Structural Study of Highly Halogenated Dihydropyridine Derivatives as Potential Calcium Channel Modulators

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Two dihydropyridines endowed with fluorine atoms (**3**) and fluorine and chlorine atoms (**4**) have been synthesized and structurally characterized by experimental X-ray analyses and theoretical calculations at the semiempirical (AM1) and *ab initio* (HF/6-31G*) levels. The results show that these compounds meet the required criteria to act as potential calcium channel modulators.

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Introduction.

Throughout recent years, the synthesis and structural characterization of novel analogues of 1,4-dihydropyridines (DHPs) calcium channel modulators has received particular attention due to the pharmacological properties they display for the treatment of cardiovascular diseases [1-7]. In this regard, crystallographic studies have played a very important role for determining receptor-ligand interactions in nifedipine and other related 1,4-DHPs [8,9].

We have reported a structural study of furo[3,4-*b*]-2(1*H*)pyridones [10] and 2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinolines [11] as potential calcium channel modulators, provided that 1,4-DHPs fused to a second heterocyclic ring have been less studied in comparison with the overwhelming number of studies carried out on differently substituted monocyclic 1,4-DHPs [12-16].

It is well-established that the fundamental requirement for the pharmacological activity of the members of this family is the presence in the 1,4-DHP ring of an aromatic substituent at position 4, alkyl groups (preferably methyl) attached at the 2 and 6 positions, ester groups on C3 and C5 atoms and an H atom on N1 [17]. Also, the absolute configuration at C-4 (*R- versus S*-enantiomer) of 1,4-DHPs is a critical factor for biological activity as antagonist or agonist of calcium ion [18]. Thus, in order to evaluate the potential interest of novel molecules as calcium channel modulators, it is important to determine the geometrical parameters in the solid state.

Recently, we have developed the experimental and theoretical structural study of 2-pyridyl- and 4-hydroxyphenyl-1,4-dihydropyridine derivatives [19] by X-ray analysis and semiempirical (AM1) calculations and both methods show a boat conformation for the 1,4-dihydropyridine ring with a pseudoaxial orientation of the aryl group in position 4. The conformational features reported for 1,4-DHP calcium modulators are preserved for these compounds. Despite the widely developed chemistry of the 1,4-DHPs, [12,20] much less is known about the structure of 1,4-DHPs bearing substituent other than hydrogen atoms or alkyl groups in C2 and C6 [21].

Recently the synthesis and pharmacological properties of novel vasorelaxant fluorinated 4-aryl-1,4-dihydropyridines was reported [22].

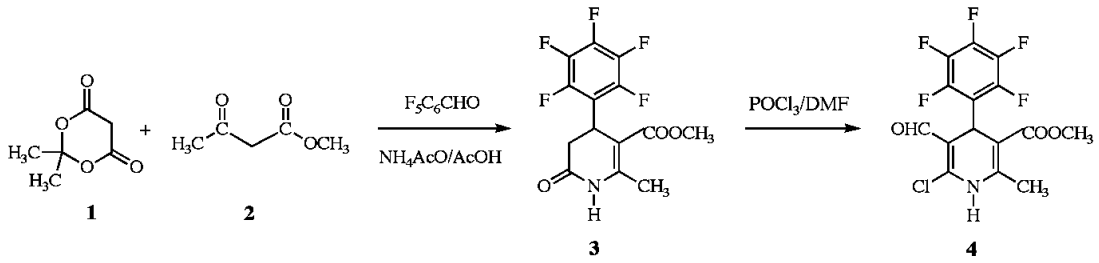
In order to extend our study to highly halogenated dihydropyridine derivatives, in this paper we report a structural study of two dihydropyridine derivatives: 5-methoxycarbonyl-6-methyl-4-(pentafluorophenyl)-3,4-dihydro-2(1*H*)pyridone (**3**) and methyl 6-chloro-4-(pentafluorophenyl)-5-formyl-2-methyl-1,4-dihydropyridine-3-carboxylate (**4**) bearing fluorine atoms, as isosteres, on the required phenyl ring at position 4 of the heterocyclic ring for biological activity. The 2-chloro-3-formyl 1,4-DHP has proved to be an excellent intermediate in the synthesis of other heterocyclic fused 1,4-DHPs like pyrazolo[3,4-*b*]-pyridines [23] and thieno[2,3-*b*]pyridines [24].

Discussion.

5-Methoxycarbonyl-6-methyl-4-(pentafluorophenyl)-3,4-dihydro-2(1*H*)pyridone (**3**) was prepared according to the procedure described by us [25], refluxing equimolecular amounts of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione), methyl acetoacetate, and pentafluorobenzaldehyde with an excess of ammonium acetate in acetic acid as solvent. After purification from ethanol, compound **3** was obtained as crystalline solid in 65 % yield. Methyl 6-chloro-4-(pentafluorophenyl)-5-formyl-2-methyl-1,4-dihydropyridine-3-carboxylate (**4**) was prepared from **3** by reaction with the Vilsmeier-Haack reagent ($POCl_3$, DMF) in good yield (70%) (See Scheme 1).

The FTIR spectrum of compound **3** shows the NH group at 3217 cm^{-1} as well as the two carbonyl groups at 1708 and 1685 cm^{-1}. The ^1H nmr spectrum shows the two protons on C3 as a part of an AMX system which was

Scheme 1



confirmed by a doublet of doublets at δ 4.58 corresponding to the proton on C4 due to the splitting by coupling with the protons on C3 ($J_{3a,4}$ = 10.2 Hz and $J_{3b,4}$ = 0.8 Hz). This last coupling suggests a *trans*-diaxial configuration between the proton on C4 and one of the protons on C3. The two methyl groups appear as singlets at δ 2.26 (CH_3-C6) and δ 3.52 (CH_3-CO).

The ^{13}C-nmr spectrum of **3** shows the signals of the carbonyl groups at δ171.0 (C=O) and 166.3 (COO) and the olefinic carbons C5 (δ = 99.1) and C6 (δ = 149.0) at unusually low and high δ values, respectively. This finding has been previously observed in other related molecules, [26] and clearly indicates a *push-pull* effect due to the electronic behavior of the substituents on both carbons.

Compound **4** shows the presence of the NH group and the two C=O groups in the FTIR spectrum at 3250, 1712 and 1640 cm^{-1} respectively. ^{1}H-nmr spectrum shows two singlets at δ 10.61 and 9.61 corresponding to NH and the formyl proton. The hydrogen atom on C4 appear as a singlet at 5.31 ppm, and the aliphatic protons appear at 3.52 (CH_3-COO) and 2.27 (CH_3-C6) ppm. The ^{13}C-nmr spectrum exhibits signals for C2 and C6 at 143.8 and 148.1 ppm and those corresponding to C3 and C5 at 108.4 and 101.1 ppm, respectively, showing the *push-pull* effect [26]. The signals of ^{1}H and ^{13}C nmr spectra for both compounds were unambiguously assigned by HMQC, HMBC, DEPT, NOE and COSY experiments.

The structural study of compounds **3** and **4** was carried out by X-ray crystallographic analysis and quantum chemical calculations at semiempirical (AM1) and *ab initio* (HF/6-31G*) levels.

We have previously confirmed that semiempirical calculations at the AM1 level reproduce adequately the geometry of 3,4-dihydropyridones [10,11] and 1,4-dihydropyridines [19]. Therefore, we have used the AM1 and HF/6-31G* methods to obtain the geometrical features of compounds **3** and **4**.

Both methods predicted that compound **3** presents two favored conformations due to the inversion of the pyridone ring, labelled **3A** when the aryl substituent at C4 lies in a pseudoaxial position, and **3B** when lies in a pseudoequatorial position. Both conformations (**3A** and **3B**) show a pyridone ring in a twisted boat conformation with the aryl group near to the orthogonal disposition to the pyridone ring pseudoplane [C5-C4-C41-C46 = -50.1 (AM1) and –60.6 (HF/6-31G*)]. Also, the stability of all possible conformers considering the *cis*/*trans* (*sp*/*ap*) disposition between the endocyclic doble bond and the C=O at C5 was calculated. AM1 calculations predicted for **3A** and **3B** conformations, *cis* (*sp*) to be more stable in 1.0 and 0.3 kcal/mol than the respective *trans* isomers (Figure 1).

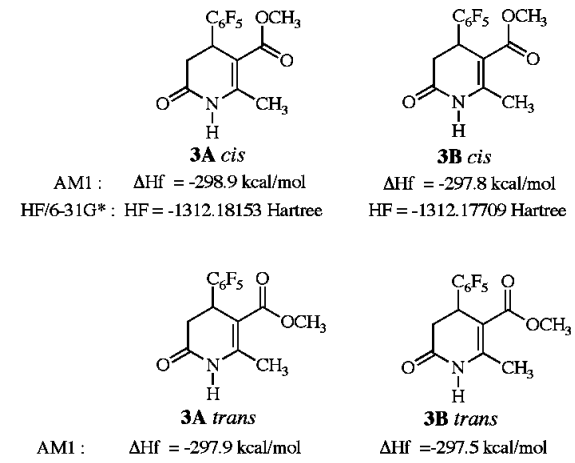
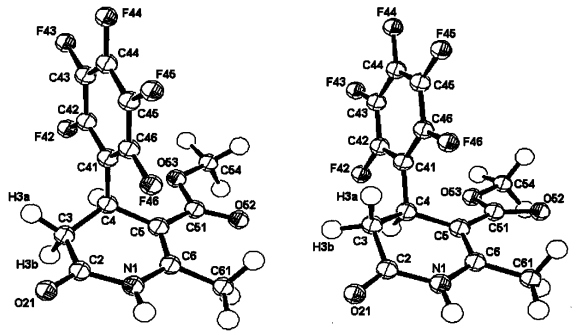


Figure 1. Stereoisomers of compound **3** showing *cis* and *trans* dispositions between the endocyclic double bond and the C=O at C5.

In this case, and in a similar way as other 2(1*H*)pyridones previously reported, [10,11] conformation **A** is 2 kcal/mol more stable than conformation **B**. Figure 2 shows both conformations predicted by AM1 and HF/6-31G* methods and the numbering scheme.

The crystal structure of compound **3** (Figure 3) shows that the pyridone ring has a screw boat conformation with puckering parameters [27] Q = 0.330(2) Å, θ = 116.4(3)° and φ = 330.7(4)° with axis through C4-C5. The dihedral angle between the least-squares planes of the substituted phenyl ring and the pyridone moiety is 89.99(10)°. The mean Csp^2-Csp^2 bond length within this ring is 1.381(1) Å. The experimental value of the dihedral angle C5-C4-C41-C46 = -44.6(3)° also shows that in the crystal the aryl group is essentially orthogonal to the pyridone ring pseudoplane. The *cis* (*sp*) disposition between the endocyclic double bond and the carbonyl group was also found in the crystal (O52-C51-C5-C6 = 2.8(3)°.



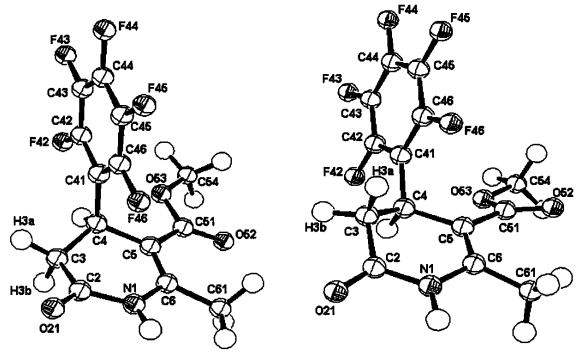


Figure 2. Most stable conformations of compound **3** calculated by AM1 and HF/6-31G* showing the atomic numbering scheme.

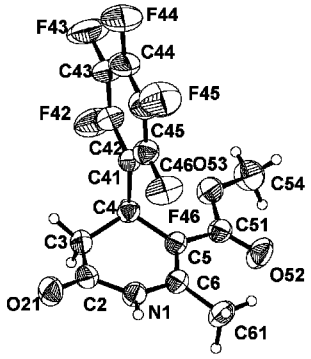


Figure 3. Crystal structure of compound **3**. Displacement ellipsoids are drawn at 50% probability level for non-H atoms.

Table 1 shows the most relevant bond distances, valence angles and dihedral angles predicted for the minimum energy conformation of **3** calculated by AM1 and HF/6-31G* and determined by X-ray analysis.

Semiempirical AM1 and *ab initio* HF/6-31G* methods showed that the 1,4-dihydropyridine ring in compound **4** adopts a flattened boat conformation, in which the carbon atoms of the olefinic double bonds are in the same boat main plane and the aryl substituent on C4 in a pseudoaxial disposition [C5-C4-C41-C46 = -62.6°

Table 1

Most Relevant Bond Distances, Valence Angles and Dihedral Angles for compound **3**. Bond distances are given in Å and angles in degrees. (Standard Deviations in parenthesis).

	AM1	HF/6-31G*	X-Ray
Bond distances			
N1-C2	1.399	1.374	1.362 (3)
C2-C3	1.502	1.506	1.488(3)
C3-C4	1.525	1.540	1.534(2)
C4-C5	1.494	1.524	1.518(3)
C5-C6	1.376	1.346	1.345(3)
C6-N1	1.387	1.380	1.397(2)
C4-C41	1.506	1.529	1.528(3)
O21-C2	1.241	1.192	1.232(2)
O52-C51	1.238	1.195	1.208(3)
O53-C51	1.374	1.328	1.336(3)
C46-F46	1.351	1.323	1.337(3)
Valence angles			
C2-N1-C6	122.6	126.0	124.8(2)
C3-C4-C5	112.9	111.1	111.3(2)
C4-C3-C2	115.4	115.3	115.6(2)
C4-C5-C6	122.1	121.3	120.4(2)
N1-C2-C3	118.3	114.5	116.5(2)
N1-C6-C5	121.1	120.7	120.6(2)
O52-C51-C5	128.9	126.3	126.9(2)
O21-C2-N1	118.8	121.2	120.8(2)
O21-C2-C3	122.9	124.1	122.6(2)
C41-C4-C3	110.9	113.0	111.2(2)
C41-C4-C5	113.2	113.1	114.4(2)
Dihedral angles			
N1-C2-C3-C4	-25.6	-33.9	-26.7(3)
C2-C3-C4-C5	31.9	38.0	37.8(2)
C3-C4-C5-C6	-21.1	-22.4	-26.3(3)
C4-C5-C6-N1	1.7	1.3	2.3(3)
C5-C6-N1-C2	6.9	4.9	12.2(3)
C6-N1-C2-C3	5.8	12.2	1.1(3)
O21-C2-N1-C6	-176.9	-172.6	177.4(2)
O52-C51-C5-C6	-8.2	0.6	2.8(3)
H3a-C3-C4-H	-89.3	-80.7	-84.7
H3b-C3-C4-H	28.5	37.5	31.6
H3a-C3-C2-O2	33.3	24.4	35.2
H3b-C3-C2-O2	-81.7	-90.0	-81.1
C6-C5-C4-C41	106.0	105.8	100.7(2)
C51-C5-C6-N1	-176.7	-178.9	-176.1(2)
C46-C41-C4-C5	-50.1	-60.6	-44.6(3)

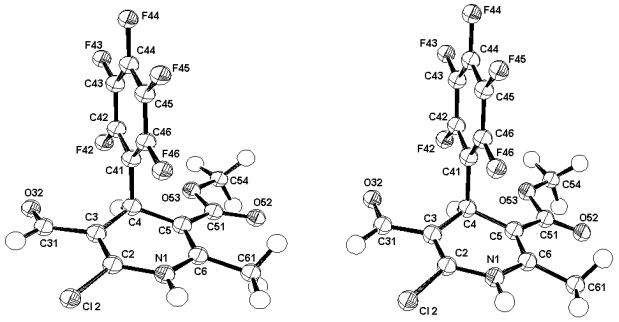


Figure 4. Most stable conformation of compound **4** calculated by AM1 and HF/6-31G* showing the atomic numbering scheme.

(AM1) and −62.8° (HF/6-31G*)].(see Figure 4 for numbering scheme).

Previously it was determined by AM1 calculations all possible disposition of the C=O group at C3 and C5 with the endocyclic double bonds, and it was found that the *trans*/*cis* (*ap*/*sp*) arrangement is the most stable one (Figure 5).

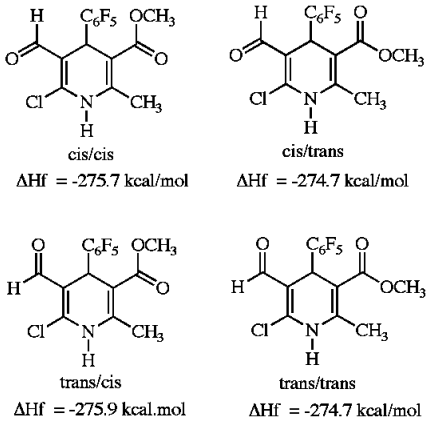


Figure 5. Stereoisomers of compound **4** showing the *cis* and *trans* dispositions between the carbonyl groups at C3 and C5 with the corresponding endocyclic double bonds.

X-ray crystallography data of compound **4**, shows that the 1,4 DHP ring can be better described as being in a boat conformation with puckering parameters [27] Q = 0.195(4) Å, θ = 110.5(12)° and φ = 354(5)° with axis through C4-C5 (See Figure 6). This ring conformation represents 14% of puckering in ideal cyclohexane chair (20% chair with N1 pointing down, 21% twist boat with axis through C5 and C4 pointing up, 59% boat with bowsprit at N1 pointing up) [28]. The dihedral angle between the least-squares planes of the substituted phenyl ring and the 1,4-DHP moiety is 86.6(2)°. The mean Csp^2-Csp^2 bond length within this ring is 1.379(3) Å. The experimental value of the dihedral angle C5-C4-C41-C46 = -67.0(5)° also shows that in the crystal the aryl group is essentially orthogonal to the pyridine ring.

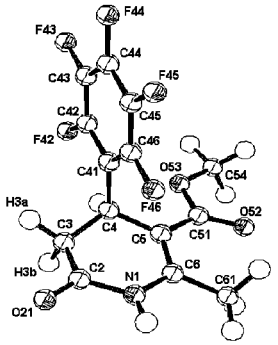


Figure 6. Crystal structure of compound **4**. Displacement ellipsoids are drawn at 50% probability level for non-H atoms.

The ester group at C5 was found to be nearly coplanar with the nearest double bond in the DHP ring (both, in AM1, *ab initio* and in the crystal structure), and having a *cis* (*sp*) orientation, as found in the majority of the more than 30 crystal structures of members of the nifedipine family [17]. It is thought that only the *sp* conformation of the ester group permits hydrogen bonding to the carbonyl O atom as acceptor atom when the drug binds to its receptor site [8,29]. Carbonyl group at C3 has a *trans* (*ap*) orientation with the endocyclic double bond.

The geometrical features predicted for the minimum energy conformation of **4** calculated by AM1, HF/6-31G*

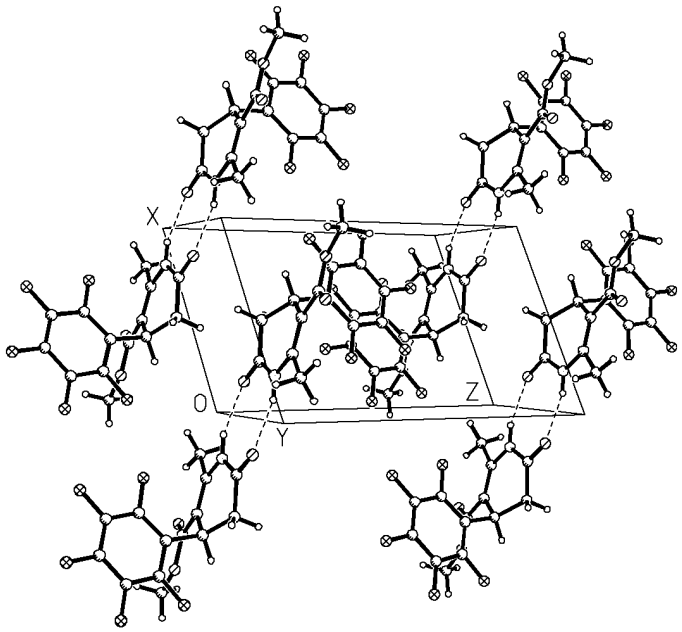
Table 2

Most Relevant Bond Distances, Valence Angles and Dihedral Angles for compound **4**. Bond distances are given in Å and angles in degrees. (Standard Deviations in parenthesis).

	AM1	HF/6-31G*	X-Ray
Bond distances			
N1-C2	1.390	1.365	1.351(6)
C2-C3	1.365	1.330	1.346(5)
C3-C4	1.502	1.521	1.511(6)
C4-C5	1.499	1.526	1.525(5)
C5-C6	1.374	1.342	1.347(6)
C6-N1	1.392	1.380	1.393(6)
C4-C41	1.510	1.531	1.522(5)
Cl 2-C2	1.717	1.733	1.723(5)
O32-C31	1.233	1.193	1.221(5)
O52-C51	1.238	1.195	1.194(6)
O53-C51	1.371	1.324	1.339(5)
C46-F46	1.352	1.324	1.340(5)
Valence angles			
C2-N1-C6	120.1	121.9	121.6(3)
C3-C4-C5	112.2	111.2	111.4(3)
C4-C3-C2	120.4	119.7	119.3(4)
C4-C5-C6	121.9	121.8	121.3(3)
N1-C2-C3	122.3	122.8	123.0(4)
N1-C6-C5	120.3	119.5	119.8(4)
Cl 2-C2-N1	115.4	112.5	113.4(3)
O32-C31-C3	123.1	122.4	124.0(4)
O52-C51-C5	128.5	126.0	127.9(4)
C41-C4-C3	110.9	111.2	111.7(3)
C41-C4-C5	111.5	112.4	112.3(3)
C2-C3-C31	122.2	123.1	122.8(4)
Dihedral angles			
N1-C2-C3-C4	-4.2	-4.3	-8.8(6)
C2-C3-C4-C5	16.1	16.7	20.2(5)
C3-C4-C5-C6	-16.5	-17.3	-19.0(5)
C4-C5-C6-N1	4.9	5.2	5.8(6)
C5-C6-N1-C2	8.8	9.5	8.2(6)
C6-N1-C2-C3	-9.2	-10.1	-6.7(6)
Cl 2-C2-N1-C6	169.4	168.5	170.9(3)
Cl 2-C2-C3-C4	177.4	177.2	173.9(3)
O32-C31-C3-C2	-163.3	-179.4	-175.3(4)
O52-C51-C5-C6	-11.3	-0.9	-3.0(7)
C2-C3-C4-C41	-109.3	-109.4	-106.2(4)
C6-C5-C4-C41	108.4	108.1	107.2(4)
C51-C5-C6-N1	-173.6	-174.9	-176.1(4)
C2-N1-C6-C61	-170.6	-169.2	-169.3(4)
C46-C41-C4-C5	-62.6	-62.8	-67.0(5)

along with the results obtained by X-ray crystallography analysis are listed in Table 2, showing the most relevant bond distances, valence angles and dihedral angles.

The flourine-substitued phenyl ring is found in a pseudoaxial position, in a near orthogonal disposition to the mean plane of the pyridone ring. The dihedral angle between the least-squares planes of boths rings is 86.6(2)° for compound **3** and 89.99(10)° for compound **4**. This pseudoaxial position of the phenyl ring at C4 is also observed in related structures [30] where the phenyl ring have other substituents rather than fluorine atoms. An intermolecular short contact of the type C-H...O between C4 and F42 (compound **3**: C4...F42 = 2.872(5) Å, and 2.798(3) Å for compound **4**), in both crystal structures, helps to keep the phenyl ring in this disposition.



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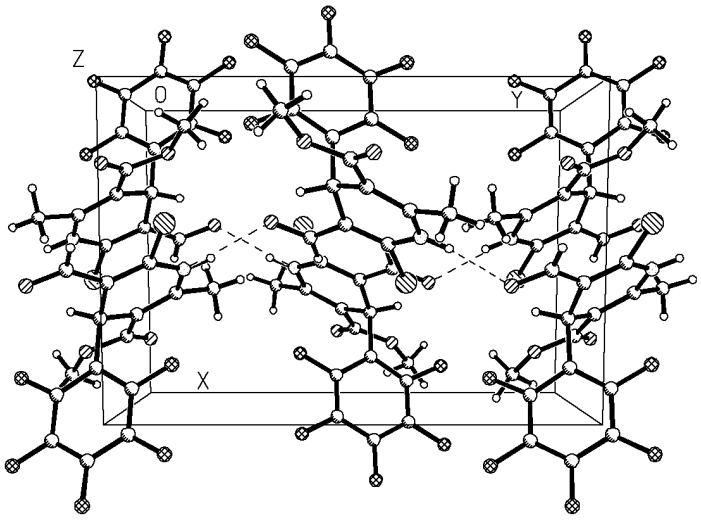

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Figure 7. Packing of the molecules in the unit cell showing the hydrogen bond scheme.

The molecules in the crystal of **3** are packed forming dimers by means of a strong hydrogen bond of the type N…O: N1…O21 = 2.907(2) Å, N1-H1…O21 = 162° (see Figure 5) also weak interactions of the type C…O, and C…F, are present. In compound **4**, the crystal structure is also stabilized by means of weak interactions of the type C…O, C…Cl and C…F, and a strong hydrogen bond of the type N…O held the molecules together forming a two-member alternated infinite chain along [010] and [0-10]: N1…O32 = 2.919(4) Å, N1-H1…O32 = 171° (Figure 7).

In summary we have synthesized and structurally characterized two new highly fluorinated dihydropyridine derivatives by following Hantzsch-like and Vilsmeier-Haack synthetic protocols. In addition to the fluorine atoms contained in these structures, the presence of a chlorine atom at C-2, in compound **4** has been less studied in this important group of calcium antagonist systems.

In the crystal structure of both compounds (**3** and **4**) the heterocyclic ring has a boat conformation with a pseudo twofold axis intercepting the C4-C5 bond, a common feature of 3,4-DHP and previously reported structures [30]. The *trans* (*ap*) disposition between the endocyclic double bond and the C=O at C3 in compound **4** is probably induced by packing interactions due to the fact that it is involved in an intramolecular hydrogen bond, as found in related structures [31]. The ester group at C5 is coplanar with the nearest double bond in the DHP ring (both, in theoretical calculations and in the crystal structure), and having a *sp* orientation as found in the majority of crystal structures of members of the nifedipine family [17].

EXPERIMENTAL

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 against tetramethylsilane as the internal standard and *J* values are given in Hz. The mass spectra were recorded at 70 eV on a HP 5989 A quadrupole instrument with a source temperature of 250 °C. The ir spectra were measured with a Shimadzu FTIR 8300 instrument as potassium bromide pellets. Microanalyses were performed in a Perkin Elmer 2400 CHN by *Servicio de Microanálisis, Universidad Complutense de Madrid*. The reactions were monitored by tlc and performed on silica-gel plates (Merck $60F_{250}$) using hexane: ethyl acetate (8:2) as the eluent. Commercially available starting materials and reagents were purchased from commercial sources (BDH and Fluka) and were used without further purification.

Synthesis of 5-Methoxycarbonyl-6-methyl-4-(pentafluorophenyl)-3,4-dihydro-2(1*H*)pyridone (**3**).

A mixture of pentafluorobenzaldehyde (40 mmoles), Meldrum's acid (40 mmoles), methyl acetoacetate (40 mmoles) and ammonium acetate (42 mmoles) in 40 mL of acetic acid was refluxed for 10 hours and then poured into ice-water. The solid that precipitated was collected by filtration. Further purification was accomplished by recrystallization from ethanol. 65 % yield. mp 193-195 °C; ir (potassium bromide): 3217 (NH), 1708 (CO), 1685 (C=O), 1612 (C=C) cm^{-1}; ^1H nmr (DMSO-d6): δ 10.15 (s, 1H, NH, deuterium oxide exchangeable), 4.58 (dd, 1H, H4, *J* = 10.2 and *J* = 0.8 Hz, X part of AMX system), 3.52 (s, 3H, OCH_3), 3.12 (dd, 1H, H3a, *J* = 10.2 and *J* = 18.2 Hz, A part of AMX system), 2.44 (dd, 1H, H3a, *J* = 18.2 and *J* = 0.8 Hz, B part of AMX system), 2.26 (s, 3H, CH_3); ^{13}C nmr (DMSO-d6): δ 168.4 (C-2), 166.3 (COO), 149.0 (C-6), 146.9 (C-2', C-6'), 142.1 (C-4'), 139.7 (C-1'), 135.3 (C-3', C-5'), 99.1 (C-5), 50.7 (OCH_3), 34.2 (C-3), 27.9 (C-4), 18.2 (CH_3); ms: m/z 335 (M^+, 100), 303 (15), 276 (95).

Anal. Calcd. $C_{14}H_{10}F_5NO_3$ (335.60): C, 50.16; H, 3.01; N, 4.18. Found C, 50.38; H, 3.27; N, 4.33.

Synthesis of Methyl 6-Chloro-4-(pentafluorophenyl)-5-formyl-2-methyl-1,4-dihydropyridine-3-carboxylate (**4**).

A solution of anhydrous *N,N*-dimethylformamide (40 mmoles, 3.1 mL) in dry chloroform (10 mL) was added dropwise to a stirred solution of phosphorus oxychloride (40 mmoles, 3.85 mL) under a nitrogen atmosphere at room temperature. After 30 minutes a solution of 5-methoxycarbonyl-6-methyl-4-(pentafluorophenyl)-3,4-dihydro-2(1*H*)pyridone (**3**) (10 mmoles) in 40 mL of dry chloroform was added. After 18 hours stirring at room temperature, a solution of sodium acetate (40 g) in water (60 mL) was slowly added. After 0.5 hours, the mixture was partitioned between water and chloroform, and the aqueous phase was extracted with ethyl acetate. The organic phases were mixed and dried with anhydrous magnesium sulfate. The organic solvent was removed *in vacuum* and the solid recrystallized from ethanol; 70 % yield; mp 243-245 °C; ir (potassium bromide): 3217 (NH), 2875 (HCO), 1712 (C=O), 1652 (C=O), 1612 (C=C) cm^{-1}; ^1H nmr (DMSO-d6): δ 10.61 (s, 1H, NH, deuterium oxide exchangeable), 9.61 (s, 1H, HCO), 5.31 (s, 1H, CH), 3.53 (s, 3H, OCH_3), 2.27 (s, 3H, CH_3); ^{13}C nmr (DMSO-d6): δ 187.3 (HC=O), 166.7 (C=O), 148.1 (C-2', C-6'), 147.1 (C-6), 143.8 (C-2), 135.3 (C-4'), 131.3 (C-3', C-5'), 110.1 (C-1'), 108.4 (C-3), 101.1 (C-5), 52.0 (OCH_3), 30.8 (C-4), 18.6 (CH_3); ms: m/z 381/383 (M^+, 53/18), 364/366 (25/9), 214/216 (100/34), 182/186 (92/32).

Anal. Calcd. (381.68): C, 47.20; H, 2.38; N, 3.67. Found C, 47.48; H, 2.49; N, 3.80.

X-ray Structure Analysis.

Crystal Data for Compound **3**.

Crystals of **3** were grown by slow evaporation from methanol. Formula: $C_{14}H_{10}NO_3F_5$, *M* = 335.23, Triclinic, *a* = 7.8153(6), *b* = 8.0090(7), *c* = 12.3431(7) Å, α = 98.287(5), β = 95.735(5), γ = 113.972(6)°, *V* = 687.76(9) $Å^3$ (by least-squares refinement on diffractometer angles for 42 automatically centered reflections with 11.57 < θ < 27.93°, λ = 1.54178 Å, *T* = 293(2) K), space group $P\bar{1}$, *Z* = 2, D_c = 1.6188(2) g cm^{-3}, μ = 1.410 mm^{-1}. A prism-like colorless crystal (0.58 x 0.26 x 0.12 mm) was used for the analysis.

Data collection and Processing for Compound **3**.

A Siemens P4 four-circle diffractometer with graphite monochromated and Cu-Kα radiation was used for data collection. The intensity data were collected using ω - *2*θ scans, with ω scan width equal to the low range plus the high range plus the separation between the $K\alpha_1$ and $K\alpha_2$ positions; 3016 reflections measured (3.71 < θ < 69.00°, -9 < *h* < 1, -9 < *k* < 9, -14 < *l* < 14), 2155 observed for $F^2 \geq 2\sigma(F)^2$ and 2471 unique reflections (merging *R* = 0.042) which were retained in all calculations. Empirical absorption correction, via ψ scan was applied [32]. Three standard reflections were monitored every 100 reflections (intensity decay: none).

Crystal Data for Compound **4**.

Crystals of **4** were grown by slow evaporation from methanol. Formula: $C_{15}H_9NO_3F_5Cl$, *M* = 361.68, Monoclinic, *a* = 9.4705(5), *b* = 13.6594(6), *c* = 11.7530(7) Å, β = 99.174(5)°, *V* = 1500.9(1)$Å^3$ (by least-squares refinement on diffractometer angles for 47 automatically centered reflections with 6.48 < θ < 42.62°, λ = 1.54178 Å, *T* = 293(2) K), space group $P2_1/c$, *Z* = 4, D_c = 1.6891(2) g cm^{-3}, μ = 2.977 mm^{-1}. A prism-like colorless crystal (0.24 x 0.14 x 0.06 mm) was used for the analysis.

Data Collection and Processing for Compound **4**.

A Siemens P4 four-circle diffractometer with graphite monochromated and Cu-Kα radiation was used for data collection. The intensity data were collected using ω - *2*θ scans, with ω scan width equal to the low range plus the high range plus the separation between the $K\alpha_1$ and $K\alpha_2$ positions; 2797 reflections measured (3.71 < θ < 69.18°, -1 < *h* < 11, -1 < *k* < 16, -14 < *l* < 14), 1395 for $F^2 \geq 2\sigma(F)^2$ and 2028 unique reflections (merging *R* = 0.034) which were retained in all calculations. Empirical absorption correction, *via* ψ scan was applied [32]. Three standard reflections were monitored every 100 reflections (intensity decay: 2%).

Structure Solution and Refinement of Compound **3** and **4**.

The structures were solved by direct methods and Fourier synthesis. Non-H atoms were refined anisotropically by full-matrix least-squares techniques. H atoms were calculated geometrically and included in the refinement, but were restrained to ride on their parent atoms. The isotropic displacement parameters of the H atoms were fixed to 1.3 times U*eq* of their parent atoms. Data collection: XSCANS [33]. Cell refinement: XSCANS [33]. Data reduction: XSCANS [33]. Program(s) used to solve structure: Sir92 [34].Program(s) used to refine structure: SHELXL97 [35]. Molecular graphics: DIAMOND [36]. Software used to prepare material for publication: PLATON [37]

Crystallographic data (excluding structure factors) for the structures in these papers have been deposited with the Cambridge Crystallographic Data Center as supplementary publication nos. CCDC 189623 and CCDC 189624. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK, (fax: + 44- (0) 1223-336033 or e-mail deposit@ccdc.cam.ac.uk).

Full geometry optimization was carried out using semiempirical AM1 [38] calculations with the aid of MOPAC 6.0 program [39]. Previously, the molecular geometry was optimized using Allinger's Molecular Mechanics [40] with PCMODEL Program [41]. The fully optimized *ab initio* geometries were obtained at the Hartree-Fock level using the 6-31G* basis set. *Ab initio* calculations were performed using the Gaussian 98 program [42] on an IBM RS/6000 workstation.

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