

## NOVEL IMIDAZOLE DERIVATIVES WITH SUBTYPE-SELECTIVE ANTIMUSCARINIC ACTIVITY (1)

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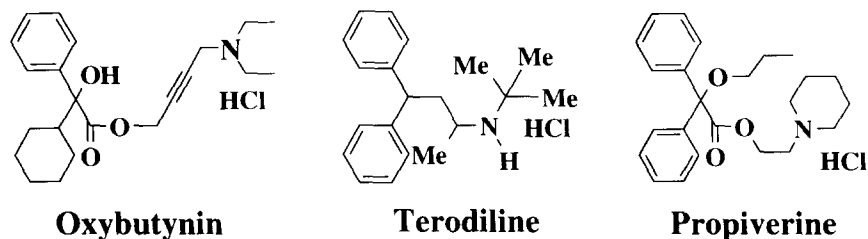
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**Abstract:** A series of *N*-substituted 4-amino-2,2-diphenylbutyramide derivatives was prepared as part of a search for subtype-selective antimuscarinic agents. The representative compound KRP-197, bearing a 2-methylimidazole ring as a surrogate of aliphatic amine, was found to be a highly potent and both  $M_1$ - and  $M_3$ -selective antimuscarinic agent. © 1998 Elsevier Science Ltd. All rights reserved.

Muscarinic acetylcholine receptors are heterogeneous and have been classified into at least three pharmacologically defined subtypes,  $M_1$ ,  $M_2$  and  $M_3$ .<sup>1</sup>  $M_1$  receptor is found in high density in neuronal tissues,<sup>2</sup> whereas  $M_2$  and  $M_3$  receptors are mainly present in peripheral effector organs such as heart ( $M_2$ ) and smooth muscle ( $M_3$ ).<sup>3</sup> This differentiation suggests that tissue-selective muscarinic agonists and antagonists might exist. Such selective agents would be extremely important not only for receptor subtype characterization, but also for the development of therapeutically useful muscarinic agonists and antagonists.<sup>4</sup> Especially,  $M_3$ -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.<sup>5</sup> Here we describe the synthesis, antimuscarinic activity, and structure-activity relationship of some novel 4-(imidazol-1-yl)-butyramide derivatives. The aim of our research was to discover structurally new muscarinic antagonists possessing a selectivity profile suitable for use in the treatment of urinary incontinence. Recently, oxybutynin,<sup>6</sup> terodiline<sup>7</sup> and propiverine (Figure 1)<sup>8</sup> have

been developed as antimuscarinic agents for the treatment of urinary incontinence.

The clinical effect of these drugs was mainly attributed to their muscarinic receptor antagonism.<sup>9</sup> But their nonselective activity in some organs was considered to be responsible for their anticholinergic side effects, such as dry mouth and mydriasis.<sup>6</sup>



**Figure 1.** Chemical structure of oxybutynin, terodiline, and propiverine.

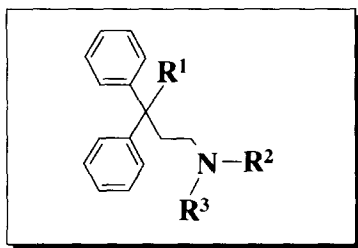
We selected terodiline as a lead compound, since it has a simple structure and a relatively long duration of action. We therefore designed and synthesized the 3,3-diphenylpropylamine derivatives and examined their antimuscarinic activity using functional tests. The compounds prepared in this study were synthesized by standard procedures and were characterized by <sup>1</sup>H-NMR, mass spectral, and elemental analyses (details and physicochemical data of the compounds will be published elsewhere). Functional activity at muscarinic receptor subtypes was estimated 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.<sup>10</sup>

## Results and discussion

The pharmacological results for the compounds prepared are listed in Tables 1 and 2. We first designed *N*-mono- and *N,N*-disubstituted 3,3-diphenylpropylamines and found that the *N,N*-disubstituted derivatives showed more potent antimuscarinic activity than the *N*-monosubstituted compounds. Interestingly, the imidazole-bearing derivative (**4**) was equipotent to the cyclic amine derivative (**3**). It is important to note that most of the aliphatic amine derivatives showed equipotent anti- $M_3$  and anti- $M_2$  activities ( $M_2/M_3 \cong 1$ ); in other words, these compounds could not discriminate between the two receptor subtypes. On the other hand, the imidazole derivative (**4**) exhibited more

potent anti-M<sub>3</sub> activity as compared to anti-M<sub>2</sub> activity, so this compound could discriminate between these receptors. Next, we synthesized diphenylacetonitrile and diphenylacetamide derivatives (**5** and **6**, respectively) and found that the introduction of a carbamoyl group at the diphenylmethyl moiety increased both anti-M<sub>3</sub> and anti-M<sub>2</sub> activities. These results prompted us to synthesize 4-(imidazol-1-yl)-2,2-diphenylbutyramide (**7**) and we found that it showed potent antimuscarinic activity, comparable to that of oxybutynin (**9**), with M<sub>3</sub>-selectivity (10-fold M<sub>3</sub>-selectivity). Therefore, we selected **7** as the next lead compound and performed further modification focused on the imidazole moiety.

**TABLE 1. Antimuscarinic Activity of Diphenylpropylamine Derivatives in Guinea-Pig Atria (M<sub>2</sub> Receptor) and Ileum (M<sub>3</sub> Receptor)**



No.	R <sup>1</sup>	NR <sup>2</sup> R <sup>3</sup>	mp (°C)	<i>K<sub>b</sub></i> (nM)		
				M <sub>3</sub>	M <sub>2</sub>	M <sub>2</sub> /M <sub>3</sub> <sup>a)</sup>
1	H	NHt Bu	203.0-204.0 <sup>b)</sup>	792	N.T. <sup>c)</sup>	-
2	H	N(Et) <sub>2</sub>	78.0-80.0 <sup>b)</sup>	197	N.T.	-
3	H	piperidine	113.0-115.0 <sup>b)</sup>	69.6	N.T.	-
4	H	imidazole	63.0-66.0	89.1	473	5.31
5	CN	pyrrolidine	d)	65.7	36.8	0.56
6	CONH <sub>2</sub>	pyrrolidine	142.0-143.0	5.59	11.0	1.97
7	CONH <sub>2</sub>	imidazole	172.0-175.0	5.07	68.4	13.5
8	Terodiline			67.7	119	1.76
9	Oxybutynin			3.44	5.00	1.45

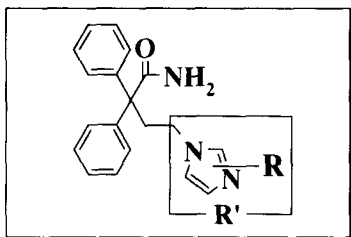
a) The selectivity ratio is the difference between the *K<sub>b</sub>* values at M<sub>2</sub> (atrium) and M<sub>3</sub> (ilium) muscarinic receptors. b) HBr salt. c) Not tested. d) Oil bp 260°C (0.8 mmHg).

As indicated in Table 2, introduction of appropriate alkyl groups at the imidazole ring strikingly affected antimuscarinic activity and subtype-selectivity. Introduction of a methyl group into position 2 of the imidazole ring increased both anti-M<sub>3</sub> and anti-M<sub>2</sub> activities. Bulkier substituents generally decreased antimuscarinic activity; for example, the 2-*n*-propylimidazole derivative (**12**) exhibited 500-fold less potent anti-M<sub>3</sub> activity as compared to that of the 2-methyl derivative (**10**), and it showed no marked M<sub>3</sub>-selectivity. On the other hand, the 4,5-di-*n*-propylimidazole derivative (**17**) retained M<sub>3</sub>-selectivity, although it exhibited decreased antimuscarinic activity. These results indicate that both the width and the length of the substituents introduced at the imidazole ring play a critical role in binding to the receptors. Next, we examined the 4-methyl- and 5-methylimidazole derivatives (**18** and **19**, respectively). The 5-methyl derivative (**19**), with half the anti-M<sub>2</sub> and anti-M<sub>3</sub> activity of the 2-methyl derivative (**10**), retained M<sub>3</sub>-selectivity. However, the 4-methyl derivative (**18**) showed not only 10-fold less potent affinity than **10** for both M<sub>3</sub>- and M<sub>2</sub>-receptors, but also decreased M<sub>3</sub>-selectivity. These data suggest the existence of a distinct regiospecificity requirement for potent antimuscarinic activity in the present series of compounds. Compounds that possessed potent and/or subtype-selective antagonism were further evaluated for anti-M<sub>1</sub>-activity.<sup>11</sup>

As can be seen from Table 2, the shape and position of the substituents at the imidazole ring strikingly affect the subtype-selectivity. The unsubstituted and 2-methyl-substituted imidazole derivatives (**7** and **10**, respectively) exhibited equipotent anti-M<sub>1</sub> and anti-M<sub>3</sub> activities, but the 2-isopropyl- and 5-methyl-substituted derivatives (**13** and **19**, respectively) showed 4- to 18-fold less potent anti-M<sub>1</sub> activity as compared to anti-M<sub>3</sub> activity. We speculate that the three-dimensional interactions between the cationic head of the imidazolylbutyramide derivatives and anionic sites of functional muscarinic acetylcholine receptor subtypes might play a critical role in subtype-selectivity.

In conclusion, a new series of *N*-substituted amino-2,2-diphenylbutyramides with subtype-selectivity at muscarinic acetylcholine receptors has been developed.

A structure-activity relationship study of these compounds led to the identification of 4-(2-methyl-1-imidazolyl)-2,2-diphenylbutyramide [KRP-197 (**10**); M<sub>1</sub>- and M<sub>3</sub>-selective] and 4-(2-isopropyl-1-imidazolyl)-2,2-diphenylbutyramide [(**13**); M<sub>3</sub>-selective] as candidate drugs for the treatment of urinary incontinence, and further pharmacological and clinical evaluations are in progress.

**TABLE 2.** Antimuscarinic Activity of Imidazole Derivatives in Rabbit Vas Deferens ( $M_1$  Receptor), Guinea-Pig Atria ( $M_2$  Receptor) and Ileum ( $M_3$  Receptor)

R	mp (°C)	$K_b$ (nM)			$M_2/M_3$ <sup>a)</sup>	$M_1/M_3$ <sup>b)</sup>
		$M_3$	$M_2$	$M_1$		
H	172.0-175.0	5.07	68.4	5.99	13.5	1.18
2-Me	189.0-190.0	0.32	4.13	0.55	13.0	1.72
2-Et	144.0-146.0	78.1	256	N.T. <sup>c)</sup>	3.30	-
2- <i>n</i> Pr	150.0-152.0	177	254	N.T.	1.43	-
2- <i>i</i> Pr	176.0-178.0	1.80	28.5	31.9	15.8	17.7
2- <i>t</i> Bu	136.0-138.0	30.2	73.9	N.T.	2.45	-
4,5-diMe	163.0-164.0	2.70	8.66	N.T.	3.21	-
4,5-diEt	194.0-196.0	3.98	90.5	N.T.	22.7	-
4,5-di- <i>n</i> Pr	147.0-148.0	100	2520	N.T.	25.2	-
4-Me	151.0-153.0	10.1	31.3	10.4	3.10	1.03
5-Me	173.0-175.0	0.86	9.59	3.40	11.1	3.95
R' = 1-benzimidazolyl	197.0-199.0	2130	6540	N.T.	3.07	-
Terodiline		67.7	119	N.T.	1.76	-
Oxybutynin		3.44	5.00	2.45	1.45	0.71

a) See footnote a in Table 1. b) The selectivity ratio is the difference between the  $K_b$  values at  $M_1$  (vas deferens) and  $M_3$  (ileum) muscarinic receptors. c) Not tested.

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