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Synthesis of new piperidine and cyclohexylamino-spiro derivatives as potential anticalcium agents

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Summary: The synthesis of new 1,3-benzodioxolo and 1,4- benzodioxan spiro derivatives containing a piperidine (**4-6**) or cyclohexylamino (**7-8**) group have been described. These compounds exhibit *in vitro* a moderate anticalcium activity.

Keywords: Spiro compounds, 1,3-benzodioxole, 1,3-benzodioxan, anticalcium activity.

The spiropiperidine derivatives have considerable importance in pharmaceutical chemistry due to their effects on different biological systems. Several synthetic drugs are based on the spiropiperidine nucleus: the *fluspirilene* **1** is a long acting agent used as a neuroleptic [1] in the treatment of psychosis but it shows also affinity by calcium channels. The *HP-406* **2** is a new antihypertensive [2] compound with selective effect on the calcium channels and the spiro(benzofuran)piperidine **3** decreases the blood pressure [3] (Fig. 1).

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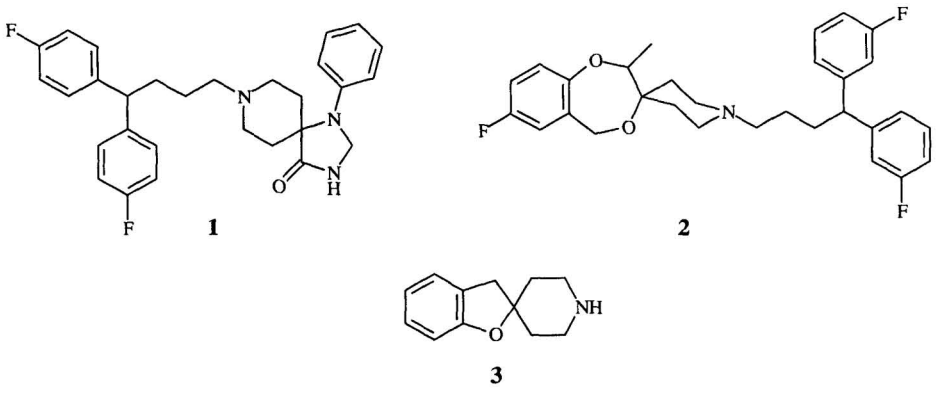


Figure 1

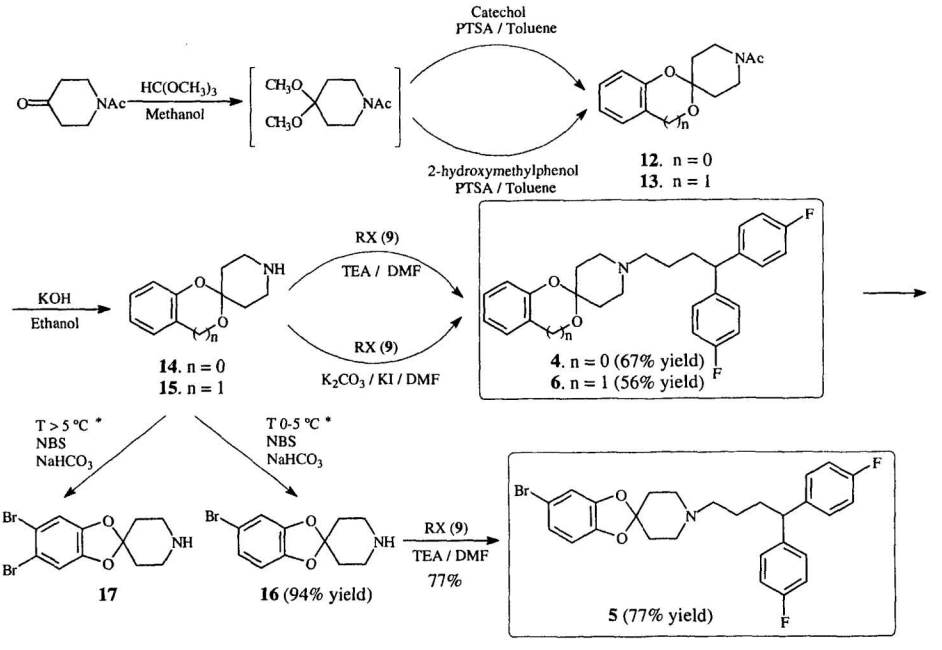
The spiropiperidine nucleus has been investigated in several occasions. By contrast, compounds with the spirocyclohexylamine nucleus have received relatively little attention. In a recent report from this laboratory, the preparation of a series of spiro compounds as adrenergic agents was described [4]. In this regard, several azadioxigenated-spiro compounds (type A) were prepared for comparison with them (Fig. 2). It is interesting to note that compounds **7** and **8** (type B) have the aminocyclohexyl group instead of the piperidine ring (Fig. 2) and the general synthetic method used for obtaining the related compounds **4**, **5** and **6** are now not applicable.

Type A Type B

Figure 2

As a part of our continued program [5][6][7] to find new calcium antagonists with non classical structures, we have undertaken the study of compounds **4-8**.

The synthesis of the alkylated amines (**4-6**) is presented in Scheme 1.



* Previous preparation of the corresponding hydrochloride

Scheme 1

The appropriate secondary amines, which proved to be useful intermediates, were conveniently prepared from the *N*-acetyl-4-piperidone. The synthesis of the corresponding alkyl halydes **9** and **10** (Fig. 3) was developed by Riom-CERM laboratories following their own methode [5] and the amine **11** was commercially available from Aldrich.

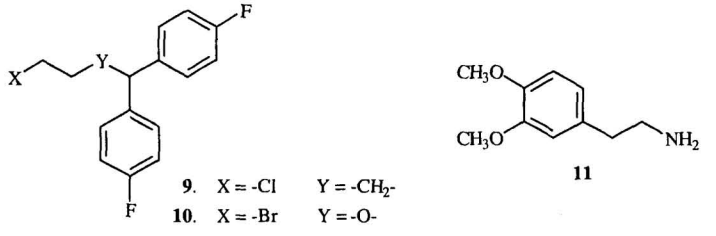


Figure 3

The amine **4** was prepared by alkylation of the secondary amine **14** in classical conditions using the arylalkylchloride **9** in the presence of TEA in dry DMF. The amine **5** was prepared in a similar manner from the corresponding amine **16**. The introduction of a

(compound **4** versus compound **6**), whereas the increasing of the lipophylicity decreased the anticalcium activity (compound **5**, obtained when compound **4** was brominated at the 5- position of the 1,3-benzodioxole).

Table I

Compound	Caffeine IC_{50} (μM)	Phenylephrine IC_{50} (μM)	Potassium IC_{50} (μM)
4	>30 (28%)	>1 (10%)	>1 (13%)
5	>30 (16%)	>1 (2%)	>1 (10%)
6	>30 (36%)	>10 (13%)	10
7	-	-	-
8	-	-	100 (37%)
Nifedipine	>10 (4%)	>10 (0%)	0.0086
Rianodine	0.039 ± 0.001	>10 (0%)	>10 (0%)
Prazosin	>30 (23%)	0.0023	>10 (0%)

Nifedipine, rianodine and prazosin were used as standards. Number of determinations varying from three to six. IC_{50} is defined as the concentration (μM) of the tested compounds that inhibited the 50% of the contractions induced by caffeine, phenylephrine or potassium.

Conclusion

On the basis of the structure, we can conclude that the substructure of spiro 1,3-benzodioxole or 1,3-benzodioxan has very few influence on the calcium antagonist activity.

The bromine introduction (compound **5**) induced a decreasing of the anticalcium activity. Compounds with the exocyclic amino group are less active than their piperidine analogues respect to the anticalcium activity in the K^+ test. However, in the caffeine test, that is indicative of the intracellular activity, compounds **7** and **8** showed an agonist effect.

Experimental

General

All melting points were determined in capillary tubes on a Gallenkamp apparatus and are uncorrected. NMR spectra were recorded either on a Varian-200 or / and Varian XL-300 MHz spectrometer. Chemical shifts are reported as δ values in parts per million downfield from tetramethylsilane as the internal standard in $CDCl_3$. The following abbreviations are used to denote signal patterns: s = singlet, d = doublet, t = triplet, bs = broad signal, m = multiplet. IR spectra were recorded on an FTIR Perkin Elmer 1600 spectrometer. Elemental analyses were performed by the Serveis Científico-Técnics de la Universitat de Barcelona. Reported analytical data are within ±0.4% of the theoretical values. Merck 60 (40-60 microns) and Merck 60 F_{254} silica gel were used for column chromatography and thin layer chromatography respectively. The organic extracts were dried over Na_2SO_4. All air and moisture sensitive reactions were carried out in an atmosphere of inert gas (argon). Yields were not optimized.

5-Bromospiro[1,3-benzodioxolo-2,4'-piperidine] **16**

A dissolution of the amine **14** hydrochloride (2.4 g; 10.47 mmol) in 20 mL of methanol was cooled under 5 ºC, then *N*-bromosuccinimide (1.8 g; 10.47 mmol) was slowly added. The mixture was stirred at room temperature for 75 min. After removing the solvent the solid obtained was dissolved in water and basified with a saturated solution of $NaHCO_3$. The basic layer was extracted with CH_2Cl_2 (3 x 40 mL) and the organic layer was several times washed with a saturated solution of NaCl. Finally it was dried, filtered and concentrated under vacuo, obtaining a brown solid identified as the brominated compound (2.64 g; 94% yield). Mp (hydrochloride): 258-259 ºC (hexane / EtOAc). IR (KBr) υ: 3400, 2910, 1480, 1220, 1120 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm): 1.93 (t, J = 5.2 Hz, 4H, CH_2C); 2.52 (s, 1H, NH); 3.08 (t, J = 5.2 Hz, 4H, CH_2N); 6.61 (d, J = 8 Hz, 1H, C7-H); 6.88 (s, 1H, C4-H); 6.92 (d, J = 8 Hz, 1H, C6-H).

Spiro[1,3-benzodioxolo-2,1'-cyclohexane-4'-one] **19**

A dissolution of the compound **18** (300 mg; 1.2 mmol) and HCl 3% (P/V) (10 mL) in 30 mL of isopropanol was stirred at reflux temperature for 2 h. Then, the solvent was removed under reduced pressure and the residue obtained was diluted with water and extracted with CH_2Cl_2 (3 x 25 mL). The organic layers were dried, filtered and concentrated under vacuo obtaining an oil which was purified by silica gel column chromatography (hexane / EtOAc 70 / 30). Compound **19** was obtained as a white solid (262 mg; 95% yield). Mp: 69-71 ºC (hexane). IR (KBr) υ: 2932, 1717, 1486, 1236, 1115 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 2.34 (m, 4H, CH_2CO); 2.56 (m, 4H, CH_2C); 6.82 (s, 4H, C4-H, C5-H, C6-H, C7-H).

4'-Aminospiro[1,3-benzodioxolo-2,1'-cyclohexane] **20**

A mixture of the ketone **19** (1.7 g; 7.37 mmol), benzylamine (3.16 g; 29.5 mmol) and a catalytic amount of *p*-toluensulfonic acid, in 150 mL of distilled toluene, was equiped with a Dean-Stark system and stirred at reflux temperature for 24 h. Following, the solvent was removed under reduced pressure and the residue obtained was dissolved in methanol (100 mL). A catalytic amount of Pd-C (170 mg; 10% P / P) and some drops of concentrated HCl were added and the resulting mixture was adapted to an hydrogenation system (atmospheric pressure). When the consumption of H_2 was finished the suspension was filtered and the solvent removed under vacuo. The solid obtained was dissolved in water, basified with a solution of NaOH 1N and extracted with CH_2Cl_2 (3 x 25 mL). The organic layers were dried, filtered and concentrated giving 650 mg (43% yield) of amine **20**. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.60 (m, 4H, CH_2C); 1.86 (m, 4H, CH_2C); 2.18 (bs, 2H, NH_2); 2.96 (m, 1H, **CH**NH_2); 6.74 (s, 4H, C4-H, C5-H, C6-H, C7-H).

General procedure of alkylation

Triethylamine freshly distilled (3 mmol) was added to a solution of the appropriate amine (1 mmol) and the corresponding alkylating reagent (2 mmol) in dry DMF. The reaction mixture was stirred under an argon atmosphere at 60-80 ºC for 48 h. After the solvent was removed, the residue was diluted with water and extracted with CH_2Cl_2. The organic layers were dried, filtered and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography, using CH_2Cl_2 or hexane as eluent, allowed us to obtain the corresponding alkylated compound.

N-[4,4-Bis(p-fluorophenyl)butyl]spiro[1,3-benzodioxolo-2,4'-piperidine] **4**

Compound **4** (914 mg; 67% yield) was obtained starting from the amine **14** (600 mg; 3.14 mmol) and 4,4-bis(*p*-fluorophenyl)butyl chloride **9** as alkylating reagent following the general procedure of alkylation described above. Mp: 230-232 ºC (hexane / EtOAc). Anal. Calc. for: $C_{27}H_{27}NO_2F_2$ Found: C 74.5%, H 6.23%, N 3.25%. IR ($CHCl_3$) υ: 3000, 2937, 1483, 1237, 1100 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.45 (m, 2H, $CH_2\mathbf{CH_2}CH_2$); 2.00 (m, 6H, $\mathbf{CH_2}CHAr$, $\mathbf{CH_2}C\mathbf{CH_2}$); 2.42 (t, *J* = 7 Hz, 2H, CH_2N); 2.56 (m, 4H, $\mathbf{CH_2}NpipC\mathbf{H_2}$); 3.87 (t, *J* = 7 Hz, 1H, CHAr); 6.74 (m, 4H, C4-H, C5-H, C6-H, C7-H); 6.96 (m, 4H, C3"-H, C5"-H); 7.16 (m, 4H, C2"-H, C6"-H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 25.6 (CH_2, $CH_2\mathbf{CH_2}CH_2$); 33.8 (CH_2, $\mathbf{CH_2}CHAr$); 34.9 (CH_2, $\mathbf{CH_2}C\mathbf{CH_2}$); 49.7 (CH, CHAr); 50.4 (CH_2, $\mathbf{CH_2}NpipC\mathbf{H_2}$); 57.7 ($CH_2$, CH_2N); 108.6 (CH, C4, C7); 115.1 and 115.4 (CH, *J* = 21 Hz, C3", C5"); 116.2 (C, Cspiro); 121.0 (CH, C5, C6); 128.9 and 129.1 (CH, *J* = 8 Hz, C2", C6"); 140.5 (C, C1"); 147.0 (C, C3a, C7a); 159.6 and 162.9 (C, *J* = 249 Hz, C4").

5-Bromo-N-[4,4-bis(p-fluorophenyl)butyl]spiro[1,3-benzodioxolo-2,4'-piperidine] **5**

Compound **5** (728 mg; 77% yield) was obtained following the general procedure of alkylation starting from the amine **16** (500 mg; 1.85 mmol) and 4,4-bis(*p*-fluorophenyl)butyl chloride **9**. Mp (hydrochloride): 108-110 ºC (EtOAc). Anal. Calc. for: $C_{27}H_{26}NO_2F_2Br$ Found: C 63.08%, H 5.05%, N 2.69%. IR ($CHCl_3$) υ: 3100, 2937, 1479, 1250, 1107 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.42 (m, 2H, $CH_2\mathbf{CH_2}CH_2$); 2.00 (m, 6H, $\mathbf{CH_2}C\mathbf{CH_2}$, $\mathbf{CH_2}CHAr$); 2.40 (t, *J* = 7 Hz, 2H, CH_2N); 2.52 (m, 4H, $\mathbf{CH_2}NpipC\mathbf{H_2}$); 3.85 (t, *J* = 7 Hz, 1H, CHAr); 6.59 (d, *J* = 7.5 Hz, 1H, C7-H); 6.87 (s, 1H, C4-H); 6.96 (m, 5H, C6-H, C3"-H, C5"-H); 7.14 (m, 4H, C2"-H, C6"-H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 26.6 (CH_2, $CH_2\mathbf{CH_2}CH_2$); 33.8 (CH_2, CH_2CHAr); 34.9 (CH_2, $\mathbf{CH_2}C\mathbf{CH_2}$); 49.7 (CH, CHAr); 50.3 (CH_2, $\mathbf{CH_2}NpipC\mathbf{H_2}$); 57.6 ($CH_2$, CH_2N); 109.5 (CH, C7); 112.2 (CH, C4); 115.1 and 115.4 (CH, *J* = 21 Hz, C5, C3", C5"); 117.8 (C, Cspiro); 123.7 (CH, C6); 129.0 and 129.1 (CH, *J* = 8 Hz, C2", C6"); 140.5 (C, *J* = 3 Hz, C1"); 146.6 (C, C3a, C7a); 159.7 and 163.0 (C, *J* = 245 Hz, C).

N-[4,4-Bis(p-fluorophenyl)butyl]spiro[1,3-benzodioxan-2,4'-piperidine] **6**

Starting from the amine **15** (506 mg; 2.47 mmol), 4,4-bis(*p*-fluorophenyl)butyl chloride **9** as alkylating reagent and operating as previously described in the general procedure of alkylation using K_2CO_3 as a base and KI (catalytic amount) was obtained compound **6** as a yellow oil (628 mg; 56% yield). Mp (hydrocloride): 182-184 ºC (EtOAc). Anal. Calc. for:

$C_{28}H_{29}NO_2F_2$ Found: C 74.78%, H 6.46%, N 3.13%. IR ($CHCl_3$) υ: 3100, 2949, 1590, 1238, 1100 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.58 (m, 2H, $CH_2\mathbf{CH_2}CH_2$); 2.07 (m, 6H, $\mathbf{CH_2}C\mathbf{CH_2}$, $\mathbf{CH_2}$CHAr); 2.57 (t, J = 7 Hz, 2H, CH_2N); 2.68 (m, 4H, $\mathbf{CH_2}$Npip $\mathbf{CH_2}$); 3.88 (t, J = 7 Hz, 1H, CHAr); 4.83 (s, 2H, C_4H); 6.90 (m, 7H, C3"-H, C5"-H, C5-H,C6-H, C8-H); 7.15 (m, 5H, C2", C6", C7). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 24.7 (CH_2, $CH_2\mathbf{CH_2}CH_2$); 32.3 (CH_2, $\mathbf{CH_2}C\mathbf{CH_2}$); 33.6 ($CH_2$, $\mathbf{CH_2}$CHAr); 49.5 (CH, CHAr); 49.7 (CH_2, $\mathbf{CH_2}N\mathbf{CH_2}$); 57.6 ($CH_2$, CH_2N); 60.3 (CH_2, C4); 97.1 (C, Cspiro); 115.2 and 115.4 (CH, J = 21 Hz, C3", C5"); 117.1 (CH, C8); 120.8 (CH, C6); 124.7 (CH, C5); 128.2 (CH, C7); 128.2 (C, C4a); 128.9 and 129.0 (CH, J = 8 Hz, C2", C6"); 140.1 (C, C1"); 150.4 (C, C8a); 159.7 and 162.9 (C, J = 245 Hz, C4").

4'-[Bis(p-fluorophenyl)methoxyethylamino]spiro[1,3-benzodioxolo-2,1'-cyclohexane] **7**

Compound **7** was obtained as a yellow oil (260 mg; 37% yield) starting from the amine **20** (305 mg; 1.5 mmol), the alkyl bromide **10** (2.45 g; 7.5 mmol) and following the general procedure of alkylation using anhydrous K_2CO_3 (1.035 g; 7.5 mmol) as a base and a catalytic amount of KI. The purification by silica gel column chromatography was carried out with hexane / EtOAc (70 / 30) as eluent. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.71 (m, 4H, $\mathbf{CH_2}$CHN); 2.15 (m, CH_2N); 2.35 (m, 2H, CH_2axC); 2.65 (m, 2H, CH_2eqC); 2.82 (bs, 2H, NH, CHN); 3.40 (m, 2H, CH_2O); 5.23 (s, 1H, CHAr); 6.75 (m, 4H, C4-H, C5-H, C6-H, C7-H); 7.01 (m, 4H, C3"-H, C5"-H); 7.26 (m, 4H, C2"-H, C6"-H).

4'-(3,4-Dimethoxyphenylethylamino)spiro[1,3-benzodioxolo-2,1'-cyclohexane] **8**

A dissolution of the ketone **19** (224 mg; 0.98 mmol), 2-(3,4-dimethoxyphenyl)ethylamine (0.7 mL; 3.92 mmol) and a catalytic amount of *p*-toluensulfonic acid in 50 mL of dry toluene was adapted to a Dean-Stark system and stirred at reflux temperature for 24 h. Then, the solvent was removed under reduced pressure, the residue diluted with water and extracted with CH_2Cl_2 (3 x 25 mL). The organic layers were dried, filtered and concentrated. The oil obtained was dissolved in methanol (20 mL), $NaBH_4$ (118 mg; 3.1 mol) was added and the mixture was stirred at room temperature for 1 h. Following, the excess of hydride was hydrolysed and the methanol removed. The crude product obtained was diluted with water and extracted with CH_2Cl_2 (3 x 25 mL). The organic layers were dried, filtered and concentrated obtaining a mixture which was purified by silica gel column chromatography (CH_2Cl_2 / methanol 90 / 10). Compound **8** was obtained as a yellow oil (146 mg: 45% yield). Anal. Calc. for: $C_{22}H_{27}NO_4$ Found: C 71.56%, H 7.40%, N 3.81%.

IR ($CHCl_3$) υ: 3100, 2938, 1484, 1250 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.85 (m, 8H, CH_2cyclohex); 2.75 (m, 1H, CHN); 2.80 (t, J = 6 Hz, 2H, CH_2N); 2.90 (t, J = 6 Hz, 2H, CH_2Ar); 3.86 (s, 6H, CH_3O); 6.75 (m, 7H, Ar). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 28.9 (CH_2, CH_2C); 32.9 (CH_2, CH_2C); 35.8 (CH_2, CH_2Ar); 48.3 (CH_2, CH_2N); 54.4 (CH, CHN); 55.9 (CH_3, CH_3O); 108.4 and 108.6 (CH, C2", C5"); 111.3 and 111.9 (CH, C4, C7); 117.5 (C, Cspiro); 120.5 and 120.9 (CH, C5, C6, C6"); 132.2 (C, C1"); 147.1; 147.2; 147.5 and 148.9 (C, C3a, C7a, C3", C4").

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