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# Synthesis and Structure of New Pyrido[2,3-d]pyrimidine Derivatives with Calcium Channel Antagonist Activity

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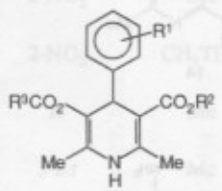
**Abstract.**- Several series of pyrido[2,3-d]pyrimidine derivatives were synthesized by reaction of aryl-methyleneacetoacetates with different aminopyrimidines. The solid-state structure of the methyl 5-(3´-chlorophenyl)-7-methyl-4-oxo-2-thioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6-carboxylate shows that these compounds can adopt some of the most important structural features of the 1,4-dihydropyridine calcium channel blockers. The scope and limitations of the synthetic procedure with different aminoheterocycles is presented together with the initial evaluation of their calcium antagonistic activity by comparison with the usual reference compound nifedipine.

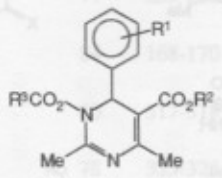
## INTRODUCTION

At the beginning of 1975 the 4-aryl-substituted 1,4-dihydropyridine-3,5-dicarboxylic esters of the nifedipine type **1** were successfully introduced for the treatment of coronary diseases.[1-3] Since then an enormous effort has been devoted to the development of newer generations of 1,4-dihydropyridines as powerful arteriolar vasodilators with relatively few effects on the heart.[4-7] All these compounds block the influx of extracellular $Ca^{+2}$ through several types of calcium channels and are known as calcium channel antagonists.[8,9]

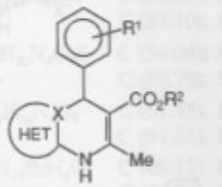



**1**

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




**2**




**3**

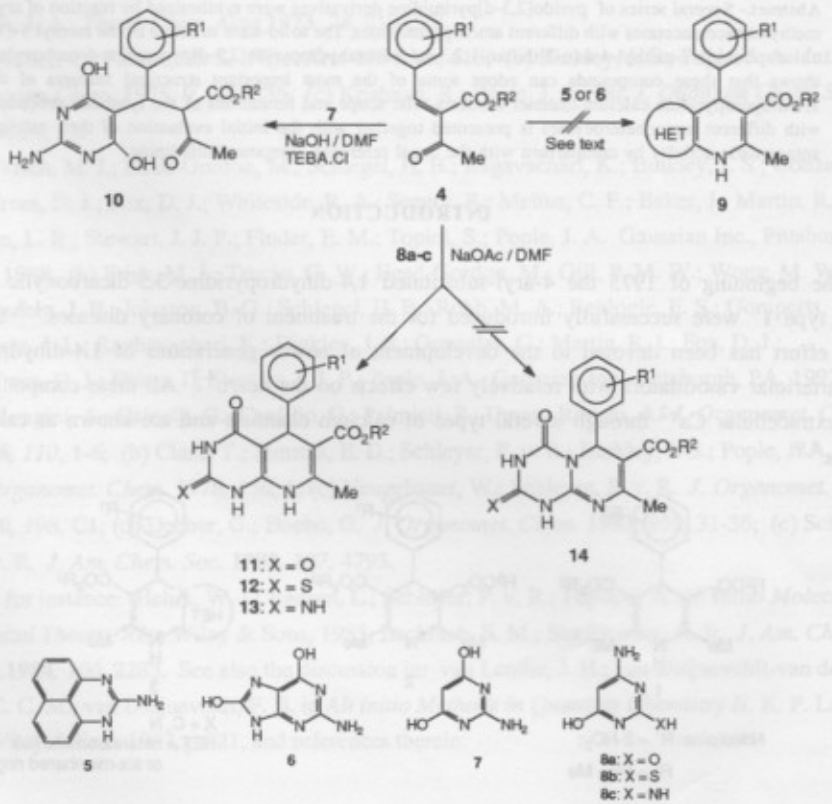
X = C, N
HET = heteroaromatic five or six-membered ring

The switch from antagonist to agonist[10-13] (compounds that enhance rather than attenuate $Ca^{+2}$ influx) can be produced by replacement of an ester group, although recent studies have shown that dihydropyrimidines **2**, fused 1,4-dihydropyridines and bicyclic dihydropyrimidines **3** imitate the vasorelaxant potency of most active 1,4-dihydropyridine calcium channel blockers.[14-16] The discovery of various subtypes of $Ca^{+2}$ channels with different tissue distribution[12] has stimulated the ongoing synthesis of these type of compounds with the aim of obtaining new derivatives with enhanced tissue selectivity.

In connection with our previously reported syntheses of furnidipine,[7] a novel and potent calcium antagonist, 4-alkyl-1,4-dihydropyridines with antithrombotic[17] or PAF-antagonistic[18] activities and bicyclic dihydropyrimidines with vasorelaxant activity,[19] we now report the synthesis and structural aspects of a series of pyrido[2,3-d]pyrimidine derivatives **11-13**. Initial vasorelaxant activity of these derivatives is also included.

## RESULTS AND DISCUSSION

For the synthesis of the desired derivatives we initially tested the condensation of several amino heterocycles **5-8** with arylmethyleneacetoacetates **4**. Attempted condensation of 2-aminoperimidine **5** and 2-aminopurine **6** with different arylmethyleneacetoacetates under a variety of reaction conditions (DMF/NaOAc/100 °C, DMF/NaOH/65 °C, DMF/$CH_2Cl_2$/t-BuOK/r. t.) gave complex mixtures with no evidence of the formation of the required derivatives **9**. Attempts to condense the 2-amino-4,6-dihydroxypyrimidine **7** with methyl 2-(3′-chlorophenylmethylene)acetoacetate under similar conditions,




**Scheme 1**

resulted in nucleophilic C5 attack and gave **10**, although in modest yield (15%). In contrast the 4-amino-2,6-dihydroxypyrimidine **8a** cleanly reacted with this arylmethylene derivative to afford the condensation product

**Table 1.** Preparation and Physical Properties of Pyrido[2,3-d]pyrimidine Derivatives **11-13**.

| Compd | X | $R^1$ | $R^2$ | yield, % | mp, °C[a] | formula[b] | analyses, calcd/found |
|---|---|---|---|---|---|---|---|
| **11a** | O | H | Me | 78 | 264-265 | $C_{16}H_{15}N_3O_4$ | C (61.33); H (4.83); N (13.41)<br>C (61.03); H (4.40); N (13.70) |
| **11b** | O | 3-Br | Me | 67 | 315-316 | $C_{16}H_{14}BrN_3O_4$ | C (49.00); H (3.60); N (10.71)<br>C (48.60); H (3.89); N (11.90) |
| **11c** | O | 3-F | Me | 89 | 269-271 | $C_{16}H_{14}FN_3O_4$ | C (58.00); H (4.26); N (12.68)<br>C (57.59); H (4.42); N (12.35) |
| **11d** | O | 3-$NO_2$ | Et | 83 | 282-284 | $C_{17}H_{16}N_4O_6$ | C (54.84); H (4.33); N (15.05)<br>C (54.61); H (4.70); N (15.31) |
| **11e** | O | 3-$NO_2$ | i-Pr | 82 | 248-250 | $C_{18}H_{18}N_4O_6$ | C (55.95); H (4.69); N (14.50)<br>C (55.68); H (5.10); N (14.13) |
| **11f** | O | 3-$NO_2$ | $(CH_2)_2$-OMe | 92 | 260-262 | $C_{18}H_{18}N_4O_7$ | C (53.73); H (4.51); N (13.93)<br>C (53.48); H (4.80); N (13.68) |
| **11g** | O | 2,3-diCl | Me | 58 | 309-310 | $C_{16}H_{13}Cl_2N_3O_4$ | C (48.38); H (3.68); N (10.75)<br>C (48.68); H (3.43); N (10.99) |
| **11h** | O | 2-$NO_2$ | Me | 70 | 284-286 | $C_{16}H_{14}N_4O_6$ | C (53.63); H (3.94); N (15.64)<br>C (53.82); H (3.80); N (15.35) |
| **11i** | O | 2-$NO_2$ | Et | 67 | 274-275 | $C_{17}H_{16}N_4O_6$ | C (54.84); H (4.33); N (15.05)<br>C (54.65); H (4.60); N (15.35) |
| **11j** | O | 2-$NO_2$ | $CH_2$THF | 65 | 247-249 | $C_{20}H_{20}N_4O_7$ | C (56.07); H (4.71); N (13.08)<br>C (55.84); H (4.43); N (12.73) |
| **12a** | S | 3-Br | Me | 84 | 258-259 | $C_{16}H_{14}BrN_3O_3S$ | C (47.07); H (3.46); N (10.29)<br>C (47.58); H (3.67); N (13.30) |
| **12b** | S | 3-Cl | Me | 87 | 257-258 | $C_{16}H_{14}ClN_3O_3S$ | C (52.82); H (3.88); N (11.55)<br>C (52.53); H (4.21); N (11.83) |
| **12c** | S | 3-$NO_2$ | i-Pr | 83 | 268-269 | $C_{18}H_{18}N_4O_5S$ | C (53.72); H (4.51); N (13.92)<br>C (53.96); H (4.87); N (14.31) |
| **12d** | S | 3-$NO_2$ | Et | 86 | 260-261 | $C_{17}H_{16}N_4O_5S$ | C (52.57); H (4.15); N (14.43)<br>C (52.70); H (4.42); N (14.36) |
| **12e** | S | 3-$NO_2$ | Me | 86 | 239-240 | $C_{16}H_{14}N_4O_5S$ | C (51.33); H (3.77); N (14.97)<br>C (51.04); H (4.01); N (15.20) |
| **12f** | S | 2-$NO_2$ | Me | 71 | 259-260 | $C_{16}H_{14}N_4O_5S$ | C (51.33); H (3.77); N (14.97)<br>C (51.10); H (4.05); N (15.21) |
| **12g** | S | 2-$NO_2$ | $CH_2$THF | 84 | 168-170 | $C_{20}H_{20}N_4O_6S$ | C (54.04); H (4.54); N (12.61)<br>C (53.79); H (4.82); N (12.91) |
| **13a** | NH | H | Me | 60 | 317-318 | $C_{16}H_{16}N_4O_3$ | C (61.53); H (5.16); N (17.94)<br>C (61.25); H (4.98); N (17.69) |
| **13b** | NH | 3-Br | Me | 78 | 325-326 | $C_{16}H_{15}BrN_4O_3$ | C (49.12); H (3.87); N (14.32)<br>C (48.88); H (3.98); N (14.68) |
| **13c** | NH | 3-Cl | Me | 77 | 309-310 | $C_{16}H_{15}ClN_4O_3$ | C (55.41); H (4.36); N (16.16)<br>C (55.14); H (4.51); N (16.52) |
| **13d** | NH | 3-$NO_2$ | Et | 71 | 284-285 | $C_{17}H_{17}N_5O_5$ | C (54.98); H (4.62); N (18.86)<br>C (54.69); H (4.58); N (19.11) |
| **13e** | NH | 3-$NO_2$ | $CH_2$THF | 80 | 305-306 | $C_{20}H_{21}N_5O_6$ | C (56.20); H (4.95); N (16.39)<br>C (55.98); H (5.10); N (16.61) |
| **13f** | NH | 2-$NO_2$ | i-Pr | 78 | 325-327 | $C_{18}H_{19}N_5O_5$ | C (56.10); H (4.97); N (18.17)<br>C (55.89); H (5.15); N (17.94) |

[a] Compounds were recrystallized from $H_2O$/DMF except **11a, 13a, 13d,e** from EtOH. *THF* = Tetrahydrofuran-2-yl
[b] Compounds crystallized as yellow powders, except for **11b,c, 11c, 11g, 12a,b, 13b,c** which were white powders.

**Table 2**. Spectral Data of Compounds **11-13**.

| Compound | Ir (KBr, $\upsilon$ $cm^{-1}$) | $^1$H-NMR (DMSO-$d_6$, $\delta$ ppm) | $M^{+\cdot}$ (rel. int) |
|---|---|---|---|
| **11a** | 1706, 1664, 1615 | 10.49 (bs, 1H, NH); 9.71 (bs, 1H, NH); 7.2-6.9 (m, 5H, Ar-H phenyl); 6.71 (bs, 1H, NH); 4.80 (s, 1H, 5-H); 3.50 (s, 3H, $CO_2Me$); 2.29 (s, 3H, Me) | 313 (32) |
| **11b** | 1712, 1673, 1536 | 10.70 (s, 1H, NH); 10.09 (bs, 1H, NH); 8.64 (bs, 1H, NH); 7.3-7.1 (m, 4H, Ar-H bromophenyl); 4.77 (s, 1H, 5-H); 3.52 (s, 3H, $CO_2Me$); 2.31 (s, 3H, Me) | 392 (38) |
| **11c** | 1706, 1672, 1539 | 10.63 (s, 1H, NH); 10-8.5 (bs, 2H, 2NH); 7.3-6.9 (m, 4H, Ar-H fluorophenyl); 4.82 (s, 1H, 5-H); 3.52 (s, 3H, $CO_2Me$); 2.31 (s, 3H, Me) | 331 (20) |
| **11d** | 1716, 1604, 1525 | 10.76 (s, 1H, NH); 10.17 (bs, 1H, NH); 8.74 (bs, 1H, NH); 8-7.5 (m, 4H, Ar-H nitrophenyl); 4.90 (s, 1H, 5-H); 3.94 (q, 2H, J= 7.1 Hz, $CO_2CH_2$); 2.33 (s, 3H, Me); 1.07 (t, 3H, J= 7.1 Hz, $CH_2\underline{Me}$) | 372 (15) |
| **11e** | 1531, 1350, 1267 | 10.75 (bs, 1H, NH); 10.32 (bs, 1H, NH); 8.90 (bs,1H, NH); 8.1-7.5 (m, 4H, Ar-H nitrophenyl); 4.90 (s, 1H, 5-H); 4.75 (hp, 1H, J=6.1 Hz, $CO_2CH$); 2.31 (s, 3H, Me); 1.16 (d, 3H, J=6.1 Hz, $CH\underline{Me}$); 0.91 (d, 3H, J=6.1 Hz, $CH\underline{Me}$) | 386 (13) |
| **11f** | 1714, 1695, 1208 | 10.67 (s, 1H, NH); 10-9 (bs, 2H, 2NH); 8-7.9 (m, 4H, Ar-H nitrophenyl); 4.89 (s, 1H, 5-H); 4-3.9 (m, 2H, $CO_2CH_2$); 3.5-3.4 (m, 2H, $CO_2CH_2\underline{CH_2}$); 3.17 (s, 3H, OMe); 2.3 (s, 3H, Me) | 402 (7) |
| **11g** | 1706, 1674, 1205 | 10.64 (s, 1H, NH); 10.08 (bs, 1H, NH); 8.68 (bs, 1H, NH); 7.4-7.2 (m, 3H, Ar-H dichlorophenyl); 5.22 (s, 1H, 5-H); 3.46 (s, 3H, $CO_2Me$); 2.26 (s, 3H, Me) | 382 (26) |
| **11h** | 1706, 1606, 1529 | 10.54 (s, 1H, NH); 9.35 (bs, 1H, NH); 8.73 (bs, 1H, NH); 7.8-7.3 (m, 4H, Ar-H nitrophenyl); 5.62 (s, 1H, 5-H); 3.40 (s, 3H, $CO_2Me$); 2.29 (s, 3H, Me) | 358 (18) |
| **11i** | 1703, 1646, 1530 | 10.64 (s, 1H, NH); 10.01 (bs, 1H, NH); 8.61 (bs, 1H, NH); 7.8-7.3 (m, 4H, Ar-H nitrophenyl); 5.69 (s, 1H, 5-H); 4-3.7 (m, 2H, $CO_2CH_2$); 2.31 (s, 3H, Me); 0.94 (t, 3H, J=7.1 Hz, $CO_2CH_2\underline{Me}$) | 372 (22) |
| **11j** | 1729, 1688, 1637 | 10.63 (s, 1H, NH); 10.08 (bs, 1H, NH); 8.71 (bs, 1H, NH); 7.8-7.3 (m, 4H, Ar-H nitrophenyl); 5.70 and 5.68 (s and s, 1H, 5-H diastereomeric); 3.9-3.7 (m, 3H, $CO_2CH_2CH$); 3.6-3.4 (m, 2H, O-$CH_2$); 2.32 (s, 3H, Me); 1.7-1.1 (m, 4H, O-$CH_2\underline{CH_2CH_2}$) | 428 (11) |
| **12a** | 1657, 1629, 1553 | 12.19 (s, 1H, NH); 11.54 (s, 1H, NH); 8.37 (s, 1H, NH); 7.4-7.1 (m, 4H, Ar-H bromophenyl); 4.77 (s, 1H, 5-H); 3.52 (s, 3H, $CO_2Me$); 2.31 (s, 3H, Me) | 408 (8) |
| **12b** | 1658, 1629, 1552 | 12.20 (s, 1H, NH); 11.53 (s, 1H, NH); 8.37 (s, 1H, NH); 7.3-7.1 (m, 4H, Ar-H chlorophenyl); 4.79 (s, 1H, 5-H); 3.52 (s, 3H, $CO_2Me$); 2.31 (s, 3H, Me) | 363.5 (11) |

**Table 2.** Spectral Data of Compounds **11-13** (cont.).

| Compound | Ir (KBr, $\upsilon$ $cm^{-1}$) | $^1$H-NMR (DMSO-$d_6$, $\delta$ ppm) | $M^{+}$ (rel. int) |
|---|---|---|---|
| **12c** | 1651, 1557, 1526 | 12.18 (s, 1H, NH); 11.56 (s, 1H, NH); 8.41 (s, 1H, NH); 8.1-7.5 (m, 4H, Ar-H nitrophenyl); 4.88 (s, 1H, 5-H); 4.76 (hp, 1H, J= 6.1 Hz, $CO_2CH$); 2.32 (s, 3H, Me); 1.15 (d, 3H, J= 6.1 Hz, CHMe); 0.91 (d, 3H, J=6.1 Hz, CHMe) | 402 (10) |
| **12d** | 1574, 1516, 1207 | 12.19 (s, 1H, NH); 11.57 (s, 1H, NH); 8.45 (s, 1H, NH); 8.1-7.5 (m, 4H, Ar-H nitrophenyl); 4.91 (s, 1H, 5-H); 3.95 (q, 2H, J= 7.1 Hz, $CO_2CH_2$); 2.34 (s, 3H, Me); 1.07 (t, 3H, J= 7.1 Hz, $CO_2CH_2Me$) | 388 (8) |
| **12e** | 1571, 1523, 1210 | 12.22 (s, 1H, NH); 11.59 (bs, 1H, NH); 8.46 (s, 1H, NH); 8.1-7.5 (m, 4H, Ar-H nitrophenyl); 4.92 (s, 1H, 5-H); 3.51 (s, 3H, $CO_2Me$); 2.34 (s, 3H, Me) | 374 (5) |
| **12f** | 1680, 1555, 1206 | 12.10 (s, 1H, NH); 11.50 (bs, 1H, NH); 8.39 (s, 1H, NH); 7.8-7.3 (m,4H, Ar-H nitrophenyl); 5.65 (s, 1H, 5-H); 3.42 (s, 3H, $CO_2Me$); 2.29 (s, 3H, Me) | 374 (5) |
| **12g** | 1650, 1526, 1205 | 12.02 (s, 1H, NH); 11.50 (bs, 1H, NH); 8.41 (s, 1H, NH); 7.8-7.3 (m, 4H, Ar-H nitrophenyl); 5.74 and 5.71 (s and s, 1H, 5-H); 3.9-3.7 (m, 3H, $CO_2CH_2CH$); 3.6-3.5 (m, 2H, O-$CH_2$); 2.31 (s, 3H, Me); 1.7-1.2 (m, 4H, O-$CH_2CH_2CH_3$) | 444 (3) |
| **13a** | 1659, 1630, 1588 | 10.31 (bs, 1H, NH); 9.07 (s, 1H, NH); 7.2-7 (m, 4H, Ar-H phenyl); 6.25 (bs, 2H, $NH_2$); 4.84 (s, 1H, 5-H); 3.48 (s, 3H, $CO_2Me$); 2.29 (s, 3H, Me) | 312 (100) |
| **13b** | 1656, 1630, 1600 | 10.35 (s, 1H, NH); 9.15 (s, 1H, NH); 7.4-7.1 (m, 4H, Ar-H bromophenyl); 6.31 (s, 2H, $NH_2$); 4.82 (s, 1H, 5-H); 3.49 (s, 3H, $CO_2Me$); 2.31 (s, 3H, Me) | - |
| **13c** | 1656, 1630, 1599 | 10.36 (s, 1H, NH); 9.16 (s, 1H, NH); 7.3-7.1 (m, 4H, Ar-H chlorophenyl); 6.31 (s, 2H, $NH_2$); 4.83 (s, 1H, 5-H); 3.49 (s, 3H, $CO_2Me$); 2.31 (s, 3H, Me) | - |
| **13d** | 1663, 1593, 1521 | 10.39 (s, 1H, NH); 9.22 (s, 1H, NH); 8.1-7.4 (m, 4H, Ar-H nitrophenyl); 6.35 (s, 2H, $NH_2$); 4.93 (s, 1H, 5-H); 3.91 (q, 2H, J= 7.1 Hz, $CO_2CH_2$); 2.31 (s, 3H, Me); 1.06 (t, 3H, J= 7.1 Hz, $CO_2CH_2Me$) | 371 (7) |
| **13e** | 1643, 1521, 1455 | 10.40 (s, 1H, NH); 9.27 (s, 1H, NH); 8.1-7.4 (m, 4H, Ar-H nitrophenyl); 6.35 (s, 2H, $NH_2$); 4.95 (s, 1H, 5-H); 4-3.7 (m, 3H, $CO_2CH_2CH$); 3.8-3.5 (m, 2H, O-$CH_2$); 2.33 (s, 3H, Me); 1.9-1.3 (m, 4H, O-$CH_2CH_2CH_3$) | 427 (3) |
| **13f** | 1670, 1523, 1459 | 10.15 (s, 1H, NH); 9.06 (s, 1H, NH); 7.8-7.2 (m, 4H, Ar-H nitrophenyl); 6.30 (s, 2H, $NH_2$); 5.74 (s, 1H, 5-H); 4.70 (hp, 1H, J= 6.1 Hz, $CO_2CH$); 2.30 (s, 3H, Me); 1.07 (d, 3H, J= 6.1 Hz, $CO_2CHMe$); 0.67 (d, 3H, J=6.1 Hz, $CO_2CHMe$) | - |

in very good yield (Scheme 1). Based on this result we condensed other substituted pyrimidines with compounds **4** containing ester and aryl groups known to impart maximum potency to previously studied dihydropyridine and dihydropyrimidine calcium antagonists. The series of bicyclic derivatives **11-13** thus obtained are shown in Table 1.

The structures of compounds **11-13** were initially assigned on the basis of the isolation of the adduct **10** and assuming a Michael attack by the C5 of the pyrimidine ring on the arylmethyleneacetoacetate followed by cyclization. Alternative structures **14** produced by Michael attack of the nitrogen atom were also considered but discarded on the basis of the $^1$H NMR spectra obtained. In particular, the presence of three acidic protons, whose interchange with $D_2O$ cleanly supports the pyrido[2,3-d]pyrimidine structure for these derivatives. This structure was confirmed by X-ray crystallographic analysis of the methyl 5-(3´-chlorophenyl)-7-methyl-4-oxo-2-thioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6-carboxylate **12b**. When this compound was crystallized in the presence of triphenylphosphine oxide, nice crystals formed in comparison with the low-quality ones obtained with this and other derivatives in the pure form. The structure showing the adopted atomic labeling[20] is given in Figures 1 and 2 and is built of discrete molecular complexes formed by one molecule of triphenylphosphine oxide linked to one molecule of **12b**. The bonding takes place through the O atom of the triphenylphosphine oxide and N1 and N2 atoms of the heterocyclic unit. The O atom supports two hydrogen bonds. The geometry of the triphenylphosphine oxide is similar to that found in the literature.[21] The crystal structure consists of alternative heterocyclic units and triphenylphosphine oxide molecules with a hydrogen bond between O1....N3 of different molecules. There are also two short intermolecular contacts between O2.....N2 (3.169 (3) Å) and O2....N3 (3.239 (3) Å).

In the solid state of **12b** the heterocyclic moiety is nearly planar with a dihedral angle between the two rings of 3.3° although the disposition of the N1 and C1 atoms confers on the dihydropyridine ring a flattened boat conformation with both atoms slightly above the main plane of the molecule. The aryl ring is in a pseudoaxial position and almost orthogonal to the main plane of the bicyclic system (93.2°). The *meta*-chloro substituent is in an antiperiplanar (*ap*) orientation with respect to H1 and points toward the dihydropyridine ring. This result is noteworthy since many X-ray structural analyses of dihydropyridines show that the sinperiplanar (*sp*) form is favoured in the crystalline state,[23] with a few exceptions.[24-26] On the other hand, the *ap* conformation has been postulated in less active bicyclic dihydropyridines.[27] The preference for the *ap* form in derivative **12b** may be a consequence of the co-crystallization with triphenylphosphine which forces the *ap* conformation over the *sp* although an intrinsic preference for the *ap* form in the solid state of compound **12b** can not be ruled out. The ester group lies above the plane of the bicyclic system (18.79°) with the carbonyl group in the *trans* conformation with respect to the double bond of the dihydropyridine ring. This latter result is in accord with previously reported studies showing a preference for this conformation in dihydropyridine derivatives without *ortho* substitution.[28] Finally, the 6-oxo and 5-thioxo forms are also favoured in the pyrimidine ring rather than the corresponding tautomeric forms. Selected distances and angles are shown in Tables 3-6.

An important aspect of the rotation of the ester groups can also be deduced by $^1$H NMR spectroscopy of some derivatives. Thus the ethyl radical of the ester group in **11i** appears as an $ABX_3$ system, the isopropyl as an $AX_3Y_3$ system in **11e**, **12c** and **13f** and the methoxyethyl as an AA'BB' in **11f**. This is consistent with severe restriction of the rotation of these ester groups in solution at room temperature, which arises as a result of the corresponding hindered rotation of the neighbouring aryl groups as was found in fused dihydropyrimidine derivatives.[19] In contrast, $^1$H NMR spectra of derivatives having an ethyl radical and

**Figure 1.** Computer-generated perspective (PLUTO) drawing of **12b** and triphenylphosphine with the atom numbering used in the crystal structure analysis (selected bond distances and angles are shown in Tables 3-5).

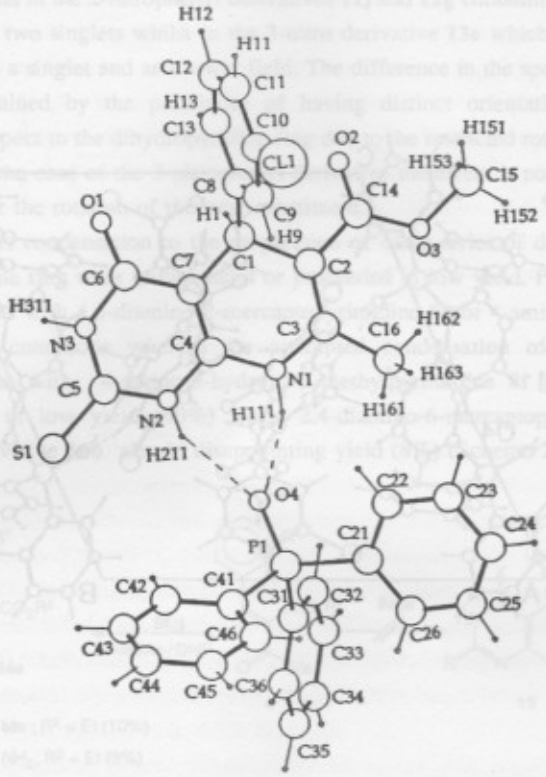



**Table 3.** Selected bond distances (Å)

| | | | |
|---|---|---|---|
| C1 - C2 | 1.536 (3) | C5 - S1 | 1.670 (2) |
| C1 - C7 | 1.509 (3) | N3 - C6 | 1.401 (2) |
| C1 - C8 | 1.531 (3) | C6 - C7 | 1.432 (3) |
| C2 - C3 | 1.356 (3) | C6 - O1 | 1.234 (2) |
| C2 - C14 | 1.479 (3) | C10 - Cl1 | 1.746 (4) |
| C3 - N1 | 1.389 (2) | C14 - O2 | 1.206 (3) |
| C3 - C16 | 1.505 (3) | C14 - O3 | 1.341 (3) |
| N1 - C4 | 1.369 (3) | O3 - C15 | 1.452 (4) |
| C4 - N2 | 1.373 (2) | P1 - O4 | 1.500 (2) |
| C4 - C7 | 1.358 (3) | P1 - C21 | 1.808 (3) |
| N2 - C5 | 1.360 (3) | P1 - C31 | 1.801 (3) |
| C5 - N3 | 1.357 (3) | P1 - C41 | 1.804 (3) |

**Table 4.** Selected bond angles (degrees)

| | | | |
|---|---|---|---|
| C7 - C1 - C8 | 111.1 (2) | C14 - O3 - C15 | 116.1 (3) |
| C2 - C1 - C8 | 111.9 (2) | C31 - P1 - C41 | 107.4 (1) |
| C2 - C1 - C7 | 110.5 (2) | C21 - P1 - C41 | 107.9 (2) |
| N2 - C5 - N3 | 114.9 (2) | C21 - P1 - C31 | 106.3 (2) |
| C5 - N3 - C6 | 126.1 (3) | O4 - P1 - C41 | 111.2 (2) |
| C2 - C14 - O3 | 114.7 (2) | O4 - P1 - C31 | 112.4 (2) |
| C2 - C14 - O2 | 122.6 (3) | O4 - P1 - C21 | 111.4 (1) |
| O2 - C14 - O3 | 122.7 (3) | | |

**Table 5.** Selected torsion angles (degrees)

| | | | |
|---|---|---|---|
| C2 - C1 - C7 - C4 | 1.6 (4) | N2 - C5 - N3 - C6 | 1.9 (4) |
| C7 - C1 - C2 - C3 | 0.1 (4) | C5 - N3 - C6 - C7 | -4.2 (4) |
| C1 - C2 - C3 - N1 | -3.1 (4) | N3 - C6 - C7 - C4 | 4.6 (4) |
| C2 - C3 - N1 - C4 | 4.7 (4) | O4 - P1 - C41 - C42 | 42.1 (3) |
| C3 - N1 - C4 - C7 | -3.1 (4) | O4 - P1 - C41 - C46 | -136.1 (3) |
| N1 - C4 - C7 - C1 | -0.2 (4) | O4 - P1 - C31 - C32 | 36.7 (3) |
| N2 - C4 - C7 - C6 | -3.3 (4) | O4 - P1 - C31 - C36 | -147.0 (3) |
| C7 - C4 - N2 - C5 | 1.0 (4) | O4 - P1 - C21 - C22 | 23.3 (3) |
| C4 - N2 - C5 - N3 | -0.2 (4) | O4 - P1 - C21 - C26 | -157.0 (3) |

**Figure 2.** Stereoview of the unit cell packing arrangement of **12b**-triphenylphosphine with intermolecular hydrogen bonds in broken lines (distances and angles are shown in Table 6).

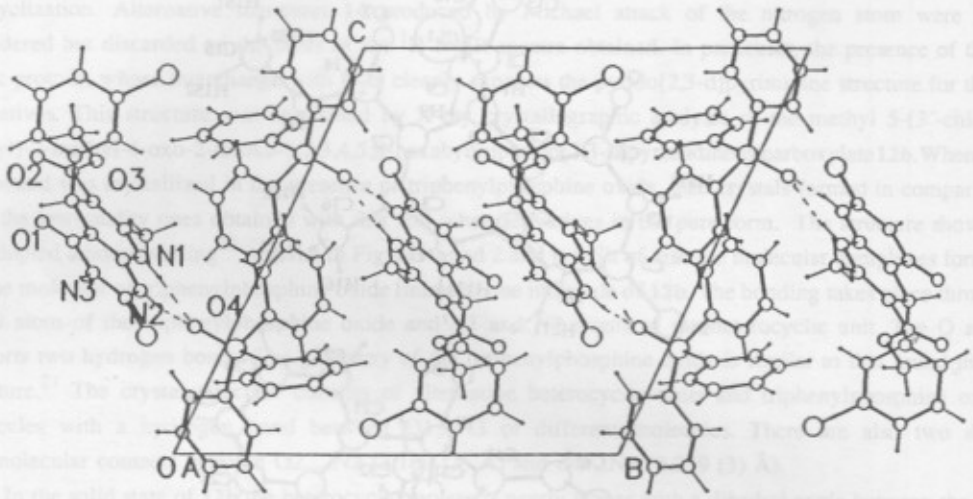



**Table 6.** Hydrogen Bonds in the Complex **12b**-Triphenylphosphine

| Donor - H | Donor .... Acceptor | H .... Acceptor | Donor - H ..... Acceptor |
|---|---|---|---|
| N1 - H111 | N1 ..... O4 (0) | H111 ..... O4 (0) | N1 - H111 ..... O4 (0) |
| 0.887(30) | 2.755 (2) | 1.919 (28) | 156.49 (3.06) |
| 1.030 | | 1.788 | 154.65 (*) |
| N2 - H211 | N2 ..... O4 (0) | H211 ..... O4 (0) | N2 - H211 ..... O4 (0) |
| 0.818 (30) | 2.821 (3) | 2.086 (32) | 149.55 (3.19) |
| 1.030 | | 1.906 | 146.31 (*) |
| N3 - H311 | N3 ..... O1 (1) | H311 ..... O1 (1) | N3 - H311 ..... O1 (0) |
| 0.847 (35) | 2.776 (3) | 1.939 (35) | 169.48 (3.13) |
| 1.030 | | 1.760 | 168.40 (*) |

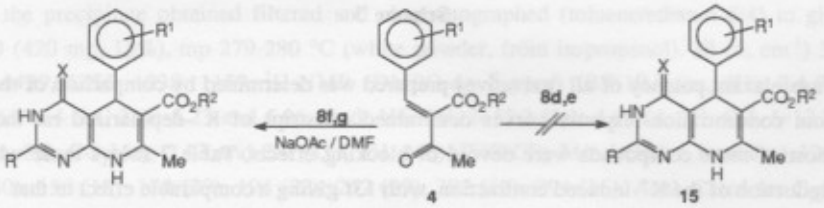
(*) Values normalized following ref. 22.

Equivalent positions: (0): X, Y, Z; (1): -X+1, -Y-1, -Z+1; (2): +X, +Y+1, +Z+1

3-phenyl substitution (**11d**, **12d** and **13d**) show for this radical the typical triplet and quadruplet signals which is in concordance with a lower energy barrier for the rotation of the ester group.

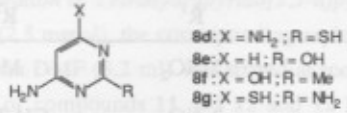
It is also noteworthy that in the 2-nitrophenyl derivatives **11j** and **12g** containing a tetrahydrofuran-2-yl methyl ester, H5 appears as two singlets whilst in the 3-nitro derivative **13e** which also has the same ester group, the proton appears as a singlet and at a lower field. The difference in the spectra of **11j** (or **12g**) and **13e** can probably be explained by the possibility of having distinct orientations in solution of the 2-nitrophenyl group with respect to the dihydropyridine ring due to the restricted rotation, thus rendering the H5 proton unequivalent. In the case of the 3-nitrophenyl derivative the effect is not observed probably due to a lower energy barrier for the rotation of this aryl substituent.

Attempts to extend this condensation to the preparation of other series of derivatives with different substitution on the pyrimidine ring were unsuccessful or proceeded in low yield. For instance, the reaction of arylmethyleneacetoacetates with 4,6-diamino-2-mercaptopyrimidine **8d** or 4-amino-2-hydroxypyrimidine **8e** failed under various conditions whereas the attempted condensation of the ethyl 2-(3´-nitrophenylmethylene)acetoacetate with 4-amino-6-hydroxy-2-methylpyrimidine **8f** gave the pyrido[2,3-d]-pyrimidine derivative **16a** in low yield (10%) while 2,4-diamino-6-mercaptopyrimidine **8g** gave the corresponding bicyclic derivative **16b** also in disappointing yield (8%) (Scheme 2).




**16a**: X = O; R = Me ; $R^2$ = Et (10%)

**16b**: X = S; R = $NH_2$; $R^2$ = Et (8%)



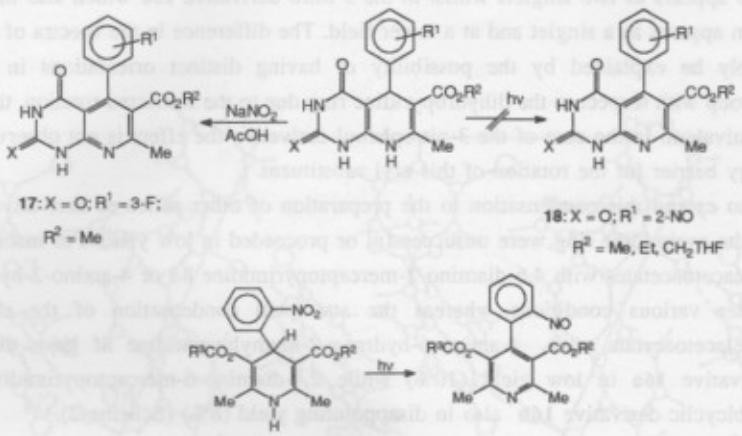
**8d**: X = $NH_2$ ; R = SH
**8e**: X = H ; R = OH
**8f** : X = OH ; R = Me
**8g**: X = SH ; R = $NH_2$

**Scheme 2**

These results show the scope of the procedure which is practically limited to the use of 6-amino-pyrimidines bearing a 2-hydroxy, 2-mercapto or 2-amino group, since changing one of these substituents for a methyl group dramatically reduced the yield of the fused derivative as proved by **16a**. On the other hand, the 6-hydroxy substituent also plays an important role in the success of the condensation as was proved with the change to a mercapto group (**13d** (71%) *vs.* **16b** (8%)). Presumably the tautomeric forms are of great importance in ensuring the nucleophilic attack and the stabilization of the bicyclic derivatives.

It is notable that derivatives **11-13**, especially those bearing a 2-nitrophenyl substituent, are stable to air oxidation when compared with dihydropyridines of the nifedipine type, which on exposure to air or sun light in alcoholic or dichloromethane solutions oxidize to the corresponding nitrosopyridine derivatives[7,29,30]

(Scheme 3). In contrast, compounds **11j**, **12g** and **13f**, *inter alia*, are stable under these conditions although they can be converted into the corresponding pyridines by oxidation with sodium nitrite in acetic acid as was proved with compound **11c**.




**Scheme 3**

The vasorelaxant potency of all derivatives prepared was determined by comparison of the $IC_{50}$ values obtained from concentration-response curves determined on strips of $K^+$-depolarized rat thoracic aortae. Although most of these compounds were devoid of blocking effects, Table 7 shows those which caused a significant reduction of the $K^+$-induced contraction, with **13f** giving a comparable effect to that of nifedipine.

**Table 7**. Significant $IC_{50}$ values for Vasorelaxant Activity of Compounds **11-13** Prepared

| Compd | X | $R^1$ | $R^2$ | $IC_{50}$(M) |
|---|---|---|---|---|
| **11h** | O | 2-$NO_2$ | Me | $5.2\times10^{-7}$ |
| **11j** | O | 2-$NO_2$ | $CH_2$THF | $1.0\times10^{-6}$ |
| **12g** | S | 2-$NO_2$ | $CH_2$THF | $8.1\times10^{-7}$ |
| **13b** | NH | 3-Br | Me | $1.0\times10^{-6}$ |
| **13f** | NH | 2-$NO_2$ | i-Pr | $2.8\times10^{-8}$ |
| **Nifedipine** | - | - | - | $1.2\times10^{-8}$ |

Compounds not included show $IC_{50}$ values $>10^{-6}$

In conclusion, compounds **11-13** mimick some of the most important conformational features of active 1,4-dihydropyridines as demonstrated by X-ray crystallography and some of them show antagonism of calcium channels. New developments are in progress to obtain pure stereoisomers of some of the pyrido[2,3-d]-pyrimidine derivatives prepared for structure-activity relationships studies and optimization of the activity.

## EXPERIMENTAL SECTION

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. $^1$H NMR spectra were recorded on a Varian Unity 300 (300 MHz) 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 all within 0.4% error. The chemical ionization (CI-MS) mass spectra were measured on a Hewlett-Packard 5988A. Chromatography was performed on a silica gel column by flash chromatography (Kieselgel 40, 0.040-0.063 mm, Merck). All chemicals were purchased from the Aldrich Chemical Co., Ltd., and purified before using when necessary. Arylmethyleneacetoacetates **4** were prepared as previously reported.[31,32]

*Methyl 2-(2´-amino-4´,6´-dihydroxypyrimidin-5-yl)-2-(3´-chlorophenyl)acetoacetate* ***10***. A mixture of the 2-amino-4,6-dihydroxypyrimidine **7** (1.02 g, 8 mmol), benzyltriethylammonium chloride (12 mg, 0.05 mmol) and sodium hydroxide (320 mg, 8 mmol) in DMF (9 ml) was stirred at room temperature for 1 h. A solution of methyl 2-(3´-chlorophenylmethylene)acetoacetate (1.90 g, 8 mmol) in DMF (1 ml) was then added and the mixture was stirred at room temperature for 24 h. The reaction mixture was poured into cold water (60 ml) and the precipitate obtained filtered and chromatographed (toluene/ethanol 6:4) to give the title compound **10** (420 mg, 15%), mp 279-280 °C (white powder, from isopropanol). IR (ν, $cm^{-1}$) 3357, 1682, 1633, 1559, 1429, 1355, 1238, 1159. $^1$H-NMR (DMSO-$d_6$, δ ppm) 10.7-10.1 (bs, 2H); 7.4-7.1 (m, 4H, aromatics); 6.8-6.4 (bs, 2H); 5.23 and 5.06 (d, d, 1H, CH, J=12.3 Hz); 4.63 (d, 1H, CH, J=12.3 Hz); 3.52 and 3.43 (s, s, 3H, $CO_2Me$); 2.13 and 2.0 (s, s, 3H, Me). (MS-CI): M/z (relative intensity) 126 (21); 128 (100); 140 (40); 156 (18); 170 (29); 194 (22); 252 (29); 292 (17); 294 (16). Anal. Calcd for $C_{16}H_{16}ClN_3O_5$: C, 52.54; H, 4.41; N,11.49. Found: C, 52.68; H, 4.55; N, 11.72.

*Typical Procedure for the Preparation of Tetrahydropyrido[2,3-d]pyrimidine Derivatives* ***11-13*** *and* ***16***. A mixture of the aminopyrimidine **8** (2.5 mmol), the corresponding arylmethyleneacetoacetate **4** (2.5 mmol), sodium acetate (431 mg, 5.25 mmol) in DMF (3.2 ml) was stirred at room temperature for 15 min and then heated at 65°C for 24 h in the case of compounds **11** and **12** and 12 h for **13**. The reaction mixture was cooled and poured into cold water (30 ml). The precipitate formed was collected by filtration, washed with water (3 x 5 ml) and recrystallized, affording pure compounds **11-13** and **16**

*Ethyl 2,7-dimethyl-5-(3'-nitrophenyl)-4-oxo-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate* ***16a***. (94 mg, 10%), mp 240-242°C (yellow powder, from ethanol). IR (ν, $cm^{-1}$) 3293, 1656, 1593, 1529, 1504, 1455, 1349, 1267, 1224, 1098. $^1$H-NMR (DMSO-$d_6$, δ ppm) 12.05 (s, 1H, NH); 9.73 (s, 1H, NH); 8.0-7.5 (m, 4H, aromatics); 5.05 (s, 1H, CH); 3.92 (q, 2H, $CO_2CH_2Me$); 2.33 (s, 3H, Me); 2.18 (s, 3H, Me); 1.07 (t, 3H, $CO_2CH_2CH_3$). MS-CI: M/z (relative intensity) 76 (4); 174 (7); 202 (7); 220 (52); 221 (6); 248 (100); 249 (14). Anal. Calcd for $C_{18}H_{18}N_4O_5$: C, 58.37; H, 4.90; N, 15.13. Found: C, 57.98; H, 4.92; N, 14.78.

*Ethyl 2-amino-7-methyl-5-(3'-nitrophenyl)-4-thioxo-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate* ***16b***. (79 mg, 8%), mp 262-264°C (yellow powder, from ethanol). IR (ν, $cm^{-1}$) 3139, 1644, 1590, 1529, 1462, 1422, 1345, 1296, 1227, 1190. $^1$H-NMR (DMSO-$d_6$, δ ppm) 11.55 (s, 1H, NH); 9.63 (s, 1H,

NH); 8.2-7.4 (m, 4H, aromatics); 6.71 (s, 2H, $NH_2$); 5.32 (s, 1H, CH); 3.97 (m, 2H, $CO_2CH_2Me$); 2.29 (s, 3H, Me); 1.09 (t, 3H), $CO_2CH_2Me$. MS-CI: M/z (relative intensity) 192 (5); 219 (6); 220 (13); 237 (44); 238 (6); 265 (100); 266 (16); 267 (12); 293 (22.5); 370 (10.5). Anal. Calcd for $C_{17}H_{17}N_5O_4S$: C, 52.70; H, 4.42; N, 18.08. Found: C, 53.02; H, 4.68; N, 17.94.

*Methyl 5-(3'-fluorophenyl)-7-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate* ***17***. To a solution of **11c** (100 mg, 0.30 mmol) in acetic acid (1 ml) and DMF (0.1 ml) was slowly added $NaNO_2$ until nitroso vapours evolved (166 mg, 2.40 mmol). The mixture was stirred at reflux for 1 h, cooled and poured into cold water (5 ml). The precipitate was collected by filtration and washed with water. Crystallization from $H_2O$/EtOH afforded 80 mg (81 %) of **17**. Mp 274-275 °C (yellow crystals). IR (KBr, $\nu$ $cm^{-1}$) 3066, 1718, 1688, 1568, 1486, 1435, 1392, 1283, 1249. $^1$H-NMR (DMSO-$d_6$, $\delta$ ppm) 11.82 (s, 1H, NH); 11.26 (s, 1H, NH); 7.5-6.9 (m, 4H, aromatics); 3.43 (s, 3H, $CO_2Me$); 2.46 (s, 3H, Me). MS-CI: M/z (relative intensity) 91 (1); 294 (2); 297 (2); 326 (4); 327 (1); 329 (6); 330 (100). Anal. Calcd for $C_{16}H_{12}N_3O_4F$ C, 58.36; H, 3.67; N, 12.76. Found: C, 58.59; H, 4.02; N, 12.58.

*Single-Crystal X-ray Structure Determination of* ***11b***. Molecular formula: $C_{34}H_{29}ClN_3O_4PS$, M=642.108, triclinic, P-1, a = 9.148 (5), b = 13.826(3) c = 14.155(3) Å, $\alpha$= 65.43(2), $\beta$ = 84.54(3)° $\gamma$= 88.82 (2)°, U = 1621(1) $Å^3$, Z =2, Dc=1.3160, g. $cm^{-3}$. Yellow, 0.26 x 0.31 x 0.35 mm,[3] Mo-K$\alpha$ radiation (graphite oriented monochromator) $\lambda$= 0.7107 Å, $\mu$(MoK$\alpha$) = 2.666 $cm^{-1}$ F(000) = 668.0. All crystallographic measurements were made on a Nonius CAD-4 four circle diffractometer, $\omega/2\theta$ scan, number of reflections measured 7610 [$2.0 \leq \theta \leq 28°$, $-12 \leq h \leq 12$, $-18 \leq k \leq 18$, $-0 \leq l \leq 18$]; 4775 observed reflections with $I > 2\sigma(I)$. The structure was solved by direct methods using MULTAN,[33] DIRDIF[34] XRAY80,[35] PESOS[36] and PARST[37] programs. Final R and Rw values are 0.041 and 0.049. Full-matrix least squares refinement with all non-H atoms anisotropic. The H-atoms were refined with fixed thermal parameters. Source of data for scattering factors are given in ref. 38 and full atomic coordinates, bond lengths and angles, thermal parameters and list of structure factors have been deposited at the Cambridge Crystallographic Data Centre.

*Determination of 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.[39] The procedure was essentially as described by Van Rosum[40] and Yousif.[41] 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.[42]

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