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Imidazo[1,5-*a*]Pyrimidine and Benzo[4,5]Imidazo-[1,2-*a*]Pyrimidine Derivatives as Calcium Antagonists

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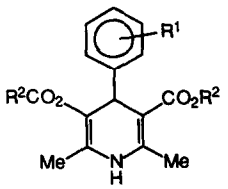
Abstract—Several bicyclic dihydropyrimidines were synthesized and evaluated for their calcium antagonistic activities by comparison with the usual 1,4-dihydropyridine calcium antagonist reference compound nifedipine. The solid-state structure of the isopropyl 2-methyl-4-(3'-nitrophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimido-3-carboxylate shows that these compounds can adopt the most important structural features of the 1,4-dihydropyridine and 1,4-dihydropyrimidine calcium channel blockers. The high-potassium depolarized rat aorta assay was used for testing the compounds as calcium channel blockers. Some compounds showed interesting vasorelaxant activity.

Introduction

Soon after the discovery of the beneficial uses of 1,4-dihydropyridines in cardiovascular medicine, it was found that these substances acted by inhibiting the entry of Ca^{2+} into the voltage-dependent calcium channels[1,2] of cardiac and vascular muscle cells. The 1,4-dihydropyridines are still the largest and most widely studied class of calcium channel blockers or 'calcium antagonists',[3] and work in this area has led to the development of many dihydropyridine derivatives, some of which have been successfully introduced as commercial products for the treatment of coronary diseases and hypertension (e.g. nifedipine, **1**).[4] More recent studies in this field have been devoted to the development of 1,4-dihydropyridines with a chiral center at C-4, with longer bioavailability or greater tissue selectivity being a characteristic feature of many of these compounds (e.g. **2**–**5**).[5]

Simultaneously, analogues of the dihydropyridine skeleton itself have been synthesized allowing for further refinement of the existing structure–activity relationships. Thus, the structural similarity between dihydropyridine and dihydropyrimidine has led to the development of a variety of dihydropyrimidines **6**[6] and **7**,[7] by several groups, as calcium channel blockers. In addition, fused dihydropyridines and dihydropyrimidines **8**[8] have recently been claimed as calcium antagonists.



1 Nifedipine : R^1 = 2-NO_2; R^2 = R^3 = Me

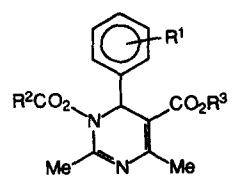
2 Nitrendipine : R^1 = 3-NO_2; R^2 = Me; R^3 = Et

3 Nimodipine : R^1 = 3-NO_2; R^2 = CH_2CH_2OMe; R^3 = i-Pr

4 Nicardipine : R^1 = 3-NO_2; R^2 = $CH_2CH_2N(Me)Bn$; R^3 = Me

5 Furnidipine : R^1 = 2-NO_2; R^2 = CH_2O–  ; R^3 = Me

6 R^2 = alkyl ; R^3 = alkyl; X = O,



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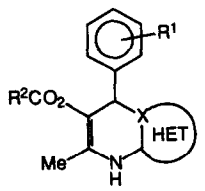


8 X = C, N

Figure 1.

In connection with previously reported work on novel calcium channel blockers[5,9] we describe here the synthesis of 1,4-dihydropyrimidine systems fused with imidazole and benzimidazole rings, their calcium channel blocking activity and the solid-state structure of a representative compound.

Results and Discussion

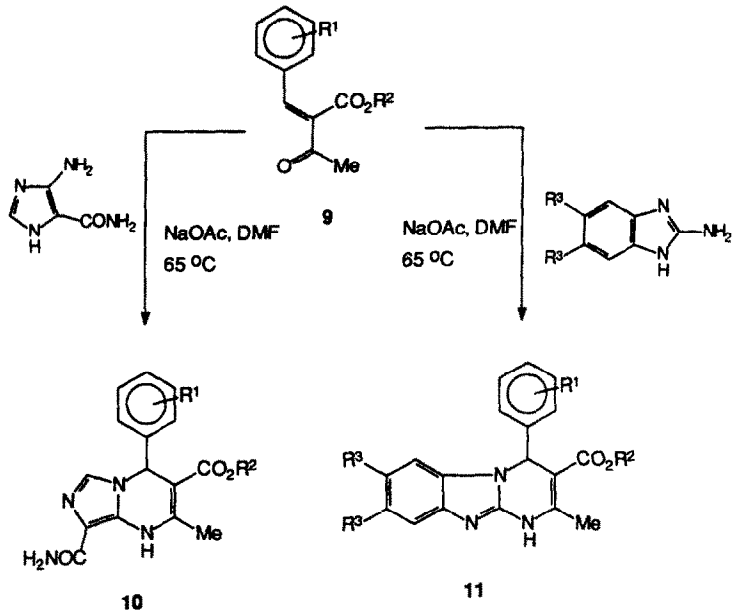
Imidazo[1,5-*a*]pyrimidine and benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives **10** and **11** shown in Table 1 were prepared following the method described by Cho and co-workers[7,10] for the synthesis of 1,4-dihydropyrimidines. In this case, commercially available 2-amino substituted imidazole and benzimidazole were condensed with the corresponding α-benzylidene-β-keto esters **9** in the presence of sodium acetate (Scheme I) in hot dimethylformamide (DMF). The method allowed for the preparation of compounds **10** and **11** in yields of 59 % to 85 %.

In order to correlate the structure of fused pyrimidines **10** and **11** with previously known calcium antagonists, the solid-state structure of isopropyl 2-methyl-4-(3'-nitrophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimido-3-carboxylate **11c** was determined by X-ray crystallography. Figure 2 shows the perspective diagram of **11c** with the corresponding atomic numbering.[11] The unit cell packing diagram (Figure 3) confirmed in each molecule,

Table 1. Physical properties of imidazo[1,5-*a*]pyrimidine and benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives **10** and **11**

compd	R^1	R^2	R^3	yield, %	mp, °C[a]	formula	analysis
10a	H	Me	-	73	241-243	$C_{16}H_{16}N_4O_3$	C (61.70); H (5.36); N (18.09)
10b	3-F	Me	-	72	260-262	$C_{16}H_{15}N_4O_3F$	C (58.42); H (4.20); N (16.69)
10c	3-NO_2	i-Pr	-	74	253-255	$C_{18}H_{19}N_5O_5$	C (55.99); H (5.20); N (18.40)
10d	3-NO_2	$(CH_2)_2OMe$	-	68	>350	$C_{18}H_{19}N_5O_6$	C (53.77); H (4.72); N (17.30)
10e	2,3-Cl_2	Me	-	61	305-307	$C_{16}H_{14}N_4O_3Cl_2$	C (50.65); H (3.90); N (15.00)
10f	2,6-Cl_2	Et	-	59	292-293	$C_{17}H_{16}N_4O_3Cl_2$	C (51.55); H (4.01); N (13.92)
10g	2-NO_2	Me	-	78	241-242	$C_{16}H_{15}N_5O_5$	C (53.58); H (4.16); N (19.30)
10h	2-NO_2	CH_2THF	-	80	267-268	$C_{20}H_{21}N_5O_6$	C (55.99); H (4.71); N (16.15)
11a	H	Me	H	74	250-251	$C_{19}H_{17}N_3O_2$	C (71.24); H (5.51); N (13.40)
11b	3-F	Me	H	76	260-261	$C_{19}H_{16}N_3O_2F$	C (67.57); H (4.83); N (12.70)
11c	3-NO_2	i-Pr	H	78	280-281	$C_{21}H_{20}N_4O_4$	C (64.10); H (5.30); N (14.24)
11d	3-NO_2	$(CH_2)_2OMe$	H	68	270-271	$C_{21}H_{20}N_4O_5$	C (61.53); H (4.72); N (13.54)
11e	2-Cl	Me	H	76	284-285	$C_{19}H_{16}N_3O_2Cl$	C (64.15); H (4.40); N (12.10)
11f	2,3-Cl_2	Me	H	65	288-289	$C_{19}H_{15}N_3O_2Cl_2$	C (59.05); H (3.50); N (10.45)
11g	2,6-Cl_2	Et	H	61	312-313	$C_{20}H_{17}N_3O_2Cl_2$	C (59.59); H (4.12); N (10.25)
11h	2-NO_2	Me	H	75	287-288	$C_{19}H_{16}N_4O_4$	C (62.89); H (4.70); N (15.60)
11i	2-NO_2	CH_2THF	H	77	270-271	$C_{23}H_{22}N_4O_5$	C (63.19); H (4.88); N (12.77)
11j	3-NO_2	i-Pr	Me	62	288-290	$C_{23}H_{24}N_4O_4$	C (65.38); H (5.99); N (13.45)
11k	2,3-Cl_2	Me	Me	70	294-296	$C_{21}H_{19}N_3O_2Cl_2$	C (60.78); H (4.70); N (9.88)
11l	2-NO_2	CH_2THF	Me	85	191-192	$C_{25}H_{26}N_4O_5$	C (64.64); H (5.45); N (12.21)

[a]All compounds were recrystallized from H_2O/DMF. THF = tetrahydrofuran-2-yl.



Scheme I.

intermolecular donor and acceptor hydrogen bonds indicated by broken lines between N-H1.....N3 (distance N-H1.....N3 = 2.95 Å, angle N1-H-N3 = 173.6 °). The crystallographic analysis demonstrates that the dihydropyrimidine ring is in a flattened boat conformation with the N1 and C11 atoms lying slightly above the plane of the benzimidazole moiety. The ester group is almost coplanar with the double bond of the dihydropyrimidine ring (angle 5.94 °) with the carbonyl group adopting the *cis* conformation with respect to this double bond. In the crystal, the 4-aryl ring adopts an almost orthogonal arrangement (99 °), occupying a pseudoaxial position with the nitro substituent twisted 16 ° with respect to the main plane of the aromatic ring and in a *synperiplanar (sp)* conformation with respect to H11.

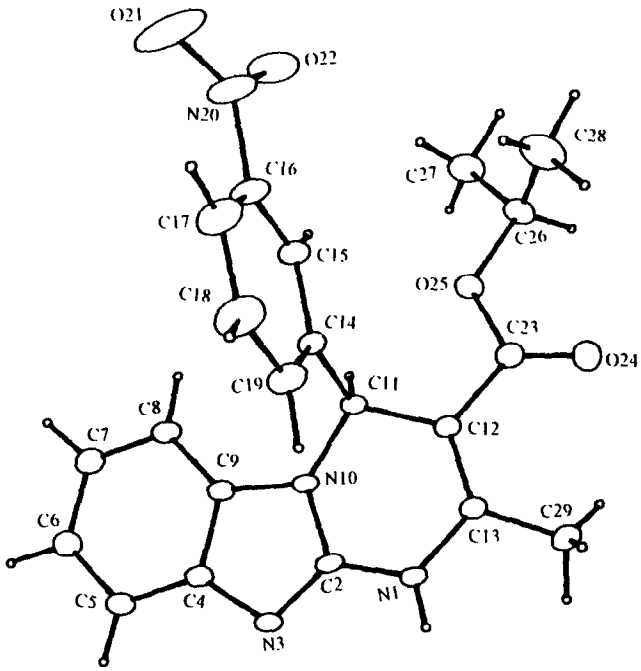


Figure 2. The solid-state structure of isopropyl 2-methyl-4-(3'-nitrophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimido-3-carboxylate (**11c**).

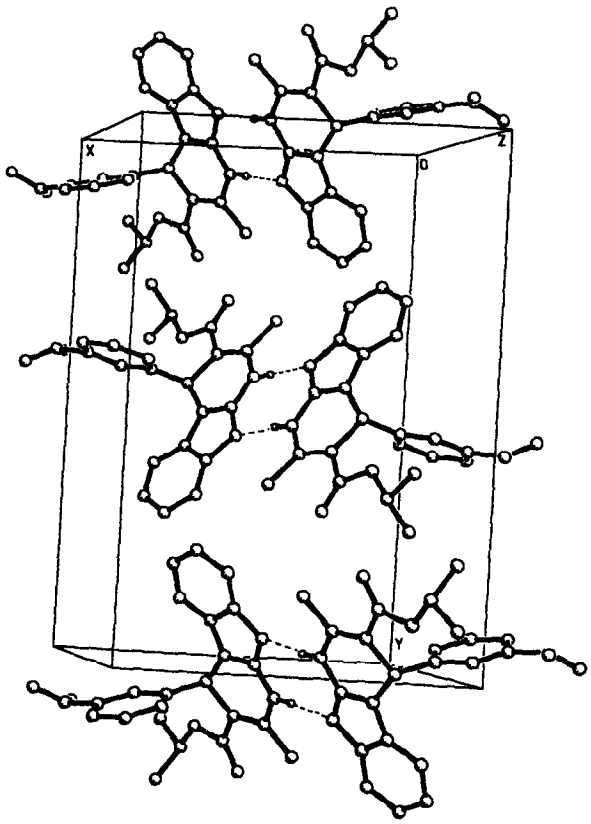


Figure 3. Unit cell packing diagram for compound **11c** (intermolecular hydrogen bonds in broken lines).

Table 2. Spectral data of compounds **10**

compd	IR (KBr, ν cm^{-1})	^{1}H-NMR (δ, ppm)	(M^{+}(rel.int.)
10a	1639, 1588, 1390	9.17 (bs, 1H, NH); 7.4-7.2 (m, 6H, Ar-H phenyl and 5-H); 7.15 and 7.02 (2 bs, 2H, $CONH_2$); 6.35 (s, 1H, 4-H);3.51 (s, 3H, CO_2Me)	312 (37)
10b	1641, 1590, 1389	9.26 (bs, 1H, NH); 7.43 (s, 1H, 5-H);7.4-7.0 (m, 6H, Ar-H fluorophenyl and $CONH_2$); 6.40 (bs, 1H, 4-H); 3.5(s, 3H, CO_2Me)	330 (45)
10c	1659, 1586, 1394	9.31 (bs, 1H, NH); 8.2-7.6 (m, 4H,Ar-H nitrophenyl); 7.41 (s, 1H, 5-H); 7.20 and 7.09 (2 bs, 2H, $CONH_2$); 6.55(s, 1H, 4-H); 4.81 (m, 1H, J= 6.1 Hz, CH); 1.20 (d, 3H, J= 6 1 Hz, Me); 0.92 (d, 3H,J= 6.1 Hz; Me)	385 (69)
10d	1663, 1595, 1529	9.24 (bs, 1H, NH); 8.1-7.5 (m, 4H, Ar-H,nitrophenyl); 7.39 (s, 1H, 5-H); 7.15 and 7.04 (2 bs, 2H, $CONH_2$); 6.48 (s, 1H, 4-H);4.1-3.9 (m, 2H, CO_2CH_2); 3.5-3.3 (m, 2H,CH_2O); 3 11 (s, 3H, OMe); 2.47 (s, 3H, =C-Me)	401 (77)
10e	3159, 1676, 1410	9,51 (s, 1H, NH); 8.2-7.5 (m, 7H, Ar-H dichlorophenyl, $CONH_2$, 4-H 3.29 and 5-H); (s, 3H, CO_2Me)	381 (5)
10f	1667, 1587, 1276	9.28 (s, 1H, NH); 7.5-7.0 (m, 6H, Ar-H dichlorophenyl, $CONH_2$ and 5-H); 6.94 (s, 1H, 4-H); 4.0-3.7 (m, 2H, OCH_2); 2.45 (s, 3H, =C-Me); 0.92 (dt, 3H, J= 7.1 and 1.2 Hz)	395 (7)
10g	1658, 1587, 1407	9.35 (bs, 1H, NH); 7.9-7.2 (m, 7H, Ar-H nitrophenyl, $CONH_2$ and 5-H); 6.68 (s, 1H, 4-H); 3.28 (s, 3H, CO_2Me)	357 (21)
10h	1658, 1586, 1525	9.37 (bs, 1H, NH); 7.9-7.3 (m, 5H, Ar-H nitrophenyl and 5-H); 7.20 and 7.11 (2 bs, 2H, $CONH_2$); 6.77 and 6.76 (2 s, 1H, 4-H diastereomeric); 3.9-3 4 (m, 5H, CO_2CH_2, 2'-CH and 5'-CH_2); 1 8-1.2 (m, 4H, 3'-CH_2 and 4'-CH_2)	427 (19)

Table 3. Spectral data of compounds **11**

compd	IR (KBr, ν cm^{-1})	^{1}H-NMR (δ, ppm)	M^{+}(rel.int)
11a	1704, 1571, 1249	11.13 (bs, 1H, NH); 7.4-6.9 (m, 9H, Ar-H phenyl and bencimidazole); 6.45 (s, 1H, 4-H); 3.58 (s, 3H, CO_2Me); 2.46 (s, 3H, =C-Me)	319 (32)
11b	1616, 1571, 1263	10.92 (bs, 1H, NH); 7.5-6.9 (m, 8H, Ar-H fluorophenyl and bencimidazole); 6.47 (s,1H, 4-H); 3.58 (s, 3H, CO_2Me); 2.45 (s, 3H, =C-Me)	337 (43)
11c	1572, 1521, 1247	10.90 (bs, 1H, NH); 8.3-7.5 (m, 4H, Ar-H nitrophenyl); 7.34 and 7.29 (2 d, 2H, J= 7.8 Hz, 5-H and 8-H); 7.03 and 6.78 (2 dt, 2H, J= 7.8 Hz, J= 1.1 Hz, 6-H and 7-H); 6.61 (s, 1H, 4-H); 4.83 (m, 1H, J= 6.2 Hz, OCH); 2.45 (s, 3H, =C-Me);1.24 (d, 3H, J= 6.2 Hz, CHMe); 0.97 (d, 3H, J= 6.2 Hz, CHMe)	392 (21)
11d	1569, 1525, 1250	11 00 (bs, 1H, NH); 8.3-6.9 (m, 8H, Ar-H nitrophenyl and bencimidazole); 6.62 (s, 1H, 4-H, CH_2-OCO); 4.2-3.9 (m, 2H), 3.6-3.3 (m, 2H, CH_2-OMe); 3.18 (s, 3H, OMe); 2.47 (s, 1H, =C-Me)	
11e	1620, 1576, 1261	10.83 (bs, 1H, NH); 7.4-6.9 (m, 8H, Ar-H nitrophenyl and bencimidazole); 6.74 (s, 1H, 4-H); 3.51 (s, 3H, CO_2Me); 2.44 (s, 3H, =C-Me)	408 (73)
11f	1708, 1618, 1574	7.5-7.1 (m, 8H, Ar-H dichlorophenyl, bencimidazole and NH); 6.96 (s, 1H, 4-H); 3.69 (s, 3H, CO_2Me); 2.71 (s, 3H, =C-Me)	388 (6)
11g	1573, 1254, 1085	7.6-7.2 (m, 9H, Ar-H dichlorophenyl, bencimidazole, NH and 4-H); 4.13 (m, 2H, CH_2OCO); 2.61 (s, 3H, =C-Me); 1.17 (t, 3H, J= 7.1 Hz, CH_2-Me)	402 (9)
11h	1570, 1256, 1077	10.90 (bs, 1H, NH); 7.9-7.2 (m, 8H, Ar-H nitrophenyl and bencimidazole); 7.09 (s,1H, 4-H); 3.56 (s, 3H, CO_2Me); 2.48 (s, 3H, =C-Me)	364 (18)
11i	1619, 1572, 1530	7.9-7.0 (m, 9H, Ar-H nitrophenyl, bencimidazole and 4-H); 4.2-3.6 (m, 5H, CO_2CH_2, 2'-CH and 5'-CH_2); 2 67 (s, 3H, =C-Me); 2.7-1.4 (m, 4H, 3'-CH_2 and 4'-CH_2)	434 (18)
11j	1530, 1350, 1266	10.80 (bs, 1H, 1N); 8.2-7.0 (m, 6H, Ar-H nitrophenyl and bencimidazole); 6.53 (s, 1H, 4-H); 4.82 (m, 1H, CO_2CH); 2.42(s, 3H, =C-Me); 2.16 (s, 3H, Me bencimidazole) 2.14 (s, 3H, Me bencimidazole); 1.23 (d, 3H,J= 6.4 Hz, CHMe); 0.98 (d, 3H, J= 6.4 Hz, CHMe)	420 (40)
11k	1583, 1265, 1246	10.89 (bs, 1H, NH); 7.5-6.7 (m, 6H, Ar-H dichlorophenyl, bencimidazole and 4-H); 3.50 (s, 1H, CO_2Me); 2.42 (s, 3H, =C-Me);2.17 (s, 3H, Me bencimidazole); 2 13 (s, 3H, Me bencimidazole)	416 (100)
11l	1579, 1464, 1265	10.98 (s, 1H, NH); 7.9-7.2 (m, 6H, Ar-H nitrophenyl and bencimidazole); 7.01 and 7.00 (2s, 1H, 4-H);4.0-3.5 (m,5H,CO_2CH_2, 2'-CH and 5'-CH_2); 2.38 (s, 3H =C-Me); 2.18 (s, 3H, Me bencimidazole), 2.12 (s, 3H, Me bencimidazole), 1 9-1.4 (m, 4H, 3'-CH_2 and 4'-CH_2)	462 (15)

Therefore, the conformational features found in these series of compounds, clearly mimic those found in active dihydropyridines and dihydropyrimidines,[12] where a flattened boat conformation of the heterocyclic ring, an orthogonal orientation of the 4-aryl substituent and a *cis* conformation for the carbonyl group have been observed and found to be crucial to confer calcium antagonistic activity.

^{1}H NMR studies also reflect some structural features of these series of compounds (Tables 2 and 3). The ethyl, isopropyl and methoxyethyl radicals of the ester groups appeared as ABX_3, AX_3 and AA'BB' systems respectively, consistent with severe restriction of the rotation of these ester groups in solution. Furthermore, in compounds having the aryl ring disubstituted in both C2' and C6' positions the NMR spectra showed that the H3' and H5' protons appeared as two different signals (e.g. 7.33 and 7.35 ppm in **10f**) with different coupling constants. This is noteworthy and is in agreement with hindered rotation of the aryl group at room temperature. Although other examples of restricted rotation of the aryl substituent in 4-aryl susbtituted dihydropyridines and dihydropyrimidines have been reported, to our knowledge this is the first time that the two signals have been observed at room temperature.[6,13]

Vasorelaxant potency was determined by comparison of the IC_{50} values obtained from concentration–effect curves determined on strips of K^+-depolarized rat thoracic aortae. In the presence of 35 mM K^+, the addition of 1.5 mM Ca^{2+} evoked contractile responses of the rat aortic strips, which were reproducible when repeated at 30 min intervals several times in the same preparation. Addition of increasing concentrations of nifedipine and most of the synthesized compounds evoked a progressive blockade of the Ca^{2+} response. The activity of the new compounds is summarized in Table 4. For structure–activity studies we chose the aromatic substituents commonly employed in active 1,4-dihydropyridines. The effect on the potency of the heteroaromatic moiety fused with the pyrimidine ring was studied by preparing imidazo[1,5-*a*]pyrimidine and benzo[4,5]imidazo[1,2-*a*]pyrimidine analogues. However, in this stage of development still few compounds are active enough to deduce consistent structure–activity relationships. As shown in Table 4, either imidazole (**10c** and **10h**) or benzimidazole (**11b** and **11d**) derivatives are in the group of the more active compounds, without showing any clear preference. Variation of the length and size of the ester group had a significant effect on calcium channel blocking activity in both series. Thus the tetrahydrofuran-2-ylmethyl ester **10h** was more potent than the corresponding methyl ester **10g** and the isopropyl ester

Table 4. The IC_{50} values for vasorelaxant activity of compounds **10** and **11** prepared

Compd	R^1	R^2	R^3	IC_{50}(nM)[a]
10a	H	Me	-	>1000
10b	3-F	Me	-	>1000
10c	3-NO_2	i-Pr	-	190±131.79
10d	3-NO_2	$(CH_2)_2OMe$	-	1000±153.76
10e	2,3-Cl_2	Me	-	>1000
10f	2,6-Cl_2	Et	-	>1000
10g	2-NO_2	Me	-	>1000
10h	2-NO_2	CH_2THF	-	24±11.39
11a	H	Me	H	>1000
11b	3-F	Me	H	150±4.06
11c	3-NO_2	i-Pr	H	3110±624.28
11d	3-NO_2	$(CH_2)_2OMe$	H	30±14.16
11e	2-Cl	Me	H	>1000
11f	2,3-Cl_2	Me	H	>1000
11g	2,6-Cl_2	Et	H	>1000
11h	2-NO_2	Me	H	>1000
11i	2-NO_2	CH_2THF	H	>1000
11j	3-NO_2	i-Pr	Me	550±1.150.29
11k	2,3-Cl_2	Me	Me	>1000
11l	2-NO_2	CH_2THF	Me	>1000
Nifedipine				12±2.30

[a]Data are mean ± standard. Number of experiments = 4.
THF: tetrahydrofuran-2-yl.

10c was more potent than the corresponding methoxyethyl ester **10d**. In contrast, the derivative **11c** was significantly less potent than **11d**. As shown in Table 4, other things being equal in the benzo[4,5]imidazo[1,2-*a*]pyrimidine series, methyl substitution on C-7 and C-8, in one instance, produced approximately a 6 fold increase in potency (**11j** versus **11c**). The most active compounds in both series show similar potency (**10h** versus **11d**)

In conclusion, compounds **10** and **11** possess the most important conformational features of active 1,4-dihydropyridines and 1,4-dihydropyrimidines as demonstrated by X-ray crystallographic analysis of **11c**. Although some of these derivatives were devoid of blocking effects, others showed significant reduction of the K^+-induced contraction in rat aorta and thus an antagonism of the calcium channel, the most active compounds being within the range of the nifedipine effect. New developments are in progress to optimize the activity of the series prepared.

Experimental Section

Chemistry

All melting points were determined on a Buchi SMP-20 apparatus and are uncorrected. IR Spectra were obtained as KBr disks on a Perkin–Elmer 1310 spectrophotometer. ^1H NMR spectra were recorded on a Varian Unity 300 and determined in $(CD_3)_2SO$ and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. Microanalyses were performed on an Heraeus CHN Rapid analyzer, and the results for all new compounds are within 0.4 % error.

Materials

All chemicals were purchased from the Aldrich Chemical Co., Ltd, and were used without further purification. The α-benzylidene-β-keto esters **9** were prepared as previously reported.[14,15]

Typical procedure for the preparation of 1,4-dihydroimidazo[1,5-a]pyrimidine derivatives 10

A mixture of 4-amino-5-carbamoylimidazole hydrochloride (2.25 mmol), the corresponding α-benzylidene-β-keto ester (2.25 mmol), triethylamine (230 mg, 2.25 mmol) and sodium acetate (380 mg, 4.72 mmol) in DMF (2.6 mL) was stirred at room temperature for 15 min and then heated at 65 °C for 24 h. The reaction mixture was cooled and poured into cold water (15 mL). The precipitate formed was collected by filtration, washed with water (3 x 5 mL) and recrystallized, affording pure compounds **10**.

Typical procedure for the preparation of 1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine derivatives 11

A mixture of 2-aminobenzimidazole or 2-amino-5,6-dimethylbenzimidazole (2.5 mmol), the corresponding α-benzylidene-β-keto ester (2.5 mmol) and sodium acetate (430 mg, 5.24 mmol) in DMF (3 mL) was heated at 65 °C for 24 h. The reaction mixture was worked up as above indicated for compounds **10**.

Single-crystal X-ray structure determination of 11c

Crystal data for compound **11c**: Molecular formula: $C_{21}H_{20}N_4O_4$ M = 391.41, space group $P2_1/c$, a = 12.369(8), b = 18.864(7), c = 8.946(6) Å, β = 109.98(3)°, U = 1974(4) $Å^3$ (by least-squares refinement on diffractometer angles for 25 automatically centred reflections), λ = 0.71073 Å, Z = 4, Dc = 1.317 g cm^{-3}. Yellow, 0.20 x 0.32 x 0.35 $mm,^3$ μ(MoKα) = 0.874 cm^{-1} F(000) = 820.0. All crystallographic measurements were made on a ENRAF–NONIUS CAD4 diffractometer, ω/2θ mode with ω scan width = 2.40 + 1.05 tan ω, ω scan speed 1.2–8.2 deg min^{-1}, graphite–monochromated MoKα radiation; number of reflections measured 6170 [$2.0 \leq \theta \leq 30$ °, $O \leq h \leq 17$, $-0 \leq k \leq 26$, $-12 \leq l \leq 12$]; 3932 observed reflections with $I \leq 2\sigma(I)$, two standard reflections were measured every 120 min and no variation was detected. The structure was solved by direct methods using MULTAN,[16] DIRDIF[17] and SPD Structure Determination Package, ENRAF–NONIUS Programms.[18] Full-matrix least squares refinement with all non-H atoms anisotropic. The H-atoms were experimentally determined with the exception of H-atoms of the methyl groups. Final R and Rw values are 0.062 and 0.085 with

$$Rw = \left[\frac{\sum w \left[|Fo| - |Fc| \right]^2}{\sum w |Fo|^2} \right]^{1/2} \quad \text{and} \quad w = 4Fo^2/\sigma\left[|Fo|^2 \right]^2$$

Highest peak in final DF map 0.4 e A^{-3}. Source of data for scattering factors is given in Reference 19.

Pharmacology. Vasorelaxant potency

Male Sprague rats weighing 250–300 g were sacrificed and the thoracic aorta removed and placed in Krebs-bicarbonate buffer. Excess fat and tissue was removed, and the aorta was cut in helicoidal strips.[20] The procedure was essentially as described by Van Rosum[21] and Yousif.[22] Strips were mounted in organ baths under a 2.5 g preload in a Krebs-bicarbonate solution at 37 °C and bubbled with 95 % O_2 + 5 % CO_2 (final pH = 7.4). Equilibration was allowed for 1 h. The aorta was washed every 20 min to avoid interference of metabolites. Afterwards, a depolarization was induced by adding 35 mmol K^+ (without osmotic adjustments), and 10 min later 1.5 mmol Ca^{2+} was added to evoke contractions. This process was repeated until a reproducible response was achieved. Strips were thereafter exposed to increasing concentrations of compounds **10** and **11** or nifedipine, 20 min before and during the Ca^{2+} addition period. Responses in the presence of each concentration were recorded and normalized with respect to initially recorded tensions. IC_{50} values were determined from concentration–response curves using the method of Finney.[23]

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