Dihydropyrimidine Calcium Channel Blockers. 4. Basic 3-Substituted-4-aryl-1,4-dihydropyrimidine-5-carboxylic Acid Esters. Potent Antihypertensive Agents

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We have examined a series of novel dihydropyrimidine calcium channel blockers that contain a basic group attached to either C5 or N3 of the heterocyclic ring. Structure–activity studies show that a 1-(phenylmethyl)-4-piperidinyl carbamate moiety at N3 and sulfur at C2 are optimal for vasorelaxant activity in vitro and impart potent and long-acting antihypertensive activity in vivo. One of these compounds (11) was identified as a lead, and the individual enantiomers **12a** (*R*) and **12b** (*S*) were synthesized. Two key steps of the synthesis were (1) the efficient separation of the diastereomeric ureido derivatives **29a/29b** and (2) the high-yield transformation of 2-methoxy intermediates **30a/30b** to the (*p*-methoxybenzyl)thio intermediates **31a/31b**. Chirality was demonstrated to be a significant determinant of biological activity, with the dihydropyridine receptor recognizing the enamino ester moiety (**12a**) but not the carbamate moiety (**12b**). Dihydropyrimidine **12a** is equipotent to nifedipine and amlodipine in vitro. In the spontaneously hypertensive rat, dihydropyrimidine **12a** is both more potent and longer acting than nifedipine and compares most favorably with the long-acting dihydropyridine derivative amlodipine. Dihydropyrimidine **12a** has the potential advantage of being a single enantiomer.

Introduction

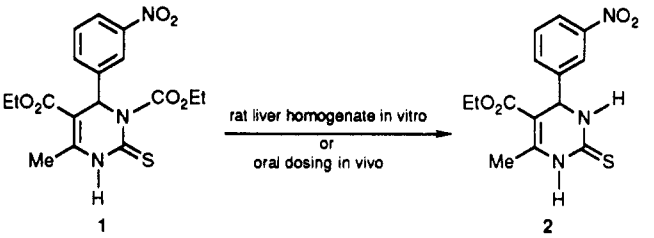
In a previous publication[1] we reported that 3-substituted-4-aryl-1,4-dihydropyrimidine-5-carboxylic acid esters are potent mimics of dihydropyridine calcium channel blockers. Despite their potent calcium channel blocking activity in vitro, most of the previously described 1,4-dihydropyrimidine analogs were devoid of antihypertensive activity when administered orally to spontaneously hypertensive rats (SHR). This lack of oral activity in the SHR was determined to result from the lability of the *N*3-(alkoxycarbonyl) group (Scheme I, biotransformation of **1** to **2**).[1]

A major objective of this work was to find a 1,4-dihydropyrimidine calcium channel blocker that possessed potent, long-acting antihypertensive activity following oral administration in the SHR,[2] an attribute of calcium channel blockers that is consistent with expected once-a-day efficacy in clinical hypertension. The chemistry[3] and initial structure–activity[1] for 3-substituted-4-aryl-1,4-dihydropyrimidine-5-carboxylic acid ester calcium channel blockers have been described. In this report, we describe the structure–activity relationship of analogs containing a basic amine group in the N3 or C5 position. Several of these compounds demonstrated potent, long-acting antihypertensive activity following oral administration in the SHR.

Chemistry[4]

Compounds **5a**, **5b**, and **9** containing amino functionality in the ester moiety, were prepared as shown in Scheme II. Benzylidene derivatives **14**, obtained from a substituted benzaldehyde and an acetoacetic acid (basic ester) as *E*/*Z* mixtures, were condensed with *S*-(*p*-methoxybenzyl)thiopseudourea to form the protected pyrimidine intermediates **15**. Reaction of **15** with ethyl chloroformate to give **16a** and **16b**, followed by deprotection and hydrochloride salt formation, gave the two carbamate derivatives **5a** and **5b**, respectively. Acylation of the N1 nitrogen was not observed.[3] Alkylation of **15** (W = 2-CF_3) with *n*-propyl bromide gave a mixture of N3 (47%) and N1 (31%) products,[3] separable by flash chromatography. Deprotection of the desired *N*3-propyl product **17** and hydrochloride salt formation afforded **9**.

Scheme I. Biotransformation of Carbamate Derivative



Preparation of derivatives containing amino functionality in the N3 carbamate group is shown in Scheme III. Protected dihydropyrimidines **18** and **19** were treated with

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(1) Atwal, K.; Rovnyak, G.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B.; Gougoutas, J. Z.; Schwartz, J.; Smillie, K.; Malley, M. Dihydropyrimidine Calcium Channel Blockers: 3-Substituted-4-aryl-1,4-dihydro-6-methyl-5-pyrimidinecarboxylic Acid Esters as Potent Mimics of Dihydropyridines. *J. Med. Chem.* **1990**, *33*, 2629–2635.
(2) Laffan, R. J.; Peterson, A.; Hitch, S. W.; Jeunelot, C. A Technique for Prolonged, Continuous Recording of Blood Pressure of Unrestrained Rats. *Cardiovasc. Res.* **1972**, *8*, 319.
(3) Atwal, K.; Rovnyak, G.; O'Reilly, B. C.; Schwartz, J. Substituted 1,4-Dihydropyrimidines. Synthesis of Selectively Functionalized 2-Hetero-1,4-Dihydropyrimidines. *J. Org. Chem.* **1989**, *54*, 5898–5907.
(4) The numbering system indicated in Figure 1 is used throughout the discussion in order to simplify discussion; proper nomenclature is assigned to each compound in the Experimental Section.
(5) Rodenkircken, R.; Bayer, R.; Steiner, R.; Bossert, F.; Meyer, H.; Moller, E. Structure-Activity Studies on Nifedipine in Isolated Cardiac Muscle. *Naunyn-Schiedeberg's Arch. Pharmacol.* **1979**, *310*, 69.
(6) Bossert, F.; Meyer, H.; Wehinger, E. 4-Aryldihydropyridines, a New Class of Highly Active Calcium Antagonists. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 762–768.
(7) Reference deleted in proof.
(8) Atwal, K.; Swanson, B.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. Dihydropyrimidine Calcium Channel Blockers: 3-Carbamoyl-4-aryl-1,2,3,4-tetrahydro-6-methyl-5-pyrimidinecarboxylic Acid Esters as Orally Effective Antihypertensive Agents. *J. Med. Chem.* **1991**, *34*, 806–811.
(9) Introduction of a bulky substituent at the α-position of the carbamate, as in α-methylbenzyl carbamate, does result in a significant effect of carbamate chirality (27×) on vasorelaxant activity (unpublished results).

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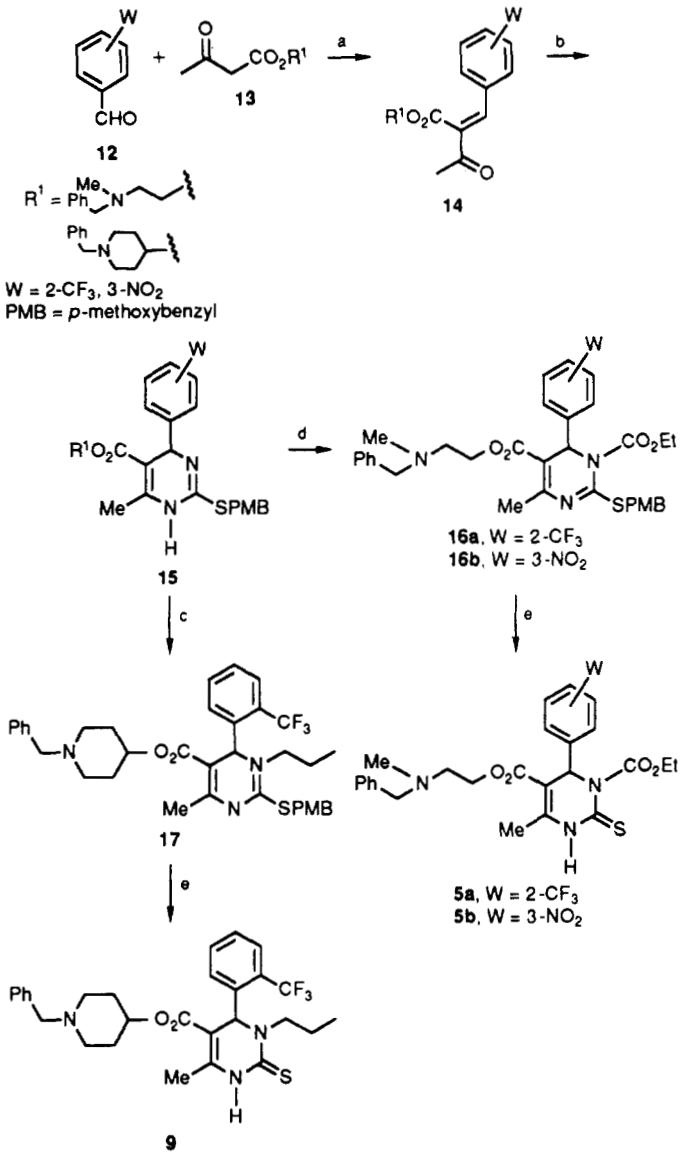
Scheme II.[a] Preparation of Basic Ester Analogs

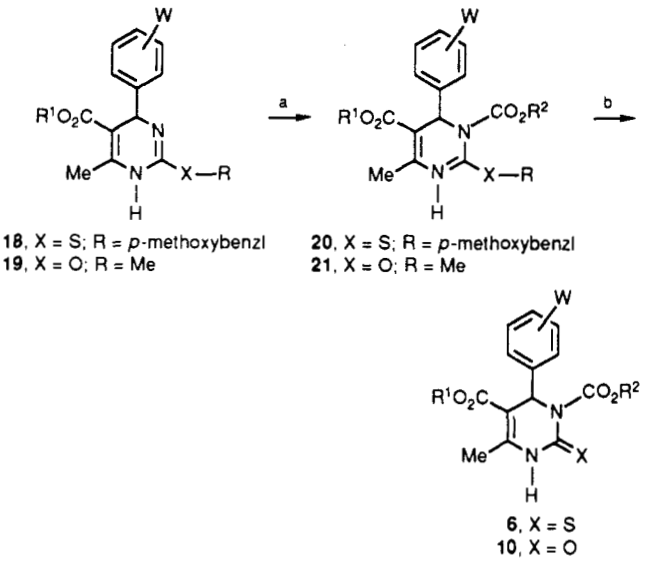


[a] (a) Piperidine/HOAc (cat.) in C_6H_6, reflux 2 h; see ref 14; (b) *S*-(*p*-methoxybenzyl)thiopseudourea hydrochloride, NaOAc, DMF, 75 °C, 4 h; see ref 3; (c) NaH, DMF, *n*-propyl bromide; (d) ethyl chloroformate in CH_2Cl_2/C_6H_5N; (e) CF_3CO_2H/C_2H_5SH in CH_2Cl_2, 16 h.

phosgene in acetonitrile/pyridine to give *N*3-(chlorocarbonyl) intermediates which were treated in situ with the appropriate amino alcohol (as its hydrochloride salt) dissolved in acetonitrile[3] to give *N*3-(alkoxycarbonyl) derivatives **20** and **21**. Use of the amino alcohol as its free base gave considerably lower yields. Deprotection employing trifluoroacetic acid/ethanethiol for the pyrimidine-2-thione analogs **20** and hydrochloric acid for the pyrimidin-2-one analogs **21**, followed by conversion to hydrochloride salts, afforded the desired products **6** and **10**, respectively.

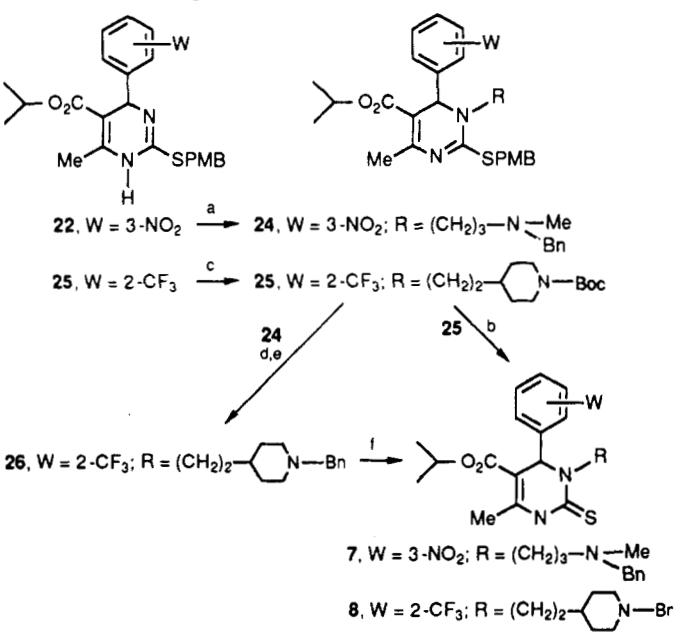
Scheme IV shows the preparation of N3 (methylbenzylamino)propyl analog **7** and N3 [1-(phenylmethyl)-4-piperidinyl]ethyl analog **8**. Alkylation of **22** with *N*-(3-chloropropyl)-*N*-methylbenzenemethanamine, followed by deprotection and hydrochloride salt formation, gave **7**; in this instance, there was no evidence for accompanying N1 alkylation. For **8** the required alkylating agent, 4-(2-bromoethyl)-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester, was prepared from the corresponding alcohol[10] with carbon tetrabromide/triphenylphosphine.

Scheme III.[a] Preparation of Basic Substituted Carbamate Derivatives (Tables I–III)



[a] (a) $COCl_2$/toluene (12.5%) in C_6H_5N/CH_3CN, followed by appropriate amino alcohol hydrochloride (R^2, Tables I and II) in CH_3CN; (b) for **20**, CF_3CO_2H/C_2H_5SH in CH_2Cl_2, 16 h; for **21**, 1 N HCl in aqueous THF, 2 h.

Scheme IV.[a] Preparation of Basic Substituted Alkyl Derivatives



[a] (a) K_2CO_3/DMF, *N*-(3-chloropropyl)-*N*-methylbenzenemethanamine; (b) CF_3CO_2H/C_2H_5SH in CH_2Cl_2, reflux 6 h; (c) NaH/DMF, 4-(2-bromoethyl)-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester; (d) HCO_2H; (e) $NaOH/H_2O/CH_2Cl_2$, $(n\text{-}Bu)_4HSO_4$, benzyl chloride; (f) CF_3CO_2H/C_2H_5SH in CH_2Cl_2, reflux 6 h.

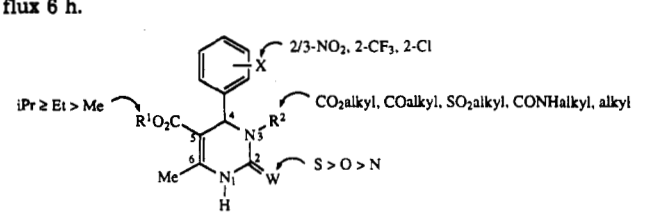
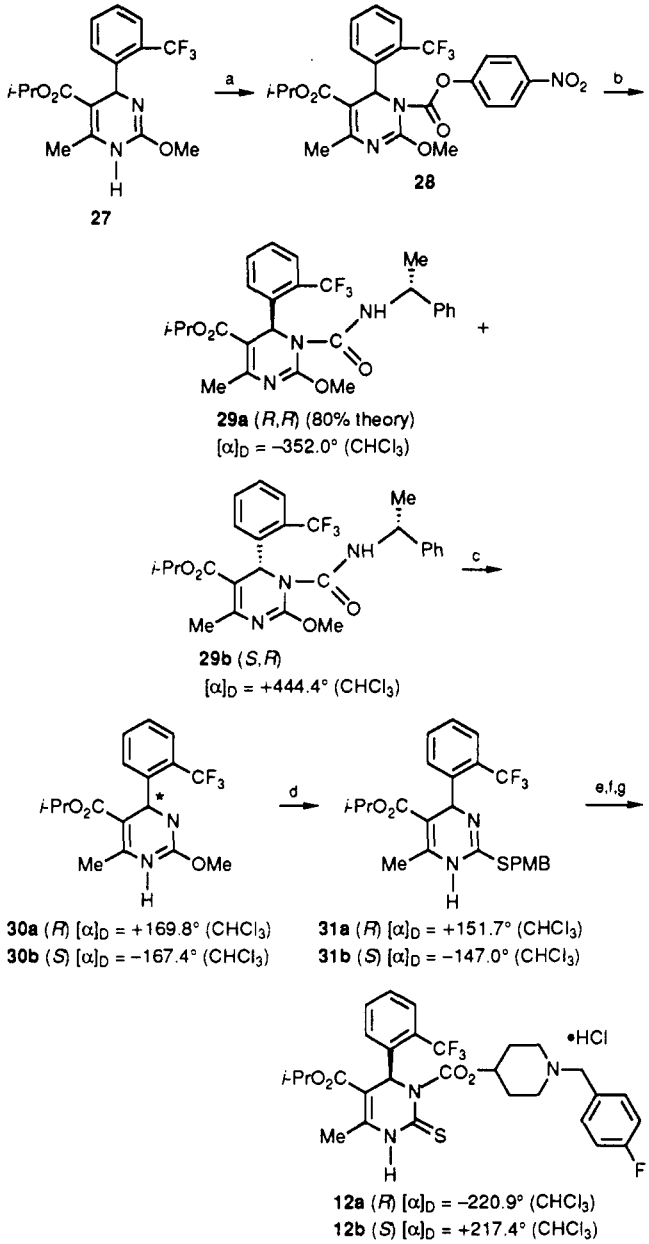


Figure 1. General structure–activity relationship of dihydropyrimidine calcium channel blockers. See refs 1 and 4.

Alkylation of pyridimine **23** proceeded in good yield to give predominantly N3 product **25** (N3/N1 ratio of 3:1). De-

Scheme V.[a] Preparation of Enantiomers **12a/12b**



[a] (a) *p*-Nitrophenyl chloroformate, C_6H_5N/CH_2Cl_2, 0–25 °C; (b) α-methylbenzylamine, EtOAc, 0–25 °C; (c) DBU, toluene, 100 °C, 1 h; (d) (4-methoxybenzyl)mercaptan, 2.5 mol% citric acid, 90 °C at 0.05 mmHg, 6 h; (e) phosgene/toluene (12.5%) in C_6H_5N/CH_3CN, followed by 1-[(4-fluorophenyl)methyl]-4-piperidinol hydrochloride in CH_3CN; (f) CF_3CO_2H/C_2H_5SH in CH_2Cl_2, 16 h; (g) HCl/IPE.

protection of **25** with formic acid and benzylation of the crude secondary amine under phase transfer conditions gave **26** in 51% overall yield. Removal of the *p*-methoxybenzyl group and salt formation provided **8**.

Enantiomers **12a** and **12b** of lead compound **11** (racemate) were prepared as outlined in Scheme V. Two key steps of the synthesis were (1) the efficient separation[1] of the diastereomeric ureido derivatives **29a/29b**; both isomers were >99.5% enantiomerically pure as determined by ^{1}H-NMR analysis[1] and (2) the high-yield transformation of 2-methoxy intermediates **30a/30b** to the (*p*-methoxybenzyl)thio intermediates **31a/31b**. N3-Acylation and deprotection as described above afforded the single enantiomers **12a** and **12b**. Stereochemical assignments of **12a** and **12b** were derived from the solid state X-ray structure determined for ureido diastereomer **29a**, which was shown to have the *R,R* configuration.

Results and Discussion

We have previously reported[1] the successful use of N3-substituted-2-hetero-1,4-dihydropyrimidines as potent mimics of 1,4-dihydropyridine calcium channel blockers. In that study, it was found that ortho and/or meta aromatic substitution (chloro, nitro, trifluoromethyl) was essential for optimal activity in vitro and that the ester alkyl group was a major determinant of potency in vitro (isopropyl > ethyl > methyl), both findings being in general accord with structure–activity relationships previously established for dihydropyridine calcium channel blockers.[5,6] Additionally, for this series of dihydropyrimidine calcium channel blockers, a substituent (alkyl, acyl, carbamate, sulfonyl, ureido) on N3 of the dihydropyrimidine ring was found to be a strict requirement for activity, and the order of potency for the 2-hetero atom was S > O > N (see Figure 1).[4]

From the initial work[1] defining basic structure–activity, we focused our attention on N3 alkyl carbamate analogs of 4-aryl-1,4-dihydro-2-thioxo(and 2-oxo)pyrimidine because this subset of compounds generally possessed the desired vasorelaxant potency in vitro. However, these compounds were ineffective for lowering blood pressure in the SHR following oral administration. Upon oral administration of ethyl carbamate compound **1** to rats, only carbamate-hydrolyzed product **2** (devoid of activity) was found in the circulation (Scheme I). This transformation was shown to occur rapidly in vitro employing rat liver homogenates. These results[1] demonstrated that metabolic biotransformation of **1** to **2** resulted in the observed lack of antihypertensive activity in the SHR.

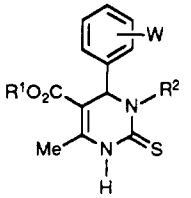
Unlike most analogs related to **1**,[1] the 4-[2-(trifluoromethyl)phenyl] N3 ethyl carbamate analog **3** showed modest antihypertensive activity in the SHR, although the duration of this effect was short. We prepared the more sterically hindered isopropyl carbamate derivative **5**, anticipating that it would undergo slower hydrolysis than the ethyl carbamate, but the duration of action of **5** in the SHR was only marginally better. Others have found that incorporation of a basic amine group into dihydropyridine calcium channel blockers, for example amlodipine,[12] resulted in prolongation of antihypertensive activity. Thus, incorporation of a basic *N*-methylbenzenemethanamine group into the N3 carbamate (**6a**) or the C5-ester (**5a**) of these dihydropyrimidine calcium channel blockers resulted in a modest improvement of the antihypertensive activity in vivo. This effect was noted for the 3-nitrophenyl analogs **6b** and **5b** as well. Replacement of the carbamate linkage with an alkyl (propyl) linkage (**7**) reduced potency in vitro,

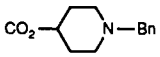
(10) Campbell, S. F.; Roberts, D. A.; Stubbs, J. K. Cyclic Sulfonamidoalkyl Substituted 4-Piperidinoquinazoline Cardiac Stimulants. U.S. Patent 4,489,075, Dec 18, 1984.

(11) Further evidence to support a nonreceptor-binding role for the N3 substituent evolves from the calcium channel blocking activity observed for a series of 2-(alkylthio)-1,4-dihydropyrimidines that lack any substitution at N3. Atwal, K.; Rovnyak, G.; Schwartz, J.; Moreland, S.; Hedberg, A.; Gougoutas, J.; Malley, M.; Floyd, D. Dihydropyrimidine Calcium Channel Blockers: 2-Heterosubstituted 4-Aryl-1,4-dihydropyrimidinecarboxylic Acid Esters as Potent Mimics of Dihydropyridines. *J. Med. Chem.* **1990**, *33*, 1510–1515.

(12) Arrowsmith, J. E.; Campbell, S. F.; Cross, P. E.; Stubbs, J. K.; Burges, R. A.; Gardiner, D. G.; Blackburn, K. J. Long Acting Dihydropyridine Calcium Antagonists. 2-Alkoxymethyl Derivatives Incorporating Basic Substituents. *J. Med. Chem.* **1986**, *29*, 1696–1702.

Table I. Effect of Nonbasic and Basic Ester/Carbamates on Biological Activity in Vitro and in Vivo



no.	W	R^1	R^2	vasorelaxation[a] IC_{50} (nM)	SHR %dec BP:[b] max/av at dose in μmol/kg, po 135	45	15	5
1[c]	3-NO_2	Et	CO_2Et	17 (16–20)	10/12	–	–	–
2[c]	3-NO_2	Et	H	>1000	6/8	–	–	–
3[c]	2-CF_3	Et	CO_2Et	41 (26–55)	25/6	–	–	–
4	2-CF_3	Et	CO_2-*i*-Pr	50 (34–92)	12/20	–	–	–
5a	2-CF_3	$(CH_2)_2N(Me)Bn$	CO_2Et	22 (14–44)	18/24	–	–	–
5b	3-NO_2	$(CH_2)_2N(Me)Bn$	CO_2Et	34 (33–35)	29/27	–	–	–
6a	2-CF_3	Et	$CO_2(CH_2)_2N(Me)Bn$	23 (18–39)	–	27/18	–	–
6b	3-NO_2	Et	$CO_2(CH_2)_2N(Me)Bn$	29 (24–33)	24/5	–	–	–
6c	2-CF_3	Et		9 (7–15)	50/50	42/41	38/33	21/20

[a] Vasorelaxant assay in vitro; concentration required to inhibit potassium-contracted rabbit aorta strips by 50%. The 95% confidence intervals are in parentheses. [b] Antihypertensive effect in the spontaneously hypertensive rat in vivo; max/ave is percent decrease (±5%) in blood pressure during 0–6/6–18-h time period postdrug administration at 135, 45, 15, and 5 μmole/kg, po (n = 6). [c] References 1 and 3.

but afforded significant activity in vivo. Combining the branched alkyl and basic amine functions in the 1-(phenylmethyl)-4-piperidinyl carbamate (N3) derivative **6c** resulted in a remarkable enhancement of antihypertensive activity in the SHR. This finding constituted a significant lead that was examined in greater detail.

Initially, we explored the lead by examining variations of N3 substituent, ester alkyl, and aromatic substitution. The five-membered 1-(phenylmethyl)-3-pyrrolidinyl carbamate analog **6d** was equally antihypertensive with the prototype **6c** (Table II); the new center of chirality in the carbamate portion is of little apparent consequence to biological activity (see also the related chiral carbamates **10i–10l**). Linkage of the 1-(phenylmethyl)-4-piperidinyl group to N3 by alkyl as in **8**, intended to enhance metabolic stability, resulted in some loss of potency in vitro but little loss of antihypertensive activity in the SHR. This result is similar to that observed for the related aminoalkyl analog **7**.

Conversion to isopropyl ester **6e** resulted in improved activity, particularly in the SHR, a result anticipated from our previous work.[1] Unlike the good calcium channel blocking activity shown by **5a** (2-CF_3-phenyl) and **5b** (3-NO_2-phenyl), having an acyclic basic amine in the C5 ester group, incorporation of the cyclic 1-(phenylmethyl)-4-piperidinyl moiety into the C5 ester group (**9**, 2-CF_3 phenyl) resulted in total loss of activity, both in vitro and in vivo. In this example, replacement of the N3 carbamate group by alkyl was justified on the basis of expected metabolic stability as well as retention of biological activity.[1,8]

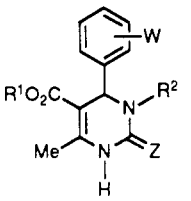
Within the series incorporating the more active isopropyl ester (C5) and 1-(phenylmethyl)-4-piperidinyl carbamate (N3) substitutions, the effect of aromatic substitution on antihypertensive activity in the SHR was determined to be 2-NO_2 (**6f**) > 2-CF_3 (**6e**) > 3-NO_2 (**6g**) ~ 2-Cl (**6h**).

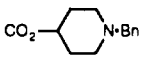
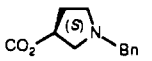
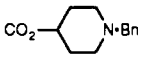
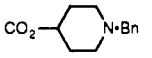
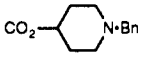
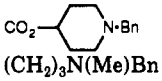
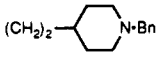
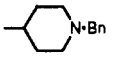
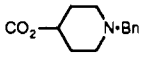
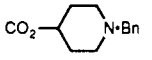
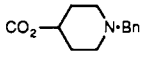
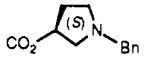
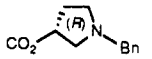
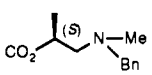
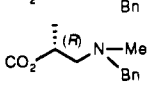
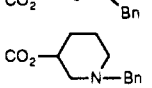
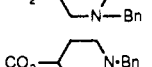
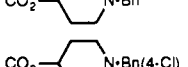
The 2-oxopyrimidine analogs **10e–g** were somewhat less active than the corresponding 2-thiopyrimidine analogs **6e–g** as vasorelaxants in vitro; however, the oxo analogs were particularly inferior to thio analogs in the SHR in vivo. To complete our structure–activity studies we explored structural variations of 2-oxopyrimidines, attempting to achieve parity of activity in the SHR with 2-thiopyrimidines such as prototype **6c**. Among modifications of the basic N3 carbamate group, we found that 1-(phenylmethyl)-3-pyrrolidinyl carbamates **10i** (*S*) and **10j** (*R*) lost significant activity in vitro, a surprising result in light of the good vasorelaxant activity in vitro observed for the corresponding 2-thiopyrimidine analog **6d** (*S*). Acyclic 1-methyl-2-[methyl(phenylmethyl)amino]ethyl carbamates **10k** (*S*) and **10l** (*R*) retained significant vasorelaxant activity in vitro but failed to reduce blood pressure in the SHR. These latter examples illustrate the minimal effect on vasorelaxant activity resulting from introduction of a chiral center at the point of attachment of the carbamate alkyl moiety.[9] Changing the position of attachment of the 1-(phenylmethyl)piperidinyl group from 4 (**10e**) to 3 (**10m**) reduced activity.

Since 2-thio-1,4-dihydropyrimidine analogs were noted to be more lipophilic than the less active 2-oxo-1,4-dihydropyrimidine analogs (thin-layer chromatography R_f's, measured octanol–water partition coefficients, and relative retention times on reverse-phase HPLC), we examined the effect on activity of structural modifications designed to enhance the lipophilicity of 2-oxo-1,4-dihydropyrimidine compounds. Attention was focussed on the C5 ester alkyl and N3 carbamate moieties to achieve enhanced lipophilicity to test this hypothesis since previous work[1,8] on these and related compounds suggested that these modifications would be least likely to adversely affect dihydropyridine receptor binding. Using 2-thio- and 2-oxodihydropyrimidine analogs **6e** and **10e**, respectively, as reference points for relative activity, increasing the size of the ester alkyl group (**10n**) or adding chlorine on the 1-(phenymethyl)-4-piperidinyl carbamate group (**10o**) in the oxo series failed to provide compounds possessing antihypertensive activity in the SHR equivalent to the reference 2-thio analog **6e**. Lipophilicity plays a minor role at most in determining activity in the SHR in vivo for this group of calcium channel blockers.

Compound **6e** was further modified by addition of a fluorine in the para position of the benzyl moiety as further protection against potential biotransformation (hydroxylation). The resulting compound **11** was equally active as the desfluoro analog **6e** and was chosen for preparation of the single enantiomers **12a** (*R*) and **12b** (*S*). Table III compares the activities of these four compounds and clearly shows the importance of chirality at C4 of the

Table II. Effect of Basic Carbamate and 2-Hetero Substituent on Biological Activity in Vitro and in Vivo

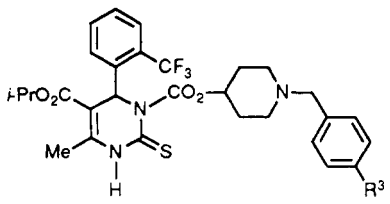


no.	Z	W	R^1	R^2	vasorelaxation[a] IC_{50} (nM)	SHR %dec BP:[b] max/av at dose in μmol/kg, po 45	15	5
6c	S	2-CF_3	Et		9 (7–15)	42/41	38/33	21/20
6d	S	2-CF_3	Et		2 (1–3)	50/31	–	–
6e[e]	S	2-CF_3	*i*-Pr		5 (1–3)	47/40	46/22	37/17
6f	S	2-NO_2	*i*-Pr		2 (1–3)	62/58	53/36	48/27
6g	S	3-NO_2	*i*-Pr		4 (3–5)	47/34	40/23	14/11
6h	S	2-Cl	*i*-Pr		5 (4–6)	32/19	41/21	25/10
7	S	3-NO_2	*i*-Pr	$(CH_2)_3N(Me)Bn$	72 (47–150)	28/23 (135 μmol/kg)		
8	S	2-CF_3	*i*-Pr		120 (56–240)	41/30	–	–
9	S	2-CF_3		*n*-Pr	>1000	0/0	–	–
10e[e]	O	2-CF_3	*i*-Pr		50 (34–74)	19/20	–	–
10f	O	2-NO_2	*i*-Pr		8 (7–9)	44/2	–	–
10g	O	3-NO_2	*i*-Pr		12 (8–18)	27/22 (135 μmol/kg)		
10i[c]	O	2-CF_3	*i*-Pr		790 (460–1300)	16/14	–	–
10j[c]	O	2-CF_3	*i*-Pr		360 (190–690)	24/18	–	–
10k	O	3-NO_2	*i*-Pr		57 (35–94)	14/10	–	–
10l[d]	O	3-NO_2	*i*-Pr		64 (41–100)	4/4	–	–
10m	O	2-CF_3	*i*-Pr		130 (92–190)	11/13	–	–
10n[e]	O	2-CF_3	*i*-Bu		98 (58–170)	12/10	–	–
10o[e]	O	2-CF_3	*i*-Pr		55 (32–95)	18/17	–	–

[a] Vasorelaxant assay in vitro; concentration required to inhibit potassium-contracted rabbit aorta strips by 50%. The 95% confidence interval is in parenthesis. [b] Antihypertensive effect in the spantaneously hypertensive rat in vivo; max/ave is percent decrease (±5%) in blood pressure during 0–6/6–18-h time period postdrug administration at 45, 15, and 5 μmol/kg, po (n = 6). [c] The intermediate (*R*)- and (*S*)-*N*-benzyl-3-hydroxypyrrolidines were prepared by literature methods.[15-17] [d] Reference 3. [e] Relative retention times on Whatman C_{18} bondapak, 30-cm reverse-phase column, pH 6.6 acetonitrile/water (1:1) buffer: **6e** (12.8 min), **10e** (8.1 min), **10n** (11.7 min), **10o** (14.6 min). Longer retention times reflect greater lipophilicity.

pyrimidine ring of 1,4-dihydropyrimidine calcium channel blockers. Consistent with previous findings,[1] the N3 (carbamate) substituent does not mimic an ester group at the receptor, the *S*-enantiomer **12b** being some 75-fold less potent as a vasorelaxant than the active *R*-enantiomer **12a**. The biological activity of **12a** was further compared with the prototypical dihydropyridine nifedipine as well as with the amino-substituted derivative amlodipine.[12] Nifedipine, while very potent in vitro, has an antihypertensive effect of short duration in the SHR mainly because of facile dihydropyridine to pyridine (inactive) ring oxidation; clinically, nifedipine requires multiple daily dosing. Amlodipine, on the other hand, causes a pronounced fall in blood pressure in the SHR that persists beyond 24 h; clinically, amlodipine is reported to be effective upon once daily administration. By comparison, dihydropyrimidine

Table III. Biological Activity of Enantiomers



no.	R^3	vasorelaxation[a] IC_{50} (nM)	SHR %dec BP:[b] max/ave at dose in μmol/kg, po 45	15	5	1.7
6e	H	5 (4–6)	47/40	46/22	37/17	–
11	F	7 (4–11)	51/32	45/18	38/15	–
12a (*R*)	F	15 (8–27)	60/46	50/28	40/18	33/16
12b (*S*)	F	>1000	–	0/0	–	–
nifedipine		2 (1–3)	33/22	26/15	12/10	–
amlodipine		3 (2–4)	46/37	34/20	23/11	–

[a] Vasorelaxant assay in vitro; concentration required to inhibit potassium-contracted rabbit aorta strips by 50%. The 95% confidence interval is in parenthesis. [b] Antihypertensive effect in the spontaneously hypertensive rat in vivo; max/ave is the percent decrease (±5%) in blood pressure during 0–6/6–18-h time period postdrug administration at 45, 15, 5, and 1.7 μmol/kg, po (n = 6).

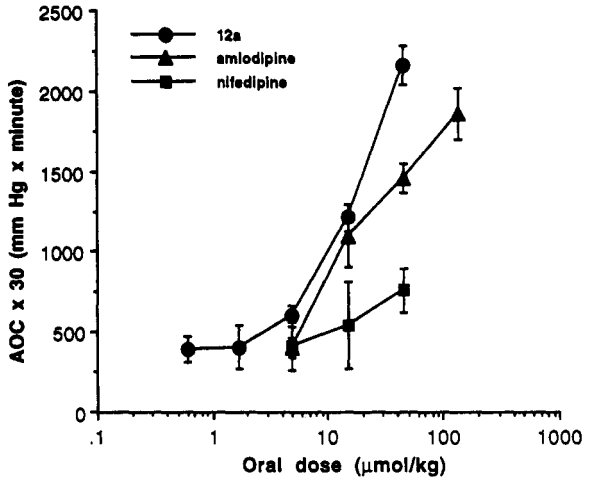


Figure 2. Antihypertensive effects of nifedipine, amlodipine and dihydropyrimidine **35a** in the spontaneously hypertensive rat. AOC = area-over-the-curve was calculated for the mean data points calculated from the peak effect (antihypertension) detected over 30-min intervals. Each data point represents the cumulative effect calculated for the first 48 such intervals (12 h) after drug administration for six animals. Vertical bars denote SEM.

compound **12a** was found to be more potent than amlodipine in the SHR, causing a pronounced fall in blood pressure that, likewise persists beyond 24 h. The antihypertensive effects of nifedipine, amlodipine, and **12a** are graphically illustrated in Figure 2.

The tolerance of various N3 substituents (as noted previously) for vasorelaxant activity, coupled with little or no effect on activity of a chiral center in the carbamate moiety, suggests that the group at N3 contributes little to specific dihydropyridine receptor binding;[1,8,11] the N3 substituent serves merely to orient the dihydropyrimidine ring and other appended groups in the conformation required for productive interaction with the receptor. This is further supported by the observation that calcium channel blocking and antihypertensive activity resides solely in the *R*-enantiomer **12a**.

In conclusion, we have examined a series of novel dihydropyrimidine calcium channel blockers that contain a basic group attached to either C5 or N3 of the heterocyclic ring. Derivatives having a 1-(phenylmethyl)-4-piperidinyl carbamate moiety attached at N3 are equipotent to nifedipine and amlodipine in the rabbit aorta smooth muscle vasorelaxant assay in vitro. Further, analogs bearing sulfur at the 2-position show greater antihypertensive activity in the SHR than the corresponding 2-oxo compounds. One of these compounds (**11**) was identified as a lead, and the individual enantiomers **12a** (*R*) and **12b** (*S*) were synthesized. Pyrimidine chirality is demonstrated to be a significant determinant of biological activity, with the dihydropyridine receptor recognizing the enamino ester moiety (**12a**) but not the carbamate moiety (**12b**). In contrast to nifedipine, dihydropyrimidine **12a** is both more potent and longer acting in the spontaneously hypertensive rat. Moreover, in this model of hypertension, **12a** compares most favorably with the long-acting derivative amlodipine. Thus, the objectives originally set forth for this work are met with dihydropyrimidine calcium channel blocker **12a**, which has both potent vasorelaxant activity in vitro and orally effective, long duration antihypertensive activity in vivo.

Experimental Section

Chemistry. All melting points were taken on a capillary melting point apparatus and are uncorrected. The infrared spectra were recorded with a Perkin-Elmer 983 spectrophotometer in KBr pellets. ^{1}H- 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 3,6-Dihydro-4-methyl-2-thioxo-6-[2-(trifluoromethyl)phenyl]-1,5(2*H*)-pyrimidinedicarboxylic Acid 5-Ethyl 1-(1-Methylethyl) Ester (4). Starting with 1,4-dihydro-2-[[(4-methoxyphenyl)methyl]thio]-6-methyl-4-[2-(trifluoromethyl)phenyl]-5-pyrimidinecarboxylic acid ethyl ester,[3] and using previously described methodology,[3] **5** was obtained in 39% yield: mp 129–130 °C; IR (KBr) 1746, 1708, 1508, 1310, 1229, 1104 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.93 (s, 1 H), 7.65 (d, J = 7.2 Hz, 1 H), 7.54 (m, 2 H), 7.44 (m, 1 H), 6.57 (s, 1 H), 5.04 (quint, J = 6.0 Hz, 1 H), 4.12 (m, 2 H), 2.41 (s, 3 H), 1.32, 1.26 (2 d, J = 6.0 Hz, 6 H), 1.16 (t, J = 7.2 Hz, 3 H); ^{13}C-NMR ($CDCl_3$) δ 174.8, 164.4, 152.3, 142.5, 138.5, 132.7, 129.3, 128.7, 127.7 (d, J_{CF} = 30 Hz), 126.8 (d, J_{CF} = 6 Hz), 105.8, 73.5, 60.6, 54.1, 21.2, 21.1, 17.6, 13.9. Anal. ($C_{19}H_{21}F_3N_2O_4S$) C, H, N, F, S.

Preparation of 3,6-Dihydro-4-methyl-2-thioxo-6-[2-(trifluoromethyl)phenyl]-1,5(2*H*)-pyrimidinedicarboxylic Acid, 1-Ethyl 5-[2-[Methyl(phenylmethyl)amino]ethyl] Ester, Monohydrochloride (5a). (a) Preparation of 14 (W = 2-CF_3, R^1 = (methylbenzylamino)ethyl]: a solution of 2-(methylbenzylamino)ethyl acetoacetate (5.0 g, 0.02 mol) and 2-(trifluoromethyl)benzaldehyde (3.5 g, 0.02 mol) in 100 mL of benzene was treated with 1 mL of piperidine and 0.5 mL of HOAc and heated at reflux for 1 h, collecting 1 equiv of water. Solvent was evaporated, and the residue, in ethyl acetate, was washed with potassium hydrogen sulfate, sodium bicarbonate, water, and brine. The dried solution was evaporated in vacuo to give 6.9 g (85%) of an oil. Anal. ($C_{22}H_{22}F_3NO_3$) C, H, N.

(b) Preparation of 15 [W = 2-CF_3, R^1 = (methylbenzylamino)ethyl]: a mixture of **14** (6.9 g, 0.017 mol) and *S*-(*p*-methoxybenzyl)thiopseudourea hydrochloride (3.96 g, 0.017 mol) in 50 mL of dimethylformamide was treated with sodium acetate (1.4 g, 0.017 mol) and heated for 4 h at 70 °C. The mixture was diluted with ethyl acetate and washed with water, sodium bicarbonate, and brine, dried, and evaporated in vacuo to give 9.6 g. Flash chromatography using ethyl acetate/hexane (1:2) yielded 3.5 g (36%) of an oil. Anal. Calcd for $C_{31}H_{32}N_3O_3F_3S$: C, 63.79; H, 5.52; N, 7.19; found: C, 63.51; H, 5.76; N, 6.36.

(c) Preparation of 16a: a solution of **15** (3.5 g, 0.006 mol) and pyridine (0.95 g, 0.012 mol) in 50 mL of dichloromethane was cooled to 5 °C and treated dropwise with a solution of ethyl chloroformate (0.78 g, 0.007 mol) in 3 mL of dichloromethane. After stirring for 4 h, additional ethyl chloroformate (0.4 g, 0.0035

mol) was added and stirring was continued for 3 h. The solution was diluted with dichloromethane, washed with water, sodium bicarbonate, and brine, and then dried and evaporated to give 3.84 g of crude product. An ether solution of this material was treated with an ether solution of 1 equiv of oxalic acid to precipitate 1.7 g of salt. This material was converted to 1.3 g of base which was flash chromatographed using ethyl acetate/hexane (1:3) to give 0.89 g (22%) of an oil. Anal. Calcd for $C_{34}H_{36}N_3F_3O_5S$: C, 62.27; H, 5.53; N, 6.40; found: C, 61.36; H, 5.50; N, 6.09.

(d) Preparation of 3,6-Dihydro-4-methyl-2-thioxo-6-[2-(trifluoromethyl)phenyl]-1,5(2*H*)-pyrimidinedicarboxylic Acid, 1-Ethyl 5-[2-[Methyl(phenylmethyl)amino]ethyl] Ester, Monohydrochloride (5a). A solution of **16a** (1.17 g, 0.0017 mol) in 20 mL of dichloromethane was treated with trifluoroacetic acid (0.68 mL, 0.0086 mol) and ethanethiol (0.28 g, 0.0044 mol) and stirred overnight at room temperature. Solvent was evaporated, and the residue, in ethyl acetate, was washed with sodium bicarbonate, water, and brine, and then dried and evaporated to give 1.1 g of crude product. Flash chromatography using EtOAc/hexane (1:2) gave 0.79 g (83%) of product as an oil. A solution of the base in acetonitrile was treated with 1 equiv of ethereal hydrochloric acid, and then concentrated to an oil which was triturated with ethyl acetate to form 0.60 g (71%) of a yellow solid: mp 188–190 °C; IR (KBr) 1720, 1697, 1505, 1317, 1230 cm^{-1}; ^1H-NMR (CD_3OD) δ 7.68 (d, J = 7.2 Hz, 1 H), 7.59 (d, J = 7.2 Hz, 1 H), 7.40–7.54 (m, 7 H), 6.59 (s, 1 H), 4.46–4.60 (m, 1 H), 4.33–4.46 (m, 1 H), 4.23–4.33 (br s, 2 H), 4.22 (q, J = 7.2 Hz, 2 H), 3.35–3.48 (m, 2 H), 2.73 (s, 3 H), 2.43 (s, 3 H), 1.22 (t, J = 7.2 Hz, 3 H); ^{13}C-NMR ($CDCl_3$, free base) δ 175.0, 164.2, 152.7, 142.7, 138.6, 132.5, 129.0, 128.6, 128.0, 126.8, 106.0, 64.4, 62.1, 55.0, 53.7, 42.0, 17.4, 13.4. Anal. ($C_{26}H_{28}N_3F_3O_4S$·HCl) C, H, N, Cl, S.

Preparation of 3,6-Dihydro-4-methyl-6-(3-nitrophenyl)-2-thioxo-1,5(2*H*)-pyrimidinedicarboxylic Acid, 1-Ethyl 5-[2-[Methyl(phenylmethyl)amino]ethyl] Ester, Monohydrochloride (5b). Using the methodology described for the preparation of **5a**, but substituting 3-nitrobenzaldehyde in the first step for the synthesis of **14** (W = 3-NO_2, R = (benzylmethylamino)ethyl, **5b** was obtained: mp 79–81 °C; IR (KBr) 1718, 1532, 1507, 1225 cm^{-1}; ^1H-NMR (CD_3OD) δ 8.20 (s, 1 H), 8.13 (d, J = 7.0 Hz, 1 H), 7.75 (d, J = 7.6 Hz, 1 H), 7.58 (dd, J = 7.6, 8.2 Hz, 1 H), 7.46 (s, 5 H), 6.35 (s, 1 H), 4.58 (br s, 2 H), 4.35 (q, J = 7.6 Hz, 2 H), 4.31 (br s, 2 H), 3.52 (br s, 2 H), 2.80 (s, 3 H), 2.40 (s, 3 H), 1.34 (t, J = 7.0 Hz, 3 H); ^{13}C-NMR ($CDCl_3$, free base) δ 176.0, 164.4, 153.4, 148.1, 143.8, 141.0, 138.4, 132.4, 129.4, 128.4, 127.9, 126.7, 122.8, 121.4, 106.0, 64.3, 62.4, 62.1, 55.8, 55.1, 41.9, 17.2, 13.6. Anal. ($C_{25}H_{28}N_4O_6S$·HCl) C, H, N, Cl, S.

Preparation of 1,2,3,6-Tetrahydro-4-methyl-1-propyl-2-thioxo-6-[2-(trifluoromethyl)phenyl]-5-pyrimidinedicarboxylic Acid, 1-(Phenylmethyl)-4-piperidinyl Ester, Monohydrochloride (9). (a) Preparation of 14 (W = 2-CF_3, R^1 = 1-(phenylmethyl)-4-piperidinyl): the procedure described above for the preparation of **5a** was used to prepare this intermediate in a similar fashion to give an oil product (86%). Anal. ($C_{24}H_{24}F_3NO_3$) C, H, N.

(b) Preparation of 15 (W = 2-CF_3, R^1 = 1-(phenylmethyl)-4-piperidinyl): the procedure described above for the preparation of **5a** was used to prepare this intermediate in a similar fashion. Purification by flash chromatography using ethyl acetate/hexane (1:1.5) gave 4.57 (41%) of product as a yellow foam. Anal. Calcd for ($C_{33}H_{34}F_3N_3O_3S$) C, H, N.

(c) Preparation of 17: a suspension of 50% NaH (0.35 g, 0.0073 mol) in 40 mL of dimethylformamide was treated with a solution of **15** (3.0 g, 0.0049 mol) in 20 mL of dimethylformamide. The mixture was heated for 30 min at 70 °C, cooled, and treated with bromopropane (1.2 g, 0.0098 mol). After stirring overnight at room temperature, ethyl acetate was added and the mixture was washed with water (2×), sodium bicarbonate, water, and brine. The dried solution was evaporated to give 3.2 g of N3/N1 product mixture as a viscous oil: R_f = 0.35, 0.45 (ethyl acetate/hexane 1:1). Flash chromatography using ethyl acetate/hexane (1:2) afforded **17** (47%) as a yellow oil (R_f = 0.45). Anal. Calcd for $C_{36}H_{40}F_3N_3O_3S$: C, 66.34; H, 6.19; N, 6.45; found: C, 67.74; N, 6.50; N, 6.21.

(d) Preparation of 1,2,3,6-Tetrahydro-4-methyl-1-propyl-2-thioxo-6-[2-(trifluoromethyl)phenyl]-5-pyrimidinedicarboxylic Acid, 1-(Phenylmethyl)-4-piperidinyl Ester, Monohydrochloride (9). Deprotection of **17** (1.8 g, 0.0027 mol) with trifluoroacetic acid and ethanethiol as described above afforded 1.76 g of an oil that was purified by flash chromatography, using ethyl acetate/hexane (1:2) to give 0.48 g (33%) of product as a viscous oil. Anal. Calcd for $C_{28}H_{32}F_3N_3O_2S$: C, 63.26; H, 6.07; N, 7.91; found: C, 63.99; H, 6.55; N, 7.02. A solution of the above free base in chloroform was treated with 1 equiv of ethereal hydrochloric acid. Solvent was stripped, and the residue was treated with ether to form 0.37 g (72%) of a cream colored solid: mp 141–145 °C dec; IR (KBr) 1702, 1645, 1534, 1461, 1307, 1216 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 7.60–7.75 (m, 3 H), 7.40–7.60 (m, 1 H), 7.50 (s, 5 H), 5.94 (s, 1 H), 4.80–5.10 (m, 1 H), 4.30 (s, 2 H), 4.10–4.30 (m, 1 H), 3.0–3.35 (m, 4 H), 3.25–3.35 (m, 2 H), 2.30 (br s, 3 H), 1.95–2.20 (m, 2 H), 1.60–1.80 (m, 1 H), 1.35–1.55 (m, 1 H), 0.85 (t, J = 7.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, free base) δ 174.2, 164.6, 142.3, 140.6, 138.0, 133.1, 130.1, 129.0, 128.6, 128.1, 127.0, 126.5, 126.3, 103.1, 71.3, 62.6, 55.7, 52.6, 50.9, 30.6, 30.4, 19.4, 18.3, 10.7. Anal. ($C_{28}H_{32}F_3N_3O_2S$·HCl·1.0H_2O) C, H, N, Cl, S.

General Method for the Preparation of Basic Substituted Carbamate Analogs 6a–h, 10e–o, and 11. Preparation of 3,6-Dihydro-4-methyl-2-thioxo-6-[2-(trifluoromethyl)-phenyl]-1,5(2*H*)-pyrimidinedicarboxylic Acid, 5-(1-Methylethyl) 1-[1-(Phenylmethyl)-4-piperidinyl] Ester, Monohydrochloride (6e). (a) Preparation of 20 (W = 2-CF_3; R^1 = iPr; R^2 = 1-(phenylmethyl)-4-piperidinyl): a solution of **18**[3] (W = 2-CF_3; R^1 = iPr) (2.0 g, 0.004 mol) in 45 mL of acetonitrile and 25 mL of pyridine under argon at room temperature was treated with phosgene (6.3 mL of 12.5% toluene soln, 0.008 mol), followed 0.5 h later with the addition of *N*-benzyl-4-hydroxypiperidine hydrochloride (2.3 g, 0.012 mol) in 5 mL of acetonitrile. After stirring overnight, volatiles were removed in vacuo and the residue dissolved in ethyl acetate and washed with 10% potassium hydrogen sulfate, water, 10% sodium carbonate, water, and brine. The dried organic solution was concentrated to give 2.4 g of an oil. Purification by flash chromatography using ethyl acetate/hexane (1:1) afforded 1.16 g (40%) of product as an oil. Anal. Calcd for $C_{37}H_{40}F_3N_3O_5S$: C, 63.87; H, 5.79; N, 6.04; found: C, 64.71; H, 5.97; N, 5.84.

(b) Preparation of 3,6-Dihydro-4-methyl-2-thioxo-6-[2-(trifluoromethyl)phenyl]-1,5(2*H*)-pyrimidinedicarboxylic Acid, 5-(1-Methylethyl) 1-[1-(Phenylmethyl)-4-piperidinyl] Ester, Monohydrochloride (6e). Deprotection of **20** (1.1 g, 1.5 mmol) with trifluoroacetic acid and ethanethiol as described above gave 1.1 g of crude material that was purified by flash chromatography using ethyl acetate/hexane (1:1) to give 0.79 g (62%) of product as a oil. This was dissolved in 10 mL of acetonitrile and treated with 1 equiv of ethereal hydrochloric acid to afford 0.58 g (62%) **6e** as yellow crystals: IR (KBr) 1716, 1708, 1501, 1311, 1234 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 12.3 (br s, 1 H), 9.1 (s, 1 H), 7.69 (d, J = 7.5 Hz, 1 H), 7.62 (br s, 2 H), 7.50 (t, J = 7.5 Hz, 1 H), 7.42 (s, 5 H), 6.83 (s, 1 H), 5.17 (br s, 2 H), 5.00 (quint, J = 6.0 Hz, 1 H), 4.08 (br s, 2 H), 2.95–3.35 (m, 4 H), 2.40–2.80 (m, 2 H), 2.52 (s, 3 H), 1.90–2.10 (m, 2 H), 1.04, 1.25 (2 t, J = 6.0 Hz, 6 H); ^{13}C-NMR ($CDCl_3$, free base) δ 174.7, 163.9, 152.2, 142.5, 138.2, 137.7, 132.4, 129.2, 128.8, 128.6, 128.0, 126.8, 126.6 (d, J_{CF} = 5 Hz), 106.2, 75.3, 68.2, 62.6, 53.8 (d, J_{CF} = 2 Hz), 50.0, 29.9, 21.5, 21.1, 17.4. Anal. ($C_{29}H_{32}F_3N_3O_4S$·HCl·0.25H_2O) C, H, N, Cl, S.

Preparation of 3,6-Dihydro-4-methyl-2-oxo-6-[2-(trifluoromethyl)phenyl]-1,5(2*H*)-pyrimidinedicarboxylic Acid, 5-(1-Methylethyl) 1-[1-(Phenylmethyl)-4-piperidinyl] Ester, Monohydrochloride (10e). (a) Preparation of 21 (W = 2-CF_3; R^1 = iPr; R^2 = 1-(phenylmethyl)-4-piperidinyl): a solution of **19**[3] (W = 2-CF_3; R^1 = iPr) (3.0 g, 0.0084 mol) in 60 mL of acetonitrile and 30 mL of pyridine at room temperature was treated with phosgene (12.5 mL of 12.5% toluene solution, 1.58 g, 0.0160 mol), followed 1 h later with *N*-benzyl-4-hydroxypiperidine hydrochloride (4.67 g, 0.0244 mol) in 15 mL of acetonitrile. After stirring overnight, volatiles were removed in vacuo and the residue, dissolved in ethyl acetate, was washed with 10% potassium hydrogen sulfate, water, 10% sodium carbonate, water, and brine. The dried organic solution was concentrated to give 4.7 g of an oil. Purification by flash chromatography using ethyl acetate/hexane (1:2) afforded 3.16 g (64%) of product as an oil. Anal. ($C_{30}H_{34}F_3N_3O_5$) C, H, N.

(b) Preparation of 3,6-Dihydro-4-methyl-2-oxo-6-[2-(trifluoromethyl)phenyl]-1,5(2*H*)-pyrimidinedicarboxylic Acid, 5-(1-Methylethyl) 1-[1-(Phenylmethyl)-4-piperidinyl] Ester, Monohydrochloride (10e). A solution of **21** (3.0 g, 0.005 mol) in 40 mL of tetrahydrofuran was treated with 30 mL of 2 N hydrochloric acid, stirred for 4 h, then evaporated in vacuo to remove most of the tetrahydrofuran. Ethyl acetate was added and the mixture was made basic by gradual addition of saturated sodium bicarbonate. The organic phase was separated and washed with water (2×) and brine. The dried organic solution was evaporated to give 2.8 g of a foam that was purified by flash chromatography using ethyl acetate/hexane (3:1) to give 1.35 g (46%) of product as an oil. This was dissolved in 20 mL of acetonitrile and treated with 1 equiv of ethereal hydrochloric acid, and then concentrated to approximately one-half volume to initiate crystallization of 1.1 g (77%) of **10e**: mp 216–218 °C; IR (KBr) 1758, 1733, 1709, 1643, 1314, 1222, cm^{-1}; ^1H-NMR (CD_3OD) δ 7.61 (d, J = 6.5 Hz, 1 H), 7.40–7.65 (m, 8 H), 6.90 (s, 1 H), 5.05–5.20 (m, 1 H), 4.97 (quint, J = 6.0 Hz, 1 H), 4.32 (s, 2 H), 3.10–3.45 (m, 4 H), 2.43 (s, 3 H), 1.90–2.30 (m, 4 H), 1.04, 1.21 (2 d, J = 6.0 Hz, 6 H); ^{13}C-NMR ($CDCl_3$, free base) δ 164.1, 151.9, 150.8, 145.5, 138.4, 137.7, 132.3, 128.8, 128.5, 128.1, 126.9, 105.8, 74.5, 68.0, 62.7, 52.6, 50.4, 30.6, 21.6, 21.3, 17.6. Anal. ($C_{29}H_{32}F_3N_3O_5$·HCl) C, H, N, Cl.

Preparation of 1,2,3,6-Tetrahydro-4-methyl-1-[3-[methyl(phenylmethyl)amino]propyl]-6-(3-nitrophenyl)-2-thioxo-5-pyrimidinecarboxylic Acid, 1-Methylethyl Ester, Monohydrochloride (7). (a) Preparation of 24: a solution of pyrimidine derivative **22**[3] (1.36 g, 3.0 mmol) and *N*-(3-chloropropyl)-*N*-methylbenzenemethanamine (0.79 g, 4.0 mmol) in 10 mL of dry dimethylformamide under argon was treated with powdered potassium carbonate (0.83 g, 6.0 mmol) and heated at 80 °C overnight. The mixture, diluted with ethyl acetate, was washed with water and saturated brine and the organic fraction dried and concentrated to give 2.3 g of an oil. Flash chromatography using ethyl acetate/hexane (1:2) gave 1.40 g (77%) of **24**. Anal. ($C_{37}H_{40}N_4O_5S$) C, H, N, S.

(b) Preparation of 1,2,3,6-Tetrahydro-4-methyl-1-[3-[methyl(phenylmethyl)amino]propyl]-6-(3-nitrophenyl)-2-thioxo-5-pyrimidinecarboxylic Acid, 1-Methylethyl Ester, Monohydrochloride (7). Deprotection of **24** (2.3 g, 3.72 mmol) with trifluoroacetic acid and ethanethiol as described above gave 2.6 g of an oil. Flash chromatography using ethyl acetate (2:3) gave 1.34 g, that, upon trituration with isopropyl ether, afforded 1.12 g (61%) of **7**. This was dissolved in 10 mL of acetone and treated with 3 mL of 1 N methanolic hydrochloric acid. Removal of volatiles in vacuo and trituration with isopropyl ether gave 1.2 g (100%) of product as an amorphous powder: mp 116–126 °C; IR (KBr) 1703, 1680, 1648, 1531, 1102 cm^{-1}; ^1H-NMR (CD_3OD) δ 8.25 (s, 1 H), 8.18 (d, J = 7.5 Hz, 1 H), 7.74 (d, J = 7.5 Hz, 1 H), 7.63 (t, J = 7.5 Hz, 1 H), 7.49 (s, 5 H), 5.63 (s, 1 H), 5.01 (quint, J = 6.0 Hz, 1 H), 4.20–4.45 (m, 3 H), 3.05–3.50 (m, 3 H), 2.79 (s, 3 H), 2.30 (s, 3 H), 2.00–2.30 (m, 2 H), 1.17, 1.29 (2d, J = 6.0 Hz, 6 H); ^{13}C-NMR (CD_3OD) δ 175.1, 164.3, 148.0, 143.8, 143.4, 138.6, 132.6, 129.8, 128.6, 128.0, 126.7, 122.9, 122.0, 101.6, 68.1, 61.5, 60.6, 53.9, 50.4, 42.0, 24.4, 21.7, 21.6, 17.7. Anal. ($C_{26}H_{32}N_4O_4S$·HCl·0.5H_2O) C, H, N, Cl, S.

Preparation of 1,2,3,6-Tetrahydro-4-methyl-1-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-2-thioxo-6-[2-(trifluoromethyl)phenyl]-5-pyrimidinecarboxylic Acid, 1-Methylethyl Ester, Monohydrochloride (8). (a) Preparation of 4-(2-bromoethyl)-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester: a solution of 4-(2-hydroxyethyl)-1-piperidinecarboxylic acid, 1,1-dimethyl ester[10] (1.66 g, 7.24 mmol) in 100 mL of ether under argon at room temperature was treated with carbon tetrabromide (4.8 g, 14.5 mmol) and then portionwise with triphenylphosphine (3.8 g, 14.5 mmol). After several minutes, a precipitate began to form. After stirring overnight, solids were filtered and washed with a small amount of ether/hexane (1:1). The filtrate was concentrated in vacuo and the residue, containing solids, was triturated with warm hexane. The hexane solution (precipitated more solids upon cooling; removed by filtration) was concentrated to give 2.7 g of an oil, containing some solids (IR: no OH absorption). The residual triphenylphosphine oxide was removed by passing through a short column of silica gel (ethyl acetate/hexane, 1:2). Residual carbon tetrabromide was removed by sublimation (60 °C at 0.005 mmHg) to give 1.66 g (78%) of product suitable for the next step: ^1H-NMR ($CDCl_3$) δ 3.53 (t, J = 9 Hz, 2 H, CH_2Br), 1.51 (s, 9 H, $C(CH_3)_3$); ^{13}C-NMR ($CDCl_3$) δ 154.6, 79.1, 43.6, 39.0, 34.3, 31.3, 30.8, 28.3.

(b) Preparation of 25: a solution of pyrimidine **23**[3] (1.06 g, 2.23 mmol) in 10 mL of dry dimethylformamide under argon at room temperature was treated with sodium hydride (120 mg, 2.98 mmol, 60% oil dispersion) and warmed at 50 °C for 15 min. Upon cooling to room temperature, 4-(2-bromoethyl)-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester (0.87 g, 2.98 mmol) was added and the mixture was stirred for 2 h at 50 °C and then at room temperature overnight. The reaction mixture, diluted with ethyl acetate, was washed with water and brine, dried, and concentrated in vacuo to give 2.1 g of an oil [TLC on silica gel, ethyl acetate/hexane, 1:2; major spot at 0.46 (N3-isomer), minor spot at 0.29 (N1-isomer)]. Flash chromatography using ethyl acetate/hexane (1:4) gave 0.99 g (64%) of desired *N*3-alkyl product **25** (R_f = 0.46). The corresponding N1-isomer (0.34 g, 22%, R_f = 0.29) was also isolated: ^1H-NMR ($CDCl_3$) δ 5.84 (s, 1 H, H4, N3-isomer); 6.10 (s, 1 H, H4, N1-isomer); ^{13}C-NMR ($CDCl_3$) δ 23.0 (pyrimidine methyl, N3-isomer); 15.0 (pyrimidine methyl, N1-isomer). Anal. ($C_{36}H_{46}F_3N_3O_5S$·0.75H_2O) C, H, N, S.

(c) Preparation of 26: the *N*3-alkyl isomer **25** (0.99 g, 1.4 mmol) under argon at room temperature was treated with 25 mL of formic acid and stirred until no more starting material remained (TLC, 20 h). The mixture, diluted with ethyl acetate, was washed with 1 N sodium hydroxide, water, and brine. The organic fraction was dried and concentrated in vacuo to give 0.87 g of an oil [^1H- and ^{13}C-NMR, loss of *N*-Boc; $(M + H)^+$ = 590] that was used in the next step without purification. The crude secondary amine (0.87 g, 1.47 mmol) in 10 mL of dichloromethane was treated with tetra-*n*-butylammonium sulfate (0.50 g, 1.47 mmol), sodium hydroxide (0.060 g, 1.47 mmol in 1.5 mL of water), and benzyl chloride (0.226 g, 1.79 mmol) and allowed to stir at room temperature overnight. The mixture, diluted with ethyl acetate, was washed with 1 N sodium hydroxide, water, and brine. The organic fraction was dried and concentrated in vacuo to give 0.84 g. Flash chromatography using ethyl acetate/hexane (1:3) gave 0.48 g (51% from **25**) of product: ^1H-NMR ($CDCl_3$) δ 5.84 (s, 1 H, H4, N3-isomer); ^{13}C-NMR ($CDCl_3$) δ 23.0 (pyrimidine methyl, N3-isomer).

(d) Preparation of 1,2,3,6-Tetrahydro-4-methyl-1-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-2-thioxo-6-[2-(trifluoromethyl)phenyl]-5-pyrimidinecarboxylic Acid, 1-Methylethyl Ester, Monohydrochloride (8). Deprotection of **25** (0.67 g, 1.0 mmol) with trifluoroacetic acid and ethanethiol as described above gave crude product as an oil. Trituration with hexane (containing a small amount of isopropyl ether) afforded 310 mg of product, mp 156–158 °C. An additional 60 mg of similar product was recovered from the mother liquor by flash chromatography using ethyl acetate/hexane (35/65) for a total yield of 370 mg (66%). For regiochemical structure determination, the N1-isomer of **25** (described above) was converted in similar fashion to the N1-isomer of **8**: ^1H-NMR ($CDCl_3$) δ 5.96 (s, 1 H, H4, N3-isomer), 5.72 (d, J = 3.0 Hz, 1 H, H4, N1-isomer); ^{13}C-NMR ($CDCl_3$) δ 18.0 (pyrimidine methyl, N3-isomer); 16.1 (pyrimidine methyl, N1-isomer). The free base of N3-isomer **8** (355 mg, 0.63 mmol) was converted to the hydrochloride salt with an excess of ethereal HCl in IPE to give a tacky solid that solidified on scratching, affording 340 mg (90%): mp 154–157 °C; IR (KBr) 1702, 1646, 1531, 1465, 1309 cm^{-1}; ^1H-NMR (CD_3OD) δ 7.60–7.70 (m, 3 H), 7.54 (t, J = 7.5 Hz, 1 H), 7.48 (s, 5 H), 5.96 (s, 1 H), 4.93 (quint, J = 6.5 Hz, 1 H), 4.65–4.80 (m, 1 H), 4.29–4.45 (m, 1 H), 4.26 (s, 2 H), 3.35–3.48 (m, 2 H), 2.88–3.06 (m, 2 H), 2.32 (s, 3 H), 2.00–2.13 (m, 1 H), 1.85–1.97 (m, 1 H), 1.35–1.75 (m, 5 H), 1.01, 1.17 (2 d, J = 6.5 Hz, 6 H); ^{13}C-NMR ($CDCl_3$, free base) δ 174.1, 164.5, 142.4, 140.7, 138.4, 133.1, 130.2, 129.1, 128.6, 128.0, 126.7, 126.6 (d, J_{CF} = 5 Hz), 103.1, 67.9, 63.3, 55.5 (d, J_{CF} = 4 Hz), 53.5, 49.4, 33.7, 32.5, 31.9, 21.6, 21.3, 18.0. Anal. ($C_{30}H_{36}F_3N_3O_2S$·HCl) C, H, N, Cl, S.

Preparation of (*R*)-3,6-Dihydro-4-methyl-2-thioxo-6-[2-(trifluoromethyl)phenyl]-1,5(2*H*)-pyrimidinedicarboxylic Acid, 1-[1-[(4-Fluorophenyl)methyl]-4-piperidinyl] 5-(1-Methylethyl) Ester, Monohydrochloride (12a) and (*S*)-Enantiomer (12b). (a) Preparation of 28: a solution of pyrimidine **27**[3] (23.8 g, 0.0667 mol) in 200 mL of dichloromethane and 25 mL of pyridine under argon was cooled in an ice bath and treated

dropwise with *p*-nitrophenyl chloroformate (14.8 g, 0.0734 mol) dissolved in 50 mL of dichloromethane. The temperature was allowed to rise to ambient over 3 h, volatiles were removed in vacuo, and the residue, dissolved in ethyl acetate, was washed with water, 10% potassium hydrogen sulfate, water, 10% aqueous bicarbonate, water, and saturated brine. The organic fraction was dried and concentrated in vacuo to give a crude solid product. Trituration with hot isopropyl ether, followed by cooling, gave 28.74 g (82%), mp 122–126 °C. Anal. ($C_{24}H_{22}F_3N_3O_7$) C, H, N.

(b) Preparation of 29a (*R*,*R*) and 29b (*S*,*R*): a solution of pyrimidine **28** (10.0 g, 0.192 mol) in 25 mL of ethyl acetate under argon was cooled to 0–5 °C and treated with *R*-(+)-α-methylbenzylamine (2.55 g, 0.211 mol). The mixture was allowed to stir overnight as the temperature rose to ambient level. The reaction mixture was diluted with ethyl acetate and washed with 10% potassium hydrogen sulfate, water, 10% sodium bicarbonate/1 N sodium hydroxide (1:1) (4×), water, and saturated brine. The organic fraction was dried, adsorbed on to 150 mL of Baker silica gel (60–200 mesh), and layered on top of a pad of LPS-1 silica gel in a Buchner funnel. Passage of toluene/ethyl acetate (10:1) eluted the mixture of diastereomers (removes small amount of base line impurities, TLC: toluene/ethyl acetate, 10:3, R_f = 0.55, 0.48). The filtrate was concentrated in vacuo and the residue crystallized from isopropyl ether/hexane to give 3.65 g. This was combined with 3.65 g from a similar run, stirred with warm isopropyl ether/hexane, cooled, and filtered to give 7.05 g (73%) of **29a** (R_f = 0.48, *R*,*R*-diastereomer, stereochemistry determined by X-ray crystallography), mp 142–6 °C. The combined mother liquors and washings gave an additional 0.58 g (7%) of similar material for a total yield of 80% of theory (chemical/resolution): $[\alpha]_D$ = −352.0° (*c* = 0.85, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 7.66 (d, *J* = 8.0 Hz, 1 H), 7.43 (t, *J* = 8.0 Hz, 1 H), 7.22–7.38 (m, 7 H), 6.58 (d, *J* = 8.0 Hz, 1 H), 5.06 (quint, *J* = 6.5 Hz, 1 H), 4.95 (quint, *J* = 6.5 Hz, 1 H), 3.91 (s, 3 H), 2.50 (s, 3 H), 1.50 (d, *J* = 6.5 Hz, 3 H), 1.23, 0.96 (2 d, *J* = 6.5 Hz, 6 H). Anal. ($C_{26}H_{28}F_3N_3O_4$) C, H, N. The residue from the above mother liquors, containing predominantly the *S*,*R*-diastereomer **29b**, was flash chromatographed using toluene/ethyl acetate/isopropyl ether (220:10:1) and crystallized from hexane to give **29b**: mp 107–109 °C (R_f = 0.55); $[\alpha]_D$ = +444.4° (*c* = 0.74, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 1 H), 7.45 (t, *J* = 8.0 Hz, 1 H), 7.40 (d, *J* = 8.0 Hz, 1 H), 7.31 (t, *J* = 8.0 Hz, 1 H), 7.26 (s, 5 H), 6.65 (d, *J* = 8.0 Hz, 1 H), 5.07 (quint, *J* = 6.5 Hz, 1 H), 4.94 (quint, *J* = 6.5 Hz, 1 H), 3.87 (s, 3 H), 2.46 (s, 3 H), 1.51 (d, *J* = 6.5 Hz, 3 H), 1.22, 0.96 (2 d, *J* = 6.5 Hz, 6 H). Anal. ($C_{26}H_{28}F_3N_3O_4$) C, H, N. Both **29a** and **29b** were diastereomerically pure (>99.5%) by 400 MHz ^{1}H-NMR.

(c) Preparation of 30a (*R*) and 30b (*S*): diastereomer **29a** (*R*,*R*) (12.0 g, 0.0238 mol) in 100 mL of toluene was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (0.75 g, 0.0049 mol) and heated at 100 °C for 1 h. Volatiles were stripped in vacuo, and the residue, dissolved in warm hexane, was layered on top of 1200 mL of flash silica gel and eluted with ethyl acetate/hexane (1:10) to give 8.0 g (87%) of **30a**: $[\alpha]_D$ = +169.8° (*c* = 0.51, $CHCl_3$). Anal. ($C_{17}H_{19}F_3N_2O_3$) C, H, N. In a similar manner, diastereomer **29b** (3.2 g, 5.9 mmol) was converted to 2.1 g (93%) of **30b**: $[\alpha]_D$ = −167.4° (*c* = 0.85, $CHCl_3$). Anal. ($C_{17}H_{19}F_3N_2O_3$) C, H, N.

(d) Preparation of 31a (*R*) and 31b (*S*): a mixture of **30a** (3.72 g, 0.0104 mol), *p*-methoxybenzylmercaptan (2.97 g, 0.0193 mol) and citric acid (0.10 g, 0.0005 mol) was heated at 90 °C at 0.05 mmHg (gentle reflux removes product methanol) for 6 h. Upon cooling, the reaction mixture was dissolved in ethyl acetate and washed with 10% sodium bicarbonate, water, and saturated brine. The organic fraction was dried and concentrated in vacuo to give an oil. Flash chromatography and elution with toluene/ethyl acetate (19:1) gave 3.61 g (72%) of **31a**: $[\alpha]_D$ = +151.7° (*c* = 0.56, $CHCl_3$). Anal. ($C_{24}H_{25}F_3N_2O_3S$) C, H, N. In a similar manner, **30b** (2.1 g, 5.9 mmol) was converted to 2.05 g (73%) of **31b**: $[\alpha]_D$ = −147.0° (*c* = 0.52, $CHCl_3$). Anal. ($C_{24}H_{25}F_3N_2O_3$) C, H, N.

(e) Preparation of (*R*)-3,6-Dihydro-4-methyl-2-thioxo-6-[2-(trifluoromethyl)phenyl]-1,5(2*H*)-pyrimidinedicarboxylic Acid, 1-[1-[(4-Fluorophenyl)methyl]-4-piperidinyl] 5-(1-Methylethyl) Ester, Monohydrochloride (12a) and (*S*)-Enantiomer (12b). Pyrimidine **31a** (3.55 g, 0.00742 mol) in 10 mL of acetonitrile and 10 mL of pyridine under argon at ambient temperature was treated with phosgene (9.6 mL of 12.5% in toluene, 1.2 g, 0.012 mol). After 1 h, additional phosgene (1.0 mL) was added, resulting in a dark green color. A solution of 1-[(4-fluorophenyl)methyl]-4-piperidinol hydrochloride (2.87 g, 0.0137 mol, hydrochloride salt of free base prepared in acetonitrile using ethereal HCl; excess HCl removed in vacuo) in 10 mL of acetonitrile was added and the mixture allowed to stir overnight. Volatiles were removed in vacuo, and the residue, dissolved in ethyl acetate, was washed with 10% potassium hydrogen sulfate, water, 10% sodium carbonate, water, and saturated brine. The dried organic fraction was concentrated in vacuo to give 5.1 g of dark oil. Flash chromatography and elution with dichloromethane/ethyl acetate (7:1) gave 3.92 g (75%) of homogeneous product: $[\alpha]_D$ = −169.7° (*c* = 0.90, $CHCl_3$). Anal. ($C_{37}H_{39}F_4N_2O_5S$) C, H, N. This product (3.90 g, 0.0056 mol) was deprotected with trifluoroacetic acid and ethanethiol as described above to give 4.8 g of an oil. Flash chromatography and elution with ethyl acetate/hexane (4 L of 3:7, then 2 L of 1:1) gave 3.2 g (96%) of **12a** (free base): $[\alpha]_D$ = −185.3° (*c* = 0.70, $CHCl_3$). Anal. ($C_{29}H_{31}F_4N_3O_4S$) C, H, N, S. This was dissolved in warm IPE (50 °C) and treated dropwise with excess ethereal hydrochloric acid. The yellow powder thus formed was collected and dissolved in 10 volumes of ethyl acetate with warming, the product salt **12a** (3.0 g, 90%) precipitating as a colorless solid: mp 178–179 °C; $[\alpha]_D$ = −220.9° (*c* = 0.75, $CHCl_3$); IR (KBr) 1710, 1513, 1311, 1235, 1099 cm^{-1}; ^{1}H-NMR (CD_3OD) δ 7.73 (d, *J* = 8.0 Hz, 1 H), 7.62 (t, *J* = 8.0 Hz, 1 H), 7.48–7.57 (m, 3 H), 7.47 (d, *J* = 8.0 Hz, 1 H), 7.22 (t, *J* = 9 Hz, 2 H), 6.78 (s, 1 H), 5.12 (br s, 1 H), 4.97 (quint, *J* = 6.5 Hz, 1 H), 4.28 (s, 2 H), 3.16–3.44 (m, 4 H), 2.42 (s, 3 H), 1.95–2.20 (m, 4 H), 1.20, 1.00 (2 d, *J* = 6.5 Hz, 6 H); ^{13}C-NMR ($CDCl_3$, free base) δ 174.8, 161.8 (d, J_{CF} = 245 Hz), 152.3, 142.6, 137.8, 134.0 (d, J_{CF} = 3 Hz), 132.5, 130.3 (d, J_{CF} = 8 Hz), 129.3, 128.7, 126.7 (d, J_{CF} = 5 Hz), 114.8 (d, J_{CF} = 21 Hz), 106.2, 75.2, 68.3, 61.9, 53.9 (d, J_{CF} = 2 Hz), 50.0, 30.0, 21.5, 21.2, 17.5. Anal. ($C_{29}H_{31}F_4N_3O_4S$·HCl) C, H, N, S. In a similar manner, **31b** (2.6 g, 0.0054 mol) was treated with phosgene and *N*-(*p*-fluorobenzyl)piperidin-4-ol hydrochloride to give the intermediate carbamate derivative (2.84 g, 75%): $[\alpha]_D$ = +166.0° (*c* = 0.51, $CHCl_3$). Anal. ($C_{37}H_{39}F_4N_2O_5S$) C, H, N. Deprotection afforded **12b** (2.06 g, 86%) free base: $[\alpha]_D$ = +179.7° (*c* = 0.66, $CHCl_3$). Anal. ($C_{29}H_{31}F_4N_3O_4S$) C, H, N, S. Formation of the hydrochloride salt afforded 2.0 g (91%) of **12b**: mp 175–177 °C; $[\alpha]_D$ = +217.7° (*c* = 1.00, $CHCl_3$). Anal. ($C_{29}H_{31}F_4N_3O_4S$·HCl) C, H, N, S. Spectral data were identical with **12a**.

Vasorelaxant and Antihypertensive Assays. Potency (IC_{50}) of test compounds was determined as the concentration of drug required to effect 50% relaxation of potassium chloride (100 mM) contracted rabbit thoracic aorta strips in the presence of calcium.[13] Antihypertensive activity was determined in male spontaneously hypertensive rats, 15 weeks of age, upon administration of drug by oral gavage. Mean arterial blood pressure was recorded via an indwelling polyethylene catheter, implanted in the abdominal aorta, and exteriorized in the intrascapular region.[2] The catheter was connected, via resistance tubing and a solenoid valve, to a disposable pressure transducer allowing for intermittent recording of each of ten animals. Blood pressure data were acquired by a

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DEC LSI-11 computer over 20-s intervals every 5 min, continuously for 24 h. Antihypertensive activity was calculated as the percent fall in blood pressure from predrug control value and is reported as the mean value acquired from six rats per dose; the maximum antihypertensive effect noted during the 0–6 h postdrug time period is an indication of drug potency, whereas the antihypertensive effect during the 6–18 h postdrug time period is an indication of duration of action of the drug (determined as the average of the maximum percent fall in blood pressure during the 6–12 and 12–18 h postdrug time periods). The antihypertensive effects for **12a**, amlodipine, and nifedipine were also evaluated as area-over-the-curve for the mean data points calculated from the peak effect (antihypertension) detected over 30-min intervals (six consecutive 5-min data intervals) and plotted against the corresponding dose levels, thereby generating a dose–response relationship (Figure 2).

Crystal Structure Analysis. Crystals of **29a** were obtained from isopropyl ether/hexane. Unit cell parameters were obtained through a least squares analysis of the experimental diffractometer settings of 25 high angle reflections using CuKα monochromatic radiation (λ = 1.5418 Å): a = 17.116 (2), b = 16.366 (2), c = 9.032 (1) Å, V = 2530.0 (9) Å^3. Space group $P2_12_12$ was assigned on the basis of systematic absences of Weissenberg films and confirmed by the full structure analysis. The crystal density, D_{obs} = 1.32 g cm^{-3} was measured by flotation in carbon tetrachloride/hexane mixtures (D_{calc} = 1.324 for Z = 4, $C_{26}H_{28}N_3O_4F_3$). A total of 2011 reflections were measured on an Enraf-Nonius CAD4 diffractometer at 23 °C with the θ–2θ variable scan technique and were corrected for Lorentz polarization factors. Background counts were collected at the extremes of the scan for half the time of the scan. Two standard reflections were monitored for decay; no decrease of intensity was observed during the course of the measurements. Calculations utilized the SDP program package with minor local modifications.[18] The structure was solved by direct methods and refined on the basis of 1499 "observed" reflections with $I \geq 3\sigma(I)$. Although some hydrogen positions were evident in difference maps, all hydrogens were introduced in idealized positions and their scattering was taken into account in the terminal stages of refinement. Least squares weights, $w = \sigma^{-2}(F_o)$ were calculated with the assumption that $\sigma^2 = \epsilon^2 + (\rho I)^2$ where ϵ is the statistical counting error and ρ = 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 $R_w = [\sum_w(|F_o| - |F_c|)^2/\sum_w|F_o|^2]^{1/2}$. The refinements converged at R = 0.044, R_w = 0.051. The final difference map contained no significant features. Tables of atomic coordinates, thermal parameters, bond distances and angles are included as supplementary material. Relative to the known configuration of the R-(+)-α-methylbenzylamine used in the synthesis, the configuration at C4 is also R.

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Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond distances and bond angles, and perspective ORTEP drawing of **29a** (6 pages). Ordering information is given on any current masthead page.

(18) SDP, Structure Determination Package, A. Frenz & Associates, College Station, TX.

Conformationally Restrained, Chiral (Phenylisopropyl)amino-Substituted Pyrazolo[3,4-*d*]pyrimidines and Purines with Selectivity for Adenosine A_1 and A_2 Receptors

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Two modes of tethering a chiral (phenylisopropyl)amino substituent in pyrazolo[3,4-*d*]pyrimidines and purines have been explored. One mode gave (*S*)-2,7-dihydro-7-phenyl-2-(phenylmethyl)-5-propoxy-3*H*-imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine (**12a**) and its corresponding *R*-enantiomer **12b**, which were selective for A_2 and A_1 adenosine receptors, respectively. The corresponding diimidazo[1,2-*c*:4′,5′-*e*]pyrimidines **12e** and **12f** were analogously selective. This is the first example where a single chiral recognition unit provides enantiomers with opposite selectivities for adenosine receptors. The second mode gave (2*S*-*trans*)-2,7-dihydro-2-methyl-3,7-diphenyl-5-propoxy-3*H*-imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine (**12c**) and its corresponding *R*-enantiomer **12d**. Compounds **12c** and **12d** were significantly less potent than **12a** and **12b** at A_1 receptors, and were nonselective.

Chiral recognition units at the C^6-N position of adenosine play a role in the determination of A_1/A_2 selectivity for adenosine receptors. Thus, N^6-[(*R*)-1-methyl-2-phenylethyl]adenosine (*R*-PIA) is more potent and selective for A_1 receptors (A_1 K_i value of 1.15 nM; A_2 K_i value of 124 nM) than is N^6-[(*S*)-1-methyl-2-phenylethyl]-adenosine (*S*-PIA) (A_1 K_i value of 47.6 nM; A_2 K_i value of 1810 nM).[1] We felt that the affinity and the selectivity for an adenosine receptor ligand bearing a chiral phenylisopropyl substituent may be enhanced by approximating the preferred spatial orientation for the relatively flexible chiral recognition unit through conformational restraint.[2]

Two different ways of tethering the chiral (phenylisopropyl)amino side chain to the pyrimidine ring were proposed. Connection of the methyl carbon to N^1 as shown by tether A in the general structure would give a ben-

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