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Synthesis and Antimuscarinic Activity of some Ether- and Thioether-bearing 1,3-Dioxolanes and Related Sulfoxides and Sulfones

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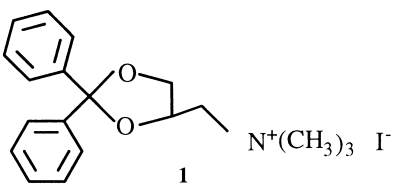
Abstract—A series of 1,3-dioxolane-based ligands, bearing ether, thioether and related sulfoxide and sulfone functionalities, were synthesised and tested as potential muscarinic antagonists. The compounds display moderate to low affinity for the three receptor subtypes M_1–M_3, with some of them showing a significant selectivity for the M_1–M_3 over the M_2 subtype.

Introduction

Molecular cloning studies have shown that muscarinic receptors consist of five molecular forms (m_1–m_5)[1,2] corresponding to the three pharmacologically-defined M_1–M_3 subtypes.[3,4] The pharmacological characterization of these receptors is thus still incomplete, most likely owing to the lack of an appropriate selective ligand. Since muscarinic receptor subtypes are variously involved in secretory and cardiovascular functions, smooth muscle control and in central nervous system transmission, selective ligands, which interfere specifically with one or other of the subtypes, would represent potential therapeutic agents. Accordingly, M_2 and M_3 antagonists have been proposed for the treatment of cardiac[5] and gastrointestinal tract disorders,[6,7] respectively, while lipophilic M_2 antagonists could serve to improve memory and learning in neurodegenerative disorders.[8,9] A potential role as selective bronchodilators has also been proposed for M_3 or combined M_1 and M_3 antagonists.[10] Hence the urgent need to discover selective antagonists which would make for a more definitive classification and represent potential therapeutic agents.

With this in mind we undertook a research project aimed at developing selective antagonists, taking as a lead compound **1**, which has been reported to be a very potent muscarinic antagonist[11–13] but lacking in significant selectivity.[14] We focused our attention on position 2 and, while keeping one of the two phenyl rings constant, replaced the other with different functionality that could cause a discriminating interaction with the receptor subtypes. Here, we report on the synthesis and pharmacological evaluation of a series of 1,3-dioxolanes carrying an ether or thioether function of varying degrees of bulkiness in position 2.



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Chemistry

The syntheses of the compounds used in this study are reported in Scheme 1. The ketones **10**–**13** were prepared from the same precursor, bromoacetophenone. In the case of compound **10**, bromoacetophenone was allowed

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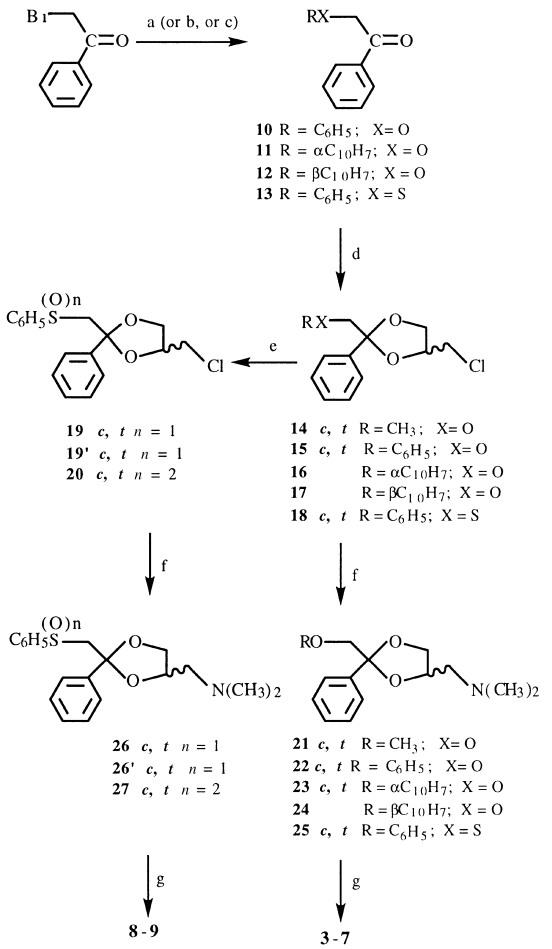


Scheme 1. (a) C_6H_5OH, K_2CO_3, $(C_2H_5)_2O$, dicyclohexyl 18-Crown ether-6, reflux; (b) C_6H_5SH, NaOH, C_2H_5OH, H_2O; (c) $\alpha C_{10}H_7OH$ (or $\beta C_{10}H_7OH$), CH_2Cl_2, H_2O, NaOH, TBAB, rt; (d) 3-chloro-propane-1,2-diol, CH_3CN (or CH_3NO_2), triflic acid, molecular sieve 4 Å, reflux; (e) MCPBA, CH_2Cl_2, −40 °C (or 0 °C to rt); (f) $(CH_3)_2$, 100 °C; (g) CH_3I, an. $(C_2H_5)_2O$, rt. When the compound number is followed by *c* (*cis*) and *t* (*trans*) the two isomers have been separated.

to react with phenol in ethereal solution, in the presence of K_2CO_3 using 18-Crown-ether-6 as phase transfer catalyst. The α-(**11**) and β-naphthoxy (**12**) derivatives were prepared in like manner; in this case the base was NaOH, the solvent a mixture of CH_2Cl_2/H_2O and the catalyst tetrabutylammonium bromide. The thiophenoxy **13**, on the other hand, was prepared in homogeneous phase (CH_3OH/H_2O) using NaOH as a base.

Compounds **10**–**13** and the commercially available 2-methoxyacetophenone were ketalized with 3-chloropropane-1,2-diol in anhydrous CH_3CN (or CH_3NO_2)[15] in the presence of molecular sieves 4 Å and a catalytic amount of triflic acid.

Compounds **14**–**18** were obtained as a mixture of diastereoisomers which, in the case of **14**, **15**, and **18**, were separated by flash chromatography. The α- and β-naphthoxy **16** and **17** were obtained as inseparable mixtures. The α-isomers were separated following the amination step (**23c**,**t**) while the β-isomers were not, and the corresponding methyl iodide **6** was a mixture 2/3 of *cis* and *trans* isomer.

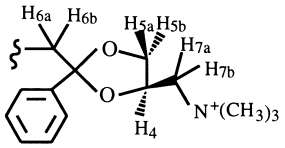
The thiophenoxy intermediates **18c**,**t** were oxidised with *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 to sulfoxides (−40 °C) **19** and to sulfones (0 °C to rt) **20**. The chloro derivatives **14**–**20** were then transformed into the tertiary amines **21**–**27** by treatment with $NH(CH_3)_2$ at 100 °C in a steel bomb. Finally, the tertiary amines were converted into the quaternary salts **3**–**9** with CH_3I in Et_2O. The configurational assignment of the diastereoisomeric pairs was obtained by 1-D Nuclear Overhaus Effect (1-D NOE)-difference experiments.[16] The ^1H chemical shifts of compounds **3**–**9** (Table 1) parallel those previously reported for some closely-related 1,3-dioxolanes[17,18] and confirm some common trends. The H-5a is always shielded with respect to its geminal partner owing to the shielding effect of the vicinal ammonium group. The difference $\Delta\delta = \delta$H-5a–δH-5b, when a 2-phenyl group is present, is greater in the *trans* than in the *cis* derivative, reflecting the remote shielding effect of the aromatic substituent on the protons in *cis* relationship with it. This effect is also seen, albeit to a lesser extent, on H-4.

The ^{13}C chemical shifts (Table 2) were obtained by direct acquisition experiments with proton decoupling, and their assignment, when not trivial, was based on the value of the coupling constant between carbons and the nitrogen atom of the $CH_2N^+(CH_3)_3$ group. In fact, C-5, C-7, and $N(CH_3)_3$ carbons display a $^3J(^{13}C, ^{14}N)$ coupling constant of the order of 1–1.5 Hz and $^1J(^{13}C, ^{14}N)$ coupling constant of the order of 3–4 Hz. The presence of these coupling constants enable us to distinguish between C-5, C-6, and C-7, which fall in a very narrow range. The detection of the $J(^{13}C, ^{14}N)$ coupling constant is due to the presence of the quaternary nitrogen.[19–21] On the other hand the H-4 signal broadens owing to an unresolved $^3J(^1H, ^{14}N)$ coupling constant, and this behaviour is characteristic of all the compounds examined.

Results and Discussion

All the newly-synthesized compounds were tested on three different preparations, namely, rabbit vas deferens, guinea pig heart and ileum for M_1, M_2, and M_3 antimuscarinic activity, respectively, and the results are reported in Table 3.

Table 1. ^{1}H Chemical shifts (ppm relative to TMS), and coupling constants, *J* (Hz), of compounds **3**–**9**[a]



	3c	3t	4c	4t	5c	5t	6c	6t	7c	7t	8c	8′c	8t	8′t	9c	9t
H-4	4.70	4.89	4.72	4.89	4.71	4.98	4.77	4.99	4.58	4.75	4.73	4.73	5.01	4.94	4.59	4.81
H-5a	3.91	3.56	3.97	3.61	4.02	3.67	4.03	3.64	3.87	3.44	4.04	3.96	3.55	3.58	3.82	3.42
H-5b	4.05	4.47	4.15	4.52	4.23	4.60	4.18	4.57	4.06	4.43	4.10	4.13	4.56	4.50	4.01	4.36
H-6a	3.66	3.65	4.28	4.27	4.45	4.45	4.41	4.41	3.54	3.51	3.41	3.45	3.44	3.48	3.98	4.02[b]
H-6b	3.66	3.66	4.31	4.32	4.55	4.49	4.44	4.44	3.59	3.60	3.45	3.48	3.47	3.52	4.03	4.02[b]
H-7a	3.62	3.67	3.53	3.48	3.61	3.57	3.71	3.66	3.57	3.42	3.59	3.65	3.61	3.51	3.57	3.51
H-7b	3.69	3.30	3.65	3.33	3.60	3.37	3.74	3.37	3.57	3.21	3.91	3.79	3.36	3.37	3.75	3.27
$N(CH_3)_3$	3.29	3.26	3.20	3.14	3.17	3.17	3.26	3.19	3.13	3.03	3.30	3.30	3.26	3.24	3.24	3.17
H-ortho ϕ	7.55	7.56	7.65	7.65	7.74	7.74	7.69	7.69	7.59	7.58	7.60	7.61	7.59	7.63	7.47	7.47
H-meta ϕ	7.45	7.45	7.49	7.49	7.52	7.53	7.50	7.50	7.47	7.47	7.47	7.47	7.47	7.49	7.41	7.41
H-para ϕ	7.45	7.45	7.49	7.49	7.49	7.48	7.52	7.52	7.44	7.46	7.47	7.47	7.47	7.49	7.41	7.41
J(H-4, H-5a)	4.75	7.71	5.29	7.94	5.78	7.89	5.31	7.93	5.65	8.66	4.60	5.58	8.85	8.63	5.76	8.64
J(H-4, H-5b)	6.89	6.35	6.91	6.26	6.98	6.29	6.92	6.28	7.28	6.11	7.47	7.41	5.97	6.46	7.49	6.31
J(H-4, H-7a)	2.15	1.46	1.76	1.52	1.6[c]	1.33	2.11	1.37	1.2[c]	1.07	1.40	1.59	1.26	1.34	1.10	1.31
J(H-4, H-7b)	9.44	9.55	9.66	9.59	9.6[c]	9.57	9.66	9.60	9.6[c]	9.71	10.14	9.81	9.52	9.46	9.86	9.68
J(H-5a, H-5b)	−8.83	−8.53	−8.81	−8.44	−8.80	−8.57	−8.82	−8.46	−8.71	−8.64	−9.16	−8.92	−8.67	−8.61	−8.76	−8.66
J(H-6a, H-6b)	−11.20	−11.10	−11.22	−11.20	−10.82	−10.72	−11.16	−11.17	−14.64	−14.83	−14.44	−14.34	−14.20	−14.32	−15.27	b
J(H-7a, H-7b)	−13.63	−13.94	−13.79	−14.02	−13.8c	−13.94	−14.00	13.99	−13.8c	−13.88	−13.69	−13.86	−13.96	−14.22	−13.75	−14.10

[a]Spectra were obtained in CD_3CN.
[b]A_2 spin system.
[c]Broad signals.

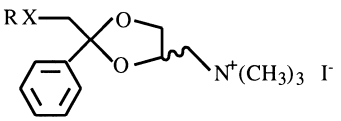
Table 2. ^{13}C Chemical shifts (ppm relative to TMS) of compounds **3**–**9**[a]

	3c[b]	3tb	4c	4t	5c	5t	6c	6t	7c	7t	8c	8′c	8t	8′t	9c	9t
C-2	111.5	111.3	110.85	110.69	110.9[b]	110.77	110.90	110.73	111.73	111.80	110.30	110.27	109.83	109.8[b]	109.15	108.72
C-4	70.6	71.4	70.74	71.60	70.56	71.72	70.85	71.79	70.45	71.80	70.62	70.80	71.63	71.4b	70.54	71.37
C-5	67.6	67.7	67.95	67.85	67.27	67.94	68.08	68.00	67.90	67.54	67.90	67.48	67.65	67.53	67.33	67.14
C-6	75.9	76.5	70.92	71.65	71.77	72.00	71.14	71.88	42.91	43.16	67.24	68.00	68.26	68.07	62.17	62.18
C-7	68.4	67.9	68.30	67.52	68.38	67.79	68.40	67.65	68.22	67.38	68.66	68.20	67.09	67.1[b]	67.96	67.09
$N(CH_3)_3$	54.4	54.2	54.27	54.09	54.20	54.14	54.35	54.14	54.19	53.97	54.41	54.36	54.24	54.23	54.37	54.15
C-1′ϕ	139.6	140.0	138.93	139.34	139.03	139.58	139.00	139.41	140.48	141.21	139.74	139.71	140.63	140.1[b]	139.29	139.92
C-ortho ϕ	125.9	125.9	126.03	125.90	126.23	126.05	126.14	126.02	125.74	125.59	125.57	125.64	125.41	125.54	125.64	125.53
C-meta ϕ	128.2	128.2	128.21	128.19	128.31	128.29	128.32	128.30	128.34	128.30	128.57	128.58	128.53	128.56	128.41	128.30
C-para ϕ	128.6	128.5	128.89	128.76	128.98	128.87	129.01	128.88	128.80	128.65	129.10	129.12	128.95	129.06	129.10	128.94

[a]Spectra were obtained in CD_3CN.
[b]Obtained from inverse detection experiments.

In a previous paper[18] we reported on compounds **2c**,**t**, which show an appreciable antimuscarinic activity at the three receptor subtypes, with some degree of diastereoselectivity. In an attempt to improve potency and selectivity, we used these compounds as a starting point. Methylation of the hydroxy group decreases activity at the M_1 and M_3 receptor subtypes, while leaving it unaffected at the M_2 subtype. The observed decrease, which is more pronounced for the *trans* isomer (**3t**), might be explained by a lack of hydrogen bonding, which may be operative in the case of compounds **2c**,**t**, or, alternatively, by a steric hindrance effect of the bulkier methoxy group. In order to determine the steric demand of the receptor subsite accommodating the substituent in position 2 more accurately, we prepared compounds **4**–**6**. Interestingly, replacement of the

Table 3. In vitro antimuscarinic activity and selectivity of compounds **1**–**9**



	R	X	pK_b (pA_2)			$\frac{M_1}{M_2}$	$\frac{M_1}{M_3}$	$\frac{M_3}{M_2}$
			M_1	M_2	M_3			
1			8.36 ± 0.07[a]	8.29 ± 0.06[a]	7.91 ± 0.07[a]	1.2	2.8	0.4
2c	H	O	6.35 ± 0.12	6.01 ± 0.15	5.97 ± 0.21	2.2	2.4	0.9
2t	H	O	7.13 ± 0.10	6.49 ± 0.21	7.01 ± 0.09	4.4	1.3	3.3
3c	CH_3	O	5.88 ± 0.07	6.05 ± 0.12	5.92 ± 0.08	0.7	0.9	0.7
3t	CH_3	O	6.49 ± 0.09	6.33 ± 0.10	6.10 ± 0.15	1.4	2.5	0.6
4c	C_6H_5	O	7.76 ± 0.05[a]	6.34 ± 0.12[a]	7.48 ± 0.10[a]	26	1.9	1.4
4t	C_6H_5	O	7.51 ± 0.15[a]	6.37 ± 0.13[a]	7.43 ± 0.07[a]	14	1.2	1.2
5c	$\alpha C_{10}H_7$	O	6.17 ± 0.13	5.30 ± 0.11	6.28 ± 0.10	7.4	0.8	1.0
5t	$\alpha C_{10}H_7$	O	6.64 ± 0.16	5.54 ± 0.09	6.17 ± 0.09	1.3	3.0	4.3
6c,t	$\beta C_{10}H_7$	O	< 5	5.85 ± 0.10	6.44 ± 0.18	0.1	—	3.8
7c	C_6H_5	S	7.04 ± 0.15[a]	5.87 ± 0.17	7.06 ± 0.11[a]	15	0.9	17
7t	C_6H_5	S	6.90 ± 0.18[a]	5.89 ± 0.12	6.97 ± 0.05[a]	10	1.2	12
8c	C_6H_5	SO	< 5	< 5	5.40 ± 0.08	—	—	—
8′c	C_6H_5	SO	5.45 ± 0.13	5.45 ± 0.18	5.91 ± 0.21	1.0	0.3	2.9
8t	C_6H_5	SO	< 5	< 5	5.35 ± 0.20	—	—	—
8′t	C_6H_5	SO	< 5	< 5	5.72 ± 0.19	—	—	—
9c	C_6H_5	SO_2	< 5	< 5	< 5	—	—	—
9t	C_6H_5	SO_2	< 5	< 5	< 5	—	—	—

[a]pA_2 values.

methyl group by a phenyl ring again leaves the M_2 antagonist activity unaffected, while a significant enhancement is observed at M_1 and M_3 receptors. A further increase in the substituent size, α-(**23**) and β-naphthyl (**24**) derivatives, reduces affinity at the three receptor subtypes.

Regarding the hydrogen-bonding interaction, evoked in the case of compounds **2c**,**t**, it can be said that, at least for M_1 and M_3 receptors, the good activity observed for the phenoxy derivatives **4c**,**t** can be explained if we allow that the decrease in activity due to the lack of hydrogen bonding is counterbalanced by a more productive interaction, probably of π–π type, between the phenyl ring and a counterpart at the receptor subsite. Bearing in mind that the compounds **2**, **3**, and **4** have similar affinities, the formation of hydrogen bonding might not take place in the case of the M_2 receptor subtype or, alternatively, the hydroxy group might behave as a hydrogen-bonding acceptor.

Isosteric oxygen/sulphur substitution was also studied, and the thioderivatives **7c**,**t** turn out to be slightly less active than the parent compounds **4c**,**t**. Finally, the oxidation of sulphur to sulfoxides **8** and **8′** and to sulfones **9** afford virtually inactive compounds.

As regard selectivity, the phenoxy derivatives **4** are the most interesting of the series. Both *cis* and *trans* forms show significantly (10–26 times) greater selectivity for the M_1–M_3 than for the M_2 subtypes. Although isosteric oxygen/sulphur substitution decreases affinity for the three receptor subtypes, it does not seem to affect selectivity, as compounds **7c**,**t** show the same selectivity profile as compounds **4t**,**c**. Although not striking, this kind of selectivity is of interest in view of a potential therapeutic application in the treatment of chronic obstructive pulmonary disease, where cholinergic tone is the only reversible component.[10] We cannot preclude that the relative affinities presented here may represent species differences or receptor tissues distribution; further measures of relative affinity against cloned human subtypes may clarify these issues. Efforts to improve selectivity are being made and findings will be reported in due course.

Experimental

Chemistry

Melting points were taken in glass capillary tubes on a Büchi apparatus and are uncorrected. Infrared (IR)

spectra were measured on a Perkin–Elmer 1600 instrument. Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR) spectra were obtained in $CDCl_3$ or CD_3CN, with Varian XL-200 and Bruker AMX-400 WB spectrometers, and peak positions are given in parts per million (δ), downfield from tetramethylsilane as the internal standard. The typical resolution for ^{1}H NMR spectra was 0.05 Hz per point. Differential steady-state NOE experiments were performed, acquiring 128 + 128 transients in groups of eight, alternately irradiating on- and off-resonance, with a presaturation time of 10 s. Fully proton-decoupled ^{13}C NMR spectra were obtained with standard pulse sequence, and the resolution being 0.05 ppm. The microanalyses were performed on a Carlo Erba 1106 Analyzer in the Microanalytical Laboratory of our department. Chromatographic separations were performed on silica gel columns (Kieselgel 40, 0.040–0.063 mm, Merck) by flash chromatography. Reaction courses and product mixture were routinely monitored by thin-layer chromatography (TLC) on silica gel-precoated F_{254} Merck plates.

2-Phenoxy-1-phenyl-ethanone (10). Bromoacetophenone (7.30 g, 35.6 mmol, 97%), in 25 mL of anhydrous diethyl ether, was added dropwise to a solution of phenol (4.5 g, 47.8 mmol), K_2CO_3 (6.0 g), and dicyclohexyl-18-crown-6 (40 mg) in 30 mL of anhydrous diethyl ether. The reaction was refluxed for 12 h under nitrogen. After cooling to rt the solid was filtered off and the solution was extracted with aqueous K_2CO_3 (3×15 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by chromatography on silica gel column using cyclohexane:EtOAc (95:5) as the eluant to give 6.52 g (30.7 mmol, 86.2%) of compound **10**: ^{1}H NMR ($CDCl_3$) δ 5.24 (s, 2H), 6.94 (m, 3H), 7.20 (m, 2H), 7.47 (m, 2H), 7.58 (m, 1H), 7.95 (m, 2H).

2-(Naphtalen-1-yloxy)-1-phenyl-ethanone (11). To 400 mL of an emulsion of H_2O:CH_2Cl_2 (1:1) were added, under vigorous stirring, 16 g (78.0 mmol) of bromoacetophenone (97%), 5.9 g (40.9 mmol) of naphthalen-1-ol, 2.4 g (60.0 mmol) of NaOH and 350 mg (1.1 mmol) of TBAB. The reaction was stirred at rt for 12 h, then the solid was filtered off and the solvent was evaporated. The residue was dissolved in diethyl ether, extracted with NaOH 2 N (3×30 mL), and dried over $MgSO_4$. Evaporation of the solvent gave a gummy residue, which was dissolved in DMF. Addition of H_2O gave 8.9 g (33.9 mmol, 82.9%) of compound **11** as a yellowish solid (mp 95–97 °C). ^{1}H NMR ($CDCl_3$): δ 5.40 (s, 2H), 6.75 (d, 1H), 7.31 (t, 1H), 7.41–750 (m, 5H), 7.59 (m, 1H), 7.78 (m, 1H), 8.03 (m, 2H), 8.32 (m, 1H).

2-(Naphthalen-2-yloxy)-1-phenyl-ethanone (12). Starting from 16 g (78.0 mmol) of bromoacetophenone (97%), following the same procedure adopted for the preparation of **11**, 8.99 g (34.3 mmol, 83.9%) of compound **12** (mp 92–94 °C) were obtained: ^{1}H NMR ($CDCl_3$) δ 5.38 (s, 2H), 7.11 (d, 1H), 7.25 (d, 1H), 7.24 (t, 1H), 7.42 (t, 1H), 7.50 (t, 2H), 7.62 (t, 1H), 7.70 (d, 1H), 7.76 (d, 2H), 8.04 (d, 2H).

1-Phenyl-2-phenylsulfanyl-ethanone (13). Benzenethiol (5.2 mL, 50.9 mmol) was added dropwise to a cooled (0 °C) solution of 2.2 g (55.0 mmol) of NaOH in 40 mL of H_2O:C_2H_5OH (1:1). After the addition of 10 g (48.9 mmol) of bromoacetophenone (97%) the reaction was refluxed for 1 h. After cooling to rt, 80 mL of H_2O were added and the solution washed with NaOH 2 N, and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was treated with anhydrous diethyl ether, cooled to −20 °C, to give 10.2 g (44.7 mmol, 91.4%) of compound **13** as a white solid (mp 54–55 °C): ^{1}H NMR ($CDCl_3$) δ 4.25 (s, 2H), 7.16–7.28 (m, 3H), 7.36 (m, 2H), 7.43 (m, 2H) 7.55 (m, 1H), 7.91 (m, 2H).

General procedure for the preparation of compounds 14–18. To a solution of methoxyacetophenone (95%) or **11–13** (1.5–10 g) and 3-chloro-propane-1,2-diol (1–5 mL) in 50–300 mL of anhydrous CH_3CN (or CH_3NO_2), cooled at 0 °C, was slowly added a catalytic amount of trifluoro-methanesulfonic acid (triflic acid) and molecular sieve 4 Å. The reaction was heated at reflux under nitrogen for 36 h. After cooling to rt, Et_2O was added and the organic phase was extracted with saturated solution of $NaHCO_3$ (3×25 mL) and dried over Na_2SO_4 (or $MgSO_4$). The solvent was evaporated and the residue was purified on a silica gel column (cyclohexane:EtOAc, 95:5), to give *cis* (c) and *trans* (t) isomer separated or as a mixture.

(2*S,4*S**) *cis*-4-Chloromethyl-2-methoxymethyl-2-phenyl-[1,3]dioxolane (14c).** (Yield 41.1%); ^{1}H NMR ($CDCl_3$) δ 3.37 (s, 3H), 3.56 (q, 2H), 3.59 (dd, 1H), 3.67 (ddd, 1H), 3.86 (ddd, 1H), 4.02 (dd, 2H), 4.25 (m, 1H), 7.33 (m, 3H), 7.47 (m, 2H).

(2*R,4*R**) *trans*-4-Chloromethyl-2-methoxymethyl-2-phenyl-[1,3]dioxolane (14t).** (Yield 19.6%); ^{1}H NMR ($CDCl_3$) δ 3.17 (dd, 1H), 3.37 (s, 3H), 3.53 (dd, 1H), 3.54 (s, 2H), 3.73 (dd, 1H), 4.34 (dd, 1H), 4.52 (m, 1H), 7.33 (m, 3H), 7.47 (m, 2H).

4-Chloromethyl-2-phenoxymethyl-2-phenyl-[1,3]dioxolane (15). (Yield 38.4%); ^{1}H NMR ($CDCl_3$) δ 3.27, 3.67 (dd, dd, 1H, 1H), 3.57, 3.70 (t, dd, 1H, 1H), 3.87, 3.96 (dd, dd, 1H, 1H), 4.13, 4.16 (s, q, 2H, 2H), 4.45, 4.12 (dd, dd, 1H, 1H), 4.61, 4.35 (m, m, 1H, 1H), 6.89 (m, 2H, 2H), 6.94 (m, 1H, 1H), 7.25 (m, 2H, 2H), 7.38 (m, 3H, 3H), 7.58 (m, 2H, 2H).

4-Chloromethyl-2-(naphthalen-1-yloxymethyl)-2-phenyl-[1,3]dioxolane (16). (Yield 40.3%); ^{1}H NMR ($CDCl_3$) δ 3.29, 3.64 (dd, dd, 1H, 1H), 3.59, 3.71 (dd, dd, 1H, 1H), 3.92, 4.01 (dd, dd, 1H, 1H), 4.28, 4.33 (s, s, 2H, 2H), 4.50, 4.37 (m, m, 1H, 1H), 4.51, 4.13 (dd, dd, 1H, 1H), 6.78 (dd, 1H, 1H), 7.30 (m, 1H, 1H), 7.43–7.32 (m, 6H, 6H), 7.64 (m, 2H, 2H), 7.75 (m, 1H, 1H), 8.14 (m, 1H, 1H).

4-Chloromethyl-2-(naphthalen-2-yloxymethyl)-2-phenyl-[1,3]dioxolane (17). (Yield 48.7%); ^{1}H NMR ($CDCl_3$) δ 4.33, 4.36 (s, q, 2H, 2H), 3.34, 3.79 (dd, m, 1H, 1H), 3.64, 3.80 (dd, m, 1H, 1H), 3.97, 4.04 (dd, dd, 1H, 1H), 4.54, 4.22 (m, m, 1H, 1H), 4.75, 4.44 (m, m, 1H, 1H), 7.20 (t, 1H, 1H), 7.25 (dd, 1H, 1H), 7.39 (m, 1H, 1H), 7.52–7.42 (m, 4H, 4H), 7.84–7.67 (m, 5H, 5H).

(2*S,4*S**) *cis*-4-Chloromethyl-2-phenyl-2-phenylsulfanyl methyl-[1,3]dioxolane (18c).** (Yield 21.3%); ^{1}H NMR ($CDCl_3$) δ 3.38 (s, 2H), 3.64 (d, 2H), 3.87 (dd, 2H), 4.02 (dd, 1H), 4.24 (m, 1H), 7.12 (m, 1H), 7.21 (m, 1H), 7.33 (m, 5H), 7.49 (m, 2H).

(2*R,4*R**) *trans*-4-Chloromethyl-2-phenyl-2-phenylsulfanyl methyl-[1,3]dioxolane (18t).** (Yield 20.6%); ^{1}H NMR ($CDCl_3$) δ 3.15 (dd, 2H), 3.40 (q, 2H), 3.51 (dd, 1H), 3.69 (dd, 1H), 4.37 (dd, 1H), 4.55 (m, 1H), 7.11 (m, 1H), 7.21 (m, 2H), 7.32 (m, 5H), 7.49 (m, 2H).

(2*S,4*S**) *cis*-(19c) and (19′c) and (2*R**,4*R**) *trans*-2-Benzenesulfinylmethyl-4-chloromethyl-2-phenyl-[1,3]dioxolane (19t) and (19′t).** To a solution of 1.1 g (3.43 mmol) of **18c,t** in 20 mL of CH_2Cl_2, cooled at −40 °C, 0.95 g (3.30 mmol) of MCPBA (60%) in 10 mL of CH_2Cl_2, were added dropwise. After 15 min the reaction mixture was extracted with saturated solution of $NaHCO_3$ (3×5 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue was purified on a silica gel column (cyclohexane:EtOAc, 60:40), to give: 0.35 g (1.04 mmol, 30.3%) of **19c**: ^{1}H NMR ($CDCl_3$) δ 3.37 (q, 2H), 3.74 (dd, 1H), 3.83 (ddd, 1H), 3.98 (ddd, 1H), 4.16 (dd, 1H), 4.33 (m, 1H), 7.33–7.40 (m, 3H), 7.45–7.53 (m, 5H), 7.46 (m, 2H); 0.38 g (1.13 mmol, 32.9%) of **19′c**: ^{1}H NMR ($CDCl_3$) δ 3.33 (q, 2H), 3.76 (dd, 1H), 3.80 (dd, 1H), 3.92 (dd, 1H), 4.14 (dd, 1H), 4.32 (m, 1H), 7.27–7.35 (m, 3H), 7.38–7.50 (m, 5H), 7.58–7.67 (m, 2H); 0.20 g (0.59 mmol, 17.2%) of **19t**: ^{1}H NMR ($CDCl_3$) δ 3.15 (dd, 1H), 3.31 (q, 2H), 3.62 (dd, 1H), 3.75 (dd, 1H), 4.49 (dd, 1H), 4.67 (m, 1H), 7.27–7.34 (m, 3H), 7.37–7.48 (m, 5H), 7.60–7.66 (m, 2H); 0.15 g (0.44 mmol, 12.8%) of **19′t**: ^{1}H NMR ($CDCl_3$) δ 3.19 (dd, 1H), 3.32 (q, 2H), 3.56 (dd, 1H), 3.71 (dd, 1H), 4.48 (dd, 1H), 4.65 (m, 1H), 7.28–7.34 (m, 3H), 7.37–7.46 (m, 5H), 7.55–7.59 (m, 2H).

(2*S,4*S**) *cis*-(20c) and (2*R**,4*R**) *trans*-2-Benzenesulfonyl methyl-4-chloromethyl-2-phenyl-[1,3]dioxolane (20t).** To a solution of 0.7 g (2.18 mmol) of **18c,t** in 10 mL of CH_2Cl_2, cooled at 0 °C, 1 g (3.48 mmol) of MCPBA (60%) in 10 mL of CH_2Cl_2, were added dropwise, and left under stirring for 30 min at rt. The reaction mixture was extracted with saturated solution of $NaHCO_3$ (3×5 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue was purified on a silica gel column (cyclohexane:EtOAc, 90:10), to give 0.4 g (1.14 mmol, 52.3%) of **20c**: ^{1}H NMR ($CDCl_3$) δ 3.56 (dd, 1H), 3.64 (ddd, 1H), 3.76 (q, 2H), 3.86 (ddd, 1H), 3.95 (dd, 1H), 4.17 (m, 1H), 7.28 (m, 3H), 7.37 (m, 2H), 7.46 (m, 2H), 7.57 (m, 1H), 7.80 (m, 2H); 0.35 g (0.99 mmol, 45.4%) of **20t**: ^{1}H NMR ($CDCl_3$) δ 3.09 (dd, 1H), 3.45 (dd, 1H), 3.62 (dd, 1H), 3.71 (q, 2H), 4.28 (dd, 1H), 4.45 (m, 1H), 7.26 (m, 3H), 7.36 (m, 2H), 7.47 (m, 2H), 7.57 (m, 1H), 7.82 (m, 2H);

General procedure for the preparation of compounds 21–27. Compounds **14–20** (0.2–1 g) and 2–10 mL of $NH(CH_3)_2$ in a steel bomb were heated at 100 °C for 24–48 h. After evaporation of the excess $NH(CH_3)_2$ the residue was chromatographed on a silica gel column [EtOAc:$NH(C_2H_5)_2$ (or NH_4OH 30%), 98:2]. In the case of compound **23**, chromatography carried out using EtOAc:C_2H_5OH:NH_4OH 30% (97:1:2) as the eluant, afforded the *cis* and *trans* isomer in pure form. The same procedure used in the attempt to separate the diastereoisomeric mixture of **24** was unsuccessful. In all cases the yields were higher than 90%.

(2*S,4*R**) (*cis*-2-Methoxymethyl-2-phenyl-[1,3]dioxolan-4-ylmethyl)-dimethyl-amine (21c).** ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 6H), 2.43 (dd, 1H), 2.64 (d, 1H), 3.38 (s, 3H), 3.58 (q, 2H), 3.77 (dd, 1H), 3.93 (dd, 1H), 4.12 (m, 1H), 7.33 (m, 3H), 7.51 (m, 2H).

(2*R,4*S**) (*trans*-2-Methoxymethyl-2-phenyl-[1,3]dioxolan-4-ylmethyl)-dimethyl-amine (21t).** ^{1}H NMR ($CDCl_3$) δ 2.25 (dd, 1H), 2.26 (s, 6H), 2.45 (dd, 1H), 3.40 (s, 3H), 3.50 (t, 1H), 3.57 (q, 2H), 4.30 (dd, 1H), 4.48 (m, 1H), 7.34 (m, 3H), 7.53 (m, 2H).

(2*S,4*R**) Dimethyl-(*cis*-2-phenoxymethyl-2-phenyl-[1,3]-dioxolan-4-ylmethyl)-amine (22c).** ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 6H), 2.48 (dd, 1H), 2.67 (dd, 1H), 3.87 (dd, 1H), 4.02 (dd, 1H), 4.17 (s, 2H), 4.23 (m, 1H), 6.94 (m, 3H), 7.24 (m, 2H), 7.41 (m, 3H), 7.64 (m, 2H).

(2*R,4*S**) Dimethyl-(*trans*-2-phenoxymethyl-2-phenyl-[1,3]-dioxolan-4-ylmethyl)-amine (22t).** ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 6H), 2.31 (dd, 1H), 2.48 (dd, 1H), 3.58 (t, 1H), 4.15 (d, 2H), 4.36 (dd, 1H), 4.57 (m, 1H), 6.93 (m, 2H), 7.26 (m, 2H), 7.38 (m, 3H), 7.63 (m, 2H).

(2*S,4*R**) Dimethyl-[*cis*-2-(naphthalen-1-yloxymethyl)-2-phenyl-[1,3]dioxolan-4-ylmethyl]-amine (23c).** ^{1}H NMR ($CDCl_3$) 2.27 (s, 6H), 2.49 (dd, 1H), 2.66 (dd, 1H), 3.88

(dd, 1H), 4.05 (dd, 1H), 4.23 (m, 1H), 4.32 (q, 2H), 6.75 (ddd, 1H), 7.28 (t, 1H), 7.46–7.29 (m, 6H), 7.65 (m, 2H), 7.73 (m, 1H), 8.15 (m, 1H).

(2*R,4*S**) Dimethyl-[*trans*-2-(naphthalen-1-yloxymethyl)-2-phenyl-[1,3]dioxolan-4-ylmethyl]-amine (23t).** ^{1}H NMR ($CDCl_3$) 2.25 (s, 6H), 2.31 (dd, 1H), 2.47 (dd, 1H), 3.61 (dd, 1H), 4.27 (q, 2H), 4.39 (dd, 1H), 4.62 (m, 1H), 6.74 (ddd, 1H), 7.29 (t, 1H), 7.45–7.29 (m, 6H), 7.65 (m, 2H), 7.72 (m, 1H), 8.15 (m, 1H).

Dimethyl-[2-(naphthalen-2-yloxymethyl)-2-phenyl-[1,3]-dioxolan-4-ylmethyl]-amine (24). ^{1}H NMR ($CDCl_3$) δ 2.24, 2.27 (s, s, 6H, 6H), 2.29, 2.46 (dd, dd, 1H, 1H), 2.48, 2.66 (dd, dd, 1H, 1H), 3.57, 3.87 (dd, dd, 1H, 1H), 4.22, 4.25 (q, s, 2H, 2H), 4.36, 4.01 (dd, dd, 1H, 1H), 4.58, 4.22 (m, m, 1H, 1H), 7.08 (m, 1H), 7.12 (m, 1H), 7.28 (m, 1H), 7.40–7.30 (m, 4H), 7.72–7.58 (m, 5H).

(2*S,4*R**) Dimethyl-(*cis*-2-phenyl-2-phenylsulfanyl-methyl-[1,3]dioxolan-4-ylmethyl)-amine (25c).** ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 6H), 2.43 (dd, 1H), 2.62 (dd, 1H), 3.40 (q, 2H), 3.76 (dd, 1H), 3.92 (dd, 1H), 4.10 (m, 1H), 7.09 (m, 1H), 7.20 (m, 2H), 7.25–7.35 (m, 5H), 7.51 (m, 2H).

(2*R,4*S**) Dimethyl-(*trans*-2-phenyl-2-phenylsulfanyl-methyl-[1,3]dioxolan-4-ylmethyl)-amine (25t).** ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 6H), 2.50 (dd, 1H), 2.91 (dd, 1H), 3.38 (q, 2H), 3.43 (dd, 1H), 4.35 (dd, 1H), 4.71 (m, 1H), 7.11 (m, 1H), 7.23 (m, 2H), 7.32 (m, 5H), 7.48 (m, 2H).

(2*S,4*R**) (*cis*-2-Benzenesulfinylmethyl-2-phenyl-[1,3]dioxolan-4-ylmethyl)-dimethyl-amine (26c).** ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 6H), 2.60 (dd, 1H), 2.76 (dd, 1H), 3.39 (q, 2H), 3.92 (m, 1H), 4.03 (dd, 1H), 4.18 (m, 1H), 7.30–7.38 (m, 3H), 7.42–7.53 (m, 5H), 7.65 (m, 2H).

(2*S,4*R**) (*cis*-2-Benzenesulfinylmethyl-2-phenyl-[1,3]dioxolan-4-ylmethyl)-dimethyl-amine (26′c).** ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 6H), 2.54 (dd, 1H), 2.85 (dd, 1H), 3.36 (q, 2H), 3.95 (dd, 1H), 3.97 (dd, 1H), 4.26 (m, 1H), 7.32–7.39 (m, 3H), 7.44–7.51 (m, 5H), 7.64 (m, 2H).

(2*R,4*S**) (*trans*-2-Benzenesulfinylmethyl-2-phenyl-[1,3]-dioxolan-4-ylmethyl)-dimethyl-amine (26t).** ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 6H), 2.27 (dd, 1H), 2.46 (dd, 1H), 3.37 (q, 2H), 3.53 (t, 1H), 4.42 (dd, 1H), 4.60 (m, 1H), 7.32–7.39 (m, 3H), 7.42–7.58 (m, 5H), 7.65 (m, 2H).

(2*R,4*S**) (*trans*-2-Benzenesulfinylmethyl-2-phenyl-[1,3]-dioxolan-4-ylmethyl)-dimethyl-amine (26′t).** ^{1}H NMR ($CDCl_3$) δ 2.21 (dd, 1H), 2.27 (s, 6H), 2.44 (dd, 1H), 3.53 (q, 2H), 3.57 (t, 1H), 4.43 (dd, 1H), 4.62 (m, 1H), 7.32–7.39 (m, 3H), 7.42–7.57 (m, 5H), 7.64 (m, 2H).

(2*S,4*R**) (*cis*-2-Benzenesulfonylmethyl-2-phenyl-[1,3]-dioxolan-4-ylmethyl)-dimethyl-amine (27c).** ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 6H), 2.46 (dd, 1H), 2.64 (dd, 1H), 3.70 (dd, 1H), 3.78 (q, 2H), 3.94 (dd, 1H), 4.08 (m, 1H), 7.24 (m, 3H), 7.39 (m, 2H), 7.46 (m, 2H), 7.58 (m, 1H), 7.82 (m, 2H).

(2*R,4*S**) (*trans*-2-Benzenesulfonylmethyl-2-phenyl-[1,3]-dioxolan-4-ylmethyl)-dimethyl-amine (27t).** ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 6H), 2.46 (dd, 1H), 2.65 (dd, 1H), 3.91 (dd, 1H), 3.75 (q, 2H), 4.21 (dd, 1H), 4.34 (m, 1H), 7.38 (m, 3H), 7.41 (m, 2H), 7.49 (m, 2H), 7.59 (m, 1H), 7.85 (m, 2H).

General procedure for the preparation of compounds 3–9c,t. Amine (100–300 mg) was dissolved in 10 mL of dry Et_2O; an excess of methyl iodide was added and the reaction left at rt for 12 h. After filtration (or evaporation of the solvent) the solid (or residue) was recrystallized to form EtOH:Et_2O (i-PrOH in the case of compound **3c**,**t**). Elemental analysis was performed for compounds **3**–**9c**,**t** and the results (not shown) are within ±0.4% of the theoretical values. For ^{1}H and ^{13}C NMR see Tables 1 and 2.

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 gr 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 agonist. The concentration of agonist in the organ bath was increased approximately threefold 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 transducer connected to a two-channel Gemini polygraph. In all cases, parallel experiments in which tissues did not receive any antagonist were run in order to check any variation in sensitivity.

Guinea pig ileum.[22,23] Two-centimetre long portions of terminal ileum were taken about 5 cm from the ileum–cecum junction and mounted in PSS at 37 °C. The composition of PSS was as follows (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

carbachol 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.[22] The heart was rapidly removed and the right and left atria were separately excised. Left atria were mounted in PSS (the same as used for ileum) at 30 °C and stimulated through platinum electrodes by square-wave pulses (1 ms, 1 Hz, 10–15 V). Inotropic activity was recorded isometrically. Tissues were equilibrated for 2 h and a cumulative dose–response curve to carbachol was constructed.

Rabbit stimulated vas deferens.[22,24] Vasa deferentia were carefully dissected free of surrounding tissue and divided into four segments, two prostatic portions of 1 cm and two epididymal portions approximately 1.5 cm in 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), and glucose (11.1); 1 μM yohimbine was included to block α_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 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 concentration [B].[25] In some cases, antagonist potency is expressed in terms of pA_2, estimated by Schild plots[26] constrained to slope −1.0, as required by the theory.[27] Values are given as mean ± standard error of four or five independent observations.

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