45 (111 mg, 97%): IR 3450 cm^{-1}; MS, m/z 396, 394 (MNH_4^+), 378, 376 (MH^+).

10β-Bromo-3α,4β,8α-triacetoxy-9α,15:12,13-diepoxytrichothecane (46) was prepared from 45 and excess Ac_2O: yield 84%; $[\alpha]_D$ +27.1° (c 0.56); IR 1745 cm^{-1}; MS, m/z 522, 520.1240 (520.1182) (MNH_4^+), 503, 501 (MH^+).

3α,4β,8α-Triacetoxy-15-hydroxy-12,13-epoxytrichothecene (47). The zinc–silver couple was prepared immediately before use as described previously.[26] To a suspension of the couple (prepared from zinc dust (30 g) and silver acetate (175 mg)) in ether (73 mL) was added **46** (942 mg, 1.87 mmol) in a tetrahydrofuran–ethanol mixture (175 mL, 5:1). The mixture was heated under reflux for 16 h. The solvents were removed in vacuo, and the residue taken up in acetone and filtered through Celite. After concentration, the residue was chromatographed (initial eluant $CHCl_3$; final eluant 2% MeOH in $CHCl_3$) to give the alcohol **47** (155 mg, 20%): $[\alpha]_D$ +30.2° (c 0.44); IR 3480, 1735 cm^{-1}; MS, m/z 442.2124 (442.2077) (MNH_4^+), 425 (MH^+). Also obtained was 4β,8α-diacetoxy-3α,15-dihydroxy-12,13-epoxytrichothec-9-ene (**48**) (151 mg, 18%): $[\alpha]_D$ +17.4° (c 0.41); IR 3500, 1730 cm^{-1}; MS, m/z 400.1992 (400.1971) (MNH_4^+).

Cytotoxicity Assay. Cultures of mouse lymphoma cells (L5178Y) were prepared from frozen stocks derived from an original culture supplied by the Central Toxicology Laboratory, ICI (Alderley Edge). Eagle's Minimum Essential Medium supplemented with 10% or 3% horse serum (10:90 HS–EMEM, 3:97 HS–EMEM) and containing sodium pyruvate (200 μg/mL) was used for routine subculture and cytotoxicity experiments, respectively. Cells were cultured in suspension in 1-oz polystyrene Universal bottles (20 mL per bottle) at 37 °C with intermittent agitation. Cells selected for use in cytotoxicity experiments were subcultured 24 h previously to ensure that immediately prior to use in an experiment the cells were in log phase growth and at a final cell density not exceeding 5×10^5 cells/mL. All media contained penicillin (100 units/mL), streptomycin (100 μg/mL), and amphotericin B (2.5 μg/mL).

Stock solutions of the compounds were made up in DMSO at initial concentrations of 1×10^{-2} g/mL. Tenfold serial dilutions were then made in DMSO to achieve concentrations down to 1×10^{-7} g/mL. These solutions (100 μL) were then diluted 200-fold with 10:90 HS–EMEM (20 mL) to achieve final concentrations in the culture media of (5×10^{-5})–(5×10^{-10}) g/mL. L5178Y cells in log-phase growth were seeded at 2×10^5 cells per 20 mL of culture medium containing the test compound or solvent control and grown up in suspension culture for 3 days. At the end of the growth period, final cell numbers were determined by plating efficiency tested on washed cells from each culture. The cells were suspended in 5 mL of 3:97 HS–EMEM (phenol red free), a further 1 in 10 dilution of the cell suspension was made in the same medium, and the crude cell concentration was determined from the standard absorbance curve for L5178Y (wavelength 540 nm). A nominal 1×10^5 cells were then transferred to 10 mL of fresh 3:97 HS–EMEM, from which 0.1 mL (ca. 1000 cells) was transferred to 23 mL of prewarmed (37 °C) 20:80 HS–EMEM. Molten 5% Noble Agar (1.6 mL) was added to the dilute cell suspension, which was then mixed vigorously, poured into a 90-mm plastic culture dish (one dish per original treated cell suspension), and allowed to gel for 15 min on an ice-cooled tray. The soft agar cultures were then incubated at 37 °C in a humidified incubator gassed with 5% CO_2 in air. The cell colonies were counted at the end of a 10-day incubation period by using an automated colony counter (System III Image Analyser, Micromeasurements Ltd.). The total viable cell yield from each original culture was calculated on the basis of the final plating efficiency in agar, and the cytotoxicity was expressed as a percentage relative to the cell yield in solvent controls. LC_{50} values were interpolated from the dose–response data for each compound. Since 10-fold serial dilutions were used in order to cover a wide range of activities, differences <0.25 log are not significant. T-2 was used as a positive control with each batch of determinations.

Registry No. 1, 21259-20-1; 1 (R_1 = OC(S)imidazole), 118143-05-8; **2**, 2270-40-8; **3**, 36519-25-2; **4**, 21259-21-2; **5**, 63148-31-2; **6**, 115589-76-9; **7**, 118142-89-5; **8**, 118142-90-8; **9**, 118204-86-7; **10**, 68165-53-7; 11, 65041-92-1; **12**, 65725-06-6; **13**, 99127-69-2; 14, 118142-91-9; **15**, 74516-69-1; **16**, 118142-92-0; **17**, 26934-87-2; **18**, 34114-98-2; **19**, 34114-99-3; **20**, 34084-03-2; **21**, 118142-93-1; **22**, 118142-94-2; **23**, 118204-87-8; **24**, 118142-95-3; **25**, 118142-96-4; **26**, 118142-97-5; **27**, 118142-98-6; **28**, 118142-99-7; **29**, 118143-00-3; **30**, 113706-92-6; **30** (R_1 = OH, R_6 = OTBDMS), 118143-06-9; **30** (R_6 = OTBDMS), 113728-56-6; **30** (R_6 = OAc), 118143-07-0; **30** (R_6 = OCOEt), 118169-52-1; **30** (R_6 = OCOPr), 118170-26-6; **30** (R_6 = OCOBu), 118143-08-1; **30** (R_6 = OCOPe), 118143-09-2; **30** (R_6 = OCOPh), 118143-10-5; **31**, 111112-47-1; **32**, 98813-18-4; **33**, 116163-74-7; **34**, 118143-01-4; **35**, 118143-02-5; **36**, 77620-47-4; **37**, 77620-53-2; 9α-**38**, 118243-15-5; 9β-**38**, 118204-88-9; 9α-**39**, 118243-16-6; 9β-**39**, 118204-89-0; **40**, 118204-90-3; **41**, 118170-22-2; **42**, 118170-23-3; **43**, 118143-03-6; 44, 76348-84-0; **45**, 118170-24-4; **46**, 118170-25-5; **47**, 118143-04-7; **48**, 65180-29-2.

Long Acting Dihydropyridine Calcium Antagonists. 2. 2-[2-Aminoheterocycloethoxy]methyl Derivatives

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A series of [(2-aminoheterocycloethoxy)methyl]dihydropyridines were prepared as selective coronary vasodilators. Results showed that a wide variety of five- and six-membered heterocycles were acceptable at the 2-position of the dihydropyridine ring and in vitro potency and tissue selectivity was independent of the basicity of these heterocycles. The SAR indicated that activity was optimum when the largest ester group was placed at the 3 rather than 5 position. 2-[[2-[(3-Amino-1*H*-1,2,4-triazol-5-yl)amino]ethoxy]methyl]-4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (**3b**) (UK-52,831) emerged as a potent (IC_{50} = 6.3×10^{-9} M) and tissue-selective calcium channel blocker with a duration of action >7 h in the anaesthetized dog.

In an earlier publication,[1] we reported the preparation and structure–activity relationship (SAR) of a series of novel dihydropyridine (DHP) calcium antagonists substituted in the 2-position by various basic side chains. The aim of our work was to modify the physicochemical properties of the DHP system such that bioavailability and duration of action were superior to currently available agents. These studies led to the identification of amlodipine (1a), which is presently in late stage clinical de-

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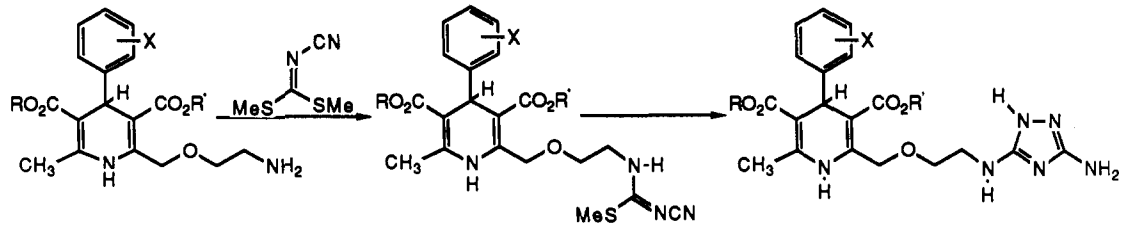
(1) Arrowsmith, J. E.; Campbell, S. F.; Cross, P. E.; Stubbs, J. K.; Burges, R. A.; Gardiner, D. G.; Blackburn, K. J. *J. Med. Chem.* 1986, *29*, 1696.

0022-2623/89/1832-0562$01.50/0

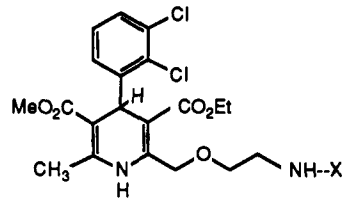
Scheme I

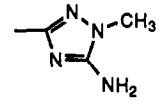
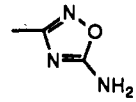
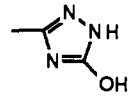
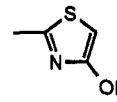


1 **2** **3**

a R = Me ; R' = Et ; X = 2-Cl b R = Me ; R' = Et ; X = 2,3-Cl_2 c R = Me ; R' = Et ; X = 3-Cl

d R = Me ; R' = Et ; X = 2-Chloropyridin-3-yl e R = Me ; R' = Et ; X = 2-Cl,3-CF_3 f R = Et ; R' = Me ; X = 2,3-Cl_2



Compound No.	X	Starting Material	Reagent
4		2 b	NH_2NHCH_3
5		2 b	NH_2OH
6	—C(S)NHCO$_2$Et	1 b	$SCNCO_2Et$
7		6	MeI /NH_2NH_2
8	—C(S)NH_2	1 b	$Cl_2C(S)$ / NH_3
9		8	$ClCH_2CO_2Et$

velopment for the once daily treatment of angina and hypertension.[2-4] Although our initial work clearly demonstrated the value of various basic side chains at the 2-position, we decided to investigate whether basicity was an important requirement for good calcium antagonist activity or if alternative hydrogen-bonding substituents were acceptable. We now report the preparation and calcium antagonist properties of a series of 2-(2-amino-heterocycloethoxy)methyl DHP derivatives in which the amino group of 1 has been replaced by a variety of five- and six-membered heterocyclic ring systems.

Chemistry

The compounds listed in Table I were prepared from the primary amines **1a–f** by the two routes shown in Schemes I and II. In route A (Scheme I), a range of five-membered heterocyclic systems were prepared by elaboration of the primary amino function of the appropriate DHP (**1a–f**). Thus, **1a–f** when reacted with dimethyl *N*-cyanoimidodithiocarbonate gave the *N*-cyano-*S*-methylisothioureas **2a–f** in good yield. These intermediates were converted to the 3,5-diaminotriazoles **3a–f**, the *N*-methyl-3,5-diaminotriazole **4**, and the 2,5-diamino-oxadiazole **5** by reaction with hydrazine, methylhydrazine and hydroxylamine, respectively. The 3-amino-5-hydroxytriazole **7** was prepared from **1b** by reaction with ethoxycarbonyl isothiocyanate to give the *N*-carbethoxythiourea (**6**), which cyclized after treatment with methyl iodide followed by hydrazine. The thiourea **8**, obtained in a two-step procedure from **1b** using thiophosgene and then ammonia, reacted with ethyl chloroacetate to afford the hydroxythiazole **9**. In route B (Scheme II), compounds **10–17** were prepared by direct nucleophilic displacement of a leaving group (X) from a heterocycle by the primary amino function of **1b**. Compounds **18**, **19**, and **20** were obtained by further reaction of **15**, **16**, and **17** with methylamine or ammonia as appropriate.

Results and Discussion

In vitro calcium antagonist activity (pIC_{50}) was assessed as inhibition of calcium-induced constriction of potassi-

(2) Burges, R. A.; Gardiner, D. G.; Gwilt, M.; Higgins, A. J.; Blackburn, K. J.; Campbell, S. F.; Cross, P. E.; Stubbs, J. K. *J. Cardiovasc. Pharmacol.* **1987**, *9*, 110.
(3) Beresford, A. P.; Humphrey, M. J.; Stopher, D. A. *Br. J. Pharmcol.* **1985**, *85*, 333P.
(4) Faulkner, J. K.; McGibney, D.; Chasseud, I. F.; Perry, J. L.; Taylor, I. W. *J. Clin. Pharmacol.* **1986**, *22*, 1.

Table I. Data for Compounds Used in This Study

no.	route	mp, °C	recryst solvent	formula	% yield	Ca IC_{50}[a,c]	neg inotropy IC_{25}[b,c]	selectivity
3a	A	137–138	EtOAc/Et_2O	$C_{22}H_{27}ClN_6O_5$	24	7.7	6.2	32
3b	A	195–196	EtOAc	$C_{22}H_{26}Cl_2N_6O_5$	69	8.2	6.3	79
3c	A	138–140	CH_3CN	$C_{22}H_{27}ClN_6O_5$	30	6.9	NT	–
3d	A	147–151	Et_2O	$C_{21}H_{26}ClN_7O_5$	53	6.5	6.0	3
3e	A	144–145	EtOAc	$C_{23}H_{26}ClF_3N_6O_5$	24	8.4	6.3	125
3f	A	173–175	EtOAc/Et_2O	$C_{22}H_{26}Cl_2N_6O_5$	39	7.0	5.5	32
4	A	118–120,5	EtOAc	$C_{23}H_{28}Cl_2N_6O_5$	35	8.4	6.8	40
5	A	124	Et_2O	$C_{22}H_{25}Cl_2N_5O_6$	22	8.5	7.3	16
6	A	144	Et_2O	$C_{24}H_{29}Cl_2N_3O_7S$	80	7.5	6.2	20
7	A	158	EtOAc	$C_{22}H_{25}Cl_2N_5O_6 \cdot H_2O$	20	8.0	6.4	40
8	A	198	EtOH	$C_{21}H_{25}Cl_2N_3O_5S$	74	9.0	7.2	63
9	A	204–205	toluene	$C_{23}H_{25}Cl_2N_3O_6S$	46	7.7	6.1	40
10	B	175–179	toluene/IPA	$C_{25}H_{30}Cl_2N_4O_6 \cdot HCl$	13	7.7	6.2	32
11	B	142–145	EtOAc	$C_{24}H_{26}Cl_2N_4O_6$	19	8.6	6.7	79
12	B	141–143	EtOAc	$C_{24}H_{26}Cl_2N_4O_6$	38	8.8	6.7	125
13	B	130–132	EtOAc	$C_{24}H_{26}Cl_2N_4O_6$	18	8.9	7.2	50
14	B	198–200	EtOAc	$C_{30}H_{30}Cl_2N_4O_6 \cdot HCl \cdot 0.5H_2O$	3	8.1	6.9	16
15	B	110	Et_2O	$C_{24}H_{25}Cl_3N_4O_5$	59	7.9	7.7	2
16	B	111–112	Et_2O	$C_{24}H_{25}Cl_3N_4O_5$	53	8.6	7.4	16
17	B	183–185	EtOAc	$C_{23}H_{26}Cl_2N_4O_7S$	22	8.0	7.1	8
18	B	158	Et_2O	$C_{25}H_{29}Cl_2N_5O_5$	44	8.5	7.2	20
19	B	88–90	Et_2O/DIPE	$C_{25}H_{29}Cl_2N_5O_5$	30	8.3	7.0	20
20	B	135	EtOAc/Et_2O	$C_{22}H_{25}Cl_2N_5O_6S \cdot 0.5H_2O$	48	7.8	7.0	6
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 isolated Langendorff-perfused guinea pig heart by 25%. Nifedipine was used as the standard compound, standard deviation ± 0.26. [c] Experiments carried out in duplicate, typical variation less than ±0.2.

um-depolarized rat aorta. Negative inotropy (pIC_{25}) was assessed in vitro, by using a Langendorff-perfused guinea-pig heart, since a high level of cardiac depression should be avoided for any potential clinical candidate.[5] It may be seen from Table I that in vitro calcium antagonist activity similar to nifedipine was achieved for many of these 2-(2-aminoheterocycloethoxy)methyl DHP derivatives, indicating that the DHP receptor is quite tolerant of structural changes around the 2-position.[6] Thus, for the five-membered heterocycles both the 2,5-diaminotriazole **3b** and the 3,5-diamino-1,2,4-oxadiazole **5** had good in vitro calcium antagonist activity; also the former compound showed minimal negative inotropy such that it had almost a 100-fold vascular/cardiac selectivity (calcium antagonist activity vs negative inotropy). Calcium antagonist potency decreased for the 3-amino-5-hydroxytriazole **7** and was further reduced for the 2-amino-4-hydroxythiazole **9** and the 2-aminoimidazolone **10**, although all these compounds displayed good tissue selectivity (>30-fold). The least selective of these five-membered ring heterocyclic DHP derivatives was the thiadiazole **20**.

For the six-membered heterocyclic compounds, results show that the three isomeric aminopyrimidinones 11–13, a diaminopyrimidine (**18**) and a diaminopyrazine (**19**) all had in vitro calcium antagonist activity similar to or better than nifedipine. However, these compounds did differ in their selectivity such that the two aminopyrimidinones (**11**, **12**) showed approximately a 100-fold vascular/cardiac selectivity, although this parameter was greatly reduced for compounds **13**, **14**, **18**, and **19**.

Consideration of the in vitro results reported above led to compounds **3b**, **5**, **11**, and **12** being selected for in vivo evaluation. These compounds (150 μg/kg) were administered intravenously to instrumented anaesthetized dogs, and effects on coronary blood flow were used as a measure

(5) Pharmacology is described in the Experimental Section of ref 1.

(6) In vitro biological activity of amlodipine (1a) is Ca IC_{50} = 8.1 ± 0.3 negative inotropy IC_{25} = 7.2 ± 0.09.

Table II. Percent Decrease in Coronary Vascular Resistance in Dogs at 150 μg/kg Intravenous Dose[a]

compd	% decrease in CVR	duration of action half-life, h[a]
3b	70	>7
5	76	0.3
11	70	4.3
12	62	3.7
nifedipine	77	0.6

[a] Time taken for 50% recovery of coronary vascular resistance

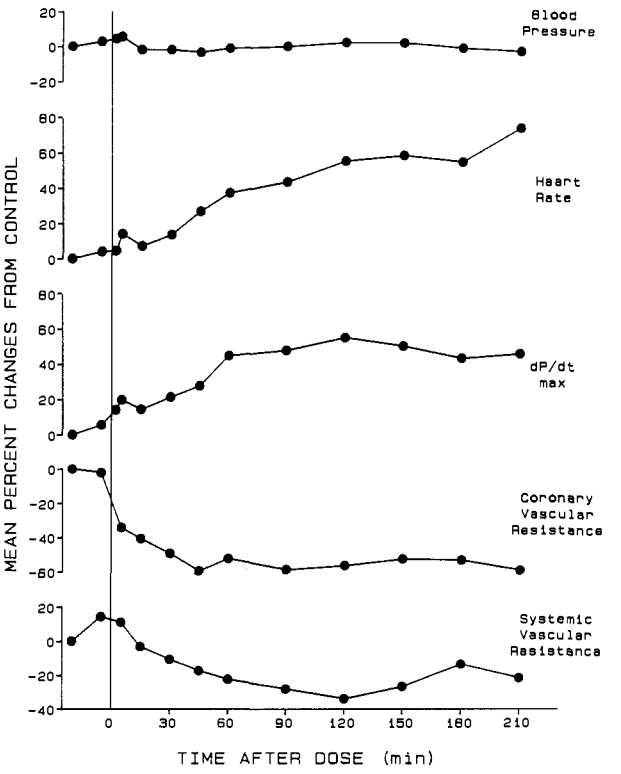
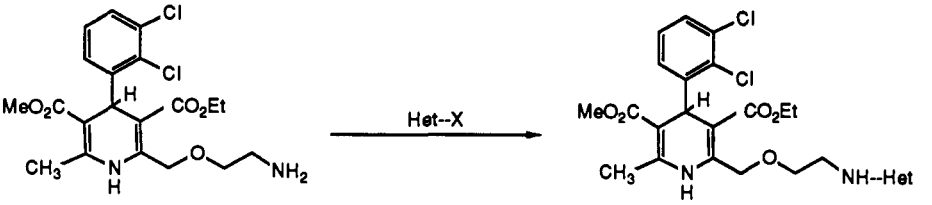
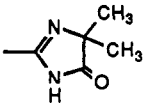
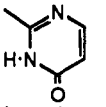
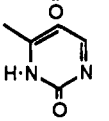
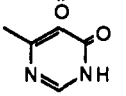
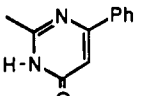
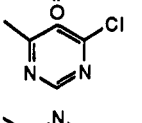
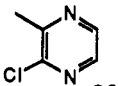
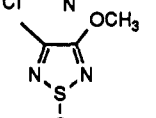
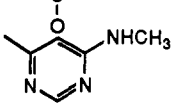
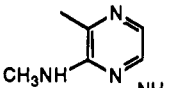
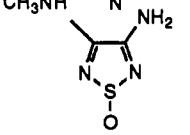


Figure 1. Duration of action of **3b** in anaesthetized dogs (n = 2).

Scheme II. Route B[a]



Compound No.	X	Het.
10	-SMe	
11	-SMe	
12	-SMe	
13	-Cl	
14	-$NHNO_2$	
15	-Cl	
16	-Cl	
17	-OMe	
[a]18	-Cl	
[a]19	-Cl	
[a]20	-OMe	

[a] 18, 19, and 20 were prepared from 15, 16, and 17 by treatment with methylamine or ammonia as appropriate.

of both calcium antagonist potency and duration of action. The results given in Table II include nifedipine as a standard. It can be seen that all compounds produce maximum or near maximum falls in coronary vascular resistance (CVR) and **3b**, 11, and 12 displayed markedly longer duration of action than nifedipine. Indeed, for **3b** a substantial reduction in CVR was still evident 7 h post dosing. Figure 1 shows that **3b** has a slow onset of action such that maximum reduction of CVR and SVR are not reached until 45 min and 2 h post dosing, respectively.

Having identified the 3,5-diaminotriazole as the heterocyclic moiety giving the most promising pharmacological profile, we further examined the SAR around **3b**. N-2 methylation of the triazole ring, as in **4**, gave a slight potency advantage over **3b** but an associated increase in negative inotropy resulted in an overall loss of selectivity. Removal of the chlorine from the 3-position on the phenyl ring of **3b** to give **3a** resulted in a reduction of calcium antagonist potency; further reduction (20-fold) occurred when the chlorine was removed from the 2-position, to give **3c**, or the 2,3-dichlorophenyl was replaced by 2-chloropyridin-3-yl as in **3d**. It was found that 2-chloro-3-(trifluoromethyl)phenyl **3e** was a satisfactory replacement for 2,3-dichlorophenyl, giving very similar calcium antagonist activity to **3b**.

We also investigated the effect of variation of the ester groups at the 3- and 5-position of the DHP on vascular vs cardiac selectivity. We found that interchanging the 3-ethyl and 5-methyl esters of **3b** to give **3f** caused a marked decrease (15-fold) in calcium antagonist activity accompanied by a smaller decrease in negative inotropic activity, resulting in an overall loss of vascular/cardiac selectivity. These two in vitro results indicate that both tissue selectivity and potency can be improved when bulky substitu-

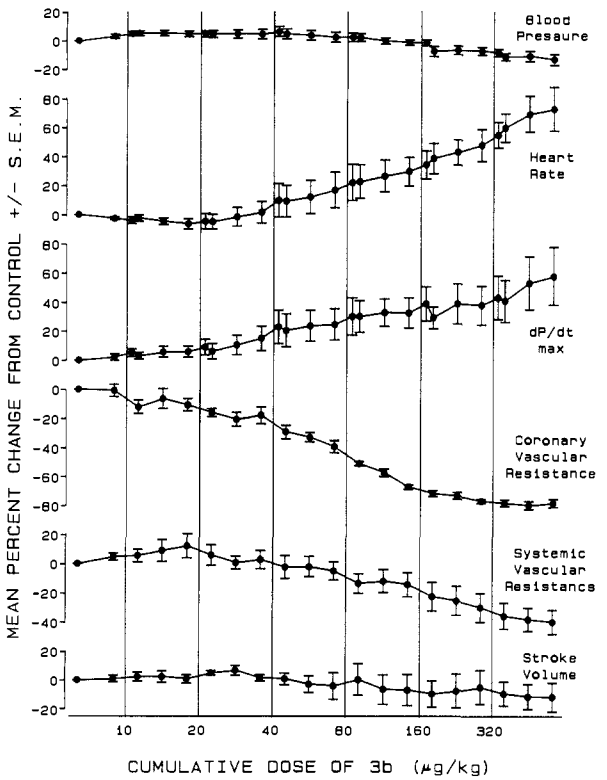


Figure 2. Haemodynamic response to **3b** in anaesthetized dogs (n = 4).

ents are adjacent to each other on the DHP ring (for example, in the 2- and 3-positions, **3b**) rather than having a transannular relationship (as in the 2- and 5-positions, e.g., **3f**). This SAR observation advances our understanding of the DHP receptor, since sterically demanding groups can only by adequately accommodated on one side of the molecule and may occupy a relatively open space on the DHP receptor.[7] A similar tolerance is seen for DHP's such as nicardipine[8,9] and niguldipine,[10] which have large substituent groups attached to the 3-position ester moiety.

Compound **3b** (UK-52, 831) was selected for further in vivo evaluation in anaesthetized dogs (n = 4). Figure 2 shows that in the cumulative dose range 10–320 μg/kg **3b** produces dose-related coronary and systemic vasodilation, coupled with reflex-induced tachycardia and an increased dp/dt max; blood pressure remained largely unaffected except for a slight decrease at higher doses. An ED_{50} of 63 μg/kg for coronary vasodilation may underestimate the potency of **3b** due to its slow onset of action (45 min to peak reduction in CVR) and the relatively short time course between doses (30 min).

In conclusion, we have found that the 2-position of the DHP ring is highly ammenable to a wide variety of substitution. Both high potency and a good tissue selectivity were obtained for a variety of 2-(2-heterocycloethoxy)-methyl compounds, which may reflect an enhanced interaction resulting from hydrogen bonding between these polar heterocycles and the DHP receptor. The basicity of these heterocycles was not considered to be important since both the 4,6-diaminopyrimidine **18** and 2,3-diaminopyrazine **19** should be substantially protonated at physiological pH,[11] yet the nonbasic aminopyrimidinones **11**, **12**, and **13** show a clear advantage in both potency and selectivity.

Experimental Section

Pharmacology. In vitro calcium antagonism IC_{50} and negative inotropy IC_{25} were measured as previously described.[1]

In vivo haemodynamic measurement were made in anaesthetized 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 (Auckland, K.; Bower, B. F.; Berliner, R. W. *Circulation* **1964**, *14*, 164–187). 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–reponse studies) or 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; ^1H NMR spectra were obtained with a Varian XL-100-5 spectrometer using $CDCl_3$ as a solvent. The preparation of the dihydropyridine primary amines I have been described in a previous publication,[1] with the exception of **1d** (R = Me; R′ = Et; X = 2-chloropyridin-3-yl) and **1f** (R = Et; R′ = Me; X = 2,3-Cl_2). These amines were prepared in a directly analogous manner by hydrolysis of the corresponding phthalimides (mp 123–125 °C and 165 °C, respectively), which were obtained directly from the Hantzsch synthesis. **1d** and **1f** were isolated and characterized as their free bases.

2-[(2-Aminoethoxy)methyl]-3-(ethoxycarbonyl)-4-(2-chloropyridin-3-yl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (1d): yield 35%; mp 129–131 °C (from Et_2O). Anal. ($C_{19}H_{24}ClN_3O_5$) C, H, N.

2-[(2-Aminoethoxy)methyl]-3-(methoxycarbonyl)-4-(2,3-dichlorophenyl)-5-(ethoxycarbonyl)-6-methyl-1,4-dihydropyridine (1f): yield 70%; mp 131–132 °C (from acetone). Anal. ($C_{20}H_{24}Cl_2N_2O_5$) C, H, N.

***N*-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-*N*′-cyano-*S*-methylisothiourea (2a).** 2-[(2-Aminoethoxy)methyl]-3-(ethoxycarbonyl)-4-(2-chlorophenyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (**1a**; 4.8 g, 10.5 mmol) and dimethyl *N*-cyanoimidodithiocarbonate (2 g, 1.37 mmol) in 2-propanol (15 mL) were allowed to stand at room temperature for 4 h. Ether (30 mL) was then added and the mixtures was allowed to stand at room temperature overnight. The crystalline precipitate was filtered, washed with ether, and dried to give the title compound **2a**: yield 5.0 g (94%); mp 177–179 °C. Anal. ($C_{23}H_{27}ClN_4O_5S$) C, H, N.

2-[[2-[(3-Amino-1*H*-1,2,4-triazol-5-yl)amino]ethoxy]methyl]-4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (3a). *N*-[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]-*N*′-cyano-*S*-methylisothiourea (**2a**; 0.4 g, 0.79 mmol) and hydrazine hydrate (0.15 mL, 3.0 mmol) were dissolved in ethanol (20 mL) and heated under reflux for 3 h. The solvent was then evaporated and toluene (10 mL) was added to the residue, and again the solution was evaporated to dryness. The residue was chromatographed on silica, eluting with 2% methanol in methylene chloride, to give a beige solid. The solid was recrystallized from ethyl acetate plus a trace of ether to give the title compound **3a**: yield 0.1 g (26%); mp 137–138 °C. Anal. ($C_{22}H_{27}ClN_6O_5$) C, H, N.

Compounds **3b–f** and **4** were prepared in a similar manner from the appropriate *N*-cyano-5-methylisothiourea and hydrazine or *N*-methylhydrazine (compound **4**). Alternatively, compounds **3b–f** and **4** were prepared without characterizing the intermediate

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isothioureas **2b–f** as exemplified for the preparation of **3b**.

2-[[2-[(3-Amino-1*H*-1,2,4-triazol-5-yl)amino]ethoxy]methyl]-4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (3b). A solution of 2-[(2-aminoethoxy)methyl]-4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (**2b**, 0.63 g, 1.4 mmol) and dimethyl *N*-cyanoimidodithiocarbonate (0.21 g, 1.4 mmol) in 2-propanol (5 mL) was stirred at room temperature for 2 h. The solution was diluted with ether and stirring continued for a further 2 h before collecting the resulting precipitate (0.75 g) by filtration. The precipitate was suspended in hot ethanol (12 mL), and hydrazine hydrate (0.22 mL) was added dropwise and heating continued for 2 h or until complete dissolution occurred. The reaction mixture was cooled and the precipitate was collected by filtration, washed with ethanol, and dried to give the title compound **3b**: yield 0.52 g (69%); mp 195–196 °C. Anal. ($C_{22}H_{26}Cl_2N_6O_5$) C, H, N.

2-[[2-[(5-Amino-1,2,4-oxadiazol-3-yl)amino]ethoxy]methyl]-4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (5). *N*-[2-[[4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]ethyl]-*N*-cyano-*S*-methylisothiourea (**2b**; 0.7 g, 1.3 mmol), hydroxylamine hydrochloride (0.3 g, 4.3 mmol), and triethylamine in ethanol (10 mL) were heated under reflux for 4 h. The solvent was then evaporated, and the residue was chromatographed on silica, eluting with ethyl acetate/methanol to give a solid, which was triturated with ether to give the title compound **5**: yield 0.15 g (22%); mp 124 °C. Anal. ($C_{22}H_{25}Cl_2N_5O_6$) C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-2-[[2-[3-(ethoxycarbonyl)thioureido]ethoxy]methyl]-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (6). To a suspension of 2-[(2-aminoethoxy)methyl]-4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (**1b**, 4.43 g, 10 mmol) in dry chloroform (50 mL) was added, dropwise, a solution of ethoxycarbonyl isothiocyanate (1.31 g, 10 mmol) in dry chloroform (25 mL). The reaction was stirred for 18 h at room temperature before evaporating the solvent and triturating the residue with ether to afford a solid, which was recrystallized from diisopropyl ether to give the title compound **6**: yield 4.6 g (80%); mp 144 °C. Anal. ($C_{24}H_{29}Cl_2N_3O_7S$) C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-2-[[2-[(5-hydroxy-1*H*-1,2,4-triazol-3-yl)amino]ethoxy]methyl]-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine Hydrate (7). To a suspension of 4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-2-[[2-[3-(ethoxycarbonyl)thioureido]ethoxy]methyl]-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (**6**; 0.25 g, 0.44 mmol) in dry tetrahydrofuran (THF) (5 mL) was added sodium hydride (0.02 g, 0.83 mmol). After being stirred for 1 h at room temperature, a solution of methyl iodide (0.07 g, 0.48 mmol) in dry THF (5 mL) was added dropwise and stirring was continued overnight. After evaporation of the solvent, the residue was taken up in methylene chloride and washed (aqueous NaCl), dried ($MgSO_4$), filtered, and evaporated to give a yellow oil (0.15 g). The oil was dissolved in 2-propanol (5 mL) containing hydrazine hydrate (0.06 g) and heated under reflux for 2 days. The solution was then evaporated and the residue was taken up in methylene chloride, washed (aqueous $NaHCO_3$), dried ($MgSO_4$), filtered, and evaporated. The residue was then chromatographed on silica, eluting with ethyl acetate/methanol (1% increments up to 20% methanol). Product-containing fractions were combined, evaporated, and recrystallized from ethyl acetate to afford the title compound **7**: yield 0.048 g (20%); mp 158 °C. Anal. ($C_{22}H_{25}Cl_2N_5O_6 \cdot H_2O$) C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-2-[[2-(thioureido)ethoxy]methyl]-1,4-dihydropyridine (8). Thiophosgene (1.71 g, 14.9 mmol) was added dropwise to a stirred mixture of 2-[(2-aminoethoxy)methyl]-4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methylcarbonyl)-6-methyl-1,4-dihydropyridine (6.0 g, 13.5 mmol) and powdered calcium carbonate (4.05 g, 40.5 mmol) in methylene chloride (40 mL) and water (50 mL). After being stirred for 18 h at room temperature, the reaction mixture was filtered and the filtrate was diluted with 2 M hydrochloric acid (100 mL) and extracted with methylene chloride (3 × 100 mL). The combined organic extracts were washed with water, dried ($MgSO_4$), filtered, and evaporated. The residue was triturated with petrol and the resulting solid was collected by filtration and dried to afford 4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-2-[[2-(isothiocyano)ethoxy]methyl]-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine [yield 6.1 g (94%); mp 154–155 °C], which was used without further purification. Thus a solution of 4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-2-[[2-(isothiocyano)ethoxy]methyl]-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (5.5 g, 10 mmol) was heated under reflux in ethanol ammonia (90 mL) for 2.5 h. The reaction was cooled, the precipitate was collected by filtration, washed with ice-cold ethanol, and dried to afford the title compound **8**: yield 4.2 g (74%); mp 198 °C. Anal. ($C_{21}H_{25}Cl_2N_3O_5S$) C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-2-[[2-[(4-hydroxythiazol-2-yl)amino]ethoxy]methyl]-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (9). Ethyl bromoacetate (0.23 g, 1.3 mmol) was added dropwise to a stirred solution of 4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-2-[[12-(thioureido)ethoxy]methyl]-1,4-dihydropyridine (0.6 g, 1.2 mmol) in methylene chloride (50 mL) containing triethylamine (0.18 g, 1.8 mmol) cooled to 0 °C. Stirring was continued for 1 h at 0 °C, 18 h at room temperature, and 2 h at 40 °C. The reaction mixture was evaporated to dryness and the residue purified by column chromatography on silica, eluting with chloroform containing ethyl acetate (a gradient from 0% up to 30%). Product containing fractions were combined and evaporated to give a solid (0.48 g), which was heated in toluene at reflux temperature for 5 h. The toluene solution was cooled, and the precipitate was collected by filtration and dried to give the title compound **9**: yield 0.30 g (46%); mp 204–205 °C. Anal. ($C_{23}H_{25}Cl_2N_3O_6S$) C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-2-[[2-[(5,5-dimethyl-3-oxo-3*H*-imidazol-2-yl)amino]ethoxy]methyl]-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine Hydrochloride (10). A solution of 5,5-dimethyl-2-(methylthio)-3*H*-imidazol-4-one (4.5 g, 28 mmol), 2-[(2-aminoethoxy)methyl]-4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (5.5 g, 11.3 mmol) and triethylamine (5 g, 5 mmol) in ethanol was heated at reflux temperature for 8 h. The reaction was cooled and the solvent evaporated. The residue was dissolved in ethyl acetate, washed with brine, dried ($MgSO_4$), and evaporated, and the residue was purified by column chromatography on silica, eluting with ethyl acetate containing methanol (a gradient from 1% up 10%). Product-containing fractions were combined and evaporated to give an oil, which was stirred in 2-propanol (5 mL); the resulting precipitate was recrystallized from methanol, then converted to its hydrochloride, which was recrystallized from 2-propanol/toluene to give the title compound **10**: yield 0.94 g, (13%); mp 175–179 °C. Anal. ($C_{25}H_{30}Cl_2N_4O_6 \cdot HCl$) C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-2-[[2-[(3,4-dihydro-4-oxopyrimidin-2-yl)amino]ethoxy]methyl]-1,4-dihydropyridine Hemihydrate (11). 2-[(2-Aminoethoxy)methyl]-3-(ethoxycarbonyl)-4-(2,3-dichlorophenyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (2 g, 4.5 mmol) and 2-(methylthio)-3,4-dihydropyrimidin-4-one (1.5 g, 10.5 mmol) were heated at reflux temperature in ethanol (25 mL) for 60 h. The reaction mixture was cooled and partitioned between ethyl acetate and water. The organic layer was separated, dried ($MgSO_4$), and evaporated in vacuo to give a foam, which was purified by column chromatography on silica, eluting with ethyl acetate. Product-containing fractions were combined and evaporated in vacuo to give a foam, which crystallized from ethyl acetate to give the title compound **11**: yield 0.45 g (19%); mp 142–145 °C. Anal. ($C_{24}H_{26}Cl_2N_4O_6 \cdot 0.5H_2O$) C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-2-[[2-[(2,3-dihydro-2-oxopyrimidin-4-yl)amino]ethoxy]methyl]-1,4-dihydropyridine (12). 2-[(2-Aminoethoxy)methyl]-3-(ethoxycarbonyl)-4-(2,3-dichlorophenyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (0.5 g, 1.1 mmol) and 4-(methylthio)pyrimidin-2-one (0.4 g, 2.8 mmol) in ethanol (5 mL) were heated at reflux temperature for 40 h. The solvent was evaporated in vacuo and the residue purified by column chromatography on alumina, eluting with ethyl acetate. Product-containing fractions were combined and evaporated in vacuo to give a gum, which crystallized from ethyl acetate to give

the title compound 12: yield 0.23 g (38%); mp 141–143 °C. Anal. ($C_{24}H_{26}Cl_2N_4O_6$) C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-2-[[2-[(3,4-dihydro-4-oxopyrimidin-6-yl)amino]ethoxy]methyl]-1,4-dihydropyridine Hemihydrate (13). 2-[(2-Aminoethoxy)methyl]-3-(ethoxycarbonyl)-4-(2,3-dichlorophenyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (1 g, 2.25 mmol), 6-chloro-3,4-dihydro-4-oxopyrimidine (0.4 g, 3.1 mmol), and 4-(dimethylamino)pyridine (0.3 g, 2.6 mmol) in butanol (10 mL) were heated on a steam bath for 17 h. The solvent was evaporated in vacuo and the residue was taken up in ethyl acetate, washed with 2 M hydrochloric acid and 5% aqueous sodium hydroxide, dried ($MgSO_4$), and evaporated. The resulting gum was dissolved in ethyl acetate and stirred at room temperature for 17 h; the precipitate was collected by filtration and dried to give the title compound 13: yield 0.22 g (18%); mp 130–132 °C. Anal. ($C_{24}H_{26}Cl_2N_4O_6 \cdot 0.5H_2O$) C, H, N.

4-(2,3-Dichlorophenyl)-2-[[2-[(3,4-dihydro-4-oxo-6-phenylpyrimidin-2-yl)amino]ethoxy]methyl]-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine Hydrochloride, Hemihydrate (14). A solution of 2-[(2-aminoethoxy)methyl]-4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-1,4-dihydropyridine (4 g, 9.0 mmol) and 3,4-dihydro-2-(nitroamino)-6-phenylpyrimidin-4-one (2.1 g, 9 mmol) in butanol (120 mL) and methanol (30 mL) was heated on a steam batch for 5 h. The reaction was cooled and evaporated to dryness and the residue was purified by column chromatography on silica, eluting with methylene chloride containing methanol (gradient 1% up to 30%). The product-containing fractions were combined and evaporated and the resulting solid was suspended in ethyl acetate and then treated with ethereal HCl. The precipitate was collected by filtration to give the title compound 14: yield 0.19 g (3%); mp 198–200 °C. Anal. ($C_{30}H_{30}Cl_2N_4O_6 \cdot HCl \cdot 0.5H_2O$), C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-2-[[2-[(4-chloropyrimid-6-yl)amino]ethoxy]methyl]-1,4-dihydropyridine (15). 2-[(2-Aminoethoxy)methyl]-3-(ethoxycarbonyl)-4-(2,3-dichlorophenyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (3.0 g, 6.75 mmol), 4,6-dichloropyrimidine (1.2 g, 8.05 mmol), and triethylamine (1.0 mL, 7.2 mmol) in ethanol (20 mL) were heated on a steam bath for 4 h. The solvent was removed by evaporation, the residue was dissolved in ethyl acetate and filtered, and the filtrate was purified by column chromatography on silica, eluting with ethyl acetate. Product-containing fractions were combined and evaporated in vacuo to give an oil, which solidified after trituration with ether. The precipitate was filtered and dried to give the title compound 15: yield 2.2 g (59%); mp 110 °C. Anal. ($C_{24}H_{25}Cl_3N_4O_5$) C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-2-[[2-[(2-chloropyrazin-3-yl)amino]ethoxy]methyl]-1,4-dihydropyridine (16). A solution of 2-[(2-aminoethoxy)methyl]-3-(ethoxycarbonyl)-4-(2,3-dichlorophenyl)-5-(methoxycarbonyl)-1,4-dihydropyridine (0.8 g, 1.8 mmol), 2,3-dichloropyrazine (0.5 g, 3.3 mmol), and triethylamine gave the title compound 16 by a method identical with that described for the previous example: yield 0.53 g, (53%); mp 111–112 °C. Anal. ($C_{24}H_{25}Cl_3N_4O_5$) C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-2-[[2-[(3-methoxy-1-oxo-1,2,5-thiadiazol-4-yl)amino]ethoxy]methyl]-6-methyl-1,4-dihydropyridine (17). A solution of 2-[(2-aminoethoxy)methyl]-4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (0.5 g, 1.1 mmol) and 3,5-dimethoxy-1,2,5-thiadiazole 1-oxide (0.2 g, 1.2 mmol) in methanol (15 mL) was heated on a steam bath for 18 h. The reaction was cooled, the solvent was evaporated, and the residue was purified by column chromatography on silica. Compound-containing fractions were combined and the resulting oil crystallized from ethyl acetate to give the title compound 17: yield 0.14 g; mp 183–185 °C. Anal. ($C_{23}H_{26}Cl_2N_4O_7S$) C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-2-[[2-[[4-(methylamino)pyrimidin-6-yl]amino]ethoxy]methyl]-1,4-dihydropyridine (18). 4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-2-[[2-[(4-chloropyrimid-6-yl)amino]ethoxy]carbonyl]-1,4-dihydropyridine (0.5 g, 0.9 mmol) and methylamine (33% in ethanol) (2 mL) were heated in a bomb for 17 h. The solvent was removed by evaporation in vacuo and the residue purified by column chromatography on silica, eluting with toluene containing ethyl acetate (0% up to 50%). Product-containing fractions were combined and evaporated in vacuo to give an oil, which was crystallized from diethyl ether, filtered, and dried to give the title compound 18: yield 0.22 g (44%); mp 158 °C. Anal. ($C_{25}H_{29}Cl_2N_5O_5$) C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-2-[[2-[[3-(methylamino)pyrazin-2-yl]amino]ethoxy]methyl]-1,4-dihydropyridine (19). 2-[[2-[(2-Chloropyrazin-3-yl)amino]ethoxy]methyl]-4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (0.3 g, 0.54 mmol) and methylamine (2 mL) were heated in a bomb at 100 °C for 18 h. The methylamine was evaporated and the residue purified by column chromatography on silica, eluting with ethyl acetate. The product-containing fractions were combined and evaporated. The resulting oil crystallized from diisopropyl ether/ether to give the title compound 19: yield 0.12 g (30%); mp 88–90 °C. Anal. ($C_{25}H_{29}Cl_2N_5O_5$) C, H, N.

2-[[2-[(3-Amino-1,2,5-thiadiazol-4-yl)amino]ethoxy]methyl]-4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine, Hemihydrate (20). A solution of 4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-2-[[2-[(3-methoxy-1-oxo-1,2,5-thiadiazol-4-yl)amino]ethoxy]methyl]-6-methyl-1,4-dihydropyridine (0.3 g, 0.52 mmol) in ethanolic ammonia (10 mL) was stirred at room temperature for 1 h. The solvent was removed and the residue purified by column chromatography on silica, eluting with ethyl acetate. The product-containing fractions were combined and evaporated, and the resulting gum crystallized from ethyl acetate/ether to give the title compound 20: yield 0.145 g (49%); mp 135 °C. Anal. ($C_{22}H_{25}Cl_2N_5O_6S \cdot 0.5H_2O$) C, H, N.

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Registry No. 1a, 88150-42-9; 1b, 88150-50-9; 1c, 118070-96-5; 1d, 103198-59-0; 1e, 93118-29-7; 1f, 103198-54-5; 2a, 93117-86-3; 2b, 93117-89-6; 3a, 93118-75-3; 3b, 93118-77-5; 3c, 118070-92-1; 3d, 118070-93-2; 3e, 93118-76-4; 3f, 118070-94-3; 4, 93118-78-6; 5, 118070-86-3; 6, 118070-87-4; 7, 93118-15-1; 8, 93848-92-1; 9, 118070-88-5; 10, 118070-89-6; 11, 93118-57-1; 12, 118070-90-9; 13, 93118-59-3; 14, 118070-91-0; 15, 93117-91-0; 16, 93118-70-8; 17, 93118-47-9; 18, 93118-09-3; 19, 93118-10-6; 20, 93118-33-3; dimethyl *N*-cyanoimidodithiocarbonate, 10191-60-3; ethoxycarbonyl isothiocyanate, 16182-04-0; 4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-2-[[2-(isothiocyano)ethoxy]methyl]-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine, 118070-95-4; 5,5-dimethyl-2-(methylthio)-3*H*-imidazol-4-one, 91121-96-9; 2-(methylthio)-3,4-dihydropyrimidin-4-one, 5751-20-2; 4-(methylthio)-pyrimidin-2-one, 35551-31-6; 6-chloro-3,4-dihydro-4-oxopyrimidine, 4765-77-9; 3,4-dihydro-2-(nitroamino)-6-phenylpyrimidin-4-one, 56741-96-9; 4,6-dichloropyrimidine, 3934-20-1; 2,3-dichloropyrazine, 4858-85-9; 3,5-dimethoxy-1,2,5-thiadiazole 1-oxide, 78441-23-3.