# Calcium Entry Blockers and Activators: Conformational and Structural Determinants of Dihydropyrimidine Calcium Channel Modulators

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Dihydropyrimidines **4**, **6**, and **15**, uniquely designed to unambiguously establish structural and conformational determinants for DHP receptor occupation and for modulation of calcium channel function, were prepared and examined for calcium channel modulation. Our results confirm and firmly establish a preference for *syn*-orientation of an unsymmetrically substituted aryl moiety at the DHP receptor (**15d** vs **15e**). We propose a normal vs capsized DHP boat model to explain structural and conformational requirements for modulation of calcium channel function that requires an obligatory left-hand side alkoxy *cis*-carbonyl interaction for maximal DHP receptor affinity, the effect on channel function being determined by orientation of the 4-aryl group. Enantiomers having an up-oriented pseudoaxial aryl group (normal DHP boat) will elicit calcium antagonist activity, whereas enantiomers having a down-oriented pseudoaxial aryl group (capsized DHP boat) will elicit calcium agonist activity. Single enantiomers of macrocyclic lactone **15b** demonstrate opposite channel activity. Antagonist activity resides in enantiomer **15b**-A (*S*-configuration, left-hand side alkoxy *cis*-carbonyl with up-oriented pseudoaxial aryl group and normal DHP boat), whereas agonist activity resides in enantiomer **15b**-B (*R*-configuration, left-hand side alkoxy *cis*-carbonyl with down-oriented pseudoaxial aryl group and capsized DHP boat). Moreover, this model is consistent with and provides a rational explanation of previous literature in this area, most notably the observation of chiral inversion and potency diminution upon replacement of ester by hydrogen in the Bay K 8644 series.

## Introduction

Dihydropyridine calcium entry blockers are clinically effective cardiovascular agents and have been intensely studied to elucidate the molecular and conformational requirements for their interaction at the receptor level. We[1] and others[2–5] examined the effect of unsymmetrically substituted 4-aryl-1,4-dihydropyridines on calcium antagonist activity, leading to the conclusion that the receptor-bound conformation positions the substituted aryl ring axially, perpendicular to and bisecting the flattened boatlike dihydropyridine ring, with the 4-aryl substituent preferring the *synperiplanar* (relative to C4-H)[1] orientation. The orientation of the ester groups at the receptor is speculated[4,5] to prefer the *cis*-orientation (ester carbonyl–DHP double bond). The discovery of dihydropyridines that possess calcium agonist activity[6] raised further questions regarding the molecular distinction at the receptor level that results in these opposing activities. Discussions[4,5,7] speculate similar orientations for an axially positioned 4-aryl-1,4-dihydropyridine for both agonist and antagonist molecules, with the molecular distinction between the opposing activities determined by the "port-side" substituent: esters for antagonists and nitro (or fused lactone or simply hydrogen) for activators (Figure 1, **A**, nifedipine; **B**, Bay K 8644). Electrostatic potential[8] and state-dependent binding[5,9] have been proposed to explain the resulting effect on the calcium channel at the molecular level. Collectively, these and other studies provide a considerable, though not complete, understanding of the molecular and conformational requirements for the observed biological activities of this class of calcium channel modulators.

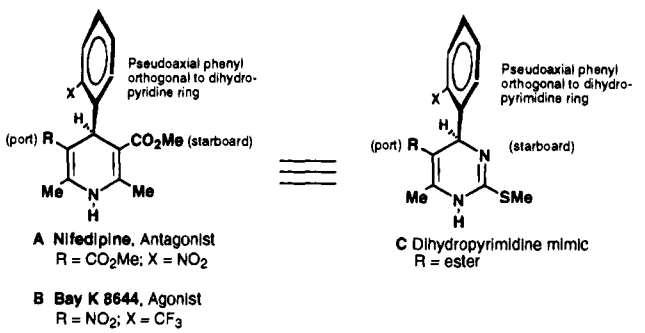


**Figure 1.** Schematic of dihydropyridine calcium antagonist nifedipine (**A**; port-side ester) and dihydropyridine calcium agonist Bay K 8644 (**B**; port-side nitro) with up-oriented pseudoaxial phenyl ring orthogonal to dihydropyridine ring and starboard-side ester. Comparison with dihydropyrimidine mimic (**C**) lacking starboard-side ester substituent.

Classical dihydropyridine calcium channel modulators possess inherent symmetry, thus making it difficult to design, synthesize, and evaluate molecules of this type that will clearly delineate receptor-bound conformation and absolute configuration requirements for both activators and antagonists. In the present study, we capitalize on the presence of a single ester group and examine individual enantiomers (C4) for calcium agonist/antagonist activity. Using our recently discovered dihydropyrimidine DHP mimics (Figure 1, **C**),[10] we prepared a consistent set of dihydropyrimidine analogs, **4**, **6**, and **15** (Figure 2, fused lactones **6** are expected to mimic calcium agonist DHP lactone CGP 28392[6c]), designed to unambiguously answer three questions: (a) the effect of ester (carbonyl) orientation on agonist/

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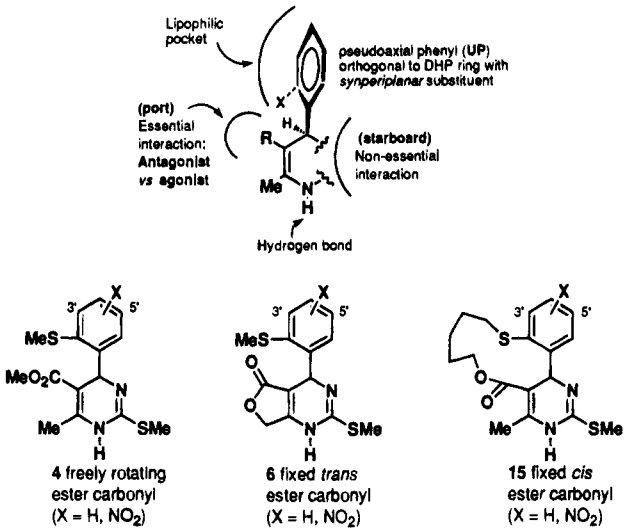



**Figure 2.** Hypothetical model showing receptor-bound dihydropyridine calcium channel modulator. Set of dihydropyrimidine mimics **4**, **6**, and **15** designed to define receptor-bound conformation and interactions of calcium channel modulators.

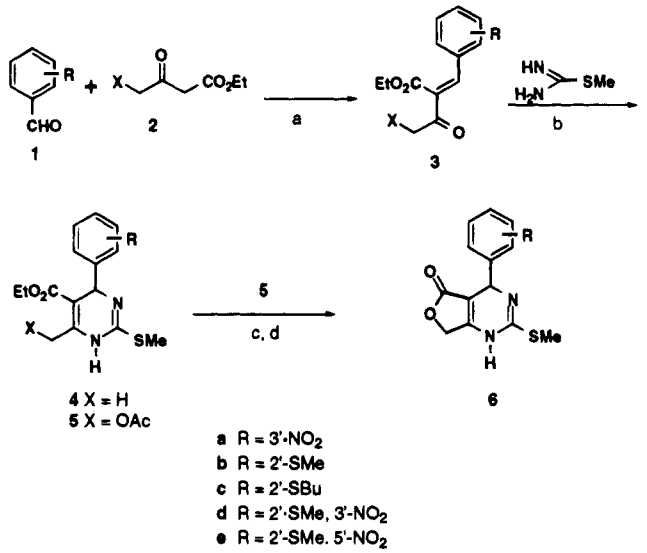
antagonist activity (**6** vs **15**), (b) the enantiomer preference of antagonist/agonist at the receptor (**4**, **6**, and **15**), and (c) the preferred orientation of an unsymmetrically substituted phenyl ring at the receptor (**15**). Previous attempts to address these questions using prototypical dihydropyridine (or DHP-derived) molecules are confounded by the presence of a second ester group, racemates, and/or a distorted dihydropyridine ring.

## Chemistry

Compounds of type **4** and **6** were prepared by the general method previously described,[10] condensing 2-methyl-2-thiopseudourea sulfate in the presence of sodium acetate with the appropriately substituted α-benzylidene β-keto ester **2** (X = H)[11] to give **4** or with the substituted α-benzylidene γ-acetoxy β-keto ester **2** (X = OAc)[11,12] to give intermediate **5**. Treatment of **5** with 1 N sodium hydroxide effected lactone formation and completed the syntheses of **6** (Scheme 1; Table 1).

Macrocyclic lactones **15** were prepared as shown in Scheme 2 (Table 1). The 3′- and 5′-nitro-substituted benzaldehydes **10** (X = 3′/5′-$NO_2$) were readily prepared

**Scheme 1.** Synthesis of Compounds **4** and **6**[a]




[a] (a) HOAc/piperidine, benzene, reflux; (b) NaOAc, DMF, 75 °C; (c) 1 N NaOH, aq EtOH, rt; (d) HCl, $Et_2O$/MeCN, rt.

by displacement of chlorine from **7** and **8**, respectively, with O-silylated 5-mercapto-1-pentanol. For benzaldehyde **10** (X = H) lacking nitro substitution, *o*-bromothiophenol (**9**) was first alkylated with O-silylated 5-chloro-1-pentanol followed by lithiation at −100 °C and formylation with dimethylformamide. Aldehydes **10** were condensed with acetoacetic acid (trimethylsilyl)-ethyl ester (**11**) using standard methodology[10] to afford benzylidenes **12**. Pyrimidine formation,[10] followed by desilylation and N-Boc formation, set the stage for the key macrocyclic lactone formation, accomplished in 52–75% yields by the method of Mukaiyama.[13] Removal of N-Boc provided target lactones **15**.

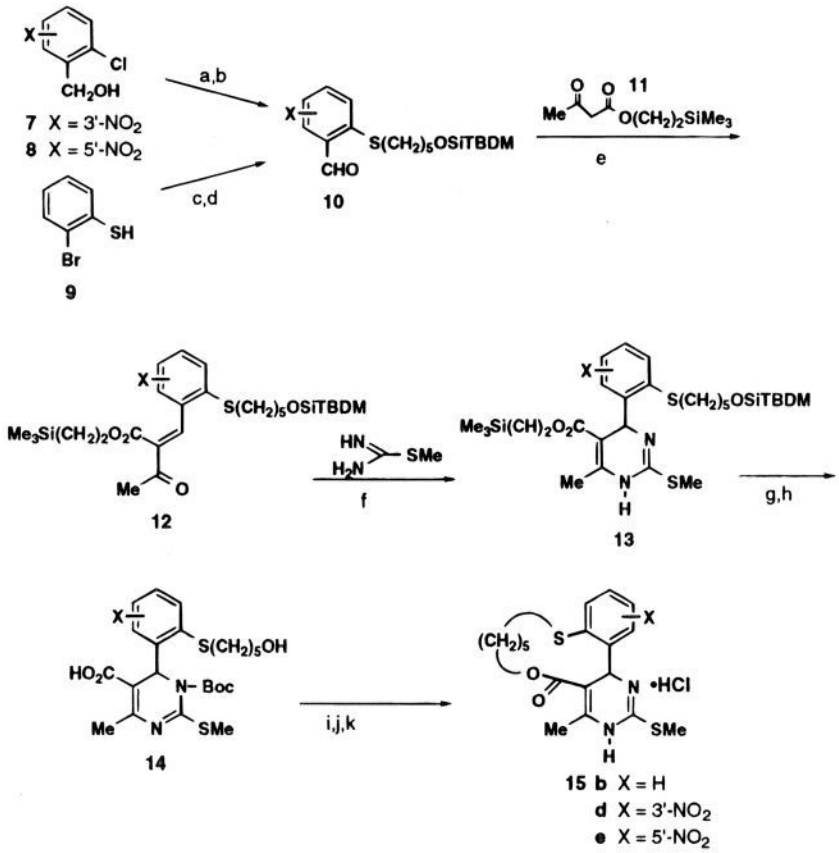
On the basis of initial biological data showing mixed agonist/antagonist activity for racemic compounds **15b,e**, we separated the individual enantiomers for one of each type of compound having similar aromatic substitution, specifically **4b, 6b**, and **15b**. Insolubility of compound in the mobile phase required for normal phase HPLC operation (preparative Chiracel OD column) and commercial unavailability of comparable preparative reverse phase columns prompted us to try[14] conversion of a normal phase column to reverse phase use. Thus, each of these three compounds was successfully sepa-

**Table 1.** Physical and Analytical Data for Compounds **4**, **6**, and **15**

| no. | yield[a] | mp (°C) | solvent | formula | anal.[b]/ee[c] | *m/z* ($MH^+$) |
|---|---|---|---|---|---|---|
| **4a** | 47 | 221–223 dec | MeCN | $C_{14}H_{15}N_3O_4S$·1.0HCl | C,H,N,S,Cl | 321 |
| **4b** | 54 | 203–205 dec | MeCN | $C_{15}H_{18}N_2O_2S_2$·1.0HCl | C,H,N,S,Cl | 323 |
| **4b-A** | – | – | – | $C_{15}H_{18}N_2O_2S_2$·1.0HCl | 99.88% | 323.0888 |
| **4b-B** | – | – | – | $C_{15}H_{18}N_2O_2S_2$·1.0HCl | 99.52% | 323.0893 |
| **4d** | 40 | 213–215 dec | $Et_2O$/MeOH trit | $C_{15}H_{17}N_3O_4S_2$·1.0HCl·0.4$H_2O$ | C,H,N,S,Cl | 368 |
| **4e** | 48 | 142–152 dec | $Et_2O$/hexane trit | $C_{15}H_{17}N_3O_4S_2$·1.0HCl | C,H,N,S,Cl | 368 |
| **6a** | 9 | 204–206 | EtOAc/acetone | $C_{13}H_{11}N_3O_4S$ | C,H,N,S | 306 |
| **6b** | 18 | 219–221 | EtOH trit | $C_{14}H_{14}N_2O_2S_2$·1.0HCl | C,H,N,S,Cl | 307 |
| **6b-A** | – | – | – | $C_{14}H_{14}N_2O_2S_2$·1.0HCl | 100% | 307.0578 |
| **6b-B** | – | – | – | $C_{14}H_{14}N_2O_2S_2$·1.0HCl | 99.32% | 307.0575 |
| **6c** | 10 | 175–178 dec | $Et_2O$ trit | $C_{17}H_{20}N_2O_2S_2$·1.0HCl | C,H,N,S,Cl | 349 |
| **6d** | 11 | 198–200 | MeOH/$CHCl_3$ | $C_{14}H_{13}N_3O_4S_2$·1.0HCl | C,H,N,S,Cl | 352 |
| **6e** | 4 | 285 dec | MeOH/$CHCl_3$ | $C_{14}H_{13}N_3O_4S_2$·1.0HCl | C,H,N,S,Cl | 352 |
| **15b** | 27 | 271–272 | MeCN trit | $C_{18}H_{22}N_2O_2S_2$·1.1HCl·0.1$H_2O$ | C,H,N,S,Cl | 363 |
| **15b-A** | – | – | – | $C_{18}H_{22}N_2O_2S_2$·1.0HCl | 99.92% | 363.1205 |
| **15b-B** | – | – | – | $C_{18}H_{22}N_2O_2S_2$·1.0HCl | 99.78% | 363.1189 |
| **15d** | 16 | >280 | MeCN trit | $C_{18}H_{21}N_3O_4S_2$·1.0HCl·0.25$H_2O$ | C,H,N,S,Cl | 408 |
| **15e** | 24 | 275 | MeCN trit | $C_{18}H_{21}N_3O_4S_2$·1.0HCl·0.25$H_2O$ | C,H,N,S,Cl | 408 |

[a] Yields are calculated from either aldehyde **1** or **10**. [b] Within ±0.4% of calculated. [c] See the Experimental Section for determination of enantiomeric purity, reported as % ee.

**Scheme 2.** Synthesis of compounds **15**[a]




[a] (a) NaOMe, DMSO/MeOH, $AcS(CH_2)_5OSiTBDM$, 0 °C to rt; (b) Swern oxidation; (c) DBU, NaI, acetone $Cl(CH_2)_5OSiTBDM$, reflux; (d) *n*-butyllithium, THF, −100 °C, DMF; (e) HOAc/piperidine, benzene, reflux; (f) NaOAc, DMF, 75 °C; (g) $(Boc)_2O$, DMAP, acetonitrile, rt; (h) TBAF, acetonitrile, 55 °C; (i) *N*-methyl-2-chloropyridinium iodide, TEA, acetonitrile, 85 °C; (j) TFA, dichloromethane, 0 °C; (k) HCl, dichloromethane/MeOH.

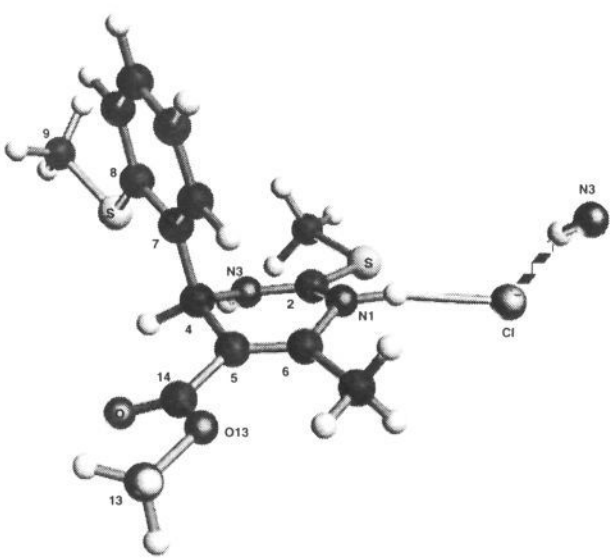


**Figure 3.** Solid state conformation **4b**-B, hydrochloride salt. The configuration at C4 is *S*. Hydrogen bond distances: N1−Cl = 3.088 Å, N3−Cl = 3.075 Å. Similar hydrogen bonds occur in the crystal structure of **15b**−A (Figure 4) with N1−Cl = 3.152 and 3.144 Å and N3−Cl = 3.011 and 3.180 Å.

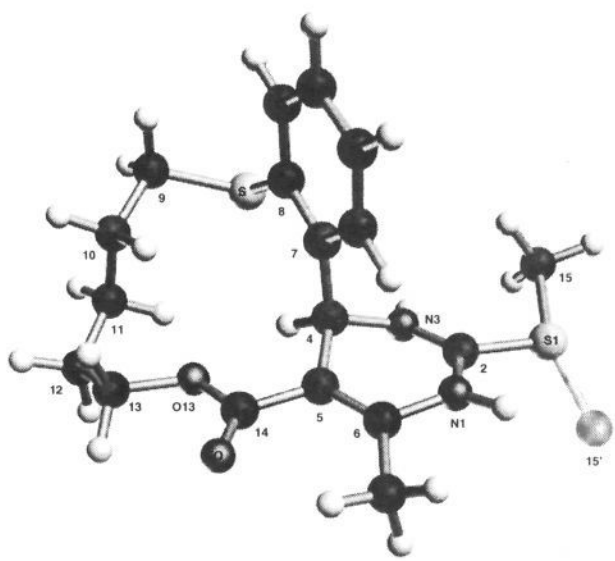


**Figure 4.** Solid state conformation of **15b**-A, hydrochloride salt. The conformations of the two crystallographically independent molecules in the crystal structure differ only through the extent of rotation of the methyl group C15 (and C15′) about the S−C2 bond. The configuration at C4 is *S*. The solid state conformation of the racemic free base **15b** is also very similar to the conformation shown above.

rated into individual enantiomers of >99.5% ee, designated as enantiomers A and B by the order of elution from the column. The absolute stereochemistries of single enantiomers **4b**-B (Figure 3) and **15b**-A (Figure 4), each possessing selective calcium antagonist activity, were both determined to be the *S*-configuration by single-crystal X-ray analysis. In addition, the solid state structures of racemic **15b,d** as well as intermediates **14b,d,e** were determined (Table 4), these data clearly establishing the pseudoaxial phenyl ring with 3′-*syn*-

**Table 2.** Biological Data for Compounds **4**, **6**, and **15**

**4** **6** **15**

| no. | X | antagonist[a] $IC_{50}$ ($\mu$M) | agonist[b] $EC_{50}$ ($\mu$M) | radioligand binding[c] $K_d$ ($\mu$M) | radioligand binding[c] slope |
|---|---|---|---|---|---|
| **4a** | 3′-$NO_2$ | 2.5 ± 0.87 | >30 | 0.48 ± 0.08 | 0.97 ± 0.08 |
| **4b** | 2′-SMe | 20.6 ± 7.9 | >30 | 1.52 ± 0.03 | 1.10 ± 0.03 |
| **4b-A**[d] | 2′-SMe | >30 | 3.55 ± 0.21 | – | – |
| **4b-B**[e] | 2′-SMe | 2.27 ± 0.38 | >30 | – | – |
| **4d** | 2′-SMe, 3′-$NO_2$ | 1.8 ± 1.1 | >30 | 0.03 ± 0.001 | 0.71 ± 0.03 |
| **4e** | 2′-SMe, 5′-$NO_2$ | 20 ± 2.2 | >30 | 2.70 ± 0.31 | 1.34 ± 0.06. |
| **6a** | 3′-$NO_2$ | >30 | >30 | 36.9 ± 4.4 | 1.61 ± 0.16 |
| **6b** | 2′-SMe | >30 | >30 | 45.2 ± 3.7 | 1.64 ± 0.28 |
| **6b-A**[f] | 2′-SMe | >30 | >30 | – | – |
| **6b-B**[f] | 2′-SMe | >30 | >30 | – | – |
| **6c** | 2′-SBu | >30 | 17.3 ± 1.8 | >50 | – |
| **6d** | 2′-SMe, 3′-$NO_2$ | >30 | >30 | 13.7 ± 1.9 | 1.40 ± 0.10 |
| **6e** | 2′-SMe, 5′-$NO_2$ | >30 | >30 | >50 | – |
| **15b** | H | 3.9 ± 1.6 | 0.82 ± 0.14 | 0.018 ± 0.002 | 0.64 ± 0.02 |
| **15b-A**[g] | H | 0.10 ± 0.02 | >30 | – | – |
| **15b-B**[h] | H | >30 | 0.59 ± 0.06 | – | – |
| **15d** | 3′-$NO_2$ | 0.036 ± 0.010 | >30 | 0.005 ± 0.001 | 0.64 ± 0.02 |
| **15e** | 5′-$NO_2$ | 26 ± 4.2 | 2.9 ± 0.46 | 0.873 ± 0.06 | 1.12 ± 0.07 |
| **A** | nifedipine | 0.019 ± 0.002 | >30 | 0.0004 ± 0.00005 | 1.02 ± 0.04 |
| **B** | Bay K 8644 | 17.1 ± 4.6[i] | 0.046 ± 0.009 | 0.018 ± 0.001 | 0.98 ± 0.06 |

[a] Dose that causes 50% relaxation of potassium-contracted rabbit aorta strips. [b] Dose that causes 50% maximal contraction of rabbit aorta strips. [c] Inhibition of [$^3$H]nitrendipine binding to guinea pig myocardial membranes. [d] **4d**-A, *R*-configuration. [e] **4b**-B, *S*-configuration. [f] Absolute configuration not determined. [g] **15b**-A, *S*-configuration. [h] **15b**-B, *R*-configuration. [i] Contraction and then relaxation.

(**14d** and **15d**) and 5′-*anti*- (**14e**) nitro substitution of the 4-aryl ring, the *synperiplanar* (C4-H) (alkylthio)-phenyl lactone bridge, and the *cis*-oriented (relative to dihydropyrimidine double bond) lactone carbonyl.

## Biological Activity

All compounds were tested *in vitro* for calcium antagonist[15] and calcium agonist[16] activity. Only racemic compounds were evaluated for [$^3$H]nitrendipine radioligand binding affinity.[1b] Open ester analogs **4** provide base line activity (Table 2) from which to compare the conformationally restricted fused lactones **6** and macrocyclic lactones **15**. Thus, aryl substitution SAR for **4** is consistent with previous work,[10] including the suggestion of a preferred *syn*-3′-nitro substituent at the DHP receptor (compare **4d** vs **4e**) assuming a bias[1b] for a *syn*-oriented 2′-substituted aryl in solution. The weak antagonist activity of 2′-SMe analog **4b** resides in one enantiomer, **4b**-B, possessing the *S*-configuration (Figure 3). Interestingly, the other enantiomer, **4b**-A, has modest calcium agonist activity. The absolute stereochemistry of antagonist enantiomer **4b**-B corresponds to related dihydropyrimidine calcium antagonists[17,18] (port-side ester).

Consistent with the model[4,5] requiring a *cis*-oriented ester carbonyl for calcium antagonist activity, none of the fused lactones **6** demonstrated antagonism (Table 2). Unexpectedly, however, calcium agonist activity was observed only for 2′-SBu analog **6c**. Neither individual enantiomer **6b**-A nor **6b**-B having 2′-SMe substitution demonstrated agonist activity. The failure of any of these fused lactones (**6c** excepted) to show calcium agonist activity was surprising in light of a previous report[6b] where 2′-SMe-aryl substitution imparted maximal agonist activity in a related dihydropyridine-fused lactone (but still possessing the typical second ester on the starboard-side). We cannot interpret our results by the model[7a] previously espoused for DHP calcium antagonist/agonist activity. Data obtained for the macrocyclic lactones **15**, however, yield clues to the interpretation of our findings as well as other results reported in the literature.

For the macrocyclic lactone series, 3′-$NO_2$ analog **15d** was 720 times more potent than 5′-$NO_2$ analog **15e**, consistent with and providing further confirmation[1,3] of a preferred *syn*-orientation (C4-H) of an unsymmetrically substituted aryl-1,4-dihydropyridine at the DHP receptor (Table 2). Expecting only calcium antagonist activity for macrocyclic lactones **15**, we were surprised that two analogs, **15b,e**, also showed relatively potent calcium agonist activity. Single-crystal X-ray analysis of enantiomer **15b**-A (Figure 4) established the *S*-configuration and, along with nuclear Overhauser NMR studies, confirmed that the bridging 2′-alkylthio group is positioned *syn* to C4-H. Further, the *S*-enantiomer **15b**-A possesses only calcium antagonist activity,[17,18] whereas the *R*-enantiomer **15b**-B possesses only calcium agonist activity.

The vasorelaxant potency for compounds of this study shows a positive correlation with [$^3$H]nitrendipine radioligand binding affinity, consistent with our previous findings,[10] and indicates a relationship between DHP receptor occupancy and functional effect.

## Discussion

The question of rotameric preference of an unsymmetrically substituted phenyl ring at the dihydropyridine receptor is addressed by macrocyclic lactones

**15d,e**, wherein the potency of the *syn*-$NO_2$ **15d** is 720 times that of the *anti*-$NO_2$ **15e**. The related nonrigid analogs **4d,e** show a modest bias (11 times) for a *syn*-substituted aryl group, the conformational bias being provided by the 2′-SMe. This supports the earlier suggestion for nonrigid dihydropyridines[1b] and confirms the results obtained for conformationally constrained dihydropyridines[3] of a preferred *syn*-orientation for an unsymmetrically substituted aryl moiety at the receptor.

We consider together the two questions regarding the effects of ester (carbonyl) orientation and sidedness of chiral dihydropyridines on calcium antagonist/agonist activity. Our results for the individual enantiomers of **4b**, **6b**, and **15b** are not consistent with previous interpretations[7] of the molecular distinction between calcium antagonists and calcium agonists. Calcium agonist activity has been reported for dihydropyridines wherein one of the two (3/5) ester groups is replaced by nitro (prototype Bay K 8644, **B**),[6a] fused lactone,[6b,c] and hydrogen.[6d] This led to a proposed DHP binding site model[7a] wherein the boatlike dihydropyridine is substituted by an axially oriented aryl group, with the port-side (3/5-position) substituted by an ester group for calcium antagonists or a nitro group[6a] (or lactone[6b,c] or hydrogen[6d]) for calcium agonists (see Figure 2, hypothetical model). For Bay K 8644 (**B**), these are the *R*- and *S*- configurations, respectively. Differentiation of antagonist/agonist activity has been attributed[6d,8] to the molecular electrostatic potential in the region of the port-side substituent, this being negative for agonist molecules.

Since fused lactone DHP calcium agonists[6b,c] (*trans*-carbonyl) appear to mimic the biological activity observed for the nitro derivative Bay K 8644 (**B**), it occurred to us that DHP mimics of type **6** (*trans*-carbonyl) and **15** (*cis*-carbonyl) might provide a means to more clearly probe the distinction between antagonists and agonists on a molecular level, since they are unencumbered with a second ester group that in previous studies has made data interpretation ambiguous. On the basis of reported SAR[6b] of dihydropyridine lactones, 2′-SMe substitution of the phenyl group should provide maximal calcium agonist activity for fused lactone compounds **6**. Yet, neither **6b** nor single enantiomers **6b**-A and **6b**-B demonstrated calcium agonism. The 2′-SBu analog **6c** was prepared for a closer comparison with the bridging "2′-S-pentyl" group as in macrocyclic lactones **15**, affording the opportunity for similar lipophilic interactions at the receptor. In contrast to 2′-SMe **6b**, 2′-SBu **6c** demonstrated weak, though reproducible, calcium agonist activity. Thus, it appears that a *trans*-oriented carbonyl on the port-side is insufficient to promote calcium agonist activity without an additional alkyl interaction, provided in **6c** by the 2′-SBu-aryl substituent. It is difficult to reconcile our observations for fused lactones **6** with the previously proposed[7a] model.

The two weaker (antagonist) macrocyclic lactones **15b** (X = H) and **15e** (X = 5′-$NO_2$) displayed mixed calcium antagonist and calcium agonist activity. For consistency **15b**, lacking aromatic nitro substitution, was separated into single enantiomers and examined for biological stereoselectivity. *S*-Enantiomer **15b**-A, having the lactone on the port-side and a pseudoaxially (up) oriented aryl ring, displayed only calcium antagonist activity, consistent with our previous[17,18] observations for biological stereoselectivity. *R*-Enantiomer **15b**-B, having the lactone on the port-side and a pseudoaxially (down) oriented aryl ring, displayed only calcium agonist activity. The lack of agonist activity observed for fused lactones **6** (excepting the very weak agonist **6c** with 2′-SBu-aryl substituent) prompted us to consider an alternative model that accommodates our findings as well as previous studies.

Our inability to demonstrate calcium agonist activity for fused lactone **6b** (*trans*-carbonyl, port-side negative electrostatic potential), as would be expected from literature precedent,[6b] was initially perplexing. However, this finding can be reconciled by the apparent requirement for both agonists and antagonists to possess a critical lipophilic interaction in a region of space accessible either by a 3/5-ester alkyl group (*cis*-carbonyl as in macrocyclic lactone **15b**) or by an appropriate 2′-aryl substituent (*trans*-carbonyl as in fused lactone **6c**, 2′-SBu).

*From our results we propose an alternate model, wherein the direction of the 4-phenyl group at the receptor serves as a molecular switch in determining state-dependent[5,9,20] affinity for the calcium channel. Viewing the DHP ring from N1 (stern) toward C4 (bow), dihydropyrimidine (and by inference dihydropyridine[19]) calcium channel modulators require an alkyl ester with* cis*-carbonyl orientation to the left of a plane perpendicular to and bisecting the DHP ring. Enantiomers having a pseudoaxially up-oriented aryl group (normal boat) will elicit calcium antagonist activity, whereas enantiomers having a pseudoaxially down-oriented aryl group (capsized boat) will elicit calcium agonist activity* (Figure 5). We depart from the nautical terms "port" and "starboard" to distinguish left and right in this proposed model of a normal vs capsized DHP boat. Furthermore, this new model accommodates and clarifies previous results reported for a series of Bay K 8644 analogs,[7b] particularly the observation of chiral inversion and diminution of potency (for both antagonist and agonist enantiomers) when the 3-carbomethoxy ester group is replaced by hydrogen (Figure 6). In our proposed model, both antagonist (*R*)-(+)-Bay K 8644 (**16a**) and agonist (*S*)-(−)-Bay K 8644 (**16b**) bind to the receptor with the 3-carbomethoxy group on the left-hand side, the orientation of the 4-aryl group determining antagonism (normal boat with aryl up, affinity for the closed channel state) or agonism (capsized boat with aryl down, affinity for the open channel state). Replacement of the 3-carbomethoxy group by hydrogen leaves a devastating void in the absence of the essential alkoxycarbonyl left-hand side receptor interaction. However, chiral inversion partially salvages the critical left-hand side interaction with a much less favorable 3-nitro group that lacks the alkyl moiety, thus accounting as well for the observed diminution of potency for both antagonist (**17a**) and agonist (**17b**) enantiomers.

Similarly, replacement of one ester function of a prototypical 3/5-diester dihydropyridine by a fused lactone (but always retaining the other ester group) results in stereoselective calcium channel modulation.[4] In the currently accepted model, the agonist enantiomer is depicted with "port-side" fused lactone and an up-oriented pseudoaxial 4-aryl group (normal boat). We propose that the agonist enantiomer binds to the receptor with the remaining ester on the left-hand side and a down-oriented pseudoaxial 4-aryl group (capsized

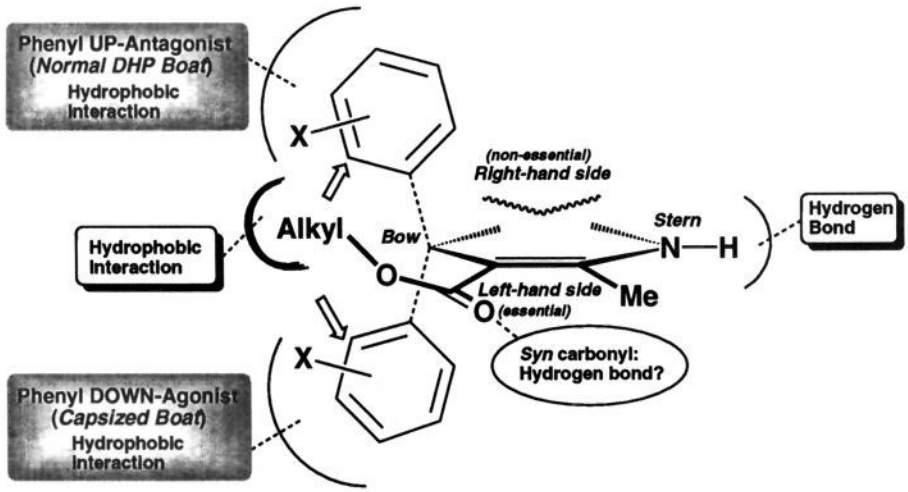



**Figure 5.** Schematic of essential left-hand side alkoxycarbonyl interaction for both calcium antagonists (phenyl up in normal DHP boat) and calcium agonists (phenyl down in capsized DHP boat). Right-hand side interactions are nonessential. Right and left are defined viewing the DHP ring from N1 (stern) toward C4 (bow).

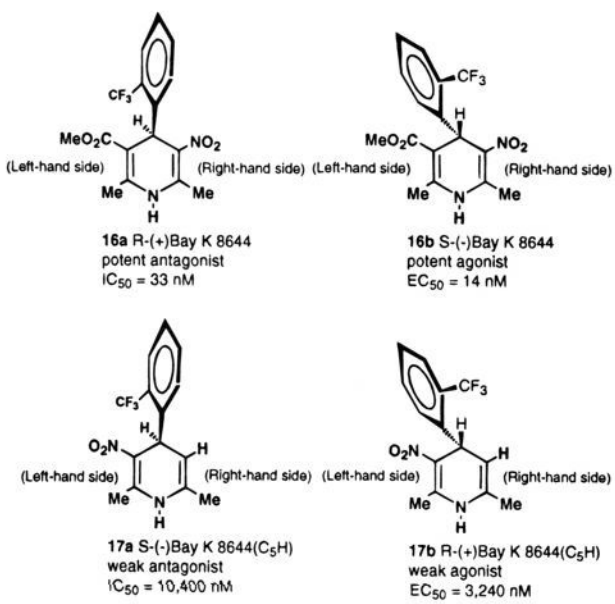
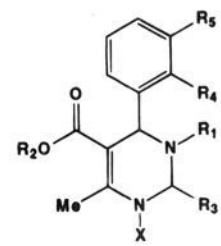



**Figure 6.** Chiral inversion of Bay K 8644(C5H) analogs (**16a,b** and **17a,b**, ref 7b).

**Table 3.** Structures and References of Compounds for Which Crystallographic Data Is Reported in Tables 4 and 5




| compound | $R_1$ | $R_2$ | X | $R_3$ | $R_4$ | $R_5$ |
|---|---|---|---|---|---|---|
| ref 10 (**8g**) | | Et | | SBn | | $NO_2$ |
| ref 17a (**3a**) | $CO_2Et$ | Et | H | =S | | $NO_2$ |
| ref 17a (**3f**) | $CO_2Et$ | Et | H | =S | $CF_3$ | |
| ref 17a (**3q**) | $CO_2Et$ | Et | H | =O | | $NO_2$ |
| ref 17a (**3s**) | $CO_2Et$ | Et | | $NH_2$ | | $NO_2$ |
| ref 17a (**20a**) | $CO_2$-menthyl | *i*-Pr | H | =S | | $NO_2$ |
| ref 17a (**21a**) | H | Et | H | =S | | $NO_2$ |
| ref 17a (**21b**) | H | Et | H | =O | | $NO_2$ |
| ref 17b (**5**) | $CON(Me)_2$ | *i*-Pr | H | =O | | $NO_2$ |
| ref 17b (**6**) | CONHMe | *i*-Pr | H | =O | | $NO_2$ |
| ref 17c (**29a**) | CONHCH(Me)Ph | *i*-Pr | | OMe | $CF_3$ | |
| ref 22 (**3f**) | N=CHC(CN)= | *i*-Pr | H | see $R_1$ | | $NO_2$ |
| ref 23 (**4**) | Bn | Et | H | =S | | $NO_2$ |

boat). Thus, from our model, we predict that replacement of the "second" ester moiety by hydrogen would result in complete abolition of calcium channel modulation (antagonism and agonism) as a result of losing the critical left-hand side alkoxycarbonyl interaction, a prediction that is consistent with our observation of lack of calcium modulation for fused lactones **6**. Finally, our model is consistent with differences that are observed for aryl ring structure–activity,[5] mainly quantitative in nature, between antagonist (phenyl up) and activator (phenyl down) molecules.

In conclusion, we have prepared a series of dihydropyrimidines, **4**, **6**, and **15**, uniquely designed to unambiguously establish structural and conformational determinants for DHP receptor occupation and for modulation of calcium channel function. Our results confirm and firmly establish a preference for *syn*-orientation of an unsymmetrically substituted aryl moiety at the DHP receptor (compare **15d** vs **15e**). We propose a normal vs capsized DHP boat model to explain structural and conformational requirements for modulation of calcium channel function that requires an obligatory left-hand side alkoxy (*cis*) carbonyl interaction for maximal DHP receptor affinity, the effect on channel function being determined by orientation of the 4-aryl group. *Enantiomers having an up-oriented pseudoaxial aryl group (normal DHP boat) will elicit calcium antagonist activity, whereas enantiomers having a down-oriented pseudoaxial aryl group (capsized DHP boat) will elicit calcium agonist activity.* Note the lack of calcium agonist activity for fused lactone **6b**, partially compensated for by increasing the size of the 4′-aryl substituent as in **6c**. Single enantiomers of **15b** demonstrate opposite channel activity. Antagonist activity resides in enantiomer **15b**-A (*S*-configuration, left-hand side alkoxy *cis*-carbonyl with up-oriented pseudoaxial aryl group and normal DHP boat), whereas agonist activity resides in enantiomer **15b**-B (*R*-configuration, left-hand side alkoxy *cis*-carbonyl with down-oriented pseudoaxial aryl group and capsized DHP boat). Moreover, this model is consistent with and provides a rational explanation of previous literature in this area, most notably the observation of chiral inversion and

**Table 4.** Crystallographic Data for Compounds of This Study and for Related Dihydropyrimidines Previously Reported (See Table 3)

| parameter | **4b**-B (HCl salt) | **15b**-A (HCl salt) | **15b** (base) | **14d** | **15d** |
|---|---|---|---|---|---|
| solvent | $MeCN/H_2O$ | $EtOH/H_2O$ | acetone | acetone | acetone/MeOH |
| $a$, Å | 14.844(2) | 10.682(2) | 10.922(2) | 29.996(3) | 7.333(1) |
| $b$, Å | 16.460(3) | 7.838(1) | 12.792(2) | 10.680(1) | 11.707(1) |
| $c$, Å | 7.267(1) | 24.133(3) | 13.875(3) | 17.996(2) | 22.434(2) |
| $\beta$, deg | – | 102.76(1) | 109.14(1) | 121.21(1) | 96.99(1) |
| $V$, Å$^3$ | 1775.7(8) | 1970.6(9) | 1831(1) | 4931(2) | 1911.4(6) |
| space group | $P2_12_12_1$ | $P2_1$ | $P2_1/c$ | $C2/c$ | $P2_1/n$ |
| formula | $C_{15}H_{19}N_2O_2S_2Cl$ | $C_{18}H_{23}N_2O_2S_2Cl$[a] | $C_{18}H_{22}N_2O_2S_2$ | $C_{23}H_{29}N_3O_6S_2$ | $C_{18}H_{21}N_3O_4S_2$ |
| $d_{calcd}$, g cm$^{-3}$ | 1.343 | 1.342 | 1.315 | 1.368 | 1.416 |
| NUNI[b] | 1962 | 4034 | 2303 | 4599 | 3560 |
| NOBS[c]/NV[d] | 1578/199 | 2736/451 | 713/107 | 3497/308 | 2025/238 |
| $R/R_w$ | 0.052/0.061 | 0.051/0.061 | 0.093/0.097 | 0.056/0.080 | 0.063/0.081 |

| parameter | ref 17a (**3s**) | ref 17a (**3f**) | ref 17a (**3g**) | ref 17a (**3a**) | ref 17b (**6**) |
|---|---|---|---|---|---|
| solvent | $CH_2Cl_2$/IPE | EtOAc/$EtOH/H_2O$ | IPE/$CH_2Cl_2$ | EtOH/petroleum ether | EtOAc/hexane |
| $a$, Å | 24.09(2) | 14.925(7) | 28.07(1) | 12.151(1) | 7.386(1) |
| $b$, Å | 8.457(4) | 8.035(4) | 9.806(1) | 12.324(1) | 28.489(5) |
| $c$, Å | 18.35(1) | 16.079(7) | 13.964(4) | 7.284(1) | 9.230(2) |
| $\alpha$, deg | – | – | – | 90.39(1) | – |
| $\beta$, deg | 102.94(6) | 99.18(3) | 110.95(2) | 103.06(1) | 109.03(2) |
| $\gamma$, deg | – | – | – | 114.04(1) | – |
| $V$, Å$^3$ | 3642(9) | 1903(3) | 3590(3) | 964.4(3) | 1836(1) |
| space group | $C2/c$ | $P2_1/c$ | $C2/c$ | $P\bar{1}$ | $P2_1/c$ |
| formula | $C_{17}H_{19}N_4O_6$ | $C_{18}H_{19}N_2O_4SF_3$ | $C_{17}H_{19}N_3O_7$ | $C_{17}H_{19}N_3O_6S$ | $C_{17}H_{20}N_4O_6$ |
| $d_{calcd}$, g cm$^{-3}$ | 1.369 | 1.453 | 1.396 | 1.355 | 1.362 |
| NUNI[b] | 2108 | 2599 | 2456 | 3292 | 3332 |
| NOBS[c]/NV[d] | 1145/245 | 1636/253 | 1246/245 | 2015/244 | 1796/245 |
| $R/R_w$ | 0.059/0.073 | 0.064/0.080 | 0.054/0.052 | 0.054/0.066 | 0.057/0.063 |

| parameter | **14b** | **14e** | ref 17a (**21a**) | ref 17a (**21b**) | ref 23 (**4**) | ref 17b (**5**) | ref 22 (**3f**) |
|---|---|---|---|---|---|---|---|
| solvent | acetone | acetone | absolute EtOH | absolute EtOH | $CHCl_3$/ether | IPE/MeCl/EtOH | EtOAc/hexane |
| $a$, Å | 12.027(1) | 11.055(1) | 8.45(1) | 8.670(1) | 7.294(1) | 9.931(1) | 13.313(4) |
| $b$, Å | 12.446(2) | 12.191(1) | 13.56(1) | 11.831(2) | 11.826(1) | 10.680(1) | 14.855(3) |
| $c$, Å | 9.473(1) | 10.033(1) | 14.47(2) | 13.759(3) | 12.507(1) | 11.040(1) | 11.235(2) |
| $\alpha$, deg | 111.43(1) | 101.32(1) | 101.35(9) | – | 98.31(1) | 82.40(1) | 76.15(1) |
| $\beta$, deg | 108.67(1) | 105.56(1) | 98.23(8) | 93.40(1) | 95.65(1) | 63.81(1) | 93.70(2) |
| $\gamma$, deg | 95.99(1) | 95.99(1) | 104.34(9) | – | 106.3(1) | 84.64(1) | 114.27(1) |
| $V$, Å$^3$ | 1210.3(7) | 1259.9(5) | 1542(7) | 1408.9(7) | 1013.4(3) | 1040.6(9) | 1965(2) |
| space group | $P\bar{1}$ | $P\bar{1}$ | $P\bar{1}$ | $P2_1/n$ | $P\bar{1}$ | $P\bar{1}$ | $P\bar{1}$ |
| formula | $C_{23}H_{30}N_2O_4S_2$ | $C_{23}H_{29}N_3O_6S_2$ | $C_{14}H_{15}N_3O_4S$[a] | $C_{14}H_{15}N_3O_5$ | $C_{21}H_{21}N_3O_4S$ | $C_{18}H_{22}N_4O_6$ | $C_{18}H_{17}N_5O_4$[a]$\cdot(C_6H_{14})_{1/2}$ |
| $d_{calcd}$, g cm$^{-3}$ | 1.269 | 1.388 | 1.38 | 1.439 | 1.35 | 1.243 | 1.314 |
| NUNI[b] | 4590 | 4708 | 4052 | 1916 | 3461 | 3076 | 4600 |
| NOBS[c]/NV[d] | 3636/281 | 3414/314 | 1877/398 | 1101/200 | 2454/263 | 2393/254 | 2691/499 |
| $R/R_w$ | 0.048/0.066 | 0.053/0.076 | 0.056/0.052 | 0.062/0.064 | 0.050/0.060 | 0.051/0.072 | 0.058/0.061 |

[a] The asymmetric unit contains two formula units. [b] Number of symmetry-independent reflections. [c] Number of reflections with $I \geq 3\sigma(I)$ used in least-squares refinement. [d] Number of refined variables.

potency diminution upon replacement of ester by hydrogen in the Bay K 8644 series.

In addition to seven compounds discussed in this work, we include here the results from single-crystal analyses of 10 closely related dihydropyrimidine derivatives from previous reports (Tables 3–5; supplemental material; refs 17, 22, and 23). This will provide interested readers the opportunity to examine solid state structures of a wide variety of substituted dihydropyrimidines which, during the course of our own studies, has led us to conclude that these are excellent mimics of prototypical dihydropyridine calcium channel modulators.

## Experimental Section

**Chemistry.** All melting points were taken on a Thomas Hoover capillary melting point apparatus and are uncorrected. $^1$H-NMR and $^{13}$C-NMR were recorded on either Jeol GX-400 or FX-270 spectrometers with tetramethylsilane as internal standard. Mass spectra were obtained with a Finnigan TSQ-4600 spectrometer. Flash chromatography was run with Whatman LPS-1 silica gel. Organic solutions were dried over anhydrous magnesium sulfate. Microanalyses of all compounds were within ±0.4% of theory unless otherwise indicated.

**Preparation of Open Ester Compounds 4a,b,d,e.** These compounds were prepared by the method reported[10] previously and are listed in Table 1.

**1,4-Dihydro-6-methyl-2-(methylthio)-4-(3-nitrophenyl)-5-pyrimidinecarboxylic Acid, Methyl Ester, Hydrochloride (4a).** $^1$H-NMR (DMSO-$d_6$): $\delta$ 8.22 (d, $J$ = 7.0 Hz, 1H), 8.20 (s, 1H), 7.84 (d, $J$ = 7.0 Hz, 1H), 7.73 (t, $J$ = 7.0 Hz, 1H), 5.83 (s, 1H), 2.65 (s, 3H), 1.76 (s, 3H), 1.49 (s, 3H). $^{13}$C-NMR ($CDCl_3$, free base): $\delta$ 166.9, 153.2, 148.2, 146.7, 133.2, 129.1, 121.7, 99.7, 58.2, 51.0 (22.6, 19.1, tautomers), 13.3.

**1,4-Dihydro-6-methyl-2-(methylthio)-4-[2-(methylthio)-phenyl]-5-pyrimidinecarboxylic Acid, Methyl Ester, Hydrochloride (4b).** $^1$H-NMR ($CD_3OD$): $\delta$ 7.50 (d, $J$ = 7.0 Hz, 1H), 7.20–7.40 (m, 3H), 6.20 (s, 1H), 3.63 (s, 3H), 2.68 (s, 3H), 2.58 (s, 3H), 2.48 (s, 3H). $^{13}$C-NMR ($CDCl_3$): $\delta$ 167.1, 127.9, 127.2, 125.9, 50.9, 17.0, 13.3 (five carbons not observed).

**1,4-Dihydro-6-methyl-2-(methylthio)-4-[2-(methylthio)-3-nitrophenyl]-5-pyrimidinecarboxylic Acid, Methyl Ester, Hydrochloride (4d).** $^1$H-NMR ($CD_3OD$): $\delta$ 7.60–7.80 (m, 3H), 6.57 (s, 1H), 3.66 (s, 3H), 2.71 (s, 3H), 2.53 (s, 3H), 2.48 (s, 3H). $^{13}$C-NMR ($CD_3OD$): $\delta$ 166.4, 165.7, 158.2, 146.9, 145.0, 132.9, 132.4, 128.6, 125.3, 106.9, 55.0, 52.4, 21.0, 17.5, 14.6.

**1,4-Dihydro-6-methyl-2-(methylthio)-4-[2-(methylthio)-5-nitrophenyl]-5-pyrimidinecarboxylic acid, Methyl Ester, Hydrochloride (4e).** $^1$H-NMR ($CD_3OD$): $\delta$ 8.20 (dd, $J$ = 2.5, 7.5 Hz, 1H), 8.10 (d, $J$ = 2.5 Hz, 1H), 7.63 (d, $J$ = 7.5 Hz, 1H), 6.18 (s, 1H), 3.65 (s, 3H), 2.72 (s, 3H), 2.69 (s, 3H), 2.52 (s, 3H). $^{13}$C-NMR ($CD_3OD$): $\delta$ 166.9, 149.4, 146.3, 138.3, 127.7, 125.8, 125.3, 124.9, 105.3, 55.1, 52.5, 17.3, 16.0, 14.7 (two carbons not observed).

**Preparation of Fused Lactone Compounds 6a–e.** These compounds were prepared by the method reported[10] previously

**Table 5.** Selected Torsional Angles for Compounds Reported in Table 4[a]

| compound | $\Phi_1$ | $\Phi_2$ | $\Phi_3$ | $\Phi_4$ | $\Phi_5$ | $\Phi_6$ | $\Phi_7$ | $\Phi_8$ | $\Phi_9$ | $\Phi_{10}$ | $\Phi_{11}$ | $\Phi_{12}$ | $\Phi_{13}$ | $\Phi_{14}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **4b**-B | −172 | 0 | 169 | | | | | | | −180 | −157 | 94 | | −3 |
| **14b** | −140 | −5 | 128 | −63 | −67 | 168 | −59 | −42 | −156 | −169 | 11 | 77 | −160 | −19 |
| **14d** | −124 | 4 | 93 | −166 | 61 | 85 | −53 | −53 | −166 | 180 | 25 | 88 | −21 | −9 |
| **14e**[b] (major) | −130 | −5 | 136 | −136 | 55 | 64 | −160 | 66 | 155 | −176 | 4 | 81 | −12 | −14 |
| (minor) | | | | −77 | −69 | 163 | −36 | −55 | −144 | | | | | |
| **15b** (free base) | −146 | 1 | 116 | −70 | −66 | 175 | −56 | −38 | −171 | −177 | 23 | 79 | | 7 |
| **15b-A** | −140 | 5 | 120 | −74 | −66 | 166 | −59 | −32 | −175 | −174 | 17 | 81 | | −4 |
| | −140 | 0 | 118 | −71 | −69 | 174 | −49 | −42 | −166 | −174 | 18 | 80 | | −5 |
| **15d**[c] | −149 | 3 | 113 | −48 | −78 | 176 | −57 | −31 | −121 | 175 | −8 | 72 | | −1 |
| | | | 75 | 40 | −169 | 56 | 67 | −90 | −121 | | | | | |
| ref 10 (**8g**) | −120 | | | | | | | | 175 | 178 | −169 | 73 | | −1 |
| ref 17a (**3a**) | 145 | | | | | | | | 92 | −176 | −8 | 96 | −168 | −14 |
| ref 17a (**3f**) | −125 | | | | | | | | −178 | 179 | −5 | 89 | −25 | −11 |
| ref 17a (**3q**) | −115 | | | | | | | | −176 | 177 | −4 | 84 | −163 | −5 |
| ref 17a (**3s**) | −140 | | | | | | | | −175 | −179 | 178 | 81 | −11 | −11 |
| ref 17a (**20a**) | 134 | | | | | | | | −164 | −176 | −7 | 94 | −160 | −16 |
| ref 17a (**21a**) | −143 | | | | | | | | −178 | −179 | 11 | 77 | | −3 |
| | −142 | | | | | | | | 177 | −178 | 4 | 78 | | −1 |
| ref 17a (**21b**) | −96 | | | | | | | | 124 | 179 | 5 | 79 | | −4 |
| ref 17b (**5**) | −132 | | | | | | | | 142 | −176 | −2 | 79 | −129 | −6 |
| ref 17b (**6**) | −117 | | | | | | | | 151 | −179 | 4 | 80 | −2 | −8 |
| ref 17c (**29a**) | −144 | | | | | | | | −167 | −179 | −22 | 84 | 165 | −12 |
| ref 22 (**3f**) | −112 | | | | | | | | 94 | 179 | 4 | 77 | | 0 |
| | −110 | | | | | | | | 86 | −175 | 20 | 73 | | −1 |
| ref 23 (**4**) | −120 | | | | | | | | 171 | 177 | 169 | 86 | | 1 |

[a] Torsional angles: $\Phi_1$ = C5−C4−C7−C8; $\Phi_2$ = C4−C7−C8−S; $\Phi_3$ = C7−C8−S−C9−C10; $\Phi_4$ = C8−S−C9−C10; $\Phi_5$ = S−C9−C10−C11; $\Phi_6$ = C9−C10−C11−C12; $\Phi_7$ = C10−C11−C12−C13; $\Phi_8$ = C11−C12−C13−O; $\Phi_9$ = C12−C13−O−C; $\Phi_{10}$ = C13−O−C−C5; $\Phi_{11}$ = O−C−C5−C4; $\Phi_{12}$ = C−C5−C4−C7; $\Phi_{13}$ = C4−N−C−O; $\Phi_{14}$ = C2−N3−C5−C6. Angles are reported in degrees. [b] Site disorder (2:1) of atoms C10 and C12 results from the presence of two conformers of the macrocycle. [c] Site disorder (1:1) of atoms C9 and C11 results from the presence of two conformers of the macrocycle.

to obtain penultimate 5-acetoxymethyl derivatives **5**, subsequently lactonized to compounds **6** by treatment with sodium hydroxide in aqueous ethanol, and are listed in Table 1.

**4,7-Dihydro-2-(methylthio)-4-(3-nitrophenyl)furo[3,4-*d*]pyrimidin-5(1*H*)-one (6a).** $^1$H-NMR (DMSO-$d_6$): $\delta$ 9.45 (br s, 1H), 8.20 (d, $J$ = 7.5 Hz, 1H), 8.14 (s, 1H), 7.78 (d, $J$ = 7.5 Hz, 1H), 7.72 (t, $J$ = 7.5 Hz, 1H), 5.77 (s, 1H), 4.88 (d, $J$ = 16 Hz, 1H), 4.77 (d, $J$ = 16 Hz, 1H), 2.46 (s, 3H). $^{13}$C-NMR (DMSO-$d_6$): $\delta$ 171.3, 147.9, 144.8, 133.3, 130.3, 122.9, 121.2, 99.2, 68.7, 52.7, 12.5 (two carbons not observed).

**4,7-Dihydro-2-(methylthio)-4-[2-(methylthio)phenyl]-furo[3,4-*d*]pyrimidin-5(1*H*)-one, Hydrochloride (6b).** $^1$H-NMR (DMSO-$d_6$): $\delta$ 7.20−7.50 (m, 4H), 6.06 (s, 1H), 4.94 (s, 2H), 2.65 (s, 3H), 2.48 (s, 3H). $^{13}$C-NMR (DMSO-$d_6$): $\delta$ 171.0, 166.9, 167.3, 166.9, 136.4, 129.1, 128.8, 128.1, 126.2, 99.2, 68.5, 51.6, 16.8, 12.5.

**4-[2-(Butylthio)phenyl]-4,7-dihydro-2-(methylthio)furo-[3,4-*d*]pyrimidin-5(1*H*)-one, Hydrochloride (6c).** $^1$H-NMR ($CD_3OD$): $\delta$ 7.89 (dd, $J$ = 2.3, 7.1 Hz, 1H), 7.70−7.80 (m, 2H), 6.75 (s, 1H), 5.08 (d, $J$ = 1.7 Hz, 2H), 2.79 (s, 3H), 2.48 (s, 3H). $^{13}$C-NMR ($CDCl_3$, free base): $\delta$ 171.7, 167.5, 165.9, 140.4, 134.5, 131.0, 129.0, 128.5, 127.2, 100.3, 69.3, 51.4, 34.7, 31.1, 21.8, 13.4, 13.1.

**4,7-Dihydro-2-(methylthio)-4-[2-(methylthio)-3-nitrophenyl]furo[3,4-*d*]pyrimidin-5(1*H*)-one, Hydrochloride (6d).** $^1$H-NMR ($CD_3OD$): $\delta$ 7.58, (d, $J$ = 7.1 Hz, 1H), 7.30−7.50 (m, 3H), 6.27 (s, 1H), 5.01 (s, 2H), 3.0 (t, $J$ = 7.1 Hz, 2H), 2.76 (s, 3H), 1.52−1.68 (m, 2H), 135−1.50 (m, 2H), 0.92 (t, $J$ = 7.1 Hz, 3H). $^{13}$C-NMR (DMSO-$d_6$): $\delta$ (167.9, 166.5) (155.8, 155.7) (149.2, 148.9), 148.6, 132.4, 131.5 (125.1, 125.0), 122.8, 99.8 (69.2, 69.0), 50.8, 20.8, 12.6 (tautomers in parentheses; one carbon not observed).

**4,7-Dihydro-2-(methylthio)-4-[2-(methylthio)-5-nitrophenyl]furo[3,4-*d*]pyrimidin-5(1*H*)-one, Hydrochloride (6e).** $^1$H-NMR ($CD_3OD$): $\delta$ 8.17 (dd, $J$ = 2.3, 8.9 Hz, 1H), 8.08 (d, $J$ = 2.3 Hz, 1H), 5.58 (d, $J$ = 8.8 Hz, 1H), 6.05 (s, 1H), 4.87 (s, 2H), 2.62 (s, 3H), 2.48 (s, 3H). $^{13}$C-NMR (DMSO-$d_6$, free base): $\delta$ 168.9, 146.0, 142.3, 123.7, 121.6, 121.3, 66.7, 50.4, 13.1, 10.6 (four carbons not observed).

**Preparation of Macrocyclic Lactones 15b,d,e Is Exemplified by Preparation of 3,8,9,10,11,16b-Hexahydro-4-methyl-2-(methylthio)-13-nitro-5*H*,7*H*-[7,1]benzoxathiacyclododecino[10,9-*d*]pyrimidin-5-one, Monohydrochloride (15d).** **(a) Preparation of 3-Nitro-2-[5-[(*tert*-butyldimethylsilyl)oxy]pentyl]thiobenzaldehyde (10d).** A solution of 2-chloro-3-nitrobenzyl alcohol (2.0 g, 10.1 mmol) and 1-(acetylthio)-5-[(*tert*-butyldimethylsilyl)oxy]pentane (3.2 g, 11.5 mmol; prepared from 5-chloropentan-1-ol by reaction with thioacetic acid followed by *tert*-butyldimethylsilyl chloride) in 15 mL of dimethyl sulfoxide:methanol (2:1) at 0 °C under argon was treated with 25% sodium methoxide/methanol (2.8 mL, 12.3 mmol). The reaction mixture was stirred at room temperature for 1.5 h and then diluted with ethyl acetate and washed with water, 1 N sodium hydroxide, water, and brine. The dried (anhydrous magnesium sulfate) organic solution was concentrated *in vacuo*, and the residue was flash chromatographed on 600 mL of LPS-1 silica gel, eluting with ethyl acetate:hexane (1:4) to give 2.43 g (63%) of 3-nitro-2-[5-[(*tert*-butyldimethylsilyl)oxy]pentyl]thiobenzyl alcohol. MS: $m/z$ 386 ($MH^+$). Anal. ($C_{18}H_{35}NO_4SSi$) C, H, N, S. The alcohol (3.35 g, 8.7 mmol) was oxidized by the method of Swern (*Tetrahedron* **1978**, *34*, 1651) to give 3.33 g (100%) of aldehyde **10d**. MS: $m/z$ 384 ($MH^+$). $^1$H-NMR ($CDCl_3$): $\delta$ 10.69 (s, 1H), 8.07 (dd, $J$ = 1.5, 7.9 Hz, 1H), 7.82 (dd, $J$ = 1.5, 7.9 Hz, 1H), 7.57 (dd, $J$ = 7.6, 8.8 Hz, 1H), 3.54 (t, $J$ = 5.9 Hz, 2H), 2.84 (t, $J$ = 7.6 Hz, 2H), 1.30−1.60 (m, 6H), 0.85 (s, 9H). $^{13}$C-NMR ($CDCl_3$): $\delta$ 190.5, 139.1, 131.7, 131.3, 129.5, 127.8, 62.6, 39.5, 32.1, 29.4, 26.2, 25.9, 25.6, 24.8, 18.3. Anal. ($C_{18}H_{33}NO_4SSi$) C, H, N, S.

**(b) Preparation of 2-[[3-Nitro-2-[[5-[(tert-butyldimethylsilyl)oxy]pentyl]thio]phenyl]methylene]-3-oxobutanoic Acid, 2-(Trimethylsilyl)ethyl ester (12d).** A solution of **10d** (2.39 g, 6.2 mmol) and 3-oxobutanoic acid 2-(trimethylsilyl)ethyl ester (1.24 g, 6.8 mmol; prepared from diketene and trimethylsilylethanol in toluene containing sodium acetate at 90 °C, bp 60−62 °C/0.3 mmHg) in 100 mL of benzene was treated with acetic acid (0.3 mL) and piperidine (0.3 mL) and heated at reflux temperature for 1 h, using a Dean−Stark trap to collect formed water. The cooled mixture, diluted with ethyl acetate, was washed with 1 N HCl, water, dilute sodium bicarbonate, and brine, dried (anhydrous magnesium sulfate), and concentrated *in vacuo* to give 3.75 g of amber oil. Flash chromatography on 400 mL of LPS-1 silica gel and elution with ethyl acetate:hexane (1:20) gave 2.92 g (82%) of product. MS: $m/z$ 585 ($MNH_4^+$). $^1$H-NMR ($CDCl_3$, $\delta$): 8.09, 8.03 (2s, 1H), 7.30−7.65 (m, 3H), 4.15−4.45 (m, 2H), 3.53 (t, $J$ = 6.1 Hz, 2H), 2.74 (t, $J$ = 7.0 Hz, 2H), 2.45, 2.27 (2s, 3H), 1.30−1.60 (m,

6H), 0.85 (s, 9H), (doubling from *E*/*Z*-isomers). Anal. ($C_{27}H_{45}NO_6SSi_2 \cdot 0.2H_2O$) C, H, N.

**(c) Preparation of 1,4-Dihydro-6-methyl-2-(methylthio)-4-[2-[[5-[(*tert*-butyldimethylsilyl)oxy]pentyl]thio]-3-nitrophenyl]-5-pyrimidinecarboxylic Acid, 2-(Trimethylsilyl)ethyl Ester (13d).** A solution of **12d** (2.9 g, 5.1 mmol) and 2-(methylthio)pseudourea hydrogen sulfate (0.75 g, 2.7 mmol) in 9 mL of dry DMF under argon at room temperature was treated with sodium acetate (0.44 g, 5.4 mmol) and heated at 75 °C for 4 h. The cooled mixture, diluted with ethyl acetate, was washed with water and brine, dried (anhydrous magnesium sulfate), and concentrated *in vacuo* to give 3.75 g of an oil. Flash chromatography on 350 mL of LPS-1 silica gel and elution with ethyl acetate:hexane (1:6) gave 2.87 g (88%) of product as a pale viscous oil. MS: *m*/*z* 639 ($MH^+$). Anal. ($C_{29}H_{49}N_3O_5S_2Si_2$) C, H, N, S.

**(d) Preparation of 1,4-Dihydro-6-methyl-2-(methylthio)-4-[2-[(5-hydroxypentyl)thio]-3-nitrophenyl]-3,5-pyrimidinedicarboxylic Acid, 3-*tert*-Butyl Ester (14d).** A solution of **13d** (2.78 g, 4.34 mmol) in 65 mL of acetonitrile under argon at room temperature was treated with di-*tert*-butyl dicarbonate (1.13 g, 5.19 mmol) followed by 4-(*N*,*N*-dimethylamino)pyridine (65 mg, 0.52 mmol). After stirring for 2 h, the mixture, diluted with ethyl acetate, was washed with 1 N hydrochloric acid, water, saturated sodium bicarbonate, and brine. The dried (anhydrous magnesium sulfate) organic solution was concentrated *in vacuo*, and the residue (2.0 g) was flash chromatographed on 300 mL of LPS-1 silica gel, eluting with methylene chloride:hexane (2:1) to give 2.14 g (67%) of homogeneous oily product. $^1$H-NMR ($CDCl_3$, $\delta$): 7.44 (dd, $J$ = 2.4, 7.1 Hz, 1H), 7.34 (t, $J$ = 7.6 Hz, 1H), 7.31 (dd, $J$ = 2.7, 8.0 Hz, 1H), 7.0 (s, 1H), 4.17 (m, 2H), 5.88 (t, $J$ = 6.0 Hz, 2H), 2.89 (t, $J$ = 7.3 Hz, 2H), 2.47 (d, $J$ = 1.2 Hz, 3H), 2.40 (s, 3H), 1.54 (s, 9H), 1.30–1.70 (m, 6H), 0.89 (s, 9H). $^{13}$C-NMR ($CDCl_3$): $\delta$ 165.8, 159.1, 156.7, 152.6, 150.8, 144.9, 131.0, 129.2, 127.3, 122.8, 111.9, 84.4, 62.9, 62.7, 60.3, 51.9, 38.0, 32.4, 29.2, 28.1, 27.3, 25.9, 25.6, 25.2, 21.0, 18.3, 17.5, 15.1, 14.1, −1.6. MS: *m*/*z* 740 ($MH^+$). Anal. ($C_{34}H_{57}N_3O_7S_2Si_2$) C, H, N, S.

A solution of the above product (1.90 g, 2.56 mmol) in 30 mL of acetonitrile containing tetra-*n*-butylammonium fluoride (10 mL of 1 M THF solution) was stirred under argon at 55 °C for 2 h. The reaction mixture, diluted with ethyl acetate, was washed with 1 N hydrochloric acid, water (twice) and brine, dried (anhydrous magnesium sulfate), and concentrated *in vacuo* to give 1.34 g of crude product. Flash chromatography on 250 mL of LPS-1 silica gel and elution with ethyl acetate:methanol (50:1) gave 1.03 g (76%) of product. Trituration with isopropyl ether/hexane gave an amorphous powder (contains some tetra-*n*-butylammonium; used in next step without further purification). $^1$H-NMR ($CDCl_3$): $\delta$ 7.46 (dd, $J$ = 1.7, 7.0 Hz, 1H), 7.33 (t, $J$ = 7.6 Hz, 1H), 7.28 (d, $J$ = 8.0 Hz, 1H), 6.99 (s, 1H), 3.62 (t, $J$ = 5.9 Hz, 2H), 2.75–3.00 (m, 2H), 2.48 (s, 3H), 2.38 (s, 3H), 1.54 (s, 9H), 1.40–1.70 (m, 6H). $^{13}$C-NMR ($CDCl_3$): $\delta$ 169.1, 159.7, 156.4, 154.2, 150.6, 144.3, 130.9, 129.1, 127.0, 122.9, 111.3, 84.4, 61.8, 51.7, 37.4, 31.5, 28.7, 27.9, 24.6, 21.1, 15.0. MS: *m*/*z* 526 ($MH^+$). Anal. Calcd for $C_{23}H_{31}N_3O_7S_2$: C, 52.55; H, 5.95; N, 7.99; S, 12.20. Found: C, 53.96; H, 7.05; N, 7.58; S, 10.10.

**(e) Preparation of 3,8,9,10,11,16b-Hexahydro-4-methyl-2-(methylthio)-13-nitro-5*H*,7*H*-[7,1]benzoxathiacyclododecino[10,9-*d*]pyrimidin-5-one, Monohydrochloride (15d).** To a solution of *N*-methyl-2-chloropyridinium iodide (1.4 g, 5.49 mmol) in 165 mL of dry acetonitrile under argon at 85 °C was added a mixture of **14d** (700 mg, 1.33 mmol) and triethylamine (1.68 mL, 1.22 g, 12.0 mmol) in 10 mL of acetonitrile via syringe pump over a period of 7 h. After stirring an additional 0.5 h at 85 °C, volatiles were stripped *in vacuo*, and the residue, dissolved in ethyl acetate, was washed with 1 N HCl, water, saturated sodium bicarbonate, and brine. The dried (anhydrous magnesium sulfate) organic solution was treated with Darco and concentrated to give 450 mg, which upon trituration with warm acetone gave 350 mg (52%) of N-Boc-protected product. Mp: 176 °C dec. $^1$H-NMR ($CDCl_3$): $\delta$ 7.46 (dd, $J$ = 1.7, 7.0 Hz, 1H), 7.34 (t, $J$ = 7.6 Hz, 1H), 7.26 (dd, $J$ = 2.7, 8.0 Hz, 1H), 7.13 (s, 1H), 4.23–4.33 (m, 1H), 3.86–3.97 (m, 1H), 3.14–3.26 (m, 1H), 2.62–2.71 (m, 1H), 2.50 (s, 3H), 2.41 (s, 3H), 1.92–2.07 (m, 1H), 1.77–1.91 (m, 1H), 1.62–1.77 (m, 1H), 1.57 (s, 9H), 1.40–1.60 (m, 2H), 1.27–1.40 (m, 1H). MS: *m*/*z* 508 ($MH^+$). Anal. ($C_{23}H_{29}N_3O_6S_2$) C, H, N, S.

A solution of the above product (300 mg, 0.59 mmol) in 1 mL of dichloromethane under argon at 0 °C was treated with 0.8 mL of trifluoroacetic acid and allowed to stir for several hours at room temperature. Volatiles were stripped *in vacuo*, and the residue, dissolved in ethyl acetate, was washed with saturated sodium bicarbonate, water, and brine. The dried (anhydrous magnesium sulfate) organic solution was concentrated and the residue triturated with hot acetone to give 233 mg (96%) of free base. Mp: 271.5–272.5 °C. MS: *m*/*z* 408 ($MH^+$). Anal. ($C_{18}H_{21}N_3O_3S_2$) C, H, N, S.

The above free base (250 mg, 0.60 mmol), dissolved in 10 mL of dichloromethane:methanol (1:1), was treated with 0.5 mL of 4 N ethereal hydrochloric acid. Volatiles were removed *in vacuo*, and the residue was triturated with hot acetonitrile, cooled, and filtered to give 238 mg (88%) of **15d**. Mp >280 °C. $^1$H-NMR ($CD_3OD$): $\delta$ 7.60–7.75 (m, 3H), 6.70 (s, 1H), 4.30–4.43 (m, 1H), 3.70–3.85 (m, 1H), 3.05–3.18 (m, 1H), 2.70–2.85 (m, 1H), 2.64 (s, 3H), 2.54 (s, 3H), 1.35–1.95 (m, 5H), 1.15–1.35 (m, 1H). MS: *m*/*z* 408 ($MH^+$). Anal. ($C_{18}H_{22}ClN_3S_2 \cdot 0.25H_2O$) C, H, N, S, Cl.

**Preparation of 3,8,9,10,11,16b-Hexahydro-4-methyl-2-(methylthio)-5*H*,7*H*-[7,1]benzoxathiacyclododecino[10,9-*d*]pyrimidin-5-one, Monohydrochloride (15b).** Following the procedure described for **15d**: mp 271–272 °C. $^1$H-NMR ($CD_3OD$, free base): $\delta$ 7.52–7.63 (m, 1H), 7.15–7.44 (m, 3H), 6.53, 6.30 (2s, 1H), 5.99, 5.62 (2s, 1H), 4.25–4.45 (m, 1H), 3.46–3.61 (m, 1H), 2.69–3.24 (m, 2H), 2.50, 2.45 (2s, 3H), 2.40, 2.30 (2s, 3H), 1.95–2.28 (m, 1H), 1.75–1.90 (m, 1H), 1.00–1.55 (m, 4H) (doubling of peaks due to pyrimidine tautomers). MS: *m*/*z* 363 ($MH^+$). Anal. ($C_{18}H_{22}N_2O_2S_2 \cdot 0.1H_2O \cdot 1.1HCl$) C, H, N, S, Cl.

**Preparation of Enantiomers 15b-A and 15b-B.** Preparative HPLC fractions containing individual enantiomers were concentrated *in vacuo* at <40 °C to remove acetonitrile. The remaining aqueous solution was basified with 5% sodium bicarbonate and extracted with ethyl acetate. The organic solution was dried and concentrated, and the residue, dissolved in ether, was treated with excess ethereal hydrochloric acid. Removal of volatiles *in vacuo* afforded the product. **15b-A**: 99.92% ee. $[\alpha]_D = -88.5°$ ($c$ = 0.26, MeOH). HRMS calcd from $C_{18}H_{23}N_2O_2S_2$, 363.1201; found, 363.1205 ($MH^+$). **15b-B**: 99.78% ee. $[\alpha]_D = +90.0°$ ($c$ = 0.27, MeOH). HRMS calcd for $C_{18}H_{23}N_2O_2S_2$, 363.1201; found, 363.1189 ($MH^+$). $^1$H-NMR for each enantiomer as for racemic **15b**.

**Preparation of 3,8,9,10,11,16b-Hexahydro-4-methyl-2-(methylthio)-15-nitro-5*H*,7*H*-[7,1]benzoxathiacyclododecino[10,9-*d*]pyrimidin-5-one, Monohydrochloride (15e).** Following the procedure described for **15d**: mp 275 °C. $^1$H-NMR ($CD_3OD$): $\delta$ 8.21 (dd, $J$ = 2.4, 8.2 Hz, 1H), 8.17 (d, $J$ = 2.4 Hz, 1H), 8.00 (d, $J$ = 8.2 Hz, 1H), 6.67 (s, 1H), 4.30–4.38 (m, 1H), 3.62–3.72 (m, 1H), 3.43–3.51 (m, 1H), 2.90–3.00 (m, 1H), 2.69 (s, 3H), 2.53 (s, 3H), 2.05–2.20 (m, 1H), 1.75–1.95 (m, 1H), 1.55–1.75 (m, 1H), 1.35–1.55 (m, 2H), 1.15–1.35 (m, 1H). MS: *m*/*z* 408 ($MH^+$). Anal. ($C_{18}H_{22}ClN_3S_2 \cdot 0.3MeCN$) C, H, N, S, Cl.

**Separation of Enantiomers and Evaluation of Enantiomeric Purity.** Analogs **4b**, **6b**, and **15b** were separated into individual enantiomers on a VersaPREP preparative liquid chromatograph (Varex, Burtonsville, MD), using a 2.0 × 25.0 cm 10 $\mu$-Chiracel OD column (Diacel Chemical Industries, Ltd., Tokyo; available from J.T. Baker, Inc., Phillipsburg, NJ) in the reverse phase mode. Because of compound insolubility in hexane/2-propanol, this column could not be used in the normal phase for which it was designed. Conversion to reverse phase use (manufacturer warranty voided) was effected by running a slow gradient from 90% hexane/10% 2-propanol (as received from manufacturer) to 100% 2-propanol, equilibrated in 100% 2-propanol (10 column volumes), followed by conversion to 100% methanol and finally to the running mobile phase of water/acetonitrile, both in the same manner as above. In a typical run, 16 mg of compound/4 mL (mobile phase) was injected onto the column and eluted with water/acetonitrile (45/55–60/40) isocratically at ambient temperature, employing flow rates of 4.5–5.0 mL/min to maintain

pressures within 300–500 psi. Detection was by UV at 220 nm wavelength. Individual enantiomers were isolated from pure column fractions as described in the chemistry experimental, with quantitative recovery.

The enantiomeric purity of individual enantiomers was determined on a Perkin-Elmer (Norwalk, CT) Series 4 liquid chromatograph, using a 4.6 × 250 mm 10 μ-Chiracel OD column, a flow rate of 0.5 mL/min, and UV detection at 210 nm. Column conversion to reverse phase use followed the same procedure as described above for the preparative column. Performance of the converted Chiracel OD analytical column paralleled that of the commercially available reverse phase Chiracel OD-R analytical column. The mobile phase employed was 50% water/20% methanol/30% acetonitrile for compound **4**, 60% water/40% acetonitrile for compound **6**, and 40% water/60% acetonitrile for compound **15**. The ee's for individual enantiomers ranged from 99.3 to 100% (Table 1).

All solvents used for preparative and analytical HPLC were from Burdick and Jackson (Muskegon, MI), and water was Milli-Q (Milford, MA) treated.

**X-ray Determination.** We include here the results from single-crystal analyses of seven compounds from this work as well as 10 closely related derivatives from previous reports (Tables 3 and 4). Except for one compound (**3f**; ref 22), the crystals contain no solvent of crystallization. Unit cell parameters were obtained through least-squares analysis of the experimental diffractometer settings of 25 high-angle reflections. Crystal densities were measured by flotation methods. Intensities were measured on a CAD4 diffractometer using Cu Kα radiation ($\lambda$ = 1.5418 Å) at 23 °C with the $\omega - 2\theta$ variable scan technique and corrected only for Lorentz-polarization factors. Background counts were collected at the extremes of the scan for half of the time of the scan. No appreciable crystal decomposition was observed during data acquisition. The structures were solved by direct methods and refined on the basis of observed reflections [$I \geq 3\sigma(I)$], using the SDP[21] software package with minor local modifications. Least-squares weights $w = \sigma^{-2}(F_o)$ were calculated with the assumption that $\sigma^2 = \epsilon^2 + (\varrho I)^2$ where $\epsilon$ is the statistical counting error and $\varrho = 0.04$. The function minimized in the least-squares refinements was $\sum_w(|F_o| - |F_c|)^2$. $R$ is defined as $\sum||F_o| - |F_c||/\sum|F_o|$, while $R_w = [\sum_w(|F_o| - |F_c|)^2/\sum_w|F_o|^2]^{1/2}$. Except for the racemic base **15b** and **3e** (ref 17a) which gave limited intensity data, all structures were refined as anisotropic models. Most hydrogen positions were evident on difference maps during the latter stages of refinement. All hydrogens on carbons were introduced in idealized positions; those on heteroatoms were introduced only if they were observed on difference maps. No hydrogen parameters were varied. Final difference maps contained no significant features.

Anomalous dispersion effects were used to establish the *S*-absolute configuration at C4 for **15b**-A and **4b**-B: (i) Identical least-squares refinements of the enantiomeric *R*-isomers converged to significantly higher *R* factors for (*S*)-**15b**-A, $R$ ($R_w$) = 0.051 (0.061); for (*R*)-**15b**-A, $R$ ($R_w$) = 0.054 (0.064); for (*S*)-**4b**-B, $R$ ($R_w$) = 0.052 (0.061); for (*R*)-**4b**-B, $R$($R_w$) = 0.059 (0.069). (ii) For each structure, pairwise comparisons of the measured and calculated intensities of ~25 Friedel pairs of reflections most sensitive to anomalous effects were found to be completely consistent with the *S*-absolute configuration.

**Pharmacology. Vasorelaxation Assay.** The thoracic aorta was removed from male New Zealand white rabbits (1.5–3 kg), cleaned of connective tissue, cut into circumferential strips, and mounted at 4 g preload for isometric force recording in an oxygenated physiological salt solution of the following composition (mM): 140 NaCl, 4.7 KCl, 1.6 $CaCl_2$, 1.2 $Na_2HPO_4$, 1.2 $MgSO_4$, 5.6 D-glucose, 2.3 (*N*-morpholino)-propanesulfonic acid, and 0.02 sodium ethylenediaminetetraacetic acid. The strips were contracted with 110 mM KCl (equimolar substitution for NaCl), and then cumulative concentration–relaxation curves were obtained with test compound. $IC_{50}$ values are reported as concentration of test compound that caused 50% relaxation.[15]

**Vasoconstriction Assay.** Aortic strips were mounted as described above and contracted with 110 mM KCl to test for viability and define maximal force. Following washout and complete relaxation, the strips were equilibrated with 10 mM KCl (to increase reactivity), and then cumulative concentration–response curves were obtained with test compound. $EC_{50}$ values are reported as concentration of test compound that caused 50% of the maximal force previously developed in response to 110 mM KCl.[16]

**Radioligand Dihydropyridine Receptor Binding Assay.** Dihydropyridine receptor affinity was determined by inhibition of [$^3$H]nitrenedipine (NTP) binding to guinea pig myocardial membranes. Values are reported as $K_d$, calculated from observed $IC_{50}$ values obtained from the concentration of test compound that caused 50% inhibition of specific binding of NTP.[16b]

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**Supplementary Material Available:** Tables of positional parameters, thermal parameters, bond distances, and bond angles (51 pages). Selected torsional angles are presented in Table 5. Ordering information is given on any current masthead page.

## References

(1) (a) Rovnyak, G.; Andersen, N.; Gougoutas, J.; Hedberg, A.; Kimball, S. D.; Malley, M.; Moreland, S.; Porubcan, M.; Pudzianowski, A. Studies Directed toward Ascertaining the Active Conformation of 1,4-Dihdyropyridine Calcium Entry Blockers. *J. Med. Chem.* **1988**, *31*, 936. (b) Rovnyak, G.; Andersen, N.; Gougoutas, J.; Hedberg, A.; Kimball, S. D.; Malley, M.; Moreland, S.; Porubcan, M.; Pudzianowski, A. Active Conformation of 1,4-Dihydropyridine Calcium Entry Blockers. Effect of Size of 2-Aryl Substituent on Rotameric Equilibria and Receptor Binding. *J. Med. Chem.* **1991**, *34*, 2521.

(2) (a) Seidel, W.; Meyer, H.; Born, L.; Kasda, S.; Dompert, W. *Abstracts of Papers*, Division of Medicinal Chemistry; 187th National Meeting of the American Chemical Society, St. Louis, MO, April 8–13; American Chemical Society: Washington, DC, 1984. (b) *Ibid.* Rigid Calcium Antagonists of the Nifedipine-type: Geometric Requirements for the Dihydropyridine Receptor. *Proc. Eur. Symp. Quant. Struct.-Act. Relat.* **1984**, *5th*, [54QWAZ], 366–399.

(3) (a) Claremon, D. A.; Lumma, P. K. Novel Rigid Calcium Entry Blockers: Intramolecular Reactions of 1,4-Dihydropyridine Derivatives. *Abstracts of Papers*, Division of Medicinal Chemistry; 187th National Meeting of the American Chemical Society, St. Louis, MO, April 8–13; American Chemical Society: Washington, DC, 1984. (b) 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. Diethyl 3,6-Dihydro-2,4-dimethyl-2,6-methano-1,3-benzothiazine 5,11-dicarboxylates as Calcium Entry Antagonists: New Conformationally Restrained Analogues of Hantzsch 1,4-Dihydropyridines Related to Nitendipine as Probes for Receptor-Site Conformation. *J. Med. Chem.* **1987**, *30*, 690.

(4) Goldmann, S.; Stoltefuss, J. 1,4-Dihydropyridines: Effect of Chirality and Conformation of the Calcium Antagonist and Calcium Agonist Activities. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1559 and references therein.

(5) Triggle, D. J.; Langs, D. A.; Janis, R. A. Calcium Channel Ligands: Structure-Function Relationships of the 1,4-Dihydropyridines. *Med. Res. Rev.* **1989**, *9*, 123.

(6) (a) Schramm, M.; Thomas, G.; Towart, R.; Franckowiak, G. Activation of Calcium Channels by Novel Dihydropyridines: A new Mechanism for Positive Inotropic Agents. *Nature* **1983**, *303*, 535. (b) Goldmann, S.; Bossert, F.; Schramm, M.; Thomas, G. New 1,4-Dihydropyridines with Calcium-Agonist Effects. *Proc. VIIth Int. Symp. Med. Chem. Upsala* **1984**, *1*, 318. (c) Erne, P.; Burgisser, E.; Buhler, F. R.; Dubach, B.; Kuhnis, H.; Merier, M.; Rogg. Enhancement of Calcium Influx in Human Platelets by CGP 28392, A Novel Dihydropyridine. *Biochem. Biophys. Res. Commun.* **1984**, *118*, 842. (d) Holtje, H. D.; Marrer, S. A Molecular Graphics Study on Structure-action Relationships of Calcium-antagonistic and Agonistic 1,4-Dihydropyridines. *J. Comput.-Aided Mol. Des.* **1987**, *1*, 20.

(7) (a) Langs, D. A.; Kwon, Y. W.; Strong, P. D.; Triggle, D. J. Molecular Level Model for the Agonist/Antagonist Selectivity of the 1,4-Dihydropyridine Calcium Channel Receptor. *J. Comput.-Aided Mol. Des.* **1991**, *5*, 95 and references therein. (b) Zheng,

W.; Stoltefuss, J.; Goldmann, S.; Triggle, D. J. Pharmacologic and Radioligand Binding Studies of 1,4-Dihydropyridines in Rat Cardiac and Vascular Preparations: Stereoselectivity and Voltage Dependence of Antagonist and Activator Interactions. *Mol. Pharmacol.* **1992**, *41*, 535 and references therein.

(8) Holtje, H.-D. Molecular Modeling Studies on 1,4-Dihydropyridines Acting at the Ca-Channel. *Quant. Struct.-Act. Relat.* **1992**, *11*, 224.

(9) Bechem, M.; Hoffmann, H. The molecular Mode of Action of the Calcium Agonist Levo Bay K 8644 on the Cardiac Calcium Channel. *Pfluegers Arch.* **1993**, *424*, 343.

(10) Atwal, K.; Rovnyak, G. C.; Schwartz, J.; Moreland, S.; Hedberg, A.; Gougoutas, J.; Malley, M.; Floyd, D. Dihydropyrimidine Calcium Channel Blockers: 2-Heterosubstituted 4-Aryl-1,4-dihydro-6-methyl-5-pyrimidinecarboxylic Acid esters as Potent Mimics of Dihydropyrimidines. *J. Med. Chem.* **1990**, *33*, 1510. For other dihydropyrimidine calcium antagonists, see: Cho, H.; Ueda, M.; Shima, K.; Mizuno, A.; Hayashimatsu, M.; Ohnaka, Y.; Takeuchi, Y.; Hamaguchi, M.; Aisaka, K.; Hidaka, T.; Kawai, M.; Takeda, M.; Ishihara, T.; Funahashi, K.; Satoh, F.; Morita, M.; Noguchi, T. Dihydropyrimidines: Novel Calcium Antagonists with Potent and Long-Lasting Vasodilative and Antihypertensive Activity. *J. Med. Chem.* **1989**, *32*, 2399.

(11) Readily prepared from the corresponding benzaldehyde and methyl acetoacetate by standard Knoevenagle condensation.

(12) Methyl $\gamma$-acetoxy acetoacetate was prepared according to the procedure of DeGraw, J. I. An Improved Synthesis of Pilocarpine. *Tetrahedron* **1972**, *28*, 967.

(13) Mukaiyama, T.; Usui, M.; Saigo, K. The facile Synthesis of Lactones. *Chem. Lett.* **1976**, 49.

(14) Compound separation on the commercially available analytical reverse phase Chiracel OD-R (Chiracel Technologies, Inc., Exton, Pa) column was determined feasible. The manufacturer suggested the possibility of converting the normal phase Chiracel OD column to reverse phase use, determined in our hands to be functionally comparable to the Chiracel OD-R column, this process voiding all warranties however. Likewise, conversion of the preparative normal phase Chiracel OD column to reverse phase use (see Experimental Section for details) was found in our hands to be most effective for efficient separation of individual enantiomers of these compounds.

(15) Moreland, S.; Ushay, M. P.; Kimball, S. D.; Powell, J. R.; Moreland, R. S. Pressor responses induced by Bay K 8644 involve both release of adrenal catecholamines and calcium channel activation. *Br. J. Pharmacol.* **1988**, *93*, 994.

(16) Moreland, S.; Moreland, R. S. Effects of dihydropyridines on stress, myosin phosphorylation, and $V_o$ in smooth muscle. *Am. J. Physiol.* **1987**, *252*, H1049.

(17) Calcium antagonist activity has been shown to reside in individual *R*-enantiomers of related dihydropyrimidines. (a) Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, J. Z.; Schwartz, J.; Smillie, K. M.; Malley, M. F. Dihydropyrimidine Calcium Channel Blockers. 2. 3-Substituted-4-aryl-1,4-dihydro-6-methyl-5-pyrimidinecarboxylic Acid Esters as Potent Mimics of Dihydropyridines. *J. Med. Chem.* **1990**, *33*, 2629. (b) Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. Dihydropyrimidine Calcium Channel Blockers. 3. 3-Carbamoyl-4-aryl-1,2,3,4-tetrahydro-6-methyl-5-pyrimidinecarboxylic Acid Ester as Orally Effective Antihypertensive Agents. *Ibid.* **1991**, *34*, 806. (c) Rovnyak, G. C.; Atwal, K. S.; Hedberg, A.; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; O'Reilly, B. C.; Schwartz, J.; Malley, M. F. Dihydropyrimidine Calcium Channel Blockers. 4. Basic 3-Substituted-4-aryl-1,4-dihydropyrimidine-5-carboxylic Acid Esters. Potent Antihypertensive Agents. *Ibid.* **1992**, *35*, 3254.

(18) Note that the designation of absolute configuration for **4b**-B (*S*) and **15b**-A (*S*) is dependent on the nature of the 2′-aryl substituent. A 2′-thioalkyl group changes substituent priorities with respect to related dihydropyrmidine enantiomers having 3′-nitro-[17a,b] and 2′-(trifluoromethyl)aryl[17c] substitution.

(19) These and related dihydropyrimidines[17] have been shown to functionally correlate with [$^3$H]nitrendipine DHP receptor binding affinity. It is reasonable that conclusions derived for dihydropyrimidine calcium modulators discussed here can be generalized to include dihydropyridine calcium modulators.

(20) We do not distinguish between the possibilities of state-dependent single-site binding and distinct two-site binding for DHP calcium channel antagonist and agonist molecules. In either case, membrane polarization appears to be an important factor. For a recent reference supporting distinct two-site binding, see: Tang, S.; Yatani, A.; Bahinski, A.; Mori, Y.; Schwartz, A. Molecular Localization of Regions in the L-Type Calcium Channel Critical for Dihydropyridine Action. *Neuron* **1993**, *11*, 1013.

(21) SDP, Structure Determination Package, Enraf-Nonius, Bohemia, NY 11716. Scattering factors, including *f′* and *f″*, in the SDP software were taken from the *International Tables for Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV, Tables 2.2A and 2.3.1.

(22) Atwal, K. S.; Moreland, S. Dihydropyrimidine Calcium Channel Bockers 5. Bicyclic Dihydropyrimidines as Potent Mimics of Dihydropyridines. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 291.

(23) Atwal, K. S.; O'Reilly, B. C.; Gougoutas, J. Z.; Malley, M. Synthesis of Substituted 1,2,3,4-Tetrahydro-6-methyl-thioxo-5-pyrimidinecarboxylic Acid Esters. *Heterocycles* **1987**, *26*, 1189.

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