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Synthesis and Antimuscarinic Activity of a Series of 4-(1-Imidazolyl)-2,2-diphenylbutyramides: Discovery of Potent and Subtype-selective Antimuscarinic Agents

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Abstract—In a study directed toward the development of new, selective agents with potential utility in the treatment of altered smooth muscle contractility and tone, for example, as seen in urinary incontinence associated with bladder muscle instability, a series of 4-(1-imidazolyl)-2,2-diphenylbutyramide derivatives was prepared. These compounds were examined for M_1, M_2, and M_3 muscarinic receptor subtype selectivity in isolated tissue assays. The compounds that showed potency and/or selectivity in these tests were further evaluated for in vivo anticholinergic effects on various organs and tissues, including urinary bladder, salivary gland, and eye in rats. The structure–activity relationships for the series of 4-(1-imidazolyl)-2,2-diphenylbutyramide derivatives are also discussed. This study led to the identification of 4-(2-methyl-1-imidazolyl)-2,2-diphenylbutyramide (KRP-197) as a candidate drug for the treatment of urinary bladder dysfunction.

Introduction

Recently, there has been much interest in the treatment of urinary dysfunction, such as urinary incontinence, owing to the rapid increase in the proportion of aged people in the population. Urinary incontinence is a pathological condition frequently affecting the elderly; epidemiological investigations indicate that 5–15% of the adult population are affected and the prevalence, particularly of urge incontinence, increases with age. The symptoms of an unstable bladder comprise urge incontinence, urgency, and frequency. Bladder instability is considered to be caused by uncontrolled detrusor contractions,[1] which are believed to be mediated by muscarinic acetylcholine receptors.[2] Consequently, muscarinic acetylcholine receptor antagonists, such as oxybutynin·HCl[3] and propiverine·HCl[4] (Fig. 1), have for years been the drugs of choice for the treatment of urinary incontinence associated with bladder muscle instability. But the use of these compounds is limited by their anticholinergic side effects, which include dry mouth, accommodation paralysis, and tachycardia.[5]

Muscarinic acetylcholine receptors, members of the huge superfamily of G protein-coupled receptors,[6–8] are heterogeneous, and have been classified into at least three pharmacologically distinct receptor subtypes (M_1–M_3).[9] The M_1 receptor is found at high density in neuronal tissues,[10] whereas M_2 and M_3 receptors are mainly present in peripheral effector organs, such as heart (M_2) and smooth muscle (M_3).[11] On the other hand, a molecular cloning study indicated that muscarinic acetylcholine receptors are composed of at least five molecularly distinct receptor proteins (m_1–m_5).[12] The pharmacologically defined M_1–M_3 receptors are thought to correspond to the cloned m_1–m_3 subtypes.

In situ hybridization[13] and immunoprecipitation[14] studies on the human urinary bladder have revealed the presence of M_2 and M_3 receptor subtypes. In spite of the predominant presence of the M_2 receptor in the bladder, the muscarinic receptor(s) responsible for the contraction of the bladder is the M_3 subtype.[15] Therefore, M_3-selective antagonists could have therapeutic potential for the treatment of diseases associated with altered smooth muscle contractility and tone, such as urinary incontinence.

In our continuing research directed toward the development of M_3-selective muscarinic antagonists, using the 3,3-diphenylpropylamine-type anticholinergic agent terodiline·HCl[16] (Fig. 1) as a lead compound, we found that incorporation of an imidazole ring as a surrogate of aliphatic amine generated M_3-selectivity, and introduction of a carbamoyl group at the diphenylmethyl moiety enhanced the anticholinergic potency.[17] On the basis of

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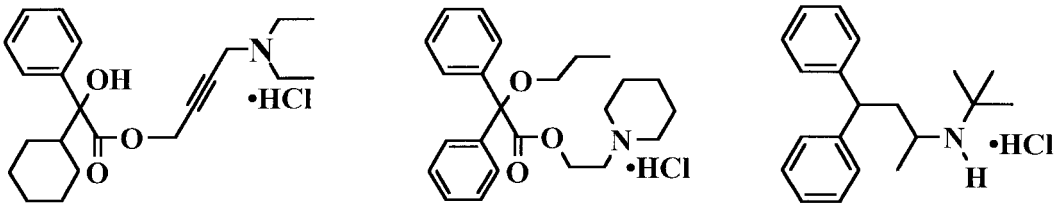


Figure 1. Structures of anticholinergic agents, oxybutynin·HCl, propiverine·HCl, and terodiline·HCl.

these observations, a series of 4-(1-imidazolyl)-2,2-diphenylbutyramides, as well as related quaternary salts, was prepared in order to obtain anticholinergic agents with greater potency and M_3-selectivity. These compounds were tested for functional muscarinic receptor subtype selectivity in rabbit vas deferens (neuronal, M_1),[18] guinea pig atrial (cardiac, M_2),[19] and guinea pig ileal (smooth muscle, M_3) preparations.[20] To evaluate the potential to cause side effects, selected compounds were also examined for in vivo anticholinergic effects in rats. The results of these studies, which led to the identification of 4-(2-methyl-1-imidazolyl)-2,2-diphenylbutyramide (KRP-197) as a candidate for the clinical treatment of bladder dysfunction,[21] are described in this article.

Chemistry

The synthetic routes to the imidazole derivatives described in this study are outlined in Chart 1. Substituted phenylacetonitriles were alkylated with the appropriate dihalogenoalkane,[22] followed by reaction with the appropriate imidazole, to form the cyanoalkylimidazoles. The cyano group was hydrolyzed with either sulfuric acid, or hydrochloric acid to give the carbamoyl derivatives (**1–23**) and the carboxylic acid derivative (**29**), respectively (in the case of **24** and **25**, alkaline hydrolysis[23] was performed to obtain carboxamide derivatives, since hydrolysis with sulfuric acid afforded only hydroxyl derivatives). The carboxylic acid derivative (**29**) was treated with thionyl chloride, then with either methanol or the appropriate amines to give the methyl ester derivative (**28**) and the amide derivatives (**31**, **32**), respectively. The hydroxymethyl derivative (**30**) was prepared by the reduction of **28** with sodium bis(2-methoxyethoxy)aluminum hydride.[24] The hydroxyl derivative (**27**) was prepared by the reaction of ethyl (2-methyl-1-imidazolyl)propionate[25] with phenyllithium.

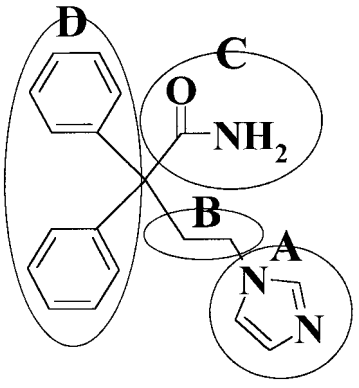


Figure 2. Structure of compound (**1**).

Imidazole derivatives (**2–5**) were treated with an excess of alkyl or benzyl halide to give the imidazolium halides (**33–40**).[26] Physical data for the present series of imidazole and imidazolium derivatives are summarized in Table 1.

Results and Discussion

The imidazole derivatives and imidazolium derivatives synthesized in this study were examined for antimuscarinic activity in tests selective for the pharmacologically defined muscarinic receptors. M_1 receptor antagonistic activity was determined as the ability to reverse the inhibitory activity of the selective M_1 agonist McN-A-343[27] on electrically stimulated contraction of isolated rabbit vas deferens.[18] M_2 receptor antagonistic activity was determined as the ability to decrease the activity of acetylcholine to inhibit the contraction of isolated guinea pig right atria.[28] M_3 receptor antagonistic activity was determined as the activity of the test compound to decrease the response of guinea pig ileum muscle strips to acetylcholine.[3,26] In each test, potency was defined as an affinity constant (Kb),[29] i.e. the calculated molar concentration of the test compound that causes a twofold increase in the EC_{50} values of the muscarinic agonists used in the functional tests. The compounds that exhibited potent and/or selective antimuscarinic activity were further evaluated in vivo. The effects were expressed as ED_{30} and ED_{50} values (dose required to reduce each in vivo effect by 30% and 50%, respectively). The pharmacological results for the compounds prepared are listed in Tables 2–9.

As already mentioned, we synthesized 3,3-diphenylpropylamine derivatives and evaluated their antimuscarinic activity and subtype-selectivity.[17] We found that the incorporation of an imidazole ring as a surrogate of aliphatic amine afforded equipotent antimuscarinic activity as compared to that of aliphatic amine derivatives, with M_3-selectivity. We also found that introduction of a carbamoyl group as a benzylic substituent enhanced the antimuscarinic activity. These results prompted us to synthesize 4-(imidazol-1-yl)-2,2-diphenylbutyramide (**1**) and we found that it showed potent

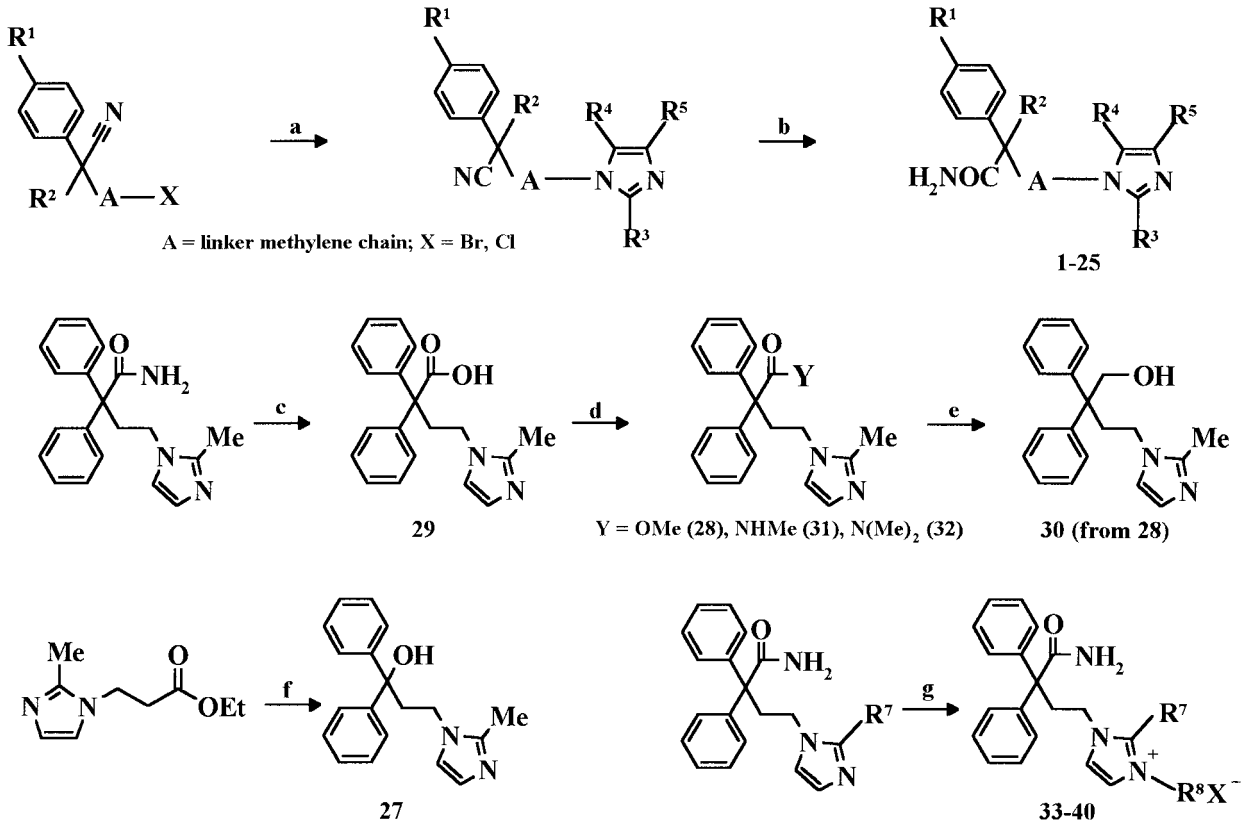


Chart 1. Schematic procedure for the synthesis of the present series of imidazole derivatives. Reagents: (a) phenylacetonitrile derivative,[22] imidazole derivative, Et_3N, *N*,*N*-dimethylformamide; (b) aq H_2SO_4 or ethanolic KOH; (c) c.HCl; (d) $SOCl_2$, methanol or amines; (e) ester derivative, sodium bis (2-methoxyethoxy)aluminium hydride, benzene; (f) ethyl (2-methyl-1-imidazolyl)propionate,[25] phenyl lithium, THF; (g) alkyl iodide or benzyl bromide, acetone.

antimuscarinic activity, comparable to that of oxybutynin, with M_3-selectivity (10-fold M_3-selectivity). Therefore, we selected **1** as the lead compound to explore M_3-selective antimuscarinic agents. Compound **1** is composed of four active regions of importance, (1) the imidazole moiety, (2) the linker moiety, (3) the benzylic substituent moiety, and (4) the diphenylmethyl moiety, so chemical modification of each part of the molecule was performed to obtain detailed structure–activity relationships.

Effect of the imidazole moiety

As indicated in Table 2, introduction of appropriate alkyl groups at the imidazole ring strikingly affected the antimuscarinic activity and subtype-selectivity. Introduction of a methyl group into position 2 or 5 of the imidazole ring increased both anti-M_3 and anti-M_2 activities, but the 4-methyl group did not appear to affect the activity. These results indicated that the substituent located near the N-1 imidazole nitrogen favorably interacted with an anionic cavity of these receptor-subtypes. On the other hand, introduction of bulkier substituents generally decreased the antimuscarinic activity; for example, the 2-*n*-propylimidazole derivative (**4**) exhibited about 500- and 60-fold less potent anti-M_3 and anti-M_2 activities as compared to those of the 2-methyl derivative (**2**), and it showed no marked M_3-selectivity. In contrast, the 4,5-di-*n*-propylimidazole derivative (**9**) retained M_3-selectivity, although it exhibited decreased antimuscarinic activity. These results prompted us to speculate that both the width and the length of the substituents introduced at the imidazole ring play a critical role in binding to the receptors, and the shape of the cavity of the anionic site cavity is different in each muscarinic receptor subtype.

Effect of the linker moiety

As can be seen from Table 3, the maximum antimuscarinic activity was obtained when the spacer was the ethylene chain, for both M_2- and M_3-subtypes, and elongation of the spacer decreased the activity. These data indicate that the distance between the cationic head (imidazole moiety) and lipophilic tail (diphenylacetamide moiety) of these molecules is important for potent antimuscarinic activity. Introduction of a methyl group into the ethylene chain decreased the activity, probably due to the consequent change of the relative orientation of the cationic head moiety and the lipophilic tail moiety. It might also be that the methyl group interfered with the proper ligand–receptor interaction. All the compounds, except **14**, listed in Table 3 exhibited about 10-fold or greater selectivity for M_3 over M_2, so the length of the spacer methylene chain and the side chain methyl group are not critical for subtype-selectivity.

Effect of the diphenylmethyl moiety

Table 4 illustrates the importance of the steric factor at the lipophilic tail part of the molecule. The presence of

Table 1. Physicochemical properties of the imidazole derivatives

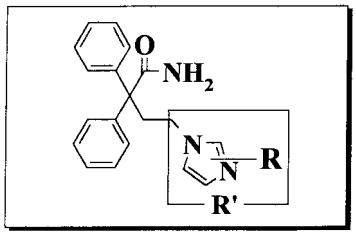
No.	mp (°C)	Mass (*m*/*z*)	Formula	Analysis (%)					
				Calcd			Found		
				C	H	N	C	H	N
1	172.0–175.0	305 (M^+)	$C_{19}H_{19}N_3O{\cdot}0.6H_2O$	72.17	6.44	13.29	72.20	6.32	12.89
2	189.0–190.0	319 (M^+)	$C_{20}H_{21}N_3O$	75.21	6.63	13.16	74.98	6.80	13.00
3	144.0–146.0	334 (M^+)	$C_{21}H_{23}N_3O$	75.65	6.95	12.60	75.42	7.08	12.43
4	150.0–152.0	347 (M^+)	$C_{22}H_{25}N_3O$	76.05	7.25	12.09	75.98	7.25	12.03
5	166.0–168.0	347 (M^+)	$C_{22}H_{25}N_3O{\cdot}0.1H_2O$	75.66	7.27	12.03	75.67	7.30	12.04
6	136.0–138.0	361 (M^+)	$C_{23}H_{27}N_3O{\cdot}0.5H_2O$	74.56	7.62	11.34	74.60	7.46	11.10
7	163.0–164.5	333 (M^+)	$C_{21}H_{23}N_3O$	75.65	6.95	12.60	75.37	7.05	12.43
8	194.0–196.0	361 (M^+)	$C_{23}H_{27}N_3O$	76.42	7.53	11.62	76.25	7.64	11.48
9	147.0–148.0	389 (M^+)	$C_{25}H_{31}N_3O{\cdot}0.2H_2O$	76.38	8.05	10.69	76.28	7.79	10.69
10	151.0–153.0	319 (M^+)	$C_{20}H_{21}N_3O$	75.21	6.63	13.16	75.32	6.79	13.07
11	173.0–175.0	319 (M^+)	$C_{20}H_{21}N_3O$	75.21	6.63	13.16	75.07	6.64	12.89
12	197.0–199.0	355 (M^+)	$C_{23}H_{21}N_3O{\cdot}0.5H_2O$	75.80	6.08	11.53	75.90	5.95	11.27
13	128.0–129.0	333 (M^+)	$C_{21}H_{23}N_3O{\cdot}0.2H_2O$	74.84	7.00	12.47	74.63	7.03	12.31
14	154.0–156.0	347 (M^+)	$C_{22}H_{25}N_3O$	76.05	7.25	12.09	75.96	7.22	11.93
15	159.0–161.0	361 (M^+)	$C_{23}H_{27}N_3O$	76.42	7.53	11.62	76.29	7.53	11.55
16	165.0–167.0	333 (M^+)	$C_{21}H_{23}N_3O{\cdot}0.4H_2O$	74.04	7.04	12.34	74.09	7.49	11.56
17	148.0–150.0	333 (M^+)	$C_{21}H_{23}N_3O$	75.65	6.95	12.60	75.48	7.16	12.50
18	206.0–207.5	355 (M^+)	$C_{20}H_{19}F_2N_3O$	67.59	5.39	11.82	67.23	5.55	11.63
19	163.0–165.0	349 (M^+)	$C_{21}H_{23}N_3O_2$	72.18	6.63	12.03	72.03	6.66	11.87
20	173.0–175.0	257 (M^+)	$C_{15}H_{19}N_3O$	70.01	7.44	16.33	69.73	7.47	16.14
21	191.0–192.5	285 (M^+)	$C_{17}H_{23}N_3O{\cdot}0.1H_2O$	71.10	8.14	14.63	71.15	8.11	14.43
22	178.0–180.0	325 (M^+)	$C_{20}H_{27}N_3O{\cdot}0.1H_2O$	73.40	8.38	12.84	73.25	8.46	12.71
23	212.0–214.0	320 (M^+)	$C_{19}H_{20}N_4O{\cdot}0.2H_2O$	70.43	6.35	17.29	70.59	6.38	17.25
24	218.0–220.0	345 (M^+)	$C_{22}H_{23}N_3O$	76.49	6.71	12.16	76.44	6.76	12.09
25	193.0–194.5	333 (M^+)	$C_{20}H_{19}N_3O_2$	72.05	5.74	12.60	72.01	5.95	12.63
26	157.0–158.5	301 (M^+)	$C_{20}H_{19}N_3{\cdot}HCl{\cdot}H_2O$	67.50	6.23	11.81	67.55	6.21	11.99
27	212.0–2.14.0 (dec.)	292(M^+)	$C_{19}H_{20}N_2O{\cdot}0.1H_2O$	77.57	6.92	9.52	77.66	6.87	9.24
28	84.0–86.0	334 (M^+)	$C_{21}H_{22}N_2O_2{\cdot}0.1H_2O$	75.02	6.66	8.33	75.00	6.80	8.36
29	237 (dec.)	320 (M^+)	$C_{20}H_{20}N_2O_2{\cdot}HCl$	67.32	5.93	7.85	67.22	5.97	7.81
30	155.0–156.5	306 (M^+)	$C_{20}H_{22}N_2O$	78.40	7.24	9.14	78.41	7.41	9.09
31	153.0–154.5	333 (M^+)	$C_{21}H_{23}N_3O{\cdot}0.1H_2O$	75.24	6.98	12.54	75.17	7.11	12.53
32	Oil	347 (M^+)	$C_{22}H_{25}N_3O{\cdot}0.4H_2O$	74.50	7.33	11.85	74.25	7.52	11.91
33	234.0–236.0	334 $(M-127)^+$	$C_{21}H_{24}IN_3O{\cdot}0.2H_2O$	54.25	5.29	9.04	54.02	5.30	9.00
34	189.0–192.0	348 $(M-127)^+$	$C_{22}H_{26}IN_3O{\cdot}0.6H_2O$	54.35	5.64	8.64	54.54	5.78	8.34
35	173.0–175.0	362 $(M-127)^+$	$C_{23}H_{28}IN_3O{\cdot}0.2H_2O$	56.04	5.81	8.52	55.89	5.68	8.51
36	164.0–166.0	376 $(M-127)^+$	$C_{24}H_{30}IN_3O$	57.26	6.01	8.35	57.08	5.94	8.23
37	230.0–232.0	410 $(M-80)^+$	$C_{27}H_{28}BrN_3O$	66.12	5.75	8.57	66.41	5.86	8.68
38	229.0–230.5	348 $(M-127)^+$	$C_{22}H_{26}IN_3O$	55.59	5.51	8.84	55.32	5.51	8.94
39	215.0–216.0	362 $(M-127)^+$	$C_{23}H_{28}IN_3O$	56.45	5.77	8.59	56.69	5.83	8.89
40	238.0–239.0	362 $(M-127)^+$	$C_{23}H_{28}IN_3O$	56.45	5.77	8.59	56.35	5.64	8.73

an unsubstituted diphenylmethyl group as a lipophilic substituent resulted in the most potent anticholinergic activity. The replacement of one phenyl group with an alkyl group (**20**, **21** and **22**) or a 2-pyridyl group (**23**) also decreased the activity. The inactivity of **20** and **21** might be due to decreased hydrophobic interaction with a lipophilic cavity. Decreased activity of **22** might indicate the importance of π–π interaction between the lipophilic tail moiety and receptor cavity hosting the diphenylmethyl group. Introduction of substituents at one or both benzene rings (**19**, **18**) decreased the activity. These results might indicate that the hydrophobic cavity hosting the diphenylmethyl group is not deep and substituents introduced at the *para* position interacted unfavorably with the cavity. The fixation of the two phenyl groups with an ethylene chain (**24**) or an ether bond (**25**) also resulted in a marked decrease in activity. These data indicate that the relative orientation of the two phenyl rings plays a critical role in the ligand-receptor interaction. We speculate that the presence of two phenyl groups located orthogonally at the lipophilic tail part of the molecule is essential for potent antimuscarinic activity. Interestingly, modification of the diphenylmethyl group decreased the antimuscarinic activity, but did not reduce the M_3 selectivity.

Effect of the benzylic substituent moiety

As shown in Table 5, the compounds bearing only the *N,N*-unsubstituted carbamoyl group (**2**) and the carboxyl group (**29**) exhibited potent antimuscarinic activity and M_3 selectivity, and the compounds possessing other functional groups lost the selectivity for the M_3 receptor (**26**, **27** and **30**) 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 *N,N*-disubstituted carbamoyl groups and the ester group (**31**, **32** and **28**, 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. These benzylic substituents may occupy a hydrophobic cavity,

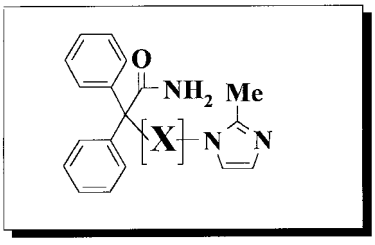
Table 2. Antimuscarinic activity of imidazole derivatives in guinea pig atria (M_2 receptor) and ileum (M_3 receptor)



No.	R	K_b (nM) M_3	M_2	M_1	M_2/M_3[a]	M_1/M_3[b]
1	H	5.07	68.4	5.99	13.5	1.18
2	2-Me	0.317	4.13	0.552	13.0	1.74
3	2-Et	78.1	258	N.T.[c]	3.30	—
4	2-*n*-Pr	177	254	N.T.	1.44	—
5	2-*i*-Pr	1.80	28.5	30.9	15.8	17.7
6	2-*t*-Bu	30.2	73.9	N.T.	2.45	—
7	4,5-diMe	2.70	8.66	N.T.	3.21	—
8	4,5-diEt	3.98	90.5	N.T.	22.7	—
9	4,5-di-*n*-Pr	100	2520	N.T.	25.2	—
10	4-Me	10.1	31.3	10.4	3.10	1.03
11	5-Me	0.862	9.59	3.40	11.1	3.94
12	R′ = 1-benzimidazolyl	2130	6540	N.T.	3.07	—
	Terodiline·HCl	67.7	119	N.T.	1.76	—
	Oxybutynin·HCl	3.44	5.00	2.45	1.45	0.712

[a]The selectivity ratio is the difference between the K_b values at M_2 (atrium) and M_3 (ilium) muscarinic receptors.
[b]The selectivity ratio is the difference between the K_b values at M_1 (vas deferens) and M_3 (ilium) muscarinic receptors.
[c]Not tested.

Table 3. Antimuscarinic activity of imidazole derivatives in guinea pig atria (M_2 receptor) and ileum (M_3 receptor)



No.	X	K_b (nM) M_3	M_2	M_2/M_3[a]
2	$(CH_2)_2$	0.317	4.13	13.0
13	$(CH_2)_3$	1.14	20.1	17.6
14	$(CH_2)_4$	43.7	148	3.39
15	$(CH_2)_5$	71.3	710	9.96
16	$CHCH_3CH_2$[b]	2.89	45.1	15.6
17	CH_2CHCH_3[b]	16.9	174	10.3

[a]See footnote a in Table 1.
[b]Assayed as a racemate.

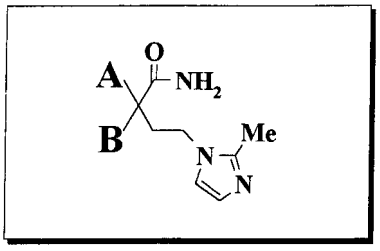
or more probably, fill a part of the cavity occupied by the two phenyl rings. So, it appears that the *N,N*-unsubstituted carbamoyl group allows optimal occupation of the hydrophobic cavity, and that further increasing the size of the substituent (**31**, **32** and **28**) leads to a decrease in activity for both M_2 and M_3 receptor-subtypes.

These structure–activity relationship studies indicated that the structure of 4-(1-imidazolyl)-2,2-diphenylbutyamide derivatives can be divided into two regions from the viewpoint of biological activity. One region, composed of the spacer methylene moiety and the diphenylmethyl moiety, is involved in the manifestation of antimuscarinic activity, and the other region, composed of the carbamoyl moiety and the imidazole moiety, contributes to both antimuscarinic activity and subtype-selectivity. A molecular modeling study of compound (**2**)[30] revealed that one of the carbamoyl hydrogens faces the imidazole moiety, probably due to a hydrogen bonding interaction between carbamoyl hydrogen and proximal imidazole nitrogen (Fig. 3). Therefore, the carbamoyl group and the imidazole moiety of **2** are located close to each other. These data indicate that the interaction of the cationic head moiety of ligands (including the imidazole moiety and carbamoyl moiety) with the anionic site cavity of muscarinic receptor-subtypes is critical for subtype selectivity.

Effect of quaternization

As can be seen from Table 6, alkyl quaternization of compound **2** (**33–37**) did not affect the anti-M_2 activity, while it considerably decreased the anti-M_3 activity. Therefore, alkyl quaternization derivatives of compound **2** showed equipotent anti-M_2 and anti-M_3 activity and decreased subtype-selectivity. In contrast, alkyl quaternization of compounds **3** and **4** (**38–40**) considerably increased both the anti-M_3 and anti-M_2 activity. This

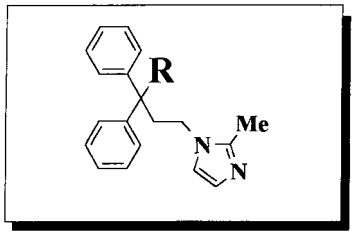
Table 4. In vitro functional activity of imidazole derivatives at M_2 receptors in guinea pig atria and M_3 receptors in guinea pig ileum



No.	A	B	K_b (nM) M_3	K_b (nM) M_2	M_2/M_3[a]
2	Ph	Ph	0.317	4.13	13.0
18	4-FPh	4-FPh	9.85	161	16.3
19	Ph	4-MeOPh[c]	24.6	744	30.2
20	Ph	Me[c]	1830	N.T.	—
21	Ph	*i*-Pr[c]	394	N.T.	—
22	Ph	Cyclohexyl[c]	19.0	603	31.7
23	Ph	2-Pyridyl[c]	2.86	50.1	17.5
24	Dibenzosuberan-5-yl		2140	N.T.	—
25	Xanthen-9-yl		> 1000	N.T.	—

[a]See footnote a in Table 1.
[b]Not tested.
[c]Assayed as a racemate.

Table 5. In vitro functional activity of imidazole derivatives at M_2 receptors in guinea pig atria and M_3 receptors in guinea pig ileum

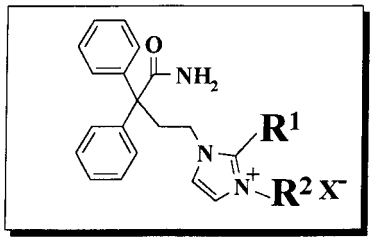


No.	R	K_b (nM) M_3	K_b (nM) M_2	M_2/M_3[a]
2	$CONH_2$	0.317	4.13	13.0
26	CN	10.4	15.5	1.49
27	OH	16.7	50.1	3.00
28	CO_2Me	> 1000	N.T.[b]	—
29	CO_2H	6.95	82.7	11.9
30	CH_2OH	25.4	83.8	3.30
31	CONHMe	5150	5870	1.14
32	$CON(Me)_2$	258	478	1.85

[a]See footnote a in Table 1.
[b]Not tested.

discrepancy is interesting but the reasons remain unknown. The benzyl quaternary salt **37** was unique in that it was much more effective at the M_3 receptor and less potent at the M_2 receptor, though overall it showed less potent activity. Contrary to the results obtained in the imidazole series, in the case of imidazolium salts, a molecular modeling study indicated that carbonyl oxygen faces the imidazolium group due to electrostatic interaction between carbonyl oxygen and the imidazolium cation (Fig. 3). This conformational change might have

Table 6. Antimuscarinic activity of imidazolium salt derivatives in guinea pig atria (M_2-receptor) and ileum (M_3-receptor)



No.	R^1	R^2	X	K_b (nM) M_3	K_b (nM) M_2	M_2/M_3[a]
33	CH_3	CH_3	I	3.78	6.34	1.68
34	CH_3	C_2H_5	I	7.11	9.24	1.30
35	CH_3	$(CH_2)_2CH_3$	I	4.07	12.3	3.02
36	CH_3	$(CH_2)_3CH_3$	I	3.12	18.2	5.83
37	CH_3	$CH_2C_6H_5$	Br	4.96	66.8	13.5
38	C_2H_5	CH_3	I	1.14	4.68	4.11
39	$(CH_2)_2CH_3$	CH_3	I	12.5	21.8	1.74
40	$CH(CH_3)_2$	CH_3	I	1.82	6.35	3.50
2	CH_3	—	—	0.317	4.13	13.0

[a]See footnote a in Table 1.

Table 7. The inhibitory effects of KRP-197 and oxybutynin·HCl on the isovolumetric bladder contraction and the decreased bladder capacity elicited by carbachol in conscious rats

Drugs	Isovolumetric bladder contraction (ED_{30}, mg/kg, id)[a]	Decreased bladder capacity (ED_{50}, mg/kg, ig)[b]
KRP-197	0.11 (0.058–0.20)[c]	0.074 (0.021–0.17)[c]
Oxybutynin·HCl	2.1 (1.2–3.5)[c]	1.1 (0.78–1.6)[c]

[a]id, Intraduodenal administration.
[b]ig, Intragastric administration.
[c]Figures in parentheses are 95% confidence limits.

resulted in unfavorable interacton with the muscarinic receptor M_3-subtype and decreased anti-M_3 activity.

Compounds that possessed potent and/or subtype-selective antagonism were further evaluated for anti-M_1 activity.[18] As can be seen from Table 2, here again, the shape and position of the substituents at the imidazole ring strikingly affect the subtype-selectivity. The unsubstituted and 2-methyl-substituted imidazole derivatives (**1** and **2**, respectively) exhibited equipotent anti-M_1 and anti-M_3 activities, but the 2-isopropyl- and 5-methyl-substituted derivatives (**5** and **11**, respectively) showed about 18- and fourfold less potent anti-M_1 activity as compared to anti-M_3 activity. These data support our hypothesis that the three-dimensional interactions between the cationic head moiety of the imidazolylbutyramide derivatives and anionic sites of functional muscarinic acetylcholine receptor subtypes play a critical role in subtype-selectivity.

On the basis of their potency as M_3 muscarinic receptor antagonists and/or their pharmacological subtype selectivity, 4-(2-methyl-1-imidazolyl)-2,2-diphenylbutyramide (**2**: **KRP-197**) was further studied in vivo. These results

Table 8. The influence of KRP-197 on the muscarinic-mediated responses in the heart, gut, urinary bladder, salivary gland, and eye in the rats

Organs	ED_{50} (mg/kg) Rat
Urinary bladder	0.11 (0.058–0.20)[a,d,e]
Gut	0.39 (0.11–1.0)[a,c,e]
Heart	1.0 (0.72–1.5)[a,e]
Salivary gland	1.1 (0.75–1.6)[b,e]
Eye (pupil diameter)	1.8 (1.2–3.1)[a,e]

[a]Intraduodenal administration.
[b]Per os.
[c]ED_{100} value (dose to prolong contraction interval by 100%).
[d]ED_{30} value (dose to prolong contraction interval by 30%).
[e]Figures in parentheses are 95% confidence limits.

Table 9. The relative selectivity of KRP-197 and oxybutynin·HCl for the urinary bladder compared with the salivary gland

Drugs	Carbachol-induced detrusor hyperreflexia (ED_{50}, mg/kg, i.g.)[b]	Salivary secretion (ED_{50}, mg/kg, p.o.)[c]	Ratio of ED_{50}S[a]
KRP-197	0.074 (0.021–0.17)[d]	1.1 (0.75–1.6)[d]	15
Oxybutynin·HCl	1.1 (0.78–1.6)[d]	3.6 (1.9–6.4)[d]	3.3

[a]Ratio of salivary secretion/carbachol-induced detrusor hyperreflexia.
[b]ig, Intragastric administration.
[c]Per os.
[d]Figures in parentheses are 95% confidence limits.

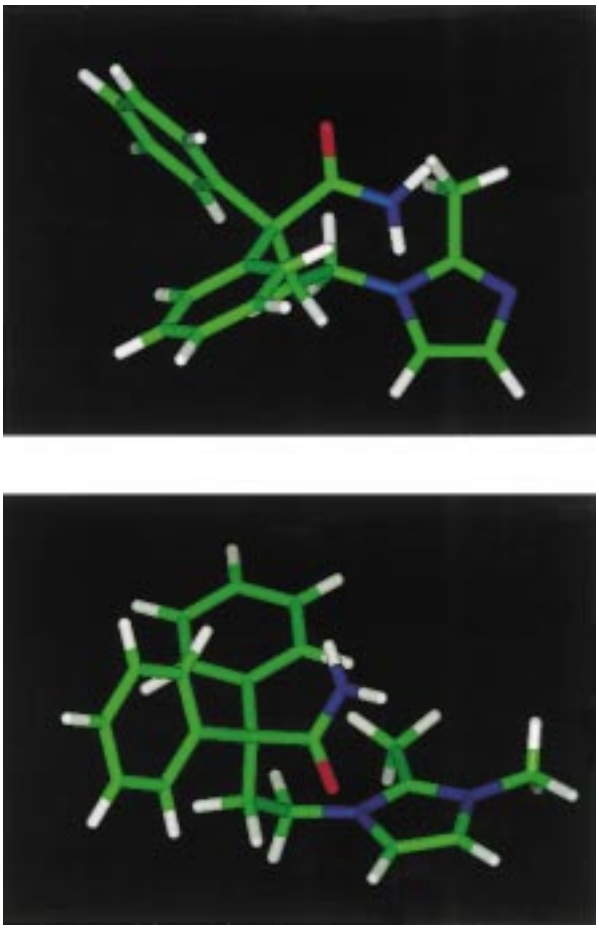


Figure 3. Energy minimized structure of **2** (KRP-197; top) and its methyl quaternary salt **33** (bottom).

are given in Tables 7–9 (although compound **5** exhibited M_3 selectivity, a preliminary in vivo study indicated that its in vivo action on urinary bladder contraction was weak and the duration of action was short, probably due to rapid metabolism, so further in vivo study was not performed).

Muscarinic-mediated bladder contraction (isovolumetric bladder contraction) and decreased bladder capacity (carbachol-induced detrusor hyperreflexia), models of pollakiuria[31] and urinary incontinence,[32] were examined in conscious rats. Intraduodenal administration of KRP-197 (0.04–0.30 mg/kg) inhibited bladder contraction dose-dependently, and the ED_{30} value was 0.11 mg/kg. The inhibitory action of KRP-197 on the bladder contraction was 19 times as potent as that of oxybutynin (Table 7), and the duration of action was similar to that of oxybutynin (data not shown). In another model of pollakiuria, KRP-197 showed preventive action against the decrease in bladder capacity induced by carbachol (ED_{50} 0.074 mg/kg, intragastric administration), and the potency of the inhibitory action was 15-fold greater than that of oxybutynin (Table 7). In both models of micturition dysfunction, KRP-197 was effective at the dose range of 0.020–0.20 mg/kg (intraduodenal or intragastric administration), being 15–19 times more potent than oxybutynin. Furthermore, the relatively potent activities in these rat models in vivo appeared to reflect those in the functional studies in vitro.

The influence of KRP-197 on the muscarinic-mediated responses in various organs or tissues was studied in rats. The muscarinic-mediated responses in heart, gut, urinary bladder, salivary gland and eye, causing vagal-induced bradycardia,[33] spontaneous ileal contraction,[31] isovolumetric bladder contraction,[31] carbachol-induced salivary secretion[34] and tonic contraction of the iris sphincter (pupil diameter),[35] respectively, were inhibited in a dose-dependent manner. As shown in Table 8, the rank order of the effective dose in rats was as follows: urinary bladder > gut > heart and salivary gland > eye (pupil size). KRP-197 exhibited selectivity for the bladder over the other organs tested in rats.

Further, in order to assess the relative selectivity of KRP-197 and oxybutynin for the muscarinic receptors in the bladder, the ED_{50} value for the inhibition of salivation was expressed as a ratio with respect to the ED_{50} value for the inhibition of bladder contraction. It can be seen from Table 9 that KRP-197 is more selective (fivefold more) for the bladder than is oxybutynin.

These in vitro and in vivo studies suggest that 4-(2-methyl-1-imidazolyl)-2,2-diphenylbutyramide (**2**; **KRP-197**) is a potent, muscarinic M_1- and M_3-selective antagonist, and shows selectivity for the bladder over the heart and the salivary gland in vitro and in vivo. Thus, KRP-197 could have therapeutic potential for the

treatment of symptoms in diseases associated with altered smooth muscle contractility and tone with a lower incidence of side effects. Clinical studies of KRP-197 are in progress.

Experimental

General

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured in $CDCl_3$ or DMSO-d_6 with TMS and the solvent peak as internal standards, on a JEOL JMN-A400 spectrometer. Mass spectra (MS) were obtained on a JEOL JMS-HX110 spectrometer. Column chromatography was carried out on Merck silica gel 60. Analytical thin-layer chromatography (TLC) was performed on Merck precoated silica gel $60F_{254}$ plates, and the compounds were visualized by UV illumination (254 nm) or by heating to 150 °C after spraying with phosphomolybdic acid in ethanol. Elemental analysis was performed in the microanalytical laboratory of Kyorin Pharmaceutical Co., Ltd.

Chemistry

4-(2-Methyl-1-imidazolyl)-2,2-diphenylbutyramide (2). A mixture of 4-bromo-2,2-diphenylbutyronitrile (3.00 g, 10.0 mmol), 2-methylimidazole (2.46 g, 30.0 mmol), triethylamine (1.40 mL, 13.5 mmol), and *N,N*-dimethylformamide (50 mL) was stirred at 150 °C for 30 h. The mixture was poured into water, and extracted with benzene, and the extract was washed, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography, eluting with CH_2Cl_2:ethanol (10:1 v/v), and treated with ethanolic HCl to give 4-(2-methyl-1-imidazolyl)-2,2-diphenylbutyronitrile (2.60 g, 77%). Then, the cyano compound (7.83 g, 26.0 mmol) was mixed with 70% sulfuric acid (50 mL) and stirred at 140–150 °C for 40 min. The mixture was carefully basified, and extracted with $CHCl_3$, then the extract was washed with brine, dried (Na_2SO_4), and concentrated. The residue was recrystallized from a mixed solvent of ethyl acetate:ethanol to give 4-(2-methyl-1-imidazolyl)-2,2-diphenylbutyramide (2.02 g, 24%) as a colorless needle: mp 189.0–190.0 °C (from ethyl acetate:ethanol); High MS (EI+) *m/z* calcd for $C_{20}H_{21}N_3O$ 319.1685, found 319.1671; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (3H, s), 2.69–2.74 (2H, m), 3.77–3.82 (2H, m), 5.33 (1H, s), 5.49 (1H, s), 6.73 (1H, s), 6.85 (1H, s), 7.31–7.42 (10H, m).

A similar procedure was employed for the preparation of compounds **1–23**. The yields (two steps) were about 5–70%. The high resolution mass spectra and the NMR data are as follows.

4-(1-Imidazolyl)-2,2-diphenylbutyramide (1). High MS (EI+) *m/z* calcd for $C_{19}H_{19}N_3O$ 305.1528, found 305.1523; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80–2.84 (2H, m), 3.88 (2H, m), 5.36 (1H, s), 5.71 (1H, s), 6.84 (1H, s), 6.99 (1H, s), 7.30–7.41 (10H, m).

4-(2-Ethyl-1-imidazolyl)-2,2-diphenylbutyramide (3). High MS (EI+) *m/z* calcd for $C_{21}H_{23}N_3O$ 333.1841, found 333.1847; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22–1.25 (3H, t, J = 7.3 Hz), 2.50–2.55 (2H, q, J = 7.3 Hz), 2.70–2.74 (2H, m), 3.77–3.81 (2H, m), 5.36 (1H, s), 5.75 (1H, s), 6.73 (1H, d, J = 1.5 Hz), 6.89 (1H, d, J = 1.0 Hz), 7.32–7.42 (10H, m).

4-(2-*n*-Propyl-1-imidazolyl)-2,2-diphenylbutyramide (4). High MS (EI+) *m/z* calcd for $C_{22}H_{25}N_3O$ 347.1998, Found 347.2014; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89–0.93 (3H, t, J = 7.3 Hz), 1.60–1.70 (2H, m), 2.46 (2H, t, J = 7.8 Hz), 2.70–2.74 (2H, m), 3.78–3.82 (2H, m), 5.34 (1H, s), 5.57 (1H, s), 6.74 (1H, d, J = 1.4 Hz), 6.89 (1H, d, J = 1.0 Hz), 7.32–7.42 (10H, m).

4-(2-*i*-Propyl-1-imidazolyl)-2,2-diphenylbutyramide (5). High MS (EI+) *m/z* calcd for $C_{22}H_{25}N_3O$ 347.1998, Found 347.1991; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21–1.22 (6H, d, J = 6.8 Hz), 2.72–2.76 (2H, m), 2.79–2.84 (1H, m), 3.80–3.84 (2H, m), 5.36 (1H, s), 5.75 (1H, s), 6.71 (1H, s), 6.90 (1H, s), 7.32–7.42 (10H, m).

4-(2-*t*-Butyl-1-imidazolyl)-2,2-diphenylbutyramide (6). High MS (EI+) *m/z* calcd for $C_{23}H_{27}N_3O$ 361.2154, Found 361.2193; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (9H, s), 2.79–2.84 (2H, m), 3.94–3.99 (2H, m), 5.36 (1H, s), 5.63 (1H, s), 6.83 (1H, s), 6.87 (1H, s), 7.34–7.43 (10H, m).

4-(4,5-Dimethyl-1-imidazolyl)-2,2-diphenylbutyramide (7). High MS (EI+) *m/z* calcd for $C_{21}H_{23}N_3O$ 333.1841, Found 333.1820; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (3H, s), 2.11 (3H, s), 2.67–2.71 (2H, m), 3.73–3.77 (2H, m), 5.36 (1H, s), 5.70 (1H, s), 7.18 (1H, s), 7.31–7.41 (10H, m).

4-(4,5-Diethyl-1-imidazolyl)-2,2-diphenylbutyramide (8). High MS (EI+) *m/z* calcd for $C_{23}H_{27}N_3O$ 361.2154, Found 361.2178; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, t, J = 7.6 Hz), 1.19 (3H, t, J = 7.6 Hz), 2.42 (2H, q, J = 7.6 Hz), 2.47 (2H, q, J = 7.6 Hz), 2.71–2.75 (2H, m), 3.74–3.78 (2H, m), 5.34 (1H, br s), 5.58 (1H, br s), 7.21 (1H, s), 7.32–7.41 (10H, m).

4-(4,5-Di-*n*-propyl-1-imidazolyl)-2,2-diphenylbutyramide (9). High MS (EI+) *m/z* calcd for $C_{25}H_{31}N_3O$ 389.2467, Found 389.2453; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (3H, t, J = 7.3 Hz), 0.92 (3H, t, J = 7.3 Hz), 1.32 (2H, hept, J = 7.3 Hz), 1.64 (2H, hept, J = 7.3 Hz), 2.34 (2H, t, J = 7.3 Hz), 2.43 (2H, t, J = 7.3 Hz), 2.72–2.76 (2H, m), 3.77–3.81 (2H, m), 5.41 (1H, br s), 5.74 (1H, br s), 7.32–7.42 (10H, m), 7.46 (1H, s).

4-(4-Methyl-1-imidazolyl)-2,2-diphenylbutyramide (10). High MS (EI+) *m/z* calcd for $C_{20}H_{21}N_3O$ 319.1685, Found 319.1685; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (3H, s), 2.78–2.82 (2H, m), 3.80–3.83 (2H, m), 5.33 (1H, br s), 5.52 (1H, br s), 6.56 (1H, s), 7.21–7.41 (11H, m).

4-(5-Methyl-1-imidazolyl)-2,2-diphenylbutyramide (11). High MS (EI+) *m/z* calcd for $C_{20}H_{21}N_3O$ 319.1685, Found 319.1667; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08

(3H, s), 2.69–2.73 (2H, m), 3.78–3.82 (2H, m), 5.33 (1H, s), 5.51 (1H, s), 6.70 (1H, s), 7.27–7.42 (11H, m).

4-(1-Benzimidazolyl)-2,2-diphenylbutyramide (12). High MS (EI+) *m/z* calcd for $C_{23}H_{21}N_3O$ 355.1685, Found 355.1693; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85–2.89 (2H, m), 4.15–4.19 (2H, m), 5.37 (1H, s), 5.59 (1H, s), 7.23–7.43 (13H, m), 7.73–7.78 (2H, m).

5-(2-Methyl-1-imidazolyl)-2,2-diphenylpentyramide (13). High MS (EI+) *m/z* calcd for $C_{21}H_{23}N_3O$ 333.1841, Found 333.1841; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62–1.70 (2H, m), 2.30 (3H, s), 2.36 (2H, m), 3.77 (2H, t, J = 7.1 Hz), 5.35 (1H, br s), 5.42 (1H, br s), 6.74 (1H, d, J = 1.0 Hz), 6.89 (1H, d, J = 1.0 Hz), 7.25–7.37 (10H, m).

6-(2-Methyl-1-imidazolyl)-2,2-diphenylhexyramide (14). High MS (EI+) *m/z* calcd for $C_{22}H_{25}N_3O$ 347.1998, Found 347.1994; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (2H, m), 1.68 (2H, dt, J = 7.8, 7.3 Hz), 2.28 (3H, s), 2.39 (2H, m), 3.71 (2H, t, J = 7.3 Hz), 5.48 (2H, br s), 6.70 (1H, d, J = 1.5 Hz), 6.84 (1H, d, J = 1.5 Hz), 7.27–7.37 (10H, m).

7-(2-Methyl-1-imidazolyl)-2,2-diphenylheptyramide (15). High MS (EI+) *m/z* calcd for $C_{23}H_{27}N_3O$ 361.2154, Found 361.2155; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.30 (4H, m), 1.63–1.66 (2H, m), 2.31 (3H, s), 2.34–2.38 (2H, m), 3.73 (2H, t, J = 7.1 Hz), 5.30–5.50 (2H, m), 6.73 (1H, s), 6.87 (1H, s), 7.28–7.35 (10H, m).

3-Methyl-4-(2-methyl-1-imidazolyl)-2,2-diphenylbutyramide (16). High MS (EI+) *m/z* calcd for $C_{21}H_{23}N_3O$ 333.1841, Found 333.1851; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (3H, d, J = 6.8 Hz), 2.29 (3H, s), 2.90–3.10 (1H, m), 3.40–3.50 (1H, m), 4.17 (1H, s), 5.46 (2H, br s), 6.84 (1H, s), 6.88 (1H, s), 7.30–7.44 (10H, m).

4-Methyl-4-(2-methyl-1-imidazolyl)-2,2-diphenylbutyramide (17). High MS (EI+) *m/z* calcd for $C_{21}H_{23}N_3O$ 333.1841, Found 333.1866; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (3H, d, J = 6.8 Hz), 1.77 (3H, s), 2.83 (1H, dd, J = 14, 5.1 Hz), 2.97 (1H, dd, J = 14, 5.1 Hz), 4.30–4.40 (1H, m), 5.29 (1H, br s), 5.55 (1H, br s), 6.80 (1H, s), 6.82 (1H, s), 7.19–7.33 (10H, m).

2,2-Bis-(4-fluorophenyl)-4-(2-methyl-1-imidazolyl)butyramide (18). High MS (EI+) *m/z* calcd for $C_{20}H_{19}F_2N_3O$ 355.1496, Found 355.1497; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (3H, s), 2.66–2.70 (2H, m), 3.83–3.87 (2H, m), 5.30 (1H, br s), 5.62 (1H, br s), 6.79 (1H, s), 6.98 (1H, s), 7.11 (4H, t, J = 8.8 Hz), 7.28 (4H, dd, J = 8.8, 5.3 Hz).

2-(4-Methoxyphenyl)-4-(2-methyl-1-imidazolyl)-2-phenylbutyramide (19). High MS (EI$^+$) *m/z* calcd for $C_{21}H_{23}N_3O_2$ 349.1790, Found 349.1790; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (3H, s), 2.66–2.70 (2H, m), 3.79–3.87 (2H, m), 3.83 (3H, s), 5.35 (1H, br s), 5.58 (1H, br s), 6.77 (1H, s), 6.91 (1H, s), 6.92 (2H, d, J = 8.8 Hz), 7.22 (2H, d, J = 8.8 Hz), 7.31–7.42 (5H, m).

2-Methyl-2-phenyl-4-(2-methyl-1-imidazolyl)butyramide (20). High MS (EI+) *m/z* calcd for $C_{15}H_{19}N_3O$ 257.1528, Found 257.1522; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67 (3H, s), 2.24 (3H, s), 2.27–2.41 (2H, m), 3.64–3.72 (1H, m), 3.74–3.82 (1H, m), 5.20 (1H, br s), 5.36 (1H, br s), 6.73 (1H, d, J = 1.5 Hz), 6.86 (1H, d, J = 1.5 Hz), 7.32–7.42 (5H, m).

2-Isopropyl-2-phenyl-4-(2-methyl-1-imidazolyl)butyramide (21). High MS (EI+) *m/z* calcd for $C_{17}H_{23}N_3O$ 285.1841, Found 285.1858; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, d, J = 6.8 Hz), 1.03 (3H, d, J = 6.8 Hz), 2.00–2.15 (1H, m), 2.22 (3H, s), 2.50–2.65 (2H, m), 3.40–3.55 (1H, m), 3.75–3.85 (1H, m), 5.38 (1H, br s), 5.65 (1H, br s), 6.72 (1H, s), 6.86 (1H, s), 7.34–7.36 (3H, m), 7.39–7.43 (2H, m).

2-Cyclohexyl-2-(4-methoxyphenyl)-4-(2-methyl-1-imidazolyl)butyramide (22). High MS (EI+) *m/z* calcd for $C_{20}H_{27}N_3O$ 325.2154, Found 325.2150; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90–1.10 (1H, m), 1.10–1.25 (2H, m), 1.40–1.60 (2H, m), 1.85–2.00 (5H, m), 2.05–2.20 (1H, m), 2.27 (1H, dt, J = 13, 4.9 Hz), 2.36 (3H, s), 2.70 (1H, dt, J = 13, 4.9 Hz), 3.67 (1H, dt, J = 13, 4.9 Hz), 3.91 (1H, dt, J = 13, 4.9 Hz), 5.54 (1H, br s), 5.72 (1H, br s), 6.87 (1H, s), 7.02 (1H, s), 7.47–7.50 (3H, m), 7.54–7.58 (2H, m).

2-Pyridyl-4-(2-methyl-1-imidazolyl)-2-phenylbutyramide (23). High MS (EI+) *m/z* calcd for $C_{19}H_{20}N_4O$ 320.1637, Found 320.1671; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (3H, s), 2.76 (1H, dt, J = 6.8, 4.9 Hz), 2.82 (1H, dt, J = 6.8, 4.9 Hz), 3.66–3.73 (1H, m), 3.86–3.92 (1H, m), 5.66 (1H, br s), 6.75 (1H, s), 6.86 (1H, s), 7.18–7.20 (2H, m), 7.26–7.37 (5H, m), 7.73 (1H, t, J = 7.8 Hz), 7.80 (1H, br s), 8.61 (1H, d, J = 3.9 Hz).

5-Carbamoyl-5-[4-(2-methyl-1-imidazoly)ethyl]dibenzosuberane (24). 5-Cyano-5-[4-(2-methyl-1-imidazoly)ethyl]dibenzosuberane (2.00 g, 6.11 mmol) was mixed with KOH (2.00 g, 35.6 mmol), EtOH (20 mL), and water (20 mL) in an autoclave and stirred for 20 h at 150 °C. The mixture was diluted with water, extracted with CH_2Cl_2 and the extract was washed, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography, eluting with CH_2Cl_2:ethanol (12:1 v/v), recrystallized from a mixed solvent of *n*-hexane and ethyl acetate to give the compound (500 mg, 24%) as a colorless powder: mp 218.0–220.0 °C; High MS (EI+) *m/z* calcd for $C_{22}H_{23}N_3O$ 345.1841, Found 345.1834; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (3H, s), 2.65–2.70 (2H, m), 3.17 (4H, s), 3.62 (2H, m), 5.10 (1H, br s), 5.45 (1H, br s), 6.66 (1H, s), 6.84 (1H, s), 7.17–7.26 (6H, m), 7.44 (2H, d, J = 6.4 Hz).

A similar procedure was employed for the preparation of compound **25**.

9-Carbamoyl-9-[4-(2-methyl-1-imidazoly)ethyl]xanthene (25). High MS (EI+) *m/z* calcd for $C_{20}H_{19}N_3O_2$ 333.1477, Found 333.1460; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (3H, s), 2.62–2.66 (2H, m), 3.36–3.41 (2H, m), 5.27 (1H, br s), 5.54 (1H, br s), 6.54 (1H, s), 6.75 (1H, s), 7.15–7.19 (4H, m), 7.34–7.40 (4H, m).

4-(2-Methyl-1-imidazolyl)-2,2-diphenylbutyronitrile HCl (26). High MS (EI+) *m/z* calcd for $C_{20}H_{19}N_3$ 301.1579,

Found 301.1578; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (3H, s), 2.75–2.79 (2H, m), 3.90–3.94 (2H, m), 6.77 (1H, s), 6.90 (1H, s), 7.35–7.42 (10H, m).

3-(2-Methyl-1-imidazolyl)-1,1-diphenylpropanol (27). To a mixture of ethyl 3-(2-methyl-1-imidazolyl) propionate (3.37 g, 18.5 mmol) and dehydrated THF (10 mL) was added a solution of phenyl lithium in cyclohexane:ether (1.8 M solution, 50 mL) at 0 °C. The mixture was stirred for 3.5 h at 10 °C, poured into water, extracted with ethyl acetate, then the extract was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography, eluting with ethyl acetate:ethanol (10:1 v/v), recrystallized from a mixed solvent of ethanol and benzene to give the product (320 mg, 6%) as a colorless needle: mp 212.0–214.0 °C; High MS (EI+) *m/z* calcd for $C_{19}H_{20}N_2O$ 292.1576, Found 292.1589; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (3H, s), 2.64–2.69 (2H, m), 2.90 (1H, br s), 3.79–3.84 (2H, m), 6.72 (1H, s), 6.80 (1H, s), 7.22–7.44 (10H, m).

Methyl 4-(2-methyl-1-imidazolyl)-2,2-diphenylbutyrate (28). A mixture of compound (**29**) (2.00 g, 5.60 mmol) and thionyl chloride (20 mL) was refluxed for 4 h and evaporated off excess thionyl chloride. Then, the residual acid chloride was mixed with methanol (100 mL), refluxed for 18 h. The solvent was evaporated and the residue was purified by silica gel column chromatography, eluting with ethyl CH_2Cl_2:ethanol (10:1 v/v), recrystallized from *n*-hexane:ethyl acetate to give the product (250 mg, 13%) as a colorless powder: mp 84.0–86.0 °C; High MS (EI+) *m/z* calcd for $C_{21}H_{22}N_2O_2$ 334.1681, Found 334.1679; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (3H, s), 2.69–2.73 (2H, m), 3.58-3.62 (2H, m), 3.75 (3H, s), 3.58–3.62 (2H, m), 3.75 (3H, s), 6.71 (1H, s), 6.87 (1H, s), 7.24–7.37 (10H, m).

4-(2-Methyl-1-imidazolyl)-2,2-diphenylbutyric acid monohydrochloride (29). A mixture of compound **2** (5.00 g, 15.7 mmol) and c.HCl (250 mL) was stirred for 18 h at 150 °C and then cooled to room temperature. The precipitate was filtrated and washed with acetone to afford 4.70 g (84%) of the product as a white powder: mp 237.0 °C; High MS (EI+) *m/z* calcd for $C_{20}H_{20}N_2O_2$ 320.1525, Found 320.1530; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.38 (3H, s), 2.80–2.84 (2H, m), 3.77–3.81 (2H, m), 7.28–7.39 (10H, m), 7.51 (1H, s), 7.55 (1H, s).

4-(2-Methyl-1-imidazolyl)-2,2-diphenylbutanol (30). To a solution of 70% sodium bis (2-methoxyethoxy)aluminium hydride and benzene (80 mL) was added dropwise a solution of compound (**28**) (2.00 g, 5.81 mmol) and benzene (20 mL) under reflux. Reflux was continued for 6 h, poured into 20% KOH solution, and the mixture was refluxed for 30 min. The mixture was poured into water and extracted with benzene. The organic solution was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography, eluting with CH_2Cl_2:ethanol (12:1 v/v), recrystallized from acetone to give the product (1.00 g, 39%) as a colorless needle: mp 155.0–156.5 °C; High MS (EI+) *m/z* calcd for $C_{20}H_{22}N_2O$ 306.1732, Found 306.1735; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53 (3H, s), 2.68–2.72 (2H, m), 3.89–3.93 (2H, m), 4.24 (2H, s), 7.13–7.35 (12H, m).

***N*-Methyl 4-(2-methyl-1-imidazolyl)-2,2-diphenylbutyramide (31).** A mixture of compound (**29**) (1.00 g, 2.80 mmol) and thionyl chloride (20 mL) was refluxed for 4 h and evaporated off excess thionyl chloride. Then, the residual acid chloride was mixed with 40% aqueous methylamine (30 mL) and CH_2Cl_2 (100 mL), stirred for 6 h under ice-cooling. The mixture was poured into water, then basified with NaOH, and extracted with CH_2Cl_2. The organic solvent was evaporated and the residue was purified by silica gel column chromatography, eluting with CH_2Cl_2:ethanol (10:1 v/v), recrystallized from ethyl acetate to give the product (800 mg, 86%) as a colorless powder: mp 153.0–154.5 °C; High MS (EI+) *m/z* calcd for $C_{21}H_{23}N_3O$ 333.1841, Found 333.1863; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (3H, s), 2.68–2.72 (2H, m), 2.80 (3H, d, J = 4.9 Hz), 3.82–3.87 (2H, m), 5.36 (1H, br s), 6.73 (1H, s), 6.84 (1H, s), 7.22–7.27 (4H, m), 7.33–7.40 (6H, m).

A similar procedure was employed for the preparation of compound **32**.

***N*,*N*-Dimethyl 4-(2-methyl-1-imidazolyl)-2,2-diphenylbutyramide (32).** High MS (EI+) *m/z* calcd for $C_{22}H_{25}N_3O$ 347.1998, Found 347.2007; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (3H, s), 2.34 (3H, s), 2.50–2.54 (2H, m), 3.03 (3H, s), 3.54–3.57 (2H, m), 6.41 (1H, s), 6.79 (1H, s), 7.32–7.35 (2H, m), 7.42–7.43 (8H, m).

4-(2,3-Dimethyl-1-imidazolyl)-2,2-diphenylbutyramide iodide (33). A mixture of compound **2** (1.00 g, 3.13 mmol), methyliodide (20 mL), acetone (100 mL) and ethanol (10 mL) was stirred for 18 h at 95 °C in a sealed tube. The solvent was evaporated and the residue was recrystallized from ethyl acetate:ethanol to afford 1.30 g (90%) of the desired salts as a yellow needle: mp 234.0–236.0 °C; High MS (FAB+) *m/z* calcd for $C_{21}H_{24}N_3O$ 334.1919, Found 334.1917; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.38 (3H, s), 2.73 (2H, m), 3.69 (3H, s), 3.77 (2H, m), 6.80 (1H, s), 7.32–7.41 (10H, m), 7.46 (1H, s), 7.53 (1H, d, J = 2.0 Hz), 7.56 (1H, d, J = 2.0 Hz).

A similar procedure was employed for the preparation of the compounds **34–40**. The yields were 40–90%.

4-(3-Ethyl-2-methyl-1-imidazolyl)-2,2-diphenylbutyramide iodide (34). High MS (FAB+) *m/z* calcd for $C_{22}H_{26}N_3O$ 348.2076, Found 348.2077; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (3H, t, J = 7.3 Hz), 2.41 (3H, s), 2.76 (2H, m), 3.80 (2H, m), 4.08 (2H, q, J = 7.3 Hz), 6.78 (1H, s), 7.33–7.41 (10H, m), 7.46 (1H, s), 7.57 (1H, s), 7.64 (1H, s).

4-(3-*n*-Propyl-2-methyl-1-imidazolyl)-2,2-diphenylbutyramide iodide (35). High MS (FAB+) *m/z* calcd for $C_{23}H_{28}N_3O$ 362.2232, Found 362.2234; ^{1}H NMR (400 MHz, DMSO-d_6) 0.86 (3H, t, J = 7.3 Hz), 1.70–1.72 (2H, m), 2.42 (3H, m), 2.77 (2H, m), 3.80 (2H, m), 4.02 (2H, t, J = 7.3 Hz), 6.78 (1H, s), 7.31–7.40 (10H, m), 7.45 (1H, s), 7.58 (1H, s), 7.63 (1H, s).

4-(3-*n*-Butyl-2-methyl-1-imidazolyl)-2,2-diphenylbutyramide iodide (36). High MS (FAB+) *m/z* calcd for $C_{24}H_{30}N_3O$ 376.2389, Found 376.2393; ^{1}H NMR (400 MHz, DMSO-d_6) 0.90 (3H, t, J = 7.3 Hz), 1.26 (2H, quint, J = 7.3 Hz), 1.66 (2H, m), 2.41 (3H, s), 2.76 (2H, m), 3.80 (2H, m), 4.05 (2H, t, J = 7.3 Hz), 6.78 (1H, s), 7.31–7.40 (10H, m), 7.45 (1H, s), 7.57 (1H, d, J = 2.4 Hz), 7.63 (1H, d, J = 2.4 Hz).

4-(3-Benzyl-2-methyl-1-imidazolyl)-2,2-diphenylbutyramide iodide (37). High MS (FAB+) *m/z* calcd for $C_{27}H_{28}N_3O$ 410.2232, Found 410.2221; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.44 (3H, s), 2.77–2.81 (2H, m), 3.80–3.84 (2H, m), 5.36 (2H, s), 6.79 (1H, s), 7.45 (1H, s), 7.30–7.43 (15H, m), 7.64 (1H, d, J = 2.4 Hz), 7.68 (1H, d, J = 2.0 Hz).

4-(2-Ethyl-3-methyl-1-imidazolyl)-2,2-diphenylbutyramide iodide (38). High MS (FAB+) *m/z* calcd for $C_{22}H_{26}N_3O$ 348.2076, Found 348.2065; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02 (3H, t, J = 7.6 Hz), 2.77–2.79 (4H, m), 3.75 (3H, s), 3.79–3.84 (2H, m), 6.82 (1H, s), 7.32–7.41 (10H, m), 7.46 (1H, s), 7.59 (1H, s), 7.61 (1H, s).

4-(3-Methyl-2-*n*-propyl-1-imidazolyl)-2,2-diphenylbutyramide iodide (39). High MS (FAB+) *m/z* calcd for $C_{23}H_{28}N_3O$ 362.2232, Found 362.2242; ^{1}H NMR (400 MHz, DMSO-d_6) 0.83 (3H, t, J = 7.3 Hz), 1.39–1.41 (2H, m), 2.69–2.73 (4H, m), 3.75 (3H, s), 3.81 (2H, m), 6.83 (1H, s), 7.34–7.42 (10H, m), 7.48 (1H, s), 7.61 (1H, s), 7.66 (1H, d, J = 2.0 Hz).

4-(2-Isopropyl-3-methyl-1-imidazolyl)-2,2-diphenylbutyramide iodide (40). High MS (FAB+) *m/z* calcd for $C_{23}H_{28}N_3O$ 362.2232, Found 362.2245; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.16 (6H, d, J = 7.3 Hz), 2.73–2.78 (2H, m), 3.24–3.30 (1H, m), 3.81–3.88 (5H, m), 6.88 (1H, s), 7.31–7.43 (10H, m), 7.46 (1H, s), 7.61 (1H, s), 7.64 (1H, s).

Pharmacology

In vitro functional antimuscarinic activity of the compounds described in this paper (rabbit vas deferens (M_1 receptor antagonism), guinea pig atrial muscle (M_2 receptor antagonism), guinea pig ileal muscle (M_3 receptor antagonism)) were determined according to the literature method.[3] In vivo antimuscarinic activity of the selected compound (KRP-197) (isovolumetric bladder contraction,[31] carbachol–induced detrusor hyperreflexia,[32] inhibition of pupil diameter,[35] inhibition of salivary gland secretion,[34] inhibition of gut motilities,[31] and inhibition of serotonin-induced bradycardia[33]) were determined according to the literature methods.

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