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Muscarinic Subtypes Profile Modulation within a Series of New Antagonists, Bridged Bicyclic Derivatives of 2,2-Diphenyl-[1,3]-dioxolan-4-ylmethyl-dimethylamine

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Abstract—A set of new muscarinic antagonists, bridged bicyclic derivatives of 2,2-diphenyl-[1,3]-dioxolan-4-ylmethyl-dimethylamine (**1**), was synthesized and tested to evaluate their affinity and selectivity for M_1, M_2, M_3 and M_4 receptor subtypes. The conformational constraint of **1** in a bicyclic structure, and the variation in distance and stereochemistry of the active functions allowed us to modulate the selectivity of interaction with the M_1–M_3 receptor subtypes. The most interesting compound was (*cis*,*trans*)-2-(2,2-diphenylethyl)-5-methyl-tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrole oxalate (**6**), which is equipotent with Pirenzepine on rabbit vas deferens (M_1-putative) but shows a better selectivity profile.

Introduction

The acetylcholine receptors, traditionally subdivided into muscarinic and nicotinic classes, play important roles both in the central and peripheral nervous systems. The muscarinic receptors, expressed in large amounts in the parasympathetic nervous system, belong to the superfamily of receptors coupled to the G proteins (GPCRs) and, by means of pharmacological and molecular biology techniques, have been divided into five subtypes, M_1–M_5, which show a high degree of homology across species (mammalian and non mammalian), as well as across receptor subtypes.[1] It has been suggested that the M_1, M_3, and M_5 subtypes couple to phosphoinositide hydrolysis leading to mobilization of intracellular calcium, whereas activation of M_2 and M_4 subtypes inhibits adenylcyclase activity.[2] Given the lack of really selective ligands in particular agonists, the physiological role of each of the different muscarinic receptor subtypes has not been fully elucitated yet. Only recently has the use of muscarinic M_1-,[3] M_2-,[4] M_3-,[5] and M_4-receptor knockout mice[6] allowed the role of these receptors in specific physiological functions to be clarified. Due to their widespread presence at the peripheral level and, in particular, the M_1 and M_3 subtypes in glandular tissue, M_2 in the heart, M_2 and M_3 in smooth muscle, and M_4 in the lung,[7–10] the muscarinic receptors are attractive therapeutic targets. M_2-selective antagonists such as, for example, AF-DX 116 may thus be useful for treating bradycardia;[11] the M_3-selective ones, such as Darifenacin, for gastrointestinal disorders,[12] and Vamicamide for urinary incontinence;[13] Revatropate, selective for the M_1 and M_3 subtypes, is useful for treating chronic obstructive pulmonary disease (COPD)[12,14] while Pirenzepine (Chart 1),[15,16] a potent M_1 antagonist, but only relatively selective for the other subtypes,[17] has proved to be efficacious in cases of peptic ulcer. Furthermore, due to their widespread presence in the central nervous system, with the M_1 and M_4 subtypes in the cerebral cortex, the M_1 subtype in the hippocampus, the M_4 one in the striatum, the M_2 one in the cerebellum and brainstem, the M_3 one in the telencephalon, the thalamic nuclei, and the brainstem, and the M_5 one in the substantia nigra,[18–22] the muscarinic receptors play a crucial role in neurodegenerative diseases.[23] Inhibitors of acetylcholinesterase,[24] as well as M_1-agonists,[25] and M_2-antagonists,[26] are useful in Alzheimer's disease, that involves a reduction of cholinergic activity.[27] Selective inhibition of M_2 presynaptic muscarinic receptors has been shown to enhance

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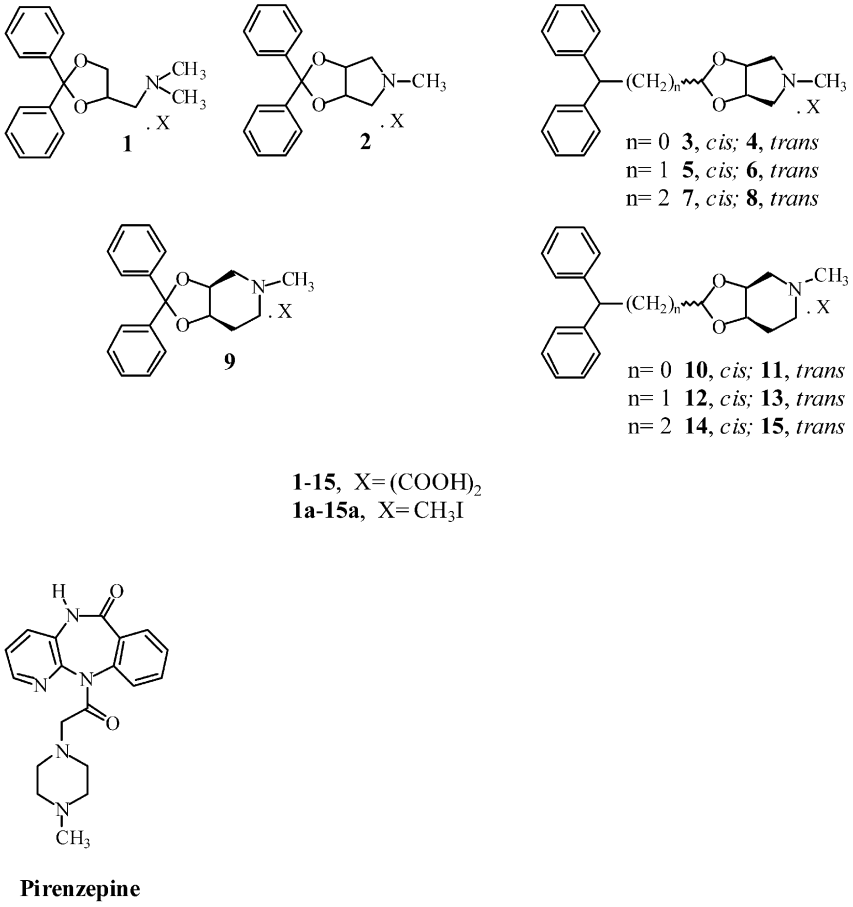
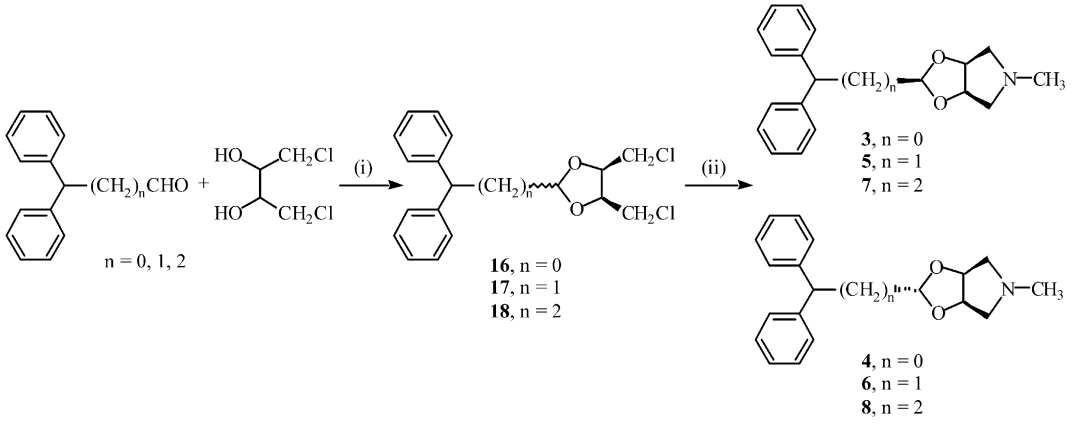


Chart 1.

acetylcholine levels.[28] Finally selective M_4-muscarinic antagonists could be useful in treating Parkinson's disease.[29]

In the present study, we have taken as reference compound 2,2 - diphenyl - [1,3] - dioxolan - 4 - ylmethyl-dimethylamine (**1**) (Chart 1), whose methiodide **1a** is known to be a potent but only slightly selective muscarinic receptor antagonist.[30] In a previous work, we demonstrated that by appropriately varying the distance and stereochemistry of the interacting functions (benzhydryl group and nitrogen atom) of **1**, M_1-selectivity could be enhanced;[31] at the same time, we had already noted that compounds with a restricted flexibility such as **2**, in which the nitrogen atom of **1** was included in a pyrrolidine ring, behave like muscarinic antagonists.[32] Therefore, knowing that compounds with a hindered conformational flexibility can lead to the identification of the bioactive conformation at the receptor[33] and, hence, to a more specific recognition of receptor-subtype binding sites, we designed and synthesized the new muscarinic antagonists **3–15** (Chart 1), bridged bicyclic derivatives of **1**. In these derivatives, the amine function of **1** was incorporated in the pyrrolidine ring,



Scheme 1. (i) TsOH, (ii) CH_3NH_2.

analogously to what had already occurred with **2**[32] (compounds **3–8**) or in the piperidine one (compounds **9–15**). In addition, the distance between essential structural moieties, and the stereochemistry of the aromatic area with respect to annulation, were modified in order to investigate their role in potency and selectivity.

Chemistry

The new compounds **3–8** were synthesized according to Scheme 1. Condensation of *meso*-1,4-dichloro-butane-2,3-diol[34] with commercially available diphenyl-acetaldehyde, 3,3-diphenyl-propionaldehyde,[35] 4,4-diphenil-butyraldehyde[36] afforded the intermediates **16–18**, respectively, which were cyclized with methylamine to give compounds **3–8**.

The structures of the amines **3** and **4** were satisfactorily determined by 1D-nuclear Overhauser effect (1D-NOE) measurements.[37] The H-2–H-4 and H2–H5 *cis* relationships in compound **3** were demonstrated by the observation that irradiation of H-2 caused NOE at H-4 and H-5 (1%) (Fig. 1). On the contrary, in compound **4** irradiation of H-2 caused no NOE effect at H-4 and H-5. Furthermore, in the pair **3–4** the H-2 of *trans* isomer **4** was deshielded with respect to the same proton in *cis* isomer **3**: δ 5.97 in **4** and δ 5.51 in **3** with a difference

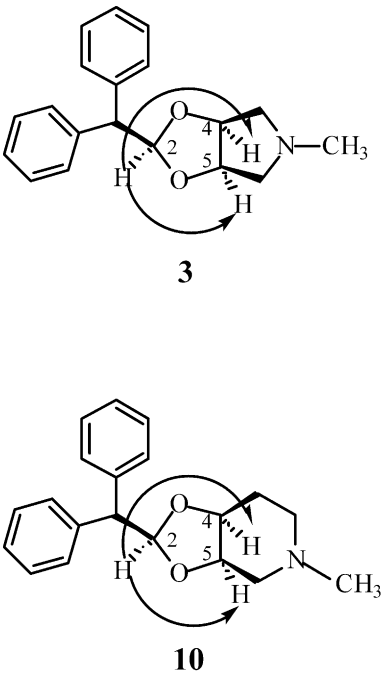
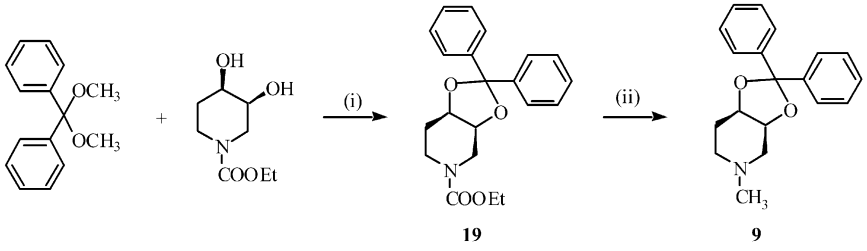
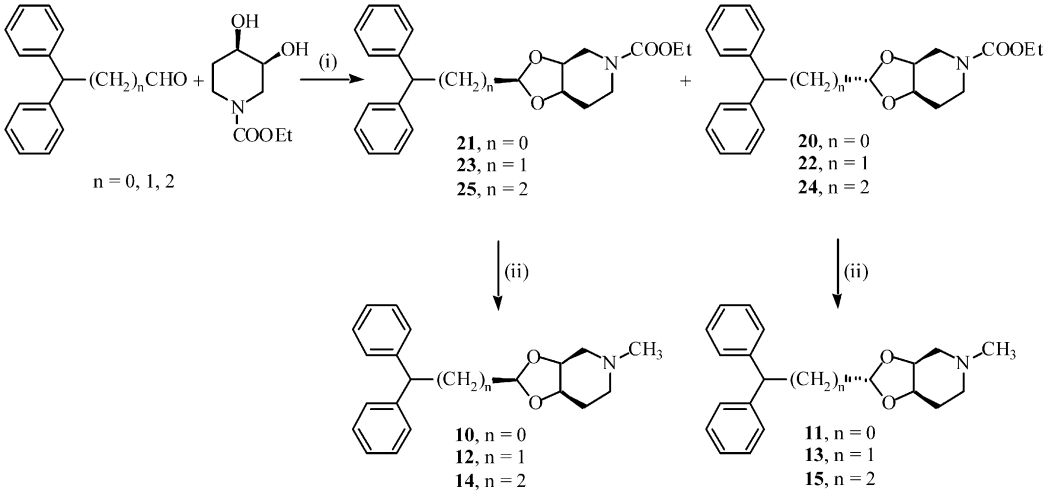


Figure 1. Principal correlations observed in the NOE spectrum of compounds **3** and **10**. The numeration refers to the dioxolane cycle and not to the bicyclic one.

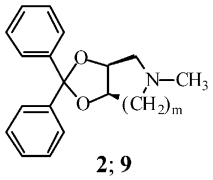


Scheme 2. TsOH, (ii) $LiAlH_4$.

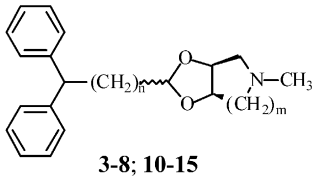


Scheme 3. (i) TsOH, (ii) $LiAlH_4$.

Table 1. Structures and affinity values[a] for the oxalate compounds **1**–**15** at muscarinic receptor subtypes



2; **9**



3-8; **10-15**

Compd	*n*	*m*	Stereoisomer	M_1	M_2	M_3	M_4
1				7.15±0.12[b]	7.11±0.03[b]	6.38±0.08[b]	5.20±0.09
2	—	1	—	5.92±0.14	6.24±0.05	6.21±0.07	<5
3	0	1	*cis*	5.80±0.09[b]	5.49±0.06[b]	7.00±0.06[b]	<5
4	0	1	*trans*	5.92±0.09[b]	6.21±0.13[b]	7.25±0.06[b]	5.43±0.06
5	1	1	*cis*	6.48±0.20	5.84±0.12	5.96±0.04	5.30±0.19
6	1	1	*trans*	7.80±0.13[b]	5.14±0.04[b]	6.18±0.12[b]	5.21±0.19
7	2	1	*cis*	6.13±0.11	5.86±0.13	5.75±0.13	<5
8	2	1	*trans*	5.48±0.17	5.24±0.13	5.78±0.12	<5
9	—	2	—	6.50±0.20 [b]	7.50±0.12[b]	6.41±0.11[b]	5.71±0.12
10	0	2	*cis*	5.79±0.14	6.98±0.01	7.00±0.06	<5
11	0	2	*trans*	6.86±0.11	7.07±0.17	7.40±0.08	5.38±0.12
12	1	2	*cis*	6.30±0.06[b]	7.30±0.08[b]	5.97±0.24[b]	5.59±0.14
13	1	2	*trans*	5.73±0.10	5.40±0.17	5.18±0.10	5.10±0.08
14	2	2	*cis*	5.88±0.13	6.30±0.03	6.06±0.13	<5
15	2	2	*trans*	5.57±0.14	5.94±0.15	5.89±0.06	<5
Pirenzepine[c]				8.05±0.014[b]	6.48±0.008[b]	6.91±0.03[b]	6.36±0.02[b]

[a]These values represent $-\log K_b$ obtained at 10 μM concentration of the antagonist from the expression $\log (DR-1) = \log [ant.] - \log K_b$ according to van Rossum.[44] Dose–ratio (DR) values represent the ratio of the potency of the (EC_{50}) in the presence of the antagonist and in its absence.
[b]pA_2 values.
[c]Pirenzepine dihydrochloride (TOCRIS).

of about 0.5 ppm. The structures of the new compounds **5**–**8** were determined by comparison of their ^{1}H NMR spectra with those of compounds **3** and **4**. In fact, in the pairs **5**–**6** and **7**–**8** the H-2 of *trans* isomers **6** and **8** were deshielded with respect to the same protons in *cis* isomers **5** and **7**: δ 5.12 in **6** and δ 4.57 in **5**; δ 5.31 in **8** and δ 4.79 in **7**.

Compound **9** was synthesized by condensation of benzophenone dimethyl acetal[38] with 1-ethoxycarbonylpiperidine-*cis*-3,4-diol[39] followed by reduction of carbamate **19** with $LiAlH_4$ (Scheme 2).

Compounds **10**–**15** were synthesized analogously to compound **9**. The *cis* and *trans* isomers **20**–**25** were separated through flash chromatography (Scheme 3).

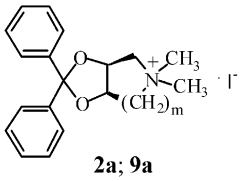
The structures of the amines **10** and **11** were determined similarly to those of compounds **3** and **4**. In fact, in compound **10** the irradiation of the doublet peak of H-2 at δ 5.59 ppm caused a NOE effect (2%) at H-4 and H-5, thus indicating a *cis* relationship between these protons and, consequently, between the benzhydryl moiety and the piperidine nucleus (Fig. 1). On the contrary, in compound **11** irradiation of the doublet peak at δ 5.90 ppm of H-2 caused no NOE effect between the same protons, indicating a *trans* relationship between the piperidine nucleus and benzhydryl moiety. Furthermore, the H-2 of *trans* isomer **11** was deshielded with respect to the same proton in *cis* isomer **10**: δ 5.90 in **11** and δ 5.59 in **10** with a difference of about 0.3 ppm. The structures of the new compounds **12**–**15** were determined in a similar way. In fact, in the ^{1}H NMR spectra of the pairs **12**–**13** and **14**–**15** the protons H-2 of *trans* isomers **13** and **15** were deshielded with respect to the same protons of *cis* isomers **12** and **14**: δ 5.11 in **13** and δ 4.79 in **12**; δ 5.31 in **15** and δ 4.98 in **14**. The same difference of about 0.3 ppm is observed in the pairs **12**–**13**, and **14**–**15**.

The free bases were transformed into the oxalates and methiodide salts using an excess of oxalic acid or CH_3I.

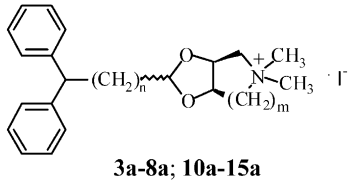
Results and Discussion

The pharmacological profiles of the new compounds, studied as oxalates (**3**–**15**) (Table 1) and methiodide salts (**3a**–**15a**) (Table 2), were determined in vitro on stimulated guinea pig left atria (M_2-subtype),[40] ileum (M_3-subtype),[41] lung (M_4-subtype),[42] and rabbit vas deferens,[43] and are expressed in terms of pK_b[44] or of pA_2[45] for the more interesting compounds (**1**, **3**, **4**, **6**, **9**, **12**, and Pirenzepine). pA_2 Values were estimated by Schild analysis constrained to slope −1.0, as required by the theory.[46] Selectivity ratios for compounds **1**, **3**, **4**, **6**, **9**, **12**, and Pirenzepine are reported in Table 3. For a long time, the contraction of rabbit vas deferens was referred to as an effect mediated by M_1-receptor subtypes,[43,47] even though some more recent studies attribute the same effect to an M_4-activation;[48] at the present moment, the pharmacological characterization still does not appear to be definitively established. Thus, in this work, the rabbit vas deferens muscarinic receptor subtype will be considered an M_1-putative. The study on lung (M_4-subtype) was extended also to compounds **1**, **1a**, **2**, and **2a**[32] for purposes of comparison.

Table 2. Structures and affinity values[a] for the methiodide compounds **1a–15a** at muscarinic receptor subtypes



2a; 9a



3a-8a; 10a-15a

Compd	*n*	*m*	Stereoisomer	M_1	M_2	M_3	M_4
1a				8.36±0.07	8.29±0.06	7.91±0.07	6.13±0.08
2a	—	1	—	7.62±0.01	7.66±0.01	7.62±0.05	5.57±0.11
3a	0	1	*cis*	6.62±0.12	7.13±0.12	7.33±0.07	6.20±0.15
4a	0	1	*trans*	7.39±0.19	7.00±0.20	7.15±0.10	5.49±0.18
5a	1	1	*cis*	6.51±0.18	6.81±0.20	6.71±0.08	5.54±0.07
6a	1	1	*trans*	6.37±0.09	6.38±0.20	6.28±0.13	5.30±0.13
7a	1	1	*cis*	6.17±0.03	5.79±0.04	5.45±0.10	5.50±0.20
8a	1	1	*trans*	5.43±0.07	5.71±0.20	6.36±0.03	<5
9a	—	2	—	7.58±0.01	7.92±0.09	7.16±0.11	5.69±0.06
10a	0	2	*cis*	7.41±0.01	7.42±0.01	7.55±0.18	5.49±0.04
11a	0	2	*trans*	8.00±0.15	7.34±0.11	7.75±0.18	5.67±0.11
12a	1	2	*cis*	7.08±0.10	6.81±0.23	6.66±0.04	6.32±0.11
13a	1	2	*trans*	5.63±0.16	6.58±0.17	6.03±0.14	<5
14a	2	2	*cis*	5.55±0.01	5.96±0.14	5.81±0.14	5.06±0.06
15a	2	2	*trans*	5.37±0.13	5.68±0.17	5.82±0.10	<5

[a]These values represent $-\log K_b$ obtained at 10 μM concentration of the antagonist from the expression $\log (DR-1) = \log [ant.] - \log K_b$ according to van Rossum.[44] Dose–ratio (DR) values represent the ratio of the potency of the (EC_{50}) in the presence of the antagonist and in its absence.

Table 3. Affinity values[a] and selectivity ratios[b] for compounds **1**, **3**, **4**, **6**, **9**, **12** and Pirenzepine

Compd	M_1	M_2	M_3	M_4	M_1/M_2	M_1/M_3	M_1/M_4	M_2/M_1	M_2/M_3	M_2/M_4	M_3/M_1	M_3/M_2	M_3/M_4
1	7.15	7.11	6.38	5.20	1	6	89		5	81			15
3	5.80	5.49	7.00	<5							16	32	>100
4	5.92	6.21	7.25	5.43							21	11	66
6	7.80	5.14	6.18	5.21	457	42	389						
9	6.50	7.50	6.41	5.71				10	12	62			
12	6.30	7.30	5.97	5.59				10	21	51			
Pirenzepine	8.05	6.48	6.91	6.36	37	14	49						

[a]pA_2 values±SEM were calculated according to Arunlakshana and Schild[45] unless otherwise specified, constraining the slope to −1.[46] Number of replications from four to six.
[b]Antilog of the difference between the pA_2 values for M_1, M_2, M_3, M_4 muscarinic receptor subtypes.

All the new compounds, analogously to the reference compound **1**, behave as muscarinic antagonists; in particular, the methiodide salts (**3a–15a**) mostly display higher potency together with a lack of selectivity for tissues with respect to the oxalates. In fact, in the basic tertiary amines, several chemical modifications (such as restricting of the conformational freedom of the methylamine chain, variation in the distance and stereochemistry of the interacting functions, and cyclohomology) to the structure of the potent but only slightly selective compound **1** have allowed the biological profile to be modified and the significantly selective antagonists to be obtained.

All the compounds examined (both oxalates and methiodide salts) display low potency at M_4-muscarinic subtype. The structure–activity relationship study of the ligands **3–15**, instead, allowed us to identify the structural characteristics which favor the interaction with the M_2-muscarinic (compounds **9** and **12**), M_3-muscarinic (compounds **3** and **4**), and the putative M_1-muscarinic (compound **6**) subtypes. With regard to ligand **4** ($M_3/M_1 = 21$-fold; $M_3/M_2 = 11$-fold; $M_3/M_4 = 66$-fold), the enhanced and more selective M_3-interaction compared with reference compound **1** can be attributed to greater rigidity of the amine function in the pyrrolidine nucleus and to a distancing of the interacting functions with a CH group, that is, to the simultaneous introduction of two variants, which individually do not produce significant selectivity.[31,32] The relative spatial arrangement between the interacting functions does not seem critical for this subtype selectivity, in so far that the *cis* isomer (compound **3**) displays similar potency and selectivity ($M_3/M_1 = 16$-fold; $M_3/M_2 = 32$-fold; $M_3/M_4 > 100$-fold). Also compounds **10** (*cis* isomer) and **11** (*trans* isomer), piperidine nucleus analogues of **3** and **4**, respectively, maintain non-negligible potency at the M_3-muscarinic subtype (pA_2 $M_3 = 7.00$ and 7.40, respectively), but display reduced selectivity, since they possess good potency also at the M_2-muscarinic subtype (pA_2 $M_2 = 6.98$ and 7.07, respectively). In compound **9** ($M_2/M_1 = 10$-fold; $M_2/M_3 = 12$-fold; $M_2/M_4 = 62$-fold) the amine function of reference compound **1** was incorporated in the piperidine nucleus: unlike what happens with the more rigid lower cyclohomologous **2**, this modification leads the ligand to assume a suitable conformation for a

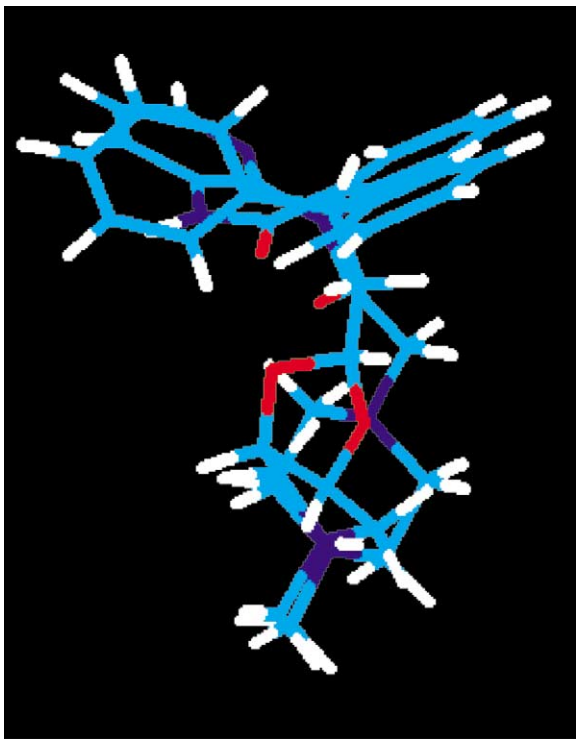


Figure 2. Overlay of pirenzepine and compound **6**.

preferred interaction with the M_2-muscarinic subtype. Compound **12** (*cis* isomer) ($M_2/M_1 = 10$-fold; $M_2/M_3 = 21$-fold; $M_2/M_4 = 51$-fold) possesses a pharmacological profile similar to that of **9**, probably because the particular configuration and increased flexibility, due to the introduction of the $CH–CH_2$ bridge between the aromatic area and the bicyclic structure, allow the interacting functions to assume a spatially similar pattern. Instead, unsuitable distances and stereochemistry seem to be responsible for the low potency of compounds **7**, **8**, **13**, **14**, and **15**.

The result of the screening of ligand **6** shows a significant selectivity on rabbit vas deferens (M_1-putative) (pA_2 $M_1 = 7.80$; $M_1/M_2 = 457$-fold; $M_1/M_3 = 42$-fold; $M_1/M_4 = 389$-fold). Its pharmacological profile is comparable to that of the well-known M_1-antagonist Pirenzepine, whose profile was determined using the same experimental protocols (pA_2 $M_1 = 8.05$; $M_1/M_2 = 37$-fold; $M_1/M_3 = 14$-fold; $M_1/M_4 = 49$-fold), and whose selectivity derives both from the tricyclic system with two aromatic areas and from the 4-methyl-1-piperazine ring.[49] Since the basic pyrrolidine ring of **6** can reproduce a spatial rigidity similar to that of the Pirenzepine piperazine ring, it can be hypothesized that, analogously to Pirenzepine, also in compound **6** the critical functions for interaction with the M_1-muscarinic subtype are present and suitably spaced. These analogies were verified by overlapping the low-energy conformations of compound **6** and Pirenzepine, which were generated using the HyperChem 'Molecular Modeling System'.[50] Their molecular overlay (Fig. 2) shows that similar spatial regions are occupied by the presumed pharmacophores, such as the basic methylated nitrogen of **6** and the one in position 4 of the Pirenzepine piperazine ring, the extensive aromatic hydrophobic area of **6** and that of Pirenzepine, the polar functions, that is, the oxygen atom of dioxolane nucleus of **6** and the nitrogen in position 1 of the Pirenzepine piperazine ring. Hence it can be hypothesized that compound **6** and Pirenzepine interact in a similar way with the M_1-muscarinic receptor.

Conclusion

In the present study, the conformational constraint of **1** in a bicyclic structure, and the variation in distance and stereochemistry of the critical functions represent fundamental operations for modulating the biological profile and obtaining muscarinic antagonists with enhanced selectivity of interaction with the M_1–M_3 receptor subtypes. In particular, the hydrophobic interactions in the basic tertiary amine derivatives allow the various receptor subtypes to be differentiated: in fact, despite marked analogies, these seem to display significant differences at the level of lipophilic binding pockets. The most interesting result of the present study is the behavior of compound **6**, which, equipotent with Pirenzepine, shows a better M_1-putative selectivity profile. Moreover, the higher lipophilicity of **6** (its calculated value of logP being 3.6, as compared with the 0.2 of Pirenzepine)[51] might facilitate bioavailability at the central level, thus making this new compound a useful tool for characterizing the central M_1-muscarinic receptor functions that govern learning acquisition and memory.[52] Similarly, due to their significant M_2/M_1 selectivity, compounds **9** (ClogP = 3.1) and **12** (ClogP = 3.8) might be useful in studies at the central level, since it is well known that this type of selectivity is crucial in the potential treatment of dementia. Finally, compounds **3** (ClogP = 3.1) and **4** (ClogP = 3.1) could be useful for determining the role played by the central M_3 receptors in orexigenic activity.[53]

Experimental protocol

Melting points were taken in glass capillary tubes on a Büchi B-540 apparatus and are uncorrected. IR and NMR spectra were recorded on Perkin-Elmer 297 and Varian EM-390 instruments, respectively. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS), and spin multiplicities are given as s (singlet), d (doublet), t (triplet), or m (multiplet). Although the IR spectra data are not included (because of the lack of unusual features), they were obtained for all compounds reported and are consistent with the assigned structures. The microanalyses were performed by the Microanalytical Laboratory of our department and the elemental compositions of the compounds agreed to within $\pm 0.4\%$ of the calculated value. Chromatographic separations were performed on silica gel columns (Kieselgel 40, 0.040–0.063 mm, Merck) by flash chromatography. The term 'dried' refers to the use of anhydrous sodium sulfate. Compounds were named following IUPAC rules as applied by Beilstein-Institut AutoNom (version 2.1), a software

for systematic names in organic chemistry. Overlay of Pirenzepine and compound **6** was obtained after global geometry optimisation and energy minimization using the HyperChem® MM+ force field method.[50]

Chemistry

***(cis,cis/cis,trans)*-2-Benzhydryl-4,5-bis-(chloromethyl)-[1,3]dioxolane (16).** A mixture of diphenyl acetaldehyde (2.0 g, 10.19 mmol), 1,4-dichloro-butane-2,3-diol[34] (1.62 g, 10.19 mmol) and *p*-toluenesulfonic acid (0.3 g) in benzene (50 mL) was refluxed with vigorous stirring and water removal for 5 h. After cooling, the solution was washed with $NaHCO_3$ sol. and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography. Eluting with cyclohexane–$CHCl_3$–EtOAc (9:1:0.1) afforded **16** as a *cis*/*trans* mixture (ratio 7:3): 2.4 g (70% yield); ^{1}H NMR ($CDCl_3$) δ 3.02–3.72 (m, 8, CH_2Cl; *cis* and *trans*), 3.94–4.46 (m, 6, OCHCHO and ArCH; *cis* and *trans*), 5.61 (d, $J=3.5$ Hz, 1, OCHO; *cis*), 5.97 (d, $J=3.9$ Hz, 1, OCHO; *trans*), 7.19–7.50 (m, 20, ArH; *cis* and *trans*).

***(cis,cis/cis,trans)*-4,5-Bis-(chloromethyl)-2-(2,2-diphenylethyl)-[1,3]dioxolane (17).** **17** was prepared as described for **16** starting from 3,3-diphenyl propionaldehyde[35] (1.25 g, 5.94 mmol). Eluting with petroleum ether–Et_2O (10:0.25) afforded **17** as a *cis*/*trans* mixture (ratio 7:3): 1.4 g (67% yield); ^{1}H NMR ($CDCl_3$) δ 2.35 (m, 2, CCH_2C; *trans*), 2.46 (m, 2, CCH_2C; *cis*), 3.66 (m, 8, CH_2Cl; *cis* and *trans*), 4.14–4.44 (m, 6, OCHCHO and ArCH; *cis* and *trans*), 4.76 (t, 1, OCHO; *cis*), 5.08 (t, 1, OCHO; *trans*), 7.12–7.30 (m, 20, ArH; *cis* and *trans*).

***(cis,cis/cis,trans)*-4,5-Bis-(chloromethyl)-2-(3,3-diphenylpropyl)-[1,3]dioxolane (18).** **18** was prepared as described for **16** starting from 4,4-diphenyl butyraldehyde[36] (1.66 g, 7.4 mmol). Eluting with cyclohexane–EtOAc (9:1) afforded **18** as a *cis*/*trans* mixture (ratio 6:4): 2.0 g (74% yield); ^{1}H NMR ($CDCl_3$) δ 1.55–2.27 (m, 8, CCH_2CH_2C; *cis* and *trans*), 3.61 (m, 8, CH_2Cl; *cis* and *trans*), 3.86–4.45 (m, 6, OCHCHO and ArCH; *cis* and *trans*), 5.01 (t, 1, ArCH; *cis*), 5.34 (t, 1, ArCH; *trans*), 7.12–7.38 (m, 20, ArH).

***(cis,cis)*- and (*cis,trans*)-2-Benzhydryl-5-methyl-tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrole oxalates (3 and 4) and methiodide salts (3a and 4a).** A solution of **16** (1.0 g, 2.97 mmol) and methylamine (0.18 g, 5.94 mmol) in dry benzene (20 mL) was heated in a sealed tube at 100 °C for 72 h. Evaporation of the solvent gave a residue, which was dissolved in $CHCl_3$; the solution was washed with 2 N NaOH. Removal of the dried solvent gave a residue, which was an isomeric mixture of the free bases **3** and **4**. These were separated by column chromatography eluting with cyclohexane–EtOAc–MeOH (1:9:0.05) as eluent. The *trans* isomer **4** eluted first: 0.25 g (28% yield); mp 113–115 °C; ^{1}H NMR ($CDCl_3$) δ 2.07 (m, 2, CH_2N), 2.27 (s, 3, NCH_3), 3.06 (d, $J=11.8$ Hz, 2, CH_2N), 4.16 (d, $J=4.7$ Hz, 1, ArCH), 4.52 (m, 2, OCHCHO), 5.97 (d, $J=4.7$ Hz, 1, OCHO), 7.15–7.40 (m, 10, ArH).

The second fraction was the *cis* isomer **3**: 0.28 g (32% yield); mp 73–75 °C; ^{1}H NMR ($CDCl_3$) δ 2.12 (m, 2, CH_2N), 2.31 (s, 3, NCH_3), 3.03 (d, $J=11.8$ Hz, 2, CH_2N), 4.40 (d, $J=8.0$ Hz, 1, ArCH), 4.58 (m, 2, OCHCHO), 5.51 (d, $J=8.0$ Hz, 1, OCHO), 7.13–7.38 (m, 10, ArH).

The free bases were transformed into the oxalates: **3** was crystallized from MeOH (mp 224–226 °C) and **4** from EtOH (mp 223–224 °C).

The free bases were transformed into the methiodide salts: **3a** was crystallized from 2-PrOH (mp 215–217 °C) and **4a** from 2-PrOH (mp 203–205 °C).

***(cis,cis)*- and (*cis,trans*)-2-(2,2-Diphenylethyl)-5-methyl-tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrole oxalates (5 and 6) and methiodide salts (5a and 6a).** **5** and **6** were prepared as described for **3** and **4** starting from **17** (1.3 g, 3.7 mmol) as a *cis*/*trans* mixture. These were separated by column chromatography eluting with cyclohexane–EtOAc–MeOH (1:9:0.05) as eluent. The *trans* isomer **6** eluted first: 0.35 g (30% yield); mp 99–101 °C; ^{1}H NMR ($CDCl_3$) δ 2.13 (m, 2, CCH_2C), 2.21 (s, 3, NCH_3), 2.32 (dd, $J=7.7$, $J=4.2$ Hz, 2, CH_2N), 2.90 (d, $J=11.5$ Hz, 2, CH_2N), 4.18 (t, 1, ArCH), 4.61 (m, 2, OCHCHO), 5.12 (t, 1, OCHO), 7.12–7.36 (m, 10, ArH).

The oxalate **6** was crystallized from MeOH (mp 214–215 °C) and the methiodide salt **6a** from MeOH (mp 205–207 °C).

The second fraction was the *cis* isomer **5**: 0.42 g (37% yield); mp 113–114 °C; ^{1}H NMR ($CDCl_3$) δ 2.03 (m, 2, CCH_2C), 2.32 (s, 3, NCH_3), 2.53 (dd, $J=8.2$, $J=4.5$ Hz, 2, CH_2N), 3.11 (d, $J=11.8$ Hz, 2, CH_2N), 4.22 (t, 1, ArCH), 4.42 (m, 2, OCHCHO), 4.57 (t, 1, OCHO), 7.10–7.37 (m, 10, ArH).

The oxalate **5** was crystallized from MeOH (mp 242 °C) and the methiodide salt **5a** from MeOH (mp 272–274 °C).

***(cis,cis)*- and (*cis,trans*)-2-(2,2-Diphenyl-propyl)-5-methyl-tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrole oxalates (7 and 8) and methiodide salts (7a and 8a).** **7** and **8** were prepared as described for **3** and **4** starting from **18** (2.0 g, 5.48 mmol) as a *cis*/*trans* mixture. These were separated by column chromatography eluting with cyclohexane–EtOAc–MeOH (1:9:0.05) as eluent. The *trans* isomer **8** eluted first: 0.2 g (11% yield); mp 89–90 °C; ^{1}H NMR ($CDCl_3$) δ 1.58 (m, 2, CH_2C), 2.06–2.39 (m, 4, CCH_2 and CH_2N), 2.32 (s, 3, NCH_3), 3.04 (d, $J=11.3$ Hz, 2, CH_2N), 3.90 (t, 1, ArCH), 4.63 (m, 2, OCHCHO), 5.31 (t, 1, OCHO), 7.10–7.36 (m, 10, ArH).

The oxalate **8** was crystallized from EtOH/Et_2O (mp 196–198 °C) and the methiodide salt **8a** from MeOH (mp 154–156 °C).

The second fraction was the *cis* isomer **7**: 0.4 g (23% yield); mp 59–60 °C; ^{1}H NMR ($CDCl_3$) δ 1.72 (m, 2, CH_2C), 2.06–2.28 (m, 4, CCH_2 and CH_2N), 2.35 (s, 3,

NCH_3), 3.09 (d, $J=11.8$ Hz, 2, CH_2N), 3.93 (t, 1, ArCH), 4.52 (m, 2, OCHCHO), 4.79 (t, 1, OCHO), 7.09–7.32 (m, 10, ArH).

The oxalate **7** was crystallized from EtOH (mp 187–188 °C) and the methiodide salt **7a** from EtOH (mp 221–222 °C).

***cis*-2,2-Diphenyl-tetrahydro-[1,3]dioxolo[4,5-*c*]pyridine-5-carboxylic acid ethyl ester (19).** A mixture of benzophenone dimethyl acetal[38] (1.21 g, 5.29 mmol), 1-ethoxycarbonylpiperidine-*cis*-3,4-diol[39] (1.0 g, 5.29 mmol) and *p*-toluenesulfonic acid (0.3 g) in toluene (50 mL) was refluxed in a Stark apparatus with vigorous stirring for 18 h. After cooling, the solution was washed with $NaHCO_3$ soln and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography. Eluting with cyclohexane–EtOAc (9:1) first and (5:5) then afforded **19** as an oil: g 1.5 (80% yield); ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3, CH_3), 1.72–2.23 (m, 2, CCH_2C), 3.31–4.05 (m, 4, CH_2NCH_2,), 4.05–4.37 (m, 4, OCHCHO and OCH_2), 7.20–7.66 (m, 10, ArH).

***(cis,cis)*- and (*cis,trans*)-2-Benzhydryl-tetrahydro-[1,3]dioxolo[4,5-*c*]pyridine-5-carboxylic acid ethyl ester (20 and 21).** **20** and **21** were prepared as described for **19** starting from 2,2-diphenyl acetaldehyde (1.55 g, 7.90 mmol). The residue was a *cis*/*trans* mixture and the two isomers were separated by column chromatography using cyclohexane–EtOAc (9:1) first and (8:2) then as eluent. The *trans* isomer **20** eluted first: 1.0 g (35% yield); ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3, CH_3), 1.62–2.0 (m, 2, CCH_2C), 3.31–3.58 (m, 4, CH_2NCH_2), 3.90 (m, 2, OCHCHO), 4.12 (q, 2, OCH_2), 4.19 (m, 1, ArCH), 5.89 (d, $J=4.8$ Hz, 1, OCHO), 7.16–7.40 (m, 10, ArH).

The second fraction was the *cis* isomer **21**: 1.6 g (55% yield); ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3, CH_3), 1.62–1.98 (m, 2, CCH_2C), 2.66–3.48 (m, 4, CH_2NCH_2), 4.12 (q, 2, OCH_2), 4.12–4.33 (m, 2, OCHCHO), 5.52 (d, $J=4.4$ Hz, 1, OCHO), 7.16–7.39 (m, 10, ArH).

***(cis,cis)*- and (*cis,trans*)-2-(2,2-Diphenyl-ethyl)-tetrahydro-[1,3]dioxolo[4,5-*c*]pyridine-5-carboxylic acid ethyl ester (22 and 23).** **22** and **23** were prepared as described for **19** starting from 3,3-diphenyl propionaldehyde[35] (1.11 g, 5.28 mmol). The residue was a *cis*/*trans* mixture and the two isomers were separated by column chromatography using cyclohexane–EtOAc (9:1) first and (8:2) then as eluent. The *trans* isomer **22** eluted first: 0.6 g (30% yield); ^{1}H NMR ($CDCl_3$) δ 1.23, (t, 3, CH_3), 1.87 (m, 2, CCH_2C), 2.3 (dd, $J=8.0$, $J=4.4$ Hz, 2, CCH_2C), 3.28–3.66 (m, 4, CH_2NCH_2), 4.12 (q, 2, OCH_2), 4.08–4.32 (m, 3, OCHCHO and ArCH), 5.07 (t, 1, OCHO), 7.13–7.36 (m, 10, ArH).

The second fraction was the *cis* isomer **23**: 1.25 g (62% yield); ^{1}H NMR ($CDCl_3$) δ 1.24, (t, 3, CH_3), 1.70–2.05 (m, 2, CCH_2C), 2.42 (dd, $J=8.2$, $J=4.5$ Hz, 2, CCH_2C), 3.26–3.80 (m, 4, CH_2NCH_2), 4.03–4.28 (m, 5, OCH_2, OCHCHO and ArCH), 4.70 (t, 1, OCHO), 7.13–7.36 (m, 10, ArH).

***(cis,cis)*- and (*cis,trans*)-2-(3,3-Diphenyl-propyl)-tetrahydro-[1,3]dioxolo[4,5-*c*]pyridine-5-carboxylic acid ethyl ester (24 and 25).** **24** and **25** were prepared as described for **19** starting from 4,4-diphenyl butyraldehyde[36] (1.8 g, 8.03 mmol). The residue was a *cis*/*trans* mixture and the two isomers were separated by column chromatography using cyclohexane–EtOAc (9:1) first and (8.5:1.5) then as eluent. The *trans* isomer **24** eluted first: 1.2 g (38% yield); ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3, CH_3), 1.50–2.22 (m, 6, CCH_2CH_2C and CCH_2C), 3.32–3.62 (m, 4, CH_2NCH_2), 3.90 (t, 1, ArCH), 4.13 (q, 2, OCH_2), 4.21 (m, 2, OCHCHO), 5.28 (t, 1, OCHO), 7.11–7.36 (m, 10, ArH).

The second fraction was the *cis* isomer **25**: 2.0 g (62% yield); ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3, CH_3), 1.58–2.26 (m, 6, CCH_2CH_2C and CCH_2C), 3.25–3.77 (m, 4, CH_2NCH_2), 3.91 (t, 1, ArCH), 3.99–4.27 (m, 4, OCH_2 and OCHCHO), 4.91 (t, 1, OCHO), 7.11–7.33 (m, 10, ArH).

***cis*-5-Methyl-2,2-diphenyl-hexahydro-[1,3]dioxolo[4,5-*c*]pyridine oxalate (9) and methiodide salt (9a).** A solution of **19** (1.5 g, 4.24 mmol) in dry Et_2O (30 mL) was added dropwise to a stirred mixture of $LiAlH_4$ (0.32 g, 8.48 mmol) in dry Et_2O (30 mL) at 0 °C over a period of 15 min. The mixture was refluxed for 2 h, then decomposed with H_2O (0.4 mL), 5 N NaOH (0.4 mL) and H_2O (2.0 mL). After stirring for 1 h, the solid was filtered off and the filtrate was dried over Na_2SO_4. Removal of solvent gave a residue, which was purified through column chromatography. Eluting with $CHCl_3$–MeOH (9.5:0.5) afforded the free base **9**: 1.1 g (88% yield); mp 133–135 °C; ^{1}H NMR ($CDCl_3$) δ 1.90–2.86 (m, 6, $CH_2CH_2NCH_2$), 2.23 (s, 3, CH_3), 4.09–4.43 (m, 2, OCHCHO), 7.20–7.60 (m, 10, ArH).

The oxalate **9** was crystallized from EtOH (mp 186–187 °C) and the methiodide salt **9a** from 2-PrOH (mp 187–188 °C).

***(cis,cis)*-2-Benzhydryl-5-methyl-hexahydro-[1,3]dioxolo[4,5-*c*]pyridine oxalate (10) and methiodide salt (10a).** **10** was prepared as described for **9** starting from **21** (1.6 g, 4.35 mmol): 1.0 g (74% yield); mp 67–68 °C; ^{1}H NMR ($CDCl_3$) δ 1.14–2.58 (m, 6, $CH_2CH_2NCH_2$), 2.07 (s, 3, CH_3), 4.10 (m, 2, OCHCHO), 4.28 (d, $J=4.4$ Hz, 1, CHAr), 5.59 (d, $J=4.4$ Hz, 1, OCHO), 7.16–7.39 (m, 10, ArH).

The oxalate **10** was crystallized from MeOH (mp 190–191 °C) and the methiodide salt **10a** from EtOH (mp 231–232 °C).

(*cis,trans*)-2-Benzhydryl-5-methyl-hexahydro-[1,3]dioxolo[4,5-*c*]pyridine oxalate (11) and methiodide salt (11a). **11** was prepared as described for **9** starting from **20** (1.0 g, 2.72 mmol): 0.7 g (83% yield); ^{1}H NMR ($CDCl_3$) δ 1.71–2.62 (m, 6, $CH_2CH_2NCH_2$), 2.28 (s, 3, CH_3), 3.68–3.98 (m, 2, OCHCHO), 4.19 (d, $J=4.0$ Hz, 1, CHAr), 5.90 (d, $J=4.0$ Hz, 1, OCHO), 7.17–7.41 (m, 10, ArH).

The oxalate **11** was crystallized from EtOH (mp 181–182 °C) and the methiodide salt **11a** from EtOH (mp 253–254 °C).

***(cis,cis)*-2-(2,2-Diphenyl-ethyl)-5-methyl-hexahydro-[1,3]dioxolo[4,5-*c*]pyridine oxalate (12) and methiodide salt (12a).** **12** was prepared as described for **9** starting from **23** (1.25 g, 3.28 mmol): 0.8 g (76% yield); mp 81–82 °C; ^{1}H NMR ($CDCl_3$) δ 1.88–2.81 (m, 8, CCH_2C and $CH_2CH_2NCH_2$), 2.28 (s, 3, CH_3), 3.92–4.14 (m, 2, OCHCHO), 4.24 (t, 1, CHAr), 4.79 (t, 1, OCHO), 7.12–7.40 (m, 10, ArH).

The oxalate **12** was crystallized from EtOH (mp 184–186 °C) and the methiodide salt **12a** from EtOH (mp 210–211 °C).

(*cis,trans*)-2-(2,2-Diphenyl-ethyl)-5-methyl-hexahydro-[1,3]dioxolo[4,5-*c*]pyridine oxalate (13) and methiodide salt (13a). **13** was prepared as described for **9** starting from **22** (0.6 g, 1.57 mmol): 0.4 g (78% yield); mp 63–64 °C; ^{1}H NMR ($CDCl_3$) δ 1.86–2.74 (m, 8, CCH_2C and $CH_2CH_2NCH_2$), 2.29 (s, 3, CH_3), 4.04–4.31 (m, 3, OCHCHO and CHAr), 5.11 (t, 1, OCHO), 7.08–7.34 (m, 10, ArH).

The oxalate **13** was crystallized from EtOH (mp 180–181 °C) and the methiodide salt **13a** from EtOH (mp 192–193 °C).

***(cis,cis)*-2-(3,3-Diphenyl-propyl)-5-methyl-hexahydro-[1,3]dioxolo[4,5-*c*]pyridine oxalate (14) and methiodide salt (14a).** **14** was prepared as described for **9** starting from **25** (2.0 g, 5.06 mmol): 1.4 g (82% yield); ^{1}H NMR ($CDCl_3$) δ 1.34–2.86 (m, 10, CCH_2CH_2C and $CH_2CH_2NCH_2$), 2.31 (s, 3, CH_3), 3.86–4.22 (m, 3, OCHCHO and CHAr), 4.98 (t, 1, OCHO), 7.11–7.33 (m, 10, ArH).

The oxalate **14** was crystallized from EtOH (mp 172–173 °C) and the methiodide salt **14a** from 2-PrOH/Et_2O (mp 97–98 °C).

(*cis,trans*)-2-(3,3-Diphenyl-propyl)-5-methyl-hexahydro-[1,3]dioxolo[4,5-*c*]pyridine oxalate (15) and methiodide salt (15a). **15** was prepared as described for **9** starting from **24** (1.2 g, 3.03 mmol): 0.7 g (69% yield); ^{1}H NMR ($CDCl_3$) δ 1.49–2.73 (m, 10, CCH_2CH_2C and $CH_2CH_2NCH_2$), 2.32 (s, 3, CH_3), 3.91 (t, 1, CHAr), 4.02–4.26 (m, 2, OCHCHO), 5.31 (t, 1, OCHO), 7.11–7.34 (m, 10, ArH).

The oxalate **15** was crystallized from EtOH/Et_2O (mp 154–155 °C) and the methiodide salt **15a** from 2-PrOH (mp 167–168 °C).

Pharmacology

General considerations. Male guinea pigs (200–300 g) and male New Zealand white rabbits (3.0–3.5 kg) were killed by cervical dislocation. The organs required were set up rapidly under 1 g of tension in 20-mL organ baths containing physiological salt solution (PSS) maintained at an appropriate temperature (see below) and aerated with 5% CO_2–95% O_2. Dose–response curves were constructed by cumulative addition of the reference agonist. The concentration of agonist in the organ bath was increased approximately 3-fold at each step, with each addition being made only after the response to the previous addition had attained a maximal level and remained steady. Following 30 min of washing, tissues were incubated with the antagonist for 30 min, and a new dose–response curve to the agonist was obtained. Contractions were recorded by means of a force displacement transducer connected to the MacLab system PowerLab/800. In addition parallel experiments in which tissues did not receive any antagonist were run in order to check any variation in sensitivity.

Guinea-pig ileum. Two-centimeter-long portions of terminal ileum were taken at about 5 cm from the ileum–caecum junction. The tissue was cleaned and the ileum longitudinal muscle was separated from the underlying circular muscle, and mounted in PSS, at 37 °C, of the following composition (mM): NaCl (118), $NaHCO_3$ (23.8), KCl (4.7), $MgSO_4.7H_2O$ (1.18), KH_2PO_4 (1.18), $CaCl_2$ (2.52), and glucose (11.7). Tension changes were recorded isotonically. Tissues were equilibrated for 30 min, and dose–response curves to arecaidine propargyl ester (APE) were obtained at 30-min intervals, the first one being discarded and the second one being taken as the control.

Guinea-pig stimulated left atria. The heart was rapidly removed, and the right and left atria were separately excised. Left atria were mounted in PSS (the same used for ileum) at 30 °C and stimulated through platinum electrodes by square-wave pulses (1 ms, 1 Hz, 5–10 V) (Tetra Stimulus, N. Zagnoni). Inotropic activity was recorded isometrically. Tissues were equilibrated for 2 h and a cumulative dose–response curve to APE was constructed.

Guinea pig lung strip. The lungs were rapidly removed and placed in Krebs–Henseleit buffer solution of the following composition (nM): NaCl (118.78), KCl (4.32), $CaCl_2.2H_2O$ (2.52), $MgSO_4.7H_2O$ (1.18), KH_2PO_4 (1.28), $NaHCO_3$ (25), glucose (5.55). Strips of peripheral lung tissue, approximately 15×2×2 mm were cut off a lower lobe with the longitudinal axis of the strip parallel to the bronchus or from the peripheral margin of the lobe. The preparations were mounted in 20-mL organ baths at 37 °C under isotonic recording with a preload of 0.3 g. Tissues were equilibrated for 60 min, and dose–response curves to arecaidine propargyl ester (APE) (0.01, 0.1, 1, 10, 100 μM) were obtained at 45-min intervals, the first one being discarded and the second one being taken as the control.

Rabbit stimulated vas deferens. This preparation was set up according to Eltze.[43] Vasa deferentia were carefully dissected free of surrounding tissue and were divided into four segments, two prostatic portions of 1 cm and two epididymal portions of approximately 1.5 cm length. The four segments were mounted in PSS with

the following composition (mM): NaCl 118.4, KCl (4.7), $CaCl_2$ (2.52), $MgCl_2$ (0.6), KH_2PO_4 (1.18), $NaHCO_3$ (25), glucose (11.1); 10^{-6} M yohimbine was included to block alpha$_2$-adrenoceptors. The solution was maintained at 30 °C and tissues were stimulated through platinum electrodes by square-wave pulses (0.1 ms, 2 Hz, 10–15 V). Contractions were measured isometrically after tissues were equilibrated for 1 h, then a cumulative dose–response curve to *p*Cl-McN-A-343 was constructed.

Determination of antagonist potency. To quantify antagonist potency, pK_b values were calculated from the equation pK_b = log(DR−1)−log[B], where DR is the ratio of ED_{50} values of agonist after and before treatment with one or two antagonist concentrations [B].[44]

In some cases, antagonist potency is expressed in terms of pA_2, estimated by Schild plots constrained to slope −1.0, as required by the theory.[45,46]

Statistical analysis. The results are expressed as mean ±SEM. Student's *t*-test was used to assess the statistical significance of the difference between two means.

Analysis of Reported Compounds

Compd	Formula	Calculated			Found		
		C%	H%	N%	C%	H%	N%
3	$C_{19}H_{21}NO_2{\cdot}H_2C_2O_4$	65.44	6.02	3.63	65.31	6.25	3.71
3a	$C_{20}H_{24}INO_2$	54.93	5.53	3.20	54.82	5.72	3.45
4	$C_{19}H_{21}NO_2{\cdot}H_2C_2O_4$	65.44	6.02	3.63	65.12	6.12	3.52
4a	$C_{20}H_{24}INO_2$	54.93	5.53	3.20	55.13	5.85	3.12
5	$C_{20}H_{23}NO_2{\cdot}H_2C_2O_4$	66.15	6.31	3.51	66.33	6.11	3.15
5a	$C_{21}H_{26}INO_2$	55.88	5.81	3.10	55.63	5.63	2.98
6	$C_{20}H_{23}NO_2{\cdot}H_2C_2O_4$	66.15	6.31	3.51	65.89	6.42	3.33
6a	$C_{21}H_{26}INO_2$	55.88	5.81	3.10	55.52	5.53	2.88
7	$C_{21}H_{25}NO_2{\cdot}H_2C_2O_4$	66.81	6.58	3.39	66.67	6.29	3.13
7a	$C_{22}H_{28}INO_2$	56.78	6.06	3.01	56.89	5.87	2.79
8	$C_{21}H_{25}NO_2{\cdot}H_2C_2O_4$	66.81	6.58	3.39	67.13	6.85	3.59
8a	$C_{22}H_{28}INO_2$	56.78	6.06	3.01	56.66	5.85	3.25
9	$C_{19}H_{21}NO_2{\cdot}H_2C_2O_4$	65.44	6.02	3.63	65.55	6.35	3.44
9a	$C_{20}H_{24}INO_2$	54.93	5.53	3.20	54.83	5.45	3.01
10	$C_{20}H_{23}NO_2{\cdot}H_2C_2O_4$	66.15	6.31	3.51	65.87	6.04	3.33
10a	$C_{21}H_{26}INO_2$	55.88	5.81	3.10	56.11	5.65	2.89
11	$C_{20}H_{23}NO_2{\cdot}H_2C_2O_4$	66.15	6.31	3.51	65.98	6.12	3.27
11a	$C_{21}H_{26}INO_2$	55.88	5.81	3.10	55.66	5.59	3.39
12	$C_{21}H_{25}NO_2{\cdot}H_2C_2O_4$	66.81	6.58	3.39	66.78	6.28	3.11
12a	$C_{22}H_{28}INO_2$	56.78	6.06	3.01	56.98	6.41	3.35
13	$C_{21}H_{25}NO_2{\cdot}H_2C_2O_4$	66.81	6.58	3.39	66.91	6.43	3.15
13a	$C_{22}H_{28}INO_2$	56.78	6.06	3.01	56.61	5.88	2.98
14	$C_{22}H_{27}NO_2{\cdot}H_2C_2O_4$	67.43	6.84	3.28	67.72	6.58	3.02
14a	$C_{23}H_{30}INO_2$	57.62	6.31	2.92	57.75	6.62	3.11
15	$C_{22}H_{27}NO_2{\cdot}H_2C_2O_4$	67.43	6.84	3.28	67.16	7.03	3.45
15a	$C_{23}H_{30}INO_2$	57.62	6.31	2.92	57.43	6.02	2.81

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