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NOVEL IMIDAZOLE DERIVATIVES WITH SUBTYPE-SELECTIVE ANTIMUSCARINIC ACTIVITY (2)

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Abstract: A series of 4-(2-methylimidazol-1-yl)-2,2-diphenylbutyramide derivatives was prepared as part of a search for subtype-selective antimuscarinic agents. On the basis of measurements of the antimuscarinic activity and subtype-selectivity for M_2 and M_3 muscarinic receptors, the structure-activity relationships of these compounds are discussed.

Numerous pharmacological studies have demonstrated that detrusor smooth muscle contraction is mediated mainly by muscarinic acetylcholine receptors.[1] Muscarinic receptors are heterogeneous, and have been classified into at least three pharmacologically defined subtypes, M_1, M_2 and M_3.[2] The M_1 receptor is found in high density in neuronal tissues,[3] whereas M_2 and M_3 receptors are mainly located in peripheral effector organs, such as heart (M_2) and smooth muscle (M_3).[4] Therefore, M_3- selective antimuscarinic agents should have therapeutic potential for the treatment of altered smooth muscle contractility and tone, for example, as seen in urinary incontinence associated with bladder muscle instability.[5] Recently, we have reported the design, synthesis and antimuscarinic activity of some novel 4-(imidazol-1-yl)-2,2-diphenylbutyramide derivatives as subtype-selective antimuscarinic agents, and we selected 4-(2-methylimidazol-1-yl)-2,2-diphenylbutyramide (KRP-197, **1**) as a candidate drug for the treatment of urinary incontinence associated with bladder muscle instability.[6] As a part of our continuing research directed toward the development of

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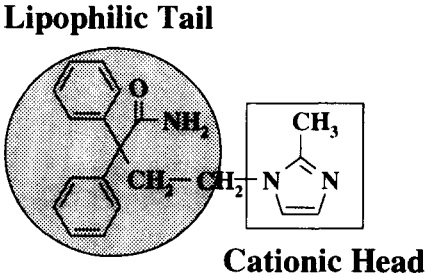
subtype-selective antimuscarinic agents, we report here the antimuscarinic activity of various derivatives of KRP-197 modified at the lipophilic tail region. We also discuss the structure-activity relationships of these compounds.



KRP-197 (1)

The compounds prepared in this study were synthesized by means of standard procedures and characterized by ^{1}H-NMR, mass spectral, and elemental analyses (details and physicochemical data of the compounds will be published elsewhere). Functional activity at receptor subtypes was studied in cardiac and smooth muscle preparations. Potencies are expressed as affinity constants (K_b), i.e. the calculated molar concentration of the compound (antagonist) required to cause a 2-fold increase in the concentration (EC_{50}) of muscarinic agonist carbachol. [7]

Results and discussion

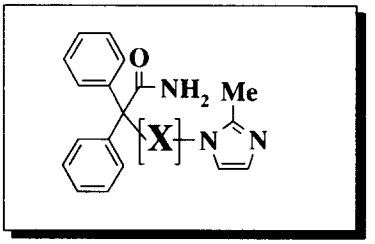
The pharmacological results for the compounds prepared are listed in Tables 1-3.

Effect of spacer methylene chain

As can be seen from Table 1, the maximum effect was obtained when the spacer was the ethylene chain (KRP-197, **1**), and elongation of the spacer decreased the activity (**2**–**6**). These results indicate that the distance between the cationic head and lipophilic tail of these molecules is important for potent antimuscarinic activity. All the compounds, except **3**, listed in Table 1 exhibited 10-fold or greater selectivity for M_3 over M_2, so the length of the spacer methylene chain is

not critical for subtype-selectivity. Introduction of a methyl group into the ethylene chain decreased the activity, but did not affect the M_3 selectivity (**5**, **6**).

TABLE 1 Antimuscarinic Activity of Imidazole Derivatives in Guinea-Pig Atria (M_2 Receptor) and Ileum (M_3 Receptor)



			K_b (nM)		
No	X	mp (℃)	M_2	M_3	M_2/M_3 [a]
1[b]	$(CH_2)_2$	186.0–187.5	4.13	0.32	13.0
2	$(CH_2)_3$	128.0-129.0	20.1	1.14	17.6
3	$(CH_2)_4$	154.0–156.0	148	43.7	3.39
4	$(CH_2)_5$	159.0–161.0	710	71.3	9.96
5	$CHCH_3CH_2$ [c]	165.0–167.0	45.1	2.89	15.6
6	CH_2CHCH_3 [c]	148.0–150.0	174	16.9	10.3

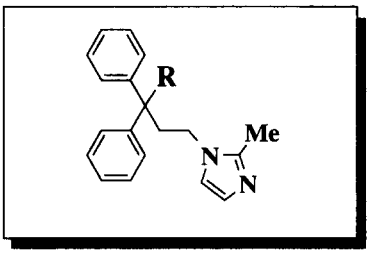
a) The selectivity ratio is the difference between the K_b values at M_2 (atrium) and M_3 (ilium) muscarinic receptors. b) KRP-197. C) Assayed as a racemate.

Effect of substituents at the benzylposition

As shown in Table 2, the compounds bearing only the *N,N*-unsubstituted carbamoyl (KRP-197, **1**) and the carboxyl groups (**10**) exhibited potent antimuscarinic activity and M_3 selectivity, and the compounds possessing the other functional groups lost the selectivity for the M_3 receptor (**7**, **8** and **11**) or showed markedly decreased M_2 and M_3 antagonist activity. It is of interest to note that the compounds bearing the *N*-

monosubstituted and the *N,N*-disubstituted carbamoyl groups and the ester group (**12**, **13** and **9**, respectively) exhibited little or no antimuscarinic activity. These results suggest that hydrogen bonding interactions may be important for potent antimuscarinic activity and M_3 selectivity.

TABLE 2 ***In Vitro*** **Functional Activity of Imidazole Derivatives at M_2 Receptors in Guinea-Pig Atria and M_3 Receptors in Guinea-Pig Ileum**



No.	R	mp(℃)	K_b (nM) M_2	M_3	M_2/M_3 [a]
1[b]	$CONH_2$	186.0–187.5	4.13	0.32	13.0
7	CN	157.0–158.5 [c]	15.5	10.4	1.49
8	OH	212.0–214.0	50.1	16.7	3.00
9	CO_2Me	84.0–86.0	N.T. [d]	>1000	-
10	CO_2H	237 (decomp)	82.7	6.95	11.9
11	CH_2OH	155.0–156.5	83.8	25.4	3.30
12	CONHMe	153.0–154.5	5870	5150	1.14
13	$CON(Me)_2$	e)	478	258	1.85

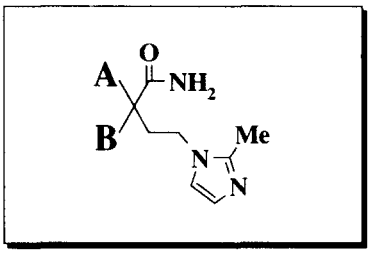
a) See footnote a in Table 1. b) KRP-197. c) HCl salt. d) Not tested. e) Oil bp 290℃ (0.8 mmHg).

Effect of diphenylmethyl moiety

As can be seen in Table 3, the unsubstituted diphenylmethyl moiety in this series of compounds has an important role in the appearance of potent antimuscarinic activity. Introduction of substituents at one or both benzene rings decreased the activity. The replacement of one phenyl group with an alkyl group (**16**, **17**, and **18**) or a 2-pyridyl group (**19**) also decreased the activity. The fixation of the two phenyl groups with an

ethylene chain (**20**) or an ether bond (**21**) resulted in a marked decrease in activity. These data indicate that the existence of the two phenyl groups located orthogonally at the lipophilic tail part of the molecule is essential for potent antimuscarinic activity, and that modification of the phenyl group decreased the antimuscarinic activity, but did not reduce the M_3 selectivity.

TABLE 3 ***In Vitro*** **Functional Activity of Imidazole Derivatives at M_2 Receptors in Guinea-Pig Atria and M_3 Receptors in Guinea-Pig Ileum.**

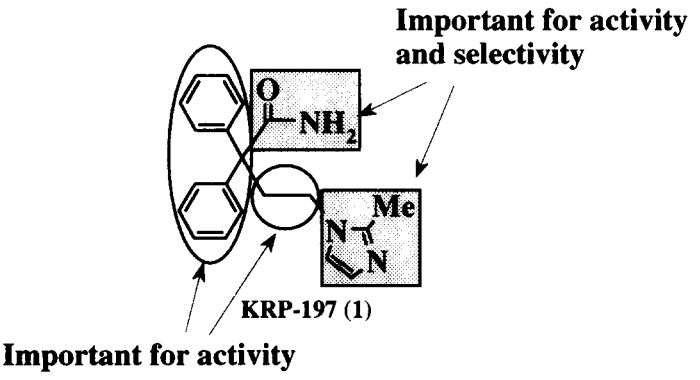


				K_b (nM)		
No.	A	B	mp (℃)	M_2	M_3	M_2/M_3 [a]
1[b]	Ph	Ph	186.0–187.5	4.13	0.32	13.0
14	4-FPh	4-FPh	206.0–207.5	161	9.85	16.3
15	Ph	4-MePh[c]	163.0–165.0	743	24.6	30.3
16	Ph	Me[c]	173.0–1757.0	N.T.[d]	1834	-
17	Ph	*i*Pr[c]	191.0–1927.5	N.T.[d]	394	-
18	Ph	Cyclohexyl[c]	178.0–180.0	603	19.0	31.7
19	Ph	2-Pyridyl[c]	212.0–214.0	50.1	2.86	17.5
20	Dibenzosuberan-5-yl		218.0–220.0	N.T.[d]	2140	-
21	Xanthen-9-yl		193.0–194.5	N.T.[d]	>300	-

a) See footnote a in Table 1. b) KRP-197. c) Assayed as a racemate. d) Not tested.

In conclusion, the antimuscarinic activity and subtype-selectivity data indicate that the structure of KRP-197 (**1**) can be divided into two regions. One region, composed of the spacer methylene moiety and the diphenylmethyl moiety, is involved in the manifestation of anticholinergic activity, and the other region, composed of the

carbamoyl moiety and the imidazole moiety, contributes to both antimuscarinic activity and subtype-selectivity.



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