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ANTIMUSCARINIC PROPERTIES OF THE STEREOISOMERS OF GLYCOPYRRONIUM BROMIDE

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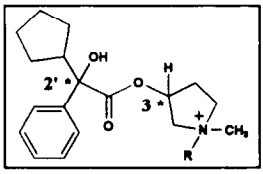

Glycopyrronium bromide (R = CH_3) is a potent muscarinic antagonist widely used in anesthesia. It contains two centres of chirality, which results in the existence of four stereoisomers. The commercially available drug (a mixture of stereoisomers) has been reported to have high selectivity for muscarinic M1 receptors (Fuder et al., NSAP 347: 591, 1993). The aim of the present study was to examine the affinity of the pure stereoisomers of glycopyrronium bromide (**3**, **4**, **7**, **8**) at muscarinic receptor subtypes, together with their corresponding tertiary amines (**1**, **2**, **5**, **6**). Antimuscarinic potency was determined in functional experiments (pA_2/pIC_{50} values) at muscarinic M1 (rabbit vas deferens), M2 (guinea-pig left atria) and M3 (guinea-pig ileum) receptors as well as in radioligand binding studies (pK_i values) at recombinant m1, m3 and m4 receptors expressed in CHO cells and native M2 receptors present in rat heart.

			M1	m1	M2		M3		m3	m4
no.	R	configuration	pA_2	pK_i	pA_2	pK_i	pA_2[a]	pIC_{50}[b]	pK_i	pK_i
1	H	3S / 2'S	7.70	8.00	7.52	7.40	7.61	6.35	7.93	7.78
2	H	3S / 2'R	9.98	9.93	9.03	9.10	-	8.80	10.20	9.93
3	CH_3	3S / 2'S	8.22	8.36	7.92	7.88	-	6.82	7.82	7.82
4	CH_3	3S / 2'R	10.40	10.50	9.39	9.74	-	9.39	10.50	10.30
5	H	3R / 2'S	8.97	9.08	8.71	8.25	-	8.47	9.18	8.93
6	H	3R / 2'R	10.00	10.18	9.45	9.22	-	9.05	10.08	9.82
7	CH_3	3R / 2'S	9.53	9.36	8.69	9.00	-	8.57	9.63	9.40
8	CH_3	3R / 2'R	10.30	10.18	9.43	9.63	-	8.76	10.20	10.27

[a]Compounds **2-8** acted as pseudoirreversible antagonists in the M3 assay. [b]Inhibition of neurogenic contractions in guinea-pig ileum.

The results demonstrate that the antimuscarinic potency of compounds **1-8** is highly (up to 1100-fold) controlled by the absolute configuration and the structure of the basic centre of the molecules. However, the pure stereoisomers of glycopyrronium bromide were not found to be M1-selective.

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PHARMACOLOGICAL CHARACTERIZATION OF PD102807: An m4 SUBTYPE SELECTIVE MUSCARINIC ANTAGONIST.

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The anti-muscarinic agent Artane (trihexyphenidyl) has been used clinically to suppress tremor and relieve rigidity associated with the early stages of Parkinson's disease (PD). However, motor benefits have been accompanied by cognitive dulling. In situ hybridization and antibody localization studies have found that the m4 subtype of muscarinic receptors predominates over m1 in the striatum, while the reverse is true for the hippocampus and cerebral cortex. Thus, an antagonist specific for the m4 receptor subtype over the m1 subtype could be efficacious against PD motor symptoms without deleterious cognitive side effects.

In the search for selective antagonists, membrane preparations from CHO cell lines transfected with each of the human muscarinic subtypes were utilized in [^{3}H]-NMS competition binding experiments. The compound PD102807 was found to have m4 (IC_{50}=90.7nM) selectivity of 72-fold against m1 (IC_{50}=6569nM), 38-fold against m2 (IC_{50}=3440nM), 10-fold against m3 (IC_{50}=951nM), and 82-fold against m5 (IC_{50}= 7412 nM). Artane, on the other hand, although found to have considerable m4 affinity, was most potent at the m1 subtype (IC_{50} values; 1.3nM for m1, 18.6nM for m2, 26.3nM for m3, 6.7nM for m4 and 10.3nM for m5). Measurement of functional activity (reversal of the effects of carbachol on PI hydrolysis for m1, m3, and m5 and cAMP accumulation for m2 and m4 receptors) correlated with this profile, as did an autoradiographic study in rat brain where PD 102807 bound with highest affinity in the striatum. In a murine *in vivo* model, PD102807 inhibited spontaneous locomotor activity after i.c.v. administration, however, it showed little effect following oral dosing. Thus, PD102807 may serve as a prototype for the development of an m4-selective antagonist to treat early PD motor symptoms.