Dihydropyrimidine Angiotensin II Receptor Antagonists

Karnail S. Atwal,* Syed Z. Ahmed, J. Eileen Bird, Carol L. Delaney, Kenneth E. J. Dickinson, Francis N. Ferrara, Anders Hedberg, Arthur V. Miller, Suzanne Moreland, Brian C. O'Reilly, Thomas R. Schaeffer, Thomas L. Waldron, and Harold N. Weller

Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, New Jersey 08543-4000

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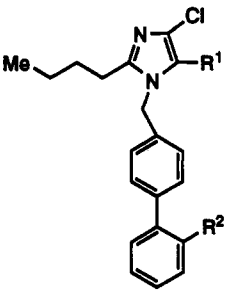
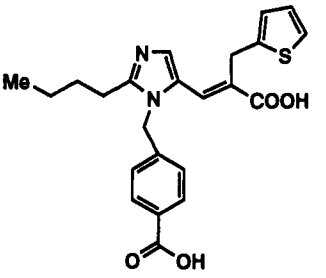
The discovery of the nonpeptidic angiotensin II (AII) receptor antagonist losartan (1), previously called DuP 753, has stimulated considerable interest in the synthesis of novel analogs of this compound. Our efforts in this area have resulted in the discovery of dihydropyrimidines (3) as potent AII receptor antagonists. The chemistry leading to this novel class of AII antagonists and their biological properties are reported in this publication. Structure–activity studies showed that a variety of substituents are tolerated on the dihydropyrimidine ring, indicating that the AII receptor is permissive in accepting this region of the nonpeptide antagonists. As reported for imidazole-based AII antagonists, the tetrazolyl dihydropyrimidine analogs were found to be more potent than the corresponding carboxylic acids. Our studies show that dihydropyrimidine analogs 2-butyl-4-chloro-1,6-dihydro-6-methyl-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]pyrimidine-5-carboxylic acid, ethyl ester (K_i = 8.3 nM), 2-butyl-4-chloro-1,6-dihydro-6-methyl-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-5-pyrimidinecarboxylic acid (K_i = 1.0 nM), and 2-butyl-6-chloro-1,4-dihydro-4,4-dimethyl-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-5-pyrimidinecarboxylic acid, ethyl ester (K_i = 1.1 nM), display affinities for the AII receptor which are comparable to or better than losartan (K_i = 9.0 nM). One of these derivatives, 2-butyl-4-chloro-1,6-dihydro-6-methyl-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]pyrimidine-5-carboxylic acid, ethyl ester, showed antihypertensive activity on oral administration to spontaneously hypertensive rats. These results demonstrate that the imidazole of losartan can be successfully replaced with a dihydropyrimidine ring.

Introduction

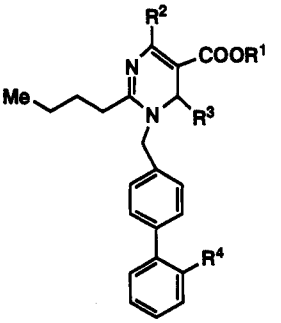
Following the pioneering discovery of the angiotensin converting enzyme (ACE) inhibitor captopril as an antihypertensive agent,[1] the renin-angiotensin system has become an important target for further drug discovery.[2] Due to the commercial success of ACE inhibitors, a large effort in medicinal chemistry has continued to focus on further manipulation of this system. Renin inhibitors[3] and angiotensin II (AII) antagonists[4] have enjoyed considerable popularity among pharmaceutical scientists. However, the use of both these classes of agents as potential cardiovascular drugs had been hampered by their peptidic nature, usually responsible for poor oral bioavailability and limited half-life.[4] With the discovery of losartan (1), previously called DuP 753, that situation has changed for AII antagonists.[5]

The discovery of losartan (1),[5] and subsequently other nonpeptidic AII antagonists (e.g., 2),[6] has generated considerable interest in the search for new analogs of 1. We focused our studies on the replacement of the imidazole





1, R^1 = CH_2OH, R^2 = tetrazole (losartan) 2
5, R^1 = CH_2OH, R^2 = tetrazole
7, R^1 = COOH, R^2 = tetrazole



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(1) Ondetti, M. A.; Rubin, B.; Cushman, D. W. Design of Specific Inhibitors of Angiotensin-Converting Enzyme: New Class of Orally Active Antihypertensives. *Science* 1977, *196*, 441–444.
(2) (a) Martin, P.; Bachmann, B.; Ganten, D. The Tissue Renin-Angiotensin System in Cardiovascular Disease. *Trends Cardiovasc. Med.* 1992, *2*, 94–99. (b) Corvol, P. New Therapeutic Prospects of Renin-Angiotensin System Inhibition. Clin. Exp. Hypertens.-Theory Pract. 1989, AII (Suppl. 2) 463–470. (c) Hollenberg, N. K. Pharmacological Interruption of the Renin-Angiotensin System. *Annu. Rev. Pharmacol. Toxicol.* 1979, *19*, 559–581.
(3) Greenlee, W. J. Renin Inhibitors. *Med. Res. Rev.* 1990, *10*, 174–236.
(4) Pals, D. T.; Denning, G. S., Jr.; Keenan, R. E. Historical Development of Saralasin. *Kidney Int.* 1979, 15 (Suppl. 9), S7-10.
(5) Timmermans, P. B. M. W. M.; Wong, P. C.; Chiu, A. T.; Herblin, W. F. *Trends Pharmacol. Sci.* 1991, *12*, 55–62 and references therein.

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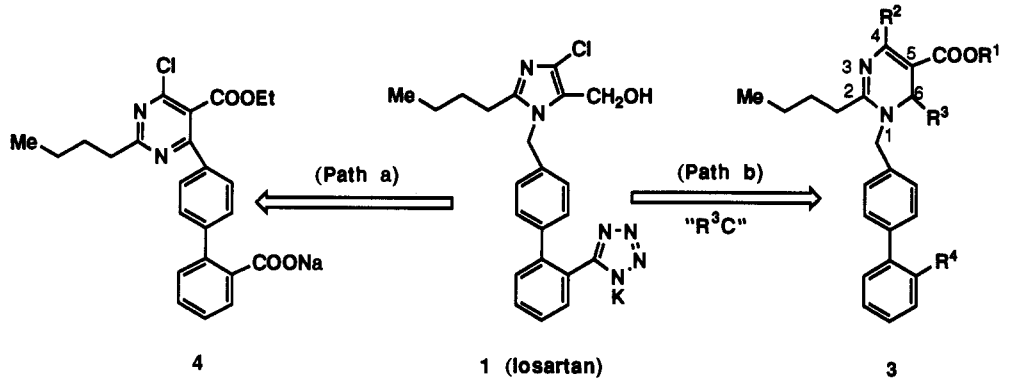
Scheme I



of losartan (1) with the homologous pyrimidine ring. Those studies led to the discovery of dihydropyrimidines (e.g., 3) as potent AII antagonists. In this publication, we describe their synthesis and biological activity. Our studies show that some dihydropyrimidine analogs (3i,j, 6b) exhibit the AII antagonistic potency of losartan (1), demonstrating that the imidazole of losartan (1) can be successfully replaced with a dihydropyrimidine ring.

Results and Discussion

A. Lead Discovery. Replacement of the imidazole ring of losartan (1) with a pyrimidine was envisioned to arise by (1) inclusion of the existing benzylic carbon of the biphenyl side chain of 1 into the imidazole ring (4, path a) and by (2) incorporation of an additional carbon atom into the carbon nitrogen bond of imidazole (3, path b) (Scheme I). It was path b that led to the discovery of dihydropyrimidines 3 as potent AII antagonists. For ease of chemical synthesis, the hydroxymethyl group of losartan (1) was changed to a carboxylic ester/acid in pyrimidines 3 and 4. This change would be expected to have a beneficial affect on biological activity, as reported previously for the imidazole series (e.g., 1).[7] For initial evaluation, it was decided to prepare 3 and 4 with a carboxylic acid group on the biphenyl portion. Although the carboxylic acid analog 5 is less potent than the corresponding tetrazole (1) in the imidazole series,[5,7] this change was not expected to have a serious impact on the identification of biologically active lead compounds.

For determination of receptor affinities, radioligand binding studies were carried out in rat adrenal cortical membranes using [^{125}I]Sar^1,Ile^8-angiotensin II as the radioligand according to the methods described in the literature.[8] For comparison of functional potencies, these compounds were tested for relaxation of the AII contracted rat aortic strips, as described previously by Wong and co-workers.[9] Results of these assays are shown in Table I. For discussion of results, the pyrimidine numbering system as displayed in formula 3 (Scheme I) is used. However, proper nomenclature is assigned to each compound as it appears in the Experimental Section.

Dihydropyrimidine analog **3a** (K_i = 41 nM) was slightly more potent than the carboxylic acid analog **5** (K_i = 95 nM) of losartan (1) for both binding to the AII receptor and antagonism of the AII contracted rat aortic smooth muscle. Losartan (1, K_1 = 9.0 nM) bound to the AII receptor with an affinity approximately 1 order of magnitude higher than either **3a** or **5**. The pyrimidine analog 4 (K_i = 44 400 nM) was 3 orders of magnitude less potent than **3a** in the binding assay and was devoid of activity in the functional assay (K_B > 10 000 nM). These preliminary studies indicated that the imidazole of losartan (1) can be replaced with a suitably substituted dihydropyrimidine ring (e.g., 3). Therefore, further work was limited to making analogs of 3.

B. Structure–Activity Relationships. Analogs prepared to explore structure–activity relationships of **3a** are given in Table I. The *n*-butyl group at C2, reported to be optimal for the imidazole series,[7] was kept constant throughout these structure–activity studies. Replacement of the methyl group of **3a** with a phenyl (**3b**) led to a large drop in binding and functional potencies, indicating that a bulky group is not tolerated at the C6 position of the pyrimidine ring. The chlorine atom at C4 appears to be optimal as the corresponding methyl (**3c**) and the phenyl (**3d**) analogs were significantly less potent. Substitution of the phenyl ring of **3d** with a chlorine atom (**3e**) led to some improvement in binding and functional potencies; however, this compound remained significantly less potent than the chloro analog **3a**.

Since we were unable to prepare the achiral protio analog of **3a** (R^3 = H) due to its instability under the reaction conditions, we focused our synthetic studies on preparing additional analogs of **3a** with either a carbonyl group (R^3 = carbonyl) or *gem*-dialkyl groups at C6. The pyrimidinone analog **3f** (K_i = 150 nM) was 6-fold more potent

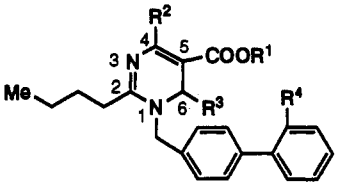
(6) Weinstock, J.; Keenan, R. M.; Samanen, J.; Hempel, J.; Finkelstein, J. A.; Franz, R. G.; Gaitanopoulos, D. E.; Girad, G. R.; Gleason, J. G.; Hill, D. T.; Morgan, T. M.; Peishoff, C. E.; Aiyar, N.; Brooks, D. P.; Fredrickson, T. A.; Ohlstein, E. H.; Ruffolo, R. R., Jr.; Stack, E. J.; Sulpizio, A. C.; Weidley, E. F.; Edwards, R. M. 1-(Carboxybenzyl)imidazole-5-acrylic Acids: Potent and Selective Angiotensin II Receptor Antagonists. *J. Med. Chem.* 1991, *34*, 1514–1517.

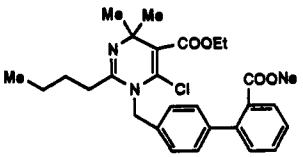
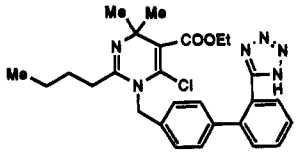
(7) (a) Duncia, J. W.; Chiu, A. T.; Carini, D. J.; Gregory, G. B.; Johnson, A. L.; Price, W. A.; Wells, G. J.; Wong, P. C.; Calabrese, J. C.; Timmermans, P. B. M. W. M. The Discovery of Potent Nonpeptide Angiotensin II Receptor Antagonists: A New Class of Potent Antihypertensives. *J. Med. Chem.* 1990, *33*, 1312–1329. (b) Carini, D. J.; Duncia, J. W.; Johnson, A. L.; Chiu, A. T.; Price, W. A.; Wong, P. C.; Timmermans, P. B. M. W. M. Nonpeptide Angiotensin II Receptor Antagonists: N-[(Benzyloxy)-benzyl]imidazoles and Related Compounds as Potent Antihypertensives. *J. Med. Chem.* 1990, *33*, 1330–1336. (c) Carini, D. J.; Duncia, J. W.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B., III; Wells, G. J.; Wexler, R. B.; Wong, P. C.; Yoo, S.-E.; Timmermans, P. B. M. W. M. Nonpeptide Angiotensin II Receptor Antagonists: The Discovery of N-(Biphenylmethyl)imidazoles as Potent, Orally Active Antihypertensives. *J. Med. Chem.* 1991, *34*, 2525–2547.

(8) Chiu, A. T.; Carini, D. J.; Johnson, A. L.; McCall, D. E.; Price, W. A.; Thoolen, M. J. M. C.; Wong, P. C.; Taber, R. I.; Timmermans, P. B. M. W. M. Non-peptide angiotensin II receptor antagonists. II. Pharmacology of S-8308. *Eur. J. Pharmacol.* 1988, *157*, 13–21.

(9) Wong, P. C.; Hart, S. D.; Zaspel, A. M.; Chiu, A. T.; Ardecky, R. J.; Smith, R. D.; Timmermans, P. B. M. W. M. Functional Studies of the Angiotensin II Receptor Subtype-Specific Ligands: DuP 753 (AII-1) and PD 123177 (AII-2). *J. Pharmacol. Exp. Ther.* 1990, *255*, 584–592.

Table I. AII Antagonistic Potencies in Vitro of Pyrimidine Analogs, EXP 7711 (5), and Losartan (1)



compd	R^1	R^2	R^3	R^4	AII binding potencies:[a] K_i, nM (±SEM)	functional potencies:[b] K_B, nM (±SEM)
3a	Et	Cl	Me	COOH	41 ± 6	70 ± 34
3b	Et	Cl	Ph	COONa	1430 ± 360	1000 ± 400
3c	Et	Me	Me	COOH	990 ± 130	660 ± 85
3d	Et	Ph	Me	COOH	850 ± 80	630 ± 300
3e	Et	4-ClC_6H_4	Me	COOH	190 ± 30	520 ± 140
3f	Et	Me	=O	COONa	150 ± 43	95 ± 40
3g	Et	Ph	=O	COONa	1600 ± 900	140 ± 19
3h	Et	H	=O	COONa	82 ± 7	610 ± 210
3i	Et	Cl	Me		8.3 ± 1.8	5.3 ± 0.63
3j	H	Cl	Me		1.0 ± 0.3	0.45 ± 0.31
6a					58 ± 7	23 ± 5
6b					1.1 ± 0.3	24 ± 9
losartan (1)					9.0 ± 3.2	2.6 ± 0.13
EXP 7711 (5)					95 ± 36	86 ± 4.4

[a] Compounds were tested in a radioligand binding assay using rat adrenal cortical membranes using [^{125}I]Sar^1,Ile^8-angiotensin II as the radioligand. [b] Functional potencies were determined by antagonism of angiotensin II induced contraction of isolated rabbit aorta as described elsewhere (see ref 9).

than the corresponding dihydropyrimidine **3c** (K_i = 990 nM) and it was less potent than the lead compound **3a** in the binding as well as the functional tests. The phenyl analog **3g**, while only slightly inferior to **3f** in the functional assay, was 10-fold less effective in displacing the radioligand from AII receptor sites. The protio analog **3h** was slightly more potent than **3f** in the binding assay but was less potent than **3f** in the functional assay. The reasons for the discrepancies between the binding and the functional potencies for **3g,h** are not clear at the present time. Nonetheless, the comparison among **3f–h** does indicate that there is some limitation as to the size of the group at C4 of the pyrimidinones. Attempts to prepare the *gem*-dimethyl analog (R^3 = Me_2) of **3a** resulted in the isolation of the regioisomeric product **6a**, which turned out to be a potent AII antagonist with a K_i value of 58 nM. Its potency compares quite favorably with those of dihydropyrimidine analog **3a** (K_i = 41 nM) and the carboxylic acid analog **5** (K_i = 95 nM) of losartan (1).

Since the tetrazole (1) is reported to be more potent than the corresponding carboxylic acid **5** for the imidazole-based AII antagonists,[5,7] we prepared tetrazole analogs of the most potent dihydropyrimidine carboxylic acid derivatives **3a** and **6a**. The tetrazole analog **3i** (K_i = 8.3 nM) of **3a** was comparable to losartan (1) (K_i = 9.0 nM) in the in vitro assays. The *gem*-dimethyl tetrazole derivative **6b** (K_i = 1.1 nM) was more potent than both the dihydropyrimidine analog **3i** and losartan (1) in the binding assay. However, the replacement of the carboxylic acid of **6a** with a tetrazole (**6b**, K_B = 23 nM) did not have a beneficial effect on its functional potency (K_B = 24 nM). In view of the improved potency and duration of action associated with the carboxylic acid analog **7** of losartan,[10] we prepared the carboxylic acid analog **3j** of dihydropyrimidine **3i**. Clearly, it was one of the most potent AII antagonist of this series in the binding (K_i = 1.0 nM) as well as the functional (K_B = 0.45 nM) tests, being 10- and 25-fold more potent than losartan (1) in the binding and the functional tests, respectively.

The above structure–activity studies show that a variety of changes are tolerated at carbons 4–6 of dihydropyrimidine AII antagonists, indicating that the requirements around the pyrimidine ring are quite flexible. These data taken together with previous reports from Du Pont scientists[7] imply that the AII receptor can accommodate significant changes in the heterocyclic portion of losartan (1). Thus, it is not surprising that numerous heterocyclic replacements for the imidazole ring of losartan (1) have already appeared in the patent literature.[11] Our studies

(10) Wong, P. C.; Price, W. A., Jr.; Chiu, A. T.; Duncia, J. V.; Carini, D. J.; Wexler, R. R.; Johnson, A. L.; Timmermans, P. B. M. W. M. Nonpeptide Angiotensin II Receptor Antagonists. XI. Pharmacology of EXP 3174: An Active Metabolite of DuP 753, An Orally Active Antihypertensive Agent. *J. Pharmacol. Exp. Ther.* **1991**, *255*, 211–217.

Table II. Biological Activity in Vivo of Pyrimidine Analogs 3i, 3j, 6b, and Losartan (1)

compd	AII antagonistic activity on intravenous admin:[a] ED_{50}, μmol/kg (n = 4)	dose, μmol/kg	antihypertensive activity on oral admin:[b] % maximum decrease in blood pressure (n = 8–10) 0–6 h	6–12 h	12–18 h	18–24 h
3i	1.65	30	23	20	19	20
		10	14	14	15	17
3j	0.076	30	8	0	2	1
6b	2.4	30	5	3	4	2
1 (losartan)	1.8	30	31	35	37	38
		10	13	20	22	24

[a] The test compounds were given intravenously to normotensive male rats followed 2 min later by AII challenge (100 ng/kg iv). The dose required to inhibit the AII pressor response by 50% (ED_{50}) was calculated by simplex curve fit of log of dose versus maximum percent inhibition. [b] The test compounds were administered orally as a suspension in agar, and blood pressure was recorded using the method described previously (see ref 21).

Table III. Physical Properties of Pyrimidine Analogs

compd	mol formula	microanalysis	physical characteristics	mp, °C (crystn solv)
3a	$C_{26}H_{29}ClN_2O_4 \cdot 0.27H_2O$	C, H, N, Cl	colorless solid	93–5 (ether)
3b	$C_{31}H_{30}ClN_2O_4Na \cdot 1.4H_2O$	C, H, N, Cl	light yellow solid	140–160 (lyphilized)
3c	$C_{27}H_{32}N_2O_4 \cdot CF_3COOH$	C, H, N, F	colorless solid	144–146 (ether)
3d	$C_{32}H_{34}N_2O_4 \cdot CF_3COOH$	C, H, N, F	colorless solid	153–155 (ether)
3e	$C_{32}H_{33}ClN_2O_4 \cdot CF_3COOH$	C, H, N, Cl, F	colorless solid	131–132 (ether)
3f	$C_{26}H_{27}N_2O_5Na \cdot 0.6H_2O$	C, H, N	colorless solid	shrinks at 115 (lyophilized)
3g	$C_{31}H_{29}N_2O_5Na \cdot 1.5H_2O$	C, H, N	colorless solid	shrinks at 135 (lyophilized)
3h	$C_{25}H_{25}N_2O_5Na \cdot 2.33H_2O$	C, H, N	off-white solid	138–140 (lyophilized)
3i	$C_{26}H_{29}ClN_6O_2K \cdot 0.5H_2O$	C, H, N, Cl	light yellow solid	shrinks at 130–135 (lyophilized)
3j	$C_{24}H_{25}N_6O_2Cl \cdot 0.79H_2O \cdot 0.81CF_3COOH$	C, H, N, Cl, F	colorless solid	108–112 (lyophilized)
4	$C_{24}H_{22}ClN_2O_4Na \cdot 1.0H_2O$	C, H, N, Cl, Na	colorless solid	shrinks at 72 (lyophilized)
6a	$C_{27}H_{30}ClN_2O_4Na \cdot 0.75H_2O$	C, H, N, Cl	colorless solid	shrinks at 190 (lyophilized)
6b	$C_{27}H_{31}ClN_6O_2Na \cdot 1.0CH_3OH$	C, H, N, Cl	colorless solid	82–85 (isopropyl ether)

also show that the tetrazole analogs of dihydropyrimidines are more potent than the corresponding carboxylic acids; results similar to those reported for imidazole-based AII antagonists.[5,7] These data indicate that the replacement of the imidazole ring of losartan (1) with a dihydropyrimidine ring (e.g., 3) does not have a major impact on the structural requirements in the biphenyl portion of losartan (1).

C. Pharmacological Studies in Vivo. The most potent dihydropyrimidine analogs, **3i**, **3j**, and **6b**, were further characterized in vivo, by comparison with the reference agent, losartan (1). For measurement of antihypertensive activity, the test compounds were given orally to salt-depleted spontaneously hypertensive rats (SdSHR) and the mean arterial blood pressure was monitored for 24 h. The AII antagonistic potency in vivo was measured by intravenous administration of the test compound to rats followed 2 min later by AII challenge. The resulting dose–response data were used to calculate ED_{50} values, doses required to inhibit the AII pressor response by 50%. As shown in Table II, only **3i** lowered blood pressure in the SdSHR on oral administration and its effect lasted for the entire 24-h period. It was slightly less potent than losartan (1) at both 10 and 30 μmol/kg doses. Neither dihydropyrimidine **3i** nor losartan (1) affected heart rates of the treated animals (data not shown). Dihydropyrimidine analogs **3j** and **6b**, in spite of being potent AII antagonists in vitro, had no effect on blood pressure in the SHR. The reasons for the lack of effect of **3j** and **6b** on blood pressure are not clear, but they may be related to their poor oral bioavailabilities or low half-lives. On intravenous administration, all three compounds, **3i** (ED_{50} = 1.65 μmol/kg), **3j** (ED_{50} = 0.08 μmol/kg), and **6b** (ED_{50} = 2.4 μmol/kg), were potent AII antagonists with potencies similar to or better than that of losartan (1) (ED_{50} = 1.8 μmol/kg) (Table II). The most potent compound in the functional assay **3j** (K_B = 0.45 nM), was also found to be the most potent AII antagonist on intravenous administration, its potency being 20-fold higher than that of losartan (1). Thus, the intravenous studies fully support the potent AII antagonistic activities of dihydropyrimidines **3i**, **3j**, and **6b** in vitro.

Chemistry

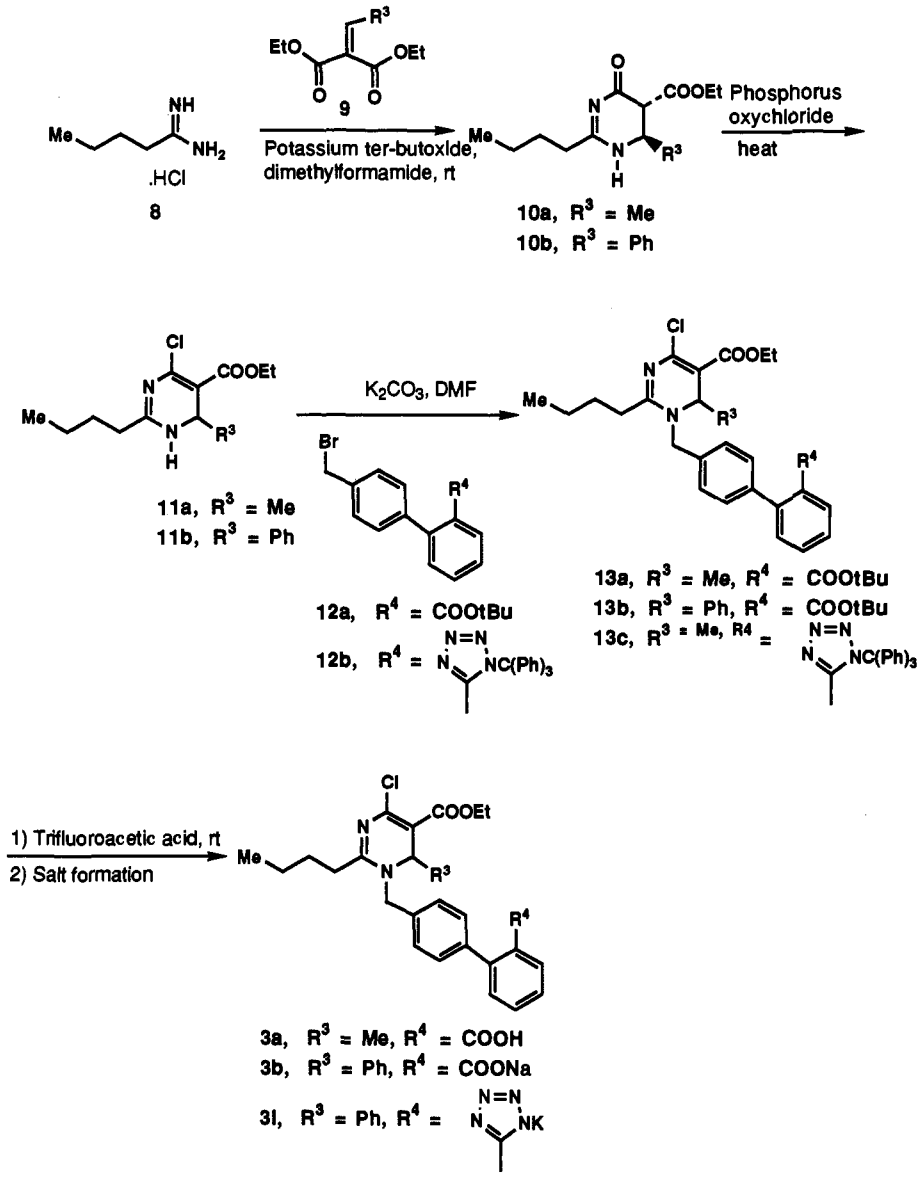
For the preparation of dihydropyrimidine analogs **3a,b,i**, pentanimidamide hydrochloride (**8**)[12] was condensed with alkylidene **9** to provide the predominantly trans pyrimidine **10** in excellent yield (Scheme II). The formation of a small amount (5-10%) of the cis product in this reaction was of insignificant importance as the mixture was converted to the homogeneous chloropyrimidine **11** by heating with phosphorus oxychloride. For the synthesis of **3a,b**, the chloropyrimidine **11a,b** was alkylated with biphenylyl bromide **12a**[13] in the presence of potassium carbonate in dimethylformamide to yield **13a,b** with complete regioselectivity. Deprotection of **13a,b** to the target compounds **3a,b** was carried out by treatment with trifluoroacetic acid. The tetrazole analog **3i** of **3a** was prepared from **11a** and the tetrazolylbiphenylyl bromide **12**[13] in an analogous

(11) (a) Carini, D. J.; Duncia, J. V.; Yoo, S.-E. Angiotensin II Receptor Blocking Benzimidazoles. U.S. Patent 4,880,804 (E. I. du Pont de Nemours and Co., November, 14, 1989). (b) Allen, E. E.; De Laszlo, S. E.; Greenlee, W. J.; Patchett, A. A.; Chakravarty, P. K.; Walsh, T. F. Substituted Quinazolinones as Angiotensin II Antagonists. EP 0411766 A1 (Merck & Co. Inc., February 6, 1991). (c) Roberts, D. A.; Russell, S. T.; Pearce, R. J. Quinoline Derivatives, Process for Their Preparation and Their Use as Medicaments. EP 0412848 A2 (Imperial Chemical Industries PLC, February 13, 1991).

(12) Yanai, M.; Naito, T. Polarization in Heterocyclic Rings with Aromatic Character. XIV. Synthesis of Pyrimidine and Bipyrimidine Homologs. *J. Pharm. Soc. Jpn.* **1941**, *61*, 99–107. (*C. A. 35*, 743).

(13) (a) Carini, D. J.; Duncia, J. V. Angiotensin II Blocking Imidazoles. *EP* 253,310 A2 (E. I. du Pont de Nemours and Co., January 20, 1988). (b) Aldrich, P. E.; Duncia, J. V.; Pierce, M. E. Tetrazole Intermediates to Antihypertensive Compounds. U.S. Patent 4,874,867 (E. I. du Pont de Nemours and Co., October 17, 1989). (c) Reference 7c.

Scheme II



manner. The regiochemistry of alkylation (**11** → **13**) was confirmed by NOE experiments on **13a–c**. For example, irradiation of the C6 proton singlet (5.48 ppm) of **13b** gave a large enhancement of the benzylic proton doublet at 4.35 ppm, indicating the alkylation took place at the N1 nitrogen of pyrimidine **11**. This regioselectivity of alkylation can be explained by the difference in the reactivities of the pyrimidine nitrogens; the more electron rich nitrogen reacts exclusively.[14]

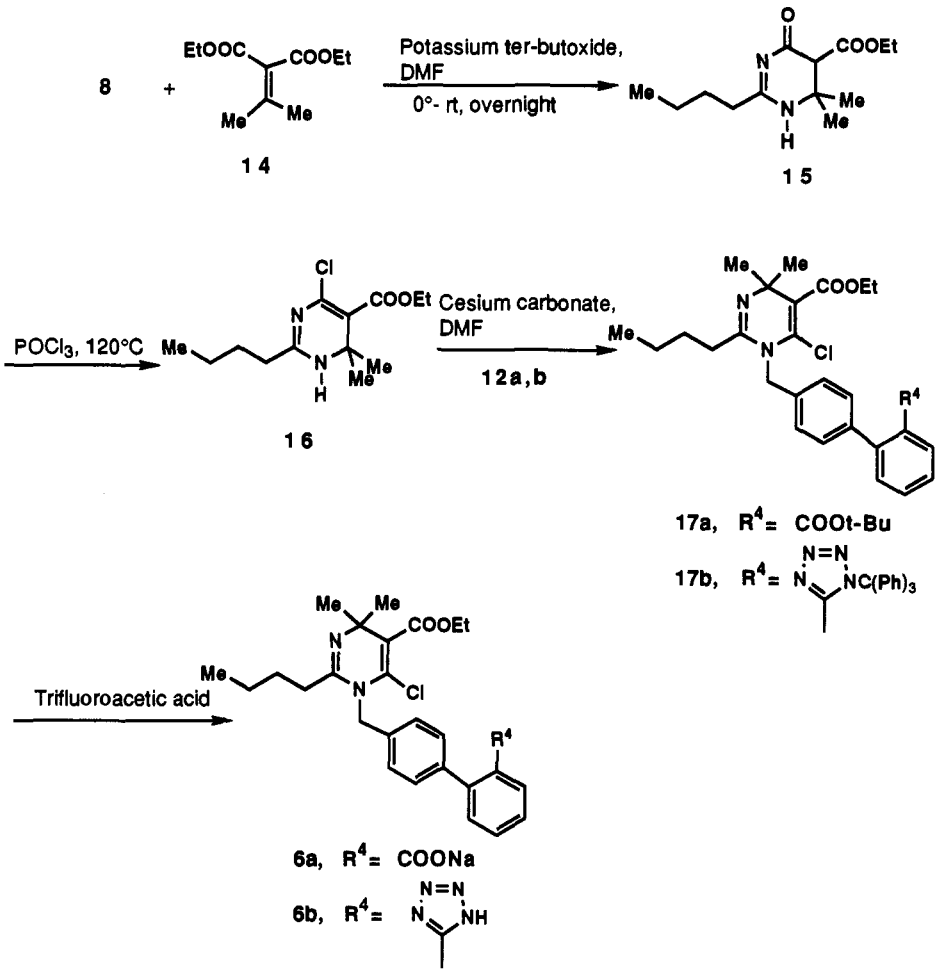
Alkylation of the *gem*-dimethyl intermediate **16**, prepared in two steps from **8** and **14**, with biphenylyl bromides **12a,b**,[13] gave **17a,b** in good yields (Scheme III). NOE experiments were performed on **17a,b** to confirm the regiochemistry of alkylation. Irradiation of the benzylic protons singlet at 4.9 ppm had no influence on the methyl singlet (1.3 ppm) due to the *gem*-dimethyl groups, indicating that the alkylation took place on the nitrogen atom remote from the *gem*-dimethyl groups. The exclusive formation of the products (**17a,b**) of alkylation on the less basic nitrogen of **16** is presumably due to the steric hindrance provided by the *gem*-dimethyl groups. Deprotection of **17a,b** to the final products **6a,b** proceeded unevenfully under acidic conditions.

Attempts to prepare **3j** directly by saponification of the ethyl ester of **3i** were unsuccessful. Therefore, the ethyl ester of **11a** had to be changed to a more labile diphenylmethyl ester which could be cleaved at the final step. Since we were unable to saponify the ethyl ester of **11a** without loss of chloropyrimidine, we resorted to enzymatic hydrolysis of **11a** with porcine liver esterase[15] to give **18** in modest 44% yield (Scheme IV). No enantioselectivity was observed during this enzymatic hydrolysis. The acid **18** was esterified with diphenyldiazomethane and the resulting product **19** was alkylated with biphenylyl bromide **12b**[13] to provide **20** in 46% yield. Both protecting groups of **20** were removed by treatment with trifluoroacetic acid to yield **3j** in 70% yield.

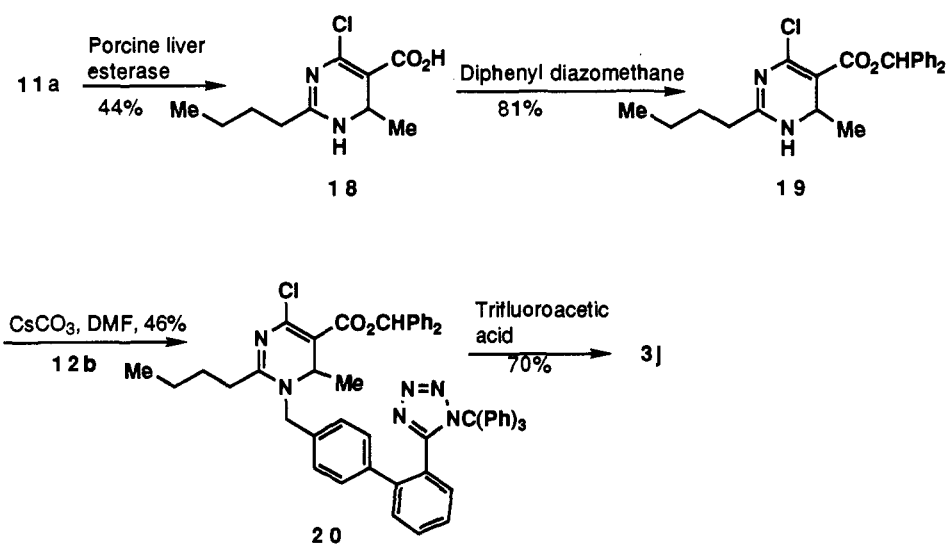
(14) Atwal, K. S.; Rovnyak, G. R.; O'Reilly, B. C.; Schwartz, J. Substituted 1,4-Dihydropyrimidines. 3. Synthesis of Selectively Functionalized 2-Hetero-1,4-dihydropyrimidines. *J. Org. Chem.* **1989**, *54*, 5898–5907. (b) Cho, H.; Shima, K.; Hayashimatsu, M.; Ohnaka, Y.; Mizuno, A.; Takeuchi, Y. Synthesis of Novel Dihydropyrimidines and Tetrahydropyrimidines. *J. Org. Chem.* **1985**, *50*, 4227–4230.

(15) Arita, M.; Adachi, K.; Ito, Y.; Sawai, H.; Ohno, M. Enantioselective Synthesis of the Carbocyclic Nucleosides (−)-Aristeromycin and (−)-Neplanocin A by a Chemicoenzymatic Approach. *J. Am. Chem. Soc.* **1983**, *105*, 4049–4055.

Scheme III



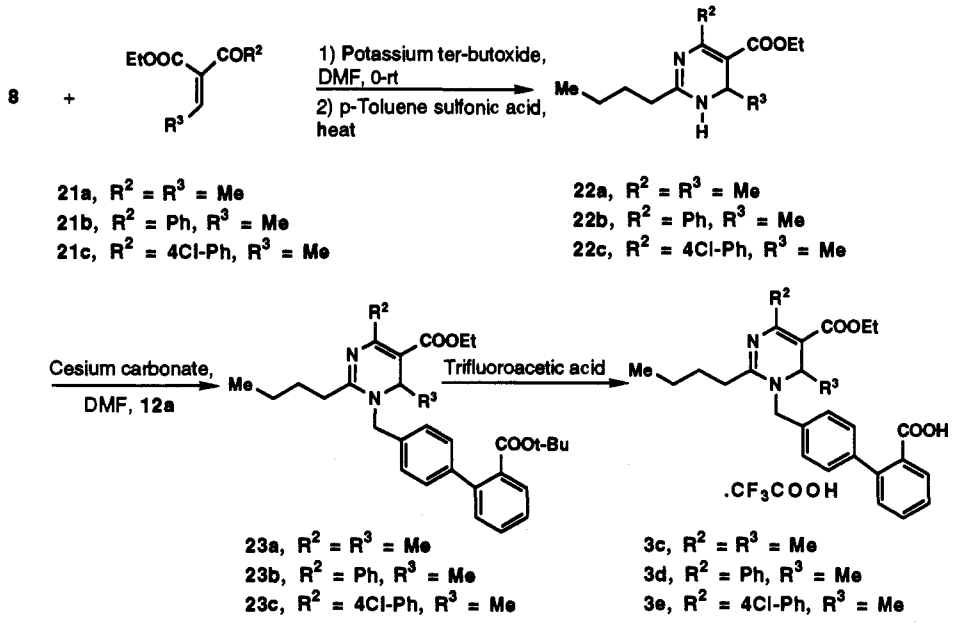
Scheme IV



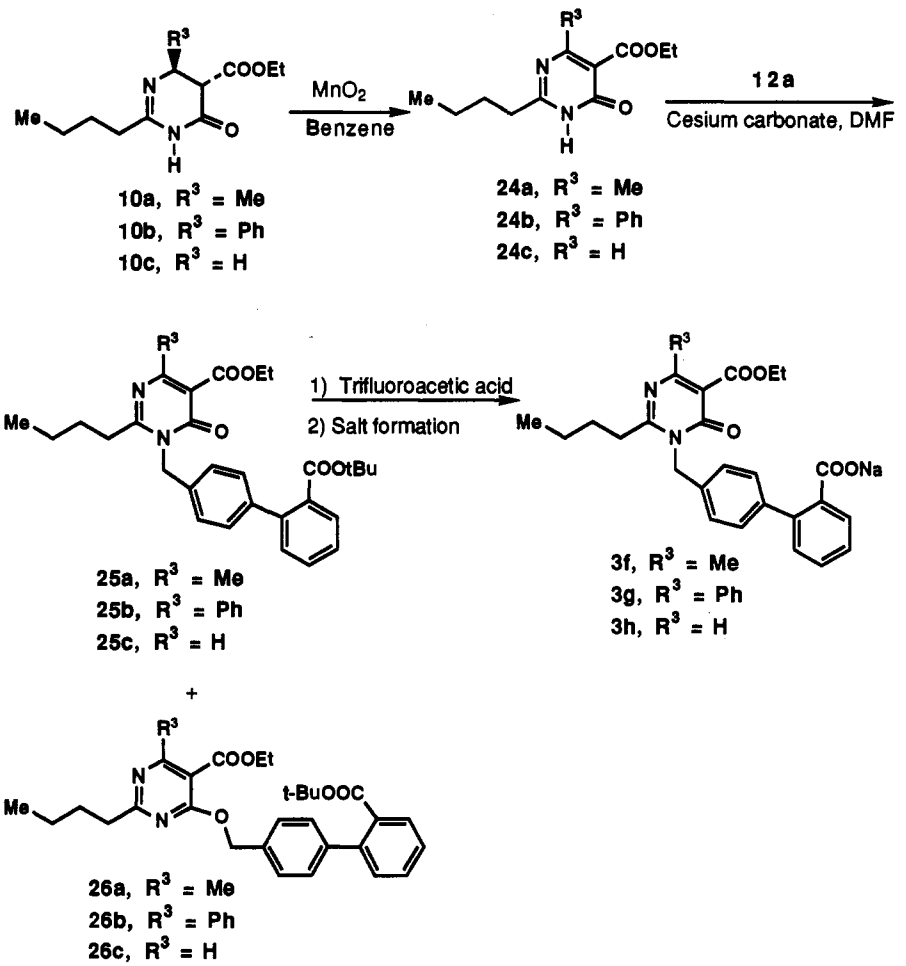
The synthesis of dihydropyrimidines **3c–e** began with alkylidenes **21a–c**, which could be easily prepared from the corresponding β-keto esters and aldehydes by the standard Knoevenagel condensation. Treatment of **21a–c** with **8** provided the intermediate dihydropyrimidines **22a–c**, which on alkylation with **12a** provided **23a–c** in a regiospecific manner. Deprotection of **23a–c** to the final product **3c–e** was carried out with trifluoroacetic acid in dichloromethane (Scheme V). The structures of **3c–e** were confirmed by NOE studies on **23a,b** similar to those described for compounds **13a–c**.

The synthesis of pyrimidinones **3f–h** is summarized in Scheme VI. The intermediate pyrimidinones **24a,b** were obtained from the corresponding dihydro compounds **10a,b** by oxidation (30–35%) with manganese dioxide. Alkylation of **24a,b** with biphenylyl bromide **12a**[13] gave, in addition to the desired products **25a,b**, the O-alkylated compounds **26a,b**. The *tert*-butyl ester of **25a,b** was

Scheme V



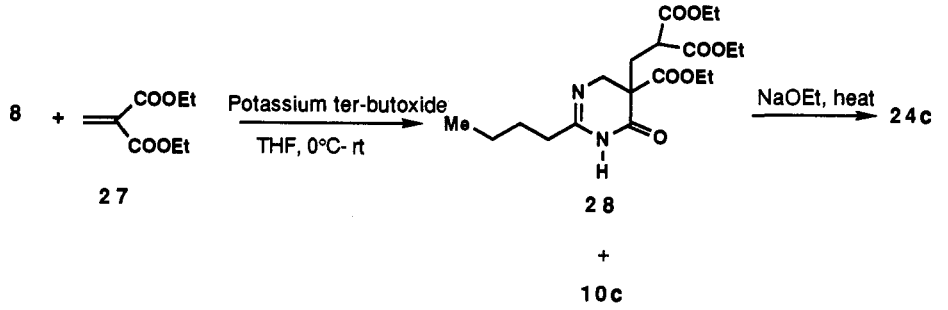
Scheme VI



cleaved by treatment with trifluoroacetic acid to provide the target compounds **3f,g**. Attempts to prepare **10c** from **8** and **27**[16] resulted largely in the formation of the bis adduct **28**, along with varying amounts (10–20%) of the desired product (Scheme VII). Treatment of **28** with sodium ethoxide gave the pyrimidinone **24c**, the product of net oxidation, presumably due to the presence of oxygen in the reaction mixture (Scheme VII). This result reflects the propensity of **10c** to air oxidation, especially in the presence of a strong base. Conversion of **24c** to the final product **3h** proceeded as described for **3f,g** (Scheme VI).

(16) Bachman, G. B.; Tanner, H. A. Diethyl Methylenemalonate. *J. Org. Chem.* **1939**, *4*, 493–501.

Scheme VII



The structures of O- and N-alkylated compounds could be easily distinguished by NMR spectroscopy. The singlets due to the benzylic protons of O-alkylated compounds **25a–c** appear slightly lowerfield (~0.15 ppm) compared to those of N-alkylated compounds **26a–c**. The benzylic carbons of the N-alkylated compounds **25a–c** (e.g., **25c**, 46 ppm) appear at significantly higher field than those of the O-alkylated compounds **26a–c** (e.g., **26c**, 68 ppm). The regiochemistry of N-alkylation was confirmed by NOE experiments on **25a–c**. For example, irradiation of the methyl singlet of **25a** had no influence on the benzylic protons of the biphenyl side chain, indicating that the alkylation took place at the nitrogen atom remote from the methyl group.

The synthesis of pyrimidine **4** began with the biphenylyl bromide **12a**, which on treatment with silver fluoroborate in dimethyl sulfoxide[17] gave the aldehyde **29**, accompanied by a small amount of the alcohol **30**. The crude product mixture was oxidized with chromium chlorochromate to furnish the aldehyde **29** in 70% overall yield. Conversion of **29** to the benzylidene **31** proceeded under standard Knoevenagel conditions. Treatment of **31** with **8** gave tetrahydropyrimidine **32**, which was oxidized to **33** with manganese dioxide in refluxing benzene. Heating of **33** with phosphorus oxychloride resulted in both chlorination of the pyrimidine ring and deprotection of the *tert*-butyl ester to give the final product **4** in 52% yield (Scheme VIII).

Conclusion

We have clearly shown that some dihydropyrimidine analogs (**3i**, **3j**, **6a**) are potent AII antagonists in vitro, their potencies being similar to or better than that of losartan (**1**). One of these compounds (**3i**) showed antihypertensive activity on oral administration to SdSHR. These data demonstrate that a dihydropyrimidine can mimic the imidazole ring of losartan (**1**). Comparison among the most potent analogs, **3i**, **3j** and **6b**, indicates that a variety of substituents are tolerated on the heterocyclic ring. These data taken together with the excellent potency of losartan (**1**) indicates that the AII receptor is quite permissive in accepting this region of the nonpeptide antagonists. This conclusion is supported by numerous reports in the patent literature, indicating that the imidazole of losartan (**1**) can be replaced by a variety of heterocycles.[11] An advantage of the dihydropyrimidine ring system (e.g., **3**) lies in the presence of an additional carbon atom which makes it possible to explore areas of the AII receptor that are not readily accessible via the use of imidazole based AII antagonists (**1**).

(17) Ganem, B.; Boeckman, R. K., Jr. Silver-assisted Dimethylsulfoxide Oxidations; an Improved Synthesis of Aldehydes and Ketones. *Tetrahedron Lett.* **1974**, *14*, 917–920.

Experimental Section

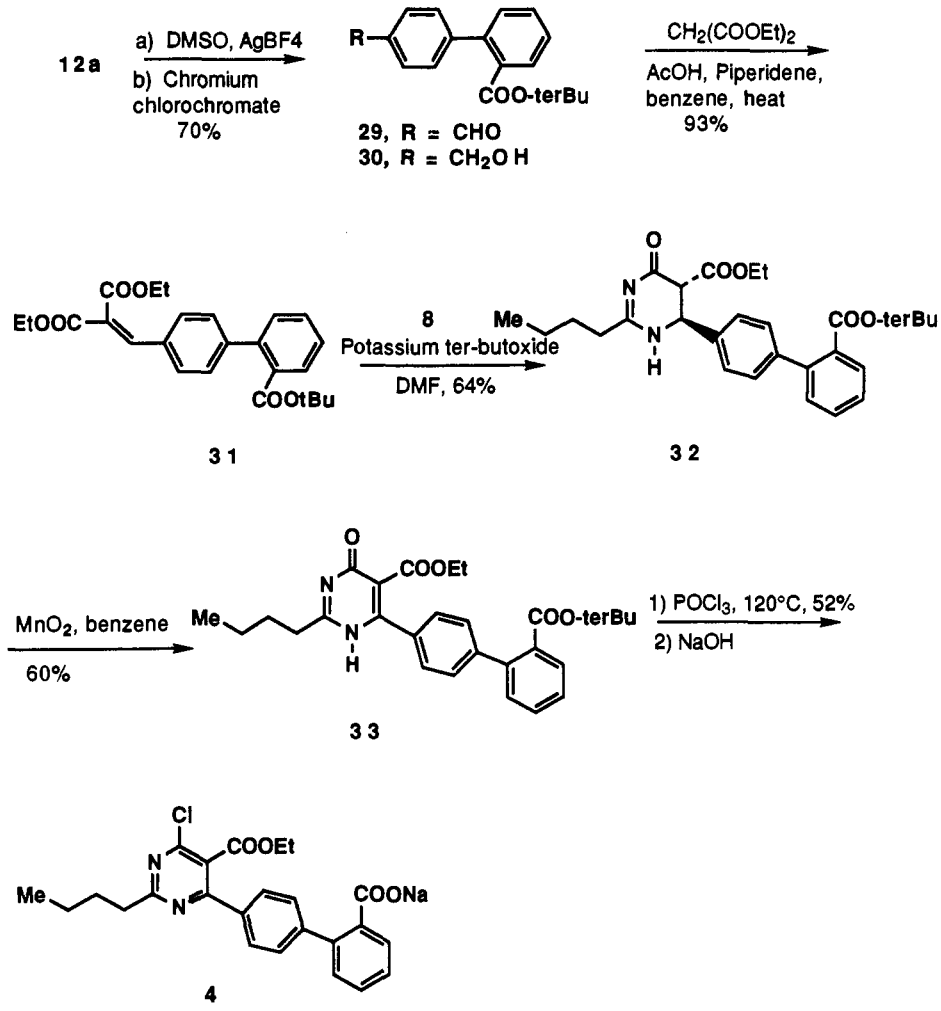
Chemistry. All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The infrared spectra were recorded with a Perkin-Elmer 983 spectrophotometer and KBr pellets. ^{1}H-NMR spectra were measured on JEOL GX-400, GX-270, and GSX-270 spectrometers. For flash chromatography, Whatman LPS-1 silica gel was used. Microanalyses of all crystalline compounds were in agreement with the structures assigned.

2-Butyl-1-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl]-4-chloro-1,6-dihydro-6-methylpyrimidine-5-carboxylic Acid, Ethyl Ester (3a). A. *trans*-2-Butyl-1,4,5,6-tetrahydro-6-methyl-4-oxo-5-pyrimidinecarboxylic Acid, Ethyl Ester (10a). To the solution of pentanimidamide hydrochloride (**8**)[12] (1.98 g, 14.5 mmol) in dimethylformamide (5.0 mL) at 0 °C under argon was added potassium *tert*-butoxide (1.57 g, 14.0 mmol). After stirring of the reaction mixture for 30 min, diethyl ethylidenemalonate (2.25 g, 12.08 mmol) was added and the cooling bath was removed. The reaction mixture was stirred at room temperature for 16 h and partitioned between ethyl acetate and water. The aqueous phase was reextracted with ethyl acetate, and the combined extracts were washed with water, saturated sodium bicarbonate, and brine. After drying over anhydrous magnesium sulfate, the solvent was evaporated to yield predominantly *trans*-2-butyl-1,4,5,6-tetrahydro-6-methyl-4-oxo-5-pyrimidine-carboxylic acid, ethyl ester (**10a**), as a light yellow oil (2.75 g, 94.8%): ^{1}H NMR ($CDCl_3$) δ 9.8 (br s, 1 H), 4.24 (q, J = 7.0 Hz, 2 H), 4.12 (m, 1 H), 3.14 (d, J = 10.0 Hz, 1 H), 2.3 (t, J = 7.6 Hz, 2 H), 1.6 (m, J = 7.6 Hz, 2 H), 1.37 (m, 2 H), 1.4–1.2 (m, 6 H), 0.92 (t, J = 7.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 168.4, 168.1, 153.4, 61.7, 52.8, 52.75, 35.0, 28.2, 22.1, 20.4, 14.0, 13.6 ppm. The product contained about 5–10% of the *cis*-2-butyl-1,4,5,6-tetrahydro-6-methyl-4-oxo-5-pyrimidinecarboxylic acid, ethyl ester. The most distinguishable signals were due to C5 protons (trans, 3.14 ppm, d, J = 10.0 Hz; cis, 3.37 ppm, d, J = 5.8 Hz).

B. 6-Butyl-4-chloro-1,2-dihydro-2-methyl-3-pyrimidinecarboxylic Acid, Ethyl Ester (11b). The reaction mixture containing 2-butyl-1,4,5,6-tetrahydro-6-methyl-4-oxo-5-pyrimidinecarboxylic acid, ethyl ester (**10a**, 1.66 g, 6.9 mmol), and phosphorus oxychloride (28 mL) was heated at reflux temperature for 6 h under argon. The excess phosphorus oxychloride was evaporated under reduced pressure and the residue was coevaporated with toluene to give **4** (1.8 g), as an oil. This material was used for the next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 7.17 (br, 1 H), 4.70 (q, J = 6.5 Hz, 1 H), 4.2 (m, 2 H), 2.4 (t, J = 7.6 Hz, 2 H), 1.7 (m, J = 7.6 Hz, 2 H), 1.4–1.2 (m, 8 H), 0.92 (t, J = 7.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 164.1, 144.6, 103.6, 60.6, 47.9, 34.2, 29.3, 23.4, 22.2, 14.1, 13.6 ppm.

C. 6-Butyl-4-chloro-1-[2′-[(1,1-dimethylethoxy)carbonyl]-[1,1′-biphenyl]-4-yl]-1,2-dihydro-2-methyl-3-pyrimidinecarboxylic Acid, Ethyl Ester (13a). The solution of 6-butyl-4-chloro-1,2-dihydro-2-methyl-3-pyrimidinecarboxylic acid, ethyl ester (**11a**, 1.9 g, crude), in dimethylformamide (14 mL) was treated with finely ground potassium carbonate (3.87 g, 27.4 mmol) and 4′-(bromomethyl)[1,1′-biphenyl]-2-carboxylic acid, 1,1-dimethylethyl ester (**12a**, 13 2.51 g, 8.3 mmol). The reaction mixture was allowed to stir at room temperature overnight. More potassium carbonate (3.8 g) and **12a** (1.1 g) were added, and the reaction mixture was stirred for 15 hours more. It was diluted with ethyl acetate and filtered. The filtrate was washed with water and brine and was dried over anhydrous magnesium sulfate.

Scheme VIII



The solvent was evaporated to yield a yellow oil which was purified by flash chromatography on silica gel (15% ethyl acetate in hexanes) to provide 6-butyl-4-chloro-1-[2′-[(1,1-dimethylethoxy)-carbonyl][1,1′-biphenyl]-4-yl]-1,2-dihydro-2-methyl-3-pyrimidinecarboxylic acid, ethyl ester (**13a**), as a yellow foam (2.58 g, 71%): ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 7.6 Hz, 1 H), 7.6–7.3 (m, 7 H), 4.92, 5.8 (AB q, J = 16.4 Hz, 2 H), 4.6 (m, 1 H), 4.25 (m, 2 H), 2.5 (m, 2 H), 1.65 (m, 2 H), 1.5–1.3 (m, 17 H), 1.0 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 167.7, 164.2, 163.9, 148.2, 141.8, 141.1, 134.1, 132.6, 130.7, 130.4, 129.7, 129.3, 129.2, 128.6, 127.3, 125.9, 101.9, 81.2, 77.2, 60.2, 54.1, 52.3, 34.0, 29.1, 27.6, 22.5, 18.4, 14.2, 13.7 ppm.

D. 2-Butyl-1-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl]-4-chloro-1,6-dihydro-6-methylpyrimidine-5-carboxylic Acid, Ethyl Ester (3a). To the solution of 6-butyl-4-chloro-1-[2′-[(1,1-dimethylethoxy)carbonyl][1,1′-biphenyl]-4-yl]-1,2-dihydro-2-methyl-3-pyrimidinecarboxylic acid, ethyl ester (**13a**, 2.58 g, 4.92 mmol), in dichloromethane (20 mL) was added trifluoroacetic acid (8.0 mL) and the reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated and to give an off-white solid (2.4 g). This material was recrystallized from ether (containing a few drops of methanol) to provide 2-butyl-1-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl]-4-chloro-1,6-dihydro-6-methyl-1-pyrimidinecarboxylic acid, ethyl ester (6, 1.14 g, 49.6%): mp 93–95 °C; ^{1}H NMR ($CDCl_3$) δ 7.94 (d, J = 6.5 Hz, 1 H), 7.5 (t, J = 7.7 Hz, 1 H), 7.5–7.2 (m, 6 H), 4.80, 4.5 (AB q, J = 15.8 Hz, 2 H), 4.45 (m, 1 H), 4.25 (m, 2 H), 2.4 (m, 2 H), 1.6 (m, 2 H), 1.36 (m, 2 H), 1.24 (d, J = 7.0 Hz, 3 H), 1.2 (t, J = 6.5 Hz, 3 H), 0.9 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 171.5, 164.5, 164.3, 147.5, 142.1, 141.5, 134.0, 131.6, 130.8, 130.5, 130.3, 129.3, 127.4, 126.2, 102.1, 77.2, 60.4, 54.0, 52.5, 33.6, 29.2, 22.5, 18.4, 14.2, 13.6 ppm.

2-Butyl-1-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl-4-chloro-1,6-dihydro-6-phenyl-1-pyrimidine-5-carboxylic acid, ethyl ester (**3b**), and 2-butyl-4-chloro-1,6-dihydro-6-methyl-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]pyrimidine-5-carboxylic acid, ethyl ester, monopotassium salt (**3i**) were prepared in a similar manner.

2-Butyl-1-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl]-1,6-dihydro-4,6-dimethyl-5-pyrimidinecarboxylic Acid, Ethyl Ester (3c). A. 2-Butyl-1,6-dihydro-4,6-dimethyl-5-pyrimidinecarboxylic Acid, Ethyl Ester (22a). To a solution of pentanimidamide hydrochloride (**8**,[12] 2.89 g, 21.1 mmol) in dimethylformamide (40 mL) at 0 °C was added potassium *tert*-butoxide (2.2 g, 19.2 mmol) under argon and the reaction mixture was stirred for ~15 min. A solution of ethyl 2-ethylideneacetoacetate (**21a**, 3.0 g, 19.2 mmol) in dimethylformamide (10 mL) was added and the reaction mixture was stirred at 0 °C for 15 min. The reaction mixture was treated with *p*-toluenesulfonic acid (7.3 g, 38.4 mmol) and heated at 80 °C for 16 h and 100 °C for 1.5 h. It was cooled to room temperature and treated with 2 N sodium hydroxide and extracted with ethyl acetate. The organic extracts were washed with water and brine. After drying over anhydrous magnesium sulfate, the solvent was evaporated and the residue was purified by flash chromatography on silica gel (30% acetone in hexane) to give a light yellow oil (**22a**) (4.0 g, 87.3%): ^{1}H NMR ($CDCl_3$) δ 7.9 (s, 1 H), 4.40 (q, J = 6.4 Hz, 1 H), 4.07 (m, 2 H), 2.18 (s, 3 H), 2.12 (t, J = 7.6 Hz, 2 H), 1.5 (qn, J = 7.6 Hz, 2 H), 1.4–1.2 (m, 5 H), 1.02 (d, J = 6.4 Hz, 3 H), 0.82 (t, J = 7.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 167.2, 155.5, 148.3, 100.8, 59.3, 48.8, 36.4, 31.4, 22.5, 22.3, 19.2, 14.4, 13.8 ppm.

B. 2-Butyl-1-[2′-[(1,1-dimethylethoxy)carbonyl][1,1′-biphenyl]-4-yl]-1,6-dihydro-4,6-dimethyl-5-pyrimidinecarboxylic Acid, Ethyl Ester (23a). The solution of 2-butyl-1,6-dihydro-4,6-dimethyl-5-pyrimidinecarboxylic acid, ethyl ester (**22a**, 1.0 g, 4.2 mmol), in dimethylformamide (14 mL) was treated with finely ground potassium carbonate (2.3 g, 16.8 mmol) and 4′-(bromomethyl)[1,1′-biphenyl]-2-carboxylic acid, 1,1-dimeth-

ylethyl ester (12a,[13a] 1.52 g, 5.0 mmol). The reaction mixture was allowed to stir at room temperature overnight. It was poured into water (100 mL) and extracted with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous magnesium sulfate. The solvent was evaporated to yield a yellow oil which was purified by flash chromatography on silica gel (5% methanol in chloroform) to provide 2-butyl-1-[2′-[(1,1-dimethylethoxy)carbonyl][1,1′-biphenyl]-4-yl]-1,6-dihydro-4,6-dimethyl-5-pyrimidinecarboxylic acid, ethyl ester (**23a**, 1.4 g, 72.5%), as a yellow foam: ^{1}H NMR ($CDCl_3$) δ 7.76 (d, J = 7.6 Hz, 1 H), 7.46–7.24 (m, 7 H), 4.80 (d, J = 16.8 Hz, 1 H), 4.47 (d, J = 16.4 Hz, 1 H), 4.33 (q, J = 6.4 Hz, 1 H), 4.10 (m, 2 H), 2.4 (m, 2 H), 2.35 (s, 3 H), 1.60 (m, 2 H), 1.5–1.1 (m, 17 H), 0.90 (t, J = 7.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 167.7, 165.2, 163.9, 155.0, 141.8, 135.1, 132.6, 129.8, 129.7, 128.5, 128.2, 127.3, 126.2, 125.9, 101.9, 81.2, 77.2, 60.2, 54.1, 52.3, 34.0, 29.1, 27.6, 22.5, 18.4, 14.2, 13.7 ppm.

C. 2-Butyl-1-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl]-1,6-dihydro-4,6-dimethyl-5-pyrimidinecarboxylic Acid, Ethyl Ester (3c). To the solution of 2-butyl-1-[2′-[(1,1-dimethylethoxy)carbonyl][1,1′-biphenyl]-4-yl]-1,6-dihydro-4,6-dimethyl-5-pyrimidinecarboxylic acid, ethyl ester (**23a**, 1.0 g, 2.2 mmol), in dichloromethane (10 mL) was added trifluoroacetic acid (3.0 mL) and the reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated and the residue was triturated with ethyl ether to provide 2-butyl-1-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl]-1,6-dihydro-6,4-dimethyl-1-pyrimidinecarboxylic acid, ethyl ester (**3c**), trifluoroacetic acid (1:1) salt (700 mg, 57%), as a colorless solid: mp 144–146 °C; ^{1}H NMR ($CDCl_3$) δ 7.97 (d, J = 7.7 Hz, 1 H), 7.59 (t, J = 7.7 Hz, 1 H), 7.5–7.2 (m, 6 H), 4.92 (d, J = 16.8 Hz, 1 H), 4.67 (d, J = 15.8, 1 H), 4.57 (q, J = 5.9 Hz, 1 H), 4.25 (q, J = 7.1 Hz, 2 H), 2.9 (m, 2 H), 2.5 (s, 3 H), 1.7 (m, 2 H), 1.48 (q, J = 7.1 Hz, 2 H), 1.25 (m, 6 H), 0.96 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 170.3, 164.8, 164.0, 144.3, 142.7, 141.4, 131.5, 130.9, 130.7, 130.6, 130.4, 129.8, 127.7, 126.5, 105.8, 61.2, 53.2, 52.9, 30.2, 29.1, 22.3, 18.9, 16.9, 14.1, 13.4 ppm.

2-Butyl-1-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl]-4-chloro-1,6-dihydro-6-methyl-4-phenyl-5-pyrimidinecarboxylic acid, ethyl ester, trifluoroacetate (1:1) salt (**3d**), and 2-butyl-1-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl]-4-chloro-1,6-dihydro-6-methyl-4-(4-chlorophenyl)-5-pyrimidinecarboxylic acid, ethyl ester, trifluoroacetate (1:1) salt (**3e**), were prepared in an analogous manner.

2-Butyl-1-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl]-1,6-dihydro-6-oxopyrimidine-5-carboxylic Acid, Ethyl Ester, Monosodium Salt (3h). A. 2-Butyl-1,4,5,6-tetrahydro-5-[2,2-bis(ethoxycarbonyl)ethyl]-4-oxo-5-pyrimidinecarboxylic Acid, Ethyl Ester (28). To a solution of pentanimidamide hydrochloride (**8**,[12] 4.56 g, 33.3 mmol) in N,N-dimethylformamide (25 mL) at 0 °C was added potassium *tert*-butoxide (3.25 g, 29.0 mmol) followed by diethyl methylenemalonate[16] (5.0 g, 29.0 mmol). The reaction mixture was stirred for 18 h at room temperature, diluted with ethyl acetate, and filtered. The filtrate was washed with water, saturated sodium bicarbonate solution, and brine and dried over magnesium sulfate. The volatiles were removed under vacuum to obtain an amber gum (5.08 g). The crude material was chromatographed on silica eluting with 15% acetone in methylene chloride to obtain 2-butyl-1,4,5,6-tetrahydro-5-[2,2-bis(ethoxycarbonyl)ethyl]-4-oxo-5-pyrimidinecarboxylic acid, ethyl ester (**28**, 3.29 g, 57%), as a colorless gum: ^{1}H NMR ($CDCl_3$) δ 9.19 (s, 1 H), 4.18 (m, 6 H), 4.03 (d, J = 15.8 Hz, 1 H), 3.74 (t, J = 5.8 Hz, 1 H), 3.48 (d, J = 15.8 Hz, 1 H), 2.59 (m, 1 H), 2.42 (dd, J = 5.0 and 14.9 Hz, 1 H), 2.28 (t, J = 7.6 Hz, 2 H), 1.59 (m, 2 H), 1.38–1.28 (m, 8 H), 0.92 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 170.01, 169.61, 169.00, 168.89, 155.59, 61.97, 61.51, 51.98, 50.74, 48.29, 34.50, 29.66, 27.82, 21.91, 13.82, 13.76, 13.53 ppm; MS $(M + H)^+$ m/z 399.

B. 2-Butyl-1,4-dihydro-4-oxo-5-pyrimidinecarboxylic Acid, Ethyl Ester (24c). To a solution of sodium ethoxide in ethanol (prepared by the addition of 0.06 g of sodium metal (0.06 g) to 4.0 mL of ethanol at 0 °C) was added 2-butyl-1,4,5,6-tetrahydro-5-[2,2-bis(ethoxycarbonyl)ethyl]-4-oxo-5-pyrimidinecarboxylic acid, ethyl ester (**28**, 0.50 g, 1.26 mmol). The reaction mixture was heated at reflux for 2 h and partitioned between saturated ammonium chloride solution and ethyl acetate. The organic fraction was washed with saturated sodium bicarbonate solution and brine and dried over magnesium sulfate. The solvent was evaporated in vacuo to obtain an off-white solid (0.23 g). The crude product was chromatographed on silica gel eluting with 5% methanol in methylene chloride to obtain 2-butyl-1,4-dihydro-4-oxo-5-pyrimidinecarboxylic acid, ethyl ester (**24c**, 90 mg, 32%), as a colorless semisolid: ^{1}H NMR ($CDCl_3$) δ 8.73 (s, 1 H), 4.36 (q, 2 H), 2.79 (t, J = 7.0 Hz, 2 H), 1.80 (m, 2 H), 1.46–1.35 (m, 5 H), 0.96 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 168.10, 163.98, 162.28, 161.25, 114.89, 61.44, 35.58, 29.56, 22.45, 14.47, 13.90 ppm.

C. 2-Butyl-1-[[2′-[(1,1-dimethylethoxy)carbonyl][1,1′-biphenyl]-4-yl]methyl]-1,6-dihydro-6-oxopyrimidine-5-carboxylic Acid, Ethyl Ester (25c), and 2-Butyl-4-[[[2′-[(1,1-dimethylethoxy)carbonyl][1,1′-biphenyl]-4-yl]methyl]oxy]-5-pyrimidinecarboxylic Acid, Ethyl Ester (26c). A solution of 2-butyl-1,4-dihydro-4-oxo-5-pyrimidinecarboxylic acid, ethyl ester (**24c**, 0.16 g, 0.71 mmol), and 4-(bromomethyl)-1,1′-biphenyl-2′-carboxylic acid, *tert*-butyl ester (**12a**,[13] 0.30 g, 0.78 mmol) in N,N-dimethylformamide (4.25 mL) containing potassium carbonate (0.20 g, 1.42 mmol) was stirred for 18 h at room temperature. The reaction mixture was partitioned between ethyl acetate and water. The organic fraction was washed with brine, dried over magnesium sulfate, and evaporated in vacuo to obtain a yellow gum (0.35 g). The crude product was chromatographed on silica eluting with hexane/ethyl acetate (4:1) to obtain 2-butyl-1-[[2′-[(1,1-dimethylethoxy)carbonyl][1,1′-biphenyl]-4-yl]methyl]-1,6-dihydro-6-oxopyrimidine-5-carboxylic acid, ethyl ester (**25c**, 185 mg, 53%), and 2-butyl-4-[[[2′-[(1,1-dimethylethoxy)-carbonyl][1,1′-biphenyl]-4-yl]methyl]oxy]-5-pyrimidinecarboxylic acid, ethyl ester (**26c**, 40 mg, 12%), as colorless gums. **25c**: ^{1}H NMR ($CDCl_3$) δ 8.75 (s, 1 H), 7.89 (d, J = 7.0 Hz, 1 H), 7.58–7.42 (m, 2 H), 7.36 (m, 5 H), 5.51 (br s, 2 H), 4.49 (q, J = 7.0 and 14.0 Hz, 2 H), 2.89 (t, J = 7.0 Hz, 2 H), 1.83 (m, 2 H), 1.51–1.42 (m, 5 H), 1.35 (s, 9 H), 1.03 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 167.54, 167.08, 163.79, 158.83, 157.56, 141.58, 141.03, 133.62, 132.58, 130.56, 130.27, 129.52, 127.16, 126.35, 114.56, 81.07, 61.02, 46.34, 35.18, 28.54, 27.45, 22.17, 14.12, 13.54 ppm. **26c**: ^{1}H NMR ($CDCl_3$) δ 8.94 (s, 1 H), 7.79 (dd, J = 1.2 and 7.6 Hz, 1 H), 7.55 (d, J = 8.21 Hz, 2 H), 7.52–7.27 (m, 5 H), 5.64 (s, 2 H), 4.38 (q, J = 7.0 and 14.1 Hz, 2 H), 2.90 (t, J = 7.6 Hz, 2 H), 1.81 (m, 2 H), 1.45–1.24 (m, 5 H), 1.21 (s, 9 H), 0.96 (t, J = 7.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 174.51, 167.91, 166.76, 160.40, 141.65, 135.00, 132.89, 130.68, 130.45, 129.67, 128.66, 127.48, 127.19, 109.71, 81.20, 68.01, 61.22, 39.08, 30.18, 27.50, 22.40, 14.22, 13.91 ppm.

D. 2-Butyl-1-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl]-1,6-dihydro-6-oxopyrimidine-5-carboxylic Acid, Ethyl Ester, Monosodium Salt (3h). 2-Butyl-1-[[2′-[(1,1-dimethylethoxy)-carbonyl][1,1′-biphenyl]-4-yl]methyl]-1,6-dihydro-6-oxopyrimidine-5-carboxylic acid, ethyl ester (**25c**, 0.30 g, 0.62 mmol), was deprotected with trifluoroacetic acid by the same procedure as described for **3a**. The crude product in ethanol was converted to its sodium salt by treatment with 1 N sodium hydroxide solution and passed through HP-20 resin eluting with methanol/H_2O (3:2). The eluant was evaporated and lyophilized to obtain 2-butyl-1-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl]-1,6-dihydro-6-oxopyrimidine-5-carboxylic acid, ethyl ester, monosodium salt (**3h**, 125 mg, 44%), as a white solid: ^{1}H NMR (CD_3OD) δ 8.60 (s, 1 H), 7.58–7.42 (m, 3 H), 7.40–7.20 (m, 3 H), 7.15 (d, J = 7.9 Hz, 2 H), 5.45 (s, 2 H), 4.35 (q, J = 7.0 Hz, 2 H), 2.82 (t, J = 7.6 Hz, 2 H), 2.68 (m, 2 H), 1.40–1.25 (m, 5 H), 0.85 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (CD_3OD) 178.28, 169.83, 165.39, 161.38, 159.15, 142.94, 141.88, 139.31, 134.95, 130.66, 130.28, 129.04, 128.38, 128.00, 127.43, 114.71, 62.38, 48.05, 36.16, 29.64, 23.27, 14.50, 14.07 ppm; MS $(M + H)^+$ m/z 433.

Using a similar reaction sequence, 2-butyl-1-[[2′-carboxy-[1,1′-biphenyl]-4-yl]methyl]-1,6-dihydro-4-methyl-6-oxo-5-pyrimidinecarboxylic acid, ethyl ester, monosodium salt (**3f**), and 2-butyl-1-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl]-1,6-dihydro-6-oxo-4-phenyl-5-pyrimidinecarboxylic acid, ethyl ester, monosodium salt (**3g**), were prepared from 2-butyl-1,6-dihydro-6-oxo-4-phenyl-5-pyrimidinecarboxylic acid, ethyl ester (**24a**), and 2-butyl-1,6-dihydro-6-oxo-4-phenyl-5-pyrimidinecarboxylic acid, ethyl ester (**24b**), respectively.

2-Butyl-1,6-dihydro-6-oxo-4-phenyl-5-pyrimidinecarboxylic Acid, Ethyl Ester (24b). To the solution of 2-butyl-1,4,5,6-tetrahydro-6-oxo-4-phenyl-5-pyrimidinecarboxylic acid, ethyl ester (**10b**, 440 mg, 1.48 mmol), in benzene (5 mL) was added manganese oxide (780, 9.0 mmol) and the reaction mixture was

heated at 70 °C for 24 h. The reaction mixture was cooled to room temperature and diluted with dichloromethane/methanol (10:1) and filtered through a pad containing silica gel and Celite. The filtrate was evaporated and the residue was crystallized from isopropyl ether to give 2-butyl-1,6-dihydro-6-oxo-4-phenyl-5-pyrimidinecarboxylic acid, ethyl ester (**24b**), as a colorless solid: mp 143–145 °C; ^{1}H NMR ($CDCl_3$) δ 7.6 (d, J = 7.0 Hz, 2 H), 4.4 (m, 3 H), 4.15 (q, J = 7.0 Hz, 2 H), 2.7 (t, J = 7.7 Hz, 2 H), 1.75 (m, 2 H), 1.4 (m, 2 H), 1.05 (t, J = 7.2 Hz, 2 H), 0.9 (t, J = 7.0 Hz, 3 H).

Using the same procedure, 2-butyl-1,6-dihydro-6-oxo-4-phenyl-5-pyrimidinecarboxylic acid, ethyl ester (**24a**), was prepared from *trans*-2-butyl-1,4,5,6-tetrahydro-6-methyl-4-oxo-5-pyrimidinecarboxylic acid, ethyl ester (**10a**).

2-Butyl-4-chloro-1,6-dihydro-6-methyl-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-5-pyrimidinecarboxylic Acid, Trifluoroacetate (1:1) Salt (3j). A. 2-Butyl-1-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl]-4-chloro-1,6-dihydro-6-methyl-5-pyrimidinecarboxylic Acid (18). A solution of 2-butyl-1-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl]-4-chloro-1,6-dihydro-6-methyl-1-pyrimidinecarboxylic acid, ethyl ester (**3a**), was prepared by warming the compound in 2500 mL of 0.1 M K_2HPO_4 solution and then filtering the hot solution. The solution was cooled to 25 °C, and the pH was adjusted to 7.8 by addition of 0.1 M KH_2PO_4 solution. Porcine liver esterase (15 000 units, 6 mL Sigma catalog #E-3128, EC 3.1.1.1) was added and the mixture was stirred at 25 °C for 17 days, during which progress of the reaction was monitored by HPLC (YMC S3 ODS column 6.0 × 150 mm, eluting with 1.5 mL/min of 30% aqueous methanol containing 0.2% phosphoric acid; UV monitoring at 300 nm). The mixture was then acidified by addition of excess trifluoroacetic acid, filtered through a 0.5-μm filter, and loaded onto a preparative HPLC column (YMC S-15 ODS, 50 × 500 mm). The column was then eluted with 100 mL/min of a linear gradient (40 min) from 10% to 90% aqueous methanol containing 0.1% trifluoroacetic acid, and fractions were monitored by UV absorbance at 330 nm. Fractions containing the major product were combined, concentrated in vacuo, and lyophilized. The gummy residue was triturated with ether to give 2-butyl-1-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl]-4-chloro-1,6-dihydro-6-methyl-1-pyrimidinecarboxylic acid (**18**) as a white solid (970 mg, 44%): mp 121–122 °C; ^{1}H NMR (CD_3OD) δ 4.90 (q, J = 6.0 Hz, 1 H), 2.65 (m, 2 H), 1.90 (m, 2 H), 1.55 (m, 2 H), 1.50 (d, J = 6.0, 3 H), 1.05 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (CD_3OD) 166.0, 165.1, 132.7, 109.0, 50.6, 32.3, 29.9, 23.1, 22.9, 13.8 ppm.

B. 2-Butyl-1-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl]-4-chloro-1,6-dihydro-6-methyl-5-pyrimidinecarboxylic Acid, Diphenylmethyl Ester (19). To a solution of 2-butyl-1-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl]-4-chloro-1,6-dihydro-6-methyl-1-pyrimidinecarboxylic acid (**18**, 240 mg, 0.75 mmol) in ethanol (3 mL) was added diphenyldiazomethane (252 mg, 1.3 mmol). The resulting red solution was stirred at 25 °C until the red color disappeared (~10 min). More diphenyldiazomethane was added (50 mg, 0.25 mmol) and the solution turned red and then slowly decolorized. After 30 min, a final portion of diphenyldiazomethane was added (70 mg, 0.36 mmol) and the mixture was stirred for 15 min. The solution was then concentrated in vacuo and the residue was purified by flash chromatography on silica gel eluting with hexane/ethyl acetate (1:1). Fractions containing the desired product were combined and concentrated to give 2-butyl-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl]-4-chloro-1,6-dihydro-6-methyl-1-pyrimidinecarboxylic acid, diphenylmethyl ester (**19**), as a colorless foam (240 mg, 81%): ^{1}H NMR ($CDCl_3$) δ 7.0–7.2 (m, 10 H), 6.85 (s, 1 H), 6.55 (br s, 1 H), 4.59 (q, J = 6.0 Hz, 1 H), 2.10 (t, J = 7.0, 2 H), 1.50 (m, 2 H), 1.25 (m, 2 H), 1.10 (d, J = 6.0 Hz, 3 H), 0.80 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 164.0, 140.4, 128.4, 127.7, 127.0, 126.8, 102.3, 77.3, 47.8, 35.5, 29.0, 23.5, 22.2, 13.6 ppm.

C. 2-Butyl-4-chloro-1,6-dihydro-6-methyl-1-[[2′-[1-(triphenylmethyl)tetrazole-5-yl][1,1′-biphenyl]-4-yl]methyl]pyrimidine-5-carboxylic Acid, Diphenylmethyl Ester (20). The title compound was prepared from 2-butyl-1-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl]-4-chloro-1,6-dihydro-6-methyl-1-pyrimidinecarboxylic acid, diphenylmethyl ester (**19**), and *N*-(triphenylmethyl)-5-[2-[4′-(bromomethyl)[1,1′-biphenyl]-yl]tetrazole (**12b**)[13] in the same manner as described for 6-butyl-4-chloro-1-[2′-[(1,1-dimethylethoxy)carbonyl][1,1′-biphenyl]-4-yl]-1,2-dihydro-2-methyl-3-pyrimidinecarboxylic acid, ethyl ester (**13a**). The residue was purified by flash chromatography on silica gel, eluting with hexane/ethyl acetate (2:1). Fractions containing the desired product were combined and concentrated to give 2-butyl-4-chloro-1,6-dihydro-6-methyl-1-[[2′-[1-(triphenylmethyl)tetrazole-5-yl][1,1′-biphenyl]-4-yl]methyl]pyrimidine-5-carboxylic acid, diphenylmethyl ester (**20**), as a colorless foam (60 mg, 46%): ^{1}H NMR ($CDCl_3$) δ 6.8–8.0 (m, 34 H), 4.62 (d, J = 16.0 Hz, 1 H), 4.52 (q, J = 6.0 Hz, 1 H), 4.30 (d, J = 16.0 Hz, 1 H), 2.35 (m, 2 H), 1.60 (m, 2 H), 1.30 (m, 2 H), 1.05 (d, J = 6.0 Hz, 3 H), 0.85 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 164.1, 164.0, 141.2, 140.6, 133.6, 130.7, 130.2, 130.0, 128.4, 128.2, 128.0, 127.7, 127.4, 127.0, 126.7, 126.2, 125.9, 101.5, 53.7, 52.2, 34.1, 29.0, 22.5, 18.3, 13.7 ppm.

D. 2-Butyl-4-chloro-1,6-dihydro-6-methyl-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-5-pyrimidinecarboxylic Acid, Trifluoroacetate (1:1) Salt (3j). Deprotection of 2-butyl-4-chloro-1,6-dihydro-6-methyl-1-[[2′-[1-(triphenylmethyl)tetrazole-5-yl][1,1′-biphenyl]-4-yl]methyl]pyrimidine-5-carboxylic acid, diphenylmethyl ester (**20**), was carried out with trifluoroacetic acid and the crude product was applied directly to a preparative HPLC column (YMC S-10 ODS, 30 × 500 mm). The column was eluted with 50 mL/min of 46% aqueous methanol containing 0.1% trifluoroacetic acid, with monitoring by UV absorbance at 300 nm. Fractions containing the major product were combined and concentrated, and the residue was lyophilized to give 2-butyl-4-chloro-1,6-dihydro-6-methyl-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-5-pyrimidinecarboxylic acid, trifluoroacetate (1:1) salt (**3j**), as a white solid (70%): mp 108–112 °C; ^{1}H NMR (CD_3OD) δ 7.3–7.9 (m, 8 H), 5.30 (d, J = 16.0 Hz, 1 H), 5.05 (d, J = 16.0 Hz, 1 H), 4.97 (q, J = 6.0 Hz, 1 H), 2.95 (m, 2 H), 1.3–1.8 (m, 4 H), 1.48 (d, J = 6.0 Hz, 3 H), 1.05 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (CD_3OD) 167.0, 164.3, 142.6, 141.7, 139.3, 133.7, 133.5, 132.6, 131.8, 131.6, 131.2, 128.8, 124.4, 108.3, 56.7, 54.4, 31.8, 30.0, 23.4, 18.6, 13.8 ppm.

2-Butyl-6-[2′-carboxy[1,1′-biphenyl]-4-yl]-4-chloropyrimidine-5-carboxylic Acid, Ethyl Ester, Monosodium Salt (4). A. 4-[2′-[(1,1-Dimethylethoxy)carbonyl]phenyl]benzaldehyde (29). To a solution of 4′-(bromomethyl)[1,1′-biphenyl]-2-carboxylic acid, 1,1-dimethylethyl ester (**12a**,[13a] 3.47 g, 10.0 mmol) in dimethyl sulfoxide (10.0 mL) at room temperature under argon were added sodium bicarbonate (1.7 g, 20.0 mmol) and silver tetrafluoroborate (2.15 g, 11.0 mmol). The reaction mixture was stirred at room temperature for 6 h and diluted with ether. The solid was filtered off using a Celite pad and the filtrate was washed with water and brine and dried over magnesium sulfate. The solvent was evaporated and the residue in dichloromethane (10 mL) was added to a suspension of chromium chlorochromate (1.5 g, 6.9 mmol) in dichloromethane (15 mL). After stirring of the reaction mixture for 1 h at room temperature, ether was added and the reaction mixture was filtered through a pad of Celite. The filtrate was washed with 1 N sodium hydroxide and brine and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (10% ethyl acetate in hexanes) to provide 4-[2′-[(1,1-dimethylethoxy)carbonyl]phenyl]benzaldehyde (**29**, 2.1 g, 74.5%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J = 8 Hz, 2 H), 7.85 (d, J = 7.0 Hz, 1 H), 7.5 (m, 4 H), 7.30 (d, J = 7.0 Hz, 1 H), 1.25 (s, 9 H); ^{13}C NMR ($CDCl_3$) 192.0, 135.0, 130.9, 130.2, 130.0, 129.8, 129.4, 129.3, 128.8, 127.9, 81.6, 27.6 ppm.

B. Diethyl [[2′-[(1,1-Dimethylethoxy)carbonyl][1,1′-biphenyl]-4-yl]methylidene]malonate (31). The reaction mixture containing 4-[2′-[(1,1-dimethylethoxy)carbonyl]phenyl]-benzaldehyde (**29**, 2.1 g, 7.45 mmol), diethylmalonate (1.2 g, 7.5 mmol), piperidene (0.6 mL), and acetic acid (0.3 mL) in benzene (25 mL) was heated at reflux temperature for 3 h using a Dean–Stark water separator. The reaction mixture was cooled to ambient temperature and most of the solvent was evaporated. The residue in ethyl acetate was washed with 1 N hydrochloric acid, 10% sodium carbonate, and brine. After drying over anhydrous magnesium sulfate, the solvent was evaporated to give diethyl [[2′-[(1,1-dimethylethoxy)carbonyl][1,1′-biphenyl]-4-yl]methylidene]malonate (**31**), 3.18 g, 100%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.85 (dd, J = 1.2 and 7.0 Hz, 1 H), 7.8 (s, 1 H), 7.3–7.55 (m, 7 H), 4.38 (m, 4 H), 1.36, 1.30 (q's, J = 6.4 Hz,

3 H each), 1.28 (s, 9 H); ^{13}C NMR ($CDCl_3$) 167.5, 166.6, 164.05, 144.3, 141.5, 140.9, 132.6, 131.5, 130.7, 130.4, 130.2, 129.8, 129.1, 129.0, 128.2, 128.05, 127.5, 126.1, 81.4, 61.6, 27.5, 13.9, 13.8 ppm.

C. *trans*-2-Butyl-6-[2′-[(1,1-dimethylethoxy)carbonyl][1,1′-biphenyl]]-4-oxo-1,4,5,6-tetrahydro-5-pyrimidinecarboxylic Acid, Ethyl Ester (32). The title compound was prepared from diethyl [[2′-[(1,1-dimethylethoxy)carbonyl][1,1′-biphenyl]-4-yl]methylidene]malonate (31) by the same procedure as described for the preparation of *trans*-2-butyl-1,4,5,6-tetrahydro-6-methyl-4-oxo-5-pyrimidinecarboxylic acid, ethyl ester (10a). The residue was purified by flash chromatography (35% ethyl acetate in hexanes) and the product was triturated with isopropyl ether to yield *trans*-2-butyl-6-[2′-[(1,1-dimethylethoxy)carbonyl][1,1′-biphenyl]-4-yl]-4-oxo-1,4,5,6-tetrahydro-5-pyrimidinecarboxylic acid, ethyl ester (32, 2.4 g, 60.8%), as a colorless solid: mp 128–129 °C; ^{1}H NMR ($CDCl_3$) δ 7.7 (d, J = 7.6 Hz, 1 H), 7.2–7.4 (m, 7 H), 5.1 (d, J = 10.5 Hz, 1 H), 4.1 (m, 2 H), 3.47 (d, J = 10.5 Hz, 1 H), 2.3 (t, J = 8.0 Hz, 2 H), 1.6 (m, 2 H), 1.3 (m, 2 H), 1.17 (s, 9 H), 0.86 (t, J = 7.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 167.8, 141.45, 141.39, 138.5, 132.8, 130.6, 130.5, 129.6, 128.9, 128.6, 127.1, 126.8, 126.5, 81.2, 61.7, 60.4, 53.4, 35.1, 28.1, 27.7, 27.6, 22.1, 14.0, 13.7 ppm.

D. 2-Butyl-6-[2′-[(1,1-dimethylethoxy)carbonyl][1,1′-biphenyl]-4-yl]-4-oxo-1,4-dihydro-5-pyrimidinecarboxylic Acid, Ethyl Ester (33). The reaction mixture containing *trans*-2-butyl-6-[2′-[(1,1-dimethylethoxy)carbonyl][1,1′-biphenyl]-4-yl]-4-oxo-1,4,5,6-tetrahydro-5-pyrimidinecarboxylic acid, ethyl ester (32 1.5 g, 3.1 mmol), and manganese dioxide (2.73 g, 31.3 mmol) in toluene (10 mL) was heated at 90 °C for 30 h. It was cooled to ambient temperature and diluted with chloroform. The suspension was filtered through a pad of silica gel and Celite. The filtrate was evaporated and the residue was triturated with ether to give a colorless solid (726 mg). The mother liquor was concentrated and triturated with isopropyl ether to give a second crop, for a total of 900 mg (60%): mp 180 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 7.6 Hz, 1 H), 7.70 (d, J = 8.2 Hz, 2 H), 7.2–7.5 (m, 5 H), 4.22 (q, J = 7 Hz, 2 H), 2.71 (t, J = 7.7 Hz, 2 H), 1.76 (qn, J = 7.0 Hz, 2 H), 1.35 (m, 2 H), 1.2 (s, 9 H), 1.18 (t, J = 7 Hz, 3 H), 0.9 (t, J = 7.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 167.7, 166.0, 163.2, 162.7, 162.0, 144.1, 141.2, 135.8, 132.8, 130.8, 130.5, 129.8, 128.7, 128.1, 127.5, 116.5, 81.5, 61.7, 35.2, 29.3, 27.6, 22.17, 13.9, 13.6 ppm.

E. 2-Butyl-6-[2′-carboxy[1,1′-biphenyl]-4-yl]-4-chloropyrimidine-5-carboxylic Acid, Ethyl Ester, Monosodium Salt (4). The solution of 2-butyl-6-[2′-[(1,1-dimethylethoxy)carbonyl][1,1′-biphenyl]-4-yl]-4-oxo-1,4-dihydro-5-pyrimidinecarboxylic acid, ethyl ester (33, 850 mg, 1.78 mmol), in phosphorus oxychloride (10 mL) was heated at 90 °C for 16 h. Most of the phosphorus oxychloride was removed under vacuum and the residue was purified by flash chromatography (3% methanol in dichloromethane) to give a colorless foam (410 mg, 52.3%). This material in methanol (5 mL) was converted to its sodium salt by treatment with 1 N sodium hydroxide (1.5 mL). Most of methanol was evaporated and the residue was passed through an HP-20 column eluting with 40% aqueous methanol. The product was lyophilized to yield 2-butyl-6-[2′-carboxy[1,1′-biphenyl]-4-yl]-4-chloropyrimidine-5-carboxylic acid, ethyl ester, monosodium salt (4), as a colorless solid (358 mg, 43.6%), which shrinks at 72 °C: ^{1}H NMR (CD_3OD) δ 7.64, 7.58 (AB q, J = 8.2 Hz, 4 H), 7.4 (m, 1 H), 7.26 (br s, 3 H), 4.22 (q, J = 7.6 Hz, 2 H), 2.9 (t, J = 7.1 Hz, 2 H), 1.75 (qn, J = 7.6 Hz, 2 H), 1.33 (qn, J = 7.6 Hz, 2 H), 1.13 (t, J = 7.1 Hz, 3 H), 0.88 (t, J = 7 Hz, 3 H).

2-Butyl-1-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl]-6-chloro-1,4-dihydro-4,4-dimethyl-5-pyrimidinecarboxylic Acid, Ethyl Ester, Monosodium Salt (6a). A. 2-Butyl-6,6-dimethyl-4-oxo-1,4,5,6-tetrahydropyrimidine-5-carboxylic Acid, Ethyl Ester (15). The title compound was prepared from pentanimidamide hydrochloride (8)[12] and diethyl isopropylidenemalonate (14) in 98% yield by the same procedure as described for *trans*-2-butyl-1,4,5,6-tetrahydro-6-methyl-4-oxo-5-pyrimidinecarboxylic acid, ethyl ester (10a). The product was obtained as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 9.6 (br s, 1 H), 4.2 (m, 2 H), 3.25 (s, 1 H), 2.3 (t, J = 7.7 Hz, 2 H), 1.6 (qn, J = 7.7 Hz, 2 H), 1.38 (m, 2 H), 1.32 (t, J = 7.1 Hz, 3 H), 1.26 (s, 6 H), 0.91 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 168.2, 167.3, 152.3, 61.13, 56.18, 55.95, 34.95, 28.27, 27.8, 25.05, 21.9, 13.85, 13.5 ppm.

B. 6-Butyl-4-chloro-1,2-dihydro-2,2-dimethyl-5-pyrimidinecarboxylic Acid, Ethyl Ester (16). The reaction mixture containing 2-butyl-6,6-dimethyl-4-oxo-1,4,5,6-tetrahydropyrimidine-5-carboxylic acid, ethyl ester (15, 3.0 g, 11.9 mmol), in phosphorus oxychloride (10 mL) was heated at 120 °C for 12 h. The reaction mixture was cooled to room temperature and most of the phosphorus oxychloride was distilled off under vacuum. The brown oily residue was taken up in ethyl acetate and washed with 10% sodium carbonate and brine and dried over magnesium sulfate. The solvent was evaporated and the residue was purified by flash chromatography (ethyl acetate/hexanes (1:2) containing 0.01% triethylamine) to give 6-butyl-4-chloro-1,2-dihydro-2,2-dimethyl-5-pyrimidinecarboxylic acid, ethyl ester (16), as a light yellow oil (1.03 g, 31.8%): ^{1}H NMR ($CDCl_3$) δ 5.85 (br s, 1 H), 4.30 (q, J = 7.6 Hz, 2 H), 2.24 (t, J = 7.6 Hz, 2 H), 1.62 (m, 2 H), 1.55 (s, 6 H), 1.44 (m, 2 H), 1.4 (t, J = 7.0 Hz, 3 H), 0.98 (t, J = 7.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 165.66, 161.95, 109.1, 60.6, 55.1, 35.65, 30.2, 29.2, 22.3, 14.05, 13.7 ppm.

C. 2-Butyl-1-[2′-[(1,1-dimethylethoxy)carbonyl][1,1′-biphenyl]-4-yl]-6-chloro-1,4-dihydro-4,4-dimethyl-5-pyrimidinecarboxylic Acid, Ethyl Ester (17a). To the solution of 6-butyl-4-chloro-1,2-dihydro-2,2-dimethyl-5-pyrimidinecarboxylic acid, ethyl ester (16, 400 mg, 1.47 mmol), in dimethylformamide (5 mL) were added cesium carbonate (1.43 g, 4.41 mmol) and 4′-(bromomethyl)[1,1′-biphenyl]-2-carboxylic acid, 1,1′-dimethylethyl ester (12a, 662 mg, 1.9 mmol) at room temperature under argon. The reaction mixture was stirred for 5 h at room temperature and diluted with ether. The solid was filtered off and the filtrate was washed with water and brine and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified by flash chromatography (20% ethyl acetate in hexanes) to yield 2-butyl-1-[2′-[(1,1-dimethylethoxy)-carbonyl][1,1′-biphenyl]-4-yl]-6-chloro-1,4-dihydro-4,4-dimethyl-5-pyrimidinecarboxylic acid, ethyl ester (17a), as a colorless oil (720 mg, 91.1%): ^{1}H NMR ($CDCl_3$) δ 7.86 (dd, J = 1.2 and 7.7 Hz, 1 H), 7.3–7.6 (m, 7 H), 5.0 (s, 2 H), 4.32 (q, J = 7.0 Hz, 2 H), 2.45 (t, J = 7.0 Hz, 2 H), 2.7 (m, 2 H), 1.35–1.5 (m, 5 H), 1.4 (s, 6 H), 1.32 (s, 9 H), 1.0 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 167.8, 165.9, 152.6, 141.4, 141.2, 136.3, 132.8, 130.6, 130.5, 130.4, 129.6, 129.0, 127.2, 126.3, 112.4, 81.2, 60.8, 55.4, 48.7, 34.0, 30.2, 29.5, 27.5, 22.32, 14.0, 13.8 ppm.

D. 2-Butyl-1-[[2′-carboxy-[1,1′-biphenyl]-4-yl]methyl]-6-chloro-1,4-dihydro-4,4-dimethyl-5-pyrimidinecarboxylic Acid, Ethyl Ester, Monosodium Salt (6a). To a solution of 2-butyl-1-[2′-[(1,1-dimethylethoxy)carbonyl][1,1′-biphenyl]-4-yl]-6-chloro-1,4-dihydro-4,4-dimethyl-5-pyrimidinecarboxylic acid, ethyl ester (17a, 785 mg, 1.46 mmol), in dichloromethane (5 mL) was added trifluoroacetic acid (4 mL) and the reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was coevaporated with toluene. The resulting oil in methanol (2 mL) was converted to its sodium salt by treatment with 1 N sodium hydroxide. Most of methanol was evaporated and the residue was passed through an HP-20 resin eluting with 30% aqueous methanol. Most of the solvent was evaporated and the product was lyophilized to provide 2-butyl-1-[[2′-carboxy[1,1′-biphenyl]-4-yl]methyl]-6-chloro-1,4-dihydro-4,4-dimethyl-5-pyrimidinecarboxylic acid, ethyl ester, monosodium salt (6a), as a colorless solid (510 mg, 69.1%) (shrinks at 190–205 °C): ^{1}H NMR (CD_3OD) δ 7.71 (d, J = 8.2 Hz, 2 H), 7.6 (m, 1 H), 7.4 (m, 5 H), 5.1 (s, 2 H), 4.37 (q, J = 7.0 Hz, 2 H), 2.6 (m, 2 H), 1.75 (m, 2 H), 1.55 (m, 2 H), 1.45 (t, J = 7.0 Hz, 3 H), 1.42 (s, 6 H), 1.08 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (CD_3OD) 178.2, 167.1, 157.1, 142.9, 139.1, 137.2, 130.7, 130.2, 128.9, 128.2, 127.9, 127.6, 114.1, 62.2, 56.5, 34.5, 30.8, 30.3, 23.28, 14.4, 14.1 ppm.

Using the same procedure, 2-butyl-6-chloro-1,4-dihydro-4,4-dimethyl-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-5-pyrimidinecarboxylic acid, ethyl ester (6b), was prepared from 6-butyl-4-chloro-1,2-dihydro-2,2-dimethyl-5-pyrimidinecarboxylic acid, ethyl ester (16), and *N*-(triphenylmethyl)-5-[2-[4′-(bromomethyl)[1,1′-biphenyl]-yl]]tetrazole (12b).

Pharmacological Studies. A. Studies in Vitro. Compounds were tested in a radioligand binding assay using rat adrenal cortical membranes which were prepared by methods described by Chiu et al.[8] Binding experiments were performed with [^{125}I]Sar^1,Ile^8-angiotensin II as the radioligand. In some cases, 0.01% BSA was used rather than the standard 0.22% to

attenuate drug binding to BSA.[18] The IC_{50} values were determined for the AT_1 receptor population using iterative curve fitting of binding data to a two-site model. Inhibition constants (K_i values) were calculated from the Cheng and Prusoff equation.[19] Compounds were also tested for functional antagonism of angiotensin II induced contraction of isolated rabbit aorta as described elsewhere.[9]

B. Studies in Vivo. For determination of antihypertensive activity, male spontaneously hypertensive rats (SHR) were prepared surgically according to the method of Weeks and Jones.[20] The rats were housed and allowed to recover for 2 weeks on regular food and water. Five days prior to testing, animals were placed on a low sodium chloride diet. Three consecutive days prior to testing, the rats were dosed with furosemide (2.5 mg/kg). The test compounds were administered orally as a suspension in agar, and blood pressure was recorded using the method described by Laffin et al.[21] For determination of AII antagonistic activity in vivo, three doses of the test compound were given intravenously to normotensive male rats followed 2 min later by AII challenge (100 ng/kg iv). The dose required to inhibit the AII pressor response by 50% (ED_{50}) was calculated by simplex curve fit of log of dose versus maximum percent inhibition.

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