Active Conformation of 1,4-Dihydropyridine Calcium Entry Blockers. Effect of Size of 2-Aryl Substituent on Rotameric Equilibria and Receptor Binding

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The conformational requisites at the receptor for unsymmetrically substituted phenyl-1,4-dihydropyridine calcium entry blockers are examined by screening a series of (2'-halophenyl)-1,4-dihydropyridines 1-4, with increasing bulk at the 2'-position of the phenyl ring, for their ability to relax potassium-contracted rabbit aortic smooth muscle and to competitively displace [^{3}H]nitrendipine from its specific binding sites on guinea pig skeletal muscle. The fraction of synperiplanar rotamer in solution for these compounds, as determined by the nuclear Overhauser enhancement method, shows a positive correlation with vasorelaxant activity and receptor binding affinity. These findings are consistent with the synperiplanar rotamer of nonrigid unsymmetrically substituted phenyl 1,4-dihydropyridine calcium channel blockers being the receptor-bound conformation.

Introduction

Unsymmetrically substituted phenyl-1,4-dihydropyridine calcium entry blockers may be oriented in either of two minimum energy conformations, with the substituent on the phenyl ring positioned either toward the C-4 hydrogen (synperiplanar, *sp*) or away from the C-4 hydrogen (antiperiplanar, *ap*) as illustrated in representations A and B, respectively, in Table I. Aside from two recent reports,[1,2] all phenyl-1,4-dihydropyridines containing a 2'-phenyl substituent have been shown to exist in the synperiplanar rotamer in the solid state. In solution, it has been generally assumed that a 2'-phenyl substituent (for example, chloro or nitro) provides a significant energetic bias for the synperiplanar rotamer,[3,4] and thus, it also seemed reasonable to assume that this must be the rotamer recognized by and bound to the dihydropyridine receptor. On this premise, we previously examined phenyldihydropyridine calcium entry blockers with a 2'-chloro substituent in addition to a nitro group at positions 3' or 5' of the phenyl ring, intending to define the receptor preference for the substituent at the 3' (5') position. In that work we described a method, using nuclear Overhauser enhancement, that permits a quantitative determination of the equilibrium fraction of synperiplanar/antiperiplanar rotamers in solution for unsymmetrically substituted phenyl-1,4-dihydropyridine calcium entry blockers.[1] Further, we demonstrated that a 2'-chloro (or 2'-nitro) phenyl substituent does not provide a significant energetic bias for the synperiplanar rotamer and, thus, the antiperiplanar rotamer could not be excluded from consideration as the active rotamer at the receptor.

In the present study, we approached the question of defining the receptor-bound conformation of unsymmetrically substituted phenyl-1,4-dihydropyridine calcium entry blockers by examining a series of (2'-halophenyl)-1,4-dihydropyridines 1-4 for their ability to relax potassium-contracted rabbit aortic smooth muscle[5] and to competitively displace [^{3}H]nitrendipine ([^{3}H]NTP) from its specific binding sites on guinea pig skeletal muscle.[6-8] For this set of compounds, we are able to show a positive correlation between the vasorelaxant activity, the receptor binding affinity, and the fraction of synperiplanar rotamer in solution as determined by the nuclear Overhauser enhancement method.[1]

Discussion and Results

We have previously[1] demonstrated that a 2'-chlorophenyl substituent does not provide a significant energetic bias toward the synperiplanar rotamer of unsymmetrically substituted 1,4-dihydropyridine calcium entry blockers. The evidence to support this conclusion was derived from a combination of NMR studies, AM1 semiempirical quantum chemical calculations, and X-ray crystallographic data. Although the fractional enhancement of synperiplanar rotamer for the monosubstituted (2'-chlorophenyl)-1,4-dihydropyridine (2) was determined in that study to be a very modest 0.73 ± 0.09, we anticipated that it might be fruitful to pursue this approach one step further. Thus, in the present study, a series of phenyl-1,4-dihydropyridines containing substituents of increasing bulk at the 2'-position of the phenyl ring were examined to determine if the vasorelaxant and receptor binding effects correlated with the experimentally determined fraction of synperiplanar conformation in solution.

We prepared the 2'-fluoro-, 2'-chloro-, 2'-bromo-, and 2'-iodo-1,4-dihydropyridines 1-4, respectively, wherein the 2'-substituent not only increases in van der Waals radius (F, 1.4 Å; Cl, 1.8 Å; Br, 2.0 Å; I, 2.2 Å) but also remains uniformly spherical within the series. The strict analogy within this series should allow simpler interpretation of the results.

The solid-state and solution rotamer preferences for compounds 1-4 are shown in Table I, and the corresponding vasorelaxant and receptor binding data are shown in Table II. In contrast to the previous study,[1] the required interproton distances for calculating the fraction synperiplanar orientation were obtained solely from AM1

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(1) Rovnyak, G.; Andersen, N.; Gougoutas, J.; Hedberg, A.; Kimball, S. D.; Malley, M.; Moreland, S.; Porubcan, M.; Pudzianowski, A. *J. Med. Chem.* **1988**, *31*, 936.
(2) Fossheim, R. *Acta Chem. Scand.* **1987**, *B41*, 581.
(3) Goldmann, S.; Geiger, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 301.
(4) Berntsson, P.; Carter, R. E. *Acta Pharm. Suec.* **1981**, *18*, 221.
(5) Ehlert, F. J.; Etoza, E.; Rocske, W. R. *Biochem. Biophys. Res. Commun.* **1982**, *104*, 931.
(6) Belleman, P.; Ferry, D., Glossman, H. *Arzneim.-Forsth.* **1981**, *31*, 2064.
(7) Depover, A.; Lee, S. W.; Matlib, M. A.; Whitmer, K.; Davis, B. A.; Powell, T.; Schwartz, A. *Biochem. Biophys. Res. Commun.* **1983**, *113*, 185.
(8) vanBreeman, C.; Fannas, B. R.; Gerba, P.; McNaughton, E. D. *Circ. Res.* **1972**, *30*, 44.

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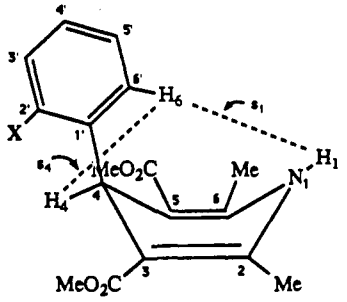
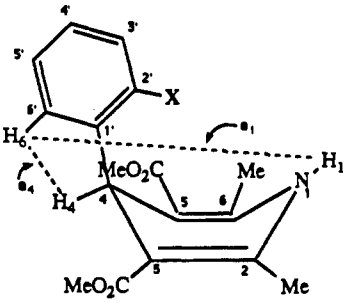
Table I. Test Compounds, Physical Data, and Rotamer Preferences (Solid State and Solution)





					rotamer preference		
					solid state[a]	soln[b]	
no.	X	mp, °C	% yield	R^c	*sp/ap*	f_s	K_{eq}
1	F	205–208	52[d]	0.12 ± 0.02	*e*	0.69 ± 0.07	2.2 ± 0.7
2	Cl	184–186	26[f]	0.28 ± 0.03	*sp/ap*	0.84 ± 0.05	5 ± 2
3	Br	164–166	33[g]	0.46 ± 0.05	*sp*	0.92 ± 0.03	12 ± 5
4	I	181.5–183.5	54[h]	0.74 ± 0.08	*sp*	0.95 ± 0.02	19 ± 8

[a] Synperiplanar (*sp*) and antiperiplanar (*ap*) from X-ray crystallographic data. [b] Fraction of synperiplanar (f_s) and *sp/ap* equilibrium ratio (K_{eq}) as determined by NOE studies in $CDCl_3$ (see Experimental Section and ref 1 for details); the model distances (a_1, s_1, a_4, s_4) used for the calculations are shown in Table IV. The same trend was observed in a parallel study of DMSO-d_6 solutions. [c] NOE ratio and experimental uncertainty limits. [d] Recrystallized from 2-propanol. Reference 14, mp 207–208 °C. [e] Crystals unsuitable for X-ray structure determination. [f] Reference 1. [g] Recrystallized from hexanes, ref 14, mp 163–165 °C. [h] Recrystallized from acetonitrile/water. Reference 14, mp 179–180 °C.

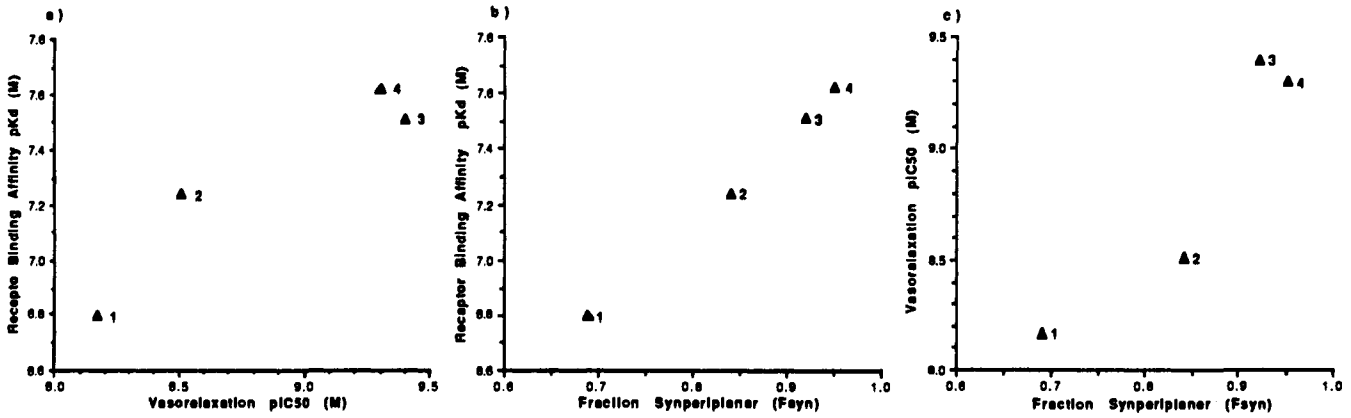


Figure 1. Graphs showing the correlation of receptor binding affinity and vasorelaxant activity (a) and the trends for increasing receptor binding affinity (b) and vasorelaxation (c) with increasing fraction of synperiplanar conformer in solution.

molecular orbital calculations (see Experimental Section for details). Comparisons of AM1-derived geometrical parameters with the sparser experimental values determined from X-ray data are acceptable (Tables III and IV). Otherwise, the fraction of synperiplanar rotamer in solution was determined for each of the (2′-halophenyl)-1,4-dihydropyridines 1–4 as previously described.[1] The data in Table I show increasing fraction of synperiplanar rotamer in solution with increasing size of the 2′-phenyl substituent, such that the rank order of fraction synperiplanar is 4 (I) > 3 (Br) > 2 (Cl) > 1 (F). The same trend is observed if we use the previous (or present) experimental values as model distances. This order and range of f_{syn} values have also been confirmed by NOESYSIM[20] calculations based on a two-rotamer model with a variable population parameter.

Table II. Vasorelaxant Activity and Receptor Binding Affinity of Test Compounds

			[^{3}H]NTP binding[a]	
no.	IC_{50},[b] nM	95% CI,[c] nM	K_d, nM	slope
1	6.8	4.3–10.6	159.2 ± 8.9	1.6 ± 0.1
2	3.1	1.4–7.2	56.9 ± 11.6	1.4 ± 0.2
3	0.4	0.2–0.8	31.1 ± 8.9	1.3 ± 0.1
4	0.5	0.3–0.8	24.0 ± 6.2	1.2 ± 0.1

[a] Radioligand–dihydropyridine receptor binding assay. [b] Vasorelaxant assay. [c] Ninety-five percent confidence interval for IC_{50}.

(9) The 4-(2,6-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid dimethyl ester was found to have an IC_{50} = 6 nM in the vasorelaxation assay and a k_d = 0.15 nM in the radioligand binding assay; unpublished results from our laboratory.

(10) Hartman, G. D.; Halczenko, W.; Phillips, B. T. *Abstracts of Papers*, 189th National Meeting of the American Chemical Society, Miami, FL; American Chemical Society: Washington, DC, 1985.

(11) Hartman, G. D.; Halczenko, W.; Phillips, B. T. *J. Org. Chem.* **1986**, *51*, 142.

(12) Claremon, D. A.; Hirshfield, J.; Lumma, P. K.; McClure, D. E.; Springer, J. P. *Syntheses* **1986**, 144.

(13) Baldwin, J. J.; Claremon, D. A.; Lumma, P. K.; McClure, D. E.; Rosenthal, S. A.; Winquist, R. J.; Faison, E. P.; Kaczorowski, G. J.; Trumble, M. J.; Smith, G. M. *J. Med. Chem.* **1987**, *30*, 690.

(14) Coburn, R. A.; Wierzba, M.; Suto, M. J.; Solo, A. J.; Triggle, A. M.; Triggle, D. J. *J. Med. Chem.* **1988**, *31*, 2103.

Table III. Experimental and Calculated Geometric Parameters of Compounds Tested

no.	conformer	source[a]	rms,[b] Å	d_N,[c] Å	d_C,[d] Å	θ,[e] deg
1	*sp*	AM1	0.001	0.146	0.249	21.04
	ap	AM1	0.000	0.082	0.205	26.36
2	*sp*	crys	0.001	0.131	0.342	14.37
		AM1	0.002	0.202	0.270	19.61
	ap	crys	0.002	0.102	0.212	29.29
		AM1	0.002	0.068	0.200	28.10
3	*sp*	crys	0.006	0.136	0.280	19.38
		AM1	0.001	0.139	0.237	21.45
	ap	AM1	0.001	0.022	0.124	33.44
4	*sp*	crys[f]	0.01	0.10	0.12	28
		AM1	0.000	0.134	0.250	20.03
	ap	AM1	0.001	0.002	0.088	36.82

[a] Parameters from molecular orbital calculation (AM1) or from crystal structures. [b] Root-mean-square deviation of atoms 2, 3, 5, and 6 from their least-squares plane. [c] Perpendicular displacement of N1 from the least-squares plane in the direction of the phenyl ring. [d] Analogous displacement of C4 from the least-squares plane. [e] Angle between C4–C1′ bond and the least-squares plane. [f] X-ray data insufficient to determine accurate geometric parameters.

Table IV. Experimental and Calculated Interproton Distances and Calculated Enthalpies of Formation

no.	conformer	source	H1–H6′,[a] Å	H4–H6′,[b] Å	ΔH_f,[c] kcal/mol
1	*sp*	AM1	3.507	3.811	−164.0
	ap	AM1	6.499	2.188	−161.5
2	*sp*	crys[d]	3.189	3.786	
		AM1	3.422	3.795	−123.7
	ap	crys[d]	6.478	2.212	
		AM1	6.487	2.148	−123.0
3	*sp*	crys[d]	3.368	3.758	
		AM1	3.469	3.779	−111.2
	ap	AM1	6.500	2.134	−110.5
4	*sp*	crys	*e*	*e*	
		AM1	3.394	3.778	−98.6
	ap	AM1	6.492	2.115	−97.4

[a] Assigned uncertainty limits[1] of ±0.16 Å for f_s calculation. [b] Assigned uncertainty limits of ±0.02 Å. [c] Calculated enthalpies of formation at 25 °C for AM1 optimized geometries. [d] Hydrogens added to the crystal structure at positions consistent with the corresponding AM1 optimized geometries (ref 1). [e] X-ray data insufficient to calculate hydrogen positions.

The vasorelaxant activity as determined in the rabbit aorta assay shows a trend toward increasing potency as the size of the 2′-halophenyl substituent increases, such that the rank order of vasorelaxant potency is 4 (I) ≥ 3 (Br) > 2 (Cl) > 1 (F). A similar trend was also observed for displacing [^{3}H]nitrendipine from its specific binding sites on guinea pig skeletal muscle (see data in Table II).

The data (Tables I and II) show that vasorelaxant potency, receptor binding affinity, and fraction of synperiplanar rotamer in solution for this set of 2′-halo-substituted phenyl-1,4-dihydropyridines (1–4) show the same trend with increasing size of the substituent. Although the data for any one of these compounds 1–4 does not support a significant energetic bias for the fraction of synperiplanar rotamer in solution, the trends observed for increasing receptor affinity and functional response (parts b and c, respectively, of Figure 1) with increasing fraction of synperiplanar rotamer in solution are consistent with this rotamer being the one recognized by and preferred at the calcium channel dihydropyridine binding site. The receptor apparently is able to accommodate an antiperiplanar 2′-substituted phenyl-1,4-dihydropyridine, as evidenced by the vasorelaxant activity and receptor binding[9] for the 2′,6′-dichloro analogue, but prefers the synperiplanar conformer.

In our previous study[1] of 2′-substituted 4-phenyl-1,4-dihydropyridine calcium entry blockers, an additional aromatic substituent was preferred at the 3′-position of the aromatic ring, relative to the 5′-position, for pharmacological potency. Using rigid analogues containing a covalent bridge between the phenyl and dihydropyridine rings, Hartman and co-workers[10,11] and Claremon and co-workers[12,13] have also provided evidence to support a preference at the receptor for a synperiplanar 3′-phenyl substituent. Taken together, results from the present study and from our previous study[1] on nonrigid (substituted phenyl)-1,4-dihydropyridine calcium channel blockers suggests that a 2′- and/or 3′-phenyl substituent is preferred in the synperiplanar orientation at the receptor.

Conclusion

We have examined a series of (2′-halophenyl)-1,4-dihydropyridine calcium channel blockers 1–4 for their solution conformation and for their ability to relax potassium-contracted rabbit aortic smooth muscle and to competitively displace [^{3}H]nitrendipine from its specific binding sites on guinea pig skeletal muscle. We are able to show a positive correlation between the vasorelaxant activity, the receptor binding affinity, and the fraction of synperiplanar rotamer in solution. These results are consistent with the synperiplanar rotamer of nonrigid unsymmetrically substituted phenyl-1,4-dihydropyridine calcium channel blockers being the receptor-bound conformation.

Experimental Section

Chemistry. Compounds employed in this study were prepared by standard methods in this laboratory and are referenced in Table I; spectral data, melting points, and microanalytical data are consistent with the assigned structures and referenced data. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL GSX-400 spectrometer and were referenced to internal TMS. Microanalyses of all compounds were within ±0.4% of the calculated values.

Crystal Structure Analyses. Crystal cell parameters and some details of data collection and refinement are summarized in Table V. Intensities were measured at 23 °C with the θ–2θ variable scan technique [Mo Kα radiation (λ = 0.710 69 Å)] and

(15) Walker, N.; Stuart, D. *Acta Crystallogr.* **1983**, *A39*, 159.
(16) Andersen, N. H.; Nguyen, K. T.; Eaton, H. L. *J. Magn. Reson.* **1985**, *63*, 365.
(17) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart J. J. P. *J. Am. Chem. Soc.* **1985**, *104*, 3902.
(18) Dewar Research Group; Stewart, J. J. P. *QCPE* **1986**, *6*, 506. This AMPAC program has been given several minor modifications. All calculations were carried out on VAX 11/750 and 11/785 computers at The Squibb Institute for Medical Research.
(19) Ferry, D. R.; Glossman, H. *FEBS Lett.* **1982**, *148*, 331.
(20) Andersen, N. H.; Lai, X.; Hammen, P. K.; Marschner, T. M. *NMR Application in Biopolymers*; Finley, et al., Eds.; Plenum Publ. Co.: New York, 1990; pp 95–134.

Table V. Crystal Data, Data Collection Parameters, and Refinement Parameters

	3 (EtOH)[a]	4 (MeCN/H_2O)[a]
formula	$C_{17}H_{18}NO_4Br \cdot H_2O$	$C_{17}H_{18}NO_4I$
a, Å	10.969 (1)	31.462 (8)
b, Å	13.883 (1)	11.709 (4)
c, Å	11.689 (2)	9.720 (3)
β, deg	95.07 (1)	90
V, Å^3	1766.7 (6)	3581 (3)
space group	$P2_1/n$	$Pbcn$
Z	4	8
D_{calcd}, g cm^{-3}	1.49	1.63
D_{obsd}, g cm^{-3}	1.50	1.61
μ, cm^{-1}	23.3	17.8
(min-max) transmission factors	0.63–1.34	0.58–1.34
NREF[b]	3499	3171
NOBS[c]	1470	987
NVAR[d]	218	97
R[e]	0.047	0.076
R_w	0.05	0.083

[a] Solvent of recrystallization. [b] Total number of symmetry independent measured reflections. [c] Total number of "observed" reflections with $I \geq 3\sigma(I)$ used for refinement. [d] Number of variables in least-squares refinement. [e] See ref 1 for further details of the analyses.

were corrected for Lorentz polarization factors and for absorption by the DIFABS[15] method. Although X-ray analysis of iodo analogue 4 clearly revealed a synperiplanar orientation of the iodine substituent in the crystal structure, the molecular geometry could not be precisely defined since the limited and relatively low quality diffraction data preclude extensive least-squares refinement.

Nuclear Magnetic Resonance Procedure. Proton NMR spectra were obtained at 400 MHz on a JEOL GSX-400 NMR spectrometer equipped with a 5-mm proton/broadband probe. All spectra used for quantitative analysis were run at 30 °C in deuteriochloroform with a transient (selective inversion) difference NOE protocol:[16]

$$\Delta\text{NOE} = \{[\text{RD} - {}^{s}\theta^{on} - \tau - {}^{ns}\theta - \text{Acq}(t_2)] - [\text{RD} - {}^{s}\theta^{off} - \tau - {}^{ns}\theta - \text{Acq}(t_2)]\}$$

using a relaxation delay (RD) of 6.7 s, an NOE buildup time (τ) of 1000 ms, and an acquisition time of 2.3 s. The selective pulse ($^{s}\theta$) corresponded to a 40-ms decoupler pulse at a power setting sufficient to produce a 180° flip angle. The nonselective pulse ($^{ns}\theta$) was set to 90°. NOE ratios (R) in Table I were calculated as previously described,[1] but reflect the greater precision available with newer instruments and probes.

Molecular Geometries, Calculations, and Error Analysis. The AM1 molecular orbital method[17,18] was used in all geometry optimizations, which were carried out as described in our previous study.[1] In that work, an overall picture emerged of 4-phenyl-1,4-dihydropyridines as intrinsically flexible molecules with respect to the geometrical relationship between the dihydropyridine (DHP) and phenyl rings. The variability of inter-ring geometry in available crystal structures was accordingly ascribed mainly to solid-state effects, and averaged geometrical parameters, with limits of uncertainty, were obtained from the crystallographic results. It was also established that similarly averaged AM1 geometrical parameters agreed very well with the averaged crystallographic values, albeit with a markedly smaller intrinsic spread.

In the present work, the amount of interaction between the phenyl and DHP rings has been directly affected by systematic variation of the 2′-halo substituent and some clear trends are evident in the AM1 results. Detailed crystallographic results, on the other hand, are available only for compounds **2** and **3**, so that averaging geometries is both unjustified and undesirable here. It is, however, reasonable to use AM1 proton–proton distances for individual conformers to calculate f_s (see eq 3 in ref 1) and to associate these with the uncertainty limits established for 2′-chloro compounds in our previous study.[1] The relevant details of molecular geometry are summarized in Tables III and IV.

Vasorelaxant Assay. The potency of the test compounds was determined as described previously[1] with two exceptions. First, cumulative concentration relaxation curves were obtained for **1**, **3**, and **4**. Force was allowed to decrease to a new steady-state force before the next increment in concentration of test compound. Noncumulative concentration relaxation curves were obtained for **2** as previously described.[1] Second, the IC_{50} values were determined from a quadration expression of the relationship between the logit transform response and the concentration of the test compound. These changes have only small effects on the calculated potency of analogous test compounds (data not shown).

Radioligand–Dihydropyridine Receptor Binding Assay. Male guinea pigs (350–450-g body weight) were sacrificed by placement in a saturated CO_2 atmosphere. The skin around the hind limbs was removed, and muscles (primarily quadriceps and gastrocnemius) were rapidly excised and placed in ice-cold 20 mM $NaHCO_3$ supplemented with 0.1 mM phenylmethanesulfonyl fluoride (PMSF). Membranes were prepared as described by Ferry and Glossman,[19] resuspended in 50 mM Tris·HCl buffer at a weight to volume ratio of 1:1 (original wet weight), snap frozen in acetone/dry ice, and stored at −70 °C until use.

On the day of the assay, the tissue was thawed and diluted 2-fold with 50 mM Tris·HCl. One hundred microliters of the ice-cold membrane solution (25–60 μg of protein) was added to 0.8–1.4 nM [^{3}H]nitrendipine from New England Nuclear (NET-741, 60–90 Ci/mmol) and the appropriate concentrations of competing drugs in a final volume of 250 μL of 50 mM Tris·HCl. The binding reaction was carried out in new disposable polypropylene tubes (Sarstedt no. 55.511), which were incubated in a water bath at 25 °C for 1 h starting immediately after addition of membrane suspension. At the end of the incubation, the samples were diluted 20-fold by addition of 5 mL of ice-cold 50 mM Tris·HCl buffer and rapidly filtered through Whatman GF/B filters by using the Brandel cell harvester MB-24. The filters were washed two times with 5 mL of 50 mM Tris·HCl and transferred to scintillation vials. Five milliliters of scintillation cocktail (OPTI-FLOUR, Packard) was added to each vial. Each sample was counted for 5 min in a Packard Tri-Carb 4640 scintillation counter. Specific binding of NTP was determined as the binding detectable in the absence ("total" binding) minus that in the presence of 2 μmol of unlabeled nifedipine ("nonspecific" binding). Specific binding routinely amounted to 80–90% of total binding.

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Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond distances, and bond angles for **3** and **4** (9 pages). Ordering information is given on any current masthead page.