Lipophilic 4-Isoxazolyl-1,4-dihydropyridines: Synthesis and Structure−Activity Relationships

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A series of 4-isoxazolyl-1,4-dihydropyridines bearing lipophilic side chains at the C-5 position of the isoxazole ring have been prepared. The calcium channel antagonistic activity of these compounds has been evaluated. A hypothetical model for binding of these compounds in the calcium channel is proposed, and the validity of this model is evaluated based on the SAR of this series of calcium binding, especially for the two most active derivatives, **1a**,**g**. The solid-state structure for the most active compound, **1a**, has also been determined, and its important features are reported.

Introduction

4-Aryl-1,4-dihydropyridines (DHPs) constitute an important class of calcium channel antagonists.[1] Several 1,4-dihydropyridine derivatives are widely used as therapeutic agents for the treatment of hypertension, angina, and other cardiovascular diseases. Synthetic interest in this class of compounds is an active area of research as new, more pharmacologically active, and tissue-selective agents are prepared.[2] The DHPs have also proven to be powerful probes of the molecular basis of antagonism and the site of action in the calcium channel.[3] We have found that bioisosteric replacement of the 4-aryl moiety with a 4-isoxazolyl group yields analogous 4-isoxazolyl-1,4-dihydropyridines (IDHPs) which retain potent calcium antagonist activity.[4] A major goal of our research is to prepare IDHPs with pharmacological activity equal to or greater than that of currently used therapeutic agents, such as nifedipine. Ideally, new drug developments arise from the detailed study of drug−receptor complexes both in the solid state (X-ray diffractometry) and in the solution phase (NMR spectroscopy). In the absence of such detailed information, drug development must proceed based on lead compounds and information on the nature of drug−receptor interactions gathered from the best-available methodology.

Photoaffinity labeling studies by Catterall and co-workers[3] using the 1,4-dihydropyridines [^{3}H]PN200-110, [^{3}H]azidopine, and diazepine have identified several binding domains in the α-1 subunit of L-type calcium channels near the extracellular end of the transmembrane segment 6 of the third and fourth membrane-spanning domains. Initially, these results conflicted with modeling studies carried out by Langs, Strong, and Triggle[5] and with the theoretical studies of Holtje and Marrer.[6] However, a more recent report from Triggle describing the use of permanently charged 1,4-DHPs and whole-cell patch clamp procedures to assay channel inhibition has seemingly reconciled some of these inconsistencies.[3c] The combined results of this experimental work indicate that the binding regions are within the channel and are closer to the extracellular membrane as opposed to the intracellular or cytoplasmic membrane. Kalasz et al. have also used photoaffinity labeling and localized the DHP binding site to S5−S6 linker peptides of repeats I, III, and IV.[7] Other recent studies by Tang and co-workers[3d] focused on using chimeric calcium channels created using the cardiac α-1 subunit as the parent protein and replacing specific segments with segments from the B1-2 calcium channel, which is insensitive to DHPs, to examine essential domains for DHP binding. Their results indicate that the S5−S6 linker in motif IV is critical for DHP action. Furthermore, their studies also indicate that several of the regions for binding determined by Catterall's photoaffinity labeling are not involved in the functional effects of DHPs, a conclusion speculated by Catterall's group.[3a] However, all of these studies indicate that there are DHP binding sites in the extracellular S5−S6 regions of motifs III and IV. Since different DHPs were used in each of these studies, it is conceivable that the structural differences in the calcium antagonists give rise to differential binding sites.

Herein we propose a model for DHP binding which attempts to reconcile some of the differences in the binding models discussed above. Catterall's photoaffinity study using PN200-110 with the photolabile group attached to the 4-aryl moiety shows the major binding site to be IIIS6. When the covalent affinity label was placed on the ester group, the major binding site was on the loop connecting IIIS5 and IIIS6. In the Tanabe primary sequence of the α-1 subunit, there is a tryptophan residue (Tryp 1016) located midway on this loop.[8] In the theoretical study by Holtje and Marrer, a strong interaction was proposed between a tryptophan and the port side ester of DHPs.[6] Solution-phase and solid-state studies have shown the 1,4-dihydropyridine ring to be in a flattened boat conformation with the 4-aryl group in the pseudoaxial position. The common nomenclature adopted for these compounds places the NH at the stern of the boat and the 4-aryl moiety at the bow.

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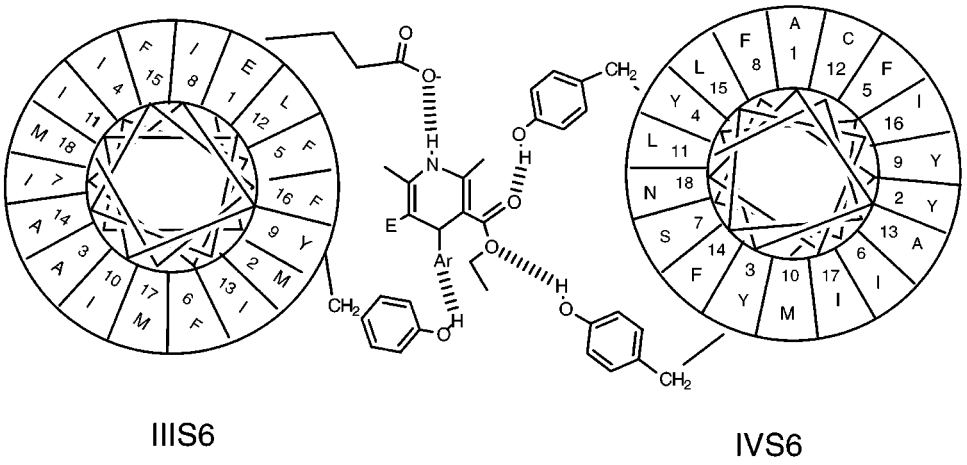
Scheme 1. Edmundson Helical Wheel Representation of the Binding Model, Based on Covalent Affinity Labeling Data, of the Hypothetical Role of the IVS6 Portion of the Calcium Channel in DHP Binding[a]



[a] The IVS6 is positioned to interact with the starboard ester functional group of the DHP.

Construction of a Working Binding Model

Langs, Strong, and Triggle carried out modeling studies which indicated that there may be important H-bond interactions between the ester groups and arginine residues which are separated by two amino acids. This sequence (Arg-X-X-Arg) is repeated 10 times in the S4 strands.[5] However, Catterall's studies do not show binding on the S4 strand. The IIIS6 strand does have the tryptophan residue and a glutamic acid residue (1040) positioned in such a way that the dihydropyridine NH can hydrogen bond to the glutamic acid and the port side ester to the tryptophan. This positions the DHP ring down with respect to the transmembrane strand.

A correlation between the flatness of the DHP boat conformation in the solid state and the binding affinity of the DHP derivatives was recognized by Triggle.[9] It has been postulated that this correlation relates to the forward presentation of the 4-aryl moiety. The current model provides an explanation for this observation: The binding site on the IIIS6 has two phenylalanines (1044 and 1045) which form a pocket between the roof of the binding site at Glu 1040 and the floor of the binding site at Tyr 1048. Thus, the flatter the DHP ring the more it presents the 4-aryl group forward making it easier for it to stretch between the two hydrogen-bonding receptor groups. There is also the potential for donor−acceptor type interactions between the electron-rich phenylalanines and the electron-poor isoxazole moiety. A schematic representation of the hypothetical binding of IDHPs within the calcium channel is shown in Scheme 1.

The interaction of the IVS6 is envisioned as a hydrogen-bonding interaction with the starboard ester, since the amino acid sequence of the IVS6 places three hydrogen-bonding residues (Tyr 1359, Tyr 1360, and Ser 1363) at approximately the right transmembrane height for interaction with an adjacent IIIS6-bound IDHP shown in Figure 1. Our model illustrates how the interaction of multiple functional groups is critical for drug−receptor binding. In our current model, the C-5 position of the isoxazole is postulated to be pointed "down" or *O-exo* when binding to the IIIS6 strand. The amino acid sequence of IIIS6 continues from residue Tyr 1048 as an α-helix until residue 1061, with the sequence

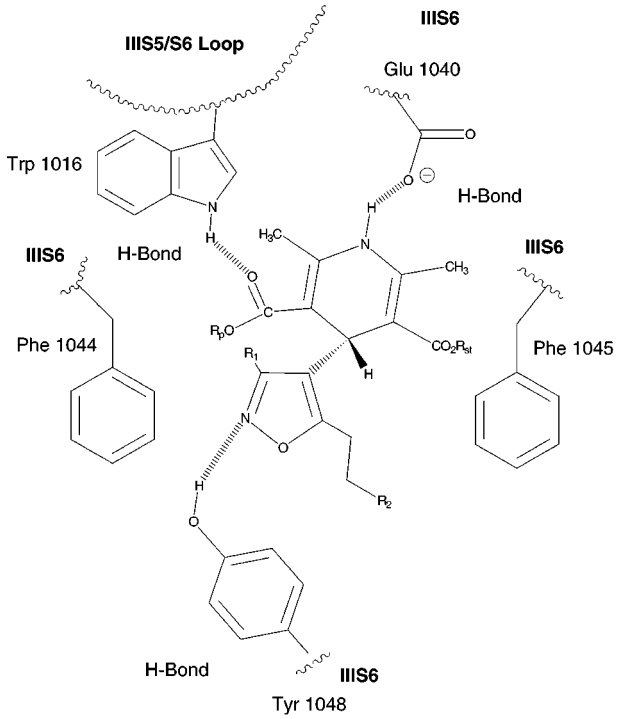
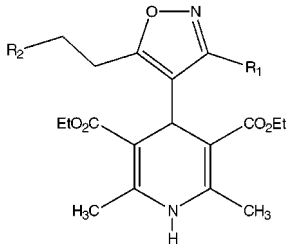


Figure 1. Hypothetical binding interactions of a 4-isoxazolyl-1,4-dihydropyridine to the IIIS6 membrane-bound strand of the calcium channel.

I-I-L-I-A-F-F-M-M-N-I-F-V. The helix should turn four amino acid residues later, and the residues placed on the same side of the α-helix would be I-A-F-F, a very lipophilic pocket. Examination of molecular models indicates that lipophilic aromatic substituents attached to the C-5 position of the isoxazole ring could be properly oriented to interact with the lipophilic pocket of our hypothesized channel. Furthermore, the pocket contains two electron-rich phenylalanine residues which may be able to undergo donor−acceptor type interactions with an electron-poor substituent such as a halo-substituted aryl ring. A final consideration is how the size of the lipophilic group will affect binding.

At the time this work was performed no crystal structure for the calcium channel was yet reported. After the completion of our work the X-ray structure of

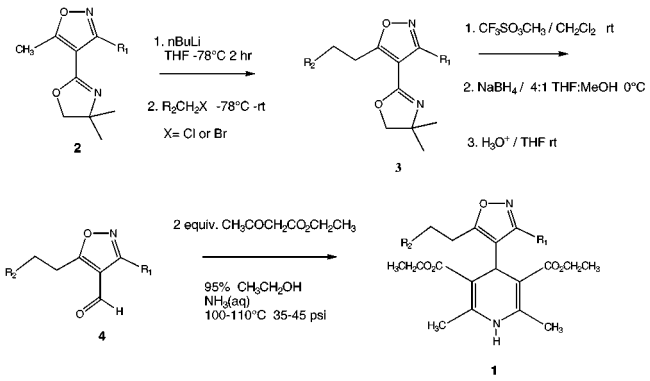
Table 1. Lipophilic IDHPs



1

entry	R_1	R_2, aryl group
1a	Me	1-naphthyl
1b	Me	2-naphthyl
1c	Me	4-biphenylyl
1d	Me	2-biphenylyl
1e	Me	phenyl
1f	phenyl	phenyl
1g	Me	*m*-Br-phenyl
1h	Me	*m*-MeO-phenyl

Scheme 2. Synthesis of Isoxazolyldihydropyridines Bearing Lipophilic Aryl Substituents



the potassium channel was reported, which is analogous in many respects to the calcium channel.[16] A prominent feature of the potassium channel's ion pore is that (1) the extracellular end of the pore contains many hydrogen-bonding residues and (2) the intracellular end of the pore is highly lipophilic. In addition, Catterall has recently reported site-directed mutagenesis studies.[17] In his study, Y1048F and Y1048A substitutions resulted in the conclusion that Y1048 is essential to DHP binding, in accordance with our current hypothesis. Thus, the information to date is consistent with our own hypothesis.

Chemistry

To test our hypothesis, we have prepared a series of IDHPs bearing lipophilic substituents at the C-5, or lateral, position of the isoxazole ring (**1a**−**f**, Table 1). We also prepared two compounds to examine whether an electron-rich or electron-poor aryl ring will affect binding affinity (**1g**,**h**, Table 1). The general synthetic route for these compounds involves lateral metalation followed by electrophilic quenching of the oxazoline-protected isoxazole **2**, Scheme 2, using methodology extensively employed in our laboratories.[10] Deprotection is smoothly accomplished by quaternization of the oxazoline nitrogen, followed by $NaBH_4$ reduction and mild acid hydrolysis to give the aldehydes **4**, Scheme 2. The aldehydes are then subjected to Hantzsch pyridine synthesis conditions in an aerosol dispersion tube at elevated pressure and temperature to give the IDHPs **1a**−**h**, in low to modest yields, Scheme 2. The low yields of IDHPs may be due to the large steric bulk and rotational mobility of the lipophilic substituents that hinder approach to the aldehyde group by the ethyl acetoacetate anion.

Table 2. Displacement of [^{3}H](+)-PN200-110 Binding by IDHPs in Rat Cardiac Membranes

compd	K_i (M), mean ± SEM	n_H, mean ± SEM
1a	$2.16 \pm 0.43 \times 10^{-9}$	1.09 ± 0.03
1b	$1.07 \pm 0.16 \times 10^{-8}$	0.93 ± 0.07
1c	$8.69 \pm 1.15 \times 10^{-9}$	0.81 ± 0.03
1d	$4.55 \pm 0.39 \times 10^{-8}$	0.84 ± 0.05
1e	$2.49 \pm 0.32 \times 10^{-8}$	1.1 ± 0.06
1f	$5.53 \pm 0.91 \times 10^{-8}$	0.83 ± 0.04
1g	$5.63 \pm 0.68 \times 10^{-9}$	0.90 ± 0.03
1h	$3.04 \pm 0.43 \times 10^{-8}$	1.13 ± 0.08

Table 3. Displacement of [^{3}H](+)-PN200-110 Binding by IDHPs in Guinea Pig Cardiac Membranes

compd	K_i (M), mean ± SEM	n_H, mean ± SEM
1a	4.11×10^{-9}	1.13
1b	2.02×10^{-8}	1.06
1c	1.82×10^{-8}	1.10
1d	9.11×10^{-8}	0.95
1e	$2.29 \pm 0.13 \times 10^{-8}$	1.06 ± 0.06
1f	$7.29 \pm 0.16 \times 10^{-8}$	0.90 ± 0.03
1g	6.89×10^{-9}	1.02
1h	3.95×10^{-8}	1.36

Results and Discussion

The results of biological evaluation of these compounds are given in Tables 2 and 3. The radioligand binding assays were carried out as previously described.[11−13] A brief general description is given in the Supporting Information. Several important features of the biological activity stand out. All of the lipophilic compounds exhibit high binding affinity, the 1-naphthyl derivative **1a** being the most potent IDHP prepared and evaluated to date. Another interesting feature is that the *m*-bromophenyl derivative **1g** is approximately 5 times more active than the derivative bearing the electron-donating methoxy substituent, **1h**. This indicates that the electron-rich character of the lipophilic pocket containing the two phenylalanine groups may indeed increase the binding affinity for the electron-poor derivative over the electron-rich compound.

The crystal structure for the most active derivative, **1a**, is shown in Figure 2, showing the thermal ellipsoids and proper numbering scheme. Important torsion angles for **1a** are listed in Table 4; crystallographic data, bond distances and angles, atomic coordinates, and anisotropic thermal parameters can be found in the Supporting Information. The crystal structure shows the isoxazole ring to be in the *O-endo* conformation with the largest group positioned over the DHP ring. We attribute this conformation to crystal packing forces. It has long been accepted that the larger substituent on the 4-aryl ring points away from the dihydropyridine nitrogen in the efficacious conformer. We have previously reported that the barrier to rotation about the dihydropyridine−isoxazole bond is on the order of 20−40 kJ, and thus ready conformational interconversion is expected in the presence of a receptor.[15] The value for $\Sigma|\rho|$ is 71.5° and

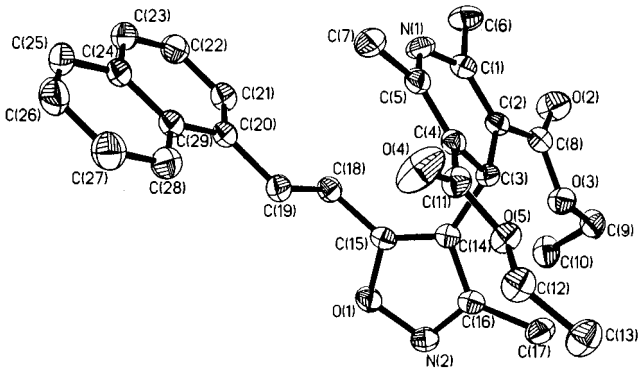


Figure 2. Single-crystal X-ray diffractometry structure for IDHP **1a**.

Table 4. Important Torsion Angles for **1a**

angle	deg
$N_1C_1C_2C_3$	4.3 (3)
$C_1C_2C_3C_4$	−18.6 (2)
$C_2C_3C_4C_5$	20.3 (2)
$C_3C_4C_5N_1$	−7.6 (3)
$C_4C_5N_1C_1$	−9.5 (3)
$C_5N_1C_1C_2$	11.2 (3)
$C_1C_2C_3C_{14}$	106.2 (2)
$C_5C_4C_3C_{14}$	−106.0 (2)

for $\Sigma|\tau|$, 106.1°. The former value is indicative of the planarity of the DHP ring which influences the binding affinity.[9] It is defined as the absolute value of the six intra-ring torsion angles. This value can be compared to the corresponding $\Sigma|\rho|$ value for nifedipine of 72.1°. The value $\Sigma|\tau|$ is a measure of how close the two rings are to perfectly bisecting one another. Finally, the solid-state structure shows both of the esters to be in the synperiplaner orientation with respect to the dihydropyridine C−C double bond.

Conclusion

The biological activity for this series of compounds is consistent with our hypothesis about the site and nature of IDHP binding in the calcium channel. Our rationale for the observation that the 1-naphthyl derivative is the most potent in this series, based on examination of molecular models, is that this derivative can slip into the hypothetical lipophilic pocket more readily than the 2-naphthyl or either biphenyl derivative. In the case of the biphenyl derivatives, it appears that their increased size may prevent them from fitting into the pocket while still allowing for the other binding interactions such as H-bonding to be optimum. The greater activity of the *m*-bromophenyl compound **1g** over that of the *m*-methoxyphenyl **1h** and the two unsubstituted phenyl derivatives **1e,f** may indicate that the electronic nature of the aryl ring is very influential on binding affinity. This result also supports our hypothesis that the lipophilic pocket plays a role in the binding of IDHPs of this type since it contains electron-rich phenylalanine residues which would tend to interact more strongly with an electron-poor aryl group. That lipophilicity can contribute to enhanced calcium channel binding is dramatically illustrated by the three-dimensional shape of the analogous potassium channel.[16] An important aspect of this structure is the overall cone shape of the channel, resulting in part from the interactions in the hydrophobic lining of the intracellular end of the channel. Finally, the site-directed mutagenesis work of Catterall supports the central focus of our working hypothesis, an essential role for Y1048 in DHP binding.[17] Furthermore, most of the amino acid residue perturbations found to affect DHP binding are in proximity to our proposed binding site. Whether these exert their effect on DHP binding by direct interaction with the DHP or by their effect on channel conformation, is a question which may be answered by the study of new synthetic analogues. Efforts are underway in our laboratory to further test our hypothesis and to obtain a better understanding of what factors are most important for isoxazolyldihydropyridine activity.

Experimental Section

All reagents used were purchased from Aldrich Chemical Co. and used without purification unless otherwise indicated, or prepared as described below. Solvents were reagent grade and dried just prior to use by standard methods. Melting points were determined in open capillary tubes on a Melt-Temp apparatus and are uncorrected. Radial chromatography was performed on a Harrison Associates chromatotron. Flash chromatography was performed using Baker flash gel using in house compressed air. All chromatography solvents were distilled prior to use. NMR spectra were recorded on a Bruker AC200 (200 MHz ^{1}H, 50 MHz ^{13}C) or an IBM Bruker AF300 (300 MHz ^{1}H, 75 MHz ^{13}C) spectrometer at ambient temperature in $CDCl_3$. Chemical shifts are reported as ppm (δ) downfield from an internal tetramethylsilane (TMS) standard. Mass spectra were obtained on a VG Micromass 70/70 HS mass spectrometer using EI or CI as indicated. Combustion analyses were performed by Desert Analytics, Tucson, AZ.

4-(4′,5′-Dihydro-4′,4′-dimethyl-Δ^2-oxazolin-2-yl)-3,5-dimethylisoxazole, **2**,[19] and 4-(4′,5′-dihydro-4′,4′-dimethyl-Δ^2-oxazolin-2-yl)-5-methyl-3-phenylisoxazole, **3f**,[19] were prepared according to literature procedures.

1-(Chloromethyl)naphthalene. A 250-mL flask with stir bar and 75 mL of concentrated HCl was cooled to 0 °C, and 1-naphthalenemethanol (1.10 g, 6.95 mmol) was added slowly with stirring. The mixture was allowed to stir uncovered and slowly warm to room temperature for 10 h, by which time the solid had been replaced by an oil suspended in the HCl. The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined CH_2Cl_2 layers were washed with water until the aqueous layers were neutral by Hydrion paper (3 × 25 mL) and then brine (1 × 25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to give 1.18 g as a light-yellow oil (97% crude yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.07 (s, 2H, CH_2Cl_2) 7.42−7.68 (m, 4H, Ar−H) 7.90 (t, 2H, Ar−H) 8.20 (d, 1H, ipso Ar H).

2-(Chloromethyl)naphthalene. A solution of 2-naphthalenemethanol in 25 mL of CH_2Cl_2 was added with stirring to 100 mL of cold (0 °C) concentrated HCl. The mixture was allowed to warm to room temperature over the course of 1 h. The layers were separated, and the HCl was extracted with CH_2Cl_2 (2 × 25 mL). Combined CH_2Cl_2 layers were washed with water until the aqueous extracts were neutral by Hydrion paper (3 × 25 mL) and brine (1 × 25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to give a light-yellow solid which was Kugelrohr distilled (0.05 mmHg, 160−180 °C) to give 2.247 g as a white powder (80%): ^{1}H NMR (200 MHz) δ 4.76 (s, 2H, CH_2) 7.45−7.53 (m, 3H, Ar H) 7.83−7.87 (m, 2H, Ar H).

General Procedure for Preparation of Compounds 3a−h. 4-(4′,5′-Dihydro-4′,4′-dimethyl-Δ^2-oxazolin-2-yl)-5-(1-naphthylethyl)-3-methylisoxazole (3a). To a stirred solution of 4-(4′,5′-dihydro-4′,4′-dimethyl-Δ^2-oxazolin-2-yl)-3,5-dimethylisoxazole, **2** (2.17 g, 11.1 mmol), in 100 mL of dry THF cooled to −78 °C under N_2 was added 1.05 equiv of 1.5 M ^{n}BuLi (7.9 mL). The yellow solution was stirred at −78 °C for 2 h. Then a solution of 1.05 equiv of 1-(chloromethyl)naphthalene (2.08 g, 11.8 mmol) in dry THF (15 mL) was added dropwise

and the mixture stirred at −78 °C for 30 min. The mixture was allowed to warm to room temperature and the solvent removed under vacuum to give a brown oil. The crude product was dissolved in CH_2Cl_2 (30 mL), washed with water (2 × 20 mL) brine (1 × 20 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The crude product was Kugelrohr distilled (0.05 mmHg, 150−170 °C) to give 3.15 g of a light-yellow solid (85%): mp 74−76 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (s, 2, 6H, oxazoline Me) 2.44 (s, 3H, isoxazole Me) 3.45 (s, 4H, CH_2CH_2) 3.85 (s, 2H, oxazoline CH_2) 7.31−7.54 (m, 4H, Ar−H) 7.70−7.83 (m, 2H, Ar−H) 8.25 (d, 1H, ipso Ar−H). Anal. ($C_{21}H_{22}N_2O_2$) C, H, N.

4-(4′,5′-Dihydro-4′,4′-dimethyl-Δ²-oxazolin-2-yl)-5-(2-naphthylethyl)-3-methylisoxazole (3b): 80% yield; mp 86−88 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (s, 6H, oxazoline Me) 2.42 (s, 3H, isoxazole Me) 3.12−3.20 (m, 2H, CH_2CH_2) 3.37−3.45 (m, 2H, CH_2CH_2) 3.89 (s, 2H, oxazoline CH_2) 7.30−7.46 (m, 3H, Ar−H) 7.62 (br s, 1H, Ar−H) 7.73−7.81 (m, 3H, Ar−H). Anal. ($C_{21}H_{22}N_2O_2$) C, H, N.

4-(4′,5′-Dihydro-4′,4′-dimethyl-Δ²-oxazolin-2-yl)-5-(4-biphenylethyl)-3-methylisoxazole (3c): 84% yield; mp 84−86 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.3 (s, 6H, oxazoline Me) 2.49 (s, 3H, isoxazole Me) 3.09 (t, 2H, J = 6 Hz) 3.4 (t, 2H, J = 6 Hz) 3.96 (s, 2H, oxazoline CH_2) 7.27−7.62 (m, 9H, Ar H). Anal. ($C_{23}H_{24}N_2O_2$) C, H, N.

4-(4′,5′-Dihydro-4′,4′-dimethyl-Δ²-oxazolin-2-yl)-5-(2-biphenylylethyl)-3-methylisoxazole (3d): 83% yield; mp 68−70 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (s, 6H, oxazoline Me) 2.40 (s, 3H, isoxazole Me) 2.99−3.04 (m, 2H, CH_2CH_2) 3.12−3.18 (m, 2H, CH_2CH_2) 3.85 (s, 2H, oxazoline CH_2) 7.20−7.43 (m, 9H, Ar H). Anal. ($C_{23}H_{24}N_2O_2$) C, H, N.

4-(4′,5′-Dihydro-4′,4′-dimethyl-Δ²-oxazolin-2-yl)-5-(phenylethyl)-3-methylisoxazole (3e): 92% yield; mp 34−38 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30 (s, 6H, oxazoline Me) 2.43 (s, 3H, isoxazole Me) 3.00 (t, 2H, J = 6 Hz, CH_2CH_2) 3.32 (t, 2H, J = 6 Hz, CH_2CH_2) 3.93 (s, 2H, oxazoline CH_2) 7.14−7.31 (m, 5H, Ar H).

4-(4′,5′-Dihydro-4′,4′-dimethyl-Δ²-oxazolin-2-yl)-5-(*m*-bromophenylethyl)-3-methylisoxazole (3g): 82% yield as a pale-yellow liquid after Kugelrohr distillation (140−150 °C, 0.05 mmHg); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (s, 6H, oxazoline Me) 2.38 (s, 3H, isoxazole Me) 2.92 (t, 2H, J = 7.5 Hz, CH_2CH_2) 3.27 (t, 2H, J = 7.5 Hz, CH_2CH_2) 3.91 (s, 2H, oxazoline CH_2) 7.04 (br s, 2H, Ar H) 7.26−7.32 (m, 2H, Ar H).

4-(4′,5′-Dihydro-4′,4′-dimethyl-Δ²-oxazolin-2-yl)-5-(*m*-methoxyphenylethyl)-3-methylisoxazole (3h): 85% yield as a pale-yellow viscous liquid after Kugelrohr distillation (140−150 °C, 0.02 mmHg); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (s, 6H, oxazoline Me) 2.41 (s, 3H, isoxazole Me) 2.92−3.0 (m, 2H, CH_2CH_2) 3.26−3.34 (m, 2H, CH_2CH_2) 3.75 (s, 3H, CH_3O−Ar) 3.92 (s 2H, oxazoline CH_2) 6.71−6.78 (m, 3H, Ar H) 7.13−7.23 (m, 1H, Ar H).

General Procedure for Preparation of Compounds 1a−h. Diethyl 2,6-Dimethyl-4-(5-[1-naphthylethyl]-3-methylisoxazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylate (1a). To a stirred solution of **3a** (2.91 g, 8.7 mmol) in 75 mL of dry CH_2Cl_2 was added 1.6 mL (2.32 g, 14.0 mmol) of $CF_3SO_3CH_3$, and the mixture stirred under N_2 until TLC (silica, 80% hexane, 20% ETOAc) showed only baseline material. The mixture was cooled to 0 °C, and a solution of 605 mg (16 mmol) of $NaBH_4$ in 20 mL of 4:1 THF:MeOH was added in one portion. This mixture was stirred at 0 °C for 30 min. Then 5 mL of saturated NH_4Cl was added and the mixture allowed to warm to room temperature. Ether, 50 mL, was added, and the layers were separated. The ether layer was washed with saturated NaCl (1 × 25 mL). The combined aqueous layers were extracted with CH_2Cl_2 (1 × 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to give an orange oil. The crude product was hydrolyzed with 15 mL of 1 M aqueous HCl in 20 mL of 4:1 THF:H_2O. The reaction mixture was poured into 50 mL of ether, and the layers were separated. The ether layer was washed with saturated $NaHCO_3$ (3 × 25 mL). Combined aqueous layers were extracted with CH_2Cl_2 (1 × 25 mL) and the combined organic layers dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude aldehyde as a yellow oil. The aldehyde was purified by flash chromatography (silica gel, 80% hexane, 15% ETOAc, 5% CH_2Cl_2) to give 1.01 g as a pale-yellow oil (44%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.40 (s, 3H, isoxazole Me) 3.30−3.45 (m, 4H, CH_2CH_2) 7.13−7.96 (m, 7H, Ar−H) 9.52 (s, 1H, aldehyde H).

The aldehyde 1.01 g (3.82 mmol) was dissolved in ethanol (10 mL) and transferred to an aerosol dispersion tube to which ethyl acetoacetate (995 mg, 7.65 mmol) and aqueous ammonia (6 mL, 28.7%) were added. The mixture was heated to 100−110 °C for 48 h, the pressure rising to 30−40 psi. After cooling the solvents were removed under vacuum to give a brown oil. The crude product was purified by flash chromatography (silica gel, 4:2:1 hexane:EtOAc:CH_2Cl_2) and crystallization by slow diffusion of hexane into a benzene−ethanol solution of the product. This gave 50 mg of pale-yellow crystals (8%): mp 156−158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (t, 6H, C*H*$_3$-CH_2O-, J = 7.1 Hz) 2.14 (s, 6H, DHP-Me) 2.29 (s, 3H, isoxazole Me) 3.06−3.11 (m, 2H, CH_2CH_2) 3.36 (m, 2H, CH_2CH_2) 4.01−4.12 (m, 4H, CH_3CH_2O-) 4.92 (s, 1H, C*H*) 5.8 (br s, 1H, N*H*) 7.30−7.51 (m, 4H, Ar−H) 7.7 (d, 1H, Ar−H, J = 7.9 Hz) 7.83 (d, 1H, Ar−H, J = 7.2 Hz) 8.13 (d, 1H, ipso Ar−H, J = 8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.2, 14.4, 19.4, 26.9, 29.1, 30.3, 59.9, 101.7, 120.2, 123.7, 125.5, 125.6, 126.9, 128.8, 131.8, 133.9, 137.3, 143.2, 159.8, 167.3, 168.8; MS (EI) 488. Anal. Calcd for $C_{29}H_{32}N_2O_5$: C, 71.29; H, 6.60; N, 5.73. Found: C, 71.38; H, 6.46; N, 5.39.

Diethyl 2,6-Dimethyl-4-(5-[2-naphthylethyl]-3-methylisoxazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylate (1b). From 3.15 g (9.4 mmol) of **3b**, 340 mg (13.7%) of purified aldehyde was obtained: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.04 (s, 3H, isoxazole Me) 3.14−3.20 (m, 2H, CH_2CH_2) 3.31−3.36 (m, 2H, CH_2CH_2) 7.24−7.78 (m, 7H, Ar−H) 9.68 (s, 1H, aldehyde-H). The aldehyde (340 mg, 1.28 mmol) was dissolved in 4 mL of ethanol and transferred to an aerosol dispersion tube to which ethyl acetoacetate (334 mg, 2.56 mmol) and aqueous ammonia (3 mL, 28.7%) were added. The mixture was heated to 100−110 °C (30−40 psi) for 48 h. The solvent was removed and the crude brown oil purified as described for **1a**. This gave 52.1 mg as pale-yellow crystals (9%): mp 174−175 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, 6H, C*H*$_3$CH$_2$O-, J = 7.1 Hz) 2.22 (s, 6H, DHP-Me) 2.30 (s, 3H, isoxazole Me) 3.04−3.08 (m, 4H, CH_2CH_2) 4.02−4.13 (m, 4H, CH_3CH_2O-) 4.92 (s, 1H, C*H*) 5.87 (br s, 1H, N*H*) 7.26−7.81 (m, 7H, Ar−H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.2, 14.4, 19.4, 27.6, 29.1, 33.5, 59.9, 101.8, 120.4, 125.3, 126.2, 126.9, 127.5, 127.6, 128.0, 132.1, 133.6, 138.7, 143.2, 159.8, 167.3, 168.7; MS (EI) 488. Anal. Calcd for $C_{29}H_{32}N_2O_5$: C, 71.29; H, 6.60; N, 5.73. Found: C, 71.03; H, 6.41; N, 5.47.

Diethyl 2,6-Dimethyl-4-(5-[4-biphenylylethyl]-3-methylisoxazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylate (1c). From 1.23 g (3.4 mmol) of **3c**, 260 mg (26%) of purified aldehyde was obtained: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3H, Me) 3.05−3.10 (m, 2H, CH_2CH_2) 3.29−3.34 (m, 2H, CH_2-CH_2) 7.19−7.56 (m, 9H, Ar−H) 9.71 (s, 1H, aldehyde-H). The aldehyde (260 mg, 0.89 mmol) was dissolved in ethanol (5 mL) and transferred to an aerosol dispersion tube to which ethyl acetoacetate (234.8 mg, 1.8 mmol) and aqueous ammonia (4 mL, 28.7%) were added. The mixture was heated to 100−110 °C (30−40 psi) for 48 h. The solvents were removed, and the crude product was purified as described above. This gave 19 mg as white crystals (4%): mp 132−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, 6H, C*H*$_3$CH$_2$O-, J = 7.1 Hz) 2.26 (s, 6H, DHP-Me) 2.30 (s, 3H, isoxazole Me) 2.99 (br s, 4H, CH_2-CH_2) 4.07−4.12 (m, 4H, CH_3CH_2O-) 4.93 (s, 1H, C*H*) 5.7 (br s, 1H, N*H*) 7.26−7.6 (m, 9H, Ar−H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.2, 14.5, 19.6, 27.6, 29.2, 32.9, 59.9, 101.9, 120.3, 127.1, 127.2, 128.6, 128.7, 139.1, 140.3, 141.0, 143.1, 159.8, 167.3, 168.7; MS (EI) 514. Anal. Calcd for $C_{31}H_{34}N_2O_5$: C, 72.35; H, 6.66; N, 5.44. Found: C, 72.28; H, 6.79; N, 5.22.

Diethyl 2,6-Dimethyl-4-(5-[2-biphenylylethyl]-3-methylisoxazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylate (1d). From 4.89 g of **3d**, was obtained 0.70 g of purified

aldehyde (18%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.35 (s, 3H, isoxazole Me) 3.00−3.05 (m, 4H, CH_2CH_2) 7.15−7.39 (m, 9H, Ar−H) 9.30 (s, 1H, aldehyde-H). The aldehyde (700 mg, 2.40 mmol) was dissolved in 5 mL of ethanol and transferred to an aerosol dispersion tube to which ethyl acetoacetate (625 mg, 4.80 mmol) and aqueous ammonia (5 mL, 28.7%) were added. The mixture was heated to 100−110 °C (30−40 psi). The solvents were removed, and the product was purified as described above. This gave 148.2 mg as white crystals (12%): mp 158−160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (t, 6H, J = 7.1 Hz, C*H*$_3$CH$_2$O) 2.21 (s, 6H, DHP-Me) 2.24 (s, 3H, isoxazole Me) 2.83−2.95 (m, 4H, CH_2CH_2) 3.99−4.11 (m, 4H, CH$_3$C*H*$_2$O) 4.88 (s, 1H, C*H*) 5.82 (s, 1H, N*H*) 7.23 (m, 9H, Ar−H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.2, 14.4, 19.4, 26.9, 29.1, 30.3, 59.8, 101.7, 119.9, 126.1, 126.9, 127.5, 128.2, 128.6, 129.1, 130.2, 138.5, 141.5, 141.9, 143.1, 159.6, 167.2, 168.7; MS (EI) 514. Anal. Calcd for $C_{31}H_{34}N_2O_5$: C, 72.35; H, 6.66; N, 5.44. Found: C, 72.08; H, 6.46; N, 5.39.

Diethyl 2,6-Dimethyl-4-(5-[phenylethyl]-3-methylisoxazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylate (1e). From 2.36 g (8.32 mmol) of **3e** was obtained 805.5 mg of purified aldehyde (45%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.42 (s, 3H, isoxazole Me) 2.89−3.10 (m, 4H, CH_2CH_2) 7.13−7.25 (m, 5H, Ar−H) 9.62 (s, 1H, aldehyde-H). The aldehyde (801 mg, 3.7 mmol) was dissolved in 6 mL of ethanol and transferred to a 20-mL round-bottom flask, to which ethyl acetoacetate (963 mg, 7.4 mmol) and aqueous ammonia (3 mL, 28.7%) were added. The mixture was refluxed for 48 h. The solvents were removed under vacuum, and the crude product was crystallized by slow diffusion of hexane into a 10:1 benzene:MeOH solution. This gave 243 mg as white crystals (15%): mp 180−182 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, 6H, J = 7.1 Hz, C*H*$_3$-CH$_2$O) 2.49 (s, 6H, DHP-Me) 2.30 (s, 3H, isoxazole Me) 2.92 (br s, 4H, CH_2CH_2) 4.03−4.16 (m, 4H, CH$_3$C*H*$_2$O) 4.91 (s, 1H, C*H*) 5.74 (br s, 1H, N*H*) 7.18−7.31 (m, 5H, Ar−H); ^{13}C NMR (75 MHz, $CDCl_3$) d 10.1, 14.4, 19.3, 27.6, 29.1, 33.2, 59.8, 101.6, 120.4, 126.1, 128.1, 141.1, 143.4, 159.8, 167.3, 168.8; MS (EI) 438. Anal. Calcd for $C_{25}H_{30}N_2O_5$: C, 68.47; H, 6.89; N, 6.38. Found: C, 68.33; H, 6.86; N, 6.46.

Diethyl 2,6-Dimethyl-4-(5-[phenylethyl]-3-phenylisoxazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylate (1f). From (3.9 g, 11.2 mmol) **3f** was obtained 1.24 g of purified aldehyde (40%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.32−3.50 (m, 4H, CH_2-CH_2) 7.20−7.69 (m, 10H, Ar−H) 9.83 (s, 1H, aldehyde-H). The aldehyde (1.20 g, 4.3 mmol) was dissolved in 7 mL of isopropyl alcohol and transferred to a 25-mL round-bottom flask to which ethyl acetoacetate (1.12 g, 8.6 mmol) and aqueous ammonia (5 mL, 28.7%) were added. The mixture was refluxed for 36 h, after which time the solvent was removed. The crude product was crystallized by slow diffusion of petroleum ether into a bezene solution. This gave 172 mg of white crystals (8%): mp 127−129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (t, 6H, J = 7.1 Hz, C*H*$_3$CH$_2$O) 1.95 (s, 6H, DHP-Me) 3.06−3.20 (m, 4H, CH_2CH_2) 3.88−4.14 (m, 4H, CH$_3$C*H*$_2$O) 5.11 (s, 1H, C*H*) 5.15 (s, 1H, N*H*) 7.20−7.45 (m, 10H, Ar−H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 14.4, 19.2, 29.4, 33.159.7, 101.2, 119.2, 126.1, 127.6, 128.1, 128.2, 128.4, 129.5, 131.0, 141.3, 143.6, 163.5, 167.3, 168.4; MS (EI) 500. Anal. Calcd for $C_{30}H_{32}N_2O_5$: C, 71.98; H, 6.44; N, 5.59. Found: C, 72.25; H, 6.37; N, 5.64.

Diethyl 2,6-Dimethyl-4-(5-[*m*-bromophenylethyl]-3-methylisoxazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylate (1g). From 6.05 g (16.6 mmol) of **3g** was obtained 556.7 mg of pure aldehyde (11%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.38 (s, 3H, isoxazole Me) 2.88−2.96 (m, 2H, CH_2CH_2) 3.23−3.31 (m, 2H, CH_2CH_2) 7.04−7.14 (m, 2H, Ar−H) 7.25−7.34 (m, 2H, Ar−H). The aldehyde (556.7 mg, 1.9 mmol) was dissolved in 4 mL of ethanol and transferred to an aerosol dispersion tube to which ethyl acetoacetate (495 mg, 3.8 mmol) and aqueous ammonia (3 mL, 28.7%) were added. The mixture was heated to 100−110 °C, 35−40 psi, for 48 h after which time the solvents were removed under vacuum. The crude product was crystallized by slow diffusion of hexane into a 8:1 benzene: ethanol solution. This gave 118 mg of white crystals (12%): mp 136−137 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, 6H, J = 7.2 Hz C*H*$_3$CH$_2$O) 2.26 (s, 6H, DHP-Me) 2.29 (s, 3H, isoxazole Me) 2.90−2.96 (m, 4H, CH_2CH_2) 4.08−4.12 (m, 4H, CH$_3$C*H*$_2$O) 4.91 (s, 1H, C*H*) 5.59 (br s, 1H, N*H*) 7.13−7.15 (m, 2H, Ar−H) 7.32−7.37 (m, 2H, Ar−H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.1, 14.4, 19.2, 27.4, 29.3, 32.8, 59.8, 101.57, 120.6, 122.5, 126.9, 128.3, 129.3, 130, 131.3, 143.4, 159.8, 167.3, 168.2; MS (EI) 516 m$^{\cdot+}$, 518 m + 2. Anal. Calcd for $C_{25}H_{29}BrN_2O_5$: C, 58.03; H, 5.65; N, 5.41. Found: C, 58.34; H, 5.69; N, 5.39.

Diethyl 2,6-Dimethyl-4-(5-[*m*-methoxyphenylethyl]-3-methylisoxazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylate (1h). From 3.50 g (11.1 mmol) of **3h** was obtained 962 mg of purified aldehyde (35%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.42 (s, 3H, isoxazole Me) 3.01 (t, 2H, J = 8 Hz, CH_2CH_2) 3.29 (t, 2H, J = 8 Hz, CH_2CH_2) 3.70 (s, 3H, CH_3O) 6.65−6.76 (m, 3H, Ar−H) 7.13−7.24 (m, 1H, Ar−H) 9.65 (s, 1H, aldehyde-H). The aldehyde (962 mg, 3.9 mmol) was dissolved in 5 mL of ethanol and transferred to a 25-mL round-bottom flask, to which ethyl acetoacetate (1.01 g, 7.8 mmol) and aqueous ammonia (5 mL, 28.7%) were added, and the mixture refluxed for 48 h. The solvents were removed under vacuum and the crude product crystallized by slow diffusion of hexane into a bezene solution. This gave 1.04 g of light-yellow crystals (57%): mp 98−100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, 3H, J = 7 Hz, C*H*$_3$CH$_2$O) 2.25 (s, 6H, DHP-Me) 2.30 (s, 3H, isoxazole Me) 2.93 (br s, 4H, CH_2CH_2) 3.78 (s, 3H, C*H*$_3$O) 4.0−4.2 (m, 4H, CH$_3$C*H*$_2$O) 4.91 (s, 1H, C*H*) 5.74 (br s, 1H, NH) 7.70−6.82 (m, 3H, Ar−H) 7.17−7.20 (m, 1H, Ar−H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.2, 14.4, 19.2, 27.4, 29.1, 33.4, 55.1, 59.9, 101.9, 111.5, 113.9, 120.33, 120.4, 129.4, 142.8, 143.1, 159.7, 167.2, 168.7; MS (EI) 468. Anal. Calcd for $C_{26}H_{32}N_2O_6$: C, 66.65; H, 6.88; N, 5.98. Found: C, 66.54; H, 6.77; N, 6.19.

Radioligand Binding. Microsomal membranes from guinea pig heart ventricles were prepared as previously described.[12,13] Binding of the 1,4-dihydropyridine (+)-[^{3}H]PN200-110 (isopropyl 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-(methoxycarbonyl)-2,6-dimethyl-3-pyridinecarboxylate) and its competition by the IDHPs were carried out as previously described. Briefly, membrane protein (40−120 μg) was incubated in 5 mL of 50 mM tri[(hydroxymethyl)amino]methane (Tris) buffer at pH 7.2 for 90 min at 25 °C with 5×10^{-11} (+)-[^{3}H]PN200-110 and varying concentrations of competing compounds. Duplicate tubes were filtered and washed rapidly with two 5-mL portions of ice-cold Tris buffer in a Brandel cell harvester (model M-24-R, Brandel Instruments Ltd., Gaithesburg, MD). Trapped radioactivity was counted by liquid scintillation spectrometry at an efficiency of 40−45%. Competing compounds were prepared in 100% ethanol as 10^{-3} stock solutions. Subsequent dilutions were made in 50% ethanol (10^{-4} M) or distilled water (10^{-5} onward). All dilutions were conducted on the day of the experiment. Concentrations of ethanol to 0.2% (v:v) did not affect specific binding. Binding data were analyzed by iterative curve-fitting programs (BDATA, CDATA, EMF Software, Knoxville, TN). (+)-[^{3}H]PN200-110 with a specific activity of 70 Ci/mol (1 Ci = 3.7×10^{10} bq) was purchased from DuPont-New England Nuclear (Boston, MA).

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Supporting Information Available: Brief description of radioligand binding assays and tables of crystallographic data. This information is available free of charge via the Internet at http://pubs.acs.org.

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