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Synthesis and structural study of new highly lipophilic 1,4-dihydropyridines†

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A new series of 1,4-dihydropyridines (1,4-DHPs) endowed with ester groups bearing long and functionalised alkoxy chains at the C3 and C5 positions of the nitrogen ring have been prepared from the corresponding β-keto esters which were in turn prepared by a lipase catalysed transesterification reaction. The structural study has been carried out by X-ray crystallography and theoretical calculations at the semiempirical (AM1), *ab initio* (HF/6-31G*) and B3LYP/6-31G* levels and reveals that the long alkyl chains do not have any influence on the required geometry of the 1,4-DHPs for biological activity. However, these chains have a strong impact on the lipophilicity and, therefore, they could be used to gain a better control of the duration of the pharmacological action.

Introduction

1,4-Dihydropyridine derivatives (1,4-DHPs) form a class of heterocyclic compounds with interesting pharmacological and biological properties.[1] It is well known that the 1,4-DHP nucleus serves as the scaffold of important cardiovascular drugs and it has been well established that the calcium modulator activity of this family of compounds is determined by structural requirements.[2] The systematic structural modification of the 1,4-DHP ring yields different compounds used in the treatment of hypertension and angina pectoris.[3] The most prominent of these compounds is nifedipine, which was the first generation calcium channel blocker marketed by Bayer.[4] Since then, a wide variety of novel compounds belonging to the second and third generations of new biologically active substances from the 1,4-DHP class have been developed in order to obtain larger bioavailabilities or greater tissue selectivity.[5] Felodipine, lercanidipine, and clinidipine are examples of newer DHP-calcium antagonists, which are effective antihypertensive compounds (see Chart 1).

Up to now, 1,4-DHPs are still the most potent group of calcium channel modulators and, therefore, the design and study of this class of compounds remains desirable.[6] Recent papers have reported novel 1,4-DHP derivatives as calcium channel modulators[7] as well as the protective effects of dihydropyridine Ca-blockers against endothelial cell oxidative injury due to combined nitric oxide and superoxide.[8] It has been determined that 1,4-dihydropyridines containing NO-donor furoxan moieties at the 3-positioned basic lateral chain present vasodilating activity.[9]

In addition, very recent papers have reported different biological activities of novel 1,4-DHP derivatives that are not connected with their calcium channel modulator properties, such as neurotropic,[10] antidiabetic,[11] antibacterial,[12] and antiviral activity.[13] New dimeric 4-aryl-1,4-dihydropyridine derivatives were developed as a third class of nonpeptide HIV-1 protease inhibitors.[14] Very recently, *N*-alkoxycarbonylmethyl derivatives of 1,4-dihydropyridine-3,5-dicarboxylate were reported to act as a new carrier system to deliver drugs to the brain.[15]

The above studies clearly show that the 1,4-DHP nucleus appears to be a unique structure interacting with a wide variety of channels and receptors, its derivatives thus being considered as a class of *privileged pharmacophoric structures*.[7]

In previous works we have described the synthesis and structural study, by X-ray crystallographic methods and quantum chemical calculations, of several 1,4-DHP derivatives. We found that, in general, the conformational features reported for 1,4-DHP calcium modulators are preserved for these compounds.[16] Very recently, we carried out the synthesis of novel fulleropyrrolidines bearing biologically active 1,4-dihydropyridines covalently connected to the fullerene core.[17]

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† Electronic supplementary information (ESI) available: Calculated conformational data for selected compounds **4**. See DOI: 10.1039/b506018d

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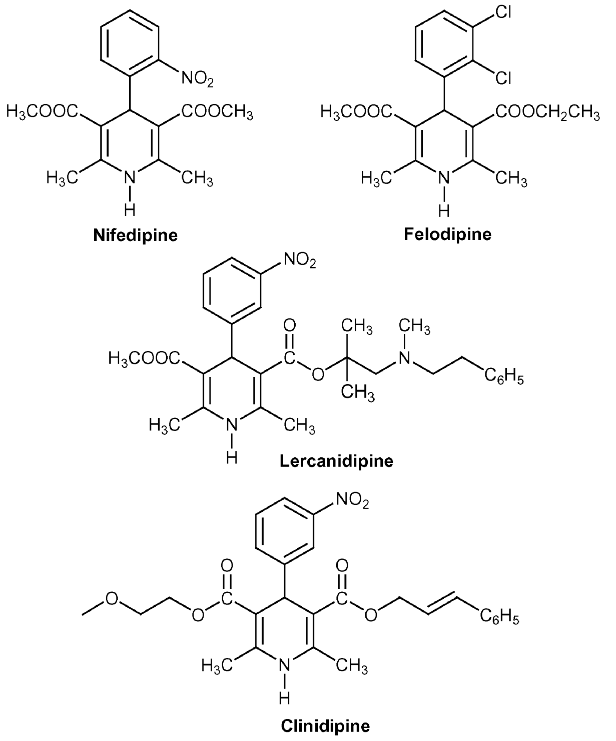


Chart 1 Representative examples of DHP-calcium antagonists.

An important drawback found for the parent nifedipine and other analogous calcium antagonists is their unfavourable kinetic profile, due to their rapid onset of vasodilator/antihypertensive action, thus leading to sympathetic activation and reflex tachycardia as a collateral effect. Because of its short duration of action, it has to be administered 3–4 times daily.[18] It has been proved that 1,4-DHP-calcium antagonists with a high degree of lipophilicity display a slow onset of action and the reflex tachycardia is not seen after administration of these compounds.[19] Accordingly, the lipophilicity of a compound might well be the major parameter governing its time of action as a calcium antagonist.[20] In addition, log *P*-values of DHP-calcium antagonists, as a measurement of the lipophilicity, can be used as a predictive parameter for the time of onset of the action.[19]

In order to gain a better understanding of the effect of the substitution pattern of the 1,4-DHP for biological activity, in this paper we describe the synthesis of novel 1,4-DHPs endowed with long and functionalised alkoxy chains, following a Hantzsch-like procedure. The β-keto esters with different acyl chains used as building blocks were synthesised as recently described by Cordova,[21] involving a transesterification reaction from the methyl β-keto ester and the corresponding alcohol in the presence of *Candida antarctica* lipase B (CALB) immobilised on a macroporous resin as a catalyst. Since the determination of the favoured conformation has been used to account for the pharmacological effect of different compounds with similar structures,[22] and in order to predict the biological activity of the compounds synthesised herein, we have carried out a structural study of these compounds, evaluating the geometry and conformational features by X-ray crystallography and theoretical calculations at the semiempirical and *ab initio* levels. Theoretical calculations have also been carried out to predict the log *P* values for the compounds obtained.

Results and discussion

Since the discovery of the pharmacological activity of 1,4-DHPs as calcium channel modulators all chemical research in this field has been devoted to the search for biologically active molecules. In spite of the extensive synthetic effort carried out on the preparation of 1,4-DHPs, the synthesis of 1,4-DHPs bearing ester groups with long and functionalised alkoxy chains at positions 3 and 5 of the nitrogen containing ring has been much less studied. All attempts to obtain these derivatives directly from the 1,4-DHP by using a classical transesterification reaction were unsuccessful. Therefore, in order to obtain this type of compound it was necessary to obtain previously the β-keto esters with the desired alkyl chain. The β-keto esters used in this work were synthesised by following the procedure described by Cordova,[21] using methyl acetoacetate (**1a**) as the acyl donor and different alcohols in the presence of *Candida antarctica* lipase B (CALB) immobilised on a macroporous resin (Scheme 1).

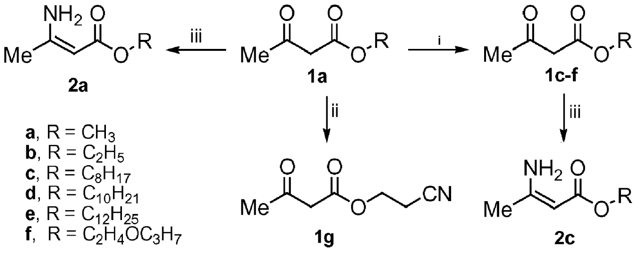
Compounds **1c–f** were thus obtained in good yields. Compound **1g** was obtained in 88% yield from **1a** and 3-hydroxypropionitrile following the same procedure. Ethyl acetoacetate (**1b**) was commercially available. From the corresponding β-keto esters **1a** and **1c**, by treatment with 25% aqueous ammonia solution in ethyl alcohol, we obtained the corresponding β-aminocrotonates **2a** and **2c** (see Scheme 1). The structures of these compounds (**1c–g**, **2a** and **2c**) were confirmed by spectroscopic methods (see Experimental).

The preparation of compounds **4a–r** was carried out by refluxing equimolar amounts of the β-keto ester **1**, alkyl 3-aminocrotonate **2** and the corresponding aromatic aldehyde **3** in absolute ethanol for 3–4 hours under a nitrogen atmosphere (see Scheme 2).

Compounds **4** were obtained as crystalline solids in 60–80% yields. Formation of the 1,4-dihydropyridine ring takes place through a Hantzsch-like mechanism *via* conjugate addition of the enamine intermediate **2** to the Knovenagel product **5** (obtained from the β-keto ester **1** and the corresponding aromatic aldehyde **3**) followed by imino–enamino tautomerism and subsequent heterocyclisation and loss of a water molecule (Scheme 3).

Compounds **4a–r** show satisfactory analytical and spectroscopic data. The FTIR spectra of compounds **4** present the amino and carbonyl signals at 3220–3260 cm^{-1} (NH) and 1690–1700 cm^{-1} (C=O). In addition to these signals, compounds **4c**, **4f**, **4i**, **4l**, **4p** and **4r** show the $C{\equiv}N$ signal at 2220–2225 cm^{-1}.

The ^{1}H NMR spectra at 300 MHz of 1,4-DHP derivatives **4a–r** show a very similar pattern. The NH and the H4 protons appear as a singlet at $\sim$9 ppm and in the range of 4.8–5.1 ppm, respectively. The methyl groups on C2 and C6 appear as singlets at $\sim$2.2 ppm, and cannot be distinguished in some compounds because of the similarity of the substituents on C3 and C5. The ^{1}H NMR spectra also show signals between 7.0–8.5 ppm corresponding to the protons of the aromatic ring on C4, showing the characteristic multiplicity depending on the position of the nitrogen atom in the pyridyl ring (2-, 3-, 4-) for compounds **4a–p**. In compounds **4q** and **4r**, endowed with a *p*-nitrophenyl ring, the aromatic protons appear at 8.1 and 7.4 ppm as an $AA'BB'$ system. The alkoxycarbonyl group



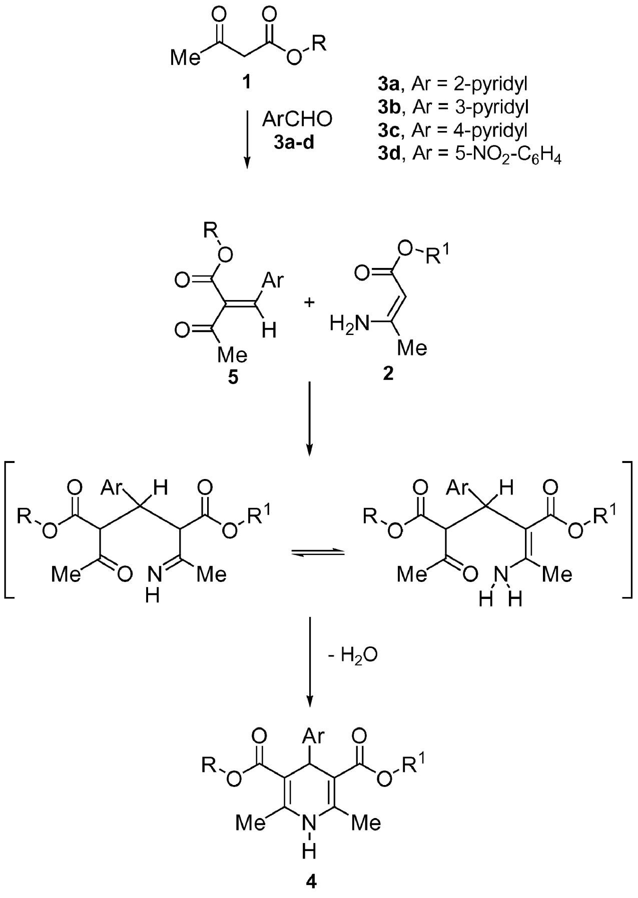
Scheme 1 Enzymatic synthesis of β-keto esters **1c–g** and aminocrotonates **2a** and **2c**. *Reagents and conditions*: i) CALB, ROH, 40 °C, 10 Torr; ii) CALB, 3-hydroxypropionitrile, 40 °C, 10 Torr; iii) conc. NH_4OH, EtOH.

4a, Ar = 2-pyridyl, R = C_8H_{17}, R^1 = CH_3
4b, Ar = 2-pyridyl, R = $C_{12}H_{25}$, R^1 = CH_3
4c, Ar = 2-pyridyl, R = C_2H_4CN, R^1 = CH_3
4d, Ar = 2-pyridyl, R = C_8H_{17}, R^1 = C_2H_5
4e, Ar = 2-pyridyl, R = C_8H_{17}, R^1 = C_8H_{17}
4f, Ar = 2-pyridyl, R = C_2H_4CN, R^1 = C_8H_{17}
4g, Ar = 3-pyridyl, R = C_8H_{17}, R^1 = CH_3
4h, Ar = 3-pyridyl, R = $C_{10}H_{21}$, R^1 = CH_3
4i, Ar = 3-pyridyl, R = C_2H_4CN, R^1 = CH_3
4j, Ar = 3-pyridyl, R = C_8H_{17}, R^1 = C_2H_5
4k, Ar = 3-pyridyl, R = $C_2H_4OC_4H_9$, R^1 = CH_3
4l, Ar = 3-pyridyl, R = C_2H_4CN, R^1 = C_8H_{17}
4m, Ar = 3-pyridyl, R = C_8H_{17}, R^1 = C_8H_{17}
4n, Ar = 3-pyridyl, R = $C_{10}H_{21}$, R^1 = C_8H_{17}
4o, Ar = 4-pyridyl, R = C_8H_{17}, R^1 = C_8H_{17}
4p, Ar = 4-pyridyl, R = C_2H_4CN, R^1 = CH_3
4q, Ar = 4-$NO_2C_6H_4$, R = C_8H_{17}, R^1 = CH_3
4r, Ar = 4-$NO_2C_6H_4$, R = C_2H_4CN, R^1 = CH_3

Scheme 2 Synthesis of 1,4-DHPs **4a–r**.

shows a number of signals which depends of the size of the chain. In these cases the methylene group of the alkoxycarbonyl chain (–O–CH_2–R) on C3 and C5 appears as a multiplet due to the presence of a stereogenic center on C4.[23] The rest of the aliphatic protons appear as a broad multiplet at ~1.2 ppm and as a triplet at ~0.8 ppm. The protons of the α-methylene group corresponding to the cyanoethyl group in compounds **4c**, **4f**, **4i**, **4l**, **4p** and **4r** appear as a multiplet at ~2.8 ppm and the β-protons as a triplet at ~4.1 ppm.

The ^{13}C NMR spectra of these compounds (**4a–g**) exhibit signals in the carbonyl, aromatic and aliphatic regions. In order to assign unequivocally the signals corresponding to the heterocyclic ring, we used 1D and 2D techniques: DEPT(135), HMQC and HMBC. The signals corresponding to the carbon atoms of the 1,4-DPH ring are relatively insensitive due to the nature of the substituent and appear at ~146 ppm (C2, C6) and at ~100 ppm (C3, C5). C4 appears between 35–40 ppm. The alkoxycarbonyl sp^2-carbon (COOR or $COOR^1$) appears at ~166 ppm. The rest of the signals are in agreement with the nature of aromatic or aliphatic carbon atoms. All the compounds showed a similar trend in the chemical shifts of the common moiety of the molecular backbone (see Experimental).



Scheme 3 Plausible mechanism for the formation of 1,4-DHPs **4a–r**.

In order to gain a better understanding of the novel compounds, we have calculated the structures of compounds **4a–r** using theoretical calculations. In previous works we have widely used theoretical calculations for determining the structural and conformational features of 1,4-DHPs and 3,4-dihydropyridone derivatives and we have demonstrated that *ab initio* and semiempirical calculations (at the AM1 level) reproduce adequately the geometry of this type of compound, taking into account the X-ray diffraction studies.[24–27]

All compounds were calculated using a semiempirical AM1 method. In the case of model compounds **4k**, **4n** and **4o** calculations were performed using *ab initio* HF/6-31G* and DFT (B3LYP/6-31G*) methods for the sake of comparison. Fig. 1 shows the most stable conformation for **4n** as a representative example, together with its numbering scheme.

Table 1 shows geometrical data calculated for compound **4n** (B3LYP/6-31G*) as well as those determined by X-ray diffraction.‡ The data for the remaining compounds, and the most stable conformations for some representative examples are collected in the ESI.†

In all cases, the distortion from planarity of the atoms comprising the 1,4-DHP ring can be clearly seen from the torsion angles calculated about the ring bonds. The greatest displacement from zero occurs from N1 and C4, indicating that the largest degree of puckering occurs at these positions, the distortion being greatest at the C4 position. The magnitudes and signs of these torsion angles indicate that both C4 and N1 (Table 1) lie above the plane formed by C2, C3, C5 and C6, which imparts a boat-like conformation to the DHP ring. Calculations predict that the substituent on C4 is in a pseudoaxial position (torsion angles C2–C3–C4–C1′ between 96° and 102°) and bisecting the plane containing the 1,4-DHP ring (torsion angles C3–C4–C1′–C2′ between 143° and 93°). In compounds **4a–f**, where the 2′-pyridyl ring is attached to C4, the values of the dihedral angle C3–C4–C1′–N2′ between 78° and 80° show the nitrogen atom of the 2′-pyridyl ring being

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‡ CCDC reference number 284120. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b506018d

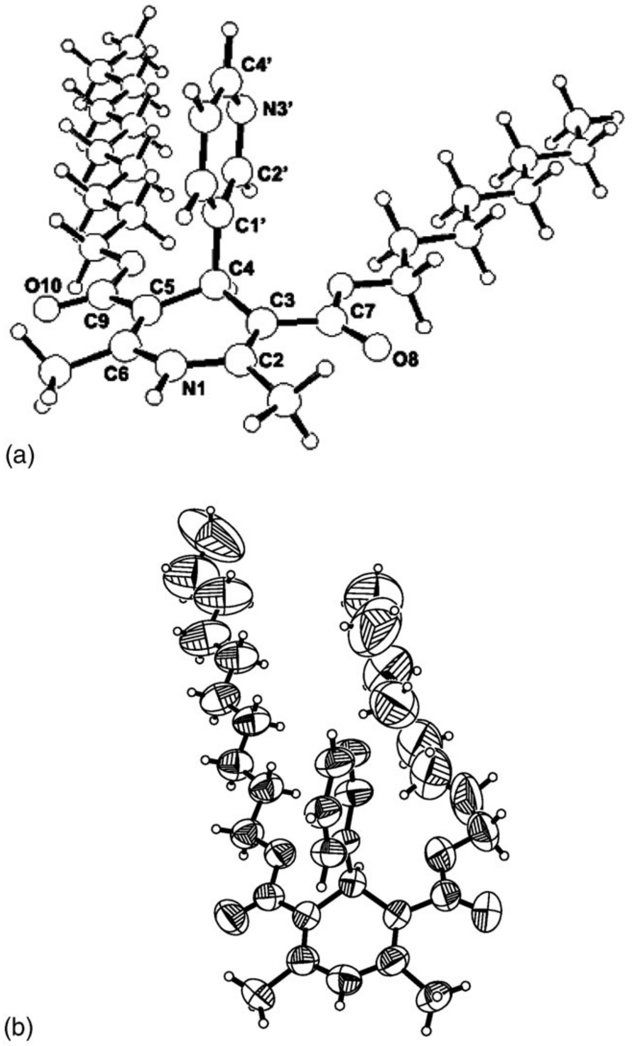

Fig. 1 (a) Most stable conformation for compound **4n** calculated at the B3LYP/6-31G* level. (b) Conformation of **4n** in the solid state showing the *sp*,*sp* orientation of the carboxylic groups with respect to the endocyclic double bonds of the 1,4-DHP ring, and the alkyl side chains are seen to fold upwards, positioned parallel to the flat face of the 3′-pyridyl ring. The carbons of the long alkyl chain are disordered in the crystal, as shown by the ellipsoids representing the high thermal motion. Displacement ellipsoids are drawn at the 50% probability level and H-atoms are represented as spheres of arbitrary size.

synperiplanar to the H4 atom on C4 in the most stable conformation. On the other hand, in compounds **4g–n** the values of the dihedral angle C3–C4–C1′–C2′ between 142° and 143°, clearly show that the nitrogen atom of the 3′-pyridyl ring lies synperiplanar to the DHP ring.

The sum, $\sum|\rho|$, of the absolute values of the internal torsion angles is a measure of its planarity (see Table 1). Compounds **4a–r** exhibit a $\sum|\rho|$ between 76° and 88°, these values are within the range of values found for compounds with biological activity.[28] In the case where the substituent on C4 is the 2-pyridyl ring the $\sum|\rho|$ shows the highest values (83°–87°), clearly due to the proximity of the nitrogen atom to the 1,4-DHP ring increasing the puckering of the ring. In all cases the C2–C3–C7–O8 and C6–C5–C9–O10 torsion angles are between 13° and −11°, showing that both carbonyl groups are *sp* (synperiplanar) to the respective endocyclic double bonds of the 1,4-DHP ring; this *sp*,*sp* orientation is 0.6 kcal mol^{-1} more stable than the *sp*,*ap* conformation and 1.3 kcal mol^{-1} more stable than the 'pure' antiperiplanar *ap*,*ap* conformation. This *sp*,*ap* conformation has also been found in felodipine and other DHP structures.[29]

Table 1 Most relevant bond distances (Å) valence angles (°) and dihedral angles (°) for the most stable conformation of compound **4n** obtained at the B3LYP/6-31G* level, as well as by X-ray diffraction

Bond distances	B3LYP/6-31G*	X-Ray
N1–C2	1.387	1.388(7)
C2–C3	1.362	1.332(8)
C3–C4	1.529	1.541(7)
C4–C5	1.529	1.515(7)
C5–C6	1.362	1.349(8)
C6–N1	1.387	1.396(8)
C4–C1′	1.533	1.540(7)
C7–O8	1.223	1.217(8)
C9–O10	1.223	1.217(8)
C2′–N3′	1.388	1.340(8)
N3′–C4′	1.339	1.330(9)
Bond angles		
C2–N1–C6	123.9	122.7(5)
O10–C9–C5	126.4	128.0(7)
O8–C7–C3	126.4	125.8(6)
C3–C4–C5	110.9	110.4(4)
C2′–N3′–C4′	117.1	117.0(5)
Torsion angles		
N1–C2–C3–C4	6.3	6.1(9)
C2–C3–C4–C5	−21.9	−24.8(7)
C3—C4–C5–C6	21.9	23.9(8)
C4–C5–C6–N1	−6.3	−4.6(9)
C5–C6–N1–C2	−12.7	−18.0(9)
C6–N1–C2–C3	12.7	17.1(9)
$\sum\|\rho\|$	81.8	94.5(8)
C3–C4–C1′–C2′	117.7	127.4(6)
C2–C3–C4–C1′	103.0	97.9(6)
C2–C3–C7–O8	−2.0	−0.9(10)
C6–C5–C9–O10	2.0	10.5(11)

The geometries for the molecules **4k**, **4n**, and **4o** were optimised by means of Hartree–Fock calculations using the basis set 6-31G*. We also decided to include electronic correlation in the form of a DFT calculation, using the B3LYP/6-31G* basis set; the results were similar to those obtained using the HF/6-31G* method. The overall analysis shows that all the methods employed (AM1, HF/6-31G* and B3LYP/6-31G*) predict the same geometry features, although the AM1 results should be analysed carefully and only allow us to characterise the systems in a qualitative way, high level calculations are necessary in order to check the validity of the approach. Therefore, taking as a reference the results from the DFT calculation (B3LYP/6-31G*) we conclude that HF/6-31G* shows basically the same results, and the AM1 semiempirical method stands as a very powerful and fast way to get reliable results.

The N1 atoms show an sp^2 hybridisation as can be seen from calculated values of the bond angles, about 120°, and the same trend is observed for the N atom in the pyridyl ring.

The compound **4n** was crystallised and its crystal structure determined by X-ray diffraction.‡ In the solid state, the 1,4-DHP ring in **4n** adopts a boat conformation with the N1 and C4 atoms defining the stern and bow positions and deviating from the least-squares plane by 0.138(5) and 0.181(5) Å, respectively. The puckering parameters[30] of the 1,4-DHP ring (N1–C2–C3–C4–C5–C6) are $Q = 0.282(6)$ Å, $\theta = 100.8(12)°$, $\varphi = 358.1(13)°$. The average ring bond distance is 1.430(3) Å. The 3′-pyridyl ring is positioned above the concave site of the 1,4-DHP ring in an axial position, perpendicular to the mean plane of the 1,4-DHP ring and bisecting it [defined by torsion angle C5–C4–C1′–C2′ = 109.9(6)°] owing to the steric hindrance of the long alkyl chains in the molecules. The conformation found in the crystal corresponds to that of the heteroatom (N) of the 3′-pyridyl ring being synperiplanar to the H atom at C4 of the 1,4-DHP moiety due to the presence of

Table 2 Calculated log *P* for compounds **4a–r**

Compound	Ar	R	R^1	log *P*
4a	2-Pyridyl	C_8H_{17}	CH_3	4.69
4b	2-Pyridyl	$C_{12}H_{25}$	CH_3	6.47
4c	2-Pyridyl	CH_2CH_2CN	CH_3	1.10
4d	2-Pyridyl	CH_2CH_3	C_8H_{17}	4.98
4e	2-Pyridyl	C_8H_{17}	C_8H_{17}	7.20
4f	2-Pyridyl	CH_2CH_2CN	C_8H_{17}	4.58
4g	3-Pyridyl	C_8H_{17}	CH_3	4.66
4h	3-Pyridyl	$C_{10}H_{21}$	CH_3	5.56
4i	3-Pyridyl	CH_2CH_2CN	CH_3	1.08
4j	3-Pyridyl	CH_2CH_3	C_8H_{17}	4.95
4k	3-Pyridyl	$(CH_2)_2O(CH_2CH_2)_2CH_3$	CH_3	2.73
4l	3-Pyridyl	CH_2CH_2CN	C_8H_{17}	4.55
4m	3-Pyridyl	C_8H_{17}	C_8H_{17}	7.19
4n	3-Pyridyl	$C_{10}H_{21}$	C_8H_{17}	7.88
4o	4-Pyridyl	C_8H_{17}	C_8H_{17}	7.20
4p	4-Pyridyl	CH_2CH_2CN	CH_3	1.12
4q	$4\text{-}NO_2C_6H_4$	C_8H_{17}	CH_3	5.24
4r	$4\text{-}NO_2C_6H_4$	CH_2CH_2CN	CH_3	1.82

a hydrogen bond between the N atom of the pyridyl and the N atom of the 1,4-DHP ring. This hydrogen bond [N1···N4′ = 3.006(6) Å, N1–H1···N4′ = 151°] holds the molecules together, forming one-dimensional infinite chains along 001. The packing diagram of **4n** is included in the ESI.† Both carbonyl groups are *sp* to the respective endocyclic double bonds of the 1,4-DHP ring, and the alkyl side chains are seen to fold upwards, positioned parallel to the flat face of the 3′-pyridyl ring, as found in *ab initio* calculations in the gas phase. The carbons in these long alkyl chains appear to be disordered in the crystal structure, as stated during the refinement by the high temperature factors.

In this matter, the presence of long carbon chains in the ester moiety of the 1,4-DHP ring does not modify significantly the geometry features of the 1,4-DHP pharmacophore, particularly the degree of puckering of the DHP ring (see Table 1).

In order to predict the influence of ester groups, on C3 and C5, endowed with long and functionalised alkoxy chains on the lipophilicity of the 1,4-DHP **4a–r**, we have calculated the log *P* values for all synthesised compounds (see Table 2) as well as for nifedipine (2.06), lecardipine (7.28), clinidipine (3.92) and felodipine (3.82). The experimental log *P* of nifedipine[31] and felodipine[32] are 2.20 and 3.86, respectively.

It is interesting to note that although log *P* values can be only considered as a guide, they clearly show that long alkyl chains on C3 and C5 significantly increase the lipophilic character of the 1,4-DHP. Therefore, they can present a low onset and long duration of the pharmacological action. In this way, the conformational features reported for 1,4-DHP calcium modulators are preserved for the compounds presented in this work, which indicates the potential activity of these compounds as biologically active systems, in spite of the long alkyl chains which also can improve the lipophilic character of the 1,4-DHPs.

Conclusions

In summary, we report a new series of 1,4-DHPs endowed with long and functionalised alkoxy chains at the C3 and C5 positions of the nitrogen ring, that strongly influence the spectroscopic as well as the lipophilic properties without modifying the required structural features for biological activity. The synthesis of the novel 1,4-DHPs bearing long alkyl chains on the ester groups at the C3 and C5 positions requires the use of a lipase catalysed transesterification for the preparation of the intermediate β-keto esters. Finally, theoretical calculations predict an interesting increase of the lipophilic character of the 1,4-DHPs bearing ester groups with long alkyl chains which may be of interest for a better control of the pharmacological action. The results obtained from the X-ray diffraction study of two representative compounds of the series correspond well with the geometrical features calculated by the different parameterisations employed in the DFT and *ab initio* theoretical calculations and the semiempirical AM1 approach. These findings corroborate the use of these theoretical methods for predicting and reproducing adequately the geometry of this type of compound.

Experimental

Commercially available starting materials and reagents were purchased from commercial sources (BDH and Fluka) and were used without further purification.

Melting points were determined in a capillary tube in an Electrothermal C14500 apparatus and are uncorrected. The NMR spectra were recorded on a Bruker DPX300 spectrometer (300 MHz-^{1}H and 75.47 MHz-^{13}C). Chemical shifts are given as δ values referred to the solvent and *J* values are given in Hz. The IR spectra were measured with a Shimadzu FTIR 8300 instrument as potassium bromide pellets. The 70 eV EI mass spectra were recorded using an HP 5989A quadrupole instrument with a source temperature of 200 °C. Microanalyses were performed in a Perkin Elmer 2400 CHN by the CAI de Microanálisis of Universidad Complutense de Madrid. The reactions were monitored by TLC performed on silica-gel plates (Merck 60F$_{250}$) and using hexane–ethyl acetate (1 : 1) as eluent. Semiempirical calculations were carried out using the AM1 method.[33] *Ab initio* calculations were carried out using the Hartree–Fock method with the 6-31G* basis set,[34] DFT were performed using a B3LYP/6-31G* basis set.[35] All calculations were carried out using the GAUSSIAN 98 program.[36] No geometry constrains were specified during the optimisation process.

The calculations of the log *P* values were carried out using the interactive analysis log *P* predictor available at www.logp.com which uses an implementation of the Molconn-Z program from Edusoft.[37] Calculations were performed on an IBM-RS6000 workstation.

Enzymatic synthesis of alkyl acetoacetates (1)

The synthesis was performed as described by Cordova[21] with some modifications. A homogeneous mixture of alcohol (30 mmol) and 3-oxobutyric acid methyl ester (**1a**) (180 mmol, 20 mL) was treated with 10% (w/w of alcohol) of *Candida antarctica* lipase B (CALB) and swirled in a 50 mL flask connected to a rotavapor at 40 °C and 10 Torr. After 5–7 hours, 10 mL of CH_2Cl_2 was added and the polymer-supported lipase removed by filtration. The solvent was removed under reduced pressure and the excess of β-keto ester was removed by distillation in the vacuum line. The crude product was purified by silica gel column chromatography with increasing amounts of ethyl acetate in hexane.

3-Oxobutyric acid octyl ester (1c). From **1a** and octan-1-ol. 6 h. Yield 90%, IR (KBr) ν 1744, 1720, 1653, 1238 cm^{-1}; ^{1}H NMR (DMSO-d_6 200 MHz) δ 4.05 (2H, t, $J = 6.6$ Hz, OCH_2), 3.59 (2H, s, CH_2), 2.18 (3H, s, CH_3), 1.55 (2H, m, CH_2), 1.27 (10H, br. s, $5 \times CH_2$), 0.87 (3H, t, $J = 6.6$ Hz, CH_3); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 201.4 (C=O), 167.3 (C=O), 64.2 (CH_2), 49.4 (CH_2), 31.0 (CH_2), 29.8 (CH_2), 29.3 (CH_2), 28.4 (CH_2), 27.8 (CH_2), 25.1 (CH_3), 21.9 (CH_2), 13.7 (CH_3); MS-EI *m*/*z*(%) 215 ([M + H]$^+$, 1), 103 (88), 85 (32), 57 (20), 43 (100). Anal. Calc. $C_{12}H_{22}O_3$ (214.30): C, 67.26; H, 10.35. Found: C, 67.38; H, 10.43%.

3-Oxobutyric acid decyl ester (1d). From **1a** and decan-1-ol. 7 h. Yield 85%, IR (KBr) ν 1743, 1718, 1650, 1238 cm^{-1}; ^{1}H NMR (DMSO-d_6 250 MHz) δ 4.13 (2H, t, $J = 7.2$ Hz, OCH$_2$), 3.44 (2H, s, CH$_2$), 2.27 (3H, s, CH$_3$), 1.62 (2H, m, CH$_2$), 1.26 (14H, br. s, 7 × CH$_2$), 0.87 (3H, t, $J = 7.2$ Hz, CH$_3$); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 201.5 (C=O), 167.1 (C=O), 65.6 (CH$_2$), 50.1 (CH$_2$), 31.8 (CH$_2$), 30.1 (CH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 29.2 (CH$_2$), 28.4 (CH$_2$), 26.4 (CH$_2$), 25.8 (CH$_3$), 22.6 (CH$_2$), 14.1 (CH$_3$); MS-EI m/z(%) 243 ([M + H]$^+$, 2), 200 (2), 103 (100), 85 (33), 70 (31), 43 (84). Anal. Calc. $C_{14}H_{26}O_3$ (242.35): C, 69.36; H, 10.81. Found: C, 69.62 H, 10.64%.

3-Oxobutyric acid dodecyl ester (1e). From **1a** and dodecan-1-ol. 7 h. Yield 96%, IR (KBr) ν 1770 (br. s), 1651, 1238 cm^{-1}; ^{1}H NMR (DMSO-d_6 250 MHz) δ 4.13 (2H, t, $J = 6.7$ Hz, OCH$_2$), 3.44 (2H, s, CH$_2$), 2.26 (3H, s, CH$_3$), 1.62 (2H, m, CH$_2$), 1.25 (18H, br. s, 9 × CH$_2$), 0.87 (3H, t, $J = 6.7$ Hz, CH$_3$); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 201.1 (C=O), 167.3 (C=O), 65.6 (CH$_2$), 50.1 (CH$_2$), 31.9 (CH$_2$), 30.1 (CH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 29.3 (CH$_2$), 29.2 (CH$_2$), 28.4 (CH$_2$), 25.8 (CH$_3$), 25.1 (CH$_2$), 22.6 (CH$_2$), 14.1 (CH$_3$); MS-EI m/z(%) 271 ([M + H]$^+$, 6), 201 (35), 103 (93), 85 (42), 69 (32), 43 (100). Anal. Calc. $C_{16}H_{30}O_3$ (270.41): C, 71.07; H, 11.18. Found: C, 71.22; H, 11.32%.

3-Oxobutyric acid 2-butoxyethyl ester (1f). From **1a** and 2-butoxyethanol. 5 h. Yield 96%, IR (KBr) ν 1747, 1718, 1247 cm^{-1}; ^{1}H NMR (DMSO-d_6 250 MHz) δ 4.28 (2H, t, $J = 5.8$ Hz, CH$_2$), 3.62 (2H, m, CH$_2$), 3.45 (4H, m, 2 × CH$_2$), 2.27 (3H, s, CH$_3$), 1.56 (2H, m, CH$_2$), 1.32 (2H, m, CH$_2$), 0.90 (3H, t, $J = 8.1$ Hz, CH$_3$); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 200.1 (C=O), 167.0 (C=O), 71.0 (CH$_2$), 68.1 (CH$_2$), 64.2 (CH$_2$), 49.9 (CH$_2$), 31.5 (CH$_2$), 29.9 (CH$_3$), 19.1 (CH$_2$), 13.7 (CH$_3$); MS-EI m/z(%) 203 ([M + H]$^+$, 63), 129 (78), 100 (22), 85 (70), 56 (100), 43 (93). Anal. Calc. $C_{10}H_{18}O_4$ (202.75): C, 59.39; H, 8.97. Found: C, 59.46; H, 8.31%.

3-Oxobutyric acid 2-cyanoethyl ester (1g). From **1a** and 3-hydroxypropionitrile. 5 h. Yield 88%, IR (KBr) ν 3504, 2230, 1751, 1717, 1655, 1630, 1271 cm^{-1}; ^{1}H NMR (DMSO-d_6 200 MHz) δ 4.24 (2H, t, $J = 6.0$ Hz, CH$_2$), 3.66 (2H, s, CH$_2$), 2.88 (2H, t, $J = 6.0$ Hz, CH$_2$), 2.20 (3H, s, CH$_3$); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 200.1 (C=O), 166.7 (C=O), 118.2 (CN), 59.3 (CH$_2$), 49.1 (CH$_2$), 29.8 (CH$_2$), 17.2 (CH$_3$); MS-EI m/z(%) 155 (M$^+$, 2), 85 (18), 43 (100); Anal. Calc. for $C_7H_9NO_3$ (155.15): C, 54.19; H, 5.85; N, 9.03. Found: C, 54.36; H, 5.68; N, 9.26%.

Synthesis of alkyl 3-aminocrotonates (2)

To 0.06 mol of β-keto ester (**1a** or **1c**) were added 0.20 mol of 25% aqueous ammonia and 25 mL of ethyl alcohol with stirring at room temperature.

3-Aminobut-2-enoic acid methyl ester (2a). After 7 h the white solid was precipitated, filtered off and rinsed with cold ethyl alcohol. Crystallisation from ethanol gives 65% yield. IR (KBr) ν 3335, 1664, 1624, 1288 cm^{-1}; ^{1}H NMR (DMSO-d_6 300 MHz) δ 7.12 (2H, br. s, NH$_2$), 4.53 (1H, s, = CH), 3.81 (3H, s, CH$_3$), 1.78 (3H, s, CH$_3$); ^{13}C NMR (DMSO-d_6, 50 MHz) 168.9 (C=O), 162.3 (C=O), 83.7 (CH$_2$), 58.6 (CH$_3$), 27.2 (CH$_3$). Anal. Calc. $C_5H_9NO_2$ (115.13): C, 52.16; H, 7.88; N, 12.17. Found: C, 52.27; H, 7.94; N, 12.25%.

3-Aminobut-2-enoic acid octyl ester (2c). After 14 h the solvent was removed under reduced pressure, obtaining the compound as a yellow liquid, 83% yield. IR (KBr) ν 3443, 3335, 1654, 1624, 1288 cm^{-1}; ^{1}H NMR (DMSO-d_6 200 MHz) δ 6.94 (2H, br s, NH$_2$), 4.29 (1H, s, = CH), 3.90 (2H, t, $J = 6.6$ Hz, CH$_2$), 1.80 (3H, s, CH$_3$), 1.55 (2H, m, CH$_2$), 1.24 (10H, br s, 5 × CH$_2$), 0.85 (3H, t, $J = 6.6$ Hz, CH$_3$); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 169.2 (C=O), 161.1 (C=O), 81.4 (CH$_2$), 61.5 (CH$_2$), 31.2 (CH$_2$), 28.7 (CH$_2$), 28.6 (CH$_2$), 28.3 (CH$_2$), 25.6 (CH$_3$), 22.1 (CH$_2$), 21.5 (CH$_2$), 14.0 (CH$_3$); MS-EI m/z(%) 213 (M$^+$, 9), 101 (30), 84 (58), 71 (30), 57 (89), 56 (28), 43 (100). Anal. Calc. $C_{12}H_{23}NO_2$ (213.32): C, 67.57; H, 10.87; N, 6.57. Found: C, 67.78; H, 10.65; N, 6.34%.

Synthesis of 1,4-dihydropyridines (4)

A mixture of the β-keto ester (**1**) (3 mmol), the corresponding aromatic aldehyde (**3**) (3 mmol) and the alkyl 3-aminocrotonate (**2**) in absolute ethanol (30 mL), was heated under reflux for 3–4 hours under a nitrogen atmosphere. After cooling to −5 °C, the precipitate was filtered and recrystallised from ethanol.

5-Methyl 3-octyl 2,6-dimethyl-4-(2′-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (4a). Obtained from **1c**, **2a** and **3a** in 65% yield, mp: 154–155 °C, IR (KBr) ν 3260 (NH), 1697 (C=O), 1643 and 1625 (C=C); ^{1}H NMR (DMSO-d_6), δ: 8.78 (1H, s, NH), 8.38 (1H, d, $J = 4.7$ Hz, H3′), 7.58 (1H, td, $J = 7.7$ Hz, $J = 1.8$ Hz, H5′), 7.11 (2H, m, H4′, H6′), 5.01 (1H, s, H4), 3.94 (2H, m, OCH$_2$), 3.53 (3H, s, OCH$_3$), 2.23 (3H, s, CH$_3$–C2), 2.22 (3H, s, CH$_3$–C6), 1.48 (2H, m, OCH$_2$*CH$_2$*), 1.24 (10H, br. s, 5 × CH$_2$), 0.85 (3H, t, $J = 6.79$ Hz, CH$_3$); ^{13}C NMR (DMSO-d_6), δ: 167.5 (C5–*C*=O), 166.9 (C3–*C*=O), 164.9 (C1′), 149.1 (C3′), 146.1, 146.1 (C2, C6); 135.6 (C5′), 121.4, 121.3 (C4′, C6′), 100.3 (C3) 100.2 (C5), 62.9 (OCH$_2$), 50.6 (OCH$_3$), 41.2 (C4), 31.2 (CH$_2$), 28.6 (2 × CH$_2$), 28.3 (OCH$_2$*CH$_2$*), 25.5 (OCH$_2$CH$_2$*CH$_2$*), 22.1 (CH$_2$), 18.3 (2 × CH$_3$), 13.9 (CH$_2$*CH$_3$*); MS-EI m/z(%) 400 (M$^+$, 1), 322 (100), 271 (4), 210 (41), 178 (8), 165 (6). Anal. Calc. $C_{23}H_{32}N_2O_4$ (400.51): C, 68.97; H, 8.05; N, 6.99. Found: C, 68.72; H, 8.21; N, 6.77%.

3-Dodecyl 5-methyl 2,6-dimethyl-4-(2′-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (4b). Obtained from **1e**, **2a** and **3a** in 75% yield, mp: 121–122 °C, IR (KBr) ν 3261 (NH), 1697 (C=O), 1645 and 1627 (C=C), cm^{-1}; ^{1}H NMR (DMSO-d_6), δ: 8.79 (1H, s, NH), 8.38 (1H, d, $J = 4.0$ Hz, H3′), 7.59 (1H, td, $J = 7.6$ Hz, $J = 1.8$ Hz, H5′), 7.09 (2H, m, H4′, H6′), 5.01 (1H, s, H4), 3.91 (2H, m, OCH$_2$), 3.53 (3H, s, OCH$_3$), 2.23 (3H, s, CH$_3$–C2), 2.21 (3H, s, CH$_3$–C6), 1.47 (2H, m, OCH$_2$*CH$_2$*), 1.23 (18H, br. s, 9 × CH$_2$), 0.85 (3H, t, $J = 6.4$ Hz, CH$_3$); ^{13}C NMR (DMSO-d_6), δ: 167.4 (C5–*C*=O), 166.9 (C3–*C*=O), 164.9 (C1′), 149.1 (C3′), 146.1, 146.0 (C2, C6); 135.5 (C5′), 121.4, 121.2 (C4′, C6′), 100.3 (C3) 100.2 (C5), 62.9 (OCH$_2$), 50.0 (OCH$_3$), 41.1 (C4), 31.3 (CH$_2$), 29.0 (2 × CH$_2$), 28.9 (CH$_2$), 28.7 (CH$_2$), 28.6 (2 × CH$_2$), 28.2 (OCH$_2$*CH$_2$*), 25.5 (CH$_2$), 22.1 (CH$_2$), 18.3 (2 × CH$_3$), 13.9 (CH$_2$*CH$_3$*); MS-EI m/z(%) 456 (M$^+$, 1), 378 (100), 271 (4), 210 (41), 178 (5), 165 (6). Anal. Calc. $C_{27}H_{40}N_2O_4$ (456.62): C, 71.02; H, 8.83; N, 6.13. Found: C, 71.29; H, 8.75; N, 6.22%.

3-(2-Cyanoethyl) 5-methyl 2,6-dimethyl-4-(2′-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (4c). Obtained from **1g**, **2a** and **3a** in 65% yield, mp: 167–169 °C, IR (KBr) ν 3260 (NH), 2225 (CN), 1690 (C=O), 1628 and 1593 (C=C); ^{1}H NMR (DMSO-d_6), δ: 8.90 (1H, s, NH), 8.40 (1H, d, $J = 4.7$ Hz, H3′), 7.58 (1H, td, $J = 7.7$ Hz, $J = 1.8$ Hz, H5′), 7.18 (1H, d, $J = 7.7$ Hz, H6′), 7.11 (1H, dd, $J = 7.7$ Hz, $J = 4.7$ Hz, H4′), 5.01 (1H, s, H4), 4.14 (2H, t, $J = 6.0$ Hz, OCH$_2$), 3.53 (3H, s, OCH$_3$), 2.83 (2H, m, CH$_2$CN), 2.25 (3H, s, CH$_3$–C2), 2.24 (3H, s, CH$_3$–C6); ^{13}C NMR (DMSO-d_6), δ: 167.4 (C5–*C*=O), 166.5 (C3–*C*=O), 164.7 (C1′), 149.1 (C3′), 147.2, 146.1 (C2, C6), 135.8 (C5′), 121.6 (C6′), 121.4 (C4′), 118.8 (CN), 100.5 (C5), 99.5 (C3), 58.4

(OCH_2), 50.6 (OCH_3), 41.0 (C4), 18.6 (CH_3–C2), 18.3 (CH_3–C6), 17.5 (CH_2–CN); MS-EI *m*/*z*(%) 341 (M^+, 2), 263 (100), 210 (26), 178 (5). Anal. Calc. $C_{18}H_{19}N_3O_4$ (341.36): C: 63.33; H: 5.61; N: 12.31. Found: C, 63.62; H, 5.33; N, 12.45%.

5-Ethyl 3-octyl 2,6-dimethyl-4-(2′-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (4d). Obtained from **1b**, **2c** and **3a** in 68% yield, mp: 133–135 °C, IR (KBr) ν 3260 (NH), 1693 (C=O), 1643 and 1626 (C=C); ^{1}H NMR (DMSO-d_6), δ: 8.76 (1H, s, NH), 8.38 (1H, br. d, J = 4.5 Hz, H3′), 7.58 (1H, td, J = 7.6 Hz, J = 1.9 Hz, H5′), 7.12 (1H, d, H6′, overlapping with 7.09), 7.09 (1H, d, H4′, overlapping with 7.12), 5.00 (1H, s, H4), 3.90 (4H, m, 2 × OCH_2), 2.23 (3H, s CH_3), 2.21 (3H, s CH_3), 1.47 (2H, m, OCH_2CH_2), 1.20 (10H, br. s, 5 × CH_2), 1.12 (3H, t, J = 7.4 Hz, CH_3), 0.84 (3H, t, J = 6.79 Hz, CH_3); ^{13}C NMR (DMSO-d_6), δ: 166.9 (C3–C=O, C5–C=O), 165.1 (C1′), 149.1 (C3′), 146.2, 145.9 (C2, C6), 135.4 (C5′), 121.7 (C6′), 121.3 (C4′), 100.4, 100.3 (C3, C5), 62.9 (OCH_2), 58.9 (OCH_2CH_3), 41.3 (C4), 31.2 (CH_2), 28.6 (2 × CH_2), 28.3 (OCH_2CH_2), 25.6 ($OCH_2CH_2CH_2$), 22.1 (CH_2), 18.3 (2 × CH_3), 14.2 (OCH_2CH_3), 13.9 (CH_2CH_3); MS-EI *m*/*z*(%) 414 (M^+, 1), 336 (100), 308 (3), 224 (20), 211 (5), 179 (5). Anal. Calc. $C_{24}H_{34}N_2O_4$ (414.54): C: 69.54; H: 8.27; N: 6.76. Found: C, 69.68; H, 8.38; N, 6.81%.

3,5-Dioctyl 2,6-dimethyl-4-(2′-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (4e). Obtained from **1c**, **2c** and **3a** in 76% yield, mp: 132–133 °C, IR (KBr) ν 3226 (NH), 1693 (C=O), 1639 and 1626 (C=C); ^{1}H NMR (DMSO-d_6), δ: 8.77 (1H, s, NH), 8.38 (1H, d, J = 4.0 Hz, H3′), 7.55 (1H, td, J = 7.6 Hz, J = 1.8 Hz, H5′), 7.10 (2H, m, H4′, H6′), 5.02 (1H, s, H4), 3.91 (4H, m, 2 × OCH_2), 2.22 (6H, s, 2 × CH_3), 1.48 (4H, m, 2 × OCH_2CH_2), 1.21 (20H, br. s, 10 × CH_2), 0.85 (6H, t, J = 6.4 Hz, 2 × CH_3); ^{13}C NMR (DMSO-d_6), δ: 166.9 (C5–C=O, C3–C=O), 165.1 (C1′), 149.1 (C3′), 146.1 (C2, C6); 135.3 (C5′), 121.6, 121.3 (C4′, C6′), 100.3 (C3, C5), 62.9 (2 × OCH_2), 41.2 (C4), 31.2 (2 × CH_2), 28.6 (4 × CH_2), 28.3 (2 × OCH_2CH_2), 25.6 (2 × CH_2), 22.1 (2 × CH_2), 18.2 (2 × CH_3), 13.9 (2 × CH_2CH_3); MS-EI *m*/*z*(%) 498 (M^+, 1), 420 (100), 308 (10), 256 (8), 178 (3). Anal. Calc. $C_{30}H_{46}N_2O_4$ (498.70): C: 72.25; H: 9.30; N: 5.62. Found: C, 72.42; H, 9.20; N, 5.77%.

3-(2-Cyanoethyl) 5-octyl 2,6-dimethyl-4-(2′-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (4f). Obtained from **1g**, **2c** and **3a** in 60% yield, mp: 133–134 °C, IR (KBr) ν 3260 (NH), 2225 (CN), 1697 (C=O), 1643 and 1625 (C=C); ^{1}H NMR (DMSO-d_6), δ: 8.99 (1H, s, NH), 8.39 (1H, br. d, J = 4.8 Hz, H3′), 7.56 (1H, td, J = 7.8 Hz, J = 1.6 Hz, H5′), 7.19 (1H, d, J = 7.8 Hz, H6′), 7.09 (1H, dd, J = 7.8 Hz, J = 4.8 Hz, H4′), 5.02 (1H, s, H4), 4.13 (2H, t, J = 5.8 Hz, OCH_2CH_2CN), 3.93 (2H, m, OCH_2), 2.83 (2H, m, CH_2CN), 2.24 (3H, s, CH_3), 2.23 (3H, s, CH_3), 1.48 (2H, m, OCH_2CH_2), 1.20 (10H, m, 5 × CH_2), 0.85 (3H, t, J = 6.7 Hz, CH_3); ^{13}C NMR (DMSO-d_6), δ: 166.9 (C5–C=O), 166.5 (C3–C=O), 164.8 (C1′), 149.1 (C3′), 147.1, 146.0 (C2, C6), 135.5 (C5′), 121.8 (C6′), 121.4 (C4′), 118.8 (CN), 100.7 (C3), 99.5 (C5), 63.0 (OCH_2), 58.4 (OCH_2CH_2CN), 41.1 (C4), 31.2 (CH_2), 28.6 (2 × CH_2), 28.2 (OCH_2CH_2), 25.5 (CH_2), 22.1 (CH_2), 18.6 (CH_3), 18.3 (CH_3), 17.5 (CH_2–CN), 13.9 (CH_2CH_3); EM *m*/*z*(%) 439 (M^+, 1), 420 (7), 361 (100), 249 (27), 211 (8), 152 (10). Anal. Calc. $C_{25}H_{33}N_3O_4$ (439.55): C: 68.31; H: 7.57; N: 9.56. Found: C, 68.52; H, 7.38; N, 9.78%.

5-Methyl 3-octyl 2,6-dimethyl-4-(3′-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (4g). Obtained from **1c**, **2a** and **3b** in 65% yield, mp: 158–160 °C, IR (KBr) ν 3265 (NH), 1692 (C=O), 1643 and 1587 (C=C); ^{1}H NMR (DMSO-d_6), δ: 8.97 (1H, s, NH), 8.35 (1H, d, J = 1.6 Hz, H2′), 8.31 (1H, dd, J = 4.7 Hz, J = 1.6 Hz, H4′), 7.47 (1H, dt, J = 7.8 Hz, J = 1.6 Hz, H6′), 7.23 (1H, dd, J = 7.8 Hz, J = 4.7 Hz, H5′), 4.89 (1H, s, H4), 3.90 (2H, m, OCH_2), 3.54 (3H, s, OCH_3), 2.28 (3H, s, CH_3–C2), 2.26 (3H, s, CH_3–C6), 1.48 (2H, m, OCH_2CH_2), 1.21 (10H, br. s, 5 × CH_2), 0.85 (3H, t, J = 6.6 Hz, CH_3); ^{13}C NMR (DMSO-d_6), δ: 167.1 (C5–C=O), 166.6 (C3–C=O), 148.5 (C2′), 147.2 (C4′), 143.2 (C1′), 146.3, 146.3 (C2, C6), 134.6 (C6′), 123.5 (C5′), 100.9, 100.8 (C3, C5), 63.2 (OCH_2), 50.8 (OCH_3), 36.8 (C4), 31.1 (CH_2), 28.6 (2 × CH_2), 28.2 (OCH_2CH_2), 25.5 (CH_2), 22.1 (CH_2), 18.2 (CH_3–C6), 18.1 (CH_3–C2), 13.9 (CH_2CH_3); MS-EI *m*/*z*(%) 400 (M^+, 3), 322 (100), 271 (4), 210 (41), 178 (7), 165 (6). Anal. Calc. $C_{23}H_{32}N_2O_4$ (400.51): C, 68.97; H, 8.05; N, 6.99. Found: C, 68.81; H, 8.16; N, 6.88%.

3-Decyl 5-methyl 2,6-dimethyl-4-(3′-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (4h). Obtained from **1d**, **2a** and **3b** in 68% yield, mp: 159–160 °C, IR (KBr) ν 3267 (NH), 1691 (C=O), 1645 and 1587 (C=C); ^{1}H NMR (DMSO-d_6), δ: 8.98 (1H, s, NH), 8.35 (1H, d, J = 1.6 Hz, H2′), 8.30 (1H, dd, J = 4.7 Hz, J = 1.6 Hz, H4′), 7.48 (1H, dt, J = 7.9 Hz, J = 1.6 Hz, H6′), 7.24 (1H, dd, J = 7.9 Hz, J = 4.7 Hz, H5′), 4.85 (1H, s, H4), 3.92 (2H, m, OCH_2), 3.54 (3H, s, OCH_3), 2.27 (3H, s, CH_3–C2), 2.25 (3H, s, CH_3–C6), 1.47 (2H, m, OCH_2CH_2), 1.22 (14H, br. s, 7 × CH_2), 0.85 (3H, t, J = 6.4 Hz, CH_3); ^{13}C NMR (DMSO-d_6), δ: 167.1 (C5–C=O), 166.5 (C3–C=O), 148.5 (C2′), 147.1 (C4′), 143.1 (C1′), 146.3, 146.2 (C2, C6), 134.6 (C6′), 123.5 (C5′), 100.9 (C5) 100.8 (C3), 63.1 (OCH_2), 50.7 (OCH_3), 37.2 (C4), 31.6 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 28.3 (OCH_2CH_2), 25.9 (CH_2), 22.5 (CH_2), 18.2 (CH_3–C2), 18.1 (CH_3–C6), 13.9 (CH_2CH_3); MS-EI *m*/*z*(%) 428 (M^+, 2), 350 (100), 287 (10), 243 (8), 210 (43), 178 (5), 165 (6). Anal. Calc. $C_{25}H_{36}N_2O_4$ (428.56): C, 70.06; H, 8.47; N, 6.54. Found: C, 70.18; H, 8.32; N, 6.59%.

3-(2-Cyanoethyl) 5-methyl 2,6-dimethyl-4-(3′-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (4i). Obtained from **1g**, **2a** and **3b** in 68% yield, mp: 186–187 °C, IR (KBr) ν 3269 (NH), 2220 (CN), 1691 (C=O), 1643 and 1600 (C=C); ^{1}H NMR (DMSO-d_6), δ: 9.08 (1H, s, NH), 8.38 (1H, d, J = 1.7 Hz, H2′), 8.32 (1H, dd, J = 4.7 Hz, J = 1.7 Hz, H4′), 7.52 (1H, dt, J = 7.7 Hz, J = 1.7 Hz, H6′), 7.24 (1H, dd, J = 7.7 Hz, J = 4.7 Hz, H5′), 4.86 (1H, s, H4), 4.15 (2H, t, J = 5.9 Hz, OCH_2), 3.54 (3H, s, OCH_3), 2.84 (2H, m, CH_2CN), 2.29 (3H, s, CH_3–C2), 2.28 (3H, s, CH_3–C6); ^{13}C NMR (DMSO-d_6), δ: 166.9 (C5–C=O), 166.1 (C3–C=O), 148.5 (C2′), 147.3 (C4′), 146.3, 146.2 (C2, C6), 142.9 (C1′), 134.7 (C6′), 123.5 (C5′), 118.7 (CN), 101.2 (C5), 100.2 (C3), 58.6 (OCH_2), 50.8 (OCH_3), 36.7 (C4), 18.5 (CH_3–C2), 18.2 (CH_3–C2), 17.4 (CH_2–CN); MS-EI *m*/*z*(%) 341 (M^+, 3), 363 (100), 243 (6), 210 (25), 178 (6). Anal. Calc. $C_{18}H_{19}N_3O_4$ (341.36): C: 63.33; H: 5.61; N: 12.31. Found: C, 63.52; H, 5.45; N, 12.49%.

5-Ethyl 3-octyl 2,6-dimethyl-4-(3′-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (4j). Obtained from **1b**, **2c** and **3b** in 70% yield, mp: 151–152 °C, IR (KBr) ν 3262 (NH), 1701 and 1690 (C=O), 1647 (C=C); ^{1}H NMR ($CDCl_3$), δ: 6.61 (1H, s, NH), 8.52 (1H, d, J = 1.6 Hz, H2′), 8.36 (1H, dd, J = 4.8 Hz, J = 1.6 Hz, H4′), 7.61 (1H, dt, J = 7.8 Hz, J = 1.6 Hz, H6′), 7.15 (1H, dd, J = 7.8 Hz, J = 4.8 Hz, H5′), 4.98 (1H, s, H4), 4.05 (4H, m, 2 × OCH_2), 2.34 (3H, s, CH_3), 2.32 (3H, s, CH_3), 1.88 (2H, m, OCH_2CH_2), 1.20 (10H, br. s, 5 × CH_2), 1.19 (3H, t, J = 7.1 Hz, CH_3), 0.88 (3H, t, J = 6.7 Hz, CH_3); ^{13}C NMR ($CDCl_3$), δ: 167.3, 167.2 (C5–C=O, C3–C=O), 149.4 (C2′), 147.1 (C4′), 143.5 (C1′), 145.0, 144.9 (C2, C6), 135.6 (C6′), 123.0 (C5′), 103.1, 103.1 (C3, C5), 64.0 (OCH_2), 59.8 (OCH_2), 37.7 (C4), 31.7 (CH_2), 29.2 (2 × CH_2), 28.6 (OCH_2CH_2), 26.0 (CH_2), 22.60 (CH_2), 19.3 (2 × CH_3), 14.2 (CH_2CH_3), 14.1 (CH_2CH_3); MS-EI *m*/*z*(%) 414 (M^+, 4), 336 (100), 257 (6), 224

(20), 179 (6). Anal. Calc. $C_{24}H_{34}N_2O_4$ (414.54): C, 69.54; H, 8.27; N, 6.76. Found: C, 69.71; H, 8.37; N, 6.52%.

5-(2-Butoxyethyl) 3-methyl 2,6-dimethyl-4-(3′-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (4k). Obtained from **1f**, **2a** and **3b** in 80% yield, mp: 158–159 °C, IR (KBr) ν 3270 (NH), 1703 and 1693 (C=O), 1645 and 1635 (C=C); ^{1}H NMR (DMSO-d_6), δ: 9.00 (1H, s, NH), 8.38 (1H, d, *J* = 1.7 Hz, H2′), 8.31 (1H, dd, *J* = 4.7 Hz, *J* = 1.7 Hz, H4′), 7.50 (1H, dt, *J* = 7.9 Hz, *J* = 1.7 Hz, H6′), 7.23 (1H, dd, *J* = 7.9 Hz, *J* = 4.7 Hz, H5′), 4.86 (1H, s, H4), 4.06 (2H, m, CH_2OCO), 3.52 (3H, s, OCH_3), 3.49 (2H, m, CH_2O), 3.35 (2H, m, CH_2O), 2.27 (3H, s, CH_3), 2.26 (3H, s, CH_3), 1.45 (2H, m, CH_2CH_2O), 1.30 (2H, m, CH_2CH_3), 0.86 (3H, s CH_3); ^{13}C NMR (DMSO-d_6), δ: 167.0 (C3–*C*=O), 166.5 (C5–*C*=O), 148.8 (C2′), 147.3 (C4′), 143.0 (C1′), 147.7 (C2, C6), 134.9 (C6′), 123.7 (C5′), 101.2 (C3), 101.0 (C5), 70.1 (CH_2), 68.3 (CH_2), 62.8 (CH_2), 50.8 (OCH_3), 36.9 (C4), 31.5 (CH_2), 19.4 (CH_2), 18.5 (CH_3), 18.5 (CH_3), 14.1 (CH_2CH_3); MS-EI *m*/*z*(%) 388 (M^+, 5), 310 (100), 287 (6), 243 (8), 210 (51), 178 (7). Anal. Calc. $C_{21}H_{28}N_2O_5$ (388.46): C, 64.93; H, 7.27; N, 7.21. Found: C, 64.81; H, 7.34; N, 7.32%.

5-(2-Cyanoethyl) 3-octyl 2,6-dimethyl-4-(3′-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (4l). Obtained from **1g**, **2c** and **3b** in 60% yield, mp: 168–169 °C, IR (KBr) ν 3271 (NH), 2223 (CN), 1701 (C=O), 1636 and 1589 (C=C). ^{1}H NMR (DMSO-d_6), δ: 9.05 (1H, s, NH), 8.39 (1H, d, *J* = 1.6 Hz, H2′), 8.30 (1H, dd, *J* = 4.7 Hz, *J* = 1.6 Hz, H4′), 7.53 (1H, dt, *J* = 7.8 Hz, *J* = 1.6 Hz, H6′), 7.23 (1H, dd, *J* = 7.8 Hz, *J* = 4.7 Hz, H5′), 4.86 (1H, s, H4), 4.16 (2H, m, OCH_2), 4.13 (2H, m, OCH_2CH_2CN), 2.84 (2H, m, CH_2CN), 2.28 (6H, s, 2 × CH_3), 1.48 (2H, m, OCH_2CH_2), 1.20 (10H, br. s, 5 × CH_2), 0.85 (3H, t, *J* = 6. 9 Hz, CH_3); ^{13}C NMR (DMSO-d_6), δ: 166.5 (C3–*C*=O), 166.1 (C5–*C*=O), 148.6 (C2′), 147.2 (C4′), 143.1 (C1′), 147.2, 146.1 (C2, C6); 123.4 (C5′), 134.8 (C6′), 118.6 (CN), 101.4, 100.3 (C3, C5), 63.2 (OCH_2), 58.6 (OCH_2CH_2CN), 36.8 (C4), 31.2 (CH_2), 28.6 (2 × CH_2), 28.2 (OCH_2CH_2), 25.5 ($OCH_2CH_2CH_2$), 22.1 (CH_2), 18.4 (CH_3), 18.1 (CH_3), 17.4 (CH_2CN), 13.9 (CH_2CH_3); MS-EI *m*/*z*(%) 439 (M^+, 3), 420 (10), 361 (100), 326 (8), 282 (10), 249 (27). Anal. Calc. $C_{25}H_{33}N_3O_4$ (439.55): C, 68.31; H, 7.57; N, 9.56. Found: C, 68.43; H, 7.50; N, 9.70%.

3,5-Dioctyl 2,6-dimethyl-4-(3′-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (4m). Obtained from **1c**, **2c** and **3b** in 64% yield, mp: 136–137 °C, IR (KBr) ν 3226 (NH), 1693 (C=O), 1639 and 1636 (C=C); ^{1}H NMR ($CDCl_3$), δ: 7.97 (1H, s, NH), 8.26 (1H, d, *J* = 1.8 Hz, H2′), 8.10 (1H, dd, *J* = 5.0 Hz, *J* = 1.8 Hz, H4′) 7.43 (1H, dt, *J* = 7.0 Hz, *J* = 1.8 Hz, H6′), 6.98 (1H, dd, *J* = 7.0 Hz, *J* = 5.0 Hz, H5′), 4.75 (1H, s, H4), 3.36 (4H, t, *J* = 6.5 Hz, 2 × OCH_2), 2.10 (6H, s, 2 × CH_3), 1.35 (4H, m, 2 × OCH_2CH_2), 1.02 (20H, m, 10 × CH_2), 0.64 (6H, t, *J* = 6.5 Hz, 2 × CH_3); ^{13}C NMR ($CDCl_3$), δ: 166.8 (C5–*C*=O, C3–*C*=O), 147.7 (C2′), 145.8 (C2, C6), 145.3 (C4′), 143.7 (C1′), 135.9 (C6′), 122.8 (C5′), 101.3 (C5, C3), 63.2 (2 × OCH_2), 37.2 (C4), 31.1 (2 × CH_2), 28.5 (2 × CH_2), 28.5 (2 × CH_2), 28.0 (2 × OCH_2CH_2), 25.4 (2 × CH_2), 21.9 (2 × CH_2), 18.2 (2 × CH_3), 13.5 (2 × CH_2CH_3); MS-EI *m*/*z*(%) 498 (M^+, 2), 420 (100), 385 (10), 308 (12), 229 (6). Anal. Calc. $C_{30}H_{46}N_2O_4$ (498.70): C, 72.25; H, 9.30; N, 5.62. Found: C, 72.38; H, 9.18; N, 5.77%.

3-Decyl 5-octyl 2,6-dimethyl-4-(3′-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (4n). Obtained from **1d**, **2c** and **3b** in 70% yield, mp: 133–134 °C, IR (KBr) ν 3265 (NH), 1699 and 1687 (C=O), 1643 and 1587 (C=C); ^{1}H NMR ($CDCl_3$), δ: 6.55 (1H, s, NH), 8.51 (1H, d, *J* = 1.8 Hz, H2′), 8.38 (1H, dd, *J* = 5.0 Hz, *J* = 1.8 Hz, H4′) 7.83 (1H, dt, *J* = 7.8 Hz, *J* = 1.8 Hz, H6′), 7.30 (1H, dd, *J* = 7.8 Hz, *J* = 5.0 Hz, H5′), 5.03 (1H, s, H4), 4.02 (4H, m, 2 OCH_2), 2.36 (6H, s, 2 × CH_3), 1.58 (4H, m, 2 × OCH_2CH_2), 1.25 (24H, m, 12 × CH_2), 0.88 (3H, t, *J* = 6.4 Hz, CH_3), 0.85 (3H, t, *J* = 6. 9 Hz, CH_3); ^{13}C NMR ($CDCl_3$), δ: 167.6 (C5–*C*=O, C3–*C*=O), 147.3 (C2′), 144.7, 144.6 (C4′, C1′), 145.5 (C2, C6), 138.1 (C6′), 123.8 (C5′), 103.2 (C5, C3), 64.5 (2 × OCH_2), 38.0 (C4), 31.9 (CH_2), 31.8 (CH_2), 29.5 (2 × CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.2 (2 × CH_2), 28.6 (2 × OCH_2CH_2), 26.0 (2 × CH_2), 22.7 (CH_2), 22.6 (CH_2), 19.5 (2 × CH_3), 14.4 (CH_2CH_3), 14.3 (CH_2CH_3); MS-EI *m*/*z*(%) 526 (M^+, 2), 476 (8), 448 (100), 420 (15), 336 (6), 178 (6). Anal. Calc. $C_{32}H_{50}N_2O_4$ (526.75): C, 72.96; H, 9.57; N, 5.32. Found: C, 72.82; H, 9.42; N, 5.44%.

3,5-Dioctyl 2,6-dimethyl-4-(4′-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (4o). Obtained from **1c**, **2c** and **3c** in 60% yield, mp: 84–85 °C, IR (KBr) ν 3290 (NH), 1703 (C=O), 1676 and 1645 (C=C); ^{1}H NMR (DMSO-d_6), δ: 8.99 (1H, s, NH), 8.38 (2H, d, *J* = 5.95 Hz, H3′, H5′), 7.10 (2H, d, *J* = 5.9 Hz, H2′, H6′), 4.88 (1H, s, H4), 3.94 (4H, m, 2 × OCH_2), 2.27 (6H, s, 2 × CH_3), 1.49 (4H, m, 2 × OCH_2CH_2), 1.21 (20H, m, 10 × CH_2), 0.85 (6H, t, *J* = 6.46 Hz, 2 × CH_3); ^{13}C NMR (DMSO-d_6), δ: 167.5 (C5–*C*=O, C3–*C*=O), 157.0 (C1′), 149.5 (C3′, C5′), 147.6 (C2, C6), 122.5 (C2′, C6′), 101.3 (C5, C3), 63.5 (2 × OCH_2), 38.6 (C4), 31.6 (2 × CH_2), 28.9 (4 × CH_2), 28.6 (2 × CH_2), 25.4 (2 × CH_2), 22.4 (2 × CH_2), 18.2 (2 × CH_3), 14.1 (2 × CH_2CH_3); MS-EI *m*/*z*(%) 498 (M^+, 1), 420 (100), 308 (11), 229 (6), 178 (3). Anal. Calc. $C_{30}H_{46}N_2O_4$ (498.70): C, 72.25; H, 9.30; N, 5.62. Found: C, 72.38; H, 9.45; N, 5.71%.

3-(2-Cyanoethyl) 5-methyl 2,6-dimethyl-4-(4′-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (4p). Obtained from **1g**, **2a** and **3c** in 70% yield, mp: 156–157 °C, IR (KBr) ν 3262 (NH), 2225 (CN), 1706 and 1683 (C=O), 1647 and 1600 (C=C); ^{1}H NMR (DMSO-d_6), δ: 9.11 (1H, s, NH), 8.40 (2H, d, *J* = 5.9 Hz, H3′, H5′), 7.14 (2H, d, *J* = 5.95 Hz, H2′, H6′), 4.88 (1H, s, H4), 4.16 (2H, t, *J* = 5.95 Hz, OCH_2), 3.55 (3H, s, OCH_3), 2.84 (2H, m, CH_2CN), 2.29 (3H, s, CH_3), 2.28 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6), δ: 167.4 (C5–*C*=O), 166.5 (C3–*C*=O), 155.8 (C1′), 149.8 (C3′, C5′), 147.1, 146.9 (C2, C6), 122.7 (C2′, C6′), 119.9 (CN), 100.9 (C3), 100.5 (C5), 58.9 (OCH_2), 51.2 (OCH_3), 38.6 (C4), 18.55 (CH_3), 18.52 (CH_3), 17.7 (CH_2–CN); MS-EI *m*/*z*(%) 341 (M^+, 2), 263 (100), 224 (52), 210 (33), 192 (10). Anal. Calc. $C_{18}H_{19}N_3O_4$ (341.36): C, 63.33; H, 5.61; N, 1231. Found: C, 63.44; H, 5.48; N, 12.43%.

5-Methyl 3-octyl 2,6-dimethyl-4-(4′-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4q). Obtained from **1c**, **2a** and **3d** in 70% yield, mp: 127–128 °C, IR (KBr) ν 3246 (NH), 1701 (C=O), 1654 and 1602 (C=C), 1560 and1344 (NO_2); ^{1}H NMR (DMSO-d_6), δ: 9.03 (1H, s, NH), 8.10 (2H, d, *J* = 8.7 Hz, H3′, H5′), 7.40 (2H, d, *J* = 8.7 Hz, H2′, H6′), 4.97 (1H, s, H4), 3.99 (1H, m, OCH_2), 3.87 (1H, m, OCH_2), 3.54 (3H, s, OCH_3), 2.29 (3H, s, CH_3–C2), 2.25 (3H, s, CH_3–C6), 1.44 (2H, m, OCH_2CH_2), 1.08 (10H, br. s, 5 × CH_2), 0.83 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (DMSO-d_6), δ: 167.0 (C5–*C*=O), 166.5 (C3–*C*=O), 155.7 (C4′), 146.6, 146.4 (C2, C6), 145.7 (C1′), 128.7 (C2′, C6′), 123.7 (C3′, C5′), 100.7, 100.6 (C3, C5), 63.6 (OCH_2), 51.2 (OCH_3), 39.6 (C4), 31.5 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 28.2 (OCH_2CH_2), 25.5 (CH_2), 22.1 (CH_2), 18.3 (CH_3–C6), 18.2 (CH_3–C2), 13.9 (CH_2CH_3); MS-EI *m*/*z*(%) 444 (M^+, 3), 331 (10), 322 (100), 287 (8), 210 (36), 178 (6). Anal. Calc. $C_{24}H_{32}N_2O_6$ (444.52): C, 64.85; H, 7.26; N, 6.30. Found: C, 64.70; H, 7.15; N, 6.37%.

3-(2-Cyanoethyl) 5-methyl 2,6-dimethyl-4-(4′-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4r). Obtained from **1g**, **2a** and **3d** in 72% yield, mp: 150–152 °C, IR (KBr) 3248 (NH), 2225 (CN), 1699, 1681 (C=O), 1651, 1602 (C=C), 1510, 1344

(NO_2); ^{1}H NMR (DMSO-d_6), δ: 9.19 (1H, s, NH), 8.09 (2H, d, $J = 8.7$ Hz, H3′, H5′), 7.44 (2H, d, $J = 8.7$ Hz, H2′, H6′), 4.98 (1H, s, H4), 4.14 (2H, t, $J = 5.3$ Hz, OCH_2), 3.53 (3H, s, OCH_3), 2.83 (2H, m, CH_2CN), 2.29 (3H, s, CH_3–C2), 2.28 (3H, s, CH_3–C6); ^{13}C NMR (DMSO-d_6), δ: 167.0 (C5–*C*=O), 166.2 (C3–*C*=O), 155.2 (C4′), 147.7 (C1′), 146.5, 146.0 (C2, C6), 128.8 (C2′, C6′), 123.8 (C3′, C5′), 119.9 (CN), 100.1 (C3, C5), 58.9 (OCH_2), 51.2 (OCH_3), 39.8 (C4), 18.8 (CH_3–C2), 18.6 (CH_3–C6), 17.7 (*C*H_2–CN); MS-EI m/z(%) 385 (M^+, 3), 263 (100), 210 (27), 178 (6). Anal. Calc. $C_{19}H_{19}N_3O_6$ (385.37): C, 59.22; H, 4.92; N, 10.90. Found: C, 59.33; H, 4.81; N, 10.83%.

Crystal structure determination of 4n

Crystal data. $C_{32}H_{50}N_2O_4$, $M = 526.74$, monoclinic, $a = 22.8754(7)$, $b = 16.1015(12)$, $c = 8.7774(16)$ Å, $\beta = 90.021(7)°$, $V = 3233.0(6)$ Å^3, $T = 293(2)$ K, space group $P2_1/c$ (no. 14), $Z = 4$, μ(Cu-Kα) = 0.542 mm^{-1}, 7434 reflections measured, 5718 unique ($R_{\text{int}} = 0.0529$) which were used in all calculations. The final $R(F^2)$ and w$R(F^2)$ values were 0.0856 and 0.2182 (observed data), respectively. The high R-values of the refinement are due to the disorder of the long alkyl side chains in the crystal structure.‡

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