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[A0013]

Design, Synthesis, and X-Ray Structure Analysis of Conformationally Restricted 4-Aryldihydropyrimidine Calcium Channel Modulators

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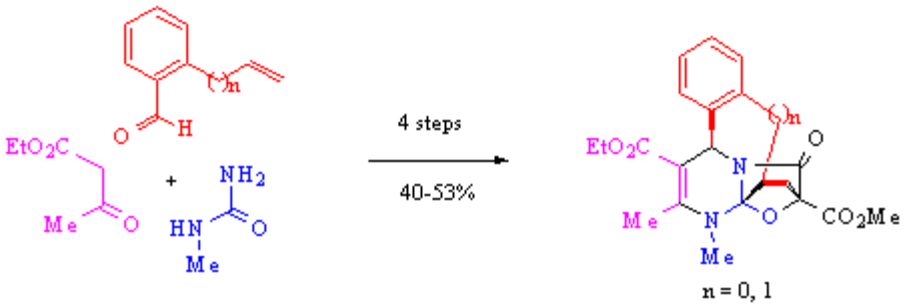
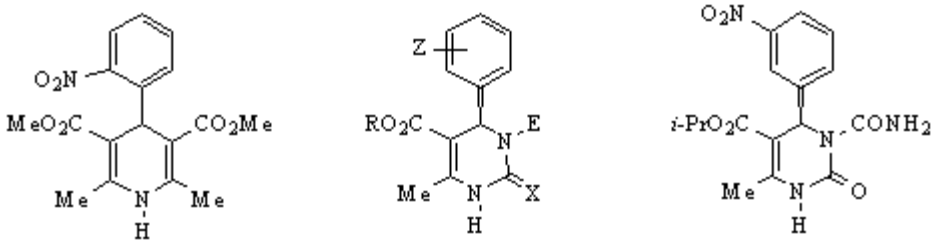
Abstract

4-Aryldihydropyrimidines (DHPMs) represent inherently chiral aza-analogs of nifedipine-type dihydropyridine (DHP) calcium channel modulators. In the context of the recently proposed new binding-site model for these types of cardiovascular drugs, conformationally rigid DHPM analogs were designed that closely mimic the receptor-bound conformation of DHP/DHPM calcium channel modulators. The synthetic methodology towards these pentacyclic DHPM analogs is based on intramolecular 1,3-dipolar cycloaddition reactions of *o*-alkenylaryl-tethered dihydropyrimidine-fused isomünchnones. Two homologs of these rigid DHPM derivatives were synthesized in good overall yield and their structure established by X-ray crystallographic analysis. Enantioseparation of these DHPMs was achieved by chiral HPLC.



Introduction

4-Aryl-1,4-dihydropyridines (DHPs, *e.g* nifedipine, **1**) 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 [1]. 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. [2] In recent years interest has also focused on aza-analogs such as dihydropyrimidines of type **2** (DHPMs) which show a very similar pharmacological profile to classical dihydropyridine calcium channel modulators [3-9]. Over the past few years several lead-compounds were developed (*e.g.* **3**, SQ 32926) [6-8] 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.[6,7] These inherently asymmetric dihydropyrimidine (DHPM) derivatives are not only very potent calcium channel modulators, but also have been studied extensively to expand the existing structure-activity relationships and to get further insight into molecular interactions at the receptor level.[3-9]



1, nifedipine

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

3

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.[10] 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.[9] 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 (aryl-group up) and agonist (aryl-group down) activity (Figure 1).[9] Furthermore, in the receptor-bound conformation the substituted aryl ring should be positioned axially, perpendicular to, and bisecting the boat-like dihydropyridine/pyrimidine ring, with the 4-aryl substitutent (X) prefering the synperiplanar (relative to C4-H) orientation.[9] 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).[9]

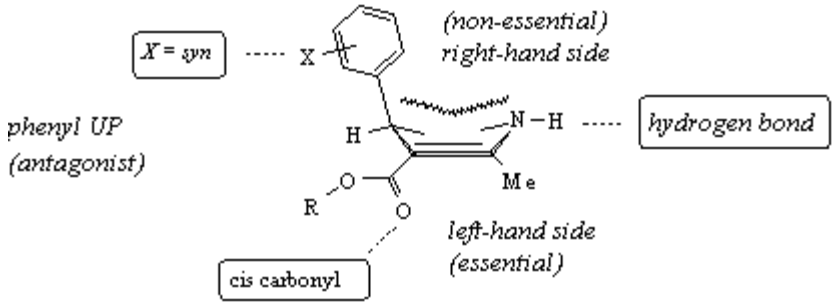
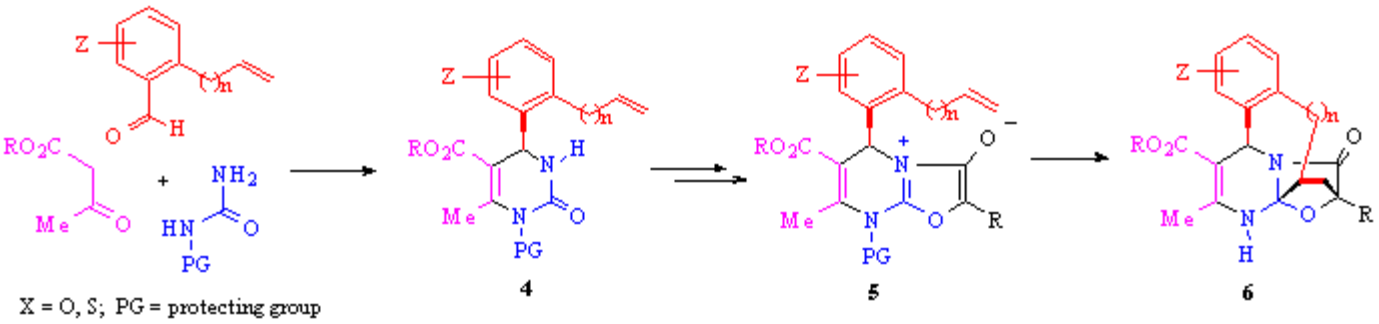


Figure 1. Proposed receptor-bound dihydropyridine/pyrimidine conformation (antagonist, for agonist activity the aryl-group should be oriented DOWN).

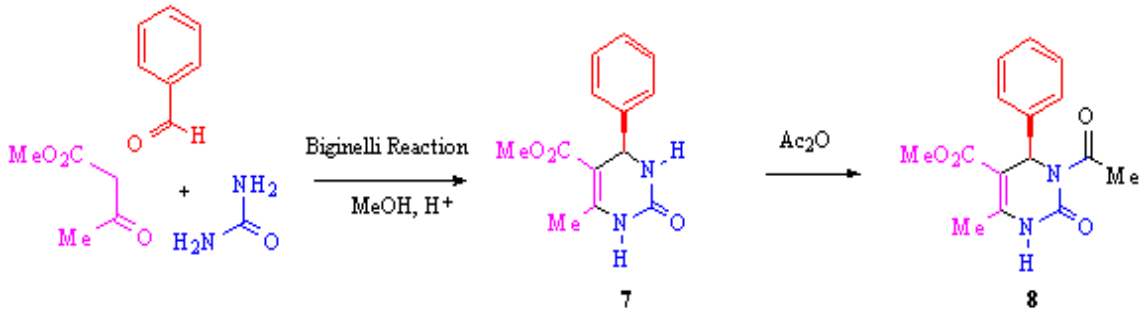
We now report synthetic methodology leading towards novel types of conformationally restricted dihydropyrimidine derivatives of type **6** that closely mimic the recently proposed receptor-bound conformation of DHP/DHPM calcium channel modulators represented in Figure 1. Molecular models of **6** indicate that these polycycles would possess a rigid framework closely resembling the receptor-bound conformation. Our strategy towards these polycyclic dihydropyrimidines involves an intramolecular 1,3-dipolar cycloaddition reaction of an *o*-alkenylaryl-tethered dihydropyrimidine-fused isomünchnone as the key step (Scheme 1). In recent years mesomeric beatines of this general type, *i.e*. isomünchnones (1,3-oxazolium-4-olates) have proven to be very useful intermediates in a variety of synthetic applications.[11] The carbonyl ylide dipoles incorporated in these mesoionics have been demonstrated to undergo both bimolecular and intramolecular cycloaddition reactions with relative ease.[11] Separation of enantiomers of the conformationally restricted DHPM derivatives **6** as described below should lead to DHPM analogs with calcium channel antagonist or agonist activity, respectively.



Scheme 1

Results and Discussion

Whereas dihydropyridines of the nifedipine type (DHPs, e.g. **1**) are generally prepared by the well-known Hantzsch synthesis,[12] the aza-analogs **2** (DHPMs) are readily available through the Biginelli dihydropyrimidine synthesis (Scheme 2) [13]. This three-component cyclocondensation reaction has been known for over 100 years and in recent years a variety of modifications [14] have been reported, including various solid-state protocols suitable for combinatorial chemistry.[15] These dihydropyrimidine derivatives are inherently asymmetric and have the advantage that the (thio)amide moiety embedded in the dihydropyrimidine ring allows a selective functionalization of the biologically less important "right-hand side" of the molecule (e.g. **8**), [16] a process that is more troublesome in the dihydropyridine series.[17]



Scheme 2

As a starting point we have carried out a detailed computational study on the conformational hypersurface of flexible 4-aryldihydropyrimidines of type **2** employing both ab initio (HF/3-21G) and semiempirical (AM1, PM3) methods [18]. The results were then compared with solid state structures obtained by X-ray crystallography. All computational treatments predict the lowest energy conformer (e.g. Figure 2) to be identical with the putative bioactive conformation (Figure 1), although the energy differences between the individual conformers are generally low [18]. In general, the conformational features previously reported for DHP calcium channel modulators were also preserved for DHPMs. The most notable difference between DHPs and DHPMs, 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 [18].

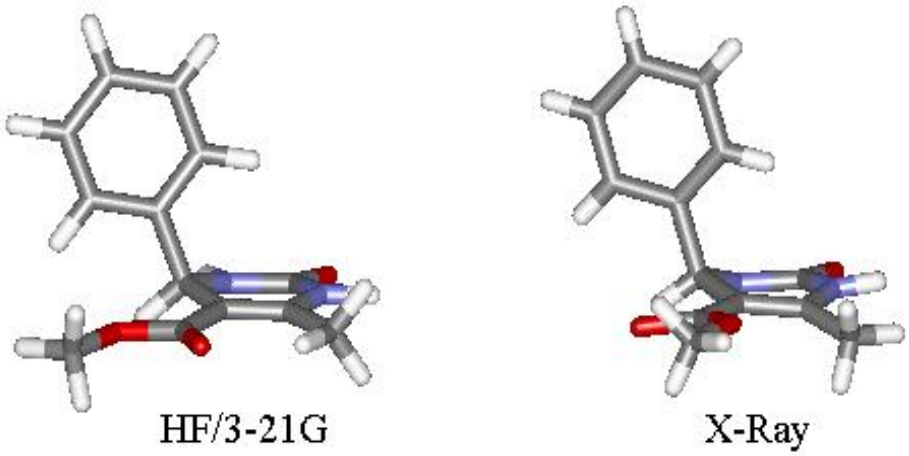
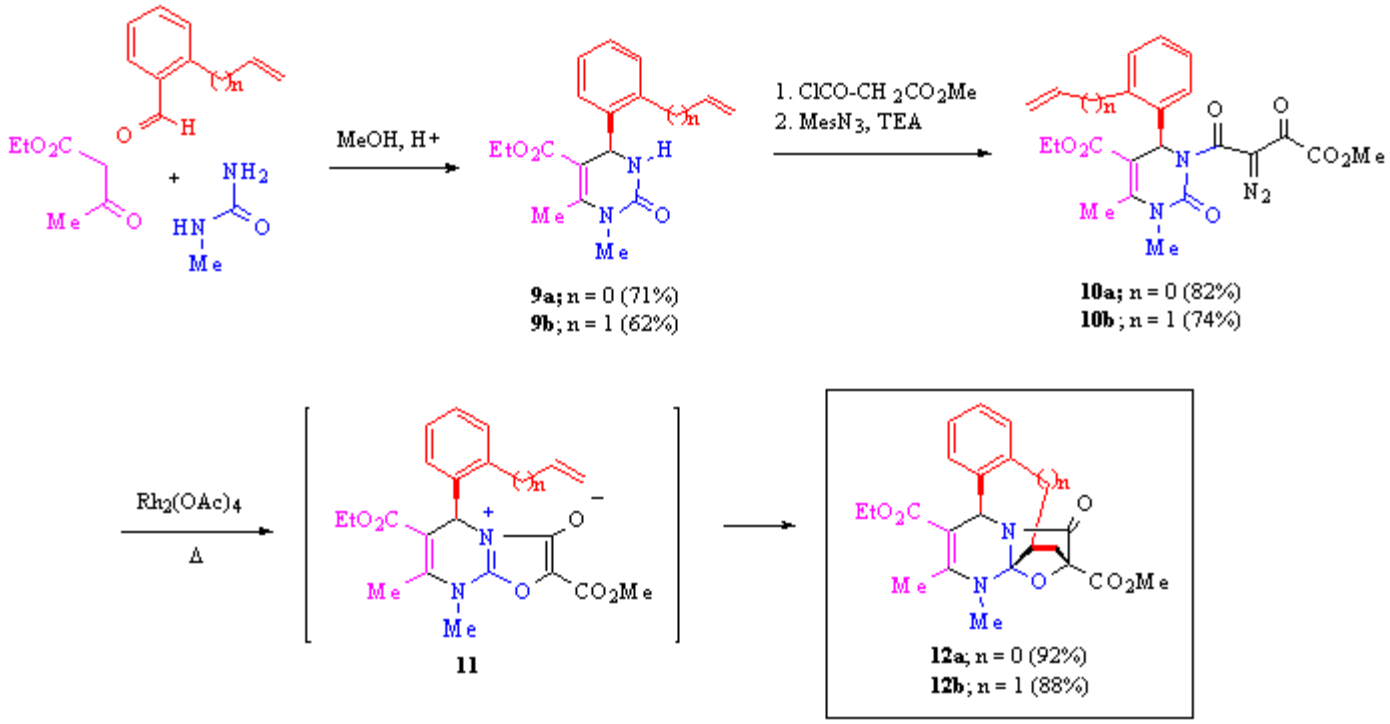


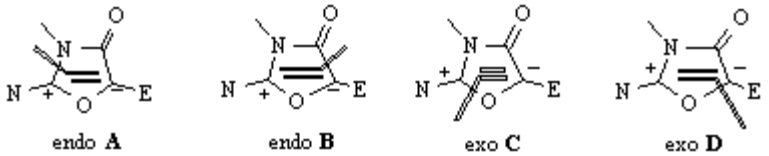
Figure 2. Comparison of an ab initio optimized geometry (HF/3-21G) and the solid state geometry of a DHPM **7** (side-view). Note the different orientation (*cis* vs. *trans*) of the ester group.

In order to construct the desired conformationally restricted polycyclic DHPM systems [19] an alkenyl tether was incorporated into the *ortho*-position of the aryl moiety in the DHPM framework. The required starting materials **9a**,**b** were obtained by classical Biginelli condensation of ethyl acetoacetate, with N-methylurea, and 2-vinylbenzaldehyde (or 2-allylbenzaldehyde, respectively). N-Malonylacylation,[11] followed by standard diazo-transfer with mesyl azide [20] produced the corresponding diazo precursors **10a**,**b** in high yield. Treatment of diazo imides **10a**,**b** with a catalytic amount of rhodium acetate in refluxing benzene [11] produced directly the desired pentacyclic dihydropyrimidine derivatives **12a,b** in high yields. In this tandem-cyclization-cycloaddition sequence [11] the initially generated transient isomünchnone dipole **11** adds spontaneously across the unactivated p-bond of the olefinic tether in a regio-and stereospecific manner. Analysis of the crude reaction mixtures for both homologs (n = 0, n = 1) by H-NMR (200 MHz) confirmed that **12a** and **12b** respectively, were the only isomers formed (within the detection limit of H-NMR spectroscopy).



Scheme 3

The stereospecificity and relative ease of these intramolecular cycloadditions are readily explained by considering molecular models (Dreiding) of the transition states involved. [21] The pseudoaxial orientation of the aryl substituent allows for an extremely favourable alignment of the double bond relative to the dipole, placing the p-bond in close proximity above the dipole. For n = 0 only an *endo* approach of the p-bond with the terminal end of the olefin directed towards the negative center of the dipole is possible (*endo* **A**). Transition states according to types **B**-**D** leading to *exo* isomers and/or different regioisomers can not be modeled at all or place a too high steric demand on the transition state. For n = 1, the *endo* **A** approach again is the most favorable, although an *endo* **B** and even an *exo* **C** approach cannot be totally excluded. The structures of both cycloadducts were unequivocally established by an X-ray crystallographic analysis (Figure 3) confirming that both cycloadducts result from an *endo* **A** type transition state.



The solid-state structures of **12a,b** (Figure 3) demonstrate that the geometry of these conformationally restricted DHPM derivatives is very similar to the receptor-bound conformation proposed in the recent binding-site model for DHP/DHPM calcium channel modulators (Figure 1). [9] The aryl group is "tied" into the axial position, is perpendicular to and bisecting (for **12b**) the boat-like dihydropyrimidine ring. Any additional substituent on the aromatic ring (*i.e.* Z in **6**) would be forced into the synperiplanar orientation relative to C4-H. Importantly, by using this cycloaddition protocol all manipulations on the DHPM system are occuring on the non essential "right-hand" side of the molecule, thereby not interfering with the receptor-sensitive groups on the "left-hand" side (Figure 1).

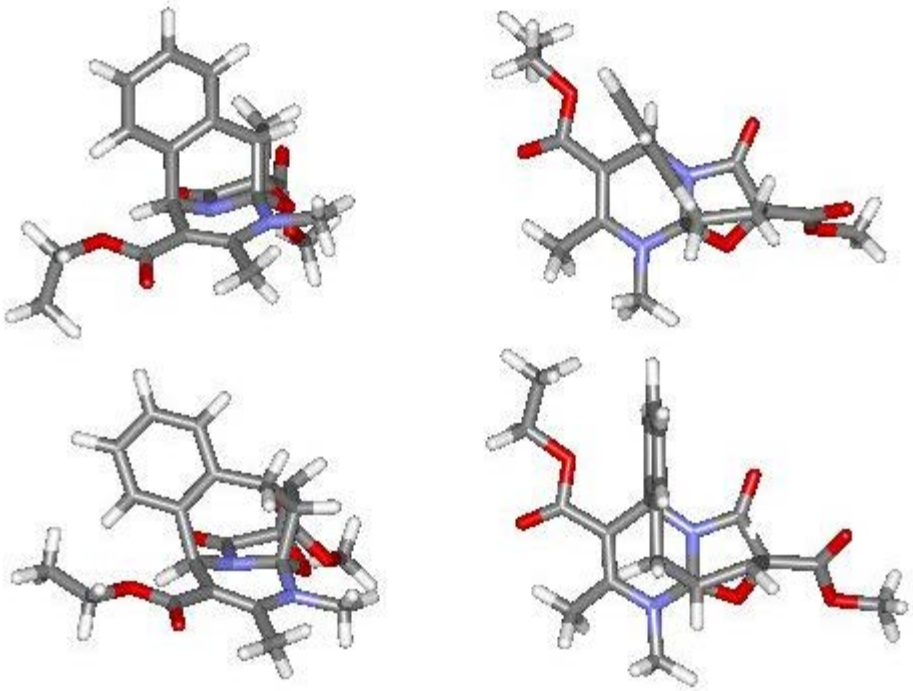


Figure 3. Solid-state geometries of DHPMs **12a** (top row) and **12b** (bottom row) from two different perspectives.

Since individual enantiomers of chiral DHPMs of type **2** have opposing pharmacological effects on the calcium channel (Figure 1), access to enantiomerically pure DHPMs is a requirement for the development of cardiovascular drugs of this structural type. Due to recent advances on chromatographic enantioseparation

techniques, enantioselective HPLC and related methods have gained importance in the preparation of single-enantiomer drugs and intermediates. In a recent study we have reported the successful chromatographic enantioseparation of DHPM derivatives of type **2** using a variety of commercially available chiral stationary phases (CSPs) in normal- and reversed-phase analytical HPLC [22]. Out of 29 racemic DHPM analogs all but one were separated on at least one of the eight CSPs tested with separation coefficients ranging from 1.08 to 8.67. For polycyclic DHPMs **12** the use of Chiralcel OD-H as CSP and 2-propanol/n-heptane (20/80) as mobile phase has proven to be an effective method for enantioseparation (Figure 4).

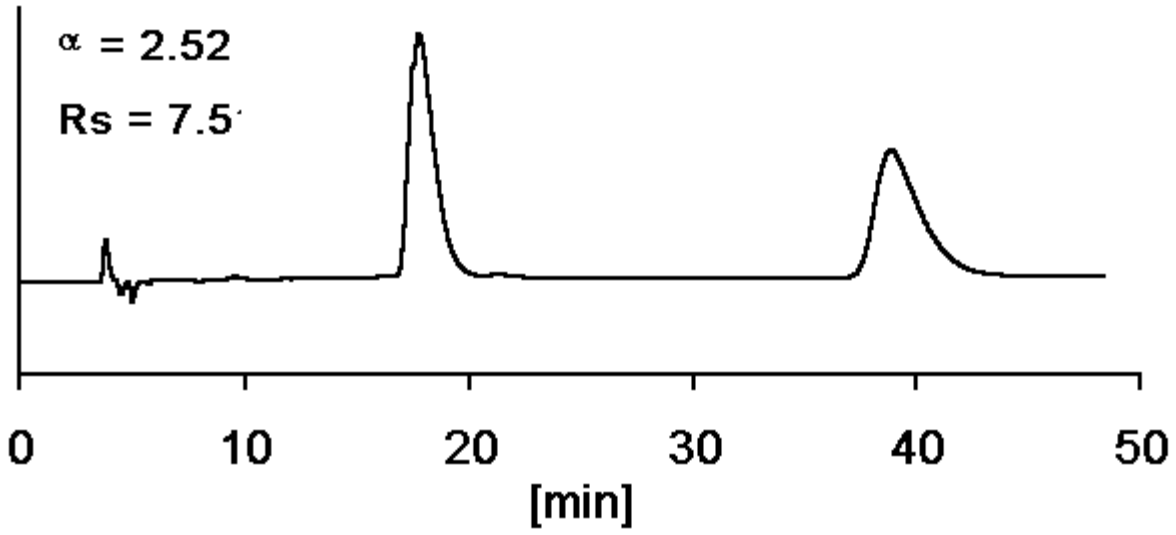


Figure 4. Enantioseparation of DHPM **12a** on Chiralcel OD-H.

Conclusion

In conclusion, the described intramolecular isomünchnone cycloaddition sequence leads to a rigid, polycyclic DHPM skeleton, that closely resembles the recently proposed receptor-bound conformation of dihydropyridine calcium channel modulators. The ease of generation of the key dipolar intermediates and the high overall yields makes this an attractive method for the preparation of pharmacologially interesting DHPM derivatives. The application and further development of this methodology for the preparation and pharmacological evaluation of properly functionalized DHPM calcium channel modulators in enantiomerically pure form is under investigation.

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