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Combinatorial Synthesis and Screening of a Chemical Library of 1,4-Dihydropyridine Calcium Channel Blockers

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Abstract—Solid-phase synthesis of a 300-member pharmacophore library of 1,4-dihydropyridines from keto ester, diketone and aldehyde building blocks on a cleavable amine polymeric support is described. Screening and serial deconvolution of the combinatorial library has resulted in identification of known and new potent calcium channel blockers.

Introduction

The 1,4-dihydropyridine (DHP) heterocyclic ring is a common feature of various bioactive compounds which include several vasodilator, antihypertensive, bronchodilator, antiatherosclerotic, hepatoprotective, antitumor, antimutagenic, geroprotective, and antidiabetic agents.[1,2] DHPs have received most attention as calcium channel blockers, as exemplified by commercial therapeutic agents such as Nifedipine,[2a] Nitrendipine,[2b] and Nimodipine.[2c] Second-generation calcium antagonists include DHPs with improved bioavailability, tissue selectivity/stability, such as as antihypertensive/antianginal drugs Elgodipine,[2d] Furnidipine,[2e,f] Darodipine,[2g] Pranidipine,[2h] Lemildipine,[2i] Dexniguldipine,[2j] Lacidipine,[2k] and Benidipine.[2l] Following the discovery of compound Bay K 8644,[2m] a number of DHPs acting as calcium agonists rather than antagonists were introduced as potential drug candidates for treatment of congestive heart failure (see refs 2n and 2o and refs therein). Among DHP's with other types of bioactivity, Cerebrocrast[2p] has been recently introduced as neuroprotectant and cognition enhancer lacking neuronal-specific calcium antagonist properties. While the majority of DHP therapeutic agents have been originally developed as cardiovascular and antihypertensive drugs, recent studies suggest several other medicinal applications. Thus, preclinical data have demonstrated the potential of Nimodipine as a cerebral antiischemic agent in the treatment of Alzheimer's disease and other dementias.[2r] Nitrendipine could be used for treatment of diabetic nephropathy.[2s] A recently discovered series of platelet anti-aggregatory DHPs[2t] include the drug Trombodipine with protective effect against *Listeria monocytogenes*.[2u] Dexniguldipine has recently entered phase I/II clinical studies as a chemosensitizer in tumor therapy with low hypotensive properties.[2j] These examples clearly demonstrate the remarkable potential of, and ongoing interest in, novel DHP derivatives as a fertile source of valuable drug candidates.

Combinatorial chemistry is playing an increasingly important role as one of the modern medicinal chemistry tools for rapid discovery of new leads.[3] While methods for the generation of combinatorial libraries of peptides and oligonucleotides are now well established, preparation of libraries of small organic molecules is less explored and rapidly evolving area of research.[4] Significantly, it is this latter aspect of combinatorial chemistry that is most relevant for efficient discovery of nonpeptidic, drug-like molecules. An important feature of combinatorial chemistry is the synthesis of compounds on solid supports, allowing Furka's[5] split and pool methodology to be employed for library construction. In this paper, we report the preparation of a 300-member DHP library and its iterative screening for the identification of 1,4-dihydropyridines with potent calcium channel binding activity.

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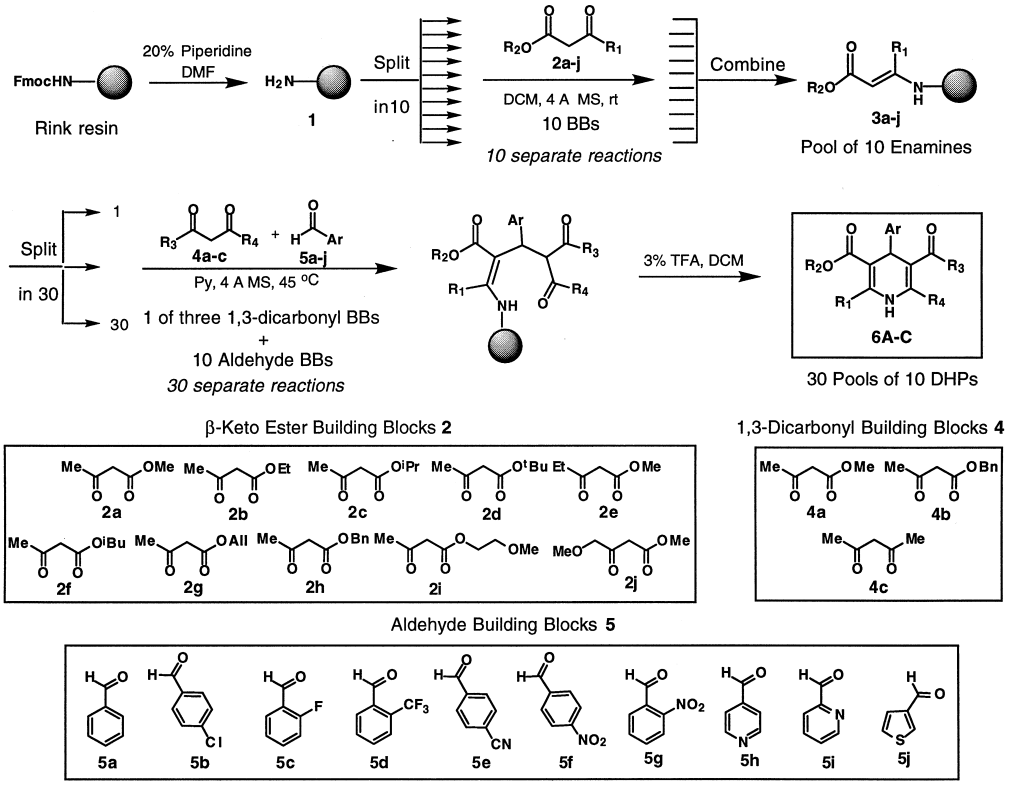
Combinatorial Chemistry

The synthesis of the 300-member DHP library involved (i) preparation of immobilized *N*-tethered enamino intermediate **3** from the Rink amine resin **1** and β-keto esters **2**, (ii) Hantzsch-type three-component condensation of the latter with β-dicarbonyls **4** and aldehydes **5**, and (iii) TFA cleavage to afford the desired DHPs **6** (Scheme 1).[6]

The library construction commences with splitting the amine resin **1** in 10 vessels, and reacting it with a single, different, β-keto ester building block (BB) **2** (from collection of **2a–j**, Scheme 1) in each vessel to form 10 separate immobilized enamino esters **3**. These are combined to form a single pool of 10 enamines **3a–j**, and the mixture is now split into three sets (A, B, and C), and each set is further divided into 10 pools (a total of 30 pools). The 10 pools within each set are treated with a common β-dicarbonyl BB **4** (methyl acetoacetate **4a** for set A, benzyl acetoacetate **4b** for set B, and acetylacetone **4c** for set C) and a single different aromatic or heteroaromatic aldehyde BB **5** in each separate vessel (from collection of aldehydes **5a–j**). Subsequent TFA cleavage of the resins gives rise to three sets of 100 member sublibraries of DHPs derived from a combination of 10 β-keto esters **2a–j**, 10 aldehydes **5a–j**, and one of the three "fixed" β-dicarbonyl component (chosen from BBs **4a–c**). Each 100-member sublibrary set thus has a common β-dicarbonyl component **4** (R_3/R_4) and exists in the form of 10 pools. Each pool within a set is a mixture of 10 compounds with a distinct aryl group (Ar, derived from the aldehyde **5**), and 10 different R_1/R_2 substituents derived from the 10 β-keto esters **2a–j** employed in preparation of immobilized enamino esters **3** (Scheme 1). Methyl acetoacetate was strategically employed at both steps of the synthesis (as BB **2a** in the enamine step, and as the 1,3-dicarbonyl component **4a** for library set **6A**) in combination with *ortho*-nitrobenzaldehyde to generate the known calcium channel blocking agent Nifedipine[2a] amongst the library members to serve as a positive control in the library evaluation (Figure 1, subset **A**). Selected pools of the the 300-member DHP library synthesized as described above.[6] have been analyzed by ESI MS and found to contain expected DHP components in most cases (for a typical DHP pool MS data, see Experimental). In addition, Nifedipine (DHP **6A–g–a**) has been independently identified in the pool **6A–g** by HPLC co-injection experiments using an authentic commercial sample of the drug.



Scheme 1.

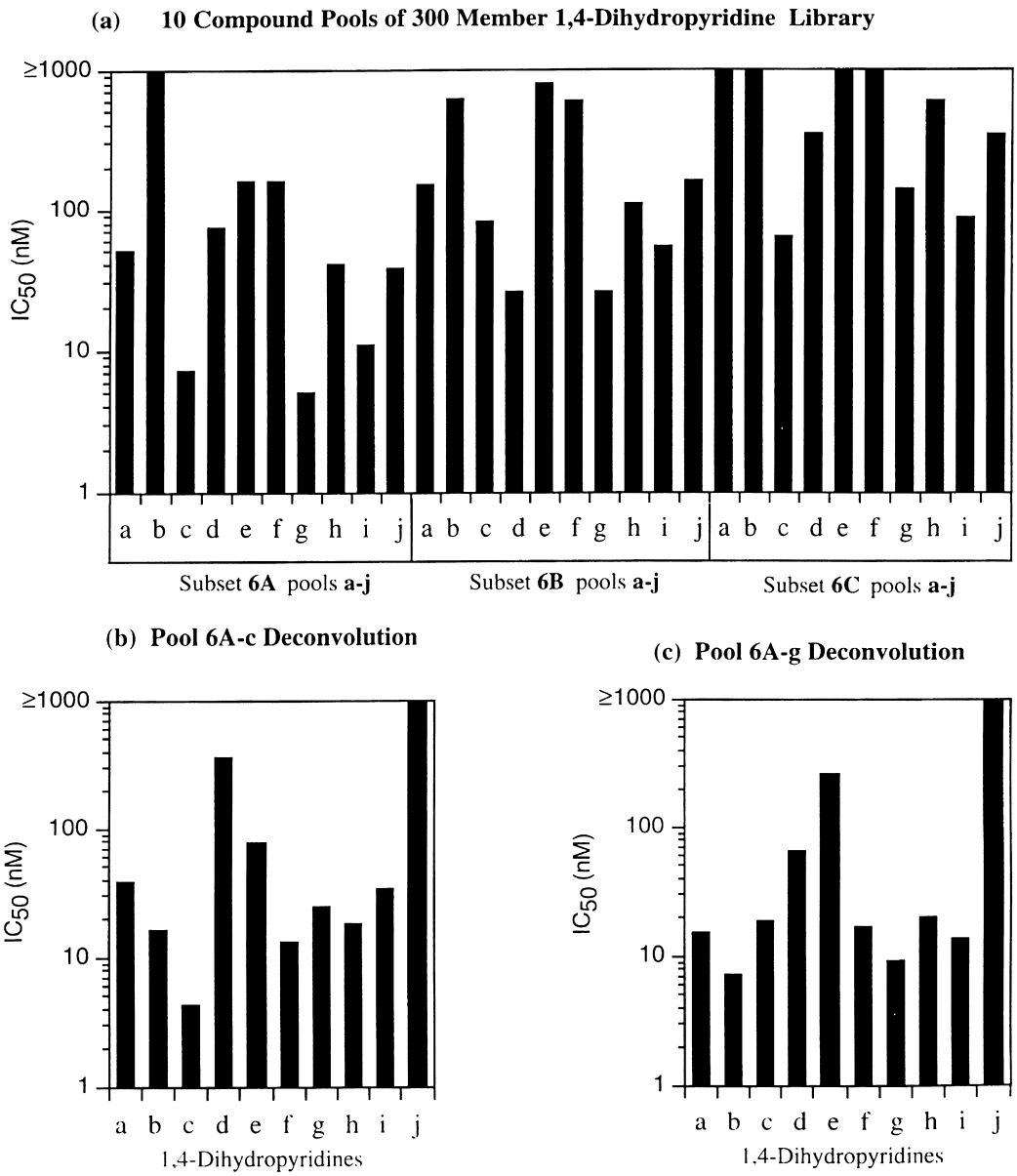


Figure 1. (a) IC_{50} for rat brain membrane binding of 10 member pools for DHP subsets **A–C** (the pool number corresponds to that of the aldehyde building block). (b) IC_{50} for the binding of 10 discrete crude DHPs comprising the pool **6A–c** (the compound number corresponds to that of the keto ester enamine precursor). (c) IC_{50} for the binding of 10 discrete crude DHPs comprising the pool **6A–g**.

Results

All 30 pools containing 10 DHPs each were analyzed separately for binding to calcium channels in rat brain membranes using a [^{3}H]-Nitrenedipine competition binding assay.[7,8] The estimated[8] IC_{50} values determined for the pools are shown in Figure 1(a).

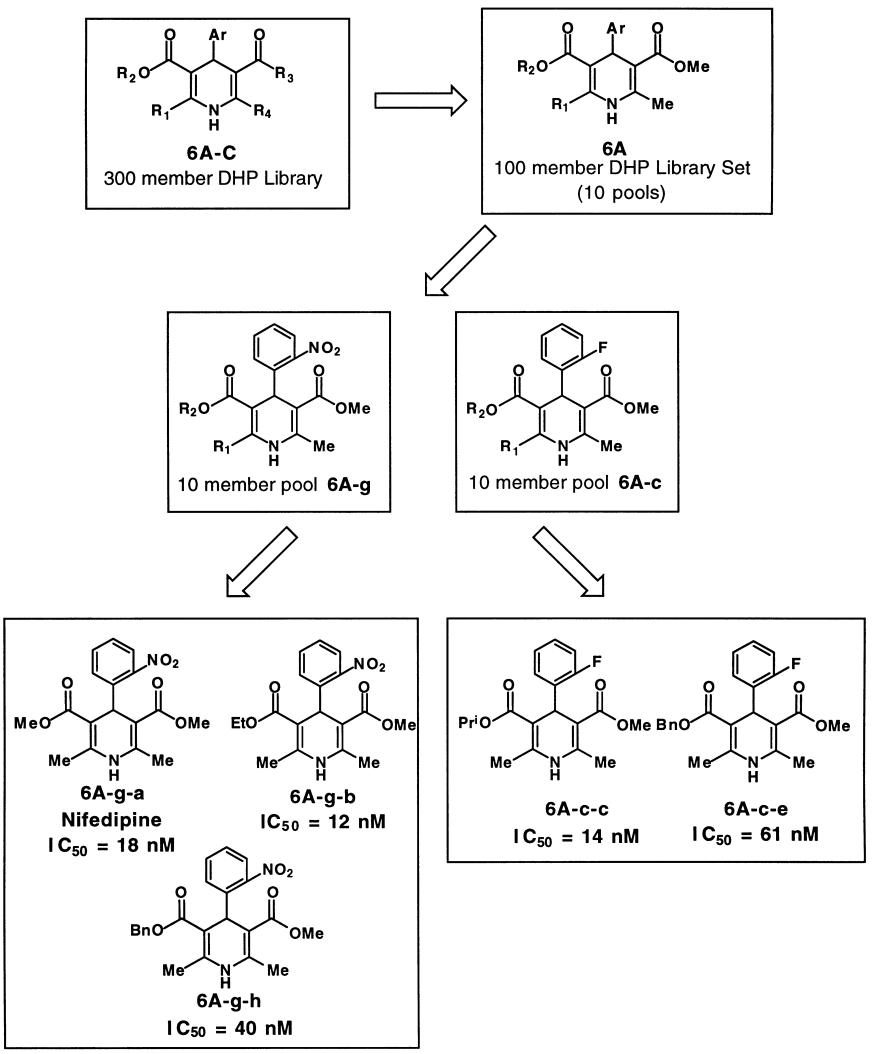
Amongst the three library sets, subset **6A** derived from methyl acetoacetate **4a** contained the most active pools. Specifically, pools **6A–c** (from *ortho*-fluorobenzaldehyde **5c**) and **6A–g** (from *ortho*-nitrobenzaldehyde **5g**) were found to display binding affinities around 10 nM, and were chosen for further deconvolution. The 10 compounds within each of these two pools (a total of 20) were resynthesized as discrete analogues and assayed as crude compounds. The inhibitory potencies of these crude compounds are shown in Figure 1(b) and (c). Based on these preliminary results, we chose to resynthesize and

purify several individual compounds in solution for accurate IC_{50} determinations. Thus, four analogues were selected to represent a cross-section of activity observed within pools **6A–c** and **6A–g**.

Discussion

The serial deconvolution process of the 300-member DHP library, and the IC_{50} data of the deconvoluted compounds are summarized in Scheme 2. The results of this deconvolution are in general agreement with known structure activity relationship (SAR) data for calcium channel blocking DHPs.[1] Thus, among the five 'most active' pools of the 300-member DHP library (see Figure 1), four possess an electron-deficient *ortho*-group in the 4-aryl moiety of the core DHP ring (*ortho*-nitrophenyl **5g** for pools **6A–g** and **6B–g**, *ortho*-fluorophenyl **5c** for pool **6A–c**, and *ortho*-trifluoromethyl **5d** for pool **6B–d**), while the fifth pool **6A–i** bears a heterocyclic electron-deficient 2-pyridyl group (from aldehyde **5i**) in this position.[1a,b,d–f] In agreement with the known SAR trend in the DHP series, acetylacetone-derived subset **6C** posessing a keto rather than an ester functionality in position 5 of the core DHP ring was significantly less active.

Individual analogues of pools **6A–c** (from *ortho*-fluorobenzaldehyde **5c**) and **6A–g** (from *ortho*-nitrobenzaldehyde **5g**) were resynthesized as discrete analogues and assayed as crude compounds. A nice spread in activity was observed, highlighting the influence of R_1/R_2



Scheme 2.

substituents around the DHP nucleus. Synthesis, purification, and accurate IC_{50} determinations of several selected analogues confirmed the SAR trend observed with the crude discrete compounds. Compound **6A–g–a** is the commercial calcium channel blocker drug Nifedipine, derived from 1,3-dicarbonyl BB methyl acetoacetate **4a**, aldehyde BB *ortho*-nitrobenzaldehyde **5g**, and β-ketoester BB methyl acetoacetate **2a**. Not surprisingly, Nifedipine **6A–g–a** is one of the most active compounds in the library (IC_{50} = 18 nM). The closely related ethyl ester analogue **6A–g–b** is equipotent or marginally better than Nifedipine (IC_{50} = 12 nM), whereas the benzyl ester analogue **6A-g-h** is twofold less active (IC_{50} = 40 nM). From the *ortho*-fluorobenzaldehyde **6A–c** pool, the isopropyl ester analogue **6A–c–c** (IC_{50} = 14 nM) is as active as Nifedipine, whereas the benzyl ester analogue is threefold less active **6A–c–e** (IC_{50} = 60 nM). These examples display consistent SAR patterns such as preference for electron withdrawing (nitro, fluoro) *ortho* substituents on the aromatic aldehyde **5** derived moiety, and good binding with small (methyl, ethyl, isopropyl) but weaker binding with large hydrophobic (benzyl) R_2 substituents derived from β-keto ester BBs **2**.

Thus, known and new potent calcium channel blockers have been successfully identified in the DHP library by rank ordering of the crude pools and components thereof. It should be noted that inherent limitations of this assay strategy,[3b] along with potential variations of the compound representation in crude specimens make it quite possible that the most potent calcium channel blocker in this library still remains to be discovered. The study also indicates that the combinatorial lead discovery may be enhanced by implementation of automated parallel synthesis and purification of discrete compounds as part of the iterative screening process.

Conclusion

In conclusion, a 300-member combinatorial library of calcium channel blocking DHPs has been synthesized on a solid phase and evaluated in a radioligand competition rat cortex membrane binding assay. An iterative screening of this library has permitted the identification of the known calcium channel blocker Nifedipine along with two DHPs of equal affinity for rat brain calcium channels, among members of the library. Thus, the present study has successfully served to validate the strategy of combinatorial drug discovery based on a solid-phase synthesis of pharmacophoric heterocyclic molecules such as 1,4-dihydropyridines.[6] Screening of combinatorial DHP libraries against other biological targets are currently under way in our laboratories.

Experimental

Chemistry

General. The ^1H spectra were recorded on a 400 MHz spectrometer with TMS as internal standard. Low resolution mass-spectra were obtained using ESI technique. All starting reagents were of the best grade available (Aldrich, Fluka, Lancaster) and were used without purification. A commercial specimen of Nifedipine **7a** was available form CalBiochem-NovaBiochem. Resin Fmoc-Rink was from CalBiochem-NovaBiochem. Solid phase preparation of the crude discreet DHPs for deconvolution studies was performed as described in ref. 6. 2-Benzylidene keto esters were prepared according to ref. 9.

General procedure for solid-phase synthesis of 300-member 1,4-dihydropyridine library. Commercial Fmoc-Rink resin (3.60 g, ca. 1.08 mmol) was deprotected by gentle vortexing with 20% piperidine in DMF for 30 min, filtered, washed liberally with DMF, CH_2Cl_2, MeOH, and dried in vacuo (0.5 Torr, 5 h). Resulted amine resin was separated into 10 equal (by weight) portions and placed into separate vials. An appropriate individual β-keto ester (3.2 mmol) in CH_2Cl_2 (2.0 mL) and 4 Å molecular sieves (0.8 g) were added in each of the reaction vials, and mixtures agitated by rotation for 3 days at r.t. Resulted immobilized enamino esters were filtered, washed liberally with DMF, CH_2Cl_2, and MeOH, and dried in vacuo (0.5 Torr, 5 h). The 10 resins were then combined and separated into 10 equal (by weight) portions and placed into separate amber vials. Solution of an appropriate individual aldehyde **5** (7.0 mmol) and a single β-dicarbonyl compound **4** (7.2 mmol) in dry Py (2.7 mL) and 4 Å molecular sieves (0.8 g) were added to each of the vials, and mixtures stirred gently at 45°C for 24 h. Resulted resins were separately filtered, washed liberally with DMF, CH_2Cl_2, and MeOH, and dried in vacuo (0.5 Torr, 5 h). Each of the 10 resin pools thus obtained was separetely stirred under argon with 3% TFA in CH_2Cl_2 (7 mL) for 45 min. Degassed acetonitrile (12 mL) was added to each reaction vessel, and the supernatant layer separated and quickly evaporated in vacuo with addition of toluene to ensure complete TFA removal. The above synthetic protocol has been repeated utilizing a total of three different "fixed" dicarbonyl components (chosen from **4a–c**) to produce the 300 member DHP library (as 30 pools of 10 components). Mass spectrum for the DHP pool generated with the 10 enamino resins **3a–j**, aldehyde **5h**, and benzyl acetoacetate **4b**: m/z 379.2 $(M+H)^+$, 393.2 $(M+H)^+$ (2 isobars), 405.2 $(M+H)^+$, 407.2 $(M+H)^+$, 409.2 $(M+H)^+$, 421.2 $(M+H)^+$ (2 isobars), 423.2 $(M+H)^+$, 455.2 $(M+H)^+$.

General procedure for solution synthesis of 1,4-dihydropyridines (6). Appropriate benzylidene keto ester **2** (2.0 mmol) and enamino ester (2.0 mmol) in EtOH

(4.0 mL) were heated under reflux for 15–24 h (until disappearance of starting materials by TLC). Solvent was evaporated in vacuo, and the crude products crystallized from EtOH (for compounds **6A–g–b** and **6A–c–c**) or hexane – ethyl ether (for compounds **6A–c–e** and **6A–g–h**).

1,4-Dihydro-4-(2-nitrophenyl)-2,6-dimethyl-3-methoxycarbonyl-5-ethoxy-carbonylpyridine (6A–g–b). Following a general procedure for solution synthesis of DHPs, 0.526 g (2.0 mmol) of ethyl 2-(*ortho*-nitro)benzylidene acetoacetate and 0.230 g (2.0 mmol) of methyl aminocrotonate yielded 0.576 g (80%) of the compound **6A–g–b**.[10] Mp 116–117°C. ^{1}H NMR ($CDCl_3$): δ 1.17 (t, J = 7.1 Hz, 3H), 2.37 (s, 3H), 2.37 (s, 3H), 3.59 (s, 3H), 4.02 (m, 1H), 4.13 (m, 1H), 5.66 (s, 1H), 5.79 (s, 1H), 7.26 (m, 1H), 7.46 (dd, J = 7.1 and 6.6 Hz, 1H), 7.51 (m, 1H); 7.71 (dd, J = 8.2 and 1.3 Hz, 1H). Mass spectrum m/z 361.0 $(M+H)^+$.

1,4-Dihydro-4-(2-nitrophenyl)-2,6-dimethyl-3-methoxycarbonyl-5-benzyl-oxycarbonylpyridine (6A–g–h). Following a general procedure for solution synthesis of DHPs, 0.325 g (1.0 mmol) of benzyl 2-(*ortho*-nitro)benzylidene acetoacetate and 0.115 g (1.0 mmol) of methyl aminocrotonate yielded 0.250 g (60%) of the compound **6A–g–h**.[11] Mp 134–135°C. ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H), 2.34 (s, 3H), 3.57 (s, 3H), 5.07 (m, 2H), 5.65 (s, 1H), 5.80 (s, 1H), 5.79 (s, 1H), 7.26 (M, 2H), 7.16 (m, 2H), 7.20–7.28 (m, 4H); 7.44 (dd, J = 8.0 and 1.3 Hz, 1H), 7.51 (m, 1H), 7.66 (dd, J = 8.1 and 1.3 Hz, 1H). Mass spectrum m/z 422.9 $(M+H)^+$.

1,4-Dihydro-4-(2-fluorophenyl)-2,6-dimethyl-3-methoxycarbonyl-5-isopro-poxycarbonylpyridine (6A–c–c). Following a general procedure for solution synthesis of DHPs, 0.444 g (2.0 mmol) of methyl 2-(*ortho*-fluoro)benzylidene acetoacetate and 0.286 g (2.0 mmol) of isopropyl aminocrotonate yielded 0.576 g (80%) of the compound **6A–c-c**. Melting point 98–100°C. ^{1}H NMR ($CDCl_3$): δ 1.04 (d, J = 6.3 Hz, 3H), 1.25 (d, J = 6.3 Hz, 3H), 2.32 (s, 3H), 2.33 (s, 3H), 3.62 (s, 3H), 4.92 (m, 1H), 5.22 (s, 1H), 5.60 (s, 1H), 6.90 (m, 1H), 6.99 (m, 1H), 7.09 (m, 1H), 7.30 (m, 1H). Mass spectrum m/z 348.0 $(M+H)^+$. Anal. ($C_{19}H_{22}FNO_4$) C, H, N.

1,4-Dihydro-4-(2-fluorophenyl)-2,6-dimethyl-3-methoxycarbonyl-5-benzyloxycarbonylpyridine (6A–c–e). Following a general procedure for solution synthesis of DHPs, 0.596 g (2.0 mmol) of the benzyl 2-(2-fluoro)benzylidene acetoacetate and 0.240 g (2.0 mmol) of methyl aminocrotonate yielded 0.392 g (50%) of the compound **6A–c–e**. Mp 120–121°C. ^{1}H NMR ($CDCl_3$): δ: 2.31 (s, 3H), 2.33 (s, 3H), 3.59 (s, 3H), 5.07 (m, 2H), 5.24 (s, 1H), 5.62 (s, 1H), 6.84–6.97 (m, 2H), 7.08 (m, 1H), 7.15–7.30 (m, 6H). Mass spectrum m/z 396.0 $(M+H)^+$. Anal. ($C_{23}H_{22}FNO_4$) C, H, N.

Pharmacology

[^{3}H]-Nitrendipine binding. Library pools, deconvolutions and purified compounds were tested for binding to calcium channels in rat cerebral cortex membranes using a modification of the assay described by Bellemann et al.[7] All steps were carried out at 4°C except as noted. Cerebral cortex from a single rat brain was homogenized in 20 mL of 0.32 M sucrose; 0.1 mM PMSF for 20 s with a polytron homogenizer. The homogenate was centrifuged at 900 *g* for 10 min. to remove coarse material and the supernatant re-centrifuged at 35,000 *g* for 20 min. The membrane pellet was washed twice by resuspending in 20 mL of assay buffer (50 mM Tris, pH 7.4; 150 mM NaCl; 1 mM $CaCl_2$; 0.1 mM PMSF) and pelleting as above, then resuspended in assay buffer to a final volume of 20 mL. Competition binding assays were carried out in 250 μL reactions containing 100 μL of the membrane preparation and [^{3}H]-Nitrendipine in assay buffer at a final concentration of 1 nM. Triplicate binding reactions containing assay buffer dilutions of library pools or individual compounds in a final concentration range from 1 μM to 1 nM were incubated at 37°C for 30 min. Non-specific binding was defined using 10 μM nimodipine. The binding reactions were filtered onto glass fiber filters (Scatron) and washed for 6 s with assay buffer at 4°C. Bound [^{3}H]-Nitrendipine was determined by liquid scintillation counting. IC_{50} values were obtained by sigmoid ± logistic curve fitting of the binding data.

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