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Conformational Analysis of 4-Aryl-Dihydropyrimidine Calcium Channel Modulators. A Comparison of Ab Initio, Semiempirical and X-Ray Crystallographic Studies.[1]

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Abstract: The conformational features of 4-aryl-dihydropyrimidine calcium channel modulators were investigated by computational and X-ray crystallographic studies. The geometries of dihydropyrimidines **8-11** were fully optimized using ab initio (HF/3-21G) and semiempirical (AM1, AM1/MM, PM3, PM3/MM) methods, and rotational barriers for important functional groups determined. All computational treatments predict the lowest energy conformation to be identical with the recently proposed receptor-bound geometry. © 1997 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

4-Aryl-1,4-dihydropyridines (DHPs, *e.g* **1-4**) are the most studied class of organic calcium channel modulators and, since their introduction into clinical medicine in 1975, have become almost indispensable for the treatment of cardiovascular diseases such as hypertension, cardiac arrhythmias, or angina.[2] More than 20 years after the introduction of nifedipine (**1**), many DHP analogs have now been synthesized and numerous second-generation commercial products have appeared on the market (*e.g.* **2-4**).[3] In recent years interest has also focused on aza-analogs such as dihydropyrimidines of type **5** (DHPMs) which show a very similar pharmacological profile to classical dihydropyridine calcium channel modulators.[4-10] Over the past few years several lead-compounds were developed (*e.g.* **6**, SQ 32926, and **7**, SQ 32547)[7-9] that are superior in potency and duration of antihypertensive activity to classical DHP drugs, and compare favorable with second-generation analogs such as amlodipine and nicardipine.[7,8] These inherently asymmetric dihydropyrimidine (DHPM) derivatives are not only very potent calcium channel modulators, but also have been studied extensively to expand the exisiting structure-activity relationships and to get further insight into molecular interactions at the receptor level.[4-10]

Despite many studies on the structure-function relationships of DHP and DHPM derivatives there still remains debate on the exact stereochemical/conformational requirements for activity.[11] In 1995 a detailed structure-activity profile for a series of DHPM calcium channel modulators was reported leading to a new general binding-site model.[10] It was proposed that calcium channel modulation (antagonist *vs.* agonist activity) is dependent on the absolute configuration at C-4, whereby the orientation of the 4-aryl group (R- versus S-enantiomer) acts as a "molecular switch" between antagonist and agonist activity (Figure 1).[10] Furthermore, in the receptor-bound conformation the substituted aryl ring should be positioned axially,

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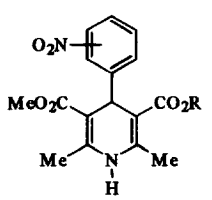
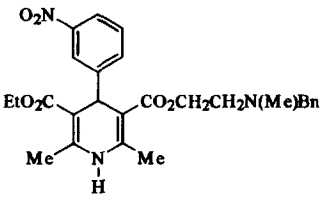
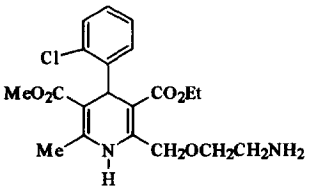


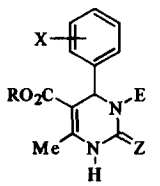
1, nifedipine: R = Me, 2-NO_2
2, nitrendipine: R = Et, 3-NO_2



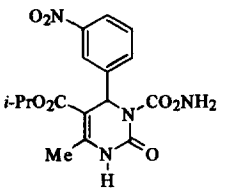
3, nicardipine



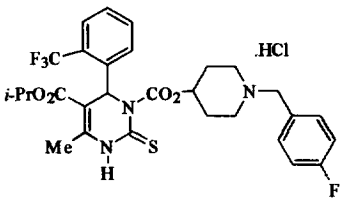
4, amlodipine



5, R = alkyl, Z = S, O, N,
X = e.g 2/3-NO_2, 2-CF_3, 2-Cl,
E = ester, acyl, amide



6, SQ 32926



7, SQ 32547

perpendicular to, and bisecting the boat-like dihydropyridine/pyrimidine ring, with the 4-aryl substitutent (X) prefering the synperiplanar (relative to C4-H) orientation.[10] A cis-carbonyl ester orientation (with respect to the C5-C6 dihydropyrimidine double-bond) was also found mandatory for optimum calcium channel modulatory activity (Figure 1).[10]

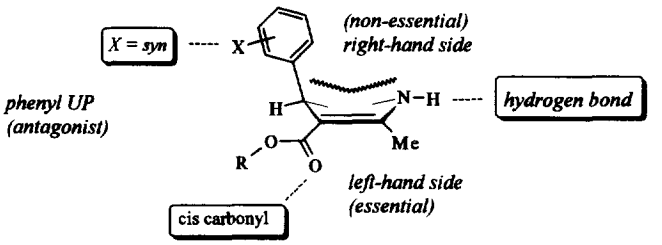


Figure 1. Proposed receptor-bound dihydropyridine/pyrimidine conformation (antagonist)[10]

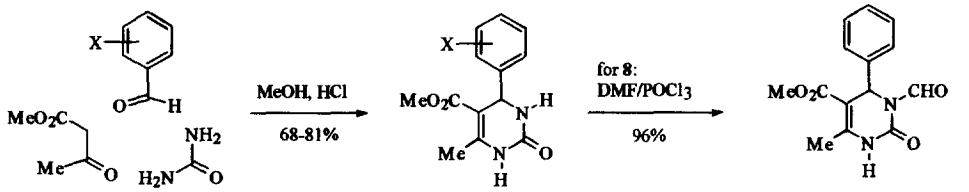
In order to develop quantitative structure-activity models or to perform molecular docking simulations on the drug-receptor interaction, it is essential to have reliable computational methods at hand to study the geometry and conformational hypersurface of molecules with interesting biological properties. In the DHP series the effects of conformational changes on the calcium channel modulatory activity are well documented by many pharmacological studies,[11] and numerous computational and experimental studies investigating the conformational hypersurface of these systems (*i.e.* **1-4**) have been reported.[11-18]

Here we report the first computational study on the geometries of dihydropyrimidines (DHPMs) **5**.[19] The results of ab initio (HF/3-21G) and semiempirical molecular orbital calculations (AM1, PM3) are compared with geometries obtained by X-ray crystallographic studies. The rotational barriers for the receptor sensitive groups on the left hand side of these systems (*i.e.* C5-ester and C4-aryl substituents) are also determined.

RESULTS AND DISCUSSION

For the present study we have selected four representative DHPM derivatives (**8-11**) as model compounds that closely mimic the critical left-hand side and C4-aryl moiety of the biologically active analogs **5**. To be able to calculate and compare the optimized geometries of all analogs at the ab initio HF/3-21G level the isopropyl (esters) and 2`or 3`-substituents in **5** were replaced by methyl groups. These substitutions should have little effect on reproducing the desired geometries and conformational features of the central dihydropyrimidine core.

DHPMs **8-10** were prepared by classical acid-catalzed Biginelli condensation of the corresponding aromatic aldehyde, methyl acetoacetate, and urea in analogy to the known ethyl ester derivatives (see Experimental).[20] Since most (but not all)[5,10] reported DHPM calcium channel modulators possess a carbonyl functionality at the N3-position (cf. **5**) the formyl analog **11**, prepared by N-formylation of **8** with $DMF/POCl_3$,[21] was included in the present study.



8; X = H
9; X = 3-Me
10; X = 2-Me

11

DHP calcium channel modulators of the nifedipine type (**1-4**) are known to be flexible molecules, in which the aryl ring and the ester groups can rotate and the conformation of the dihydropyridine ring can change. However, distinct local minima are found for geometries where the ester groups are in coplanar arrangement with the dihydropyridine ring (*cis* or *trans*) and where the substituent on the aryl ring (i.e. X) adopts either a syn- or antiperiplanar orientation with respect to C4-H. For DHPMs **8-11** analogous types of conformers were considered.[22] The conformations of dihydropyrimidines **8-11** are classified according to the conventions shown in Figure 2. The ester at C5 is considered to be *cis* if its carbonyl groups eclipses the adjacent double bond of the dihydropyrimidine ring and *trans* if its carbonyl group is oriented anti to the adjacent double bond. The conformation of the phenyl ring is classified according to the orientation of the phenyl substituent X with the C4-H bond on the dihydropyrimidine ring. Thus, a conformation in which the phenyl substituent lies above the dihydropyrimidine ring (X at C5') is antiperiplanar (*ap*); that in which it is oriented away from the ring (X at C3', cf. also Figure 1) and eclipses the C4-H bond is synperiplanar (*sp*). The formyl (amide) group at N3 is defined as being either *cis* or *trans* in analogy to the ester group at C5.

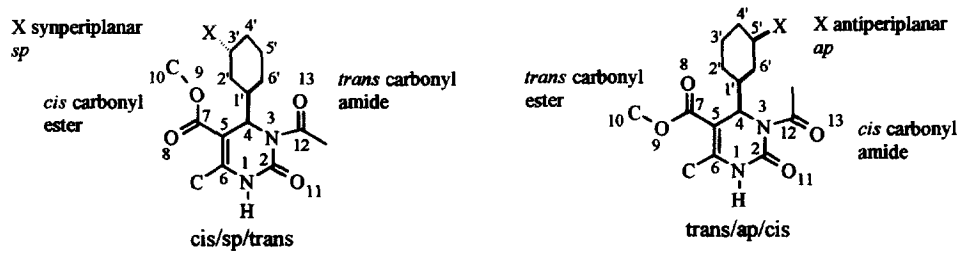


Figure 2. Numbering scheme and conformational nomenclature of dihydropyrimidines **8-11** (schematic).

In the first phase of this study structures **8-11** were fully optimized using ab initio calculations at the HF/3-21G level. Single-point energy calculations at the HF/6-31G*//HF/3-21G level were also performed. All possible conformers for each of the DHPMs (Figure 2) were considered. In order to compare these results with the performance of semiempirical methods, the 3-21G geometries were then reoptimized employing the AM1 and PM3 Hamiltonians. Due to the presence of an amide functionality in dihydropyrimidines of this type, and the well known underestimation of amide rotational barriers by AM1 and PM3, these calculations were also performed applying a force field correction method for both Hamiltonians (AM1/MM and PM3/MM). Relative energies for the individual conformers are given in Table 1.

Table 1. Relative Energies[a] [kcal/mol] for Individual Dihydropyrimidine (DHPM) Conformers.

		3-21G	6-31G*//3-21G	AM1	AM1/MM	PM3	PM3/MM
8	*cis*	0.00	0.00	0.00	0.00	0.00	0.00
	trans	1.53	1.36	0.47	0.48	0.01	0.04
9	*cis/sp*	0.00	0.00	0.00	0.00	0.00	0.00
	trans/sp	1.49	1.32	0.43	0.45	0.00	0.02
	cis/ap	-0.01	0.00	-0.05	-0.04	-0.02	-0.02
	trans/ap	1.53	1.39	0.46	0.46	0.00	0.04
10	*cis/sp*	0.00	0.00	0.00	0.00	0.00	0.00
	trans/sp	1.27	1.04	0.43	0.43	-0.06	-0.01
	cis/ap	1.93	1.45	2.33	2.21	3.61	2.99
	trans/ap	3.98	2.84	2.86	2.74	3.54	3.03
11	*cis/trans*	0.00	0.00	0.00	0.00	0.00	0.00
	trans/trans	2.90	2.28	1.09	1.09	0.04	0.09
	cis/cis	9.59	11.01	4.13	4.08	3.71	3.51
	trans/cis	10.94	11.01	4.51	4.46	3.59	3.46

[a] Total energies/heats of formation for selected conformers: **8** *cis*: -829.3315104 a.u. (3-21G), -76.68 kcal/mol (AM1), 89.09 kcal/mol (PM3); **9** *cis/sp*: -868.1523031 a.u. (3-21G), -84.25 kcal/mol (AM1), -98.46 (PM3); **10** *cis/sp*: -868.1495664 a.u. (3-21G), -82.86 kcal/mol (AM1), -97.66 kcal/mol (PM3); **11** *cis/trans*: -941.4379138 a.u. (3-21G), -102.25 kcal/mol (AM1), -121.12 kcal/mol (PM3).

Overall, the energy differences among conformers were not large; differences less than 4 kcal/mol between the highest and lowest energy conformer for each compound were typical. One notable exception was found for conformers of **11** where the N3-formyl group was placed in *cis*-orientation (**11** cis/cis and *trans/cis*), *syn* to the adjacent urea carbonyl functionality.[23] The lowest energy conformation was generally one in which the ester group was oriented *cis*, the aryl group *sp*, and the aldehyde (amide) functionality *trans*. Energy differences between aryl conformers (*sp* vs *ap*) were only notable for *ortho* substitution (*e.g.* in **10**) with the *ap* conformations being ca. 1.5-3.6 kcal/mol higher in energy. In the case of *meta* substitution (*e.g.* in **9**) both rotamers had virtually identical energies. The energy differences between *cis* and *trans* ester orientations were 0.0-2.9 kcal/mol . In general, the highest differences were obtained with ab initio methods, followed by AM1 and PM3. The inability of PM3 to reflect energy differences in the ester conformations is a result of the poor geometries delivered by PM3 (in particular with respect to the coplanarity of the ester functionality with the dihydropyrimidine ring, see Table 3).

Although the energy differences between the individual conformers of these dihydropyrimidines are small it should nevertheless be pointed out that the lowest energy conformer (*cis/sp/trans*) corresponds to the proposed receptor-bound geometry shown in Figure 1. For the following discussion of individual dihydropyrimidine geometries only these, lowest energy, "bioactive" conformers were considered.

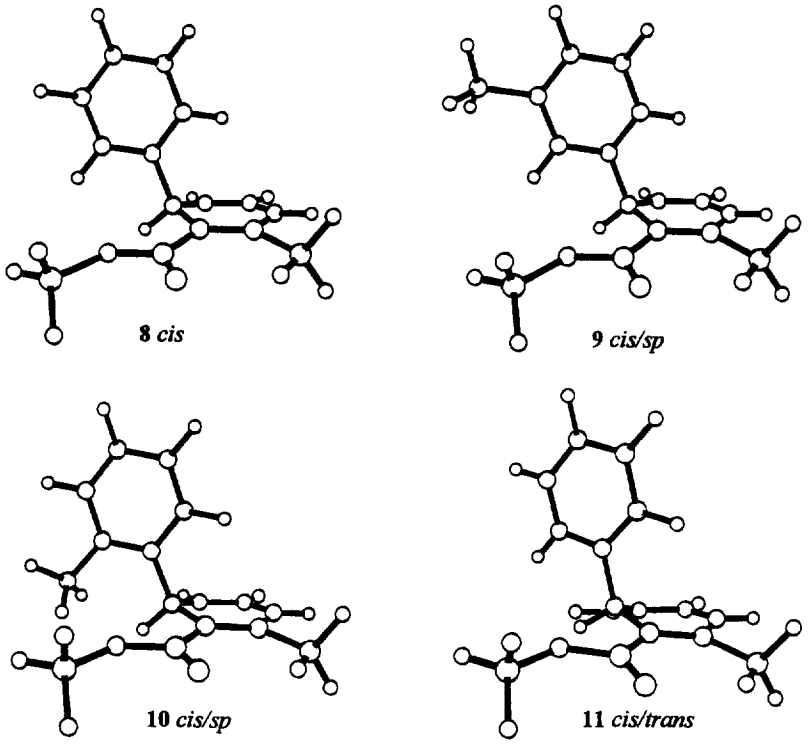


Figure 3. HF/3-21G optimized geometries for lowest energy conformers of DHPMs **8-11**.

The fully optimized 3-21G geometries for dihydropyrimidines **8-11** are shown in Figure 3. The pseudo-boat conformation for the dihydropyrimidine ring with the pseudoaxial orientation of the aryl group is evident in all four cases, although the dihydropyrimidine ring is extremely flattended around N1.[24] Due to the amide-type character of the N1-C2 bond the enforced planarity of this region of the dihydropyrimidine ring is not surprising. Any attempt to locate a minimum for an equatorial aryl arrangement failed. The conformation of the dihydropyrimidine ring was further evaluated by the following puckering descriptors (Table 2): (i) $\Sigma|\tau|$, the sum of the absolute values of the six internal dihydropyrimidine torsional angles, (ii) the distance of C4 and N1 from a least-squares plane through C2/N3/C5/C6, and (iii) ϕ, the angle between the C2/N3/C5/C6 and the N3/C1'/C5 planes. Whereas $\Sigma|\tau|$ provides a general measurement of ring pucker, the distance of the C4 and N1 atoms from the C2/N3/C5/C6 plane allows a more specific quantification of the degree of boat-type conformation of the dihydropyrimidine ring. The angle ϕ provides a probe for the orthogonal arrangement of the 4-aryl ring with the dihydropyrimidine ring, a ϕ value of ca. 145° representing a fully orthogonal arrangement. For all geometries and computational methods a strict correlation between the $\Sigma|\tau|$ value and the angle ϕ was observed, a larger sum of torsional angles correlating with a smaller ϕ value. The degree of puckering of the dihydropyrimidine ring and the deviation from an ideal pseudo-boat conformation can be derived from the data in Table 2. A comparison of the (almost identical) data for structures **8** and **9** demonstrates the close structural similarity between DHPM **8** and its 3'-methyl derivative **9**. For the 2'-methyl analog **10** however, a small but significant flattening of the dihydropyrimidine ring was observed, reflected in a smaller $\Sigma|\tau|$ value, a closer distance of C4 and N1 from the C2/N3/C5/C6 plane, and a larger ϕ value. This trend is reproduced by the 3-21G, AM1, and AM1/MM methods, but not by PM3 and PM3/MM which gave

nearly identical puckering values for all three structures. On the other hand the introduction of a carbonyl functionality at N3 as in **11** resulted in a stronger puckered dihydropyrimidine ring, reflected by larger $\Sigma|\tau|$, C4 and N1 values and a smaller ϕ value indicating a more pronounced orthogonal arrangement of the 4-aryl and dihydropyrimidine rings (see Figure 3). Again, this trend was reproduced by all computational methods except for PM3. In general, AM1 and PM3 produced the strongest puckering of the dihydropyrimidine ring for all derivatives, clearly indicated by the large $\Sigma|\tau|$ values. This is in part due to the underestimation of the amide rotational barriers for the N1-C2 and C2-N3 bonds which also lead to the strongest deviation from true boat-type conformations. As expected, the use of the AM1/MM and PM3/MM methods partly corrects this inherent problems of AM1 and PM3, producing more "flattened" geometries.

The data for crystal geometries are also included in Table 2. However, due to the limited number of available X-ray structures representing the lowest energy conformer a clear correlation with the calculated geometries is difficult. Therefore, crystal geometries are discussed separately (see below).

Table 2. Ring Puckering Analysis for the Dihydropyrimidine Ring.

	descriptor[a]	3-21G	AM1	AM1/MM	PM3	PM3/MM	crystal
8 *cis*	$\Sigma\|\tau\|$	68.1	86.0	75.8	108.8	69.7	95.7[b]
	rms	0.008	0.045	0.031	0.066	0.052	0.042[b]
	C4	0.229	0.313	0.273	0.342	0.245	0.319[b]
	N1	0.082	0.054	0.050	0.152	0.043	0.116[b]
	ϕ	164.5	157.6	160.6	156.1	162.8	157.9[b]
9 *cis/sp*	$\Sigma\|\tau\|$	69.1	86.1	76.0	108.5	69.5	91.7[b]
	rms	0.008	0.045	0.031	0.065	0.052	0.040[b]
	C4	0.233	0.314	0.274	0.341	0.245	0.314[b]
	N1	0.082	0.053	0.050	0.152	0.042	0.096[b]
	ϕ	164.2	157.5	160.5	156.1	162.8	158.5[b]
10 *cis/sp*	$\Sigma\|\tau\|$	58.9	76.1	67.3	107.2	70.2	138.2
	rms	0.015	0.044	0.031	0.064	0.053	0.024
	C4	0.201	0.277	0.242	0.335	0.247	0.454
	N1	0.063	0.046	0.043	0.148	0.042	0.206
	ϕ	166.4	160.2	162.8	156.5	162.7	148.3
11 *cis/trans*	$\Sigma\|\tau\|$	102.1	93.4	90.2	108.0	90.2	121.6[c]
	rms	0.033	0.024	0.028	0.026	0.046	0.030[c]
	C4	0.353	0.322	0.320	0.328	0.325	0.418[c]
	N1	0.109	0.108	0.082	0.244	0.091	0.145[c]
	ϕ	155.7	157.1	157.3	157.3	157.4	151.3[c]

[a] $\Sigma|\tau|$ is defined as the sum of the absolute torsional angles about the dihydropyrimidine ring [°]. The values for C4 and N1 (in Å) indicate the distance of these atoms from a least-squares plane through C2/N3/C5/C6 (the rms value provides a measure of the goodness-of-fit of the plane). ϕ is the angle between the C2/N3/C5/C6 and the N3/C1'/C5 planes and provides a probe for the orthogonal arrangement of the 4-aryl ring with the dihydropyrimidine ring, a value of ca. 145° representing a fully orthogonal arrangement.

[b] values shown are for the **8/9** *trans* ester isomers as obtained by the X-ray analyses (Figure 5); see discussion below.

[c] values for the **11** *trans/trans* isomer: $\Sigma|\tau|$ 106.1; rms 0.030; C4 0.356; N1 0.115; ϕ 155.6; see discussion below.

Another important factor influencing the pharmacological activity of DHPs and DHPMs is the geometry and orientation of the ester group (Figure 1).[10,11] In the DHP series (*i.e.* **1-4**) all X-ray structures show the ester groups coplanar with the dihydropyridine ring either in *cis* or *trans* arrangement with only minimal deviation.[11] For DHPMs **8-11** the 3-21G geometries produced a minimal deviation of the C5-ester group (2-7°) from planarity, as reflected by the torsional angle C6-C5-C7-O8 (Table 3). AM1 and AM1/MM typically

gave torsional angles around 13°, however PM3 and PM3/MM predicted values of ca. 65°. The performance of the semiempirical methods AM1 and PM3 here is in close agreement with similar calculations recently carried out in the DHP series (AM1 20°, PM3 60° deviation from planarity).[12] No significant differences between the individual DHPM derivatives could be observed.

Table 3. Conformation of Ester Group at C5.[a]

		3-21G	AM1	AM1/MM	PM3	PM3/MM	crystal
8	*cis*	7.1	12.1	12.9	66.4	62.5	-166.4[b]
9	*cis/sp*	7.2	12.3	13.1	66.1	62.3	-165.4[b]
10	*cis/sp*	6.2	15.1	15.7	65.5	62.1	12.6
11	*cis/trans*	2.2	12.7	12.8	68.6	66.1	1.3[c]

[a] The angle reported is the C6-C5-C7-O8 torsional angle [°]. The postive values indicate that the carbonyl oxygen (O8) is placed above the plane of the dihydropyrimidine ring.
[b] values shown are for the **8/9** *trans* ester isomers as obtained by the X-ray analyses (Figure 5); see discussion below.
[c] value for **11** *trans/trans*: -163.5; see discussion below.

Table 4 indicates the ability of the various computational methods to predict rotation about the C4-N1' bond in dihydropyrimidines **8-11**. In the receptor-bound geometry the aryl group is proposed[10] to bisect the dihydropyrimidine ring (N1-C4-C1'-C2' = 180°). The close similarity between the dihedral angles for **8** and **9** is again noteworthy, although there are substantial differences between the prediction of the 3-21G, AM1, and AM1/MM methods on one hand, and the PM3 and PM3/MM treatments on the other. The largest deviations from 180° are found for the N3-formyl derivative **11**. No correlation was found between the X-ray and calculated structures (see also discussion below).

Table 4. Orientation of Pseudoaxial Aryl Ring.[a]

		3-21G	AM1	AM1/MM	PM3	PM3/MM	crystal
8	*cis*	-170.5	-160.4	-161.9	147.4	154.5	165.6[b]
9	*cis/sp*	-170.8	-160.8	-162.3	147.6	154.5	171.9[b]
10	*cis/sp*	169.3	174.1	174.0	151.7	153.9	129.3
11	*cis/trans*	148.1	151.4	151.3	162.8	163.6	151.6[c]

[a] The angle reported is the N1-C4-C1'-C2' dihedral angle. The attached ring eclipses the N1-C4-C1' plane of the molecule if the torsional angle is 180°. Smaller positive values indicate that the aryl ring is rotated clockwise, smaller negative values indicate a counterclockwise rotation.
[b] values shown are for the **8/9** *trans* ester isomers as obtained by the X-ray analyses (Figure 5); see discussion below.
[c] value for **11** *trans/trans*: 170.8, see discussion below.

Profiles for rotation of both the aryl- as well as the ester group in **8-11** were calculated by the semiempirical AM1 and PM3 methods. The results (energies relative to the lowest energy conformation and positions of minima and barriers are summarized in Table 5). As a typical example the rotational profiles obtained for **10** are depicted in Figure 4. As can be seen from the data of Table 5 both semiempirical methods yield quite similar results for rotational barriers of the aryl groups with respect to both height as well as position (generally the PM3 barriers are slightly higher and shifted to larger τ - values). For compounds **8**, **9** and **11** with either unsubstituted or *meta* substituted phenyl groups the rotational barrier is $\approx$ 2-3 kcal/mol, that for the *ortho* substituted compound **10** is twice to three times this value. As already mentioned above, with PM3 for ester rotation a considerably too high twisting ($\tau \approx 60°$) is obtained. PM3 barriers are also significantly lower than those obtained by the AM1 method. Except for **10**, with AM1, barriers for ester rotation are calculated to be higher than those for phenyl rotation.

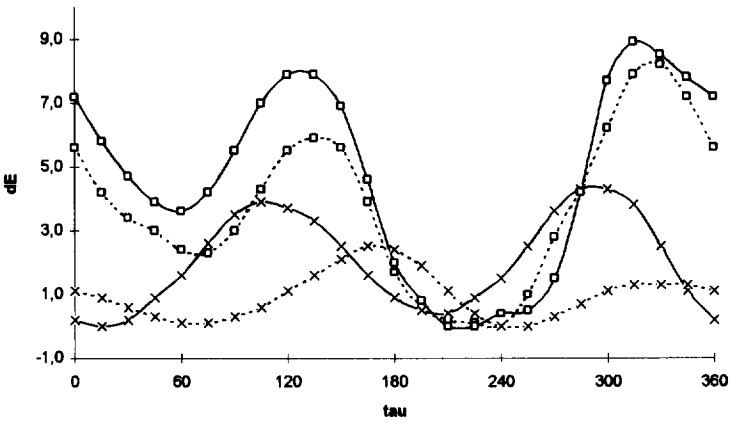


Figure 4. Rotational energies (kcal/mol) for the 4-aryl (AM1 · ·□· ·, PM3 —□—, C5/C4/C1'/C2' as torsional angle) and the ester group (AM1—X—, PM3 · ·X· ·, C6/C5/C7/O8 as torsional angle) in **10**.

Table 5. Calculated (AM1 and PM3) Energies and Approximate Positions of Minima and Barriers (ΔE) for Rotation of Aryl- and Ester Groups in **8-11**.[a]

	C4-Aryl rotation				C5-Ester rotation			
	AM1		PM3		AM1		PM3	
	ΔE	τ	ΔE	τ	ΔE	τ	ΔE	τ
8	0.0	80	0.0	30	0.0	15	0.0	70
	2.3	150	2.8	135	3.9	105	2.4	170
	0.0	260	0.0	210	0.5	195	0.1	250
	2.2	230	2.7	315	4.2	290	1.2	320
9	0.0	80	0.0	30	0.0	15	0.0	60
	2.3	150	2.6	135	3.8	105	2.4	170
	0.0	260	0.1	220	0.4	195	0.0	250
	2.2	320	2.5	315	4.1	290	1.2	0[b]
10	2.3	75	3.6	60	0.0	15	0.1	75
	5.9	135	7.9	130	3.9	105	2.5	165
	0.0	240	0.0	220	0.4	210	0.0	250
	8.2	330	8.9	315	4.3	290	1.3	330
11	0.0	30	0.0	45	0.0	15	0.0	70
	2.2	140	2.3	135	3.4	130	2.7	180
	0.0	210	0.0	225	1.1	200	0.0	225
	2.3	315	2.3	315	3.7	185	1.2	0[b]

[a] Energies are given in kcal/mol; The positions of minima and barriers refer to τ (C5/C4/C1'/C2') and τ (C6/C5/C7/O8) for aryl- and ester rotation, respectively. [b] Energy essentially constant in the range -30° to + 30°.

In the past X-ray crystallography has been utilized extensively for the conformational analysis of dihydropyridine calcium channel modulators.[11] Therefore the literature is rich with X-ray structures for this series of compounds and attempts to correlate features of the solid state structures with biological activity.[11] In sharp contrast only a limited number of X-ray data for dihydropyrimidines of type **8-12** have been

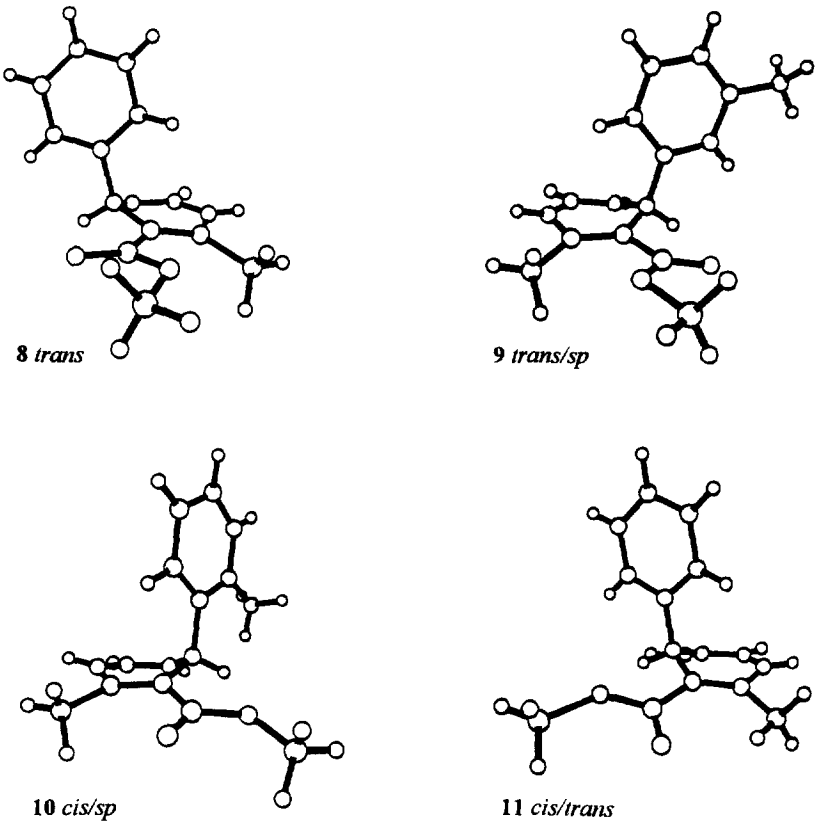


Figure 5. Solid state structures of dihydropyrimidines **8-11**. For **11** only the *cis/trans* isomer is shown (see discussion below). Note that **9** and **10** are displayed in the enantiomeric form.

published.[1,10] For comparision purposes we therefore determined the solid state structures of **8-12** by single crystal X-ray analysis (Figure 5).

The solid state structures show some interesting deviations from the predictions of the theoretical models: (i) all X-ray structures show a more pronounced boat-type conformation of the dihydropyrimidine ring than predicted by theory. In particular the N1 atom is placed further above the plane of the dihydropyrimidine ring (C2/N3/C5/C6) than predicted by the 3-21G, AM1, and AM1/MM geometries (PM3 and PM3/MM have proven to be unreliable (see above) and were therefore not included in these comparisons). (ii) The orthogonal arrangement of the 4-aryl ring with the dihydropyrimidine ring is more pronounced in the solid state structures, reflected by lower ϕ values than those found for calculated geometries (see Table 2). (iii) Despite the slight preference for a *cis* ester orientation predicted by all computational methods (Table 1) the X-ray structures of **8** and **9** show the C5-ester group in *trans* orientation, coplanar with the dihydropyrimidine ring. Remarkably, the asymmetric unit of **11** containes both rotamers (*i.e.* two molecules) with *cis* and *trans* ester orientations! Despite these ambiguos results with respect to ester orientation we believe that the computational methods correctly predict a small preference for the *cis* geometry. The deviations observed in the crystal structures are likely to be an artefact of the crystal packing forces, rather than an intrinsic property of the molecule itself. This is supported by an investigation of the

crystal packing of **8** (Figure 6) which shows intermolecular H-bonding between the O8 *trans* carbonyl oxygen and the N1-H atom of the neighboring molecule (C=O · · ·H-N = 2.10 Å), apparently overriding the inherent preference for *cis* ester orientation. A comparision of the two solid state conformers found for **11** reveals substantial differences with respect to the overall dihydropyrimidine geometries between the *cis* and *trans* ester solid state structures (Tables 2-4). Due to the relatively small number of X-ray crystallographic structure determinations available for dihydropyrimidines of this type a more detailed comparision of solid state and calculated geometries is not feasable at this time.[25]

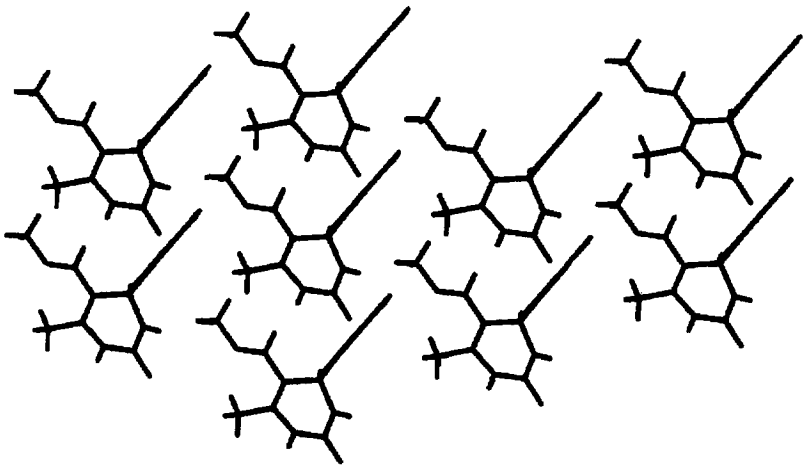


Figure 6. Crystal packing diagram of structure **8**.

SUMMARY AND CONCLUSION

In the present study geometry optimizations and conformational analyses for four 4-aryl-dihydropyrimidines, DHPMs **8-11**, were performed employing different computational methods. All computational treatments predict the lowest energy conformer to be identical with the putative bioactive conformation (Figure 1)[10] although the energy differences between the individual conformers are generally low. Whereas *meta* substitution on the 4-aryl ring had no effect on the overall geometries, *ortho* substitution led to a significant flattening of the dihydropyrimidine ring. In general, the conformational features previously reported for DHP calcium channel modulators[11-18] were also preserved for DHPMs **8-11**. The most notable difference between dihydropyridines and dihydropyrimidines, however, is the extreme flattening of the boat-type dihydropyrimidine ring around N1 as a result of the amide-type bonds present in these heterocycles.

A critical evaluation and comparison of the computational methods indicate that both PM3 and PM3/MM do not reproduce DHPM geometries adequately. On the other hand there is good qualitative agreement with the results obtained by the ab initio (HF/3-21G) , AM1, and AM1/MM methods (Tables 1-4). Since the use of ab initio calculations is impractical for geometry optimizations of large numbers of analogs, we suggest the use of the AM1 Hamiltonian, in particular the AM1/MM method for further structural and conformational investigations on these pharmacologically important systems.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus Mod. MFB-595 and are uncorrected. ^1H and ^{13}C NMR spectra were obtained on a Varian XL-200 Gemini instrument at 200 MHz and 50 MHz, respectively. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer. Micro-analyses were obtained on a Fisons Mod. EA 1108 elemental analyzer. Reactions were monitored by thin layer chromatography on 0.2 mm silica gel F-252 (Merck) plates.

Methyl 4-Aryl-6-methyl-4-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates (8-10), General Procedure: A mixture of urea (0.60 g, 10 mmol), methyl acetoacetate (1.16 g, 10 mmol), the appropriate aromatic aldehyde (10 mmol), and 10 mL of MeOH containig 2 drops of HCl conc. was heated under reflux for 4 h. The reaction mixture was cooled and the precipitated product filtered off and washed with cold MeOH. Analytical samples were obtained by recrystallization from EtOH.

Methyl 6-Methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (8); 81% yield, mp 215-217 °C; IR (KBr) 3340, 3220, 3100, 1695, and 1665 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 2.28 (s, 3H), 3.54 (s, 3H), 5.16 (d, J = 4.0 Hz, 1H), 7.20-7.40 (m, 5H), 7.78 (br s, 1H), and 9.23 (br s, 1H). Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.51; H, 5.64; N, 11.28.

Methyl 6-Methyl-4-(3-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (9); 78% yield, mp 216-218 °C; IR (KBr) 3330, 3220, 3100, 1695, and 1665 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 2.26 (s, 3H), 2.30 (s, 3H), 3.55 (s, 3H), 5.12 (d, J = 4.0 Hz, 1H), 7.02-7.29 (m, 4H), 7.72 (br s, 1H), and 9.20 (br s, 1H). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H,6.20; N, 10.76. Found: C, 64.72; H, 6.13; N, 10.56.

Methyl 6-Methyl-4-(2-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (10); 68% yield, mp 240-242 °C ; IR (KBr) 3230, 3100, 1700, and 1645 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 2.31 (s, 3H), 2.43 (s, 3H), 3.48 (s, 3H), 5.41 (d, J = 4.0 Hz, 1H), 7.11-7.22 (m, 4H), 7.62 (br s, 1H), and 9.19 (br s, 1H). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; H, 10.76. Found: C, 64.72; H, 6.13; N, 10.56.

Methyl 3-Formyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (11). To a suspension of dihydropyrimidine **8** (2.46 g, 10 mmol) in 10 mL of dry DMF, $POCl_3$ (1.54 g, 10 mmol) was added dropwise with cooling at 0 °C. The resulting solution was heated at 70 °C for 40 min, and then was poured into 100 mL of ice-water to yield 2.65 g (96%) of **11**, mp 234-237 °C (DMF/EtOH); IR (KBr) 3240, 3140, 1710, 1690, and 1650 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 2.38 (s, 3H), 3.65 (s, 3H), 6.21 (s, 1H), 7.22-7.40 (m, 4H), 9.19 (s, 1H), and 10.40 (br s, 1H). Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.13; H, 5.15; N, 10.21. Found: C, 61.13; H, 4.98; N, 10.07.

Computational Methods

Ab initio calculations were carried out using the SPARTAN (Version 4.0) package[26] on Silicon Graphics INDIGO 2 and IRIS workstations. Starting geometries were obtained using SPARTANS interactive buliding mode, and preoptimized using the SYBYL force field. Starting geometries for individual conformers were obtained by performig systematic bond rotations (180°) around the C5-C7, C4-C1', and N3-C12 single bonds. Ab initio geometry optimizations were performed using SPARTANS HF/3-21G(*) basis-set, which employs 3-21G representation for all first-row main-group elements. Convergence was achieved in all optimizations.

Semiempirical AM1[27] and PM3[28] calculations were done by the VAMP[29] and MOPAC[30] program packages. Geometries were completely optimized (keyword PRECISE) using the eigenvector following method[31] either with (*i.e.* for AM1/MM) or without molecular mechanics corrections for amide bonds (keywords MMOK and NOMM, respectively). Rotational profiles were obtained by the reaction coordinate method using 15° steps for the torsional angles C5/C4/C1'/C2' and C6/C5/C7/O8 (for numbering see Figure 2) as reaction coordinates.

Table 6. X-Ray Crystallographic Data for **8-11**.[25]

parameter	8	9	10	11
solvent	EtOH/H_2O	EtOH/H_2O	EtOH/H_2O	acetone/H_2O
empirical formula	$C_{13}H_{14}N_2O_3$	$C_{14}H_{16}N_2O_3$	$C_{14}H_{16}N_2O_3$	$C_{28}H_{28}N_4O_8$
formula weight	246.26	260.29	260.29	548.54
crystal size, mm	0.10 x 0.04 x 0.02	0.10 x 0.10 x 0.05	0.01 x 0.09 x 0.10	0.40 x 0.20 x 0.35
crystal system	monoclinic	monoclinic	orthorhombic	triclinic
space group	C2/c	$P2_1/n$	Pbca	P1
a, Å	16.129(2)	11.5330(7)	15.729(4)	8.521(3)
b, Å	7.2313(7)	7.2303(4)	7.2076(12)	11.386(3)
c, Å	22.522(2)	16.763(1)	22.567(4)	13.707(5)
α, deg	90	90	90	90.16(2)
β, deg	110.125(2)	109.163(1)	90	92.29(2)
γ, deg	90	90	90	93.03(2)
V, $Å^3$, Z	2466.4(4), 8	1320.4(1), 4	2558.4(9), 8	1326.9(7), 2
d_{calc}, g cm^{-3}	1.326	1.309	1.352	1.373
wavelength, Å	0.71073	0.71073	0.71073	0.71073
temperature, K	213(2)	213(2)	213(2)	213(2)
theta range, deg	1.93-23.04	1.89-23.41	1.80-26.07	1.49-26.48
limiting indices, h	$-16 \rightarrow 16$	$-12 \rightarrow 11$	$-19 \rightarrow 2$	$-10 \rightarrow 7$
k	$-7 \rightarrow 7$	$-3 \rightarrow 8$	$-8 \rightarrow 8$	$-13 \rightarrow 14$
l	$-21 \rightarrow 24$	$-16 \rightarrow 18$	$-24 \rightarrow 25$	$-16 \rightarrow 16$
reflections collected	4947	3898	6125	6567
independent reflections	1707	1870	2391	4858
data/restraints/parameters	1707/0/164	1870/0/173	2391/0/173	4857/0/362
refinement method	full-matrix LSQ F^2	full-matrix LSQ F^2	full-matrix LSQ F^2	full-matrix LSQ F^2
goodness-of-fit on F^2	1.381	1.091	1.085	1.100
final R indices [$I>2\sigma(I)$]	R1 = 0.0705, wR2 = 0.1430	R1 = 0.0692, wR2 = 0.1951	R1 = 0.0746, wR2 = 0.1863	R1 = 0.0541, wR2 = 0.1607
R indices (all data)	R1 = 0.0941, wR2 = 0.1523	R1 = 0.0941, wR2 = 0.2352	R1 = 0.1225, wR2 = 0.2244	R1 = 0.0666 wR2 = 0.1773
extinction coefficient	0.0031(7)	0.019(6)	0.0025(12)	0.016(3)
largest difference peak, e $Å^{-3}$	0.332	0.374	0.365	0.435
largest difference hole, e $Å^{-3}$	-0.378	-0.362	-0.322	-0.373

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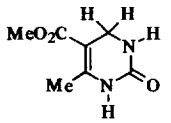
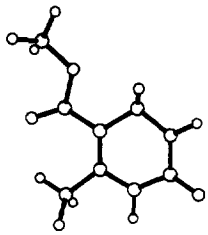
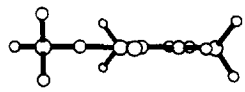
22. A conformational search within MACROMODEL (MM3* force-field, Monte Carlo method, TNCG minimization) for **10** also produced four local minima corresponding to the structures in Figure 2.
23. The large energy difference between **11** *cis/trans* and **11** *cis*/cis is not surprising given the unfavourable interactions of the adjacent *syn* carbonyl groups in **11** *cis/cis*, see also: Challis, B. C.; Challis, J. A. in *Comprehensive Organic Chemistry;* Barton, D.; Ollis, W. D. Eds.; Pergamon Press: Oxford, 1979; vol.2, p. 999.
24. We have also performed ab initio calculations on the 4-unsubstituted DHPM analog **12**. Calculations at the HF/3-21G level of theory predict the dihydropyrimidine ring to be flat ($\Sigma|\tau|$ 0.0 deg). Interestingly, by performing full geometry optimizations with larger basis sets these values increase dramatically (HF/3-21G*: $\Sigma|\tau|$ 45.36 deg; HF/6-31G*: $\Sigma|\tau|$ 78.72 deg). However, a density functional theory method (DFT, B3LYP/3-21G*) produced a $\Sigma|\tau|$ value of only 1.97 deg. In the dihydropyridine series it is well-known that the dihydropyridine ring in such unsubstitued derivatives (*i.e.* NADH analogs) is practically flat.[11] These results are under further investigation and full details will be reported at a later point in time.



12



HF/3-21G top view



HF/3-21G side view

25. Crystallographic data for compounds **8-11** have been deposited at the Cambridge Crystallographic Data Center. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. Atomic coordinates for X-ray and ab initio structures will also be made available by the authors in electronic format upon request.
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