Dopaminergic Receptor Binding ([^{3}H]Spiperone). The assay was carried out in the striatum of the calf brain according to the method described previously.[23]

Muscarinic Cholinergic Receptor Binding ([^{3}H]QNB). This assay was also carried out on male Olac rat brain by the method previously described.[4]

Acknowledgment. We thank Dave Rackham, Sarah Morgan, Juliet Brown, and Julie Smith for the spectroscopic data and Nick Moore, Francesca Risius, Susan Wedley, Linda Horsman, and Jeremy Findlay for pharmacological assays. Elemental analyses were carried out at the Lilly Microanalytical Lab, Indianapolis, IN.

Registry No. **5**, 83448-96-8; **6**, 83448-87-7; **7**, 83448-93-5; **8**, 83448-94-6; **9**, 83448-95-7; **10**, 83448-90-2; **11**, 121845-20-3; **12**, 83448-97-9; **13**, 83448-98-0; **14**, 121845-21-4; **15**, 121845-22-5; **16**, 121845-23-6; **17**, 121865-29-0; **18**, 121845-24-7; **19**, 121845-25-8; **20**, 121845-26-9; **20**·maleate, 121845-27-0; **21**, 83449-02-9; **22**, 83448-99-1; **23**, 83448-88-8; **24**, 83449-00-7; **25**, 83449-01-8; **26**, 83448-91-3; **27**, 121845-28-1; **28**, 83449-03-0; **29**, 83449-04-1; **30**, 121845-29-2; **31**, 121845-30-5; **32**, 83449-08-5; **33**, 83449-05-2; **34**, 83448-89-9; **35**, 83449-06-3; **36**, 83449-07-4; **37**, 83448-92-4; **38**, 121845-31-6; **39**, 83449-09-6; **40**, 83449-10-9; **41**, 121845-32-7; **42**, 121845-33-8; **43**, 121845-34-9; **44**, 121845-35-0; **45**, 121845-36-1; **46**, 121845-37-2; **47**, 121845-38-3; 5-amino-4-cyano-2-methyl-2*H*-1,2,3-triazole, 28539-27-7; 5-amino-4-cyano-2-ethyl-2*H*-1,2,3-triazole, 121845-39-4; *o*-fluoronitrobenzene, 1493-27-2; 2,5-dichloronitrobenzene, 89-61-2; 2,5-difluoronitrobenzene, 364-74-9; 2,5-dibromonitrobenzene, 3460-18-2; 2-fluoro-5-(trifluoromethyl)nitrobenzene, 367-86-2; 2,4,5-trifluoronitrobenzene, 89-69-0; 5-amino-4-carbethoxy-1-cyclohexyl-1*H*-imidazole, 37842-61-8; 5-amino-4-cabethoxy-1-ethyl-1*H*-imidazole, 121845-40-7; 5-amino-4-carbethoxy-1-methyl-1*H*-imidazole, 54147-04-5; 4-amino-5-cyano-1-methyl-1*H*-imidazole, 40637-80-7; 4-amino-5-cyano-1,2-dimethyl-1*H*-imidazole, 58192-81-7; 5-amino-4-cyano-1-methyl-1*H*-1,2,3-triazole, 23085-12-3; 1-methylpiperazine, 109-01-3; ethyl 5-[(2-amino-4-fluorophenyl)amino]-1-methyl-1*H*-imidazole-4-carboxylate, 121845-41-8; 6*H*-pyrido[2,3-*b*][1,5]benzodiazepin-5(11*H*)-one, 10189-78-3; 8,9-dichloro-6*H*-pyrido[2,3-*b*][1,5]benzodiazepin-5(11*H*)-one, 10321-11-6.

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Long-Acting Dihydropyridine Calcium Antagonists. 3. Synthesis and Structure–Activity Relationships for a Series of 2-[(Heterocyclylmethoxy)methyl] Derivatives

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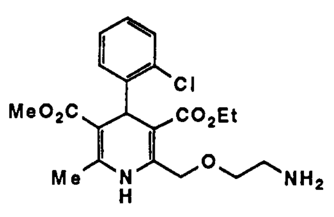
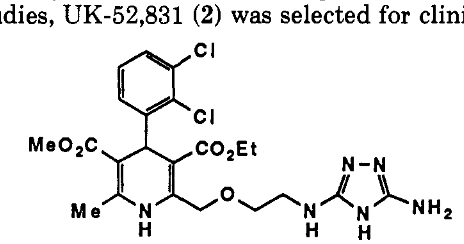
The preparation of 1,4-dihydropyridines containing (heterocyclylmethoxy)methyl groups in the 2-position is described and the structural identification of certain of the compounds using ^{1}H NMR spectroscopic methods is reported. The calcium antagonist activity of the compounds on rat aorta is listed and is compared with the negative inotropic potency as determined by using a Langendorff-perfused guinea pig heart model. Several compounds are more potent than nifedipine and show greater selectivity for the vasculature over the heart. One compound, 2-[[(2-amino-4-hydroxypyrimidin-6-yl)methoxy]methyl]-4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (**27**, UK-56,593), was identified as a potent ($IC_{50} = 1.6 \times 10^{-9}$ M), tissue-selective calcium antagonist which proved to have a markedly longer duration of action (>4.5 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 bearing basic side chains at the 2-position of the DHP ring. Our aim in this study was to modify the physicochemical properties of the DHP system so as to improve bioavailability and duration of action over the agents available at that time. Amlodipine (1) was identified as fulfilling our objectives



1,amlodipine

and is currently in late-stage clinical evaluation for the once-daily treatment of angina and hypertension.[2–4] In a subsequent publication,[5] we reported that a basic center in the amlodipine series was not an absolute requirement for good calcium antagonist activity and that the amino group could be substituted by a number of five- or six-membered heterocycles. The excellent calcium antagonist potency and selectivity for the vasculature over cardiac tissue seen for these compounds was thought to arise from enhanced hydrogen-bonding interactions between the polar heterocycles and the DHP receptor. As a result of these studies, UK-52,831 (2) was selected for clinical develop-



2

ment. In order to extend these SARs and to identify additional structural features compatible with potent

† Department of Chemistry.
‡ Department of Biology.

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Table I. Data for Compounds Used in the Study

no.	route	mp, °C	recrystn solvent[a]	formula	% yield	Ca pIC_{50}[b]	neg inotropy pIC_{25}[c]	selectivity index[d]
16	A	118–120	EtOAc	$C_{22}H_{23}Cl_2N_3O_6$	26	9.4	7.6[e]	63
17	B	140–144	Et_2O	$C_{22}H_{23}Cl_2N_3O_5S$	48	9.0	7.4	40
18	C	194	EtOAc	$C_{21}H_{22}Cl_2N_4O_5S$	24	8.6	7.1	32
19	D	112–114	Et_2O	$C_{20}H_{21}Cl_2N_5O_5$	81	6.5	NT	–
20	D	62–64	Et_2O	$C_{21}H_{23}Cl_2N_5O_5$	23	9.0	7.2	63
21	D	141–142	Et_2O	$C_{21}H_{23}Cl_2N_5O_5$	23	8.5	7.2	20
22	E	225–230	EtOAc	$C_{24}H_{25}Cl_2N_3O_6$	52	8.6	6.9	50
23	E	190–193	Et_2O/EtOAc	$C_{24}H_{25}Cl_2N_3O_7$	45	8.3	6.2	126
24	E	200–204	EtOAc	$C_{27}H_{31}Cl_2N_3O_6$	18	7.5	<6.0	>32
25	E	169–170	Et_2O	$C_{28}H_{26}Cl_2N_4O_6$	51	8.7	7.1	40
26	E	130–135	Et_2O	$C_{28}H_{32}Cl_2N_4O_7$	15	8.4	6.9	32
27	E	222–225	EtOAc/EtOH	$C_{23}H_{24}Cl_2N_4O_6$	63	8.8	6.7	126
28	E	230–234 dec	Et_2O	$C_{24}H_{25}Cl_2N_3O_6S$	48	8.7	<6.0	>50
29	E	219–222	EtOAc	$C_{25}H_{28}Cl_2N_4O_6$	26	8.8	6.3	316
30	E	147–150	Et_2O	$C_{28}H_{32}Cl_2N_4O_6$	34	8.1	6.9	16
31	F	175–177	EtOAc	$C_{29}H_{29}Cl_2N_5O_6$	28	9.1	6.9	200
32	F	140–147	Et_2O	$C_{29}H_{29}Cl_2N_5O_6$	14	7.8	7.4	2.5
33	G	202–205	EtOAc	$C_{24}H_{26}Cl_2N_4O_6$	43	9.2	7.1	126
34	G	144–147	DIPE	$C_{26}H_{32}Cl_2N_4O_6$	24	7.8	6.6	16
35	G	125–130	Et_2O	$C_{25}H_{28}Cl_2N_4O_7$	13	8.5	7.0	32
36	G	135–138	EtOAc	$C_{27}H_{33}Cl_2N_5O_6$	4	7.9	7.2	5
37	G	122–125	Et_2O	$C_{29}H_{29}Cl_2N_5O_6$	17	9.2	7.5	50
38	H	160–162	Et_2O	$C_{24}H_{26}Cl_2N_4O_6$	8	9.0	6.2	631
nifedipine						8.4 ± 0.01	7.5 ± 0.26	8

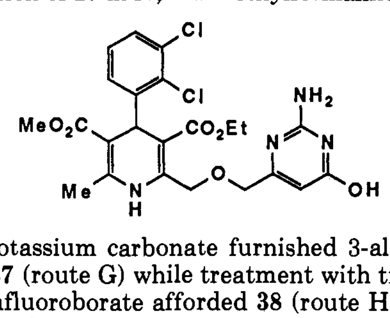
[a] DIPE, diisopropyl ether. [b] Negative logarithm of the molar concentration required to block Ca^{2+}-induced contraction of K^+-depolarised rat aorta by 50%. Nifedipine was used as the standard compound. [c] Negative logarithm of the molar concentration required to depress contraction in the Langendorff-perfused guinea pig heart by 25%. Nifedipine was used as the standard compound. [d] Selectivity index = Ca IC_{50}/neg inotropy IC_{25}. [e] $n = 2$ (±0.3).

calcium antagonist activity, we have now prepared a series of 2-(heterocyclylmethoxy)methyl DHPs for evaluation as calcium antagonists.

Chemistry

The synthesis of the starting materials **8**, **9**, **11**, and **12** required for the preparation of compounds **16–38** (Table I) was achieved with the series of transformations indicated in Scheme I. Knoevenagel condensation of methyl 3-aminocrotonate (**3**) with β-keto ester **4** followed by treatment with 2,3-dichlorobenzaldehyde (**5**) and base-catalyzed hydrolysis afforded **6**. Treatment of **6** with 1,1′-carbonyldiimidazole (CDI) gave imidazolide **7**, which was reacted in situ with acetylhydrazine, thiosemicarbazide, and ammonia to give **8**, **9**, and **10**, respectively. Compound **11** was obtained in good yield from **10** by dehydration with trifluoroacetic anhydride in pyridine. Reaction of **7** with Meldrum's acid/piperidine followed by heating in ethanol gave β-keto ester **12**.[6] An alternative route to **12**, which proved more amenable to large-scale preparation, involves the Hantzsch synthesis of **14** from β-keto ester **13**, **3**, and **5**. Metalation of the terminal acetylene in **14** with *n*-butyllithium proceeded smoothly and quenching with carbon dioxide followed by esterification[7] afforded **15**. Mild, two-step hydration[8] of **15** resulted in a good yield of **12**.

The compounds **16–38** listed in Table I were obtained as described in Scheme II. Thus, dehydration of **8** with P_2O_5 yielded **16** (route A) while with Lawesson's reagent[9] **17** was obtained (route B). Dehydration of **9** with $POCl_3$ gave 2-amino-1,3,4-thiadiazole **18** (route C). Unsubstituted tetrazole **19** was prepared by heating **11** with tri-*n*-butyltin azide followed by acid-catalyzed removal of the tri-*n*-butyltin group. Reaction of **19** with iodomethane in the presence of potassium carbonate gave a 1:1 mixture of the 1-methyl (**20**) and 2-methyl (**21**) substituted products (route D); the formation of both *N*-methyl isomers (**20** and **21**) is in accord with literature precedent.[10] The structures of **20** and **21** were assigned from their ^1H NMR spectra since it has been demonstrated[11] for a series of *N*-methyltetrazoles that the chemical shift of the methyl protons occurs at significantly higher field (0.09–0.34 ppm) in the 1-isomer compared to the 2-isomer. Thus, the chemical shift of the NMe group in **20** is 4.08 ppm while in **21** it is 4.39 ppm. The pyrimidin-6-yl derivatives (**22–38**) were prepared by routes E–H. Reaction of **12** with a suitable amidine or guanidine resulted in **22–30** (route E) while nucleophilic displacement of the methylthio group in **28** by 2-(aminomethyl)pyridine and 4-(aminomethyl)pyridine afforded **31** and **32**, respectively (route F). Alkylation of **27** in *N,N*-dimethylformamide in the presence



27

of potassium carbonate furnished 3-alkylated products **33–37** (route G) while treatment with trimethyloxonium tetrafluoroborate afforded **38** (route H).

Alkylation of **27** can in principle occur at either ring nitrogen atom or the exocyclic oxygen or nitrogen atom. Since compounds **31** and **37** are not identical and reaction of **12** with (2-pyridylmethyl)guanidine affords a mixture containing **31** and **37**, it is apparent that alkylation must

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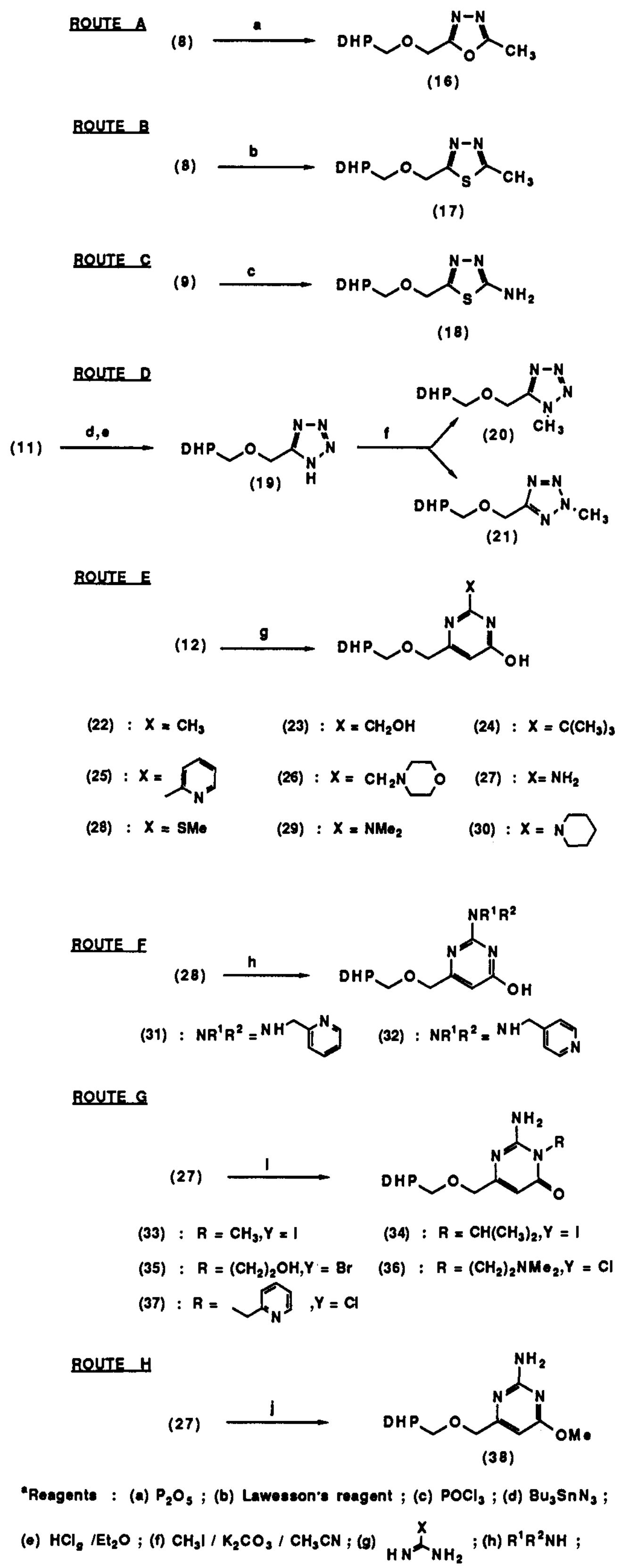
Scheme I[a]



[a]Reagents: (a) P_2O_5; (b) Lawesson's reagent; (c) $POCl_3$; (d) Bu_3SnN_3; (e) HCl_g/Et_2O; (f) CH_3I/K_2CO_3/CH_3CN; (g) $HN{=}C(X)NH_2$; (h) R^1R^2NH; (i) R-Y/K_2CO_3/DMF; (j) $Me_3O^+ BF_4^-$

have occurred on one of the pyrimidine ring nitrogen atoms. This conclusion is in agreement with the reported regiochemistry of methylation of isocytosine[12] and 6-methylisocytosine.[13] Although we were confident that 33–37 arose from alkylation of 27 on N3, NOE experiments on 33 and 37 confirmed our assignment. Thus, for both 33 and 37 significant NOE enhancements were seen between the 2-amino group and the protons on the ring nitrogen substituent whereas no enhancements were seen between methylene (a) and the ring nitrogen substituent protons (see Table II).

Results and Discussion

In vitro calcium antagonist activity was assessed as the inhibition of calcium-induced contraction of potassium-depolarized rat aorta. Negative inotropy was determined in vitro with a Langendorff-perfused guinea pig heart. The ratio of these two activities was used as an index of selectivity for vascular smooth muscle over cardiac muscle. From the data in Table I, it is apparent that in vitro calcium antagonist activity similar to that of nifedipine was achieved for many of these 2-(heterocyclylmethoxy)methyl DHP derivatives. For example, oxadiazole **16** is 10-fold more potent than nifedipine and is 63-fold selective for vascular tissue over the heart, while 1-methyltetrazole **20**, which has a significant potency and selectivity advantage over its 2-methyl isomer **21**, is only slightly less active and of equivalent selectivity. Interestingly, unsubstituted tetrazole **19** is almost completely inactive, indicating that the presence of an acidic proton is not tolerated by the DHP receptor. Many of the pyrimidine derivatives (**22**–**38**) are also potent and selective calcium antagonists. Thus, **31**, **33**, and **37** are all at least 5-fold more potent than nifedipine while **23**, **27**, **29**, **31**, and **38** exhibit tissue selectivities in favor of the vasculature in excess of 100-fold. The 2-substituent on the pyrimidine ring can be alkyl (**22**), amino (**27**) or 2-pyridyl (**25**) without markedly affecting the activity on the vasculature. In addition, replacement of both protons of the amino group in **27** by methyl substituents as in **29** does not lead to any substantial loss of activity. However, incorporation of bulky substituents in the 2-position of the pyrimidine ring does lead to less potent compounds (cf. **22** with **24** and **29** with **30**). The reasons why 4-pyridyl derivative **32** is relatively weak and nonselective are not clear, particularly since 2-pyridyl isomer **31** is one of the most potent and selective compounds. In certain cases the presence of a 3-substituent in the pyrimidine ring is also compatible with good calcium antagonist activity although the introduction of bulk close to the pyrimidine ring as in **34** or the presence of a basic center in the 3-substituent as in **36** both lead to decreased activity and selectivity. The excellent in vitro profile of **38** demonstrates that the potential for keto–enol tautomerism in the 4-hydroxypyrimidine ring is not a requirement for good calcium antagonist activity.

These results confirm that the presence of considerable bulk in the 2-position of the DHP is compatible with calcium antagonist activity. Both five- and six-membered ring 2-(heterocyclylmethoxy)methyl DHPs are potent calcium antagonists which have good vascular selectivity. That both five- and six-membered heterocyclic rings bearing a variety of functionality can be accommodated

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Scheme II[a]

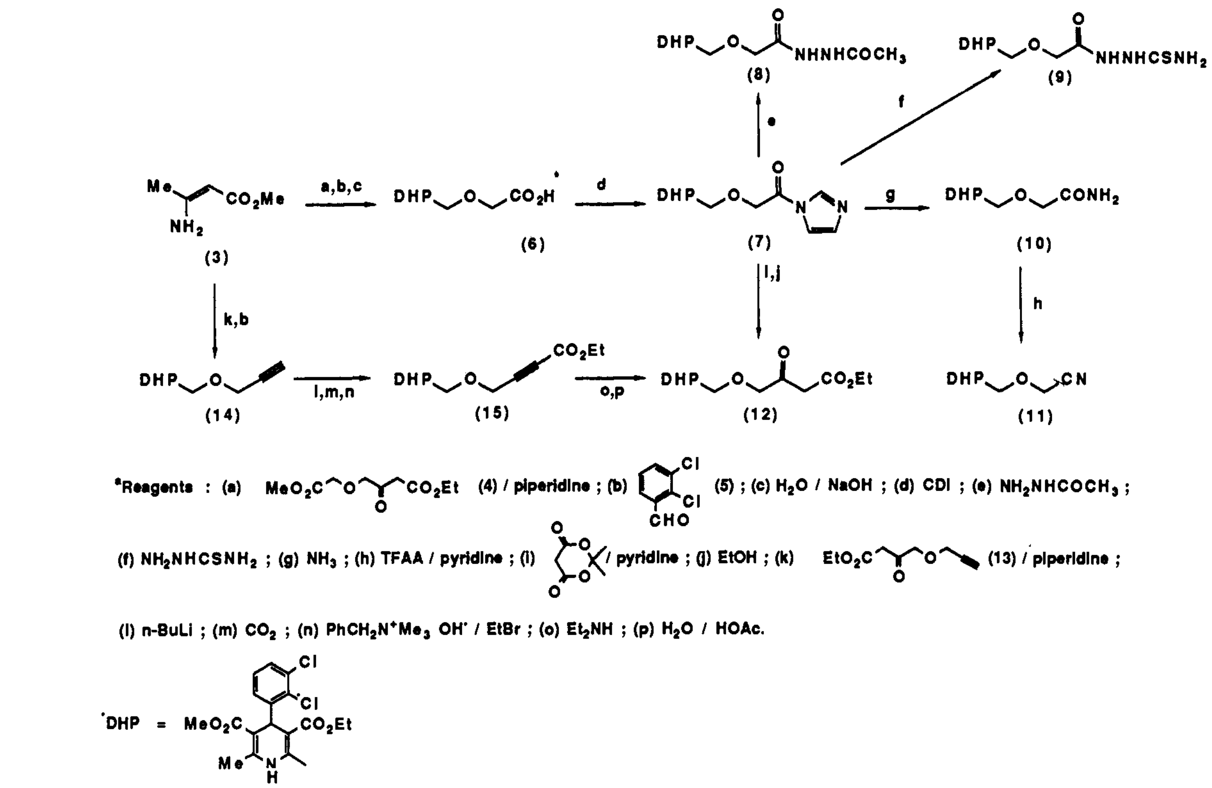
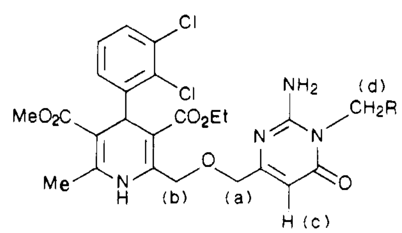
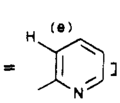


Table II. NOE Percentage Enhancements Observed for 33 and 37



compd	irradiated multiplet: proton assignment	irradiated multiplet: chem shift, δ	NOE observations: proton assignment	NOE observations: chem shift, δ	NOE observations: % change in signal
33 [R = H]	NCH_3 (d)	3.44	NH_2	5.38	1.9
	CH_2 (a)	4.30	CH_2 (b)	4.80	3.3
			H (c)	6.00	10.4
	CH_2 (b)	4.80	CH_2 (a)	4.30	4.7
			H (c)	6.00	3.1
	NH_2	5.38	NCH_3 (d)	3.44	4.3
37 [R = ]	CH_2 (a)	4.28	CH_2 (b)	4.80	3.5
			H (c)	5.97	12.5
	CH_2 (b)	4.80	CH_2 (a)	4.28	4.4
			H (c)	5.97	4.2
	NCH_2 (d)	5.26	H (e)	7.69	9.4
	NH_2	6.73	NCH_2 (d)	5.26	1.8

into the DHP active site suggests that, although the receptor has strict structural requirements for the DHP ring, it will tolerate considerable bulk in the substituents on at least one side of the DHP ring. In addition, the good in vitro profile of oxadiazole **16** and tetrazoles **20** and **21** indicate that the presence of groups on the 2-position capable of being involved in hydrogen-bonding interactions with the DHP receptor is not an absolute requirement for potent, vascular selective calcium antagonist activity.

Compounds **17**, **18**, **20–22**, **25**, and **27** were selected for in vivo evaluation in instrumented, anesthetized dogs. The compounds were administered intravenously and their calcium antagonist potency and duration of action were determined from the effects on coronary blood flow. Compounds **17**, **18**, and **20–22** showed maximum or near-maximum falls in coronary vascular resistance (CVR) at 150 μg kg^{-1} while **27** was more potent and **25** was only slightly weaker (see Table III). However, only compound **27** had a markedly longer duration of action than nifedipine, showing a significant reduction of CVR even 4.5 h after dosing.

Compound **27** (UK-56,593) was evaluated further in the anesthetized dog. In Figure 1, the results of a cumulative dose study (10–40 μg/kg^{-1}) are depicted. Compound **27** produced dose-related falls in both CVR and SVR (systemic vascular resistance) and an increase in dP/dt_{max}. Notably, blood pressure was unaffected over the dose-range studied. The ED_{50} for coronary vasodilation determined

Table III. Coronary Vasodilator Activity in Anesthetized Dogs following a 150 $\mu g\ kg^{-1}$ Intravenous Dose

compd	% decrease in CVR	duration of action:[a] half-life, min
17	85	30
18	61	45
20	61	15
21	78	20
22	79	65
25	38	10
27[b]	82	>270
nifedipine	77	36

[a] Time taken for 50% recovery of CVR. [b] Dose of 45 $\mu g\ kg^{-1}$.

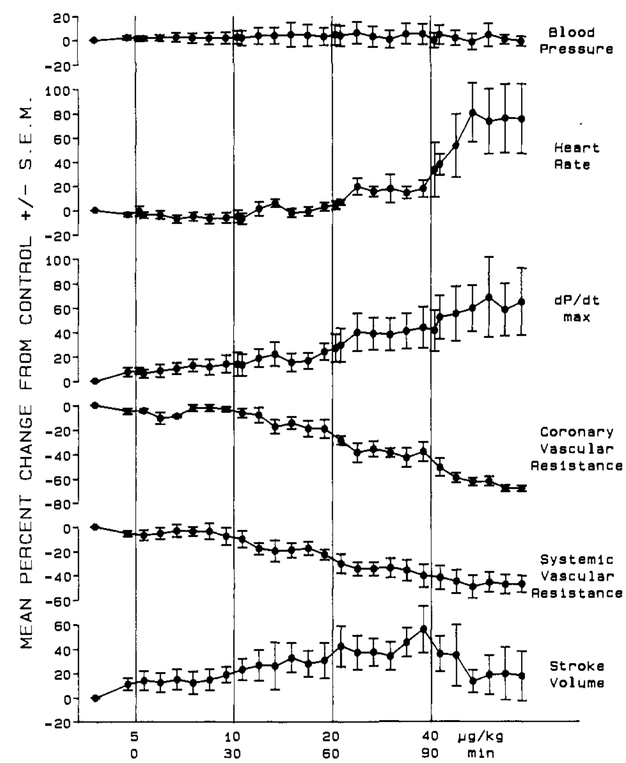


Figure 1. Hemodynamic effects of **27** in anesthetized dogs (n = 4) (±SEM).

from the data in Figure 1 is 35 $\mu g\ kg^{-1}$; this may well underestimate the potency of **27** because of its markedly slow onset of action (approximately 2 h to peak effect; the onset of action was determined in a preliminary experiment by measuring the time course of the reduction in CVR caused by the administration of a single dose of 45 $\mu g\ kg^{-1}$ of **27** to an anesthetized dog) and the relatively short time courses between doses (30 min).

In conclusion, we have demonstrated that the 2-position of the DHP ring may be substituted by an alkoxyalkyl chain carrying a range of heterocycles to give potent, highly tissue-selective calcium antagonists. This work led to the identification of **27**, which is a more potent and vascular selective calcium antagonist than nifedipine in vitro and in vivo and which has a markedly longer duration of action in the anesthetized dog.

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 with the hydrogen-clearance technique using platinum electrodes positioned in the coronary sinus and femoral artery as described in the literature.[14] Cardiac output was determined by the thermodilution method. All other parameters were derived from these measurements. Compound was administered in either ascending doses at fixed time intervals (for dose–response studies) or as one single dose to assess duration of action.

Chemistry. All melting points are uncorrected. The structures of all the compounds used in the study were determined by ^1H NMR and microanalysis. Microanalytical data was not obtained for intermediates **4**, **8**, **9**, and **12–15**. 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 a solvent.

Ethyl 4-[(Methoxycarbonyl)methoxy]acetoacetate (4). 2-[(Methoxycarbonyl)methoxy]acetyl chloride[15] (216.6 g, 1.31 mol) was added over 45 min to a stirred solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (173.9 g, 1.21 mol) and pyridine (189.6 g, 2.4 mol) in CH_2Cl_2 (1 L) while the temperature was kept below 5 °C. The mixture was stirred at 5 °C for 1.5 h, washed with 2 M HCl and water, dried over $MgSO_4$, and evaporated. The resulting brown oil was dissolved in EtOH (300 mL) and the solution was heated under reflux for 2.5 h and evaporated. The residual oil was distilled to give the title compound **4**: yield 32.5 g (12%); bp 138–140 °C (1 Torr); ^1H NMR ($CDCl_3$) δ = 4.27 (2 H, s), 4.20 (2 H, q, J = 7 Hz), 4.16 (2 H, s), 3.75 (3 H, s), 3.54 (2 H, s), 1.29 (3 H, t, J = 7 Hz).

2-[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]acetic Acid (6). A solution of **3** (52.9 g, 0.46 mol), **4** (100 g, 0.46 mol), and **5** (80.2 g, 0.46 mol) in MeOH (300 mL) was heated under reflux for 16 h and evaporated. The residue was treated with 10% aqueous NaOH solution (350 mL) and the mixture was heated under reflux for 1.5 h, washed three times with CH_2Cl_2, acidified with concentrated HCl, and extracted into CH_2Cl_2. The organic extracts were washed with water, dried over $MgSO_4$, and evaporated. Recrystallization of the residue from EtOAc gave title compound **6**: yield 23.1 g (11%); mp 160–162 °C. Anal. ($C_{20}H_{21}Cl_2NO_7$) C, H, N.

1-Acetyl-2-[[[4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]acetyl]hydrazine (8). Carbonyldiimidazole (1.15 g, 7.1 mmol) was added to a solution of **6** (3.00 g, 6.55 mmol) in THF (80 mL) and the mixture stirred for 2 h, treated with acetylhydrazine (2.00 g, 27 mmol), stirred for 5 h, and evaporated. The residue was partitioned between EtOAc and water and the organic layer was washed with water, dried over $MgSO_4$, and evaporated to give title compound **8**: 3.1 g (92%); oil; ^1H NMR ($CDCl_3$) δ = 6.90–7.40 (4 H, m), 5.46 (1 H, s), 4.80 (2 H, s), 4.23 (2 H, s), 4.06 (2 H, q, J = 7 Hz), 3.62 (3 H, s), 2.36 (3 H, s), 2.09 (3 H, s), 1.24 (3 H, t, J = 7 Hz).

1-[[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]acetyl]thiosemicarbazide (9). Stirring a solution of **6** (3.20 g, 7.0 mmol) and carbonyldiimidazole (1.25 g, 7.7 mmol) in THF (100 mL) for 2 h and then adding thiosemicarbazide (1.80 g, 20 mmol) gave title compound **9** by a method identical with that described for the previous example: yield 3.10 g (83%); mp 95–100 °C; ^1H NMR ($CDCl_3$) δ = 7.5–8.5 (4 H, exchangeable with D_2O), 6.90–7.45 (4 H, s), 5.44 (1 H, s), 4.83 (2 H, s), 4.33 (2 H, s), 4.15 (2 H, q, J = 7 Hz), 3.60 (3 H, s), 2.33 (3 H, s), 1.22 (3 H, t, J = 7 Hz).

2-[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]acetamide (10). Carbonyldiimidazole (3.6 g, 22 mmol) was added to a solution of **6** (9.2 g, 20 mmol) in THF (200 mL) and the mixture was stirred for 2 h. Gaseous ammonia was bubbled rapidly through the solution for 30 min and the mixture was evaporated. Workup as described above for compound **8** afforded an oil which was crystallized from Et_2O/hexane to give title compound **10**: yield 8.0 g (87%); mp 55–60 °C. Anal. ($C_{20}H_{22}Cl_2N_2O_6$) C, H, N.

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2-[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]acetonitrile (11). A solution of trifluoroacetic anhydride (4.20 g, 21 mmol) in dioxane (20 mL) was added over 10 min to a stirred solution of **10** (6.8 g, 15 mmol) and pyridine (3.6 g, 46 mmol) in dioxane (160 mL). The mixture was stirred for 16 h, diluted with water, and extracted into EtOAc. The organic extract was washed successively with 1 M HCl, 10% aqueous Na_2CO_3 solution and water, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica using CH_2Cl_2 plus 0–50% EtOAc as eluant. Appropriate fractions were combined and evaporated, and the resulting oil was crystallized from Et_2O to give title compound 11: yield 4.75 g (72%); mp 117–118 °C. Anal. ($C_{20}H_{20}Cl_2N_2O_5$) C, H, N.

Ethyl 4-[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]acetoacetate (12). **Method A from Acid 6.** Carbonyldiimidazole (5.20 g, 32 mmol) was added to a solution of **6** (14.00 g, 30.5 mmol) in CH_2Cl_2 (200 mL), and the mixture was stirred for 2 h and then added to a solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (4.56 g, 32 mmol) and pyridine (2.40 g, 30 mmol) in CH_2Cl_2 (200 mL). The mixture was stirred for 2.5 h, washed successively with water, 2.5 M HCl, and saturated brine, dried over $MgSO_4$, and evaporated. The residual oil was dissolved in EtOH (200 mL) and the solution was heated under reflux for 2.75 h and evaporated. The residue was crystallized from Et_2O to give the title compound **2**: yield 9.0 g (60%); mp 99–102 °C; ^1H NMR ($CDCl_3$) δ = 7.55–7.70 (1 H, br s), 6.9–7.4 (3 H, m), 5.48 (1 H, s), 4.82 (2 H, s), 4.41 (2 H, s), 4.29 (2 H, q, J = 7 Hz), 4.10 (2 H, q, J = 7 Hz), 3.66 (3 H, s), 3.55 (2 H, s), 2.47 (3 H, s), 1.34 (3 H, t, J = 7 Hz), 1.20 (3 H, t, J = 7 Hz).

Method B from Acetylenic Ester 15. Diethylamine (477 g, 6.52 mol) was added to a solution of **15** (2.22 kg, 4.34 mol) in THF (11.1 L) and the mixture was stirred for 1.5 h and evaporated. The residue was triturated with methanol to give a solid which was stirred in a mixture of acetic acid (7.5 L) and water (3.75 L) for 6 h, diluted with water, and extracted into CH_2Cl_2. The organic extract was washed successively with water, saturated aqueous $NaHCO_3$ solution, and water, dried over $MgSO_4$, and evaporated. The residual solid was recrystallized from Et_2O to give title compound **15**, whose spectral data was identical with those of the material obtained above.

Ethyl 4-(Prop-2-ynyloxy)acetoacetate (13). A solution of ethyl 4-chloroacetoacetate (294 g, 1.79 mol) in THF (200 mL) was added over 3 h to a stirred, ice-cooled suspension of NaH (150 g, 5.0 mol; 80% dispersion in oil) in THF (500 mL) and the mixture was treated over 2 h with ice-cooling with a solution of prop-2-ynol (100 g, 1.79 mol) in THF (200 mL). The mixture was stirred for 16 h and poured into 2 M HCl (900 mL), and the layers were separated. The organic layer was evaporated and the resulting red oil was separated from the mineral oil. This red oil was dissolved in CH_2Cl_2 and the solution was washed with water, dried over Na_2SO_4, and evaporated to give title compound **13**: yield 313 g (95%); oil; ^1H NMR ($CDCl_3$) δ = 4.1–4.4 (6 H, m), 3.56 (2 H, s), 2.48 (1 H, t, J = 2.5 Hz), 1.27 (3 H, t, J = 7 Hz).

1-[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]-2-propyne (14). Piperidine (2.4 g, 28 mmol) was added dropwise over 10 min to a mixture of **5** (60 g, 0.34 mol) and **13** (63 g, 0.34 mol) in 2-propanol (600 mL). The mixture was stirred for 24 h, treated with **3** (39 g, 0.34 mol), stirred for 4 days, and evaporated. The residue was crystallized from MeOH to give title compound 14: yield 29.5 g (21%); mp 104–105 °C; ^1H NMR ($CDCl_3$) δ = 7.35 (1 H, dd, J = 8 and 2 Hz), 7.28 (1 H, dd, J = 8 and 2 Hz), 7.09 (1 H, t, 3 = 8 Hz), 7.02 (1 H, br s), 5.52 (1 H, s), 4.81 (2 H, AB system), 4.33 (2 H, d, J = 2 Hz), 4.04 (2 H, q, J = 7 Hz), 3.60 (3 H, s), 2.57 (1 H, t, J = 2 Hz), 2.38 (3 H, s), 1.21 (3 H, t, J = 8 Hz).

Ethyl 4-[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]-2-butynoate (15). A 1.6 M solution of n-BuLi (360 g, 5.62 mol) in hexane was added over 40 min to a stirred, cooled (−65 °C) solution of **14** (1.10 kg, 2.51 mol) in THF (11 L) and the mixture was stirred at −65 °C for 2.5 h. Carbon dioxide was bubbled through the mixture for 2 h while it was allowed to warm to 0 °C. The layers were separated, and the aqueous layer was washed with Et_2O, acidified with concentrated HCl, and extracted into CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and evaporated. The resulting solid was dissolved in DMSO (800 mL) and the solution was treated with a solution of Triton B (304 g, 1.82 mol) in DMSO (900 mL). After 10 min EtBr (218 g, 2.0 mol) was added and the mixture was stirred for 48 h, diluted with water, and extracted into EtOAc. The organic extracts were washed with saturated brine, dried over $MgSO_4$, and evaporated. The residual solid was recrystallized from MeOH to give title compound **15**: yield 780 g (82%); mp 123–125 °C; ^1H NMR ($CDCl_3$) δ = 7.14–7.38 (2 H, m), 7.09 (1 H, t, J = 8 Hz), 6.92 (1 H, br s), 5.51 (1 H, s), 4.70–4.97 (4 H, m), 4.43 (2 H, s), 4.25 (2 H, q, J = 7 Hz), 4.06 (2 H, q, J = 7 Hz), 3.62 (3 H, s), 2.39 (3 H, s), 1.30 (3 H, t, J = 7 Hz), 1.18 (3 H, t, J = 7 Hz).

2-[[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]methyl]-5-methyl-1,3,4-oxadiazole (16). A mixture of **8** (1.33 g, 2.58 mmol) and P_2O_5 (1.55 g, 10.9 mmol) in $CHCl_3$ (70 mL) was stirred for 72 h, washed with water, dried over $MgSO_4$, and evaporated. The residual oil was crystallized from Et_2O and recrystallized from EtOAc to give the title compound **16**: yield 0.33 g (26%); mp 118–120 °C. Anal. ($C_{22}H_{23}Cl_2N_3O_6$) C, H, N.

2-[[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]methyl]-5-methyl-1,3,4-thiadiazole (17). A mixture of **8** (1.50 g, 2.91 mmol) and Lawesson's reagent (1.18 g, 2.91 mmol) in CH_3CN (50 mL) was stirred for 24 h and evaporated. The residue was chromatographed on silica using CH_2Cl_2 plus 0–1% MeOH as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from Et_2O to give title compound 17: yield 0.82 g (48%); mp 140–144 °C. Anal. ($C_{22}H_{23}Cl_2N_3O_5S$) C, H, N.

5-Amino-2-[[[4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]methyl]-1,3,4-thiadiazole (18). A solution of **9** (1.00 g, 1.88 mmol) in $POCl_3$ (50 mL) was stirred for 7 h and evaporated. The residue was partitioned between water and $CHCl_3$ and the organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica using CH_2Cl_2 plus 0–5% MeOH as eluant. Appropriate factions were combined and evaporated, and the residue was crystallized from EtOAc to give the title compound **18**: yield 0.23 g (24%); mp 194 °C. Anal. ($C_{21}H_{22}Cl_2N_4O_5S$) C, H, N.

5-[[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]methyl]tetrazole (19). A solution of **11** (3.52 g, 8.0 mmol) and tri-n-butyltin azide (3.00 g, 9.0 mmol) in dioxane (100 mL) was heated under reflux for 21.5 h and evaporated. The residue was dissolved in Et_2O (200 mL) and gaseous HCl was passed through the solution for 50 min. The resulting precipitate was collected, washed with Et_2O, and dried to give title compound **19**: yield 3.14 g (81%); mp 112–114 °C. Anal. ($C_{20}H_{21}Cl_2N_5O_5$) C, H, N.

5-[[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]methyl]-1-methyltetrazole (20) **and 5-[[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]methyl]-2-methyltetrazole** (21). A mixture of **19** (0.96 g, 2.0 mmol), CH_3I (0.72 g, 5.0 mmol), and K_2CO_3 (0.69 g, 5.0 mmol) in CH_3CN (40 mL) was heated under reflux for 8 h, filtered, and evaporated. The residue was chromatographed on silica using CH_2Cl_2 plus 0–50% EtOAc as eluant. In each case, appropriate fractions were combined and evaporated, and the residues were crystallized from Et_2O to give title compounds **20** and **21**. **20**: yield 228 mg (23%); mp 62–64 °C. Anal. ($C_{21}H_{23}Cl_2N_5O_5$) C, H, N (more polar isomer). **21**: yield 229 mg (23%); mp 141–142 °C. Anal. ($C_{21}H_{23}Cl_2N_5O_5$) C, H, N (less polar isomer).

General Route to 2-Substituted Pyrimidines (22–30). A solution of **12**, the appropriate amidine or guanidine derivative, and DBN in ethanol was stirred at room temperature or heated under reflux and then evaporated. The residue was dissolved in $CHCl_3$ and the solution was washed successively with 0.1 M HCl, water, and saturated aqueous Na_2CO_3 solution, dried over $MgSO_4$, and evaporated.

6-[[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]-

methyl]-4-hydroxy-2-methylpyrimidine Hydrate (22). A solution of 12 (0.53 g, 1.0 mmol), acetamidine hydrochloride (0.10 g, 1.06 mmol), and DBN (0.25 g, 2.0 mmol) in EtOH (5 mL) was stirred for 18.5 h. Crystallization of the residue from EtOAc gave title compound 22: 0.27 g (52%); mp 225–230 °C. Anal. ($C_{24}H_{25}Cl_2N_3O_6 \cdot H_2O$) C, H, N.

6-[[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]methyl]-4-hydroxy-2-(hydroxymethyl)pyrimidine (23). A solution of 12 (0.53 g, 1.0 mmol), 2-hydroxyacetamidine hydrochloride[16] (0.13 g, 1.0 mmol), and DBN (0.14 g, 1.1 mmol) in EtOH (20 mL) was stirred for 72 h. Crystallization of the residue from EtOAc/Et_2O gave title compound 23: yield 0.24 g (45%); mp 190–193 °C. Anal. ($C_{24}H_{25}Cl_2N_3O_7$) C, H, N.

2-*tert*-Butyl-6-[[[4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]methyl]-4-hydroxypyrimidine (24). A solution of 12 (0.53 g, 1.0 mmol), 2,2-dimethylpropanamidine hydrochloride (0.14 g, 1.0 mmol), and DBN (0.14 g, 1.1 mmol) in EtOH (20 mL) was stirred for 48 h. Crystallization of the residue from EtOAc gave title compound 24: yield 0.10 g (18%); mp 200–204 °C. Anal. ($C_{27}H_{31}Cl_2N_3O_6$) C, H, N.

6-[[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]methyl]-4-hydroxy-2-(2-pyridyl)pyrimidine (25). A solution of 12 (0.53 g, 1.0 mmol), pyridine-2-carboxamidine hydrochloride[17] (0.16 g, 1.0 mmol), and DBN (2.0 mmol) in EtOH (5 mL) was stirred for 24 h. Crystallization of the residue from Et_2O gave title compound 25: yield 0.30 g (51%); mp 169–170 °C. Anal. ($C_{28}H_{26}Cl_2N_4O_6$) C, H, N.

6-[[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]methyl]-4-hydroxy-2-(morpholinomethyl)pyrimidine (26). A solution of 12 (1.58 g, 3.0 mmol), 2-morpholinoacetamidine hydrochloride (prepared as follows: a solution of 2-chloroacetamidine hydrochloride (0.5 g, 3.35 mmol) in morpholine (10 mL) was stirred for 18 h, filtered, and evaporated to give essentially pure product containing traces of morpholine by TLC and ^1H NMR) (1.00 g, 5.6 mmol), and DBN (1.10 g, 8.9 mmol) in EtOH (40 mL) was stirred for 72 h. Crystallization of the residue from Et_2O gave title compound 26: yield 0.25 g (15%); mp 130–135 °C. Anal. ($C_{28}H_{32}Cl_2N_4O_7$) C, H, N.

2-Amino-6-[[[4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]methyl]-4-hydroxypyrimidine (27). A solution of 12 (0.74 g, 1.4 mmol), guanidine hydrochloride (0.14 g, 1.5 mmol), and DBN (0.25 g, 2.0 mmol) in EtOH (30 mL) was heated under reflux for 5.5 h. Crystallization of the residue from EtOAc/EtOH gave the title compound 27: yield 0.46 g (63%); mp 222–225 °C. Anal. ($C_{23}H_{24}Cl_2N_4O_6$) C, H, N.

6-[[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]methyl]-4-hydroxy-2-(methylthio)pyrimidine (28). A solution of 12 (1.00 g, 1.89 mmol), 2-methylisothiouronium sulfate (0.53 g, 1.90 mmol), and DBN (0.35 g, 2.82 mmol) in EtOH (30 mL) was stirred for 5 days. Crystallization of the residue from Et_2O gave title compound 28: yield 0.50 g (48%); mp 230–234 °C dec. Anal. ($C_{24}H_{25}Cl_2N_3O_6S$) C, H, N.

6-[[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]methyl]-2-(dimethylamino)-4-hydroxypyrimidine (29). A solution of 12 (0.82 g, 1.55 mmol), *N,N*-dimethylguanidine hydrochloride (0.20 g, 1.62 mmol), and DBN (0.30 g, 2.4 mmol) in EtOH (40 mL) was stirred for 72 h. Crystallization of the residue from EtOAc gave title compound 29: yield 0.22 g (26%); mp 219–222 °C. Anal. ($C_{25}H_{28}Cl_2N_4O_6$) C, H, N.

6-[[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]methyl]-4-hydroxy-2-piperidinopyrimidine (30). A solution of 12 (0.80 g, 1.5 mmol), piperidinoformamidine hydriodide (0.39 g, 1.5 mmol), and DBN (0.25 g, 2.0 mmol) in EtOH (20 mL) was stirred for 24 h. Crystallization of the residue from Et_2O gave title compound 30: yield 0.30 g (34%); mp 147–150 °C. Anal. ($C_{28}H_{32}Cl_2N_4O_6$) C, H, N.

A solution of 12 (0.53 g, 1.0 mmol), (2-pyridylmethyl)guanidinium sulfate[18] (0.25 g, 1.26 mmol), and DBN (0.20 g, 1.61 mmol) in EtOH (20 mL) was stirred for 72 h. TLC and ^1H NMR analysis of the crude product showed it to be an approximately equimolar mixture of 31 and 37.

6-[[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]methyl]-4-hydroxy-2-(2-pyridylmethyl)pyrimidine (31). A mixture of 28 (0.50 g, 0.92 mmol) and 2-(aminomethyl)pyridine (2.0 g) was heated at 75 °C for 7 h, dissolved in EtOAc, washed with water, dried over $MgSO_4$, and evaporated. the residue was chromatographed on silica using CH_2Cl_2 plus 0–1% MeOH as eluant. Appropriate fractions were combined and evaporated, and the residual solid was recrystallized from EtOAc to give title compound 31: yield 0.17 g (28%); mp 175–177 °C. Anal. ($C_{29}H_{29}Cl_2N_5O_6$) C, H, N.

6-[[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]methyl]-4-hydroxy-2-(4-pyridylmethyl)pyrimidine Hemihydrate (32). A mixture of 28 (0.50 g, 0.92 mmol) and 4-(aminomethyl)pyridine (5.0 mL) was heated at 95 °C for 60 h, dissolved in $CHCl_3$, washed successively with 2 M HCl and 10% aqueous Na_2CO_3 solution, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica using CH_2Cl_2 plus 0–4% MeOH as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from Et_2O to give title compound 32: yield 80 mg (14%); mp 140–147 °C. Anal. ($C_{29}H_{29}Cl_2N_5O_6 \cdot 0.5H_2O$) C, H, N.

General Route to 3-Substituted Pyrimidines 33–37. A mixture of 27 (0.52 g, 1.0 mmol), the appropriate alkylating agent (1.0 mmol), and K_2CO_3 (0.14 g, 1.0 mmol) in DMF (20 mL) was stirred for 4 days (in the synthesis of 34 the mixture was heated at 80 °C for 18 h) and evaporated. The residue was dissolved in CH_2Cl_2 and the solution was washed with water, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica using CH_2Cl_2 plus 0–5% MeOH as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from the appropriate solvent.

2-Amino-6-[[[4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]methyl]-4-hydroxy-3-methylpyrimidine (33). Compound 27 was reacted with CH_3I and the residue was crystallized from EtOAc to give title compound 33: yield 0.23 g (43%); mp 202–205 °C. Anal. ($C_{24}H_{26}Cl_2N_4O_6$) C, H, N.

2-Amino-6-[[[4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]methyl]-4-hydroxy-3-(2-propyl)pyrimidine (34). Compound 27 was reacted with 2-bromopropane and the residue was crystallized from DIPE to give title compound 34: yield 135 mg (24%); mp 144–147 °C. Anal. ($C_{26}H_{32}Cl_2N_4O_6$) C, H, N.

2-Amino-6-[[[4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]methyl]-4-hydroxy-3-(2-hydroxyethyl)pyrimidine (35). Compound 27 was reacted with 2-bromoethanol and the residue was crystallized from Et_2O to give title compound 35: yield 74 mg (13%); mp 125–130 °C. Anal. ($C_{25}H_{28}Cl_2N_4O_7$) H, N; C: calcd, 52.92; found, 52.33.

2-Amino-6-[[[4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]methyl]-3-[2-(dimethylamino)ethyl]-4-hydroxypyrimidine Hydrate (36). Compound 27 was reacted with (2-bromoethyl)dimethylamine and the residue was crystallized from EtOAc to give title compound 36: yield 25 mg (4%); mp 135–138 °C. Anal. ($C_{27}H_{33}Cl_2N_5O_6 \cdot H_2O$) H, N; C: calcd, 52.94; found, 53.53.

2-Amino-6-[[[4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydro-

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pyridin-2-yl]methoxy]methyl]-4-hydroxy-3-(2-pyridylmethyl)pyrimidine (37). Compound **27** was reacted with 2-(chloromethyl)pyridine and the residue was crystallized from Et_2O to give title compound **37**: yield 102 mg (17%); mp 122–125 °C. Anal. ($C_{29}H_{29}Cl_2N_5O_6$) C, H, N.

2-Amino-6-[[[4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]methyl]-4-methoxypyrimidine (38). Trimethyloxonium tetrafluoroborate (0.85 g, 5.7 mmol) was added to a stirred suspension of **27** (1.00 g, 1.9 mmol) in CH_2Cl_2 (100 mL) at 0 °C, and the mixture was stirred at room temperature for 24 h, washed with 5% aqueous Na_2CO_3 solution, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica using CH_2Cl_2 plus 0–1% MeOH as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from Et_2O to give title compound **38**: yield 80 mg (8%); mp 160–162 °C. Anal. ($C_{24}H_{26}Cl_2N_4O_6$) C, H, N.

Acknowledgment. We thank S. M. Denton and S. F. Tickner for their able technical assistance, A. J. Pettman and I. W. Sinclair for the large-scale synthesis of **12**, and A. G. Swanson for performing the NOE experiments on **33** and **37**. We are also grateful to P. J. Wadsworth and his staff for analytical and spectral data.

Substituted 5-Amino-4,5,6,7-Tetrahydroindazoles as Partial Ergoline Structures with Dopaminergic Activity

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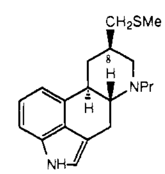
Two series of tetrahydroindazoles were synthesized and evaluated for dopaminergic activity. A number of these partial ergoline analogues possess substituents that could mimic the C-8 substituent of the dopaminergic ergolines. Of the unsymmetrically substituted amine series **7a–k**, the (monopropylamino)tetrahydroindazole **7b** was most interesting as it was found to selectively activate the dopamine (DA) autoreceptor at a dose of 5 mg/kg in rats. The disubstituted amines **7g–k** had significant DA postsynaptic activity as measured by increases of serum corticosterone levels in rats. The 6-substituted-5-aminotetrahydroindazoles **10a–d** were found to possess only marginal dopaminergic activity.

Classical neuroleptics are believed to exert their therapeutic effect by blocking the postsynaptic dopamine (DA) receptor.[1] This same pharmacological property is thought to be responsible for the development of undesirable extrapyramidal side effects and dyskinesias. A selective DA autoreceptor agonist which decreases synthesis and release of DA as well as the firing rate of DA neurons[2] might decrease dopaminergic function sufficiently to have antipsychotic activity without causing extrapyramidal side effects or tardive dyskinesias resulting from direct blockage of postsynaptic DA receptors. In this way, a new class of neuroleptic drugs devoid of extrapyramidal side effects might emerge.

Pergolide (1), a semisynthetic ergot alkaloid, preferentially activates the DA autoreceptor at low doses.[3] Martin and co-workers[4] found that pergolide showed the highest selectivity for the autoreceptor seen for the series of compounds tested. Therefore, we were interested in synthesizing partial pergolide analogues in an effort to increase selectivity for the presynaptic versus postsynaptic D_2 receptor.

A number of workers have synthesized a variety of partial ergoline compounds in order to determine the dopaminergic pharmacophore present in the ergoline skeleton. Originally,[5] it was thought that the phenethylamine portion was responsible for DA activity (Chart I, structure A). However, Nichols[6] noted that a comparison of the



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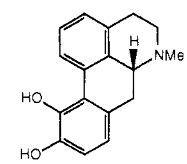

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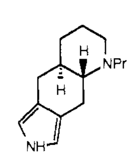

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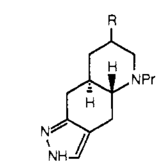
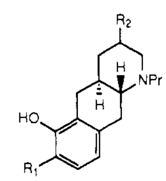
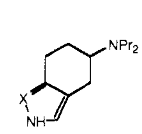


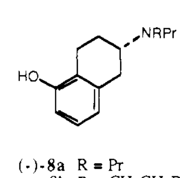
4a R = H
4b R = CH_2SMe



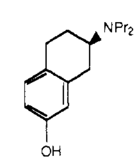
5a R_1 = OH; R_2 = H
5b R_1 = H; R_2 = CH_2SMe
5c R_1 = H; R_2 = $CH_2NHSO_2NEt_2$



6 X = CH
7l X = N



(–)-8a R = Pr
8b R = CH_2CH_2Ph
8c R = CH_2CH_2-2-thienyl
8d R = $(CH_2)_nX$



(+)-9

absolute configuration of the ergoline skeleton with that of the classical DA agonist, apomorphine (2), suggested that it was the rigid pyrroleethylamine moiety which was the DA pharmacophore (Chart I, structure B). Kornfeld[7] had also come to this conclusion and tested this hypothesis by synthesizing a number of partial ergoline structures. The octahydropyrrolo- and pyrazolo[3,4-*g*]quinolines 3 and

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