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PREPARATION AND *IN VITRO* BIOLOGICAL EVALUATION OF THE ENANTIOMERS OF THE DIHYDROPYRIDINE BMY 20014, A COMBINATION CALCIUM AND α_1-ADRENORECEPTOR ANTAGONIST

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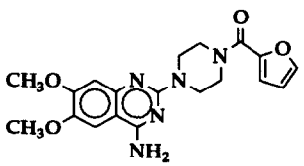
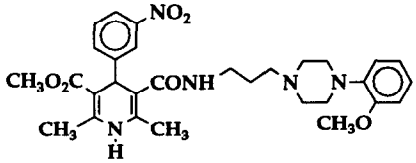
Abstract The R and S enantiomers of the 1,4-dihydropyridine amide BMY 20014 (**1**) were prepared from the corresponding chiral carboxylic acids via carbonyldiimidazole couplings. Pharmacologically, the R-(-)-amide **5a** demonstrates more potent Ca^{++} channel and α_1-adrenoreceptor antagonist properties than the S-(+) isomer.

Coronary heart disease (CHD) is the primary cause of death in the United States.[1] Among the risk factors for CHD are hypertension and abnormal plasma lipid levels. Two types of pharmacological agents which are known to beneficially affect these risks factors are calcium (Ca^{++}) entry blockers and α_1-adrenoreceptor antagonists.[2] Both types of drugs have been reported to control hypertension while α_1-adrenoreceptor antagonists also favorably modify plasma lipids.[3] Earlier, we prepared a series of compounds designed to incorporate structural features of both the Ca^{++} antagonist nifedipine and the α_1-adrenoreceptor antagonist prazosin.[4] From this series of compounds the combination Ca^{++} and selective α_1-adrenoreceptor antagonist BMY 20014 (**1**) and related agents were identified.[5,6] This report describes the chemical preparation and preliminary *in vitro* pharmacologic examination of both the R and S enantiomers of **1**.

Nifedipine

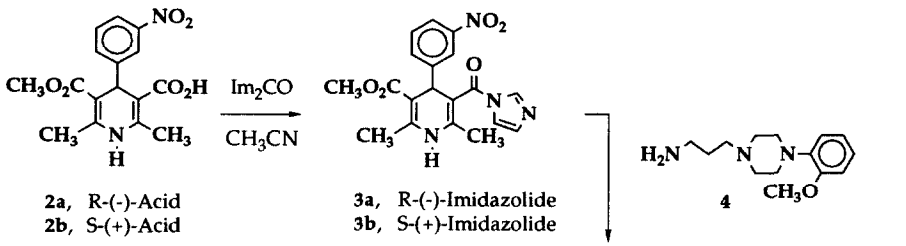


Prazosin



BMY 20014 (**1**)

As shown below, BMY 42803 (**5a**) and BMY 42804 (**5b**) were prepared from the corresponding R-(-) and S-(+) 1,4-dihydropyridine carboxylic acids **2a** and **2b**, respectively. The chiral acids were obtained by fractional crystallizations of the racemic acid[7] via their alkaloid salts.[8] The quinidine salt of the racemic acid afforded the R-(-)-acid **2a** and the (-)-cinchonidine salt gave the S-(+)-acid **2b**.[9] X-ray crystallographic studies on derivatives of these chiral dihydropyridines have been reported previously, allowing confident configurational assignments to be made.[10] Both chiral acids were subsequently converted to the intermediate imidazolides **3a** and **3b** using carbonyldiimidazole (Im_2CO).[11,12] Because of their vinylogous urea character, the resulting imidazolides were surprisingly stable intermediates which could be purified by recrystallization in refluxing alcoholic solvents. The final R and S amides **5a** and **5b** were obtained by treatment of the intermediate



2a, R-(-)-Acid
2b, S-(+)-Acid

3a, R-(-)-Imidazolide
3b, S-(+)-Imidazolide

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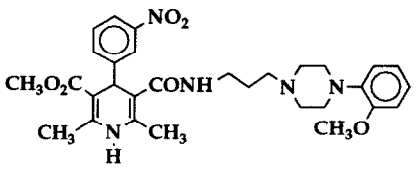


5a, R-(-)-Amide (BMY 42803)
5b, S-(+)-Amide (BMY 42804)

imidazolides with aminopropylpiperazine **4**[13] in CH_3CN. As expected, no loss of enantiomeric purity was observed during the conversion of the acids to the amides.[14,15]

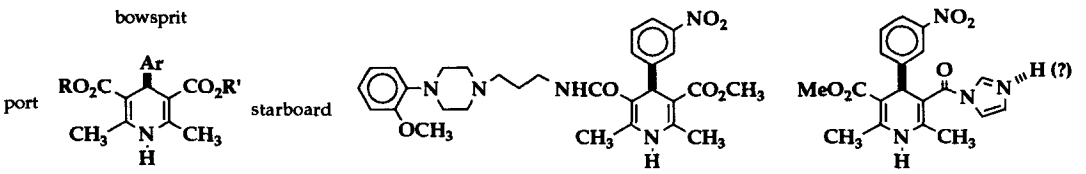
The *in vitro* Ca^{++} channel and α_1-adrenergic pharmacologic effects of **1** and enantiomers **5a** and **5b** are summarized in the Table. The standard reference agents nifedipine and prazosin and the chiral imidazolides **3a** and **3b** are also included. These data show that **5a**, the R-(-)-enantiomer of **1**, has the stereochemical configuration which favors binding in rat brain synaptosomes, while the S-(+)-enantiomer **5b** is considerably less interactive at this site (K_i's 16 vs 338 nM). This relationship is also maintained in a functional vascular assay against calcium-induced contractions in rat dorsal aorta (K_b's of 2.9 vs 107 nM). In addition to the calcium results, the R-enantiomer **5a** also displays a higher affinity for the α_1-receptor in rat brain synaptosomes than does the S-enantiomer demonstrating a eudismic ratio of 8.9 (K_i's 4.7 vs 42 nM). Similarly, **5a** exhibits more potent functional α_1-adrenergic antagonism in the inhibition of phenylephrine-induced contractions in rabbit dorsal aorta (K_b's, 8.3 vs 50 nM) than does **5b**. At this time, the origin of these α_1-adrenergic effects are unclear considering that the center of stereochemical difference between **5a** and **5b** is in the dihydropyridine portion of the molecule and is remote from the arylpiperazine terminus. Glossman has reported similar stereoselective α_{1a}-adrenergic binding differences with the enantiomers of niguldipine.[17]

The distinctly greater Ca^{++} channel potency of **5a** vs **5b** is consistent with and supports the *Goldmann dihydropyridine boat hypothesis*.[18] As proposed, the the Goldmann model predicts that when the C-4 dihydropyridine substituent is depicted as a β-aryl *bowsprit*, the more active enantiomer should have the *larger* ester (or amide) group located on the so-called *port* side of the molecule. Thus for the more potent enantiomer R-(-)-**5a**, the larger amide grouping is indeed located on the designated *port* side of the boat and is in agreement with the model. Interestingly, the precursor imidazolides **3a** and **3b** did not afford the expected results. Their observed Ca^{++} binding affinities in synaptosomes and functional Ca^{++} antagonism in vascular

Table. *In Vitro* Pharmacological Results[a]

Compounds	Receptor Binding		Functional Vascular Effects	
	Ca^{++} (K_i, nM)[b]	α_1 (K_i, nM)[c]	Ca^{++} (K_b, nM)[d]	α_1 (K_b, nM)[e]
R-Amide **5a**	16 (13-19)	4.6 (3.1-6.6)	2.9 (1.6-6.3)	8.3 (3.6-19)
S-Amide **5b**	338 (152-695)	36 (31-43)	107 (79-158)	50 (21-117)
R,S-Amide **1**	35 (27-44)	13 (9-18)	6.3 (4-12)	--
R-Imidazolide **3a**	181 (153-213)	>1000	31 (19-54)	--
S-Imidazolide **3b**	7.8 (6.9-8.4)	>1000	3.6 (2.2-5.5)	--
Nifedipine	0.53 (0.4-0.64)	>1000	0.50 (0.2-1.6)	>1000
Prazosin	>1000	0.3 (±0.1)[f]	>1000	1.6 (0.5-5.5)

[a] Values in parentheses represent the 95% confidence limits. [b] Displacement of [^{3}H]-PN-200-110 in rat brain synaptosomes, (Janis, R. A.; Maurer, S. C.; Sarmiento, J. G.; Bolger, G. T.; and Triggle, D. J. *Eur. J. Pharmacol.* **1982**, *82*, 191). [c] Displacement of [^{3}H]-prazosin in rat brain synaptosomes, (Miach, P. J.; Dausse, J. P.; Cardot, A.; and Meyer, P. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1980**, *312*, 23). [d] Contractions induced by K^+ depolarization in rat dorsal aorta, (reference 5c). [e] Contractions induced by phenylephrine in rabbit dorsal aorta, (reference 16). [f] SEM, (n=4).



Goldmann Dihydropyridine Boat BMY 42803 (**5a**) **3b**

strips were opposite to those of the corresponding amides **5a** and **5b**! Thus the configurational-activity relationship of the R-(-)- and S-(+)-imidazolides **3a** and **3b** does not appear to fit the same hypothesis as the amides. A possible explanation for this observation which is consistent with the Goldmann model might be that hydrogen bonding interactions between the imidazolide ring in **3b** and the receptor site are more important for proper orientation than steric fit for these types of heterocyclic substituted 1,4-dihydropyridines.

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6. BMY 20014 (**1**) displayed no significant affinity for the α_2-adrenoreceptor site in [^{3}H]-clonidine binding studies using rat brain synaptosomes. For an example of this type of binding, see: Braunwalder, A; Stone, G.; and Lovell, R. A. *J. Neurochem.* **1981**, *37*, 70.
7. Wehinger, E. *U.S. Patent* 4,285,955, **1981**.
8. Genain, G. *U.S. Patent* 4,920,225, **1990**.
9. R-(-)-Acid **2a**: mp 188-189 °C; $[\alpha]_D$ -18.84° (c=1.01, acetone). S-(+)-Acid **2b**: mp 187-188 °C; $[\alpha]_D$ +19.60° (c=0.954, acetone).
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12. R-(-)-Imidazolide **3a**: mp 194-195 °C; $[\alpha]_D$ -139.0° (c=0.790, CH_3OH); *Anal.* Calcd for $C_{19}H_{18}N_4O_5$: C, 59.69; H, 4.75; N, 14.66. Found: C, 59.49; H, 4.48; N, 14.56. S-(+)-Imidazolide **3b**: mp 195-196 °C; $[\alpha]_D$ + 139.0° (c=0.782, CH_3OH); *Anal.* Calcd for $C_{19}H_{18}N_4O_5$: C, 59.69; H, 4.75; N, 14.66. Found: C, 59.60; H, 4.55; N, 14.69.
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14. R-(-)-Amide **5a**•HCl: mp 216.5-218.5 °C; $[\alpha]_D$ -10.81° (c=1.10, CH_3OH); *Anal.* Calcd for $C_{30}H_{37}N_5O_6$•HCl•0.3 H_2O: C, 59.51; H, 6.43; N, 11.57; H_2O, 0.89. Found: C, 59.16; H, 6.66; N, 11.26; H_2O, 0.73. S-(+)-Amide **5b**•HCl: mp 218.5-220.5 °C; $[\alpha]_D$ +10.74° (c=1.10, CH_3OH); *Anal.* Calcd for $C_{30}H_{37}N_5O_6$•HCl•0.2 H_2O: C, 59.60; H, 6.42; N, 11.61; H_2O, 0.60. Found: C, 59.61; H, 6.68; N, 11.41; H_2O, 0.61.
15. The amides **5a** and **5b** were found to be >98% enantiomerically pure as determined by chiral HPLC analysis. The analysis was performed on a Baker Chiracel OD column (250x4.6 mm) using a mobil phase of 92:8 hexane:*n*-propanol containing 0.1% diethylamine at a flow rate of 1.8 mL/min.
16. Cylindrical rabbit dorsal aorta rings were suspended in tissue baths containing modified Tyrode solution and maintained at 3-g tension. Concentration-response curves to the agonist phenyephrine were conducted in the presence or absence of test compound after an incubation period of 1 h. The K_b values reported in the Table were determined from the dose-response curves. For K_b value calculations, see: Tallarida, R. J. and Murray, R. B. *Manual of Pharmacologic Calculations*, Springer-Verlag, 1987, p 297.
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