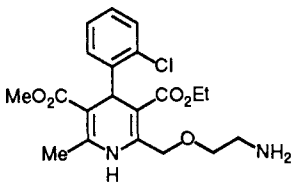
Long-Acting Dihydropyridine Calcium Antagonists. 4. Synthesis and Structure-Activity Relationships for a Series of Basic and Nonbasic Derivatives of 2-[(2-Aminoethoxy)methyl]-1,4-dihydropyridine Calcium Antagonists

David Alker,*,† Simon F. Campbell,† Peter E. Cross,† Roger A. Burges,‡ Anthony J. Carter,‡ and Donald G. Gardiner‡

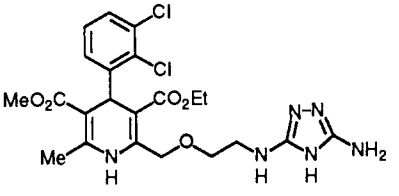
Pfizer Central Research, Sandwich, Kent CT13 9NJ, United Kingdom. *Received May 1, 1989*

The preparation of a series of 1,4-dihydropyridines (DHPs) which have polar, acyclic, nonbasic substituents on an ethoxymethyl chain at the 2-position is described. In addition, in order to assess the effects of incorporating a basic center into DHPs of this type, a series of glycinamides were also prepared. The calcium antagonist activity on rat aorta of both these classes of DHP is compared with their negative inotropic activity as determined by using a Langendorff perfused guinea pig heart model. A number of the compounds evaluated have activity of the same order as nifedipine although those with more extended substituents have lower potency, particularly when a basic substituent is present. The compounds examined displayed a wide variation in selectivity for vascular over cardiac tissue. A number of structure-activity relationship trends were identified and possible explanations to account for the differences in selectivity observed are advanced. One of the compounds, 2-[[2-[[4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]amino]acetamide (**26**, UK-51,656), was identified as a potent ($IC_{50} = 4 \times 10^{-9}$ M) calcium antagonist which is 20-fold selective for vascular over cardiac tissue and which has a markedly longer duration of action (>5 h) than nifedipine in the anesthetized dog on intravenous administration. The pharmacokinetic half-life of **26** was established as 4.7 h and possible explanations are advanced to account for **26** having a shorter plasma half-life than amlodipine and a longer plasma half-life than felodipine.

Calcium antagonists are a well-established therapeutic class of agents which are finding increasing use in the treatment of angina and hypertension. One of the major structural series with this mode of action is the 1,4-dihydropyridines (DHPs). We have recently reported[1] the synthesis and structure-activity relationships (SARs) of a series of DHP calcium antagonists which have a basic side chain linked to the 2-position of the DHP ring. From this work we identified amlodipine (1), a compound with improved bioavailability and duration of action over currently available calcium antagonists. Amlodipine is now in late-stage clinical development as a once-daily treatment for angina[2,3] and hypertension.[4,5] Subsequent work established that the basic center in amlodipine was not an absolute requirement for calcium antagonist activity and that the amino function could be replaced by polar heterocycles as in **2**[6] and **3**.[7] The much higher potency of **2** and **3** for vascular rather than cardiac tissue was thought to arise from favorable hydrogen-bonding interactions between the nonbasic polar heterocyclic group on the side chain on the 2-position and the DHP receptor. In order to establish whether structural modification of **2** and **3** was consistent with calcium antagonist activity, we decided to investigate DHPs (I) containing acyclic, polar functionality



1, amlodipine



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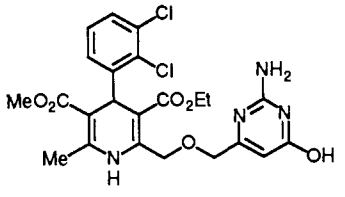

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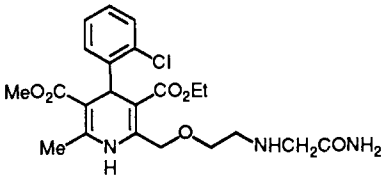

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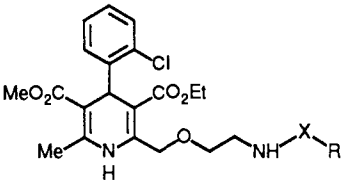
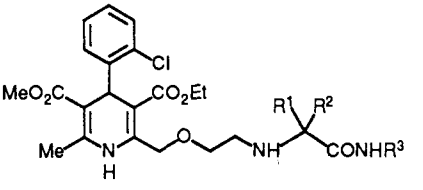


I: X = C=O, SO_2, C=N(CN); R = alkyl, heterocyclyl; NH-alkyl, NH-heterocyclyl



II: R^1, R^2 = H, CH_3; R^3 = H, alkyl

† Department of Chemistry.
‡ Department of Biology.

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also capable of hydrogen-bonding to the DHP receptor. The effect of combining basic and nonbasic functionality in the 2-position of the DHP ring was probed by synthesizing a series of hybrid structures (II). It was expected that the favorable pharmacokinetics displayed by amlodipine might also be expressed in this series.

Chemistry

The synthesis of the DHP derivatives **4–23** was achieved by the transformations shown in Scheme I. Acetylation of **1** gave **4** (route A) while **5–7** were prepared by using a peptide-coupling procedure[8] involving 1-hydroxybenzotriazole hydrate, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, and 4-methylmorpholine (route B). Reaction of **1** or **8** with isocyanates gave **9–11** (route C) while the more complex ureas (**13–16**) were synthesized in good yield by a two-step procedure (route D). Thus, reaction of **1** with CDI gave [(1-imidazolyl)-carbonyl]amino derivative **12** as a stable, isolable solid which could be transformed smoothly into ureas **13–16** by treatment with the appropriate primary amines. This method represents a convenient means of preparing unsymmetrical ureas containing functionality which is not compatible with an isocyanate or carbamoyl chloride intermediate, e.g. **13**. Sulfamoylamino analogues **17** and **18** were obtained by heating **1** and **8**, respectively, with sulfamide in dioxane (route E) while the cyanoguanidines **21–23** were prepared in a two-step sequence via **19** or **20** (route F) as outlined in a previous paper of this series.[6]

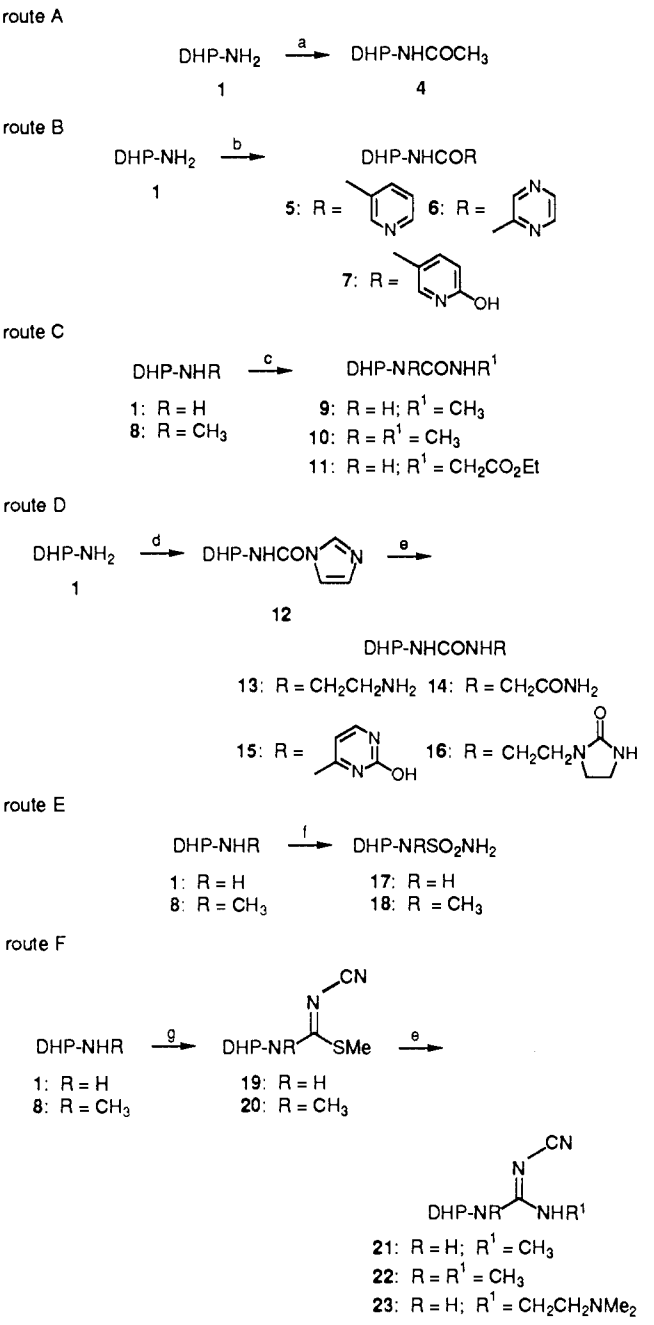
The preparation of **24–33** was accomplished by the routes summarized in Scheme II. Alkylation of **1** with 1 equiv of methyl bromoacetate gave approximately equal amounts of the mono- (**24**) and bis-alkylated (**25**) products, which were readily separable by chromatography. Reaction of **24** and **25** with concentrated aqueous ammonia afforded **26** and **27**, respectively. Alternatively, direct alkylation of **1** with 1.1 equiv of 2-chloroacetamide in refluxing acetonitrile resulted in a modest yield of **26**, together with **27**, which could be separated by chromatography. Bis-alkylated product **27** was obtained more efficiently by heating **1** with 2.7 equiv of 2-chloroacetamide in DMF at 110–120 °C. Stirring **24** with the appropriate primary amine led to **28–30**. Alkylation of **1** with ethyl 2-bromopropionate gave **31** (a small amount of a second product, observed by TLC but not isolated, was presumed to be bis-alkylated material), which on reaction with concentrated aqueous ammonia gave **32** (as a mixture of diastereomers). Compound **33** was formed in poor yield by heating **1** with 2-bromo-2-methylpropionamide.[9]

Results and Discussion

In vitro calcium antagonist activity (expressed as an IC_{50}) 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 IC_{25}) was determined in vitro using a Langendorff perfused guinea pig heart preparation. An examination of the data for compounds **4–23** suggests that the DHP receptor can accommodate DHPs with a range of substituents in the 2-position without marked adverse effects on activity (see Table I). For example there is only a 5-fold difference in in vitro activity within the wide range of structural prototypes **4**, **9**, **17**, and **21**. However, certain SAR trends are apparent from the data. In ureas **9**, **11**, and **13–16**, greatest potency is seen for **9**, which has the smallest N3 substituent, whereas larger groups as in **11**, **14**, and **16** lead to lower activity. The comparable activity seen for **11**, **14**, and **16**, which have structurally diverse N3 substituents, confirms the tolerance of the DHP receptor to structural variation in the 2-position of the DHP ring.

Urea derivatives **13** and **15**, where the N3 substituent contains a basic center or is a heterocycle, respectively, are both markedly less active. The detrimental effect of introducing a substituent containing a basic center is also seen by comparing cyanoguanidines **21** and **23**. This is in contrast to amlodipine, where the presence of a basic

Scheme I[a,b]



[a] Reagents: (a) CH_3COCl, pyridine; (b) 1-hydroxybenzotriazole hydrate, 4-methylmorpholine, $Me_2N(CH_2)_3N{=}C{=}NEt$ HCl, RCO_2H; (c) RNCO; (d) CDI, 4-methylmorpholine; (e) RNH_2; (f) $NH_2SO_2NH_2$; (g) $(MeS)_2C{=}NCN$.

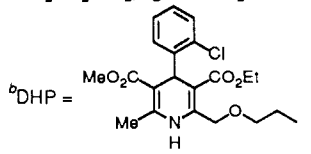


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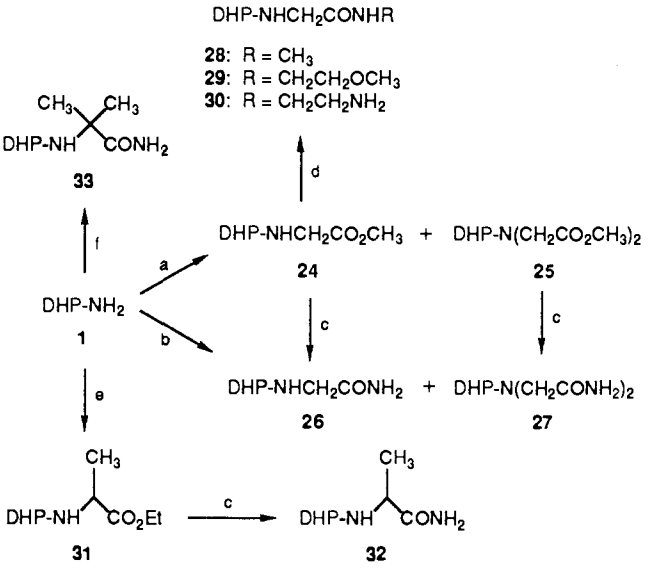
Table I. Data for Compounds Used in Study

no.	route	mp, °C	recryst[n] solvent	formula	% yield	Ca pIC_{50}[a]	neg inotropy pIC_{25}[b]	selectivity index[c]
4	1A	97–99	Et_2O	$C_{22}H_{27}ClN_2O_6$	75	7.8[d]	7.6	1.6
5	1B	81–84	Et_2O	$C_{26}H_{28}ClN_3O_6$	57	7.8	7.6	1.6
6	1B	117–118	Et_2O	$C_{25}H_{27}ClN_4O_6$	42	7.4	7.5	0.8
7	1B	125–130 dec	Et_2O	$C_{26}H_{28}ClN_3O_7$	63	8.2	7.0	16
9	1C	75–90 dec	Et_2O	$C_{22}H_{28}ClN_3O_6$	85	8.5	7.6	13
10	1C	160–162	EtOAc/Et_2O	$C_{23}H_{30}ClN_3O_6$	53	7.7	7.0	5
11	1C	125–127	EtOAc/hexane	$C_{25}H_{32}ClN_3O_8$	41	8.0	7.0	10
13	1D	90 dec	EtOAc/EtOH	$C_{23}H_{31}ClN_4O_6 \cdot C_4H_4O_4$	58	7.3	7.1	1.6
14	1D	114–116	EtOAc	$C_{23}H_{29}ClN_4O_7$	23	7.7	6.4	20
15	1D	140–143	EtOAc	$C_{25}H_{28}ClN_5O_7 \cdot H_2O$	16	6.8	7.7	0.1
16	1D	75–77	EtOAc	$C_{26}H_{34}ClN_5O_7$	32	7.8	6.2	40
17	1E	150–152	Et_2O	$C_{20}H_{26}ClN_3O_7S$	77	8.1	7.1	10
18	1E	117–120	Et_2O	$C_{21}H_{28}ClN_3O_7S$	88	7.6	6.7	8
21	1F	188–190	EtOH	$C_{23}H_{28}ClN_5O_5$	64	8.2	7.5	5
22	1F	131–136	Et_2O	$C_{24}H_{30}ClN_5O_5$	74	7.6	6.6	10
23	1F	202–204 dec	EtOAc	$C_{26}H_{35}ClN_6O_5$	79	7.3	6.8	3
26	2	136–138	EtOAc	$C_{22}H_{28}ClN_3O_6$	31[e]/62[f]	8.4	7.1	20
27	2	125–128	EtOAc	$C_{24}H_{31}ClN_4O_7$	77[g]/64[h]	7.2	6.0	16
28	2	123–124	Et_2O	$C_{23}H_{30}ClN_3O_6$	62	7.6	6.9	5
29	2	87–88	Et_2O	$C_{25}H_{34}ClN_3O_7$	41	8.3	7.5	6
30	2	93–99	EtOAc	$C_{24}H_{33}ClN_4O_6$	40	7.0	7.0	1
32	2	124–126	EtOAc	$C_{23}H_{30}ClN_3O_6$	59	8.0	7.2	6
33	2	79–81	MeOH	$C_{24}H_{32}ClN_3O_6 \cdot H_2O$	9	8.5	7.6	8
nifedipine					8.4	7.5	8	

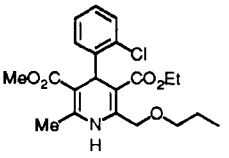
[a] Negative logarithm of the molar concentration required to block Ca^{2+}-induced contraction of K^+-depolarized rat aorta by 50%. Nifedipine was used as the standard compound, standard deviation ±0.01. [b] Negative logarithm of the molar concentration required to depress contraction in the Langendorff perfused guinea pig heart by 25%. Nifedipine was used as the standard compound, standard deviation ±0.26. [c] Selectivity index = $IC_{50}(Ca^{2+})/IC_{25}$(negative inotropy). [d] $n = 2$ (±0.3). [e] Yield obtained from alkylation of 1 with 1.1 equiv of chloroacetamide. [f] Yield obtained from reaction of **24** with concentrated aqueous ammonia. [g] Yield obtained from alkylation of 1 with 2.7 equiv of chloroacetamide. [h] Yield obtained from reaction of **25** with concentrated aqueous ammonia.

Scheme II[a,b]



[a] Reagents: (a) $BrCH_2CO_2CH_3$, K_2CO_3, heat; (b) $ClCH_2CONH_2$, K_2CO_3, heat; (c) concentrated aqueous ammonia; (d) RNH_2; (e) $BrCH(CH_3)CO_2Et$, K_2CO_3, heat; (f) $BrC(CH_3)_2CONH_2$, K_2CO_3, heat.

[b] DHP =



center is tolerated.[1] It is also apparent that alkyl substitution on the nitrogen atom causes a reduction in activity in **9**, **17**, and **21**, as exemplified by **10**, **18**, and **22**.

From the data for the glycinamide derivatives (**26–33**), it is apparent that the presence of both a basic center and a polar, nonbasic amide group is compatible with good calcium antagonist potency. The tolerance of the DHP receptor to the presence of bulky substituents on the 2-position of the DHP ring is reflected by the fact that **26** is equipotent with nifedipine. The in vitro activity seen for **33** and **29** demonstrates that neither substituent of the methylene adjacent to the carboxamide group nor the introduction of substituents on the amide group, respectively, have any significant effect on calcium antagonist activity. However, in parallel with the observations above, both **30**, in which the carboxamide substituent contains a second basic center, and **27**, in which the nitrogen attached to the ethoxymethyl chain is disubstituted, are markedly less potent than **26**.

It is now generally accepted that the voltage-dependent calcium channel can exist in one of three states (open, resting, and inactivated) and that DHP antagonists bind preferentially[10,11] to the inactivated state. Because the inactivated state is favored by increasingly negative resting potentials, DHPs would thus be expected to be intrinsically more effective in smooth-muscle tissue than cardiac tissue, since the latter normally exhibits a more negative resting potential and undergoes only brief periods of depolarization during the cardiac cycle. This reasoning has been put forward[12] to account for the apparent inherent selectivity of DHPs for vascular over cardiac tissue. In support of this view is the observation that amlodipine and nifedipine, which have structurally, sterically, and physicochemically different substituents on the DHP 2-position, exhibit similar (ca. 10-fold) selectivity for vascular over cardiac tissue.[1] However, an examination of the data in Table I reveals that tissue selectivity is also dependent on structure, at least to some degree. Thus, while many of the compounds have the same selectivity index as nifedipine,

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Table II. Coronary Vasodilator Activity for **10**, **11**, **26**, **32**, **33**, and Nifedipine in Anesthetized Dogs following Intravenous Administration (150 $\mu g\ kg^{-1}$)

compound	percentage decrease in CVR	duration of action,[a] min
10	68	15
11	61	15
26	88	>300
32	73	150
33	85	210
nifedipine	77	36

[a] Time taken for 50% recovery of CVR.

certain derivatives are markedly more or less selective. In general, the most highly tissue-selective compounds **7**, **14**, **16**, **26**, and **27** contain an amide group at the terminus of the 2-substituent. However, in contrast to amlodipine,[1] the presence of a basic center at the terminus of the 2-substituent as in **13**, **23**, and **30** causes a loss of selectivity for vascular over cardiac tissue. Remarkably urea **15** exhibits "reversed" selectivity, being some 10-fold more active on cardiac tissue. Literature evidence is also available which demonstrates that DHPs can exhibit a range of tissue selectivities. Thus, it has been reported that nisoldipine shows vascular selectivity 100 times that seen for nifedipine[13] while it has recently been claimed[14] that certain halogenated derivatives of nitrendipine are 10-fold more vascular selective than nitrendipine itself.

The mechanism by which the presence of certain structural features in DHPs alters the tissue selectivity is not fully understood. It has been suggested[13,15] that increased potency per se leads to more pronounced selectivity. However, this is not entirely the case for the compounds in Table I since the pairs of compounds **4** and **16** and **6** and **27** have equivalent IC_{50}'s on vascular tissue but exhibit markedly different selectivities. It has also been suggested[14] that improved vascular selectivity may at least in part be a consequence of differences in lipophilicity. We believe that the differences in selectivity index seen for the compounds in Table I cannot be explained simply on the grounds of potency or overall lipophilicity and that structural differences in the 2-substituent lead directly to variations in selectivity between vascular and cardiac tissue. Two possible mechanistic explanations for this phenomenon can be advanced. Firstly, it is possible that DHP binding to the inactivated state of the channel[10,11] may not be exclusive; a higher degree of open-state binding by certain derivatives would lead to relatively higher affinity for the cardiac channel, and thus reduced vascular selectivity. Alternatively, by analogy with the well-described heterogeneity of hormone receptors into subtypes with different primary protein structures, it may be that similar structural differences exist for the DHP-sensitive calcium channels in vascular and cardiac tissues. While the primary sequences of the various subunits of the calcium channel have now been established,[16] the location and sequence of the DHP binding site has yet to be elucidated. Further advances are thus required in order to fully understand the reasons for variation in tissue selectivity among DHPs.

Table III. Pharmacokinetic Data for Compound **26** in Comparison with Felodipine[19] and Amlodipine[1] in Dogs after Intravenous Administration

compound	plasma clearance, mL min^{-1} kg^{-1}	vol of distribution, L kg^{-1}	plasma half-life, h
26	7.0	3.0	4.7
felodipine	38	3.6	1.0
amlodipine	11	25	30

On the basis of their potency and selectivity, compounds **10**, **11**, **26**, **32**, and **33** were selected for in vivo evaluation in instrumented, anesthetized dogs. These compounds were administered intravenously and their calcium antagonist potency and duration of action were determined from the effects on coronary vascular resistance (CVR). As might be expected on the basis of their in vitro activity, all compounds were of similar potency to nifedipine and produced maximum or near-maximum falls in CVR at a dose of 150 $\mu g\ kg^{-1}$ (Table II). However, there were significant differences in the durations of action of the compounds examined. The effect of **10** and **11** on CVR was relatively short-lived, while **26**, **32**, and **33**, which all contain a basic center, had markedly longer durations of action than nifedipine. The duration of action of **26** was particularly noteworthy, being over 5 h. These results illustrate that the presence of a basic center in the 2-substituent on the DHP ring has a beneficial effect on duration of action, as might be expected from SAR studies with amlodipine.

In order to clarify these observations, a pharmacokinetic study in dogs was performed on **26**. Compound **26** has an elimination half-life of 4.7 h (Table III), which is consistent with its duration of action in the anesthetized dog (Table II). Thus, the compound has a markedly longer half-life than felodipine, although its half-life is much shorter than that of amlodipine. Amlodipine and **26** have similar plasma clearance values, which are each significantly lower than that of felodipine. Although other factors may also be important, it is possible that the extended 2-substituent present in both **26** and amlodipine hinders their binding to the cytochrome p450 enzymes responsible for metabolic oxidation of DHPs to the corresponding pyridines,[17] thereby reducing plasma clearance.

The shorter half-life of **26** compared to that of amlodipine is a consequence of its much lower volume of distribution, which is approximately equal to that seen for felodipine. Amlodipine has a remarkably large volume of distribution[1] and a hypothesis to explain this phenomenon has recently been proposed.[18] Thus, it has been suggested from the results of X-ray diffraction studies that the position adopted by amlodipine within biological membrane bilayers favors the existence of a charge–charge interaction between the protonated amino group on amlodipine and a region of negative charge in the phosphate head group of the membrane phospholipid. This interaction, which arises because of the discrete position of the basic center on the 2-substituent in amlodipine, is suggested to account for the high partition coefficient of amlodipine, as measured in biological membranes,[18] and possibly the large volume of distribution observed in animals and man. Although **26** has a basic center in the same relative position as that in amlodipine, its much lower volume of distribution suggests that a charge–charge interaction within the membrane of the type proposed for

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amlodipine is not as favorable for this compound. This may be a consequence of an unfavorable steric interaction between the carboxamidomethyl group in **26** and the phosphate head group of the membrane phospholipid. Alternatively, the lower pK_a of **26** compared to that of amlodipine may reduce the charge–charge interaction between the protonated amino group of **26** and the phosphate head group.

In conclusion, we have established that the incorporation of polar, nonbasic, acyclic substituents on the 2-position of the DHP ring can give compounds which exhibit calcium antagonist activity equivalent to that seen for nifedipine. In addition we have shown that combining the basic center of amlodipine with amide groups gives potent calcium antagonists with good selectivity for vascular tissue over cardiac tissue. One of these compounds, **26** (UK-51,656) has a duration of action in excess of 5 h on intravenous administration to an anesthetized dog and its pharmacokinetic half-life was shown to be markedly longer than that of felodipine.

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 implanted with catheters for the measurement of blood pressure and left ventricular pressure and for the intravenous administration of test compound. Coronary blood flow was measured by the hydrogen-clearance technique using platinum electrodes positioned in the coronary sinus and femoral artery as reported in the literature.[20] Cardiac output was determined by the thermodilution method. All other parameters were derived from these measurements. Compound was administered as one single dose to assess duration of action.

Chemistry. All melting points are uncorrected. The structures of all the compounds were determined by ^1H NMR spectroscopy and microanalysis. Microanalytical data were not obtained for intermediates **11**, **20**, and **24**. However, the ^1H NMR spectrum of each of these compounds was wholly compatible with its proposed structure and TLC data established the purity of each compound. ^1H NMR spectra were obtained with a Varian XL-100-5 spectrometer using $CDCl_3$ as the solvent.

All compounds were obtained as racemic mixtures. The preparation of amines **1** and **8** has been described in a previous publication.[1] The preparation of *S*-methylisothiourea **19** has also been reported.[6] *S*-Methylisothiourea **20** was prepared in a directly analogous manner by reacting **8** with *N*-cyanoimidodithiocarbonate.

2-[[2-(*N*-Acetylamino)ethoxy]methyl]-4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (4). CH_3COCl (0.22 g, 3.0 mmol) was added dropwise to a stirred, ice-cooled solution of **1** (0.82 g, 2.0 mmol) in pyridine (5 mL), and the mixture was stirred at room temperature for 14 h, poured into 2 M HCl, and extracted with EtOAc. The EtOAc extract was washed successively with 2 M HCl and water, dried over Na_2SO_4, 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 crystallized from Et_2O to give title compound **4**: yield 0.68 g (75%); mp 97–99 °C. Anal. ($C_{22}H_{27}ClN_2O_6$)C, H, N.

General Route to Amides (5–7). 4-Methylmorpholine was added dropwise to a stirred, ice-cooled mixture of **1**, 1-[(3-dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, 1-hydroxybenzotriazole hydrate, and the appropriate carboxylic acid in CH_2Cl_2. The mixture was stirred at room temperature for 16 h, diluted with CH_2Cl_2, washed successively with water, 2 M HCl, water, 10% aqueous Na_2CO_3 solution and water, dried over Na_2SO_4, 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 Et_2O.

4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-2-[[2-[*N*-(3-pyridylcarbonyl)amino]ethoxy]methyl]-1,4-dihydropyridine (5). Addition of 4-methylmorpholine (0.61 g, 6.0 mmol) to a mixture of **1** (0.4 g, 1.0 mmol), 1-[(3-dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.42 g, 2.2 mmol), 1-hydroxybenzotriazole hydrate (0.17 g, 1.1 mmol), and nicotinic acid (0.14 g, 1.1 mmol) in CH_2Cl_2 (40 mL) followed by workup as described above gave title compound **5**: yield 0.29 g (57%); mp 81–84 °C. Anal. ($C_{26}H_{28}ClN_3O_6$) C, H, N.

4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-2-[[2-[*N*-(2-pyrazinylcarbonyl)amino]ethoxy]methyl]-1,4-dihydropyridine (6). Addition of 4-methylmorpholine (1.22 g, 12.0 mmol) to a mixture of **1** (0.82 g, 2.0 mmol), 1-[(3-dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.84 g, 4.4 mmol), 1-hydroxybenzotriazole hydrate (0.34 g, 2.2 mmol), and pyrazine-2-carboxylic acid (0.28 g, 2.2 mmol) in CH_2Cl_2 (80 mL) followed by workup as described above gave the title compound **6**: yield 0.46 g (42%); mp 117–118 °C. Anal. ($C_{25}H_{27}ClN_4O_6$) C, H, N.

4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-2-[[2-[*N*-(pyrid-6-on-3-ylcarbonyl)amino]ethoxy]methyl]-1,4-dihydropyridine (7). Addition of 4-methylmorpholine (0.91 g, 9.0 mmol) to a mixture of **1** (0.82 g, 2.0 mmol), 1-[(3-dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.84 g, 4.5 mmol), 1-hydroxybenzotriazole hydrate (0.3 g, 2.2 mmol), and 6-hydroxypyridine-3-carboxylic acid (0.28 g, 2.0 mmol) in CH_2Cl_2 (40 mL) followed by workup as described above gave title compound **7**: yield 0.68 g (63%); mp 125–130 °C dec. Anal. ($C_{26}H_{28}ClN_3O_7$) C, H, N.

1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-3-methylurea (9). MeNCO (0.5 mL) was added to a solution of **1** (0.41 g, 1.0 mmol) in CH_2Cl_2 (50 mL) and the mixture stirred at room temperature for 2 h and evaporated. The residue was crystallized from Et_2O to give title compound **9**: yield 0.40 g (85%); mp 75–90 °C dec. Anal. ($C_{22}H_{28}ClN_3O_6$) C, H, N.

1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-1,3-dimethylurea (10). MeNCO (100 mg, 1.45 mmol) was added to a solution of **8** (200 mg, 0.47 mmol) in CH_2Cl_2 (8 mL) and the mixture was stirred at room temperature for 2 h and evaporated. The residue was purified by chromatography on SiO_2 using CH_2Cl_2 plus 0–10% EtOAc as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from Et_2O/EtOAc to give title compound **10**: yield 120 mg (53%); mp 160–162 °C. Anal. ($C_{23}H_{30}ClN_3O_6$) C, H, N.

1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-3-[(ethoxycarbonyl)methyl]urea (11). A solution of **1** (0.41 g, 1.0 mmol) and (ethoxycarbonyl)methyl isocyanate (0.30 mL) in acetonitrile (5 mL) was heated under reflux for 2.5 h and evaporated. The residue was triturated with Et_2O and the resulting solid was collected, dried, and recrystallized from EtOAc/hexane to give title compound **11**: yield 220 mg (86%); mp 125–127 °C; ^1H NMR ($CDCl_3$) δ = 6.85–7.55 (5 H, m), 5.35 (1 H, s), 5.2–5.6 (1 H, br s), 4.64 (2 H, s), 4.10 (2 H, q, J = 7 Hz), 3.93 (2 H, q, J = 5 Hz), 3.88 (2 H, q, J = 7 Hz), 3.53 (3 H, s), 3.2–3.6 (4 H, m), 2.28 (3 H, s), 1.20 (3 H, t, J = 7 Hz), and 1.09 (3 H, t, J = 7 Hz).

4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-2-[[(1-imidazolyl)carbonyl]amino]-6-methyl-1,4-dihydropyridine (12). A solution of **1** (20.49 g, 50 mmol) in THF (150 mL) was added dropwise over 45 min to a stirred solution of CDI (8.9 g, 54 mmol) and 4-methylmorpholine (20 mL) in THF (350 mL) and the mixture was stirred at room temperature for 2 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 crystallized from Et_2O to give title compound **12**: yield 16.6 g (66%); mp 149–151 °C. Anal. ($C_{24}H_{27}ClN_4O_6$) C, H, N.

General Route to Ureas 13–16. A mixture of **12** (0.98 g, 2.0 mmol) and the appropriate amine in CH_3CN (10 mL) was stirred at room temperature for 16 h and then evaporated. The residue

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was purified by chromatography on SiO_2 using CH_2Cl_2 plus 0–3% MeOH as eluant. Appropriate fractions were combined and evaporated.

3-(2-Aminoethyl)-1-[2-[[4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]urea (13). Reacting **12** with 1,2-diaminoethane (120 mg, 2.0 mmol) and workup as described above gave the title compound **13** as a colorless oil: yield 0.56 g (58%). A portion of this oil was converted to an analytically pure maleate salt by treatment with 1 equiv of maleic acid in EtOAc and recrystallization of the resulting solid from EtOAc/EtOH: mp 90 °C dec. Anal. ($C_{23}H_{31}ClN_4O_6 \cdot C_4H_4O_4$)C; H: calcd, 5.81; found, 6.31; N.

3-[(Aminocarbonyl)methyl]-1-[2-[[4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]urea (14). Reacting **12** with glycinamide (0.22 g, 3.0 mmol) and workup as described above gave, after crystallization of the residue from EtOAc, title compound **14**: yield 0.25 g (23%); mp 114–116 °C. Anal. ($C_{23}H_{29}ClN_4O_7$) C, H, N.

1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-3-(2-hydroxy-4-pyrimidinyl)urea (15). Reacting **12** with 4-amino-2-hydroxypyrimidine (0.22 g, 2.0 mmol) and workup as described above gave, after crystallization of the residue from EtOAc, title compound **15**: yield 0.18 g (16%); mp 140–143 °C. Anal. ($C_{25}H_{28}ClN_6O_5 \cdot H_2O$) C, H, N: calcd, 12.42; found, 11.84.

1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-3-[2-(2-oxoimidazolidin-1-yl)ethyl]urea (16). Reacting **12** with 1-(2-aminoethyl)imidazolidin-2-one (0.26 g, 2.0 mmol) and workup as described above gave, after crystallization from EtOAc, title compound **16**: yield 0.355 g (32%); mp 75–77 °C. Anal. ($C_{26}H_{34}ClN_5O_7$) C, H; N: calcd, 12.42; found, 11.50.

1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]sulfamide (17). A solution of **1** (0.82 g, 2.0 mmol) and sulfamide (0.96 g, 10 mmol) in dioxane (30 mL) was heated under reflux for 70 min and evaporated. The residue was partitioned between EtOAc and water, and the organic layer was dried over Na_2SO_4 and evaporated. The residue was crystallized from Et_2O to give title compound **17**: yield 0.75 g (77%); mp 150–152 °C. Anal. ($C_{20}H_{26}ClN_3O_7S$) C, H, N.

1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-1-methylsulfamide (18). A solution of **8** (0.42 g, 1.0 mmol) and sulfamide (0.96 g, 10 mmol) in dioxane (40 mL) was heated under reflux for 2 h, diluted with CH_2Cl_2 (100 mL), washed with water, dried over Na_2SO_4, and evaporated. The residue was crystallized from Et_2O to give title compound **18**: yield 0.44 g (88%); mp 117–120 °C. Anal. ($C_{21}H_{28}ClN_3O_7S$) C, H, N.

1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-3-cyano-2-methylisothiourea (20): 87% yield; foam.

1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-2-cyano-3-methylguanidine (21). A suspension of **19** (0.40 g, 0.8 mmol) in 33% ethanolic methylamine (10 mL) was stirred at room temperature for 18 h and evaporated. The residue was crystallized from EtOH to give title compound **21**: yield 0.25 g (64%); mp 188–190 °C. Anal. ($C_{23}H_{28}ClN_5O_5$) C, H, N.

1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-2-cyano-1,3-dimethylguanidine (22). A solution of **20** (0.64 g, 1.2 mmol) in 33% ethanolic methylamine (25 mL) was stirred at room temperature for 30 min and evaporated. The residue was taken up in toluene, evaporated, and 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 Et_2O to give title compound **22**: yield 0.46 g (74%); mp 131–136 °C. Anal. ($C_{24}H_{30}ClN_5O_5$) C, H, N.

1-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-2-cyano-3-[2-(dimethylamino)ethyl]guanidine (23). A mixture of **19** (0.35 g, 0.7 mmol) and 2-(dimethylamino)ethylamine (5 mL) was heated at 95 °C for 1.5 h and evaporated. The residue was crystallized from EtOAc to give title compound **23**: yield 0.30 g (79%); mp 202–204 °C dec. Anal. ($C_{26}H_{35}ClN_6O_5$) C, H, N.

4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-2-[[2-[*N*-[(methoxycarbonyl)methyl]amino]ethoxy]methyl]-6-methyl-1,4-dihydropyridine (24) and 2-[[2-[*N*,*N*-Bis[(methoxycarbonyl)methyl]amino]ethoxy]methyl]-4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (25). A mixture of **1** (4.08 g, 10 mmol), methyl bromoacetate (1.53 g, 10 mmol), and K_2CO_3 (2.76 g, 20 mmol) in CH_3CN (100 mL) was heated under reflux for 2 h, filtered, and evaporated. The residue was partitioned between CH_2Cl_2 and water, and the organic layer was dried over $MgSO_4$ 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 to give the title compounds. **24** (more polar compound): yield, 1.50 g (31%); oil. Anal. ($C_{23}H_{29}ClN_2O_7$) C, H, N. **25** (less polar compound): yield 1.45 g (30%); mp 40 °C. Anal. ($C_{26}H_{33}N_2O_9$) C, H, N.

2-[[2-[*N*-[(Aminocarbonyl)methyl]amino]ethoxy]methyl]-4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (26). A solution of **24** (2.40 g, 5.0 mmol) and concentrated aqueous ammonia (40 mL) in MeOH (80 mL) was stirred at room temperature for 3 days and evaporated. The residue was partitioned between EtOAc and water, and the organic layer was dried over Na_2SO_4 and evaporated. The residue was crystallized from EtOAc to give title compound **26**: yield 1.44 g (62%); mp 136–138 °C. Anal. ($C_{22}H_{28}ClN_3O_6$) C, H, N.

2-[[2-[*N*,*N*-Bis[(aminocarbonyl)methyl]amino]ethoxy]methyl]-4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (27). A solution of **25** (1.32 g, 2.5 mmol) and concentrated aqueous ammonia (30 mL) in MeOH (15 mL) was stirred at room temperature for 2 h and evaporated. The residue was partitioned between EtOAc and water, and the organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by chromatography on SiO_2 using CH_2Cl_2 plus 0–10% MeOH as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from EtOAc to give title compound **27**: yield 0.80 g (64%); mp 125–128 °C. Anal. ($C_{24}H_{31}ClN_4O_7$) C: calcd, 55.12; found, 54.37; H, N.

Reaction of 1 with 2-Chloroacetamide. A mixture of **1** (2.04 g, 5.0 mmol), 2-chloroacetamide (0.50 g, 5.5 mmol), and K_2CO_3 (1.36 g, 10 mmol) in acetonitrile (80 mL) was heated under reflux for 14 h, filtered, and evaporated. The residue was partitioned between CH_2Cl_2 and water, and the organic layer was dried over Na_2SO_4 and evaporated. The residue was chromatographed on SiO_2 using CH_2Cl_2 plus 0–10% MeOH as eluant. Appropriate fractions were combined and evaporated to give **26**: yield 0.71 g (31%). A second product whose TLC characteristics were identical with those of **27** was also isolated from this reaction.

A mixture of **1** (0.41 g, 2.7 mmol), 2-chloroacetamide (0.25 g, 2.7 mmol), and K_2CO_3 (0.42 g, 3 mmol) in DMF (20 mL) was heated at 115 °C for 4 h, filtered, and evaporated. The residue was worked up and purified as described above to give **27**: yield 0.40 g (77%). A small amount of product whose TLC characteristics were identical with those of **26** was also isolated from this reaction.

2-[[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]amino]-*N*-methylacetamide (28). A mixture of **24** (0.39 g, 0.80 mmol) and 40% aqueous methylamine solution (5 mL) in MeOH (10 mL) was stirred at room temperature for 3 days 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 0–5% MeOH as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from Et_2O to give title compound **28**: yield 0.24 g (62%); mp 123–124 °C. Anal. ($C_{23}H_{30}ClN_3O_6$) C, H, N.

2-[[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]amino]-*N*-(2-methoxyethyl)acetamide (29). A solution of **24** (0.39 g, 0.8 mmol) and 2-methoxyethylamine (5 mL) in MeOH (10 mL) was stirred at room temperature for 18 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 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 Et_2O to give title compound **29**: yield 0.17 g (41%); mp 87–88 °C. Anal. ($C_{25}H_{34}ClN_3O_7$) C, H, N.

***N*-(2-Aminoethyl)-2-[[2-[[4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]amino]acetamide (30).** A solution of **24** (0.58 g, 1.2 mmol) and 1,2-diaminoethane (5 mL) in MeOH (10 mL) was stirred at room temperature for 18 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 purified by chromatography on SiO_2 using CH_2Cl_2 plus 10–30% MeOH as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from EtOAc to give title compound **30**: yield 0.16 g (40%); mp 93–99 °C. Anal. ($C_{24}H_{33}ClN_4O_6$)C: calcd, 56.63; found, 56.00; H, N.

Ethyl 2-[[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]amino]propionate (31). A mixture of **1** (4.08 g, 10 mmol), ethyl 2-bromopropionate (2.00 g, 11 mmol), and K_2CO_3 (2.8 g, 20 mmol) in acetonitrile (120 mL) was heated under reflux for 24 h, filtered, and evaporated. The residue was partitioned between EtOAc and water, and the organic layer washed with water, dried over Na_2SO_4, and evaporated. The residue was purified by chromatography on SiO_2 using CH_2Cl_2 plus 0–2% MeOH as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from Et_2O to give title compound **31**: yield 1.40 g (28%); mp 89–90 °C. Anal. ($C_{25}H_{33}ClN_2O_7$) C, H, N.

2-[[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]amino]propionamide (32). A solution of **31** (1.02 g, 2.0 mmol) and concentrated aqueous ammonia (25 mL) in EtOH (30 mL) was stirred at room temperature for 14 days 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 0–5% MeOH as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from EtOAc to give title compound **32**: yield 0.56 g (59%); mp 124–126 °C. Anal. ($C_{23}H_{30}ClN_3O_6$) C, H, N.

2-[[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]amino]-2-methylpropionamide (33). A mixture of **1** (4.08 g, 10 mmol), 2-bromo-2-methylpropionamide (1.66 g, 10 mmol), and K_2CO_3 (2.07 g, 15 mmol) in CH_3CN (50 mL) was heated under reflux for 18 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 0–5% MeOH as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from MeOH to give title compound **33**: yield 0.45 g (9%); mp 79–81 °C. Anal. ($C_{24}H_{32}ClN_3O_6 \cdot H_2O$)C: calcd, 56.30; found, 56.89; H, N.

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Registry No. **1**, 88150-42-9; **4**, 123700-09-4; **5**, 123700-10-7; **6**, 123700-11-8; **7**, 123700-12-9; **8**, 103069-16-5; **9**, 123700-13-0; **10**, 123700-14-1; **11**, 123700-15-2; **12**, 123700-16-3; **13**, 123700-17-4; **13**·maleate, 123700-18-5; **14**, 123700-19-6; **15**, 123700-20-9; **16**, 123700-21-0; **17**, 123700-22-1; **18**, 123700-23-2; **19**, 123700-24-3; **20**, 123700-25-4; **21**, 123700-26-5; **22**, 123700-27-6; **23**, 123700-28-7; **24**, 123700-29-8; **25**, 123700-30-1; **26**, 123700-31-2; **27**, 123700-32-3; **28**, 123700-33-4; **29**, 123700-34-5; **30**, 123700-35-6; **31**, 123700-36-7; **32**, 123700-37-8; **33**, 123700-38-9; EtO_2CCH_2NCO, 2949-22-6; $H_2NCH_2CH_2NH_2$, 107-15-3; $H_2NCH_2CONH_2$, 598-41-4; $NH_2SO_2NH_2$, 7803-58-9; $MeOCH_2CH_2NH_2$, 109-85-3; $H_3CCH(Br)CO_2Et$, 41978-69-2; nicotinic acid, 59-67-6; 2-pyrazinecarboxylic acid, 98-97-5; 6-hydroxypyrazine-3-carboxylic acid, 5006-66-6; 4-amino-2-hydroxypyrimidine, 71-30-7; 1-(2-aminoethyl)-imidazolidin-2-one, 6281-42-1; 2-bromo-2-methylpropionamide, 7462-74-0.

Novel Glutamic Acid Derived Cholecystokinin Receptor Ligands

R. M. Freidinger,* W. L. Whitter, N. P. Gould, M. K. Holloway, R. S. L. Chang, and V. J. Lotti

Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486. *Received May 11, 1989*

Novel aryl amide analogues of glutamic acid dialkylamide have been synthesized to test for a possible structural analogy between glutamic acid and benzodiazepine CCK antagonists such as compounds **2** and **24** (lorglumide and MK-329, respectively). In support of the structural model, certain of these hybrid compounds are more potent in pancreas CCK radioligand binding assays than corresponding lorglumide-type reference compounds. Modifications previously found in the benzodiazepine antagonists to result in brain CCK/gastrin receptor selectivity were also incorporated to produce an aryl urea series of glutamic acid analogues. None of these compounds were brain CCK/gastrin selective; however, one was potent and selective in the pancreas binding assay. The model appears to be most useful in the design of selective ligands for the pancreas type CCK receptor.

Cholecystokinin (CCK) was originally discovered as a gastrointestinal peptide,[1] and more recently it has been implicated as a neurotransmitter or neuromodulator.[2] The effects of CCK on pancreatic secretions, gut motility, and satiety have been studied intensively.[3,4] These and other actions are mediated by at least two CCK receptor subtypes termed CCK-A and CCK-B.[5] The former receptor is found primarily in tissue types such as pancreas, gall bladder, and colon, although isolated regions have been localized in the central nervous system (CNS).[5,6] The CCK-A receptors in the pancreas have been shown to be linked to phosphatidylinositol turnover.[7] The primary CCK receptor subtype in the CNS is CCK-B,[8] which has

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