Crystal Structure of a 1,4-Dihydropyridine with Enantiomers Showing Opposite Effects on Calcium Channels: Structural Features of Calcium Channel Agonists and Antagonists

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The structure of the calcium channel modulator isopropyl 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-5-nitro-3-pyridinecarboxylate has been determined by X-ray analysis. Structural and stereochemical features are discussed in relation to previously determined structures of calcium agonists and antagonists of the 1,4-dihydropyridine type, and in relation to a newly proposed model for the dihydropyridine binding site.

Derivatives of 1,4-dihydropyridine (DHP) that are closely related in structure (Fig. 1) can act as calcium channel antagonists or agonists. DHP's that are antagonists (DHPI) block transmembrane Ca^{2+} influx, thereby causing relaxation of smooth and cardiac muscle.[1–3] Well-known compounds include nifedipine (R = R′ = Me, X = 2-NO_2) and nitrendipine (R = Me, R′ = Et, X = 3-NO_2). The DHP agonists enhance Ca^{2+} influx across the cell membrane and thus produce quite opposite pharmacological effects.[4–5] Direct measurements of Ca^{2+} single-channel currents in cardiac cells suggest that antagonist binding promotes a state of the calcium channel characterized by brief opening times. Agonist binding on the other hand promotes a state in which the calcium channel has a higher probability of being open.[6] Radioligand binding assays suggest that DHP antagonists and agonists bind to the same receptor site.[7,8]

Even the enantiomers of a chiral DHP may exhibit opposite pharmacological effect.[9,10] The *R* enantiomer of the title compound, isopropyl 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-5-nitro-3-pyridinecarboxylate (DHPII) acts as a calcium antagonist, whereas the *S* enantiomer is an agonist. The absolute configuration of this compound has been established by X-ray analysis of a quaternary ammonium salt precursor PREDHPII: (−)-(*S*)-4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-5-nitro-3-pyridinecarboxylic acid [2-(trimethylammonio)ethyl] ester iodide.[9] When tested as a racemate, the title compound shows both agonistic and antagonistic properties, depending on the experimental conditions. The enantiomers of DHPIV also show opposite pharmacological effects; the enantiomer with *R* configuration has antagonist properties, whereas the *S* enantiomer has agonist properties.[10] This compound is predominantly an agonist when tested as a racemate, but at high concentrations it shows antagonist properties. The compounds DHPIII (CGP 28392), DHPV (YC 170) and DHPVI (BAY F 6653 = H 160/51) are reported agonists. To this authors knowledge, pure enantiomers of these compounds have not been prepared.

Comparative crystallographic studies of DHP agonists (DHPIII and DHPIV) and antagonists show that several conformational features are shared by these compounds.[11] The DHP ring is relatively flat in both potent antagonists and agonists. Structural differences, including hydrogen-bonding strength of the DHP ring amine

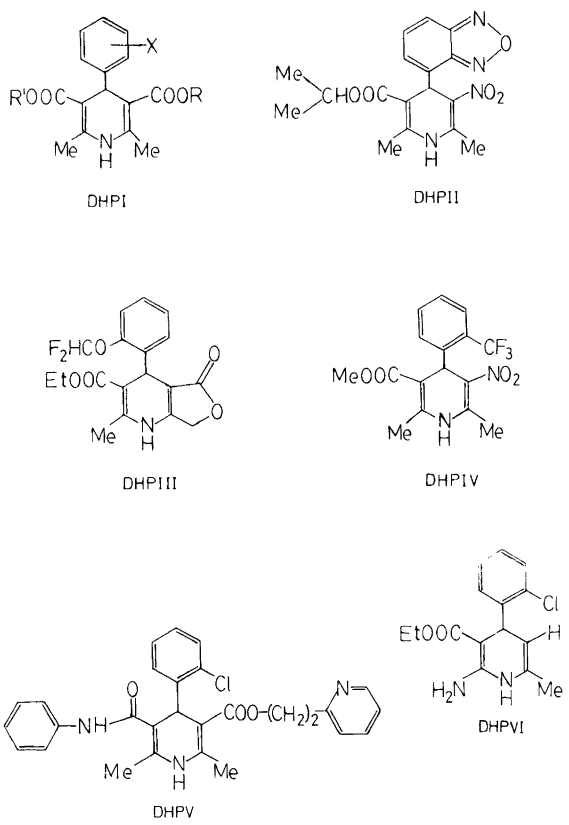

Fig. 1. Structural formulas for various 1,4-dihydropyridine Ca^{2+} channel antagonists and agonists.

group, ester group orientation and hydrophobic fit of the ester groups are suggested as factors that may control the availability of the Ca^{2+} channel open and closed states.

In the crystal lattice, the carbonyl groups of diesters (DHPI) are either twisted in opposite directions, one anti- the other synperiplanar (*ap,sp*), or they are both synperiplanar (*sp,sp*) with respect to the DHP ring double bonds. An examination of hydrogen-bonding patterns in crystal structures of DHP diesters suggested that the distinction between antagonists and agonist response might be related to the *sp* and *ap* conformational difference.[12]

Recent theoretical calculations on DHP agonists and antagonists have demonstrated a conformational distinction between these compounds.[13] The conformational preference of the ester side-chains in antagonists corresponds to both carbonyl groups being synperiplanar with respect to the DHP ring double bonds. A receptor model that allows DHP antagonists and agonists to bind to the same binding site and yet produce opposite pharmacological effects has been proposed. The model involves at least three binding sites: (a) the aromatic or heteroaromatic ring binds to a flat part of the receptor; (b) the DHP N atom is donor in a hydrogen bond; (c) one *sp* carbonyl group in diesters (DHPI) acts as H-bond acceptor in binding that produces antagonist response and the *ap* lactone carbonyl (DHPIII) or the *ap* oxygen of the nitro group (DHPII, DHPIV) act as H-bond acceptor in binding that produces agonist response.

The crystal structure of the pharmacologically active DHPII has been determined in order to investigate further structural features of DHP agonists and antagonists. Since the absolute configurations of several DHP agonists and antagonists now are known, this permits further investigations of stereochemical features that allow DHP agonists and antagonists to bind to the same site and yet produce opposite pharmacological effects.

Experimental

Single crystals of the racemic title compound were grown by slow evaporation from a diethyl ether solution. Data concerning the experimental conditions are given in Table 1.

Cell parameters were obtained from a least-squares fit of the diffractometer settings for 24 general reflections. The measured intensities were corrected for Lorentz and polarisation effects. Correction for absorption effects was not deemed necessary. The structure was solved by direct methods using the program package MITHRIL[14] and refined by full-matrix least-squares techniques. The weights in least-squares were calculated from the standard deviations in intensities $\sigma(I)$, taken as $\sigma(I) = [C_1 + (0.02C_2)^2]^{1/2}$, where C_1 is the total number of counts and C_2 is the net peak count. Hydrogen atoms were introduced on the basis of stereochemical considerations. Non-hydrogen atoms were refined anisotropically and hydrogen atoms isotropically using a common thermal parameter for H atoms belonging to the same methyl group. Refinement resulted in relatively large thermal parameters for the methyl C atoms of the isopropyl group. It was not possible to locate the methyl H atoms of this group. The positions of the H atoms were calculated and the H atoms were assigned a common thermal parameter which was not refined. The final R-value was 0.074 (R_w = 0.064) for 2060 reflections. A difference Fourier map showed no peaks or holes exceeding 0.3 eÅ^{-3} after the last refinement cycle. Final positional coordinates are given in Table 2. Thermal parameters, and tables of observed and calculated structure factors are available from the author on request.

Table 1. Experimental conditions.

Instrument	NICOLET P3/F
Radiation	Graphite-monochromated MoKα (λ = 0.71069 Å)
Crystal dimensions/mm	0.2×0.2×0.3
Scanning mode	θ/2θ
Scan speed/°min^{-1}	3.0
Background counts	for 35 % of scan time at scan limits
Temperature/°C	approx. −150
2θ range/°	2.5–70.0
No. of refl.	4093
No. of obs. refl. $I > 2.5\sigma(I)$	2060

Table 2. Fractional atomic coordinates. Estimated standard deviations in parentheses.

Atom	*x*	*y*	*z*
O32	0.5013	0.5766(3)	−0.1738
O33	0.3650(4)	0.7059(4)	−0.2772(5)
O52	0.2193(4)	0.8078(3)	0.0793(5)
O53	0.2365(4)	0.9030(3)	−0.0567(5)
O82	0.6983(4)	0.9264(3)	0.3191(5)
N1	0.4958(4)	0.6226(3)	0.1738(5)
N51	0.2673(4)	0.8255(3)	0.0244(5)
N81	0.6034(5)	0.8594(3)	0.2262(6)
N91	0.7070(5)	1.0105(4)	0.2516(6)
C2	0.5069(5)	0.6051(4)	0.0687(6)
C3	0.4477(5)	0.6692(4)	−0.0458(6)
C4	0.3829(5)	0.7688(4)	−0.0536(6)
C5	0.3567(5)	0.7579(3)	0.0494(6)
C6	0.4171(5)	0.6902(3)	0.1615(6)
C7	0.4505(5)	0.8702(4)	−0.0328(6)
C8	0.5538(5)	0.9039(3)	0.1023(6)
C9	0.6179(5)	0.9958(4)	0.1174(7)
C10	0.5862(6)	1.0604(5)	0.0011(7)
C11	0.4882(6)	1.0270(5)	−0.1265(7)
C12	0.4214(6)	0.9343(4)	−0.1408(7)
C21	0.5827(6)	0.5101(4)	0.0989(7)
C31	0.4450(5)	0.6440(4)	−0.1670(6)
C34	0.3549(7)	0.6943(6)	−0.4052(7)
C35	0.2303(7)	0.7218(8)	−0.5237(8)
C36	0.4411(9)	0.7624(8)	−0.3934(8)
C61	0.4137(6)	0.6852(4)	0.2831(6)
H11	0.526(5)	0.576(5)	0.237(6)
H41	0.297(5)	0.774(4)	−0.153(6)
H101	0.638(6)	1.124(6)	0.006(7)
H111	0.466(5)	1.073(5)	−0.210(6)
H121	0.352(5)	0.913(4)	−0.233(6)
H211	0.624(5)	0.491(5)	0.185(7)
H212	0.540(5)	0.438(5)	0.055(6)
H213	0.610(5)	0.504(5)	0.054(6)
H341	0.351(4)	0.616(4)	−0.426(5)
H351	0.172	0.667	−0.523
H352	0.213	0.804	−0.510
H353	0.215	0.715	−0.622
H361	0.527	0.735	−0.306
H362	0.432	0.757	−0.489
H363	0.430	0.845	−0.376
H611	0.437(7)	0.606(7)	0.332(9)
H612	0.397(7)	0.750(7)	0.300(9)
H613	0.339(7)	0.635(7)	0.250(8)

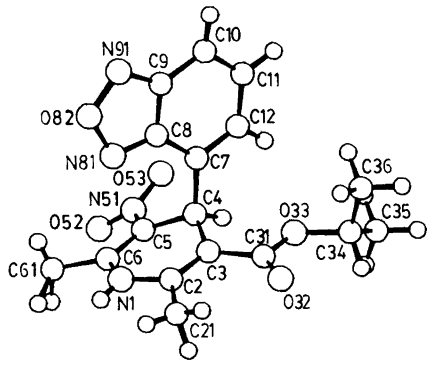

Fig. 2. A schematic drawing of the *S* configuration of the title compound: isopropyl 4-(2,3,1-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-5-nitro-3-pyridinecarboxylate (DHPII).

Crystal data

Isopropyl 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-5-nitro-3-pyridinecarboxylate, $C_{17}H_{18}O_5N_4$; monoclinic, a = 14.483(3), b = 12.386(3), c = 12.118(2) Å, β = 127.95(1)°, V = 1714 Å^3, M = 358.34, Z = 4, $F(000)$ = 752, space group *Cc* (No. 9).

Results and discussion

Fig. 2 shows a schematic drawing of DHPII with the adopted atomic labelling scheme. The molecule shown has the *S* absolute configuration and is the enantiomer which has Ca^{2+} agonist properties. Selected torsion angles in DHPII and in the ammonium salt precursor PREDHPII[9] are given in Table 3. An examination of the sign and magnitude of these torsion angles shows that the conformation adopted by the DHP ring and the inter-ring conformation are almost identical in the two compounds. The only appreciable conformational difference is exhibited by the torsional distortions of the C3 and C5 substituents. The deviations of the C6–C5–N51–O52 and C2–C3–C31–O32 torsion angles from synplanarity show that the torsional distortion of the nitro group is somewhat larger in DHPII, whereas the carbonyl group has a greater torsional distortion in PREDHPII. These minor differences are most likely caused by intramolecular hydrogen-bonding. In DHPII there is a weak bifurcated hydrogen bond between N1(donor) and O32 and O53 of two neighbouring molecules. The N1···O32 distance is 3.054 Å and the N1–H···O32 angle is 148°. Corresponding values for the N1···O53 distance and the N1–H···O53 angle are 2.986 Å and 118°.

Table 3. Selected torsion angles (°) in the title compound (DHPII) and in the ammonium salt precursor (PREDHPII).

Torsion angle	DHPII	PREDHPII[a]
C2 –N1 –C6 –C5	−10.6(6)	−8.0
C3 –C2 –N1 –C6	9.7(6)	8.2
N1 –C2 –C3 –C4	8.4(6)	9.0
C2 –C3 –C4 –C5	−21.7(6)	−22.6
C3 –C4 –C5 –C6	21.1(6)	22.9
C4 –C5 –C6 –N1	−6.5(6)	−9.5
C21–C2 –C3 –C31	5.2(7)	0.2
C61–C6 –C5 –N51	−9.0(7)	−7.1
C2 –C3 –C31–O32	−8.9(7)	−18.1
C3 –C31–O33–C34	177.4(5)	−176.8
C31–O33–C34–C35	151.4(6)	
C31–O33–C34–C36	−84.9(7)	
C6 –C5 –N51–O52	−18.7(6)	−4.6
C3 –C4 –C7 –C8	−75.5(5)	−75.2

[a]Standard deviations are not available.

Structural studies of the Ca^{2+} agonists DHPIII and DHPIV showed that substitution of one of the ester groups with a nitro group, or covalent constraint of one carbonyl group in a lactone ring leads to relatively large perturbations in some of the bond distances pertaining to the DHP ring as compared to diestes (DHPI).[11] This is illustrated further in Table 4, where selected bond distances in DHPII and other Ca^{2+} agonists and antagonists are compared. Since agonist or antagonist action is determined by chirality in DHPII and DHPIV, the differences in bond distances shown in Table 4 cannot be decisive in determining whether a DHP is predominantly an agonist or an antagonist.

The sum of the magnitudes of the six DHP ring torsion angles is 78° in DHPII. The DHP ring is thus more puckered than in the dihydropyridines DHPIII (47°) and DHPIV (39°). The fact that the DHP ring is not flattened as much in the title compound as in DHPIV, which also contains a nitro group, is in part related to the conformation adopted by the benzoxadiazole ring. The oxadiazole moiety resides directly over the DHP ring. In phenyl-substituted antagonists and agonists with an *ortho* substituent the *ortho* substituent is

Table 4. Selected bond distances (Å) in Ca^{2+} antagonists and agonists.

Bond	DHPI[a]	DHPII	PREDHPII[b]	DHPIII[b]	DHPIV[b]
N1–C2	1.384(6)	1.394(6)	1.417	1.404	1.390
N1–C6	1.380(5)	1.348(6)	1.350	1.345	1.350
C2–C3	1.359(8)	1.352(6)	1.325	1.344	1.355
C5–C6	1.359(8)	1.361(6)	1.366	1.319	1.375
C3–C31	1.469(8)	1.479(6)	1.463	1.485	1.477
C5–C51	1.468(5)			1.446	
C5–N51		1.409(6)	1.419		1.404

[a]Mean value of the bond lengths in the six most precisely determined structures of Ca^{2+} antagonists (Fig. 1: DHPI). The standard deviations in bond lengths range from 0.001 to 0.004 Å. The numbers in parentheses are standard deviations from the mean. [b]Standard deviations are not given in the original Refs.

always found to point away from the DHP ring such that the phenyl ring approximately bisects the DHP ring. This phenyl ring conformation subsequently flattens the DHP ring. The conformation adopted by the benzoxadiazole ring is achieved without imposing non-bonded contacts with the DHP ring atoms that are significantly shorter than van der Waals contact distances. In the *ortho*-substituted phenyl derivatives the steric strain imposed by the *ortho* substituent residing over the DHP ring would have to be partly relieved by opening of the C7–C8–X exocyclic bond angle. Due to ring strain, the C7–C8–N81 angle (128.9°) is already opened in the title compound. Since 2,6-, 2,3- and 2,5-disubstituted phenyl DHPI derivatives are generally potent antagonists, binding of the present benzoxadiazole ring conformation is apparently not precluded by steric limitations at the DHP binding site.

According to the model for the DHP binding site,[13] the distinction between DHP antagonists and agonists is based on the conformational preference of the hydrogen bond-accepting carbonyl or nitro groups located on the same side of the DHP boat. Agonistic binding corresponds to the presence of an *ap* H-bond acceptor whereas antagonistic binding corresponds to the presence of a *sp* H-bond acceptor. The nitro group containing the *ap* H-bond acceptor is on C5 in the agonists DHPII (Fig. 2) and DHPIV with *S* configuration. Looking down into the DHP boat and defining C4 as the bow, this means that the nitro group is located on the left hand or port side of the DHP boat. Theoretical calculations suggest that the agonist (*ap*) conformation is not accessible to the C3 carbonyl group in DHPIV. If so, the receptor model is wrongly illustrated in terms of chirality in Ref. 13 since the *ap* or *sp* H-bond acceptors are shown located on the right- hand or starboard side of the DHP boat (C3 position) in this reference and chirality is implied by the fact that three binding sites are involved. This model should therefore rather be illustrated as in Figs. 3A and 3B.

The agonist properties of DHPVI[8] cannot easily be explained in terms of this model, suggesting that some qualifications are needed. In DHPVI it would be expected that intramolecular hydrogen-bonding between the amino group and the carbonyl group favours a *sp* orientation of the carbonyl group. This may suggest that an *ap* hydrogen bond acceptor at C5 is not necessary in order to produce a conformational change in the DHP receptor that results in increased availability of the Ca^{2+} channel open state(s). Even when an *ap* H-bond acceptor at C5 is lacking, agonist response may be produced (Fig. 3C).

In general, the agonistic or antagonistic activity exhibited by racemic DHP's with different C3 and C5 substituents will depend on several factors. The extent to which these substituents fit the surmised antagonist binding mode (Fig. 3A) and the agonist binding modes (Figs. 3B or 3C) will depend on the configurational and conformational properties of both the C3 and the C5 substituent, since the substituent located on the port side of the DHP boat is interchanged for the two enantiomers. Furthermore, other factors, including the extent to which agonist and antagonist binding enhances and inhibits Ca^{2+} influx, respectively, will also play a decisive role in determining the pharmacological response. The inter-

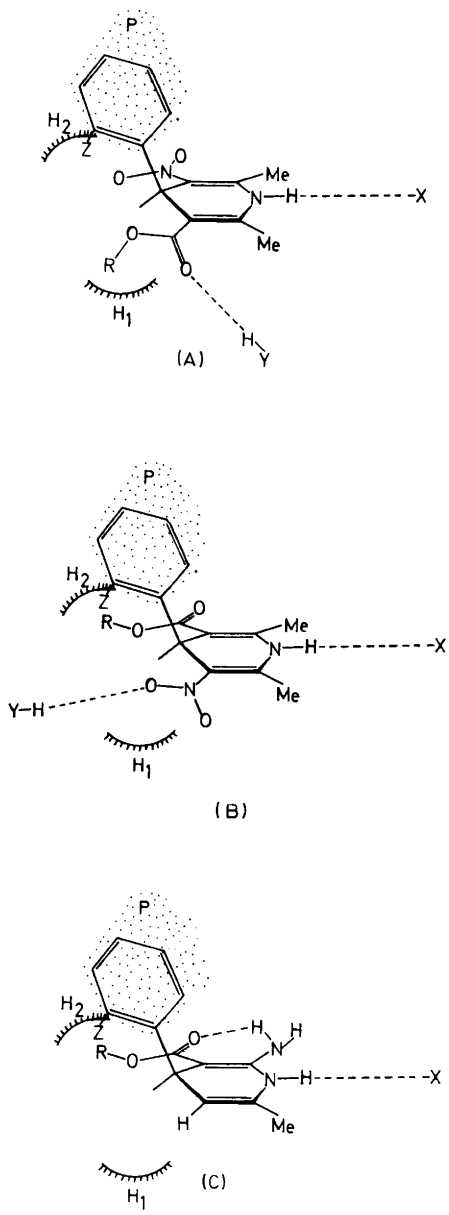

Fig. 3. A model for the DHP antagonist (A) and agonist (B) binding modes obtained by inverting the configuration of the model suggested in Ref. 8. Broken lines indicate hydrogen bonds and P a planar region of the DHP receptor. Additional features of this model are the hydrophobic regions designated by H_1 and H_2. Even when an *ap* H-bond acceptor (C) is lacking, binding may result that produces agonistic response.

play between these factors is illustrated by the mixed effects produced by DHPII and DHPIV when tested as racemates.

The thesis that agonist or antagonist response can be distinguished by the adopted conformation of the C3 and C5 side-chain suggests that marked effects on the pharmacological activity of a DHP may be produced by chemical changes that affect this conformational equilibrium. The 2-amino analogue of nifedipine (Fig. 1: R = R′ = Me; X = 2–NH_2) may provide one such example. In the crystal structure of this compound, the amino group is involved in intramolecular hydrogen-bonding to the *ap* carbonyl group, thus stabilizing this conformation.[15] Although the antagonistic potency of this compound is reduced by the hydrophilic amino group, this reduction is much greater for the 2-amino isomer than the 3-amino isomer. For a wide range of electropositive and electronegative substituents, the 2-X isomer is more potent than the 3-X isomer.[3,16] Only in the case of nitro substitution are the isomers approximately equipotent. The fact that the 2-amino derivative, judged by IC_{50}-values, is a factor of approximately 0.05 less potent than the 3-amino derivative in inhibiting the contraction of ileal smooth muscle[17] is not likely to be caused by differences in lipophilicity. Intramolecular hydrogen-bonding should make the 2-amino derivative less hydrophilic than the 3-amino. This anomalous activity ratio may rather be related to the fact that the antiperiplanar carbonyl conformation is more accessible owing to intramolecular hydrogen-bonding. Accordingly, a larger fraction of the molecules may adopt the conformation of an agonist, suggesting that the pharmacological activity of this compound also has an agonistic component.

Some possible additional features of the DHP binding site are discussed below in the light of available structure-activity data, binding data and crystal structures of DHP's.

X-ray crystallographic data show that the DHP N atom is essentially sp^2 hybridized in these compounds. The sum of the bond angles around N1 is always close to 360°. The H atom is thus located only slightly below the plane containing C2, C6 and N1 (Fig. 2). For this reason, the requirements for a strong linear hydrogen bond are best fulfilled when the acceptor atom of the receptor lies approximately in the DHP ring plane, as illustrated in Fig. 3. Deviations from planarity in

the DHP ring are generally small in potent antagonists and agonists. This common conformational feature may be a prerequisite for both good antagonist and agonist binding.[11] In effect, the degree of puckering in the DHP ring describes the relative orientation of the various ring substituents; as the DHP ring becomes more puckered, the C2, C3, C5 and C6 substituents bend down below the DHP ring plane, whereas the C4 ring adopts a more "priapic" orientation above the DHP ring plane. Presumably, this affects both the geometry of hydrogen-bonding to a receptor site and the steric fit of the various DHP ring substituents.

Conformational calculations suggest that the torsional distortions of the C3 and C5 substituents are relatively large in antagonists; the carboxy groups are preferentially oriented in a plane which intersects the plane of the DHP ring with an angle of between 30 and 60°. In the solid state, the carbonyl groups are always less torsionally distorted; the C2–C3–C31–O32 and C6–C5–C51–O52 torsion angles seldom deviate more than 10° from anti- or synplanar values in 25 crystal structures investigated.[18] The torsional distortions of the nitro groups in DHPII and DHPIV are also small, as shown both by crystal structure data and theoretical calculations. In DHPIII, the lactone ring forces the carbonyl group to adopt an antiplanar conformation. Conformationally restricted DHP analogues having the distal *ortho* position of the phenyl ring covalently linked to an ester group, thus forcing the carbonyl group to be *sp*, are potent antagonists provided the linking chain is long enough to permit the phenyl ring to adopt an orientation bisecting the DHP ring.[19] It remains to be determined to what extent the strong conformational preference for the *sp* and *ap* conformations seen in the crystal structures is conserved in the receptor binding modes illustrated in Fig. 3. The crystal and pharmacological activity data discussed above are, at least, consistent with the thesis that the conformations adopted by the H-bond acceptors involved in the antagonist and agonist binding modes do not deviate much from syn- and antiplanar values, respectively.

Large variations in terms of branching, steric size, degree of saturation and heterosubstitution are permitted in the alcohol moiety of the ester groups in diesters without significant loss of antagonist activity.[8,20] This suggests that there are relatively large hydrophobic regions at the binding site that can accomodate these groups, designated by H_1 and H_2 in Fig. 3.

The stereoselectivity of antagonism observed when the ester groups are different may be related to differences in the spatial layout of the H_1 and H_2 regions. The *S* configurated isomer is always more potent and has higher binding affinity than the *R* isomer.[8,20] Stereoselectivity becomes more pronounced the more the alkyl groups differ in terms of steric bulk. It may be noted that in the *S* isomers, the bulkier alkyl group is located on the C5 ester group that is presumed to be involved in hydrogen-bonding at the receptor site. However, the nature of the C3 alcohol moiety is also important in determining binding and activity. Further studies are needed to clarify the role played by ligand interactions involving both the C3 and C5 substituents in determining the pharmacological activity of DHP's.

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