Natick, MA), 10 μM (vs [³H]ADTN); cis-(Z)-flupenthixol (a gift of Dr. John Hyttel of Lundbeck Labs., Copenhagen, Denmark), 300 nM (vs [³H]SCH-23390), and (+)-butaclamol (from RBI, Natick, MA), 1 μM (vs [³H]spiperone) for the agonist, $D_1$, and $D_2$ assays, respectively. Half-maximal inhibitory concentrations (IC50 ± SEM) of each test agent were determined by using nonlinear least squares[23-25] analysis and converted to $K_i$ according to Cheng and Prusoff.[26] All results were repeated at least twice, and the repeated values are means.

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# Long-Acting Dihydropyridine Calcium Antagonists. 5. Synthesis and Structure–Activity Relationships for a Series of 2-[[(N-Substituted-heterocyclyl)ethoxy]methyl]-1,4-dihydropyridine Calcium Antagonists

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The synthesis of a series of 1,4-dihydropyridines which have N-linked heterocycles at the terminus of an ethoxymethyl chain at the 2-position is described. The calcium antagonist activity on rat aorta of this class of DHPs is compared with their negative inotropic activity as determined by using a Langendorff-perfused guinea pig heart model. The compounds examined show a wide range of selectivity for vascular over cardiac tissue, with those analogues which possess an amide group at the terminus of the 2-substituent proving the most selective. From the in vitro data obtained for a series of 1,2,3-triazoles, it is possible to conclude that the SARs for binding to the calcium channels in vascular and cardiac tissue are different. One of the compounds, 2-amino-1-[2-[[4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-4(3H)-imidazolone (20b, UK-55,444), was identified as a potent ($IC_{50}$ = 8 × 10⁻⁹ M) calcium antagonist which is 40-fold selective for vascular over cardiac tissue and which has a significantly longer duration of action (>3 h) than nifedipine in the anesthetized dog on intravenous administration.

We have recently reported[1] the synthesis and structure–activity relationships (SARs) of a series of novel 1,4-dihydropyridine (DHP) calcium antagonists which contain a basic side chain on the 2-position of the DHP ring. The aim of this program was to modify the physicochemical properties of the DHP 2-substituents in order to improve bioavailability and duration of action over existing agents. From this work we identified amlodipine (1a), which fulfilled our objectives, and this compound is
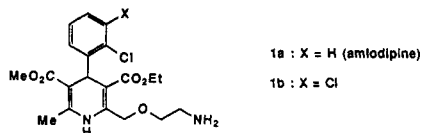
currently in late-stage clinical development for the treatment of angina[2,3] and hypertension.[4,5] We subsequently reported that the presence of a basic center on the substituent on the 2-position of the DHP ring was not an absolute requirement for either calcium-antagonist activity or selectivity for vascular tissue over the heart. For example, DHPs of general structure I in which the alkoxyalkyl group in the 2-position is substituted at its terminus
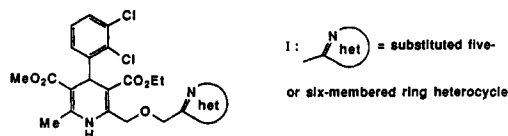
by heterocycles are also potent, selective calcium antagonists.[6,7] Morever, in the previous paper in this series[8] we demonstrated that the primary amino group in 1a could be replaced by polar functionality such as ureas and glycinamides. From this work we identified UK-51,656 (2) as having equivalent in vitro activity to nifedipine but with markedly longer duration of action in anesthetized dogs (of the order of 5 h). In order to extend the SARs in this

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2

20b
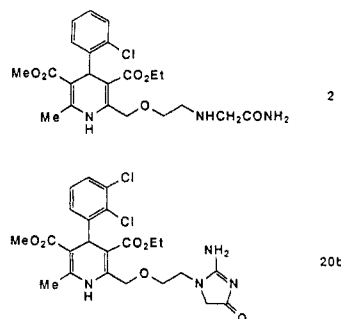
area we have now prepared a series of DHPs (II) which

II : H , Cl

N het = substituted

five-membered ring heterocycle
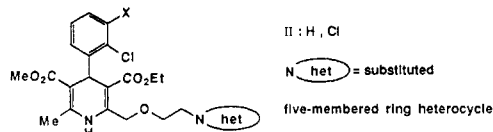
have a heterocyclic substituent linked through a ring nitrogen atom to an ethoxymethyl chain in the 2-position of the DHP ring. In addition it was hoped that, by evaluating a range of substituted and unsubstituted heterocyclic substituents in II, we may shed further light on the structural features affecting the tissue selectivity of DHPs.
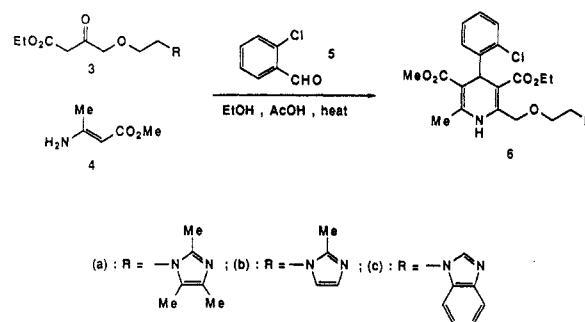
## Chemistry

Compounds 6 were prepared by the route shown in Scheme I. 4-Alkoxy-β-keto esters 3 were obtained by reacting the enolate of ethyl 4-chloroacetoacetate with an appropriately substituted sodium ethoxide.[9] Hantzsch condensation of 3 with methyl 3-aminocrotonate (4) and 2-chlorobenzaldehyde (5) then afforded 6.
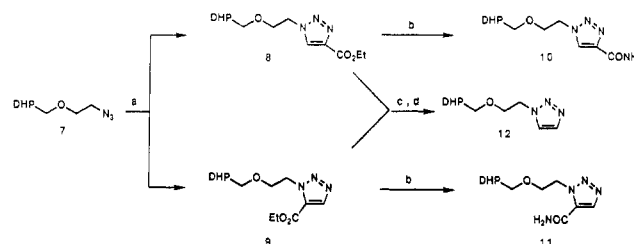
The synthesis of 1,2,3-triazoles 8–12 is summarized in Scheme II. Thus, 1,3-dipolar cycloaddition of azides 7[1] with ethyl propynoate afforded mixtures of the two possible regioisomers, 8 and 9 (similar formation of regioisomeric mixtures of products from the reaction of alkyl azides with methyl propynoate has been reported[10]). It did not prove possible to assign the structures of the esters 8 and 9 from an inspection of their ^{1}H NMR spectra. However, the regiochemistry of the adducts 8a and 9a was readily elucidated from NOE experiments. A significant NOE enhancement is seen between the 5-proton on the 1,2,3-triazole ring and the N-1 proton on the DHP ring in the ^{1}H NMR spectrum of 8a while no such effect is seen in the ^{1}H NMR spectrum of 9a. It follows therefore that the ethoxycarbonyl group in 8a must be on the 4-position of the 1,2,3-triazole ring while 9a is the 5-(ethoxycarbonyl) analogue. Stirring 8 and 9 with concentrated aqueous ammonia gave the corresponding amides 10 and 11, while saponification of mixtures of 8 and 9 followed by decarboxylation in refluxing N,N-dimethylaniline afforded 12.

Imidazolidine analogues 16, 17, 20, 24a, 25a, 27a, and 30a were obtained as shown in Scheme III. Reaction of N-substituted glycine esters 13[8] with potassium cyanate and methyl isocyanate gave 14 and 15, which on base-catalyzed cyclization afforded 16 and 17, respectively (route A). In similar fashion, treatment of glycine esters 18 with cyanogen bromide followed by cyclization of 19 with concentrated aqueous ammonia yielded 20 (route B). Reaction of 1a with chloroacetonitrile gave a 45% yield of 21a (a second product, which was detected by TLC but which was

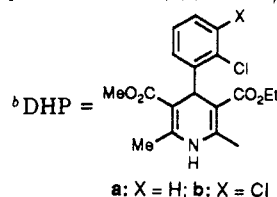(9) Troostwijk, C. B.; Kellogg, R. M. *J. Chem. Soc., Chem. Commun.* 1977, 932.

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## Scheme I

3

5

4

EtOH , AcOH , heat

6

(a) : R = ; (b) : R = ; (c) : R =

## Scheme II[a,b]

7

8

9

10

11

12

[a] Reagents: (a) ethyl propynoate/toluene/heat; (b) concentrated aqueous ammonia; (c) NaOH/H₂O/dioxane; (d) PhNMe₂/heat.

[b] DHP =

a: X = H; b: X = Cl

not isolated, is presumed to be bis-alkylated material). Treatment of 21a with potassium cyanate and methyl isocyanate followed by base-catalyzed cyclization afforded 24a and 25a, respectively (route C). Stirring urea 26a[8] with concentrated aqueous ammonia furnished imidazolidine-2,5-dione 27a (route D) while 30a was prepared by stirring 28a (obtained by reacting 1a with CDI[8]) with aminoacetonitrile hydrochloride and cyclizing the resulting urea 29a in the presence of base (route E).

## Results and Discussion

In vitro calcium antagonist activity (expressed as an IC₅₀) was assessed as the concentration of the compound required to inhibit the calcium-induced contraction of potassium-depolarized rat aorta by 50%. Negative inotropy (expressed as an IC₂₅) was determined in vitro by using a Langendorff-perfused guinea pig heart preparation. In agreement with our previous results, examination of the data in Table I suggests that the DHP receptor can accommodate DHPs bearing a range of heterocyclic substituents at the terminus of an ethoxymethyl chain on the 2-position of the DHP ring. Thus, the activity seen for compounds 8a–30a, which have a 4-(2-chlorophenyl) group on the DHP ring, is approximately 5-fold less than that observed for nifedipine and is generally insensitive to the nature of both the heterocycle and the substituents attached to it. For example, parent 1,2,3-triazole 12a has equivalent calcium antagonist activity to its 4-carbethoxy (8a) and 4-carboxamido (10a) analogues. Similarly 12a is also essentially equiactive with the range of imidazolidine derivatives 16a, 17a, 20a, 24a, 25a, and 27a. Certain SAR trends are, however, apparent from the data in Table I. Thus, the 1,2,3-triazole derivatives with a 5-carbethoxy (9a) and 5-carboxamido (11a) substituent are some 5-fold less active as calcium antagonists than their corresponding

**Scheme III**[a,b]

Route A

Route B

Route C

Route D

Route E
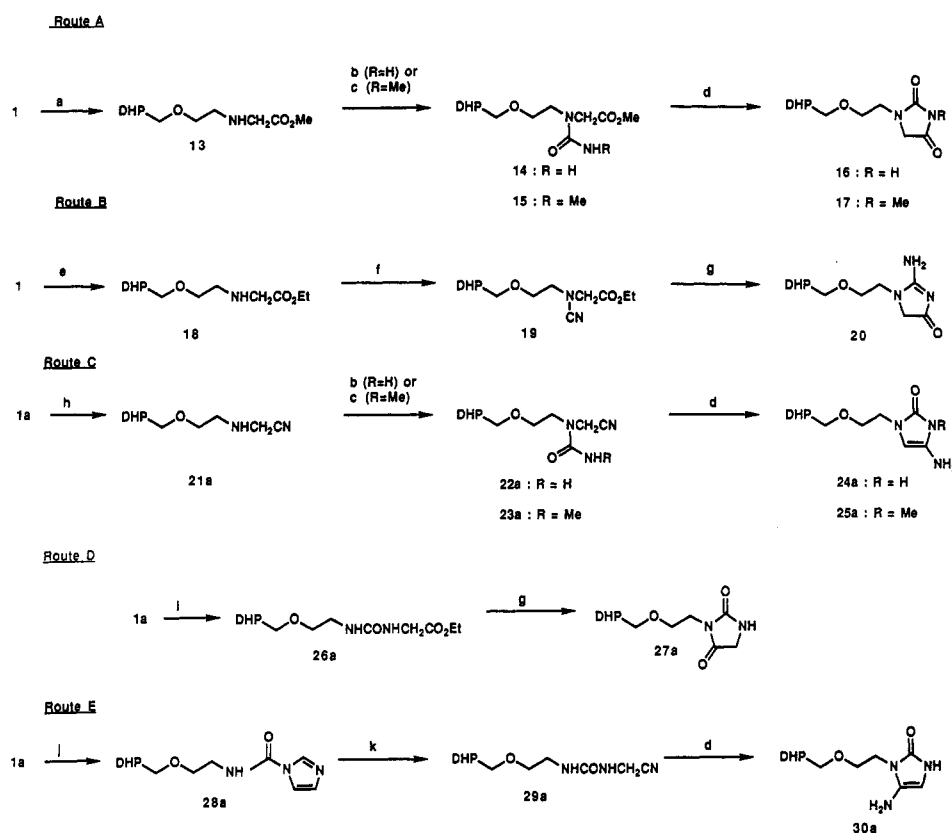
[a] Reagents: (a) $BrCH_2CO_2Me/K_2CO_3/MeCN$; (b) $KCNO/AcOH/H_2O$/dioxane; (c) $MeNCO/CH_2Cl_2$; (d) $NaH/MeOH$; (e) $BrCH_2CO_2Et/K_2CO_3/MeCN$; (f) $BrCN/NaHCO_3/CHCl_3$; (g) concentrated aqueous ammonia; (h) $ClCH_2CN/K_2CO_3/MeCN$; (i) $EtO_2CCH_2NCO/MeCN$; (j) CDI/THF; (k) $NH_2CH_2CN\cdot HCl/N$-methylmorpholine/MeCN.
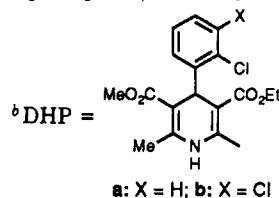
[b] DHP =

a: X = H; b: X = Cl

**Table I.** Data for Compounds Used in the Study

| no. | route | mp, °C | recrystn solvent | formula | % yield | Ca pIC$_{50}$[b] | neg inotropy pIC$_{25}$[c] | selectivity index[d] |
|---|---|---|---|---|---|---|---|---|
| 6a | 1 | 167–168[a] | EtOAc | $C_{26}H_{32}ClN_3O_5$ | 10 | 8.3 | 7.5 | 6 |
| 6b | 1 | 124 | EtOAc/Et$_2$O | $C_{24}H_{28}ClN_3O_5$ | 6 | 8.6 | 7.8 | 6 |
| 6c | 1 | 162 | EtOAc/Et$_2$O | $C_{27}H_{28}ClN_3O_5$ | 1.5 | 7.7 | 7.2 | 3 |
| 8a | 2 | 116–118 | Et$_2$O | $C_{25}H_{29}ClN_4O_7$ | 46 | 7.3 | 7.0 | 2 |
| 9a | 2 | 146–147 | Et$_2$O | $C_{25}H_{29}ClN_4O_7$ | 27 | 7.0 | 6.9 | 1.3 |
| 10a | 2 | 215–217 | Et$_2$O | $C_{23}H_{26}ClN_5O_6$ | 92 | 7.7 | <6.0 | >50 |
| 10b | 2 | 148–151 | Et$_2$O | $C_{23}H_{25}Cl_2N_5O_6$ | 68 | 8.5 | 6.6 | 80 |
| 11a | 2 | 125–128 | Et$_2$O | $C_{23}H_{26}ClN_5O_6$ | 40 | 7.0 | 6.3 | 5 |
| 11b | 2 | 163–166 | Et$_2$O | $C_{23}H_{25}Cl_2N_5O_6$ | 60 | 7.8 | 6.5 | 20 |
| 12a | 2 | 134–140 | Et$_2$O | $C_{22}H_{25}ClN_4O_5$ | 57 | 7.8 | 7.3 | 3 |
| 12b | 2 | 155–156 | Et$_2$O | $C_{22}H_{24}Cl_2N_4O_5$ | 64 | 8.3 | 7.3 | 10 |
| 16a | 3A | 105–107 | Et$_2$O | $C_{23}H_{26}ClN_3O_7$ | 80 | 7.7 | 6.3 | 25 |
| 16b | 3A | 116–118 | MeOH | $C_{23}H_{25}Cl_2N_3O_7$ | 31 | 8.5 | 7.1 | 25 |
| 17a | 3A | 166–167 | MeOH | $C_{24}H_{28}ClN_3O_7$ | 84 | 7.6 | 6.4 | 16 |
| 17b | 3A | 115–116 | Et$_2$O | $C_{24}H_{27}Cl_2N_3O_7$ | 34 | 8.3 | 7.2 | 13 |
| 20a | 3B | 110–113 | EtOH | $C_{23}H_{27}ClN_4O_6$ | 65 | 7.7 | 6.1 | 40 |
| 24a | 3C | 132–134 | – | $C_{23}H_{27}ClN_4O_6$ | 53 | 7.5 | <6.0 | >32 |
| 25a | 3C | 135–137[a] | EtOH | $C_{24}H_{29}ClN_4O_6$ | 25 | 7.6 | 6.2 | 25 |
| 27a | 3D | 140 | Me$_2$CO/EtOAc | $C_{23}H_{26}ClN_3O_7$ | 21 | 7.5 | 6.8 | 5 |
| 30a | 3E | 138–139[a] | EtOAc/hexane | $C_{23}H_{27}ClN_4O_6$ | 29 | 6.8 | 6.0 | 6 |
| nifedipine | | | | | | 8.4 | 7.5 | 8 |
| amlodipine | | | | | | 8.1 | 7.2 | 8 |

[a] Hydrochloride salts. [b] Negative logarithm of the molar concentration required to block $Ca^{2+}$-induced contraction of K$^+$ depolarized rat aorta by 50%; $n = 2$ ($\pm$0.3). Nifedipine was used as the standard compound. [c] Negative logarithm of the molar concentration required to depress contraction in the Langendorff-perfused guinea pig heart by 25%; $n = 2$ ($\pm$0.3). Nifedipine was used as the standard compound. [d] Selectivity index = Ca pIC$_{50}$/neg inotropy pIC$_{25}$.

4-isomers (**8a** and **10a**, respectively). 5-Amino analogue **30a** is likewise approximately 5-fold less active than its 4-isomer **24a**. In contrast, imidazole **6a** is more potent than **8a–30a** and has similar calcium antagonist activity to that of both nifedipine and amlodipine. This result demonstrates that replacement of the amino group in amlodipine with a basic heterocycle (the p$K_a$ of **6a** has been determined to be 7.7 by potentiometric titration in 40% aqueous methanol) is not detrimental to activity. 2-Methyl analogue **6b** has similar activity on the vasculature as **6a** while benzimidazole analogue **6c** is 4–8 times weaker than **6a** and **6b**.

As suggested by our previous SAR,[6] replacement of the 4-(2-chlorophenyl) group on the DHP ring by 4-(2,3-dichlorophenyl) caused a consistent 3–6-fold increase in potency. This change resulted in compounds such as **10b**, **12b**, **16b**, **17b**, and **20b**, which all have essentially equivalent calcium antagonist activity on the vasculature to nifedipine.

DHPs are proposed[11,12] to bind preferentially to the inactivated state of the voltage-dependent calcium channel. They would thus be expected to be intrinsically more effective in smooth muscle tissue than in cardiac tissue,[13] since the latter normally exhibits a more negative resting potential and undergoes only brief periods of depolarization during the cardiac cycle. The view that tissue selectivity is, to some extent, an inherent feature of DHP calcium antagonist activity is supported by the observation that nifedipine, amlodipine, and **6a** exhibit similar selectivity for vascular over cardiac tissue. However, an examination of the data in Table I reveals that structural features can significantly affect tissue selectivity. Thus, while 4-carbamoyl-1,2,3-triazole **10a** has 50-fold selectivity for vascular over cardiac tissue, the selectivity indices of the corresponding 4-ester **8a** and parent 1,2,3-triazole **12a** are only 2-fold and 3-fold, respectively. In general, compounds which contain amide groups at the terminus of the 2-substituent such as **10a**, **16a**, **20a**, **24a**, and **25a** tend to exhibit high tissue selectivity. Literature evidence is also available which demonstrates that DHPs can exhibit markedly different tissue selectivities. Thus, it has been reported[14] that nisoldipine exhibits vascular selectivity 100 times that seen for nifedipine while it has recently been claimed[15] that certain halogenated derivatives of nitrendipine are 10-fold more vascular selective than nitrendipine itself.

The mechanism by which certain structural features in DHPs affect tissue selectivity is not fully understood. It has been suggested[14,16] that increased potency per se leads to more pronounced selectivity. While that may be true in certain series, the data in Table I suggest that additional factors are also important. Thus, **8a** and **10a** are equipotent on the vasculature but exhibit markedly differing tissue selectivities. Likewise, compound **10a** has a selectivity index in excess of 50 and yet it is 5-fold less potent than nifedipine. It has also been suggested[15] that the improved vascular selectivity of two haloethyl ester analogues of nitrendipine may in part be due to their increased lipophilicity. Although lipophilicity may affect tissue se-

**Table II.** Coronary Vasodilator Activity in Anesthetized Dogs following a 150 μg/kg Intravenous Dose[a]

| compound | % decrease in CVR | duration of action:[b] half-life, min |
|---|---|---|
| **10b** | 54 | 20 |
| **12b** | 79 | 30 |
| **16b** | 65 | 30 |
| **17b** | 50 | 10 |
| **20b** | 60 | >180 |
| nifedipine | 77 | 36 |

[a] $n$ = 2. [b] Time taken for 50% recovery of CVR.

lectivity for certain DHPs, we see no evidence for a similar trend from the data in Table I. On the contrary, those compounds in Table I with the highest selectivity indices are the ones which have relatively polar amide groups at the terminus of the 2-substituent on the DHP ring.

We believe that the data in Table I for 1,2,3-triazoles **8–12** support the hypothesis that the environments of the calcium channels in vascular and cardiac tissue are in some way different and that this leads to a difference in the relative activities of DHP analogues on each of these tissues. Thus, the selectivity indices for **12a** and **10a** are 3 and greater than 50, respectively, although they are equipotent on the vasculature. Their differing tissue selectivities are a consequence of the much lower activity of **10a** on cardiac tissue, suggesting that the cardiac DHP receptor cannot easily accommodate polar functionality at the terminus of the 2-substituent on the DHP ring. The poor activity of **10a** on cardiac tissue is not a consequence of steric factors since **8a** and **10a** have essentially equivalent vascular activity, but **10a** has at least 10-fold lower calcium antagonist activity on cardiac tissue. In contrast, the poor tissue selectivity seen for **11a** in comparison with that of **10a** arises from its lower relative activity on vascular tissue since **10a** and **11a** have very similar activity on cardiac tissue. These results indicate that the presence of polar functionality at the terminus of the 2-substituent on the DHP ring generally leads to lower activity at the cardiac DHP receptor and therefore greater tissue selectivity. Evidence in support of a difference between the environments of the verapamil-type receptors in cardiac and vascular tissue has recently been provided.[17] However, it must be noted that, since DHP binding to the inactivated state of the channel[11,12] is not exclusive, the presence of certain structural features in DHPs may alter their relative binding to the open and inactivated states of the DHP channel, thereby causing the differences in tissue selectivity observed.

On the basis of their in vitro profiles, compounds **10b**, **12b**, **16b**, **17b**, and **20b** were selected for in vivo evaluation in instrumented, anesthetized dogs. These compounds were administered intravenously at a dose of 150 μg/kg and calcium antagonist potency and duration of action were determined from their effects on coronary vascular resistance (CVR). All compounds showed substantial (50% or greater) falls in CVR which were essentially equivalent to that seen for nifedipine (see Table II). However, of the compounds evaluated, only **20b** had a markedly longer duration of action than nifedipine. Compound **20b** still exhibited a substantial reduction (approximately 50%) in CVR 3 h after dosing, indicating that the half-life for its duration of action may be well in excess of 3 h. The reason for the improved duration of action of **20b** over the structurally related compounds **16b** and **17b** is not apparent.

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(17) Osterrieder, W.; Holck, M. *J. Cardiovasc. Pharmacol.* **1989**, *13*, 754.

In conclusion, we have again established that the incorporation of a heterocyclic ring at the terminus of the 2-substituent of the DHP ring affords compounds with good calcium antagonist activity and superior vascular tissue selectivity to that of nifedipine. One of the compounds, **20b** (UK-55,444), had a duration of action in excess of 3 h on intravenous administration to an anesthetized dog. In addition, we have provided evidence that the environments of the vascular and cardiac DHP receptors are different.

## Experimental Section

**Pharmacology.** In vitro calcium antagonism $IC_{50}$ and negative inotropy $IC_{25}$ were measured as previously described.[1] In vivo hemodynamic measurements were made in anesthetized beagle dogs as described previously.[8]

**Chemistry.** All melting points are uncorrected. The structures of all the compounds were determined by $^1H$ NMR spectroscopy and microanalysis. $^1H$ NMR spectra were obtained with a Varian XL-100-5 spectrometer using $CDCl_3$ as a solvent. The preparation of amines **1** and azides **7** has been described in a previous publication.[1] The preparations of glycine methyl ester **13a**, urea **26a**, and imidazolide **28a** have all been previously reported.[8] 4-Alkoxy-β-keto esters **3** were prepared by the method of Troostwijk and Kellogg[9] as described previously.[1] The structure and purity of products **3** were confirmed by $^1H$ NMR and they were used directly in the preparation of **6**.

**1-[2-[[4-(2-Chlorophenyl)-3(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-2,4,5-trimethylimidazole Hydrochloride (6a).** A mixture of **3a** (6.41 g, 23 mol; prepared by the general procedure previously described[1]), **4** (2.61 g, 23 mmol), **5** (3.18 g, 23 mmol), and AcOH (1 mL) in EtOH (15 mL) was heated under reflux for 4.5 h and evaporated. The residue was partitioned between 10% aqueous $Na_2CO_3$ solution and $CH_2Cl_2$ and the organic layer was washed with water, dried over $Na_2SO_4$, and evaporated. The residue was purified by chromatography on $SiO_2$ using $CH_2Cl_2$ as eluant. Appropriate fractions were combined and evaporated and the residue was taken up in EtOAc and treated with saturated ethereal HCl. The resulting solid was collected and recrystallized from EtOAc to give title compound **6a**: yield 1.18 g (10%); mp 167–168 °C. Anal. $(C_{26}H_{32}ClN_3O_5 \cdot HCl)$ H, N; C: calcd, 57.99; found 57.30.

**1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-2-methylimidazole Hemihydrate (6b).** A mixture of **3b** (9.0 g, 35 mmol; prepared by the general procedure described previously[1]), **4** (4.0 g, 35 mmol), **5** (4.6 g, 33 mmol), and AcOH (2 mL) in EtOH (20 mL) was heated under reflux for 4.5 h and then was worked up and chromatographed as described for **6a**. Appropriate fractions were combined and evaporated, and the residue was recrystallized from $Et_2O$/EtOAc to give title compound **6b**: yield 0.90 g (6%); mp 124 °C. Anal. $(C_{24}H_{28}ClN_3O_5 \cdot 0.5H_2O)$ C, H, N.

**1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-2-methylbenzimidazole (6c).** A mixture of **3c** (12.5 g, 43 mmol; prepared by the general procedure described previously[1]), **4** (5.0 g, 43 mmol), **5** (6.0 g, 43 mmol), and AcOH (4 mL) in EtOH (40 mL) was heated under reflux for 3.5 h and was then worked up and chromatographed as described for **6a**. Appropriate fractions were combined and evaporated, and the residue was recrystallized from $Et_2O$/EtOAc to give title compound **6c**: yield 0.30 g (1.5%); mp 162 °C. Anal. $(C_{27}H_{28}ClN_3O_5)$ C, H, N.

**1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-4-(ethoxycarbonyl)-1,2,3-triazole (8a) and 1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-5-(ethoxycarbonyl)-1,2,3-triazole (9a).** A mixture of **7a** (2.17 g, 5.0 mmol) and ethyl propynoate (1.1 g, 11 mmol) in toluene (80 mL) was heated under reflux for 8 h and evaporated. The residue was chromatographed on $SiO_2$ using $CH_2Cl_2$ plus 0–2.5% MeOH as eluant. In each case, appropriate fractions were combined and evaporated, and the residue was crystallized from $Et_2O$ to give title compounds **8a** and **9a**. **8a**: yield 1.71 g (46%); mp

116–118 °C. Anal. $(C_{25}H_{29}ClN_4O_7)$ C, H, N (more polar isomer). **9a**: yield 0.99 g (27%); mp 146–147 °C. Anal. $(C_{25}H_{29}ClN_4O_7)$ C, H, N (less polar isomer).

Fractions from the chromatography containing both **8a** and **9a** were combined and evaporated and the residue was used in the preparation of **12a**.

**1-[2-[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-4-(ethoxycarbonyl)-1,2,3-triazole (8b) and 1-[2-[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-5-(ethoxycarbonyl)-1,2,3-triazole (9b).** A mixture of **7b** (2.40 g, 5.0 mmol) and ethyl propynoate (0.74 g, 7.5 mmol) in toluene (80 mL) was heated under reflux for 6 h and evaporated. The residue was chromatographed on $SiO_2$ using $CH_2Cl_2$ plus 0–2% MeOH as eluant. In each case, appropriate fractions were combined and evaporated, and the residue was crystallized from $Et_2O$ to give title compounds **8b** and **9b**. **8b**: yield 0.82 g (29%); mp 134–136 °C. Anal. $(C_{25}H_{28}Cl_2N_4O_7)$ C, H, N (more polar isomer). **9b**: yield 0.41 g (14%); mp 147–148 °C. Anal. $(C_{25}H_{28}Cl_2N_4O_7)$ C, H, N (less polar isomer).

Fractions from the chromatography containing both **8b** and **9b** were combined and evaporated, the residue was used in the preparation of **12b**.

**General Route to Amides 10 and 11.** A mixture of the appropriate ester and concentrated aqueous ammonia (20 mL) in dioxane (10 mL) was stirred at room temperature for 24 h and evaporated. The residue was partitioned between EtOAc and water and the layers were separated. The organic layer was washed with water, dried over $Na_2SO_4$, and evaporated, and the residue was crystallized from $Et_2O$.

**4-Carbamoyl-1-[2-[[4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-1,2,3-triazole (10a).** Reacting **8a** (0.53 g, 1.0 mmol) with concentrated aqueous ammonia and workup as described above gave title compound **10a**: yield 0.46 g (92%); mp 215–217 °C. Anal. $(C_{23}H_{26}ClN_5O_6)$ C, H, N.

**4-Carbamoyl-1-[2-[[4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-1,2,3-triazole (10b).** Reacting **8b** (0.57 g, 1.0 mmol) with concentrated aqueous ammonia and workup as described above gave title compound **10b**: yield 0.37 g (68%); mp 148–151 °C. Anal. $(C_{23}H_{25}Cl_2N_5O_6)$ C, H, N.

**5-Carbamoyl-1-[2-[[4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-1,2,3-triazole (11a).** Reacting **9a** (0.21 g, 0.4 mmol) with concentrated aqueous ammonia and workup as described above gave title compound **11a**: yield 80 mg (40%); mp 125–128 °C. Anal. $(C_{23}H_{26}ClN_5O_6)$ C, H; N: calcd, 13.90; found, 13.33.

**5-Carbamoyl-1-[2-[[4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-1,2,3-triazole (11b).** Reacting **9b** (0.35 g, 0.6 mmol) with concentrated aqueous ammonia and workup as described above gave title compound **11b**: yield 0.20 g (60%); mp 163–166 °C. Anal. $(C_{23}H_{25}Cl_2N_5O_6)$ C, H, N.

**1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-1,2,3-triazole (12a).** A solution of a mixture of esters **8a** and **9a** (0.68 g, 1.25 mmol) and a 1 M aqueous NaOH solution (5 mL) in dioxane (25 mL) was stirred at room temperature for 15 h and evaporated. The residue was taken up in water, treated with AcOH (2 mL), and extracted into EtOAc. The EtOAc extract was dried over $Na_2SO_4$ and evaporated. The residual oil was taken up in *N,N*-dimethylaniline (5 mL), and the solution was heated under reflux for 15 min, allowed to cool to room temperature, and purified by chromatography on $SiO_2$ using $CH_2Cl_2$ plus 0–4% MeOH as eluant. Appropriate fractions were combined and evaporated. The residue crystallized from $Et_2O$ to give title compound **12a**: yield 0.25 g (57%); mp 134–140 °C. Anal. $(C_{22}H_{25}ClN_4O_5)$ C, H, N.

**1-[2-[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-1,2,3-triazole (12b).** A solution of a mixture of esters **8b** and **9b** (0.96 g, 1.7 mmol) and a 1 M aqueous NaOH solution (10 mL) in dioxane (25 mL) was stirred at room temperature for

2 h and evaporated. The residue was dissolved in water, treated with AcOH (2 mL), and extracted into EtOAc. The EtOAc extract was washed with water, dried over $Na_2SO_4$, and evaporated. The residue was taken up in *N,N*-dimethylaniline (5 mL) and the solution was heated under reflux for 15 min, allowed to cool to room temperature, and purified by chromatography on $SiO_2$ using $CH_2Cl_2$ plus 0–2% MeOH as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from $Et_2O$ to give the title compound **12b**: yield 0.54 g (64%); mp 155–156 °C. Anal. ($C_{22}H_{24}Cl_2N_4O_5$) C, H, N.

**Methyl 2-[[2-[[4-(2,3-Dichlorophenyl)-3-(ethoxy-carbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]amino]acetate (13b).** A mixture of amine **1b** (4.42 g, 10 mmol), $BrCH_2CO_2Me$ (1.53 g, 10 mmol), and $K_2CO_3$ (2.76 g, 20 mmol) in $CH_3CN$ (80 mL) was heated under reflux for 3 h, filtered, and evaporated. The residue was partitioned between EtOAc and water and the organic layer was washed with water, dried over $Na_2SO_4$, and evaporated. The residue was purified by chromatography on $SiO_2$ using $CH_2Cl_2$ plus 0–3% MeOH as eluant. Appropriate fractions were combined and evaporated to give title compound **13b**: yield 2.10 g (41%); mp 96–98 °C. Anal. ($C_{23}H_{28}Cl_2N_2O_7$) C, H, N.

**1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-1-[(methoxycarbonyl)methyl]urea (14a).** AcOH (0.37 g, 6.0 mmol) was added to a solution of KCNO (0.24 g, 3.0 mmol) and **13a**[8] (0.96 g, 2.0 mmol) in a mixture of dioxane (10 mL) and water (10 mL) and the mixture was stirred at room temperature for 70 min and evaporated. The residue was partitioned between EtOAc and water and the organic layer was washed with water, dried over $Na_2SO_4$, and evaporated. The residue was crystallized from EtOAc to give title compound **14a**: yield 0.77 g (74%); mp 166–169 °C. Anal. ($C_{24}H_{30}ClN_3O_8$) C, H, N.

**1-[2-[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-1-[(methoxycarbonyl)methyl]urea (14b).** AcOH (0.54 g, 9 mmol) was added to a solution of KCNO (0.36 g, 4.5 mmol) and **13b** (1.40 g, 2.8 mmol) in a mixture of dioxane (15 mL) and water (15 mL) and the mixture was stirred at room temperature for 16 h and evaporated. The residue was worked up as described above for **14a** to give, after crystallization from $Et_2O$, title compound **14b**: yield 0.90 g (58%); mp 176–178 °C. Anal. ($C_{24}H_{29}Cl_2N_3O_8$) C, H, N.

**[1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-1-[(methoxycarbonyl)methyl]-3-methylurea (15a).** MeNCO (1.0 mL) was added to a solution of **13a**[8] (2.40 g, 5.0 mmol) in $CH_2Cl_2$ (80 mL) and the mixture was stirred at room temperature for 2 h and evaporated. The residue was crystallized from $Et_2O$ to give title compound **15a**: yield 2.62 g (97%); mp 174–176 °C. Anal. ($C_{25}H_{32}ClN_3O_8$) C, H, N.

**1-[2-[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-1-[(methoxycarbonyl)methyl]-3-methylurea (15b).** MeNCO (0.5 mL) was added to a stirred solution of **13b** (0.50 g, 0.97 mmol) in $CH_2Cl_2$ (50 mL) and the mixture was stirred at room temperature for 3 h and evaporated. The residue was crystallized from $Et_2O$ to give title compound **15b**: yield 0.40 g (75%); mp 118–120 °C. Anal. ($C_{25}H_{31}Cl_2N_3O_8$) C, H, N.

**General Route to 16 and 17.** A solution of the appropriate urea in MeOH was treated with NaH (80% dispersion in oil) and the mixture was stirred at room temperature and then evaporated. The residue was partitioned between EtOAc and water and the organic layer was washed with water, dried over $Na_2SO_4$, and evaporated.

**1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]imidazolidine-2,4-dione (16a).** Stirring a mixture of **14a** (0.52 g, 1.0 mmol) and NaH (60 mg, 2 mmol) in MeOH (40 mL) at room temperature for 1 h and workup as described above gave, after crystallization of the residue from $Et_2O$, title compound **16a**: yield 0.41 g (80%); mp 105–107 °C dec. Anal. ($C_{23}H_{26}ClN_3O_7$) C, H, N.

**1-[2-[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]imidazolidine-2,4-dione Hemihydrate (16b).**

Stirring a mixture of **14b** (1.12 g, 2.0 mmol) and NaH (0.36 g, 12 mmol) in MeOH (20 mL) at room temperature for 2 h and workup as described above gave, after crystallization from MeOH, title compound **16b**: yield 325 mg (31%); mp 116–118 °C. Anal. ($C_{23}H_{25}Cl_2N_3O_7$·0.5 $H_2O$), C, H, N.

**1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-3-methylimidazolidine-2,4-dione (17a).** Stirring a mixture of **15a** (0.54 g, 1.0 mmol) and NaH (60 mg, 2 mmol) in MeOH (40 mL) at room temperature for 1 h and workup as described above gave, after crystallization from MeOH, title compound **17a**: yield 0.42 g (84%); mp 166–167 °C. Anal. ($C_{24}H_{28}ClN_3O_7$) C, H, N.

**1-[2-[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-3-methylimidazolidine-2,4-dione Hemihydrate (17b).** Stirring a mixture of **15b** (0.40 g, 0.74 mmol) and NaH (60 mg, 2 mmol) in MeOH (15 mL) at room temperature for 4 h and workup as described above gave, after crystallization from $Et_2O$, title compound **17b**: yield 129 mg (34%); mp 115–116 °C. Anal. ($C_{24}H_{27}Cl_2N_3O_7$·0.5 $H_2O$), C, H, N.

**Ethyl 2-[[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]amino]acetate (18a).** A mixture of amine **1a** (4.08 g, 10 mmol), $BrCH_2CO_2Et$ (1.67 g, 10 mmol), and $K_2CO_3$ (4.2 g, 30 mmol) in $CH_3CN$ (160 mL) was heated under reflux for 2.5 h, filtered, and evaporated. The residue was partitioned between EtOAc and water and the organic layer was washed with water, dried over $Na_2SO_4$, and evaporated. The residue was purified by chromatography on $SiO_2$ using $CH_2Cl_2$ plus 0–3% MeOH as eluant. Appropriate fractions were combined and evaporated to give title compound **18a**: yield 3.35 g (68%); mp 78–80 °C. Anal. ($C_{24}H_{31}ClN_2O_7$) C, H, N.

**Ethyl 2-[[2-[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]amino]acetate (18b).** A mixture of amine **1b** (4.42 g, 10 mmol), $BrCH_2CO_2Et$ (1.67 g, 10 mmol), and $K_2CO_3$ (4.49 g, 30 mmol) in $CH_3CN$ (100 mL) was heated under reflux for 3.5 h and worked up as described above to give title compound **18b**: yield 3.00 g (57%); oil. Anal. ($C_{24}H_{30}Cl_2N_2O_7$) C, H, N.

**Ethyl 2-[*N*-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-*N*-cyanoamino]acetate Hemihydrate (19a).** BrCN (0.35 g, 3.3 mmol) was added to a mixture of **18a** (1.25 g, 2.5 mmol) and $NaHCO_3$ (0.3 g) in $CHCl_3$ (10 mL) and the mixture was stirred at room temperature for 20 h, filtered, and evaporated. The residue was crystallized from $Et_2O$ to give title compound **19a**: yield 0.81 g (62%); mp 132–134 °C. Anal. $C_{25}H_{30}ClN_3O_7$·0.5 $H_2O$) C, H, N.

**Ethyl 2-[*N*-[2-[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-*N*-cyanoamino]acetate Hemihydrate (19b).** BrCN (0.40 g, 3.7 mmol) was added to a mixture of **18b** (1.33 g, 2.5 mmol) and $NaHCO_3$ (0.40 g) in $CHCl_3$ (30 mL) and the mixture was stirred at room temperature for 7.5 h and evaporated. The residue was crystallized from $Et_2O$ to give title compound **19b**: yield 0.86 g (62%); mp 148–150 °C. Anal. ($C_{25}H_{29}Cl_2N_3O_7$·0.5 $H_2O$) C, H, N.

**2-Amino-1-[2-[[4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-4(5*H*)-imidazolone Hemihydrate (20a).** A solution of **19a** (0.60 g, 1.15 mmol) in MeOH (50 mL) was treated with concentrated aqueous ammonia (20 mL) and the mixture was stirred at room temperature for 16 h and evaporated. The residue was crystallized from EtOH to give title compound **20a**: yield 0.37 g (65%); mp 110–113 °C. Anal. ($C_{23}H_{27}ClN_4O_6$·0.5 $H_2O$) C, H, N.

**2-Amino-1-[2-[[4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-4(5*H*)-imidazolone Hemihydrate (20b).** A solution of **19b** (0.70 g, 1.3 mmol) in MeOH (20 mL) was treated with concentrated aqueous ammonia (10 mL) and the mixture was stirred at room temperature for 16 h and evaporated. The residue was crystallized from EtOH to give title compound **20b**: yield 0.46 g (69%); mp 134–138 °C. Anal. ($C_{23}H_{26}Cl_2N_4O_6$·0.5 $H_2O$) C, H; N: calcd, 10.48; found, 10.02.

[[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxy-carbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-amino]acetonitrile (21a). A mixture of 1a (4.08 g, 10 mmol), chloroacetonitrile (1.0 g, 13.2 mmol), and $K_2CO_3$ (1.2 g) in MeCN (40 mL) was heated under reflux for 20 h and evaporated. The residue was crystallized from $Et_2O$ to give title compound 21a: yield 2.0 g (45%); mp 104–105 °C. Anal. ($C_{22}H_{26}ClN_3O_5$) C, H, N.

1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(meth-oxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]-ethyl]-1-(cyanomethyl)urea (22a). AcOH (0.5 g) was added to a solution of 21a (1.0 g, 2.25 mmol) and KCNO (0.35 g, 4.3 mmol) in a mixture of dioxane (15 mL) and water (15 mL), and the mixture was stirred at room temperature for 16 h and evaporated. The residue was partitioned between EtOAc and water and the organic layer was washed with water, dried over $Na_2SO_4$, and evaporated. The residue was chromatographed on $SiO_2$ using $CH_2Cl_2$ plus 0–5% MeOH as eluant. Appropriate fractions were combined and evaporated to give title compound 22a: yield 53 mg (5%); mp 190–191 °C. Anal. ($C_{23}H_{27}ClN_4O_6$) C, H, N.

1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(meth-oxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]-ethyl]-1-(cyanomethyl)-1-methylurea (23a). MeNCO (0.20 g) was added to a solution of 21a (1.0 g, 2.25 mmol) in $CH_2Cl_2$ (10 mL) and the mixture was stirred at room temperature for 3 h and evaporated. The residue was crystallized from $Et_2O$ to give title compound 23a: 285 mg (25%); mp 64–66 °C. Anal. ($C_{24}H_{29}ClN_4O_6$) C, H, N.

4-Amino-1-[2-[[4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]meth-oxy]ethyl]-2(3H)-imidazolone Hydrate (24a). A solution of 22a (49 mg, 0.1 mmol) in MeOH (5 mL) was treated with NaH (12 mg, 0.4 mmol; 80% dispersion in oil) and the mixture was stirred at room temperature for 1 h and evaporated. The residue was partitioned between EtOAc and water and the organic layer was dried over $Na_2SO_4$ and evaporated to give title compound 24a: yield 26 mg (53%); mp 132–134 °C. Anal. ($C_{23}H_{27}ClN_4$-$O_6·H_2O$) H, N, C: calcd, 54.28; found, 54.77.

4-Amino-1-[2-[[4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]meth-oxy]ethyl]-3-methyl-2(3H)-imidazolone Dihydrochloride (25a). NaH (51 mg, 1.7 mmol; 80% dispersion in oil) was added to a solution of 23a (1.0 g, 2.0 mmol) in MeOH (10 mL) and the mixture was stirred at room temperature for 30 min and evaporated. The residue was partitioned between EtOAc and 2 M HCl and the organic layer was dried over $MgSO_4$ and evaporated. The residue was crystallized from EtOH to give title compound 25a: yield 255 mg (25%); mp 135–137 °C. Anal. ($C_{24}H_{29}Cl_2N_4O_6·2HCl$) H, N, C: calcd, 50.04; found 49.23.

1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(meth-oxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]-ethyl]imidazolidine-2,5-dione (27a). A solution of 26a[8] (1.08 g, 2.0 mmol) in MeOH (5 mL) was treated with concentrated aqueous ammonia (2 mL) and the mixture was stirred at room

temperature for 16 h and evaporated. The residue was purified by chromatography on $SiO_2$ using $CH_2Cl_2$ plus 0–4% MeOH as eluant. Appropriate fractions were combined and evaporated and the residue was recrystallized from $EtOAc/Me_2CO$ to give title compound 27a: yield 0.20 g (21%); mp 140 °C. Anal. ($C_{23}$-$H_{26}ClN_3O_7$) C, H, N.

1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(meth-oxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]-ethyl]-3-(cyanomethyl)urea Hemihydrate (29a). A mixture of 28a[8] (0.98 g, 2.0 mmol), 2-aminoacetonitrile hydrochloride (0.30 g, 3.3 mmol), and N-methylmorpholine (0.44 g, 4.4 mmol) in MeCN (5 mL) was stirred at room temperature for 22 h and evaporated. The residue was purified by chromatography on $SiO_2$ using $CH_2Cl_2$ plus 0–5% MeOH as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from EtOH to give title compound 29a: yield 390 mg (40%); mp 145–147 °C. Anal. ($C_{23}H_{27}ClN_4O_6·0.5\ H_2O$) C, H, N.

5-Amino-1-[2-[[4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]meth-oxy]ethyl]-2(3H)-imidazolone Hydrochloride Dihydrate (30a). NaH (60 mg, 2 mmol; 80% dispersion in oil) was added to a suspension of 29a (0.36 g, 0.73 mmol) in MeOH (10 mL) and the mixture was stirred at room temperature for 1 h and evaporated. The residue was partitioned between EtOAc and 2 M HCl and the organic layer was dried over $MgSO_4$ and evaporated. The residue was crystallized from EtOAc/hexane to give title compound 30a: yield 129 mg (29%); mp 138–139 °C. Anal. ($C_{23}H_{27}ClN_4O_6·HCl·2H_2O$) C, H, N.