide was added to a solution of 0.01 mol (2.25 g) of *N*-methyl-3,3-diphenylpropylamine [41] in 6 mL of MeOH and the reaction mixture was kept at 15–20 °C in a plugged round bottomed flask for 3 days. An additional amount of propylene oxide (0.11 g) was added and the mixture was kept in the same manner for 24 h. The solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel eluting with $CHCl_3$–MeOH (100:0 to 95:5) gradient mixture, to give 2 g (70%) of the pure oily compound. The analytical sample was obtained after drying at 40 °C/0.5 mmHg. Anal. $C_{19}H_{25}NO$ (C, H, N). ^{1}H-NMR ($CDCl_3$): 7.2 (s, 10H, aromatics), 3.95 (t, 1H, CH–C–C), 3.65 (m, 1H, CH–O), 3.6 (s, 1H, OH), 2.6–1.8 (m, 9H, NCH_3 and 3 CH_2s), 1.05 (d, 3H, C–CH_3).

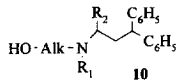
6.8.2. 1,N-(3,3-Diphenylpropyl)amino-2-methyl-2-propanol•HCl ***10b***

A mixture of 0.02 mol (4.23 g) of 3,3-diphenylpropylamine, 0.005 mol (0.54 g) of 1-chloro-2-methyl-2-propanol and 5 mL of xylene was stirred at reflux temperature for 8 h. After cooling to room temperature, the suspension was filtered, the filtrate was evaporated to dryness and the oily residue was purified by flash chromatography eluting with a $CHCl_3$–MeOH, 85:15 mixture to give 1.37 g of the pure base. This was converted into its HCl salt that was crystallized from a EtOAc–EtOH, 3:1 mixture to give 1.13 g (71%) of the compound. M.p. 199–200 °C. Anal. $C_{19}H_{25}NO$•HCl (C, H, N, Cl). ^{1}H-NMR (DMSO-d_6): 9.5–9.0 (m, 1H, $^+$NH), 7.70–7.2 (m, 10H, aromatics), 5.35 (bs, 1H, OH), 4.25 (t, 1H, CH), 3.15–2.5 (m, 4H, CH_2CH_2N), 2.29 (bs, 2H, N–CH_2–C–O), 1.3 (s, 6H, gem-CH_3s).

6.8.3. 1-[N-(3,3-Diphenylpropyl)-N-methylamino]-2-methyl-2-propanol ***10c***

A mixture of 0.2 mol (45 g) of *N*-methyl-3,3-diphenylpropylamine, 0.08 mol (8.68 g) of 1-chloro-2-methyl-2-propanol and

Table VI. *N*-(Hydroxyalkyl) diphenylalkylamines **10**.



Compound	Alk	R_1	R_2	Yield (%)	M.p. or b.p. (°C)/mmHg	Anal.
10a	$-CH(CH_3)CH_2-$	CH_3	H	70	Oil	C, H, N
10b	$-C(CH_3)_2CH_2-$	H	H	71	199–200[a]	C, H, N, Cl
10c	$-C(CH_3)_2CH_2-$	CH_3	H	80	145/0.2	C, H, N
10d	$-CH(CH_3)(CH_2)_2-$	CH_3	H	83	Thick oil	C, H, N
10e	$-C(CH_3)_2(CH_2)_2-$	CH_3	H	56	194–196[a]	C, H, N, Cl
10f	$-CH_2C(CH_3)_2CH_2-$	CH_3	H	65	147–148[a]	C, H, N, Cl
10g	$-(CH_2)_2C(CH_3)_2-$	CH_3	H	99	167–168[a]	C, H, N, Cl
10h	$-C(CH_3)_2CH_2-$	CH_3	=O	83	88–89	C, H, N

[a]As HCl salt.

70 mL of xylene was stirred at reflux temperature for 8.5 h. After cooling to room temperature, 450 mL of Et_2O was added, the suspension was filtered and the filtrate was evaporated to dryness. The oily residue was purified by flash chromatography on silica gel eluting with $CHCl_3$–MeOH (100:0 to 90:10) gradient mixture to give 19 g (80%) of the pure compound. A sample was distilled to give the analytical sample. B.p. 145 °C/0.2 mmHg. Anal. $C_{20}H_{27}NO$ (C, H, N). ^{1}H-NMR ($CDCl_3$): 7.15 (s, 10H, aromatics), 3.9 (t, 1H, CH), 2.8 (bs, 1H, OH), 2.8–1.9 (m, 4H, CH_2CH_2N), 2.3 (s, 3H, NCH_3), 2.2 (s, 2H, N–CH_2–C–O), 1.05 (s, 6H, gem-CH_3s).

6.8.4. 4-[N-(3,3-Diphenylpropyl)-N-methylamino]-2-butanone•HCl ***13***

0.045 mol (3.3 g) of 95% methyl vinyl ketone was dropped in 20 min into a stirred solution of 0.035 mol (7.87 g) of *N*-methyl-3,3-diphenylpropylamine in 7 mL of Et_2O at –5/+3 °C. Afterwards, the solvent was evaporated at room temperature to give 9.2 g (90%) of the pure base. A sample was converted to its HCl salt that was crystallized to give the analytical sample. M.p. 133–135 °C (Me_2CO or *i*-PrOH or MeCOEt). Anal. $C_{20}H_{25}NO$•HCl (C, H, N, Cl). ^{1}H-NMR ($CDCl_3$): 13.3–12.5 (bs, 1H, $^+$NH), 7.3 (s, 10H, aromatics), 4.0 (t, 1H, CH), 3.4–2.9 (m, 4H, CH_2NCH_2), 2.9–2.4 (m, 4H, CH_2–C–N–C–CH_2), 2.7 (s, 3H, NCH_3), 2.15 (s, 3H, $COCH_3$).

6.8.5. 4-[N-(3,3-Diphenylpropyl)-N-methylamino]-2-butanol ***10d***

0.024 mol (0.9 g) of $NaBH_4$ was added in small portions and at 0 °C into a solution of 0.031 mol (9.16 g) of **13** in 30 mL of MeOH. At the end of the addition (about 5 min), the solvent was evaporated at reduced pressure, the residue was treated with H_2O (100 mL) and extracted with Et_2O. The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated to dryness to give 9.28 g of the oily product, that was dried in vacuo (about 0.4 mmHg at room temperature) to give 7.73 g (83%) of the pure compound. Anal. $C_{20}H_{27}NO$ (C, H, N). ^{1}H-NMR ($CDCl_3$): 7.35–7.0 (m, 10H, aromatics), 5.6–5.2 (m, 1H, OH), 4.05–3.6 (m, 2H, 2 x CH), 2.6–1.9 (m, 9H, $CH_2CH_2N(CH_3)CH_2$), 1.55–1.15 (m, 2H, N–C–CH_2–C–O), 1.1 (d, 3H, CH_3–C–O).

6.8.6. 4-[N-(3,3-Diphenylpropyl-N-methylamino]-2-methyl-2-butanol•HCl ***10e***

A solution of 0.051 mol (7.23 g) of methyl iodide in 6 mL of anhydrous Et_2O (distilled from $LiAlH_4$) was slowly dropped (30 min) into a mixture of 0.051 mol (1.24 g) of Mg, 10 mg of I_2 and 5 mL of anhydrous Et_2O. Then, the mixture was heated at reflux temperature for 15 min until complete Mg dissolution and, after cooling to –5 °C, a solution of 0.042 mol (12.5 g) of **13** in 45 mL of anhydrous Et_2O was added dropwise in 25 min, without exceeding the temperature of 10 °C. After 18 h stirring at room temperature, the mixture was cooled, 10 mL of H_2O, 150 mL of EtOAc and 4.5 mL of 50% AcOH were added until complete dissolution. After separation of the organic layer, the aqueous phase was re-extracted with EtOAc and the collected organic layers were washed with 5% aqueous Na_2CO_3 solution followed with brine. The residue obtained from EtOAc evaporation was purified by flash chromatography, eluting with a $CHCl_3$–MeOH, 98:2 mixture, to give 7.4 g (56%) of the pure base. A sample was converted into its $^+$HCl salt to give the analytical sample. M.p. 194–196 °C (*i*-PrOH). Anal.

$C_{21}H_{29}NO$•HCl (C, H, N, Cl). ^{1}H-NMR (DMSO-d_6): 12.5–11.0 (bs, 1H, $^+$NH), 7.5 (s, 10H, aromatics), 4.7 (bs, 1H, OH), 4.4–4.0 (m, 1H, CH), 3.8–2.3 (m, 6H, $CH_2CH_2NCH_2$), 2.75 (s, 3H, NCH_3), 2.0–1.5 (m, 2H, CH_2C–O), 1.15 (s, 6H, gem-CH_3s).

6.8.7. 2,2-Dimethyl-3-[N-(3,3-diphenylpropyl)-N-methylamino]-propanol•HCl ***10f***

A mixture of 0.01 mol (2.61 g) of *N*-methyl-3,3-diphenylpropylamine•HCl, 0.011 mol (0.9 mL) of 37% HCHO and 1 mL of Ac_2O was stirred at 100 °C for 30 min. A solution of 0.012 mol (1.08 mL) of *i*-butyraldehyde in 1 mL of Ac_2O was dropped at the same temperature and heating was continued for additional 30 min. The solvent was almost completely distilled at 50 °C (1 mmHg), the residue was dissolved in H_2O and the solution was alkalinized and extracted with Et_2O. The crude obtained after solvent evaporation was purified by flash chromatography eluting with CH_2Cl_2–MeOH (100:3 to 100:4) gradient mixture to give 1.55 g (50%) of pure 3-[*N*-(3,3-diphenylpropyl)-*N*-methylamino]-2,2-dimethylpropionaldehyde. ^{1}H-NMR ($CDCl_3$): 9.5 (s, 1H, CHO), 7.3 (s, 10H, aromatics), 4.0 (t, 1H, CH), 2.7–1.9 (m, 9H, 3 CH_2s and NCH_3), 1.0 (s, 6H, gem-CH_3s).

0.065 mol (0.25 g) of $NaBH_4$ was added at 0/3 °C to a stirred solution of 0.005 mol (1.5 g) of the above aldehyde in 7 mL of MeOH. The mixture was stirred for 30 min at the same temperature and for 1 h at room temperature. The reaction could be monitored by TLC (toluene–Me_2CO, 7:3). 35 mL of H_2O was then added and the mixture was extracted with Et_2O. The organic phase was extracted with a solution of 0.6 g of oxalic acid in 25 mL of H_2O, the aqueous solution was washed twice with Et_2O, alkalinized with 1 mL of concentrated NaOH to give the base that was extracted with Et_2O. After drying and evaporation of the solvent, 1.38 g (80%) of the pure oily base was obtained. This was converted into its HCl salt that was crystallized from Me_2CO to give 1.26 g (65%) of **10f**. M.p. 147–148 °C. Anal. $C_{21}H_{29}NO$•HCl (C, H, N, Cl). ^{1}H-NMR ($CDCl_3$): 10.8–9.9 (m, 1H, $^+$NH), 7.7–7.2 (m, 10H, aromatics), 5.0–4.4 (m, 1H, OH), 4.1 (t, 1H, CH), 3.7 (s, 2H, CH_2O), 3.5–2.5 (m, 9H, $CH_2CH_2N(CH_3)CH_2$), 1.1 (s, 6H, gem-CH_3s).

6.8.8. Ethyl 3-[N-(3,3-diphenylpropyl)amino]-3-methylbutyrate•HCl ***15***

A mixture of 0.088 mol (11.27 g) of ethyl 3-methylcrotonate **14** [42], 0.08 mol (17.43 g) of 3,3-diphenylpropylamine and 60 mL of EtOH was refluxed for 57 h. The reaction was monitored by GLC, that showed a 50% maximum rate of **15** formation. The mixture was evaporated to dryness in vacuo and the residue was purified by flash chromatography eluting with $CHCl_3$–CH_3OH (100:0 to 98:2) gradient mixture. Yield 9.8 g (36%) as base. A sample was converted into its hydrochloride salt. M.p. 126–130 °C (EtOAc). Anal. $C_{22}H_{29}NO_2$•HCl (C, H, N, Cl). ^{1}H-NMR ($CDCl_3$): 10.0–9.3 (bs, 2H, $^+NH_2$), 7.3 (s, 10H, aromatics), 4.2–4.0 (m, 1H, CH), 4.15 (q, 2H, OCH_2–C), 3.0–2.6 (m, 4H, CH_2CH_2N), 2.7 (s, 2H, CH_2COO), 1.4 (s, 6H, gem-CH_3s), 1.2 (t, 3H, O–C–CH_3).

6.8.9. Ethyl 3-[N-(3,3-diphenylpropyl)-N-methylamino]-3-methylbutyrate ***16***

A mixture of 0.036 mol (12.35 g) of **15**, 0.04 mol (5.7 g) of methyl iodide, 0.0547 mol (7.56 g) of anhydrous K_2CO_3 and 48 mL of anhydrous DMF (dried on 4 Å molecular sieves) was stirred at room temperature for 6 h. Afterwards, the mixture was poured into 350 mL H_2O and the separated oil was extracted with Et_2O (4 x 70 mL). The residue obtained after solvent evaporation was purified by flash chromatography eluting with a petroleum ether–Me_2CO, 95:5 mixture. Yield 9.6 g (74%). A sample was distilled to give the analytical sample; b.p. 190–195 °C/0.7 mmHg. Anal. $C_{23}H_{31}NO_2$ (C, H, N). ^{1}H-NMR ($CDCl_3$): 7.35 (s, 10H, aromatics), 4.15 (q, 2H, $COOCH_2$), 4.2–3.9 (m, 1H, CH), 2.4–2.15 (m, 6H, CH_2CH_2N–C–CH_2), 2.25 (s, 3H, NCH_3), 1.25 (t, 3H, COO–C–CH_3), 1.1 (s, 6H, gem-CH_3s).

6.8.10. 3-[N-(3,3-Diphenylpropyl)-N-methylamino]-3-methylbutanol•HCl ***10g***

A solution of 0.017 mol (6 g) of **16** in 20 mL of Et_2O (distilled from $LiAlH_4$) was dropped in 15 min into a stirred suspension of 0.0255 mol (0.97 g) of $LiAlH_4$ in 20 mL of Et_2O, mantaining a gentle reflux. After 3 h at 25 °C, 1 mL of H_2O, 1 mL of 35% NaOH and 3 mL of H_2O were cautiously added and the mixture was stirred for 15 min. The suspension was filtered, washed with Et_2O and the solvent was evaporated to dryness to give 5.25 g (99%) of **10g** base. A sample of this thick oil was converted into its HCl salt to give the analytical sample. M.p. 167–168 °C (Me_2CO). Anal. $C_{21}H_{29}NO$•HCl (C, H, N, Cl). ^{1}H-NMR ($CDCl_3$): 11.0–10.5 (bs, 1H, $^+$NH), 7.55 (s, 10H, aromatics), 5.3–5.0 (bs, 1H, OH), 4.4–3.8 (m, 3H, CH and CH_2O), 3.0–2.5 (m, 4H, CH_2CH_2N), 2.8 (s, 3H, NCH_3), 2.1–1.8 (m, 2H, N–C–CH_2–C–O), 1.6–1.3 (m, 6H, gem-CH_3s).

6.8.11. 3,3-Diphenyl-N-(2-hydroxy-2-methylpropyl)-N-methylpropanamide ***10h***

A solution of 0.05 mol (12.2 g) of 3,3-diphenylpropionyl chloride [43] in 30 mL of 1,4-dioxane was added at 30–35 °C to a stirred solution of 0.05 mol (5.15 g) of 1-methylamino-2-methyl-2-propanol [44] in 0.0525 mol (25 mL) of 2.1 N NaOH. The mixture was stirred at room temperature for 3 h and then poured into 200 mL of H_2O kept at 5–10 °C. The precipitate was extracted with 200 mL of Et_2O, the ethereal solution evaporated to dryness and the residue redissolved in $CHCl_3$. This solution was dried ($CaCl_2$), filtered, evaporated to dryness and the residue was washed repeatedly with petroleum ether to give 12.9 g (83%) of the pure compound. A little amount was crystallized from cyclohexane to give the analytical sample. M.p. 88–89 °C. Anal. $C_{20}H_{25}NO_2$ (C, H, N). ^{1}H-NMR ($CDCl_3$): 7.2 (s, 10H, aromatics), 4.7 (t, 1H, CH), 3.9 (s, 1H, OH), 3.3 (s, 2H, NCH_2), 3.05 (d, 2H, CH_2CO), 3.0 (s, 3H, NCH_3), 1.0 (s, 6H, gem-CH_3s).

6.9. Preparation of intermediates ***11*** *(table VII)*

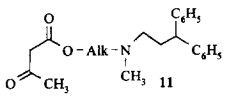
6.9.1. 1-[N-(3,3-Diphenylpropyl)-N-methylamino]-2-propyl acetoacetate ***11a***

0.084 mol (7 g) of diketene was dropped at 95 °C into a stirred solution of 0.08 mol (22.67 g) of 1-[*N*-(3,3-diphenylpropyl)-*N*-methylamino]-2-propanol **10a** in 22 mL of toluene. After cooling to room temperature, the solvent was evaporated in vacuo and the residue was purified by flash chromatography eluting with EtOAc to give 20 g (68%) of pure compound containing about 10% of the enolic form. The analytical sample was obtained by repeating flash chromatography. Anal. $C_{23}H_{29}NO_3$ (C, H, N). ^{1}H-NMR ($CDCl_3$): 7.1 (s, 10H aromatics), 5.15–4.7 (m, 1.1H, CH–O and enolic CHCOO), 4.1–3.8 (m, 1H, N–C–C–CH), 3.3 (s, 1.8H, CH_2COO), 2.55–1.8 (m, 12H, NCH_3, $CH_2NCH_2CH_2$, CH_3CO), 1.2 (d, 3H, COO–C–CH_3).

6.9.2. 1-[N-(3,3-Diphenylpropyl)-N-methylamino]-2-methyl-2-propyl acetoacetate ***11b***

0.046 mol (3.8 g) of diketene was dropped in 10 min at 85–100 °C into a stirred solution of 0.044 mol (13.1 g) of

Table VII. *N*-(3,3-Diphenylpropyl)methylaminoalkyl acetoacetates **11**.



Compound	Alk	Yield	M.p. (°C)	Anal.
11a	$-CH(CH_3)CH_2-$	68	Oil	C, H, N
11b	$-C(CH_3)_2CH_2-$	72	Oil	C, H, N

1-[*N*-(3,3-diphenylpropyl)-*N*-methylamino]-2-methyl-2-propanol **10c** in 10 mL of toluene. After 2 h stirring at 80 °C, the mixture was cooled to room temperature, the solvent was evaporated in vacuo and the residue was purified by flash chromatography, eluting with $CHCl_3$–Me_2CO (100:0 to 98:2) gradient mixture, to give 12.3 g (72%) of the ester. Anal. $C_{24}H_{31}NO_3$ (C, H, N). ^{1}H-NMR ($CDCl_3$): 7.35 (s, 10H, aromatics), 4.0 (t, 1H, CH), 3.2 (s, 2H, $COCH_2$), 2.55 (s, 2H, COO–C–CH_2), 2.55–2.1 (m, 4H, N–CH_2CH_2), 2.3 (s, 3H, NCH_3), 2.2 (s, 3H, CH_3CO), 1.45 (s, 6H, gem-CH_3s).

*6.10. Preparation of intermediates **12** (table VIII)*

*6.10.1. 1-[N-(3,3-Diphenylpropyl)-N-methylamino]-2-propyl 2-(3-nitrobenzylidene)acetoacetate•HCl **12a***

A mixture of 0.01 mol (1.51 g) of 3-nitrobenzaldehyde and 0.01 mol (3.67 g) of 1-[*N*-(3,3-diphenylpropyl)-*N*-methylamino]-2-propyl acetoacetate **11a** in 14.5 mL of $CHCl_3$ was saturated with HCl at 0 °C. After 3 days at 15 °C, the mixture was diluted with $CHCl_3$, washed with diluted NaOH until neutrality and the organic phase dried over $CaCl_2$. The residue obtained after solvent evaporation was dissolved in Et_2O and an excess of 3.2 N HCl in Et_2O was added at 0 °C. The precipitate obtained after Et_2O addition was decanted and washed repeatedly with Et_2O to give 4.3 g (80%) of the product as *E/Z* isomers mixture of the HCl salt as a glassy solid. Anal. $C_{30}H_{32}N_2O_5$•HCl (C, H, N, Cl). ^{1}H-NMR ($CDCl_3$): 8.35 and 8.2 (2s, 1H, CH–C–CO), 8.0–6.9 (m, 14H, aromatics), 5.8–5.2 (m, 1H, COOCH), 4.2–3.8 (m, 1H, N–C–C–CH), 3.6–2.2 (m, 12H, $CH_2N(CH_3)CH_2CH_2$ and CH_3CO), 1.4 and 1.2 (2d, 3H, COO–C–CH_3).

*6.10.2. 1-[N-(3,3-Diphenylpropyl)-N-methylamino]-2-methyl-2-propyl 2-(3-nitrobenzylidene)acetoacetate **12b***

Same procedure as for **12a**, but using **11b**. The analytical sample was obtained by treatment of the hydrochloride salt with diluted NaOH, extraction with EtOAc and purifing the crude base by flash chromatography eluting with a $CHCl_3$–EtOAc, 95:5 mixture. Yield 91%, m.p. 65–80 °C. Anal. $C_{31}H_{34}N_2O_5$ (C, H, N). ^{1}H-NMR ($CDCl_3$): 8.5–8.2 (m, 2H, aromatics at positions 2,4 of $C_6H_4NO_2$), 8.0–7.5 (m, 3H, aromatics at positions 5,6 of $C_6H_4NO_2$ and CO–C–CH), 7.3 (s, 10H, other aromatics), 4.1–3.8 (m, 1H, N–C–C–CH), 2.7–2.1 (m, 12H, $CH_2N(CH_3)CH_2CH_2$ and $COCH_3$), 1.52 and 1.48 (2s, 6H, gem-CH_3s).

*6.10.3. 1-[N-(3,3-Diphenylpropyl)-N-methylamino]-2-propyl 2-(2,3-dichlorobenzylidene)acetoacetate **12c***

A mixture of 0.01 mol (3.67 g) of 1-[*N*-(3,3-diphenylpropyl)-*N*-methylamino]-2-propyl acetoacetate **11a**, 0.01 mol (1.75 g) of 2,3-dichlorobenzaldehyde in 12 mL of $CHCl_3$ was saturated with HCl at 0 °C. After 1 day at room temperature, the solvent was evaporated to dryness, the residue was dissolved into CH_2Cl_2 and the solution was neutralized by washing with diluted $NaHCO_3$ aqueous solution. Evaporation of the organic layer gave 4.88 g (93%) of the compound as a glassy solid as *E/Z* isomers mixture. Anal. $C_{30}H_{31}Cl_2NO_3$ (C, H, N, Cl). ^{1}H-NMR ($CDCl_3$): 7.9 and 7.8 (2s, 1H, CO–C–CH), 7.7–7.0 (m, 13H, aromatics), 5.4–4.8 (m, 1H, COOCH), 4.3–3.8 (m, 1H, N–C–C–CH), 2.8–1.9 (m, 12H, $CH_2N(CH_3)CH_2CH_2$ and CH_3CO), 1.25 and 1.1 (2d, 3H, COO–C–CH_3).

*6.10.4. 1-[N-(3,3-Diphenylpropyl)-N-methylamino]-2-methyl-2-propyl 2-(2,3-dichlorobenzylidene)acetoacetate•HCl **12d***

Same procedure as for **12c**, but using **11b**. The residue after $CHCl_3$ evaporation was treated with *i*-Pr_2O until solidification. The solid was washed with a *i*-Pr_2O–EtOAc, 95:5 mixture and dried in desiccator to give the hydrochloride salt as a glassy solid. Yield 100%. Anal. $C_{31}H_{33}Cl_2NO_3$•HCl (C, H, N, Cl). ^{1}H-NMR ($CDCl_3$): 10.8 (bs, 1H, $^+$NH), 7.9–7.6 (m, 1H, CO–C–CH), 7.55–7.0 (m, 13H, aromatics), 4.2–3.7 (m, 1H, N–C–C–CH), 3.6–2.0 (m, 12H, $CH_2N(CH_3)CH_2CH_2$ and CH_3CO), 1.6 and 1.5 (2s, 6H, gem-CH_3s).

*6.11. General procedure for the synthesis of 1,4-dihydropyridines **9** (table I)*

6.11.1. Method A

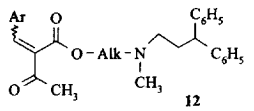
A mixture of the monohaloalkyl ester of general formula **6** (0.02 mol), a diphenylalkylamine **8** (0.04–0.06 mol) and toluene or xylene (15–30 mL) was stirred at reflux temperature for 1–24 h. After cooling to room temperature, the mixture was diluted with Et_2O in order to precipitate the formed **8**•HCl. The filtrate was evaporated in vacuo and the residue was purified by flash chromatography. The purified base was converted into its •HCl salt by usual methods; the product was isolated as amorphous material or washed or crystallized from a suitable solvent or solvents mixture. The following compounds were synthesized by this route.

*6.11.1.1. 2-[N-(3,3-Diphenylpropyl)-N-methylamino]ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate•HCl•H_2O **9a**:* m.p. 118–125 °C (EtOAc or Me_2CO); Anal. $C_{34}H_{37}N_3O_6$•HCl•H_2O (C, H, N, Cl, H_2O); ^{1}H-NMR (DMSO-d_6): 11.3–10.0 (bs, 1H, $^+$NH), 9.45 (s, 1H, pyridine–NH), 8.0–7.3 (m, 14H, aromatics), 5.65 (s, 1H, pyridine–H_4), 4.7–3.9 (m, 3H, N–C–C–CH and $COOCH_2$), 3.65 (s, 3H, $COOCH_3$), 2.75 (s, 3H, NCH_3), 2.4 (s, 6H, 2,6 CH_3s), 3.7–2.2 (m, 8H, $CH_2NCH_2CH_2$ and H_2O).

*6.11.1.2. 2-[N-(3,3-Diphenylpropyl)-N-methylamino]ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl **9b**:* m.p. 108–113 °C (amorphous); Anal. $C_{34}H_{37}N_3O_6$•HCl (C, H, N, Cl); ^{1}H-NMR ($CDCl_3$): 12.3 (bs, 1H, $^+$NH), 8.0 (s, 1H, pyridine–NH), 8.1–7.0 (m, 14H, aromatics), 5.0 (s, 1H, pyridine–H_4), 4.48 (m, 2H, $COOCH_2$), 3.98 (m, 1H, N–C–C–CH), 3.6 (s, 3H, $COOCH_3$), 3.4–2.2 (m, 6H, $CH_2NCH_2CH_2$), 2.69 (s, 3H, NCH_3), 2.39 (s, 6H, 2,6 CH_3s).

*6.11.1.3. 2-[N-(3,3-Diphenylpropyl)-N-methylamino]ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate•HCl•0.6H_2O **9c**:* m.p. 161 °C (EtOH + Et_2O); Anal. $C_{34}H_{36}Cl_2N_2O_4$•HCl•0.6 H_2O (C, H, N, Cl, H_2O); ^{1}H-NMR ($CDCl_3$): 7.85 (bs, 1H, pyridine–NH), 7.4–6.8 (m, 13H, aromatics), 5.2 (s, 1H, pyridine–H_4), 4.5–4.1 (m, 2H,

Table VIII. *N*-(3,3-Diphenylpropyl)methylaminoalkyl 2-arylideneacetoacetates **12**.



12

Compound	Ar	Alk	Yield	M.p. (°C)	Anal.
12a	3-NO_2–C_6H_4	–$CH(CH_3)CH_2$–	80[a]	Glassy	C, H, N, Cl
12b	3-NO_2–C_6H_4	–$C(CH_3)_2CH_2$–	91	65–80	C, H, N
12c	2,3-Cl_2–C_6H_3	–$CH(CH_3)CH_2$–	93	Glassy	C, H, N, Cl
12d	2,3-Cl_2–C_6H_3	–$C(CH_3)_2CH_2$–	100[a]	Glassy	C, H, N, Cl

[a]As HCl salt.

$COOCH_2$), 4.0–3.7 (m, 1H, N–C–C–CH), 3.5 (s, 3H, $COOCH_3$), 2,45 (s, 3H, NCH_3), 2.3 (s, 6H, 2,6 CH_3s), 3.3–2.1 (m, 7H, $CH_2NCH_2CH_2$ and H_2O).

6.11.1.4. 2-[N-(3,3-Diphenylpropyl)-N-methylamino]ethyl methyl 4-(benzofurazan-4-yl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate•HCl ***9d****:* m.p. 161–166 °C (MeOAc or MeCN); Anal. $C_{34}H_{36}N_4O_5$•HCl (C, H, N, Cl); ^{1}H-NMR ($CDCl_3$): 11.5–10.5 (bs, 1H, $^+$NH), 8.0–7.2 (m, 13H, aromatics and benzofurazan–H_5, H_6, H_7), 6.6 (s, 1H, pyridine–NH), 5.6 (s, 1H, pyridine–H_4), 4.3–3.9 (m, 3H, $COOCH_2$ and N–C–C–CH), 3.6 (s, 3H, $COOCH_3$), 2.7–1.9 (m, 15H, 2,6 CH_3s and $CH_2N(CH_3)CH_2CH_2$).

6.11.1.5. 2-[N-(3,3-Diphenylpropylamino)]ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl ***9e****:* m.p. 128–132 °C (*i*-PrOAc or EtOAc); Anal. $C_{33}H_{35}N_3O_6$•HCl (C, H, N, Cl); ^{1}H-NMR ($CDCl_3$) of the base: 8.55–7.25 (m, 14H, aromatics), 6.55 (s, 1H, pyridine–NH), 5.35 (s, 1H, pyridine–H_4), 4.4–4.0 (m, 3H, $COOCH_2$ and N–C–C–CH), 3.8 (s, 3H, $COOCH_3$), 3.0–2.0 (m, 6H, $CH_2NCH_2CH_2$), 2.45 (s, 6H, 2,6 CH_3s), 1.55 (s, 1H, NH).

6.11.1.6. 2-[N-(4,4-Diphenyl-2-butyl)-N-methylamino]ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl ***9f****:* m.p. 113–120 °C (amorphous); Anal. $C_{35}H_{39}N_3O_6$•HCl (C, H, N, Cl); ^{1}H-NMR ($CDCl_3$): 12.2 (bs, 1H, $^+$NH), 8.3–7.0 (m, 14H, aromatics), 6.8 (bs, 1H, pyridine–NH), 4.9 (bs, 1H, pyridine–H_4), 4.7–4.3 (m, 2H, $COOCH_2$), 4.2–3.8 (m, 1H, N–C–C–CH), 3.6 (s, 3H, $COOCH_3$), 3.4–2.8 (m, 4H, O–C–CH_2–N–C–CH_2–C), 2.6 (s, 3H, NCH_3), 2.4 (s, 6H, 2,6 CH_3s), 2.2–1.8 (m, 1H, N–CH–C), 1.6–1.1 (m, 3H, N–C–CH_3).

6.11.1.7. 2-[N-(3,3-Diphenylpropyl)-N-methylamino]ethyl ethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl ***9g****:* m.p. 164–167 °C (Me_2CO); Anal. $C_{35}H_{39}N_3O_6$•HCl (C, H, N, Cl); ^{1}H-NMR (DMSO-d_6): 11.3 (bs, 1H, $^+$NH), 9.35 (bs, 1H, pyridine–NH), 8.0–7.3 (m, 14H, aromatics), 5.0 (s, 1H, pyridine–H_4), 4.5–3.9 (m, 5H, 2 x $COOCH_2$ and N–C–C–CH), 3.6–2.25 (m, 6H, $CH_2NCH_2CH_2$), 2.75 (s, 3H, NCH_3), 2.35 (s, 6H, 2,6 CH_3s), 1.2 (t, 3H, COO–C–CH_3).

6.11.1.8. 2-[N-(3,3-Diphenylpropyl)-N-methylamino]ethyl 1-methylethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl ***9h****:* m.p. 160–164 °C (Me_2CO); Anal. $C_{36}H_{41}N_3O_6$•HCl (C, H, N, Cl); ^{1}H-NMR (DMSO-d_6): 12.0–11.5 (bs, 1H, $^+$NH), 9.5 (s, 1H, pyridine–NH), 8.3–7.6 (m, 4H, aromatics of 3-nitrophenyl ring), 7.5 (s, 10H, other aromatics), 5.1 (s, 1H, pyridine–H_4), 5.2–4.8 (m, 1H, COOCH), 4.7–4.3 (m, 2H, $COOCH_2$), 4.3–3.9 (m, 1H, N–C–C–CH), 3.8–2.2 (m, 6H, $CH_2NCH_2CH_2$), 2.8 (s, 3H, NCH_3), 2.4 (s, 6H, 2,6 CH_3s), 1.25 and 1.15 (2d, 6H, COO–C–$(CH_3)CH_3$).

6.11.1.9. 2-[N-(3,3-Diphenylpropyl)-N-methylamino]ethyl 2-methylpropyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl ***9i****:* m.p. 123–124 °C (EtOAc or EtOAc + Me_2CO); Anal. $C_{37}H_{43}N_3O_6$•HCl (C, H, N, Cl); ^{1}H-NMR (DMSO-d_6): 11.7–11.25 (bs, 1H, $^+$NH), 9.55 (s, 1H, pyridine–NH), 8.35–7.65 (m, 4H, aromatics of 3-nitrophenyl ring), 7.5 (s, 10H, other aromatics), 5.15 (s, 1H, pyridine–H_4), 4.7–4.05 (m, 3H, $COOCH_2$–C–N and N–C–C–CH), 4.05–3.75 (d, 2H, $COOCH_2$–C–$(C)_2$), 3.65–2.25 (m, 6H, $CH_2NCH_2CH_2$), 2.8 (s, 3H, NCH_3), 2.45 and 2.4 (2s, 6H, 2,6 CH_3s), 2.05–1.65 (m, 1H, COO–C–CH), 1.9 and 0.85 (2d, 6H, COO–C–$C(CH_3)_2$).

6.11.1.10. 2-[N-(3,3-Diphenylpropyl)-N-methylamino]ethyl 2-propoxyethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl ***9j****:* m.p. 124–129 °C (EtOAc); Anal. $C_{38}H_{45}N_3O_7$•HCl (C, H, N, Cl); ^{1}H-NMR (DMSO-d_6): 11.8–11.3 (bs, 1H, $^+$NH), 9.5 (s, 1H, pyridine–NH), 8.3–7.7 (m, 4H, aromatics of 3-nitrophenyl ring), 7.45 (s, 10H, other aromatics), 5.1 (s, 1H, pyridine–H_4), 4.7–4.0 (m, 5H, 2 x $COOCH_2$ and N–C–C–CH), 3.8–3.2 (m, 8H, CH_2NCH_2 and CH_2OCH_2), 3.2–2.3 (m, 2H, N–C–CH_2–C), 2.8 (s, 3H, NCH_3), 2.4 (s, 6H, 2,6 CH_3s), 1.8–1.2 (m, 2H, O–C–CH_2–C), 0.85 (t, 3H, O–C–C–CH_3).

6.11.1.11. 3-[N-(3,3-Diphenylpropyl)-N-methylamino]propyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl ***9k****:* m.p. 100–107 °C (amorphous); Anal. $C_{35}H_{39}N_3O_6$•HCl (C, H, N, Cl); ^{1}H-NMR ($CDCl_3$): 8.0–6.8 (m, 16H, aromatics, $^+$NH and pyridine–NH), 5.0 (s, 1H, pyridine–H_4), 4.2–3.8 (m, 3H, N–C–C–CH and $COOCH_2$), 3.47 (s, 3H, $COOCH_3$), 3.1–2.2 (m, 8H, $CH_2CH_2NCH_2CH_2$), 2.62 (s, 3H, NCH_3), 2.35 (s, 6H, 2,6 CH_3s).

6.11.1.12. 3-[N-(4,4-Diphenyl-2-butyl)-N-methylamino]propyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl ***9l****:* m.p. 113–118 °C (H_2O); Anal. $C_{36}H_{41}N_3O_6$•HCl (C, H, N, Cl); ^{1}H-NMR ($CDCl_3$): 8.15–7.1 (m, 15H, aromatics and pyridine–NH), 5.05 (s, 1H, pyridine–H_4), 4.25–3.8 (m, 3H, N–C–C–CH and $COOCH_2$), 3.61 (s, 3H, $COOCH_3$), 2.6 (s, 3H, NCH_3), 2.4 (s, 6H, 2,6 CH_3s), 2.4–1.7 (m, 7H, O–C–CH_2CH_2 and $NCHCH_2$), 1.5–1.2 (m, 3H, N–C–CH_3).

6.11.1.13. 4-[N-(3,3-Diphenylpropyl)-N-methylamino]butyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl•0.5H_2O ***9m****:* the reaction was carried out in DMF at room temperature for 16 h. M.p. 91–103 °C (amorphous); Anal. $C_{36}H_{41}N_3O_6$•HCl .0.5H_2O (C, H, N, Cl, H_2O); ^{1}H-NMR ($CDCl_3$): 11.6–11.2 (bs, 1H, $^+$NH), 9.3 (s, 1H, pyridine–NH), 8.5–8.1 (m, 4H, aromatics of 3-nitrophenyl ring), 7.35 (s, 10H, other aromatics), 5.05 (s, 1H, pyridine–H_4), 4.2–3.8 (m, 3H, $COOCH_2$ and N–C–C–CH), 3.6 (s, 3H, $COOCH_3$), 3.4 (s, 1H, H_2O), 3.3–2.0 (m, 6H, $CH_2NCH_2CH_2$), 2.8 (s, 3H, NCH_3), 2.35 (s, 6H, 2,6 CH_3s), 1.7–1.4 (m, 4H, O–C–CH_2CH_2).

6.11.1.14. 2-[N-(3,3-Diphenylpropyl)-N-methylamino]-1-methylethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl ***9n****:* m.p. 114–123 °C (amorphous); Anal. $C_{35}H_{39}N_3O_6$•HCl (C, H, N, Cl); ^{1}H-NMR ($CDCl_3$): 8.1–7.0 (m, 16H, aromatics, $^+$NH and pyridine–NH), 5.3 (m, 1H, COOCH), 5.05 and 5.00 (2s, 1H, pyridine–H_4), 4.1–3.5 (m, 1H, N–C–C–CH), 3.6 (s, 3H, $COOCH_3$), 3.5–2.2 (m, 9H, $CH_2N(CH_3)CH_2CH_2$), 2.4 (s, 6H, 2,6 CH_3s), 1.6–1.0 (m, 3H, COO–C–CH_3).

This compound was also synthesized by *method* B_1 and the diastereoisomers were separated by repeated flash chromatography, eluting with $CHCl_3$ containing increasing amounts of EtOAc (0 to 50%). In these conditions $\mathbf{9n}_2$ base was collected before $\mathbf{9n}_1$. Each crude base was dissolved into Et_2O–Me_2CO mixture and HCl in Et_2O was added to the solution. Each hydrochloride salt was collected by filtration and crystallized from EtOAc.

6.11.1.15. 2-[N-(3,3-Diphenylpropyl)-N-methylamino]-1-methylethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl•H_2O $\mathbf{9n}_1$ (diastereomer at lower R_F in $CHCl_3$–5 N methanolic NH_3, 99:1 eluent mixture): m.p. 143–147 °C (EtOAc); Anal. $C_{35}H_{39}N_3O_6$•HCl•H_2O (C, H, N, Cl, H_2O); ^{1}H-NMR (DMSO-d_6): 11.5–10.0 (bs, 1H, $^+$NH), 9.25 (s, 1H, pyridine–NH), 8.2–7.5 (m, 4H, aromatics of 3-nitrophenyl ring), 7.35 (s, 10H, other aromatics), 5.2 (m, 1H, COOCH), 5.05 (s, 1H, pyridine–H_4), 4.0 (m, 1H, N–C–C–CH), 3.55 (s, 3H, $COOCH_3$), 3.7–3.2 (m, 4H, H_2O and COO–C–CH_2–N), 2.75 (s, 3H, NCH_3), 2.35 (s, 6H, 2,6 CH_3s), 3.2–2.2 (m, 4H, N–CH_2CH_2), 1.05 (d, 3H, COO–C–CH_3).

6.11.1.16. 2-[N-(3,3-Diphenylpropyl)-N-methylamino]-1-methylethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl•0.5H_2O $\mathbf{9n}_2$ (diastereomer at higher R_F in $CHCl_3$–5 N methanolic NH_3, 99:1 eluent mixture): m.p. 196–198 °C (dec.) (EtOAc); Anal. $C_{35}H_{39}N_3O_6$•HCl•0.5H_2O (C, H, N, Cl, H_2O); ^{1}H-NMR (DMSO-d_6): 11.0–10.0 (bs, 1H, $^+$NH), 9.35 (s, 1H, pyridine–NH), 8.1–7.5 (m, 4H, aromatics of 3-nitrophenyl ring), 7.35 (s, 10H, other aromatics), 5.25 (m, 1H, COOCH), 5.0 (s, 1H, pyridine–H_4), 4.0 (m, 1H, N–C–C–CH), 3.6 (s, 3H, $COOCH_3$), 3.7–3.0 (m, 3H, H_2O and COO–C–CH_2–N), 3.0–2.1 (m, 7H, $CH_2CH_2NCH_3$), 2.35 (s, 6H, 2,6 CH_3s), 1.25 (d, 3H, COO–C–CH_3).

The analysis of the diastereoisomers $\mathbf{9n}_1$ and $\mathbf{9n}_2$ was performed also by HPLC method, under the following conditions:

Column:	Nova-pak C-18 4μ (Waters); 150 x 3.9 mm
Mobile phase:	CH_3CN (63 vol) – NORMEX buffer pH 7.4 (37 vol)
Elution:	isocratic
Flow:	1.2 mL/min
Temperature:	room temperature
Detector:	UV (240 nm)
Attenuation:	0.02 AUFS

Under these conditions a good separation was observed: $\mathbf{9n}_1$, R_T = 11.10 min and $\mathbf{9n}_2$, R_T = 11.85 min.

6.11.1.17. 2-[N-(3,3-Diphenylpropyl)-N-methylamino]-1-methylethyl 2-methylpropyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate•HCl ***9r****:* m.p. 162–164 °C (EtOAc); Anal. $C_{38}H_{44}Cl_2N_2O_4$•HCl (C, H, N, Cl); ^{1}H-NMR ($CDCl_3$): 7.85 (s, 1H, pyridine–NH), 7.6–7.0 (m, 13H, aromatics), 5.6–5.1 (m, 1H, COOCH), 5.35 (s, 1H, pyridine–H_4), 4.2–3.7 (m, 3H, $COOCH_2$ and N–C–C–CH), 3.6–1.4 (m, 16H, $CH_2N(CH_3)CH_2CH_2$, 2,6 CH_3s and COO–C–CH), 0.95 (d, 3H, COO–C–CH_3), 0.8 (2d, 6H, COO–C–$C(CH_3)_2$).

6.11.2. Method B_1

A mixture of the appropriate 4-aryl-1,4-dihydropyridine-3-carboxylic acid **7** (0.01 mol), aminoalcohol **10** (0.01 mol), dicyclohexylcarbodiimide (0.011 mol), 4-dimethylaminopyridine (0.0011 mol) and DMF (8.5–20 mL) was stirred under N_2 atmosphere at 75 °C for 8–48 h. After cooling to room temperature the mixture was diluted with Et_2O, the precipitated *N,N*-dicyclohexylurea was filtered and the filtrate was washed with H_2O. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to dryness to give the crude that was purified by flash chromatography. The purified base was converted into •HCl salt by usual methods; the product was obtained as amorphous material, then was washed or crystallized from a suitable solvent or solvent mixtures. The following compound was synthesized by this route.

6.11.2.1. 4-[N-(3,3-Diphenylpropyl)-N-methylamino]-2-butyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl•H_2O ***9ab****:* m.p. 93–110 °C (amorphous); Anal. $C_{36}H_{41}N_3O_6$•HCl•H_2O (C, H, N, Cl, H_2O); ^{1}H-NMR (DMSO-d_6): 11.5–10.8 (bs, 1H, $^+$NH), 9.35 (s, 1H, pyridine–NH), 8.3–7.6 (m, 4H, aromatics of 3-nitrophenyl ring), 7.4 (s, 10H, other aromatics), 5.1 (s, 1H, pyridine–H_4), 5.2–4.7 (m, 1H, COOCH), 4.4–3.9 (m, 1H, N–C–C–CH), 3.6 (s, 3H, $COOCH_3$), 3.5 (s, 2H, H_2O), 3.3–2.2 (m, 6H, $CH_2NCH_2CH_2$), 2.65 (s, 3H, NCH_3), 2.35 (s, 6H, 2,6 CH_3s), 2.2–1.7 (m, 2H, COO–C–CH_2), 1.4–0.9 (m, 3H, COO–C–CH_3).

6.11.3. Method B_2

A mixture of the appropriate 4-aryl-1,4-dihydropyridine-3-carboxylic acid **7** (0.01 mol), anhydrous CH_2Cl_2 (35 mL) and anhydrous DMF 9 mL) was stirred under N_2 atmosphere at –10 °C and added with $SOCl_2$ (0.012 mol). After 1 h stirring at 0/5 °C, a solution of the suitable aminoalcohol **10** (0.02 mol) in anhydrous CH_2Cl_2 (10 mL) was dropped into the mixture in about 10 min without exceeding 3 °C. After 3 h at 0 °C, the solvent was evaporated, the residue dissolved in EtOAc and washed repeatedly with brine, 1 N HCl, 10% Na_2CO_3, H_2O. The residue obtained after solvent evaporation was purified by flash chromatography. The purified base was converted into •HCl salt by usual methods; the product was isolated as amor-

phous material or washed or crystallized from a suitable solvent or solvents mixture. The following compounds were synthesized by this route.

6.11.3.1. 2-[N-(3,3-Diphenylpropyl)amino]-1,1-dimethylethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl ***9t:*** m.p. (118) 130 °C dec. (amorphous); Anal. $C_{35}H_{39}N_3O_6$•HCl (C, H, N, Cl); ^{1}H-NMR (DMSO-d_6): 9.55–9.15 (m, 3H, $^+NH_2$ and pyridine–NH), 8.25–7.55 (m, 4H, aromatics of 3-nitrophenyl ring), 7.4 (s, 10H, other aromatics), 5.05 (s, 1H, pyridine–H_4), 4.3–3.9 (m, 1H, N–C–C–CH), 3.6 (s, 3H, $COOCH_3$), 3.5–3.2 (m, 2H, N–C–CH_2–C), 3.0–2.4 (m, 4H, CH_2NCH_2), 2.35 and 2.3 (2s, 6H, 2,6 CH_3s), 1.42 (s, 6H, COO–C$(CH_3)_2$).

6.11.3.2. 2-[N-(3,3-Diphenylpropyl)-N-methylamino]-1,1-dimethylethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl ***9u:*** m.p. 185–190 °C (EtOH); Anal. $C_{36}H_{41}N_3O_6$•HCl (C, H, N, Cl); ^{1}H-NMR (DMSO-d_6): 10.8–9.4 (bb, 1H, ^+NH), 9.5 (bs, 1H, pyridine–NH), 8.30–8.05 (m, 2H, 3-nitrophenyl–H_2–H_4), 7.85–7.60 (m, 2H, 3-nitrophenyl–H_5–H_6), 7.55–7.20 (m, 10H, other aromatics), 5.05 (s, 1H, pyridine–H_4), 4.15–3.35 (m, 6H, N–C–CH_2–CH, $COOCH_3$), 3.20–2.15 (m, 13H, $CH_2N(CH_3)CH_2$ and 2,6 CH_3s), 1.50 (s, 6H, COO–C$(CH_3)_2$).

This compound was also prepared by method C giving 36% yield, after crystallization from H_2O containing a slight excess of hydrochloric acid.

6.11.3.3. 2-[N-(3,3-Diphenylpropyl)-N-methylamino]-1,1-dimethylethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl•0.5H_2O ***9u$_1$:*** m.p. 119–123 °C (H_2O); Anal. $C_{36}H_{41}N_3O_6$•HCl•0.5H_2O (C, H, N, Cl, H_2O).

6.11.3.4. 2-[N-(3,3-Diphenylpropyl)-N-methylamino]-1,1-dimethylethyl methyl 1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine-3,5-dicarboxylate•HCl ***9v:*** m.p. 119–121 °C (amorphous); Anal. $C_{36}H_{41}N_3O_6$•HCl (C, H, N, Cl); ^{1}H-NMR (DMSO-d_6): 10.1–10.4 (bs, 1H, ^+NH), 9.5 (bs, 1H, pyridine–NH), 8.3 and 7.6 (2dd, 4H, 4-nitrophenyl AA'BB' system), 7.43 (s, 10H, other aromatics), 5.05 (s, 1H, pyridine–H_4), 4.3–3.7 (m, 1H, N–C–C–CH), 3.67 (s, 3H, $COOCH_3$), 3.0–2.2 (m, 6H, $CH_2NCH_2CH_2$), 2.75 (s, 3H, NCH_3), 2.4 and 2.3 (2s, 6H, 2,6 CH_3s), 1.5 (s, 6H, COO–C$(CH_3)_2$).

6.11.3.5. 3-[N-(3,3-Diphenylpropyl)-N-methylamino]-1,1-dimethylpropyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl ***9ac:*** m.p. 201–203 °C (EtOH); Anal. $C_{37}H_{43}N_3O_6$•HCl (C, H, N, Cl); ^{1}H-NMR (DMSO-d_6): 12.0–11.0 (bs, 1H, ^+NH), 9.4 (bs, 1H, pyridine–NH), 8.2–7.9 (m, 2H, 3-nitrophenyl–H_2–H_4), 7.8–7.5 (m, 2H, 3-nitrophenyl–H_5–H_6), 7.4 (s, 10H, other aromatics), 5.05 (s, 1H, pyridine–H_4), 4.3–3.9 (m, 1H, N–C–C–CH), 3.6 (s, 3H, $COOCH_3$), 2.7 (s, 3H, NCH_3), 2.35 (s, 6H, 2,6 CH_3s), 3.2–1.9 (m, 8H, $CH_2CH_2NCH_2CH_2$), 1.35 (bs, 6H, COO–C$(CH_3)_2$).

6.11.3.6. 3-[N-(3,3-Diphenylpropyl)-N-methylamino]-2,2-dimethylpropyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl•0.5H_2O ***9ad:*** m.p. (119) 130–140 °C (amorphous); Anal. $C_{37}H_{43}N_3O_6$•HCl•0.5H_2O (C, H, N, Cl, H_2O); ^{1}H-NMR ($CDCl_3$): 10.5–9.5 (m, 1H, ^+NH), 8.6–7.2 (m, 15H, aromatics and pyridine–NH), 5.2 (s, 1H, pyridine–H_4), 4.1 (s, 2H, OCH_2), 4.2–3.7 (m, 1H, N–C–C–CH), 3.7 (s, 3H, $COOCH_3$), 3.2–2.2 (m, 9H, NCH_3 and $CH_2NCH_2CH_2$), 2.5 and 2.4 (2s, 6H, 2,6 CH_3s), 1.2 and 1.0 (2s, 6H, COO–C–C$(CH_3)_2$).

6.11.3.7. 3-[N-(3,3-Diphenylpropyl)-N-methylamino]-2,2-dimethylpropyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate•HCl ***9ae:*** m.p. 117–119 °C (Me_2CO); Anal. $C_{37}H_{42}Cl_2N_2O_4$•HCl (C, H, N, Cl); ^{1}H-NMR (DMSO-d_6): 10.5 (m, 1H, ^+NH), 9.4 (s, 1H, pyridine–NH), 7.7–7.1 (m, 13H, aromatics), 5.4 (s, 1H, pyridine–H_4), 4.2–3.8 (m, 3H, N–C–C–CH and OCH_2), 3.6 (s, 3H, $COOCH_3$), 3.2–2.2 (m, 15H, $CH_2N(CH_3)CH_2CH_2$ and 2,6 CH_3s), 1.0 (s, 6H, COO–C–C$(CH_3)_2$).

6.11.3.8. 3-[N-(3,3-Diphenylpropyl)-N-methylamino]-3,3-dimethylpropyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl•0.5H_2O ***9af:*** m.p. 112–117 °C (amorphous); Anal. $C_{37}H_{43}N_3O_6$•HCl•0.5H_2O (C, H, N, Cl, H_2O); ^{1}H-NMR (DMSO-d_6): 11.2–10.6 (bs, 1H, ^+NH), 9.5 (s, 1H, pyridine–NH), 8.3–8.0 (m, 2H, 3-nitrophenyl–H_2–H_4), 7.8–7.6 (m, 2H, 3-nitrophenyl–H_5–H_6), 7.45 (s, 10H, other aromatics), 5.1 (s, 1H, pyridine–H_4), 4.5–3.9 (m, 3H, N–C–C–CH and OCH_2), 3.65 (s, 3H, $COOCH_3$), 3.55 (s, 1H, 0.5 H_2O), 3.2–2.2 (m, 7H, $CH_2CH_2N(CH_3)$), 2.4 (s, 6H, 2,6 CH_3s), 2.2–1.8 (m, 2H, O–C–CH_2), 1.3 (s, 6H, N–C$(CH_3)_2$).

6.11.3.9. 2-[N-(3,3-Diphenyl-1-oxopropyl)-N-methylamino]-1,1-dimethylethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate ***9ag:*** m.p. 158 °C (EtOH 95); Anal. $C_{36}H_{39}N_3O_7$ (C, H, N); ^{1}H-NMR ($CDCl_3$): 8.4–7.2 (m, 14H, aromatics), 6.6 (s, 1H, pyridine–NH), 5.2 (s, 1H, pyridine–H_4), 4.75 (t, 1H, N–C–C–CH), 3.85 (s, 2H, NCH_2), 3.7 (s, 3H, $COOCH_3$), 3.1 (d, 2H, $NCOCH_2$), 2.8 (s, 3H, NCH_3), 2,3 (s, 6H, 2,6 CH_3s), 1.2 (s, 6H, COO–C$(CH_3)_2$).

6.11.4. Method C

A mixture of the appropriate aminoalkyl 2-arylideneacetoacetate of general formula **12** (0.01 mol), alkyl 3-aminocrotonate **5** (0.01 mol) and *i*-PrOH (10–40 mL) was stirred at reflux temperature for 3–6 h under N_2 atmosphere. After cooling to room temperature the solvent was evaporated and the residue was purified by flash chromatography. When **12** was used as •HCl salt, the residue was dissolved in a suitable solvent (CH_2Cl_2 or EtOAc) and the solution was washed with 20% Na_2CO_3 aqueous solution followed by H_2O. The organic layer was dried, filtered and evaporated to dryness to give the residue for flash chromatography. The following compounds were synthesized by this route.

6.11.4.1. 2-[N-(3,3-Diphenylpropyl)-N-methylamino]-1-methylethyl 1-methylethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl ***9o:*** m.p. 108–110 °C (amorphous); Anal. $C_{37}H_{43}N_3O_6$•HCl (C, H, N, Cl); ^{1}H-NMR ($CDCl_3$): 12.00–11.50 (bs, 1H, ^+NH), 8.4–7.2 (m, 15H, aromatics and pyridine–NH), 5.6–4.8 (m, 2H, 2 x O–CH), 5.05 (s, 1H, pyridine–H_4), 4.2–3.7 (m, 1H, N–C–C–CH), 3.4–2.2 (m, 6H, $CH_2NCH_2CH_2$), 2.8 (s, 6H, 2,6 CH_3s), 1.5–1.0 (m, 9H, O–C$(CH_3)_2$ and O–C(CH_3)–C).

6.11.4.2. 2-[N-(3,3-Diphenylpropyl)-N-methylamino]-1-methylethyl 2-propoxyethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl•0.5H_2O ***9p:*** m.p. 85–92 °C (amorphous); Anal. $C_{39}H_{47}N_3O_7$•HCl•0.5 H_2O (C, H, N, Cl, H_2O); ^{1}H-NMR ($CDCl_3$): 8.2–7.0 (m, 14H, aromatics), 6.0 (s, 1H, pyridine–NH), 5.3–4.6 (m, 1H, COOCH), 5.1 (s, 1H, pyridine–H_4), 4.3–3.7 (m, 3H, N–C–C–CH and $COOCH_2$), 3.7–3.15 (m, 4H, CH_2OCH_2), 2.6–1.85 (m, 9H, $CH_2N(CH_3)$-

CH_2CH_2), 2.3 (s, 6H, 2,6 CH_3s), 1.75–1.3 (m, 2H, O–C–CH_2–C), 1.2 and 1.0 (2d, 3H, O–C–CH_3), 0.85 (t, 3H, O–C–C–CH_3).

6.11.4.3. 1,1-Dimethyl-2-propoxyethyl 2-[N-(3,3-diphenylpropyl)-N-methylamino]-1-methylethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl•0.5H_2O ***9q****:* m.p. 86–95 °C (amorphous); Anal. $C_{41}H_{51}N_3O_7$•HCl•0.5H_2O (C, H, N, Cl, H_2O); ^{1}H-NMR ($CDCl_3$): 11.0–10.5 (bs, 1H, $^+$NH), 8.1–7.0 (m, 14H, aromatics), 5.7 (s, 1H, pyridine–NH), 5.2–4.7 (m, 1H, COOCH), 5.0 (s, 1H, pyridine–H}$_4$), 4.1–3.6 (m, 1H, N–C–C–CH), 3.4 (s, 2H, OCH_2–C–C), 3.25 (t, 2H, OCH_2–C(C_2), 2.5–1.9 (m, 10H, $CH_2N(CH_3)CH_2CH_2$ and 0.5H_2O), 2.25 (s, 6H, 2,6 CH_3s), 1.75–1.2 (m, 2H, O–C–CH_2–C), 1.35 (s, 6H, COO–C(CH_3)$_2$), 1.2 and 1.0 (2d, 3H, COO–C–CH_3), 0.8 (t, 3H, O–C–C–CH_3).

6.11.4.4. 2-[N-(3,3-Diphenylpropyl)-N-methylamino]-1-methylethyl 2-propoxyethyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate•HCl ***9s****:* m.p. 108–118 °C (amorphous); Anal. $C_{39}H_{46}Cl_2N_2O_5$•HCl (C, H, N, Cl); ^{1}H-NMR ($CDCl_3$): 12.0–11.5 (bs, 1H, $^+$NH), 8.0 (s, 1H, pyridine–NH), 7.8–7.1 (m, 13H, aromatics), 5.7–5.3 (m, 1H, COOCH), 5.45 (s, 1H, pyridine–H_4), 4.4–3.8 (m, 3H, N–C–C–CH and $COOCH_2$), 3.8–2.1 (m, 13H, $CH_2N(CH_3)$-CH_2CH_2 and CH_2OCH_2), 2.4 (s, 6H, 2,6 CH_3s), 1.8–1.2 (m, 5H, COO–C–CH_3 and O–C–CH_2–C), 1.0–0.7 (t, 3H, O–C–C–CH_3).

6.11.4.5. 2-[N-(3,3-Diphenylpropyl)-N-methylamino]-1,1-dimethylethyl ethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl ***9w*** (the reaction was carried out in anhydrous DMF at 80 °C for 5 h): m.p. 135–145 °C (EtOAc); Anal. $C_{37}H_{43}N_3O_6$•HCl (C, H, N, Cl); ^{1}H-NMR (DMSO-d_6): 11.0–10.0 (bs, 1H, $^+$NH), 9.45 (s, 1H, pyridine–NH), 8.2–7.6 (m, 4H, aromatics of 3-nitrophenyl ring), 7.4 (s, 10H, other aromatics), 5.0 (s, 1H, pyridine–H_4), 4.3–3.8 (m, 3H, N–C–C–CH and $COOCH_2$), 3.8–3.3 (m, 2H, O–C–CH_2–N), 2.4 and 2.3 (2s, 6H, 2,6 CH_3s), 3.2–2.1 (m, 7H, $N(CH_3)CH_2CH_2$), 1.45 (s, 6H, COO–C(CH_3)$_2$), 1.2 (t, 3H, COO–C–CH_3).

6.11.4.6. 2-[N-(3,3-Diphenylpropyl)-N-methylamino]-1,1-dimethylethyl 1-methylethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl•0.5H_2O ***9x****:* m.p. 100–115 °C (amorphous); Anal. $C_{38}H_{45}N_3O_6$•HCl•0.5H_2O (C, H, N, Cl, H_2O); ^{1}H-NMR (DMSO-d_6): 11.2–10.5 (bs, 1H, $^+$NH), 9.45–9.25 (s, 1H, pyridine–NH), 8.3–7.6 (m, 4H, aromatics of 3-nitrophenyl ring), 7.45 (s, 10H, other aromatics), 5.05 (s, 1H, pyridine–H_4), 5.2–4.75 (m, 1H, COOCH), 4.2–3.8 (m, 1H, N–C–C–CH), 3.5 (s, 1H, 0.5H_2O), 3.8–2.0 (m, 6H, $CH_2NCH_2CH_2$), 2.7 (s, 3H, NCH_3), 2.4 and 2.3 (2s, 6H, 2,6 CH_3s), 1.5 (s, 6H, COO–C(CH_3)$_2$–C), 1.2 (t, 6H, COO–C(CH_3)$_2$).

6.11.4.7. 2-[N-(3,3-Diphenylpropyl)-N-methylamino]-1,1-dimethylethyl 2-propoxyethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl•0.5H_2O ***9y****:* m.p. 87–92 °C (amorphous); Anal. $C_{40}H_{49}N_3O_7$•HCl•0.5H_2O (C, H, N, Cl, H_2O); ^{1}N-NMR (DMSO-d_6): 10.6–10.1 (bs, 1H, $^+$NH), 9.3 (s, 1H, pyridine–NH), 8.2–7.5 (m, 4H, aromatics of 3-nitrophenyl ring), 7.35 (s, 10H, other aromatics), 5.0 (s, 1H, pyridine–H_4), 4.3–3.8 (m, 3H, N–C–C–CH and $COOCH_2$), 3.8–2.1 (m, 20H, $CH_2N(CH_3)CH_2CH_2$, 2,6 CH_3s, CH_2OCH_2 and 0.5 H_2O), 1.6–1.2 (m, 8H, O–C–CH_2–C and COO–C(CH_3)$_2$), 0.8 (t, 3H, O–C–C–CH_3).

6.11.4.8. 1,1-Dimethyl-2-propoxyethyl 2-[N-(3,3-diphenylpropyl)-N-methylamino]-1,1-di-methylethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate•HCl•0.5H_2O ***9z****:* m.p. 88–92 °C (amorphous); Anal. $C_{42}H_{53}N_3O_7$•HCl•0.5H_2O (C, H, N, Cl, H_2O); ^{1}H-NMR (DMSO-d_6 at 80 °C): 10.5–9.3 (bs, 1H, $^+$NH), 9.25 (s, 1H, pyridine–NH), 8.4–7.7 (m, 4H, aromatics of 3-nitrophenyl ring), 7.6 (s, 10H, other aromatics), 5.3 (s, 1H, pyridine–H_4), 4.5–4.1 (m, 1H, N–C–C–CH), 3.8 (s, 3H, COO–C–CH_2–O and 0.5H_2O), 3.6 (t, 2H, COO–C–C–O–CH_2), 2.9 (s, 3H, NCH_3), 2.6 and 2.55 (2s, 6H, 2,6 CH_3s), 3.5–2.3 (m, 6H, $CH_2NCH_2CH_2$), 1.65 and 1.6 (2s, 12H, 2 COO–C–(CH_3)$_2$), 1.8–1.3 (m, 2H, O–C–CH_2–C), 0.95 (t, 3H, O–C–C–CH_3).

6.11.4.9. 2-[N-(3,3-Diphenylpropyl)-N-methylamino]-1,1-dimethylethyl methyl 4-(2,3-di-chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate•HCl•0.75H_2O ***9aa****:* m.p. 124–140 °C (amorphous); Anal. $C_{36}H_{40}Cl_2N_2O_4$•HCl•0.75H_2O (C, H, N, Cl, H_2O), ^{1}H-NMR (DMSO-d_6): 10.7–10.2 (bs, 1H, $^+$NH), 9.35 (s, 1H, pyridine–NH), 7.55 (s, 13H, aromatics), 5.45 (s, 1H, pyridine–H_4), 4.2–3.9 (m, 1H, N–C–C–CH), 3.65 (s, 3H, $COOCH_3$), 3.5 (s, 1.5H, 0.75H_2O), 3.3–2.1 (m, 9H, $CH_2N(CH_3)CH_2CH_2$), 3.35 and 3.25 (2s, 2,6 CH_3s), 1.4 (s, 6H, COO–C(CH_3)$_2$).

6.11.5. Determination of apparent dissociation constant for ***9u***

The apparent dissociation constant (pK_a') of **9u** was determined by potentiometric titration according to Albert and Serjeant [45]. 10^{-3} M Ethanolic–aqueous solutions (80:20 to 50:50) of the compound were titrated in a double run with 0.02 N NaOH at 37 °C using a glass–calomel electrode system. Only the pK_a values obtained in the range of 20–80% of titrating solution were taken into account and used to determine the regression line, which gave the extrapolated pK_a' of **9u** in pure water. The value found was pK_a' = 6.83.

By the same method a pK_a' value of 7.05 was obtained for nicardipine, in agreement with the value of 7.0 from the literature [46].

6.11.6. Determination of the partition coefficient for ***9u***

Log *P* determination of **9u** was carried out at 25 °C in *n*-octanol–phosphate buffer using a modified procedure based on the shake-flask method [47]. *n*-Octanol and aqueous phosphate buffers (pH 2.5 and 3) were mutually saturated by stirring equal volumes of each component at 25 °C for 2 h, and the two layers were separated after standing for 1 h.

Isotonic phosphate buffer solutions at pH 2.5 and 3 were prepared using 0.05 M KH_2PO_4 solutions adjusted to desired pH by H_3PO_4 addition. A shaking time of 5 min was used, followed by centrifugation at 3000 rpm for 10 min to completely separate the two layers, and the concentration of compound **9u** was determined by HPLC on the aqueous phase.

The determinations were made using 10^{-3} M solutions of **9u** base in *n*-octanol and volumetric *n*-octanol/aqueous buffer ratios 1:1 and 1:10 for each pH value. The concentration of compound **9u** in the aqueous layer was quantitated by HPLC using a Waters 3.9 x 300 mm reverse-phase μ-Bondapack C-18 column with UV detection at 240 nm and with MeCN–0.15 M $NaClO_4$ aqueous solution adjusted to pH 3 by $HClO_4$ addition (61:39, v/v) as the mobile phase at a flow rate of 1.5 mL/min (isocratic elution at 25 °C).

The distribution coefficient *D* was calculated from the equation

$$D = \frac{\text{(total concentration – concentration in aqueous layer)}}{\text{concentration in aqueous layer}}$$

Table IX. Results from pharmaco-toxicological screening for 1,4-dihydropyridines **9**.

Compound	^{3}H-Nitrendipine binding, IC_{50} (nM)	SHR ED_{25} p.o. (μmol/kg)	Indicative toxicity, LD_{50} (μmol/kg)		
			i.p. (mouse)	p.o. (mouse)	i.v. (rat)
9a	9.6	16.0	114	396	
9b	0.4	10.0	200	250	11
9c	7.1	22.0	149	570	
9d	2.6	23.6[a]	116	275	
9e	1.8	12.0	112	460	
9f	1.5	13.0	270	180	
9g	1.4	5.0[a]	99	200	
9h	0.6	4.1	77	179	7
9i	1.3	5.1	95	605	16
9j	1.1	10.0	320	3170	18
9k	2.3	5.3	270	400	
9l	7.8	8.0	170	290	
9m	1.0	11.0	150	750	11
9n	1.0	3.5	113	310	7
9n$_1$	0.8	3.4			5
9n$_2$	14.0	43.0			32
9o	3.4	7.4	110	190	11
9p	1.5	6.6	94	75	6
9q	8.0	11.0	375	> 4000	40
9r	4.0	4.9		> 770	19
9s	4.5	6.6		1860	10
9t	2.0	8.2	81	312	
9u	0.5	3.9	114	440	39
9v	380.0	> 154	710	> 4000	
9w	1.3	3.5[a]	520	4530	
9x	1.3	11.8	320		39
9y	0.6	5.2	71	515	23
9z	31.6	10.0	132	990	100
9aa	11.7	12.0	218	> 4000	28
9ab	1.4	6.6	150	230	
9ac	13.3	49.8	759	> 4000	
9ad	0.45	1.1	18	89	38
9ae	2.9	5.5	104	> 4000	
9af	20.8	18.4	320	> 4000	
9ag	4.3	> 160	> 1600	> 4800	
Nifedipine	2.3	18.0[a]	660	810	56
Nicardipine ·HCl	0.4	14.0	390	890	48
Felodipine	0.2	16.0	350	320	22
Prenylamine lactate	470.0	> 100			

[a]Peak effect at 1 hour after administration.

The partition coefficient was calculated by the formula

$$\log P = \log D - \log [1/1 + (10^{pKa-pH})]$$

and proved to be 6.0–6.1.

6.12. Pharmaco-toxicology

6.12.1. ^{3}[H]nitrendipine binding

Radioreceptor binding studies on 1,4-dihydropyridines binding site in the Ca^{2+} channels were carried out in membranes of rat brain. Male Sprague Dawley rats (200–300 g, Charles River, Italy) were killed by cervical dislocation and brains (minus cerebella) were excised and homogenized (2 x 20 sec) in 50 vol. of cold Tris-HCl buffer pH 7.7, using a Politron homogenizer (speed 7). Homogenates were centrifuged at 1000 *g* for 10 min and supernatants recentrifuged at 48000 *g* for 10 min; pellets were resuspended in 50 vol. of the same buffer and centrifuged once more.

The final pellets were suspended in 75 vol. of 50 mM Tris-HCl buffer pH 7.7; membranes were incubated in a final volume of 1 mL for 1 h at 25 °C with 0.2–0.5 nM ^{3}[H]nitrendipine, in the absence or presence of competing drugs; non-specific binding was determined in the presence of 1 μM nifedipine.

The incubation was stopped by addition of ice-cold Tris-HCl buffer and rapid filtration through Whatman GF/B. The filters were then washed with ice-cold buffer and the radioactivity retained on the filters was counted by liquid scintillation spectrometry. The inhibition of specific binding of the radioligands by the tested drugs was analyzed to estimate the IC_{50} value by using the non-linear curve-fitting program Allfit [48].

6.12.2. Effects on blood pressure in Spontaneously Hypertensive Rats (SHR)

Male spontaneously hypertensive rats of the Okamoto Strain, age 12–16 weeks, weighing 250–300 g were obtained from Charles River Italia, Calco, Como. Animals were housed with free access to food and water and maintained under standard conditions of temperature and humidity with a 12 h light–dark cycle, at least for 5 days before the experiment. Systolic arterial pressure (SBP) was non-invasively recorded (tail-cuff method) using a W&W 8006 BP Recorder and a piezoelectric pulse transducer (U. Basile, Italy). The animals were trained to comply unstressfully to the recording procedure for three days before the beginning of the experiment and only those having SBP values over 200 mmHg were used.

Animals were pre-warmed for 15 min at 37 °C before recording SBP. Compounds were dissolved or suspended in an aqueous solution of 0.5% Methocel A4C Premium, and administered by oral gavage in a volume of 5 mL/kg; the effects on blood pressure were monitored at 1, 3, 5 and 7 h after administration. The decrease in SBP recorded at different times were calculated as % changes versus the basal values, and the ED_{25} values (extrapolated dose inducing 25% decrease of SBP) were evaluated by linear regression analysis at time of peak effect.

6.12.3. Acute toxicity in mice and rats

Female Albino Swiss mice (28–34 g), and male Sprague–Dawley rats (180–220 g), obtained from Charles River Italia, Calco, Como, were used. Animals were housed with free access to food and water and maintained on standard conditions of temperature and humidity with a 12 h light–dark cycle, at least for 5 days before the experiment. The acute toxicity of tested compounds in mice was evaluated after intraperitoneal and oral administration, in groups of 3 mice (fasted for 4 h) at the maximal dose of 2000 mg/kg/30 mL (oral) or 500 mg/kg/20 mL (intraperitoneal). Compounds were dissolved or suspended in an aqueous solution of 0.5% Methocel A4C Premium. When necessary, logarithmic scaled doses of the compounds were administered to different groups of mice. Mortality was recorded for 14 days after the administration. LD_{50} values were evaluated by the method of Weil [49].

Intravenous toxicity in rats was evaluated as reported above. Compounds were dissolved in polypropylene glycol 400–water 1:1 and administered in the caudal vein (1 mL/kg).

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