Synthesis and Antimuscarinic Properties of Some N-Substituted 5-(Aminomethyl)-3,3-diphenyl-2(3*H*)-furanones

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In a study aimed toward developing new, selective antimuscarinic drugs with potential utility in the treatment of urinary incontinence associated with bladder muscle instability, a series of N-substituted 5-(aminomethyl)-3,3-diphenyl-2(3*H*)-furanones, conformationally-constrained lactone relatives of benactyzine, was prepared. The compounds were examined in several paradigms that measure muscarinic (M_1, M_2, and M_3) receptor antagonist activity. Selected members of the series that displayed potency and/or selectivity in these tests were studied for their effects on urinary bladder contraction, mydriasis, and salivation in guinea pigs. These studies revealed that incorporation of the amino functionality into an imidazole or pyrazole ring resulted in some novel, potent, and selective antimuscarinic agents. Appropriate alkyl substitution of position 2 of the imidazole strikingly affected muscarinic, particularly M_3, receptor activity and may reflect a complementary site of interaction. Some of the compounds selectively reduced bladder pressure in a cystometrogram (CMG) model without producing concomitant mydriatic and salivary effects. The separate and distinct action of several compounds of this series in these in vivo protocols suggests the possibility of subtypes of muscarinic receptors that may correspond to previously characterized molecular cloned subpopulations. In this article, structure–activity relationships for the series of substituted lactones are discussed. These studies led to the identification of (*R*)-[(2-isopropyl-1*H*-imidazol-1-yl)methyl]-4,5-dihydro-3,3-diphenyl-2(3*H*)-furanone (**23**) as a clinical candidate for treating urinary bladder dysfunction.

On the basis of the action of antagonists in radioligand binding and functional studies in various tissue preparations, three subpopulations of muscarinic receptors, M_1, M_2, and M_3, have been defined.[1] In contrast, molecular cloning studies have identified five unique sequences, m_1–m_5, coding for muscarinic receptors.[2-4] Although not unequivocally established, it is likely that the m_1 sequence corresponds to that of the M_1 receptor, m_2 to the M_2 receptor, and m_3 to the M_3 receptor. To date, unambiguous assignment of a pharmacological M_4 or M_5 receptor subtype has not been possible.[1]

An objective of the present research was to develop new, selective antimuscarinic agents. Such compounds with M_3 receptor selectivity may have advantageous therapeutic applications, for example, in treating urinary incontinence associated with bladder muscle instability. Their selectivity of action might obviate side effects, such as dry mouth (xerostomia) and blurred vision (resulting from mydriasis), which are commonly produced by nonselective muscarinic receptor antagonists.[5] As increased selectivity of action might reasonably be expected for agents that are selective for subtypes of muscarinic receptors, a series of N,N-disubstituted 5-(aminomethyl)- (**1–14**), 5-(1-imidazolylmethyl)- (**15–60**), 5-(1*H*-pyrazol-1-ylmethyl)- (**61–70**), and 5-(1,2,4-triazol-1-ylmethyl)- (**71**) 4,5-dihydro-3,3-diphenyl-2(3*H*)-furanones, as well as related bridged bicyclic quaternary salts (**72–83**), was prepared. These compounds are conformationally constrained relatives of a prototypical nonselective antimuscarinic drug, benactyzine (**84**). The lack of selectivity of antimuscarinics such as **84** may be the result of interaction of different conformations of the ligand with the different receptor subtypes. Thus, conformational restriction of the molecule as in the cyclic structures **1–83** might be anticipated to result in increased receptor selectivity.

The furanones **1–83**[6,7] were examined for muscarinic receptor subtype selectivity in tests utilizing rabbit vas deferens (nerve, M_1),[8] guinea pig atrial (cardiac, M_2),[1,6,7,9,10] and guinea pig ileal (smooth muscle, M_3)[11-15] preparations. Selected compounds with potency and/or selectivity in

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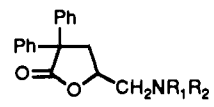
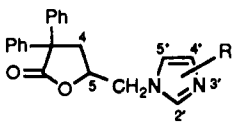
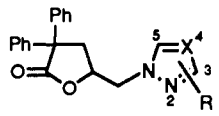


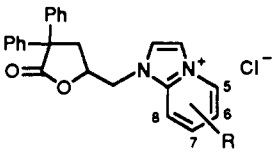
1–14 (Table I)



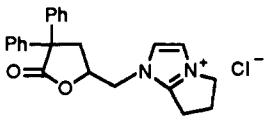
15–60 (Table II)



X = CH: 60–70 (Table III)
X = N: 71 (Table III)



72–76 (Table IV)



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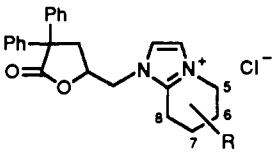
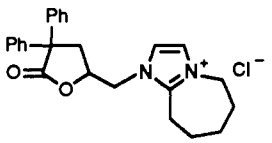
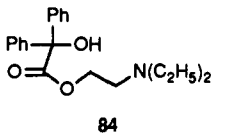


78–82 (Table IV)



83 (Table IV)



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these paradigms were examined for their in vivo effects on urinary bladder contraction, mydriasis, and salivary secretion in guinea pigs. Some of the furanones were selective for the pharmacologically defined muscarinic receptor subtypes and affected volume-induced urinary bladder contractions, as measured by cystometrogram (CMG) parameters, without concomitant production of xerostomia and mydriasis in the in vivo protocols. The results of these studies, which led to the identification of (*R*)-[(2-isopropyl-1*H*-imidazol-1-yl)methyl]-4,5-dihydro-3,3-diphenyl-2(3*H*)-furanone (**23**) as a clinical candidate for the treatment of bladder dysfunction, are described in this article.

Chemistry

Preparation of 5-[(diethylamino)methyl]-4,5-dihydro-3,3-diphenyl-2(3*H*)-furanone (**7**) from diphenylacetonitrile and 3-(diethylamino)-1,2-epoxypropane followed by hydrolysis of the derived valeronitrile and lactonization of the resulting carboxylic acid has been described previously.[16] The substituted (aminomethyl)furanones **1–13** (Table I) were prepared in a related fashion as illustrated in Scheme I (method A). Accordingly, the dilithio derivative of diphenylacetic acid (**85**) was allylated to afford 2,2-diphenyl-4-pentenoic acid (**86a**).[17–19] Alkaline bromination of **86a** resulted in cyclization to the corresponding bromomethylfuranone **87a**,[18–21] which was also prepared via **88c**.[22] Amination of **87a** with the required secondary amines gave **1–13** (Table I). The quaternary methiodide **14** (Table I) was prepared by treatment of **1** with methyl iodide.

Similar alkylation (method A) of imidazole or the appropriately substituted derivative[23–34] with **87a** gave **15–17**, **25**, **46**, and **48**; **47** was obtained by alkylation of 2-methylimidazole with **87b**, which was prepared via **86b**[17] as previously described.[18] Alternatively, as outlined in Scheme I (method B), **86a** was epoxidized and the product was hydrolytically cyclized to the lactone–alcohol **88a**.[22] This alcohol was converted to the triflate **88b**, which was utilized to alkylate the requisite substituted imidazole[23] to afford **20**, **22**, **26–29**, **36**, **37**, and **45** (Table II). The appropriately substituted imidazole was converted to its sodio derivative before alkylation with **88b** (method C) to provide **34**, **35**, and **38–40** (Table II).

4,5-Dihydro-3,3-diphenyl-5-[(2-formyl-1-imidazolyl)-methyl]-2(3*H*)-furanone (**38**) and its acetyl homologue **39** were utilized as precursors for the preparation of several

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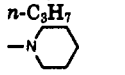
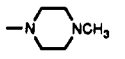
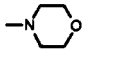
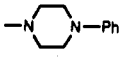
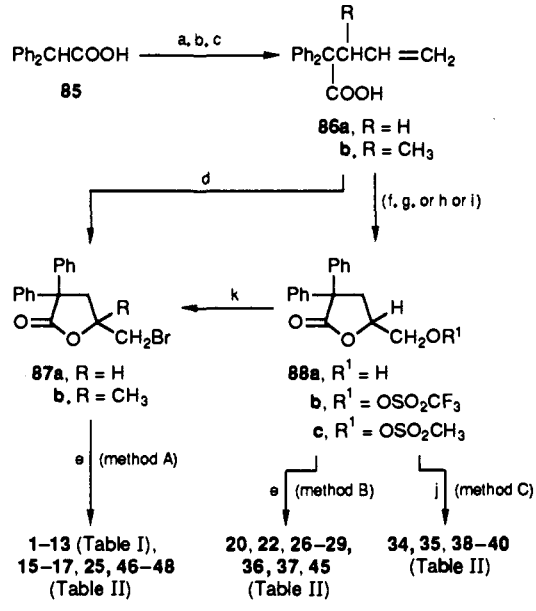
Table I. Physical and Pharmacological Data for N,N-Disubstituted 5-(Aminomethyl)-4,5-dihydro-3,3-diphenyl-2(3H)-furanones (1–14)[a]

compd	R_1	R_2	yield, %	mp, °C	formula[b]	recrystn solvent	antimuscarinic activity: vas deferens rabbit, K_b, nM ± SEM (M_1)[c]	antimuscarinic activity: atria, guinea pig, K_b, nM ± SEM (M_2)[c]	antimuscarinic activity: ileum, guinea pig, K_b, nM ± SEM (M_3)[c]
1	CH_3	CH_3	41	223–225	$C_{19}H_{21}NO_2$·HCl	EtOH–Et_2O		1764 ± 107	278 ± 43
2[d]	CH_3	CH_3	58	230–232	$C_{19}H_{21}NO_2$·HCl	EtOH–Et_2O		2641 ± 380	386 ± 52
3	CH_3	C_2H_5		oil	$C_{20}H_{23}NO_2$			1657 ± 570	471 ± 85
4	CH_3	n-C_3H_7	40	oil	$C_{21}H_{25}NO_2$			>10000	2000 (n = 2)
5	CH_3	i-C_3H_7	43	89–91	$C_{21}H_{25}NO_2$	Et_2O		1188 ± 427	299 ± 46
6	CH_3	$(CH_2)_2Ph$		oil	$C_{20}H_{27}NO_2$			>10000	913 (n = 1)
7	C_2H_5	C_2H_5	91	202–204	$C_{21}H_{25}NO_2$·HCl	EtOH–EtOAc		612 ± 29	143 ± 58
8	n-C_3H_7	n-C_3H_7	93	oil	$C_{23}H_{29}NO_2$			>10000	>1320
9	NR_1R_2 = 		90	oil	$C_{21}H_{23}NO_2$			1636 ± 252	189 ± 42
10	NR_1R_2 = 		75	253 dec	$C_{22}H_{26}N_2O_2$·2HCl·H_2O[e]	EtOH–Et_2O		3411 ± 1284	946 ± 116
11	NR_1R_2 = 		63	238–240 dec	$C_{21}H_{23}NO_3$·HCl	EtOH–EtOAc		>10000	>10000
12	NR_1R_2 = 		71	170–175 dec	$C_{27}H_{25}N_2O_2$·HCl[f]	EtOH–Et_2O		>10000	>10000
13	CH_3	CH_2Ph	67	160 dec	$C_{23}H_{25}NO_2$·HCl·0.5H_2O	EtOH–Et_2O		>10000	>10000
14	NR_1R_2 = $N^+(CH_3)_3I^-$		87	271–273	$C_{20}H_{24}INO_2$	MeOH–Et_2O		616 ± 4	203 ± 56
atropine							0.4 ± 0.1	1.5 ± 0.2	1.7 ± 0.26
oxybutynin							10 ± 1	98	9 ± 2

[a] Unless otherwise noted, all compounds were prepared as described in the Experimental Section, general method A. [b] All compounds gave elemental analyses (C, H, N, Cl) within 0.4% of theoretical values unless indicated otherwise. [c] See Experimental Section, Pharmacology, for description of method, K_b, ID_{50}, and EC_{50} definitions. [d] (R)-Enantiomer. [e] C: calcd, 59.86; found, 60.34. [f] C: calcd, 69.44; found, 69.89. [g] Prepared from 1 as described in the Experimental Section, general method E.

Scheme I. Methods A–C[a]



[a] (a) 2 equiv of n-BuLi, THF, 0 °C; (b) CH_2=$CHCH_2Br$ (**86a**) or CH_2=$CH_2CHClCH_3$ (**86b**); (c) 10% HCl; (d) $NaHCO_3$, Br_2, THF; (e) HNR_1R_2 or (R)-imidazole; (f) H_2O_2, HCOOH, 70 °C; (g) NaOH, MeOH/H_2O, 70 °C, then HCl; (h) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2 (**88a** → **88b**); (i) $(CH_3SO_2)_2O$, pyridine, CH_2Cl_2 (**88a** → **88c**); (j) (R)-imidazole, NaH, DMF; (k) LiBr, DMF (**88c** → **87a**).

other 2-substituted imidazolylmethyl lactones **30–33, 41,** and **42** listed in Table II. Accordingly, addition of methylmagnesium chloride to **38** and **39** gave the alcohols **32** and **33**. DAST fluorination of **33** provided **31**. Sodium borohydride reduction of **38** followed by similar DAST fluorination of the resulting alcohol produced **30**. Reductive amination of **38** with methylamine and dimethylamine afforded the 2-(aminomethyl) derivatives **41** and **42**, respectively.

Synthesis of the enantiomers, **18, 19, 21, 23,** and **24** was achieved as outlined in Scheme II (method D). This procedure was facilitated by the commercial availability of (R)- and (S)-2,2-dimethyl-1,3-dioxolane-4-methanol [(R)- and (S)-**89**],[35] which were sequentially converted to the S[36,37] and R tosylates[38] and to the S and R iodides [(S)- and (R)-**90**].[37] Alkylation of the dilithio dianion of diphenylacetic acid with (S)- and (R)-**90** gave (R)- and (S)-**91**, respectively. Aqueous acid hydrolysis of the acetonides (R)- and (S)-**91** produced (R)- and (S)-5-(hydroxymethyl)-4,5-dihydro-3,3-diphenyl-2(3H)-furanones [(R)- and (S)-**88a**), which were converted to the corresponding R and S triflates [(R)- and (S)-**88b**]. Triflate displacement afforded the indicated enantiomers.

The unsaturated lactone derivatives **43** and **44** (Table II) were prepared from the (bromomethyl)furanone **87a** as illustrated in Scheme III. Dehydrobromination of **87a** gave a mixture of endocyclic **92**[35] and exocyclic **93** olefins in a 7:3 ratio. The mixture was brominated to afford a 6:4 mixture of bromination products **94** and **95**. Treatment of this mixture with 2-ethyl- and 2-isopropylimidazole afforded **43** and **44** as the only basic products. The quaternary salts **49–60** (Table II) were prepared by several methods. Reaction of **15** with ethyl iodide afforded **50**. Similarly, reaction of **17, 20, 22, 35–37,** and **27** with methyl iodide provided **53–59**, respectively (method E). The methochloride **60** was prepared by similar reaction of **29** with methyl triflate followed by passage of the resulting

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(36) These isomers are commercially available from International Bio-Synthetics (IBIS), names R- and S-IPG [(R)- and (S)-α,β-isopropylideneglycerol].

(37) Nelson, W. L.; Wennerstrom, J. E.; Sankar, S. R. Absolute Configuration of Glycerol Derivatives. 3. Synthesis and Cupra A Circular Dichroism Spectra of Some Chiral 3-Aryloxy-1,2-propanediols and 3-Aryloxy-1-amino-2-propanols. *J. Org. Chem.* **1977**, *42*, 1006–1012.

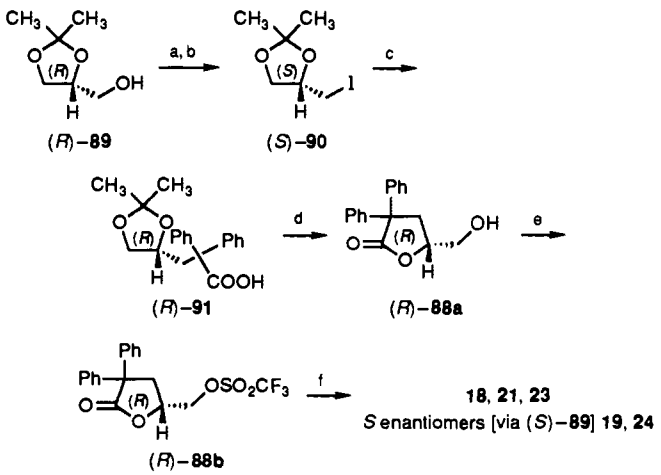
(38) Jung, M. E.; Shaw, T. J. Total Synthesis of (R)-Glycerol Acetonide and the Antiepileptic and Hypotensive Drug (−)-γ-Amino-β-hydroxybutyric Acid (GABOB): Use of Vitamin C as a Chiral Starting Material. *J. Am. Chem. Soc.* **1980**, *102*, 6304–6311.

Table II. Physical and Pharmacological Properties of 4,5-Dihydro-3,3-diphenyl-5-(1-imidazolylmethyl)-2(3*H*)-furanone and Related Compounds (15–60)

compd	R	method[a]	yield, %	mp, °C	formula	recrystn solvent	antimuscarinic activity: vas deferens rabbit, K_b, nM ± SEM (M_1)[b]	antimuscarinic activity: atria, guinea pig, K_b, nM ± SEM (M_2)[b]	antimuscarinic activity: ileum, guinea pig, K_b, nM ± SEM (M_3)[b]
15	H	A	48	146–148	$C_{28}H_{18}N_2O_2$	Et_2O		2057 ± 310	373 ± 42
16	2′-CH_3	A	51	268–270	$C_{21}H_{20}N_2O_2$·HCl·0.25H_2O	MeOH–Et_2O	59 ± 0.4	>10000	107 ± 51
17	2′-C_2H_5	A	56	266–270	$C_{21}H_{22}N_2O_2$·HCl·0.25H_2O	EtOAc–Et_2O[c]	92 ± 9	400 ± 38	50 ± 6
18[d]	2′-C_2H_5	D	67	275–278	$C_{22}H_{22}N_2O_2$·HCl·0.25H_2O	EtOAc[c]		255 ± 27	25 ± 4
19[e]	2′-C_2H_5	D	44	276.5–279	$C_{22}H_{22}N_2O_2$·HCl·0.25H_2O	EtOAc–Et_2O[c]		1288 ± 179	226 ± 16
20	2′-*n*-C_3H_7	B	57	232–234	$C_{23}H_{24}N_2O_2$·HCl	*i*-PrOH	541 ± 64	336 ± 47	18 ± 2
21[d]	2′-*n*-C_3H_7	D	41	235–236	$C_{23}H_{24}N_2O_2$·HCl	*i*-PrOH		116 ± 39	4.1 ± 0.3
22	2′-*i*-C_3H_7	B	66	250–251	$C_{23}H_{24}N_2O_2$·HCl·0.25H_2O	EtOAc–Et_2O[c]	207 ± 21	162 ± 17	30 ± 4
23[d]	2′-*i*-C_3H_7	D	82	228–230	$C_{23}H_{24}N_2O_2$·HCl	EtOAc–Et_2O[c]	133 ± 15	115 ± 7	8 ± 1
24[e]	2′-*i*-C_3H_7	D	73	228–230	$C_{23}H_{24}N_2O_2$·HCl·0.5H_2O	*i*-PrOH	1802 ± 340	1062 ± 109	228 ± 11
25	2′-*n*-C_4H_9	A	18	134–135	$C_{24}H_{20}N_2O_2$	*i*-PrOH[c]	1343 ± 306	2756 ± 477	113 ± 16
26	2′-*i*-C_4H_9	B	54	223–227	$C_{24}H_{20}N_2O_2$·HCl	EtOAc–Et_2O[c]	320	503 ± 55	489 ± 109
27	2′-*t*-C_4H_9	B	51	118–130	$C_{24}H_{20}N_2O_2$·HCl·0.25H_2O	*i*-PrOH	3 ± 0.2	20 ± 2	3.9 ± 0.8
28	2′-Ph	B	16	189–190.5	$C_{28}H_{22}N_2O_2$	*i*-PrOH		>3000	5920 (n = 1)
29	2′-CH_2Ph	B	74	256–260	$C_{27}H_{24}N_2O_2$·HCl	*i*-PrOH–Et_2O[c]	972 ± 112	>10000	223 ± 9
30	2′-CH_2F	*f*	30	240–280 dec	$C_{21}H_{19}FN_2O_2$·HCl	*i*-PrOH–Me_2CO		>10000	1045 ± 156
31	2′-$CF(CH_3)_2$	*f*	58	158–161	$C_{23}H_{23}FN_2O_2$·HCl	Me_2CO–Et_2O		1899 ± 346	168 ± 7
32	2′-$CH(OH)CH_3$	*f*	39	174–177	$C_{22}H_{22}N_2O_3$·HCl	*i*-PrOH–EtOAc	>1000	>10000	285 ± 12
33	2′-$C(OH)(CH_3)_2$	*f*	44	192–194	$C_{23}H_{24}N_2O_3$·HCl	EtOAc	1521	>1000	357 ± 24
34	2′-CH_2OH	C	44	211–213	$C_{22}H_{22}N_2O_3$·HCl	*i*-PrOH	775 ± 85	4000 ± 842	291 ± 7
35	2′-CH_2OCH_3	C	67	196–199	$C_{22}H_{22}N_2O_3$·HCl	EtOH	>1000	>10000	299 ± 10
36	2′-$CH_2OC_2H_5$	B	69		$C_{23}H_{24}N_2O_3$·HCl	EtOAc–Et_2O[c]		>3000	>1000
37	2′-$(CH_2)_2OCH_3$	B	74	235–236	$C_{23}H_{24}N_2O_3$·HCl	EtOAc–Et_2O[c]	1354 ± 340	2142 ± 47	166 ± 12
38	2′-CHO	C	68		$C_{21}H_{16}N_2O_3$	*e*			
39	2′-$COCH_3$	C	50	203–208	$C_{22}H_{20}N_2O_3$·HCl	EtOAc	>10000	>10000	4296 ± 1162
40	2′-$COOCH_3$	C	91	151–152	$C_{23}H_{20}N_2O_4$·HCl	EtOAc[c]	1642 ± 227	>10000	435 ± 11
41	2′-CH_2NHCH_3	*f*	16	185–186	$C_{23}H_{23}N_3O_2$·2HCl	*i*-PrOH	4743	>10000	166 ± 15
42	2′-$CH_2N(CH_3)_2$	*f*	80	235–236	$C_{23}H_{25}N_3O_2$·2HCl	MeOH–Et_2O[c]	532 ± 74	>10000	509 ± 21
43	4,5-dehydro-2′-C_2H_5	*f*	14	102–103	$C_{22}H_{20}N_2O_2$	Et_2O[c]		90.6 ± 13.4	8.2 ± 1.0
44	4,5-dehydro-2′-*i*-C_3H_7	*f*	13	209–211.5	$C_{23}H_{24}N_2O_2$·HCl·0.75H_2O	MeOH–Et_2O		86 ± 7	31 ± 6
45	4′-Ph	B	43	223.5–225.5	$C_{28}H_{22}N_2O_2$·HCl·0.75H_2O	Me_2CO–Et_2O	919 ± 107	>10000	140 ± 13
46	4′,5′-benzo	A	34	160–162	$C_{24}H_{20}N_2O_2$	EtOAc		>10000	1281 ± 192
47	2′,5-$(CH_3)_2$	A	54	166–167	$C_{22}H_{22}N_2O_2$·0.25H_2O	EtOAc–hexane		3005 ± 517	590 ± 96
48	2′-C_2H_5,4′-CH_3	A	30	291–292	$C_{23}H_{24}N_2O_2$·HBr	MeOH	40 ± 4	1649 ± 203	86 ± 20
49	3′-$CH_3{}^+Br^-$	G	41	148–152	$C_{21}H_{21}BrN_2O_2$·H_2O	Me_2CO[c]	355	1071 ± 141	208 ± 12
50	3′-$C_2H_5{}^+I^-$	E	36	155–160	$C_{22}H_{23}IN_2O_2$	Me_2CO[c]			229 ± 60
51	2′-CH_3,3′-$CH_3{}^+Br^-$	G	20	242.5–244	$C_{22}H_{23}BrN_2O_2$·0.5H_2O	Me_2CO[c]	38 ± 4	341 ± 18	71 ± 4
52	2′-CH_3,3′-$CH_2Ph^+Br^-$	G	75	218.5–220.5	$C_{28}H_{27}BrN_2O_2$	MeOH–Et_2O	4 ± 0.3	3.7 ± 0.5	403 ± 80
53	2′-C_2H_5,3′-$CH_3{}^+I^-$	E	30	219.5–221	$C_{23}H_{25}IN_2O_2$	*i*-PrOH	14 ± 0.4	49 ± 3	8 ± 0.6
54	2′-*n*-C_3H_7,3′-$CH_3{}^+I^-$	E	92	210–211	$C_{24}H_{27}IN_2O_2$	CH_2Cl_2[c]	16 ± 0.8	39 ± 5	23 ± 2
55	2′-*i*-C_3H_7,3′-$CH_3{}^+I^-$	E	50	216–217	$C_{24}H_{27}IN_2O_2$	Me_2CO[c]	0.6 ± 0.1	2.7 ± 0.6	1.6 ± 0.2
56	2′-$CH_2OC_2H_5$,3′-$CH_3{}^+I^-$	E			$C_{24}H_{27}IN_2O_3$	CH_2Cl_2[c]	245	1114 ± 100	253 ± 35
57	2′-$(CH_2)_2OCH_3$,3′-$CH_3{}^+I^-$	E	31	179–183	$C_{24}H_{27}IN_2O_3$·H_2O	*i*-PrOH[c]	48 ± 0.5	105 ± 70	39 ± 2
58	2′-CH_2OCH_3,$CH_3{}^+I^-$	E			$C_{23}H_{23}IN_2O_3$	CH_2Cl_2[c]		317 ± 56	40 ± 5
59	2′-*t*-C_4H_9,3′-$CH_3{}^+I^-$	E	54	213–214.5	$C_{24}H_{27}IN_2O_2$	*i*-PrOH	2.6 ± 0.3	3.4 ± 0.4	4 ± 0.9
60	2′-CH_2Ph,3′-$CH_3{}^+Cl^-$	F	56	216.5–218.5	$C_{28}H_{27}ClN_2O_2$	Me_2CO[c]	54 ± 3	767 ± 72	40 ± 2

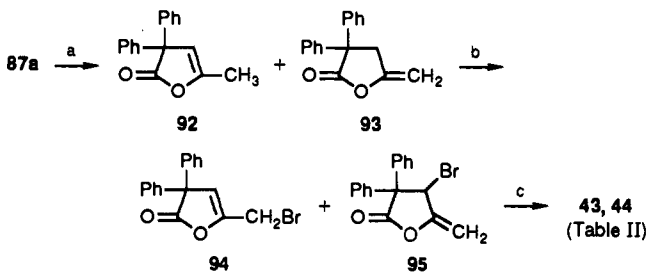
[a] See Experimental Section, general methods. [b] See Experimental Section, Pharmacology. [c] Crystallized from this solvent. [d] (*R*)-Enantiomer. [e] (*S*)-Enantiomer. [f] See Experimental Section for method of synthesis.

Scheme II. Method D[a]



[a] (a) TsCl, Et_3N, CH_2Cl_2; (b) NaI, DMF; (c) $Ph_2CHCOOH$, LDA; (d) HCl; (e) $(CF_3SO_2)_2O$, pyridine; (f) (*R*)-imidazole, KO-*t*-Bu.

Scheme III[a]



[a] (a) DBU, C_6H_6, reflux; (b) NBS, 2,2′-azobis(2-methylpropionitrile) (ABMP), CCl_4, reflux; (c) (*R*)-imidazole, Na_2CO_3, DMF, 115 °C.

triflate salt through chloride exchange resin (method F). The quaternary bromides **49**, **51**, and **52** were obtained by treatment of **87a** with 1-methylimidazole,[23] 1,2-dimethylimidazole,[23] and 1-benzyl-2-methylimidazole,[23] respectively (method G).

4,5-Dihydro-3,3-diphenyl-5-(1*H*-pyrazol-1-ylmethyl)-2(3*H*)-furanone (**61**, Table III) and its methyl-substituted derivatives (**62–64**, Table III) were prepared by alkylation of pyrazole[23] or its methylated homologues[23] with the triflate **88b** according to general method B. These pyrazoles **61–64** were treated with methyl or ethyl triflate, and the resulting quaternary triflate was passed through

Table III. Physical and Pharmacological Data for 4,5-Dihydro-3,3-diphenyl-5-(1*H*-pyrazol-1-ylmethyl)-2(3*H*)-furanones (61–70) and 4,5-Dihydro-3,3-diphenyl-5-(1,2,4-triazol-1-ylmethyl)-2(3*H*)-furanone (71)

								antimuscarinic activity		
compd	R	X	method	yield, %	mp, °C	formula	recrystn solvent	vas deferens rabbit, K_b, nM ± SEM (M_1)[b]	atria, guinea pig, K_b, nM ± SEM (M_2)[b]	ileum, guinea pig, K_b, nM ± SEM (M_3)[b]
61	H	CH	B	43	141.5–142.5	$C_{26}H_{18}N_2O_2 \cdot 0.25H_2O$	MeOH–Me_2CO	106 ± 17	>3000	50 ± 6
62	3-CH_3	CH	B	18	112–113	$C_{21}H_{20}N_2O_2$	EtOH	337 ± 26	>10000	239 ± 14
63	4-CH_3	C	B	45	100.5–102	$C_{21}H_{20}N_2O_2$	EtOH	1793 ± 255	>10000	251 ± 33
64	3,5-$(CH_3)_2$	CH	B	46	176.5–179	$C_{22}H_{22}N_2O_2 \cdot HCl$	EtOH–Me_2CO		>10000	>10000
65	$CH_3^+Cl^-$	CH	F		216–218.5	$C_{21}H_{21}ClN_2O_2 \cdot 0.25H_2O$	EtOH–Et_2O	74 ± 12	475 ± 65	100 ± 5
66	2-$CH_3^+Cl^-$, 3-CH_3	CH	F	85	214–216	$C_{22}H_{23}ClN_2O_2$	EtOH	118 ± 6	508 ± 29	142 ± 21
67	2-$CH_3^+Cl^-$, 4-CH_3	C	F	85	118–121	$C_{22}H_{23}ClN_2O_2 \cdot H_2O$	MeOH–Et_2O	101 ± 16	714 ± 83	117 ± 10
68	$C_2H_5^+Cl^-$	CH	F	80	239–241	$C_{22}H_{23}ClN_2O_2$	EtOH–Et_2O	184 (n = 2)	229 ± 47	49 ± 2
69	2-$C_2H_5^+Cl^-$, 3-CH_3	CH	F	20	213–215.5	$C_{22}H_{23}ClN_2O_2 \cdot H_2O$	EtOH–Et_2O	52 (n = 2)	112 ± 19	52 ± 3
70	2-$C_2H_5^+Cl^-$, 4-CH_3	C	F	37	240.5–242	$C_{23}H_{25}ClN_2O_2 \cdot 0.75H_2O$	EtOH–Et_2O	114 ± 22	504 ± 60	148 ± 6
71[c]	H	N	C	57	165–170	$C_{19}H_{17}N_3O_2 \cdot HCl$	MeOH	>10000	>10000	366 (n = 2)

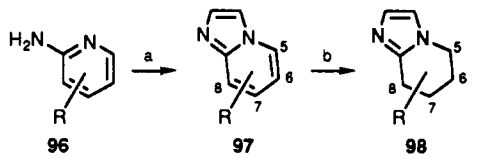
[a] See Experimental Section, general methods, for description of method. [b] See Experimental Section, Pharmacology, for description of method, K_b, ID_{50}, and ED_{50} definitions. [c] The structure of this product was not established; it may be a regioisomer.

Table IV. Physical and Pharmacological Properties of Bridged Cyclic Quaternary Salts of 4,5-Dihydo-3,3-diphenyl-5-(1-imidazolylmethyl)-2(3*H*)-furanone (72–82) and Related Compound (83)[a]

						antimuscarinic activity		
compd	R	yield, %	mp, °C	formula[b]	recrystn solvent	vas deferens rabbit, K_b, nM ± SEM (M_1)[c]	atria, guinea pig, K_b, nM ± SEM (M_2)[c]	ileum, guinea pig, K_b, nM ± SEM (M_3)[c]
72	H	73	266–268	$C_{24}H_{21}ClN_2O_2 \cdot 0.5H_2O$	EtOH	135 ± 7	289 ± 29	45 ± 4
73	5-CH_3	37	272–274	$C_{25}H_{23}ClN_2O_2 \cdot 0.5H_2O$	Me_2CO	76 ± 14	479 ± 59	40 ± 3
74	6-CH_3	96	249.5–251.5	$C_{25}H_{23}ClN_2O_2 \cdot 0.5H_2O$	*i*-PrOH	290	750 ± 48	109 ± 6
75	7-CH_3	77	249–251	$C_{25}H_{23}ClN_2O_2 \cdot 0.75H_2O$	Me_2CO	271 ± 18	1392 ± 160	59 ± 5
76	8-CH_3	67	232.5–234.5	$C_{25}H_{23}ClN_2O_2 \cdot 0.25H_2O$	Me_2CO	95 ± 6	266 ± 13	74 ± 5.4
77	H	63	245–246	$C_{23}H_{23}ClN_2O_2 \cdot 0.75H_2O$	*i*-PrOH	91 ± 6	361 ± 87	33 ± 6
78	H	58	235.5–237	$C_{24}H_{25}ClN_2O_2 \cdot 0.5H_2O$	Me_2CO	139 ± 5.1	289 ± 34	41 ± 1.5
79	5-CH_3	37	135–136.5	$C_{25}H_{27}ClN_2O_2$	Me_2CO	79 ± 4	631 ± 85	47 ± 3
80	6-CH_3	61	224–226.5	$C_{25}H_{27}ClN_2O_2 \cdot 0.75H_2O$	Me_2CO	1182	881 ± 56	170 ± 15
81	7-CH_3	48	249–251	$C_{25}H_{27}ClN_2O_2$	Me_2CO	731 ± 160	606 ± 42	204 ± 8
82	8-CH_3	44	208–227	$C_{25}H_{27}ClN_2O_2 \cdot 0.75H_2O$	Me_2CO	3.4 ± 0.1	20 ± 2	3.5 ± 0.6
83			153–155	$C_{25}H_{31}ClN_2O_2 \cdot H_2O$	MeOH			>1000

[a] All compounds were prepared by method B followed by chloride exchange of the derived triflate (method F). See Experimental Section, general methods. [b] All compounds gave elemental analyses within 0.4% of theoretical values. [c] See Experimental Section, Pharmacology, for description of method, K_b, ID_{50}, and ED_{50} definitions.

Scheme IV. Method H[a]



R = H, 5–, 6–, 7–, or 8–CH_3

[a] (a) $ClCH_2CHO$, $NaHCO_3$, H_2O; (b) Raney Ni, *n*-BuOH/EtOH, 65 °C, 60 psi.

a chloride exchange resin according to general method F to afford the quaternary chlorides **65–70** (Table III). 4,5-Dihydro-3,3-diphenyl-5-(1,2,4-triazol-1-ylmethyl)-2(3*H*)-furanone (**71** or a regioisomer, Table III) was derived from the (bromomethyl)furanone **87a** and the sodio derivative of 1,2,4-triazole[23] according to general method C.

The bridged bicyclic quaternary salts of 4,5-dihydro-3,3-diphenyl-5-(1-imidazolylmethyl)-2(3*H*)-furanone (**72–83**, Table IV) were prepared by alkylation of the appropriate imidazo[1,2-*a*]pyridine, 6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazole, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine, or 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepine (DBU) with the triflate **88b** by general method B followed by chloride exchange (method F). The required imidazo-[1,2-*a*]pyridines were obtained as indicated in Scheme IV (method H). Accordingly, the appropriate 2-aminopyridine **96** underwent cyclic condensation with chloroacetaldehyde to give the imidazo[1,2-*a*]pyridines **97**, which were hydrogenated to the corresponding 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridines **98**.

5,6,7,8-Tetrahydroimidazo[1,2-*a*]pyridine (**98**, R = H) was obtained via Finkelstein cyclization of 2-(4-chlorobutyl)imidazole.[23] Similarly, 6,7-dihydro-5*H*-pyrrolo[1,2-*a*]-imidazole precursor to **77** was derived from 2-(3-chloropropyl)imidazole.[23]

Results and Discussion

Antimuscarinic potency of the present series was evaluated pharmacologically in tests selective for M_1, M_2, and M_3 muscarinic receptor subtypes. M_1 receptor antagonist activity was evaluated by the ability of compounds to reverse the effect of a selective M_1 receptor agonist McN-A-343[40,41] on electrically-stimulated isometric contractions of rabbit vas deferens. Potency in this test is defined as an affinity constant (K_b), i.e. the calculated[42] molar concentration of compound (antagonist) required to cause a 2-fold increase in the concentration (EC_{50}) of McN-A-343 that inhibits electrically-induced twitching by 50%. M_2 receptor antagonist potency was also expressed as a K_b value. In this case, the affinity constant is the calculated molar concentration of compound that

(39) Baer, E.; Fischer, H. O. L. L(+)-Propylene Glycol. *J. Am. Chem. Soc.* **1948**, *70*, 609–610.
(40) Willfert, B.; Davidesko, D.; Timmermans, P. B. M. W. M.; van Zwieten, P. A. Differential Role of M-1 and M-2 Receptors in Sympathetic Ganglia of the Pithed Normotensive Rat in *Alpha* Adrenoceptor-Mediated Vasconstriction. *J. Pharmacol. Exp. Ther.* **1983**, *226*, 855–860.
(41) Purchased from Research Biochemicals, Inc., Natick, MA.

causes a 2-fold increase in the EC_{50} of the muscarinic agonist carbachol for inhibiting the rate of contraction of isolated guinea pig right atria.[4,5,43] M_3 receptor antagonist activity was also determined as a K_b value; it is a measure of a compound's ability to attenuate the response of guinea pig ileum muscle strips to carbachol.[5,13]

Compounds demonstrating potent and/or selective antagonism of the muscarinic receptor subtypes were further evaluated in a guinea pig cystometrogram (CMG) model in which functional detrusor muscle contraction strength was measured as peak intravesical bladder pressure (P_{ves} P). ID_{50} values are the calculated dose of antagonist that inhibits P_{ves} P by 50%.[44] The propensity of selected compounds to produce mydriasis[5,45] or to attenuate carbachol-stimulated salivation[5,46] was evaluated in guinea pigs. ED_{50} values in the mydriasis test are the calculated dose of compound that produces an increase of pupil diameter that is equal to 50% of the maximum increase that is produced by atropine. Salivation ID_{50}s are defined as the dose of antagonist that inhibits carbachol-induced salivation in 50% of guinea pigs.[5]

As indicated by the data tabulated in Table I, N,N-disubstitution of 5-(aminomethyl)-4,5-dihydro-3,3-diphenyl-2(3*H*)-furanone with alkyl or aralkyl groups (**1–8, 13**), incorporation of substituents into a saturated heterocycle (**9–12**), or quaternization (**14**) afforded compounds that were less potent than oxybutynin in tests for M_2 and M_3 receptor antagonism. As a result of their limited potency in these tests **1–14** were not studied for M_1 receptor antagonism. Similarly, as indicated by pharmacological data presented in Table II, incorporation of the N-substituent into an imidazole ring, i.e. to give **15**, resulted in only modest M_2 and M_3 receptor antagonist activity. Introduction of appropriate substituents into position 2 of the imidazole ring, however, strikingly affected antimuscarinic activity. Introduction of alkyl groups into this location increased M_3 antagonist potency in the order: isobutyl (**26**) < *n*-butyl (**25**) < methyl (**16**) < ethyl (**17**) < isopropyl (**22**) < *n*-propyl (**20**) < *tert*-butyl (**27**), whereas phenyl (**28**), benzyl (**29**), fluoroalkyl (**30, 31**), oxoalkyl (**32–40**), or aminoalkyl (**41, 42**) substituents generally decreased or had little effect on M_3 receptor antagonist potency. This general order of potency of 2-imidazole substituents is similar to that observed upon N-substitution of norepinephrine to give β-adrenoreceptor agonists.[47] Similarly, striking enantioselectivity is noted in this series of muscarinic receptor antagonists. Activity resides primarily in the *R* enantiomers (compare **18** vs **17**, **21** vs **20**, and **23** vs **22**). The achiral furanones **43** and **44** retain potent antimuscarinic activity.

Table V. Effects of Selected N-Substituted 5-(Aminomethyl)-3,3-diphenyl-2(3*H*)-furanones on Urinary Bladder Contraction, Mydriasis, and Salivary Secretion in Guinea Pigs

compd	cystometrogram, ID_{50}, mg/kg, sc[a]	mydriasis, ED_{50}, mg/kg, sc[a]	salivation inhibn, ID_{50}, mg/kg, sc[a]
1	>10[b]	91.3	61.6
7	16.2 ± 5.5[b]	60	>100
14	0.64 ± 0.06[b]	2.2	4.6
16	29 ± 8	69.2	29
17	8.5 ± 1.7	75	4.1
18	1.3 ± 0.3[b]	26.6	5.3
20	12.5 ± 5	14.9	>100
22	3.6 ± 0.6	49	152
23	1.9 ± 0.2	48	167
27	1.3 ± 0.4	0.55	0.74
43	20 ± 6	73.3	39.1
44	30	27.9	>100
53	0.27 ± 0.06[b]	0.65	0.67
54	0.9 ± 0.001	2.93	0.54
55	0.03 ± 0.01[b]	0.17	0.02
59	0.28 ± 0.05	0.48	0.29
61	>10	4.1	3.8
72	5.2 ± 0.6	11.7	8
76	1.7 ± 0.3[b]	6.23	4.42
77	2.1 ± 0.5	12.1	5.5
82	0.045 ± 0.01	0.08	0.12
atropine	0.15 ± 0.01[c]	0.05	0.14
oxybutynin	0.7 ± 0.1[d]	0.6	0.87

[a] See Experimental Section, Pharmacology for description of method, ID_{50} and EC_{50} definitions. [b] Iv administration. [c] ID_{50} = 0.01 ± 0.005 mg/kg, iv. [d] ID_{50} = 0.14 ± 0.003 mg/kg, iv.

In some instances, methyl or ethyl quaternization had little effect on overall antimuscarinic activity (compare **49** and **50** vs **15**, **51** vs **16**, and **54** vs **20**); however, in many cases methyl quaternization increased potency several fold (compare **53** vs **17**, **55** vs **22**, **56** vs **36**, **57** vs **37**, **58** vs **35**, **59** vs **27**, and **60** vs **29**). The benzyl quaternary salt **52** was unique in that it was much more effective at M_1 and M_2 receptors and less potent at M_3 receptors.

Substitutions at positions 4 and/or 5 of the imidazole ring of the imidazole lactone series had an inconsistent effect on antimuscarinic activity (compare **45** and **46** vs **15** and **48** vs **17**).

Pyrazole isomers (**61–70**) of the imidazole lactones, as indicated by the pharmacological data listed in Table III, generally retained significant antimuscarinic activity. The pyrazole analogue **61** of the imidazole **15** was noteworthy. Although it was more effective than **15** at M_3 receptors and was also active at M_1 receptors, it was ineffective at M_2 receptors. In general, the pyrazoles paralleled the imidazole series in that substitution of position 2 (**65–70**) increased potency, whereas substitutions at other positions of the ring (**62–64**) had little effect. This is consistent with the location of an M_3 receptor binding site complementary to this substitution. The 1,2,4-triazole **71**, an aza analogue of **15**, was equipotent with the imidazole at M_3 receptors, but was ineffective in the tests for M_1 and M_2 receptor antagonist activity.

Cyclic quaternary salts **72–83** of the imidazole lactones, as evidenced by the pharmacological data presented in Table IV, retained significant antimuscarinic activity. In conformity with the suggestion that a binding site complementary to a branched alkyl may be present in the muscarinic receptors **82**, which bears a structural relationship to the 2-isopropylimidazole **55**, was the most potent antimuscarinic agent in the series of cyclic quaternary salts.

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Several of the compounds, e.g. **16**, **41**, **44**, and **61**, were greater than 50-fold selective for M_3 vs M_2 receptors; however, this observation was not pursued.

On the basis of their potency as M_3 muscarinic receptor antagonists and/or their pharmacological subtype selectivity, some of the described compounds were studied in vivo for their action on urinary bladder contraction, mydriasis, and salivation. These results are tabulated in Table V. In general, ID_{50} values in the cystometrogram (CMG) model, ED_{50}s in the mydriasis test, and ID_{50}s in the salivation assay in guinea pigs were similar; however, several exceptions are noteworthy. For example, **22** was about 10- and 40-fold more potent in the CMG paradigm than in the mydriasis and salivation tests. Interestingly, this effect appears stereoselective in the CMG model, but not in the mydriasis and salivation protocols. Thus, potency of the *R* enantiomer **23** is about twice that of the racemate **22** in the former test while that of the enantiomer and racemate are nearly the same in the latter two procedures. The separation of its activity on the bladder relative to propensity to produce mydriasis and to inhibit salivation led to the selection of (*R*)-[(2-isopropyl-1*H*-imidazol-1-yl)methyl]-4,5-dihydro-3,3-diphenyl-2(3*H*)-furanone (**23**) as a clinical candidate for the treatment of bladder dysfunction. The selective pharmacological responses to **22** and **23**, coupled with the striking difference in potencies of **18**, **20**, **44**, and **55** in the in vivo tests, further suggest that mydriasis and salivation may be modulated by different muscarinic receptors distinct from the smooth muscle M_3 receptor. Although metabolic and pharmacokinetic events could play a role in the selectivity observed, the data suggest that mydriasis and salivation may be mediated by distinct receptor subtypes, e.g. M (mydriasis) and M (salivation), which may represent pharmacological counterparts of the molecular cloned m_4 and m_5 receptors. If this is the case, compounds of the present series that show selective CMG, mydriasis, and salivation activity in vivo may provide pharmacological tools for investigation of muscarinic receptor subpopulations.

Experimental Section

Melting points were determined in open glass capillaries on a Thomas-Hoover UniMelt apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Beckman FT 1300 spectrophotometer. Proton magnetic resonance (^{1}H NMR) spectra were recorded on a General Electric QE-300 spectrometer. Chemical shifts are reported in parts per million (δ) downfield relative to tetramethylsilane as standard. Chromatographic separations were performed on a silica gel column (Kieselgel 60, finer than 230 mesh, Merck). Analytical thin-layer chromatography (TLC) was carried out on precoated glass plates (silica gel, 60 F-254). TLC spots were visualized with UV light or iodine vapor. Elemental analyses were performed by Atlantic Microlabs, Inc., Atlanta, GA, and were within 0.4% of the theoretical values unless indicated otherwise.

Method A. 5-[(Dimethylamino)methyl]-4,5-dihydro-3,3-diphenyl-2(3*H*)-furanone Hydrochloride (1). Crystalline **87a** (5.0 g, 15.1 mmol) was added to a solution of 2.7 g (60 mmol) of dimethylamine in 12 mL of THF with stirring. The resulting solution was heated at 130 °C in a sealed tube for 24 h. To the mixture was added an excess of a saturated aqueous solution of sodium bicarbonate, and then it was extracted with methylene chloride. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated to give 4.4 g (99%) of an orange oil: TLC (hexane/EtOAc/Et_3N 70:25:5) R_f = 0.27; NMR ($CDCl_3$) δ 2.30 (s, 6 H), 2.60–2.72 (m, 3 H), 3.02 (dd, 1 H), 4.48 (sextet, 1 H), 7.22–7.36 (m, 10 H). A solution of the oil in 20 mL of ethanol was acidified with ethereal hydrogen chloride, ether was added to the cloud point, and the solution was cooled to 0 °C for 24 h to give **1** as colorless crystals.

Method B. 4,5-Dihydro-3,3-diphenyl-5-[[[(trifluoromethyl)sulfonyl]oxy]methyl]-2(3*H*)-furanone (88b). To a stirred solution of 5.5 mL (32.5 mmol) of trifluoromethanesulfonic anhydride in 14 mL of methylene chloride at −40 °C under argon was added 2.3 g (22 mmol) of finely powdered, oven-dried sodium carbonate. The mixture was stirred while a solution of 6.7 g (25 mmol) of **88a**[22] in 15 mL of methylene chloride was added dropwise. After being stirred at −40 °C for 2 h, the mixture was stirred for 30 min at 0 °C. Water (10 mL) was added dropwise at 0 °C to quench the reaction. The layers were separated. The organic layer was washed with brine, dried, and concentrated in vacuo to give a glassy tan solid, 9.18 g (92%), that was used for further reaction without additional purification: TLC (ethyl acetate/hexane 80:20) R_f = 0.46; NMR ($CDCl_3$) δ 2.77–2.83 (m, 1 H), 3.05–3.14 (m, 1 H), 4.51–4.71 (m, 2 H), 4.7–4.75 (m, 1 H), 7.25–7.45 (m, 10 H).

4,5-Dihydro-3,3-diphenyl-5-[(2-*n*-propylimidazol-1-yl)methyl]-2(3*H*)-furanone Hydrochloride (20). A solution of 5.2 g (13 mmol) of **88b** and 3.0 g (28 mmol) of 2-*n*-propylimidazole in 15 mL of methylene chloride under argon was heated at 120 °C in a sealed tube for 16 h. The cooled solution was poured into water, and the organic layer was separated, washed with dilute aqueous potassium carbonate solution, and brine. After being dried ($MgSO_4$), the solution was concentrated in vacuo to provide an oily residue. Chromatography of the residue over silica using methylene chloride/methanol 8:2 gave 3.0 g (64%) of a colorless oil. A solution of this oil in 2-propanol was acidified with 1 N ethereal hydrogen chloride. After cooling at 0 °C for 4 h, the colorless crystals, mp 232–234 °C, were collected: NMR (DMSO-d_6) δ 0.9 (t, J = 7.4 Hz, 3 H), 1.63–1.79 (m, 2 H), 2.79–2.89 (m, 1 H), 2.95 (t, J = 7.4 Hz, 2 H), 3.23–3.33 (m, 1 H), 4.48–4.70 (m, 3 H), 7.23–7.43 (m, 10 H), 7.61 (d, J = 1.8 Hz, 1 H), 7.66 (d, J = 1.8 Hz, 1 H); IR (KBr) 3062, 2957, 2933, 2872, 1761, 1493, 1445, 1277, 1169, 1069, 696 cm^{-1}; TLC (methylene chloride/methanol 95:5) R_f = 0.39.

Method C. 5-[(2-Carbomethoxyimidazol-1-yl)methyl]-4,5-dihydro-3,3-diphenyl-2(3*H*)-furanone Hydrochloride (40). To a stirred solution of 0.11 g (0.87 mmol) of 2-carbomethoxyimidazole[33] in 5 mL of dimethylformamide, under argon, was added 0.034 g (1.5 mmol) of sodium hydride. The mixture was stirred until solution was completed (about 1 h) and then 0.5 g (1.2 mmol) of **88b** was added. After being stirred for 20 h, the solution was concentrated in vacuo. The residual semisolid was partitioned between methylene chloride and water. The organic layer was separated, washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was applied to a preparative TLC plate (silica, 2 mm × 20 cm × 20 cm) using methanol/methylene chloride 5:95. Elution of the major spot gave 0.3 g (91%) of a colorless oil. A solution of this oil in 10 mL of ethyl acetate was acidified with 1 N ethereal hydrogen chloride to afford colorless crystals: mp 151–152 °C; NMR ($CDCl_3$) δ 2.62–2.76 (m, 1 H), 3.20–3.28 (m, 2 H), 4.07 (s, 3 H), 4.65–4.77 (m, 2 H), 5.14–5.23 (m, 1 H), 7.22–7.40 (m, 10 H), 7.56 (s, 1 H), 7.63 (s, 1 H); IR (KBr) 3432, 2519, 1756, 1745, 1460, 1447, 1270, 1172, 960, 699 cm^{-1}; TLC (methylene chloride/methanol 96:4) R_f = 0.55.

Method D. (*S*)-(−)-2,2-dimethyl-4-(iodomethyl)-1,3-dioxalane [(*S*)-90)] was obtained from (*R*)-89[35] via the *S* tosylate[36,37] as described previously for the racemate.[37] Following column chromatographic purification, (*S*)-**90** was obtained as a colorless liquid: $[\alpha]^{22}_D$ −27.0° (*c* 1.8, EtOH); NMR ($CDCl_3$) δ 1.34 (s, 3 H), 1.45 (s, 3 H), 3.11–3.17 (m, 1 H), 3.23–3.28 (dd, J = 6.3 Hz, 8.7 Hz, 1 H), 3.76–3.81 (dd, J = 6.37 Hz, 8.7 Hz, 1 H), 4.12–4.17 (dd, J = 6.3 Hz, 8.7 Hz, 1 H), 4.23–4.35 (m, 1 H); IR (neat) 2987, 2869, 1450, 1378, 1252, 1218, 1149, 1059, 845 cm^{-1}. Anal. ($C_6H_{11}IO_2$) C, H, I.

(*R*)-(−)-**90** was prepared in an identical fashion: $[\alpha]^{22}_D$ +34.0° (*c* 10.7, EtOH).

(*R*)-(+)-3-[(2,2-Dimethyl-1,3-dioxolanyl)methyl]-2,2-diphenylpropionic Acid ((*R*)-91]. To a solution of 39.2 g (0.185 mol) of diphenylacetic acid in 100 mL of tetrahydrofuran was added a solution of 310 mL (0.47 mol) of 1.5 M lithium diisopropylamide in tetrahydrofuran at 0 °C. The resulting mixture was stirred at 25 °C for 30 min and then at 70 °C for 1 h. After the mixture was cooled to 0 °C, 67.1 g (0.277 mol) of

(*S*)-**90**[37] was added dropwise. Stirring was continued at 0 °C for 30 min and then at ambient temperature for 20 h. The reaction mixture was poured into 800 mL of ice–water, and then it was extracted with ethyl acetate. After being washed with brine, the extracts were dried and concentrated to give 44.5 g (74%) of a red oil: NMR ($CDCl_3$) δ 1.23 (s, 3 H), 1.25 (s, 3 H), 2.30–2.35 (m, 1 H), 2.90–2.95 (m, 1 H), 3.15–3.30 (m, 1 H), 3.85–3.95 (m, 1 H), 7.25–7.38 (m, 10 H), This material was used without further purification.

(*S*)-(–)-**91** was prepared from (*R*)-**90**[37] using an identical procedure.

(*R*)-(+)-4,5-Dihydro-3,3-diphenyl-5-(hydroxymethyl)-2-(3*H*)-furanone [(*R*)-88a]. A solution of 44.5 g (0.136 mol) of (*R*)-**91** in 300 mL of water was acidified with concentrated hydrochloric acid. After the reaction mixture was stirred at 25 °C for 2.5 h, it was concentrated in vacuo. The residue was extracted into ether. After the extracts were washed with 10% aqueous sodium bicarbonate and brine, they were dried ($MgSO_4$) and concentrated to afford 29.1 g (80%) of a yellow liquid: TLC (ethyl acetate/methylene chloride 1:9) gave a single spot R_f = 0.40; $[\alpha]^{23}_D$ +54.6° (*c* 1.9, EtOH); NMR ($CDCl_3$) δ 2.30 (br s, 1 H), 2.85–3.01 (dd, J = 4.13 Hz, J = 2.88 Hz, 2 H), 3.69 (dd, J = 4.56 Hz, 1 H), 3.98 (dd, J = 2.80 Hz, 1 H), 4.42–4.52 (m, 1 H), 7.24–7.37 (m, 10 H); IR (neat) 3420, 2972, 2860, 1746, 1498, 1448, 1177, 1110, 699, 675 cm^{-1}. Anal. ($C_{17}H_{16}O_3$) C, H.

(*S*)-**88a** was prepared from (*S*)-**91** in an identical manner: $[\alpha]^{23}_D$ –61.6° (*c* 3.7, EtOH).

(*R*)-(+)-4,5-Dihydro-3,3-diphenyl-5[[[(trifluoromethyl)-sulfonyl]oxy]methyl]-2(3*H*)-furanone [(*R*)-88b]. To a stirred solution of 50 g (0.177 mol) of trifluoromethanesulfonic acid anhydride in 50 mL of argon at –60 °C was added 10.1 g (0.095 mol) of sodium carbonate followed by dropwise addition of a solution of 29 g (0.11 mol) of (*R*)-**88a** in 100 mL of methylene chloride. After the mixture was stirred for 2 h at –60 °C and 1 h at 0 °C, 35 mL of water was added slowly. The organic layer was separated, washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give 37.8 g (88%) of an oily product: TLC (hexane/ethyl acetate 7:3) R_f = 0.51; $[\alpha]^{23}_D$ +48.6° (*c* 18.5, $CHCl_3$) NMR δ 2.81 (dd, J = 10.14 Hz, 1 H), 3.05 (dd, J = 5.10 Hz, 1 H), 4.53–4.59 (m, 1 H), 4.60–4.64 (m, 1 H), 4.71 (dd, J = 2.19 Hz, 1 H), 7.24–7.39 (m, 10 H).

(*S*)-(–)-**88b** was prepared by the same procedure described for the *R* enantiomer: $[\alpha]^{22}_D$ –53.5° (*c* 4.76, CH_2Cl_2); $[\alpha]^{22}_D$ –48.5° (*c* 4.6, $CHCl_3$).

(*R*)-(+)-4,5-Dihydro-3,3-diphenyl-5-[(2-isopropylimidazol-1-yl)methyl]-2(3*H*)-furanone hydrochloride (23) was prepared from (*R*)-**88b** and 2-isopropylimidazole in the same manner described in general method A for the synthesis of **20**. **23** base was obtained as a pale yellow foam: TLC (methanol/methylene chloride 1:9) R_f = 0.76; $[\alpha]^{23}_D$ +36.15° (*c* 0.78, EtOH). The hydrochloride (*R*)-**23** (Table II) had the following: $[\alpha]^{21}_D$ +20.3° (*c* 0.75, EtOH); NMR ($CDCl_3$) δ 1.47–1.58 (m, 6 H), 2.68–2.72 (m, 1 H), 3.33–3.41 (m, 2 H), 4.28–4.38 (m, 1 H), 4.62–4.73 (m, 2 H), 7.20–7.37 (m, 11 H), 7.43 (d, J = 1.6 Hz, 1 H); IR (KBr) 3435, 2499, 1767, 1600, 1180, 753, 700 cm^{-1}.

24 was prepared from (*S*)-**88b** and 2-isopropylimidazole in the same manner as described for **23**.

Method E. 4,5-Dihydro-3,3-diphenyl-5-[(3-methyl-2-*n*-propylimidazol-1-yl)methyl]-2(3*H*)-furanone Iodide (54). A mixture of 2.75 g (7.6 mmol) of **20** base and 10 mL of iodomethane was heated in a sealed tube for 20 h at 120 °C. After the solution was cooled to 25 °C, it was concentrated in vacuo. Trituration of the residual solid with acetone afforded 3.5 g (92%) of colorless crystals of **54** (Table II): TLC (methylene chloride/methanol 95:5) R_f = 0.5; NMR ($CDCl_3$) δ 0.95 (t, J = 7.2 Hz, 3 H), 1.52–1.68 (m, 2 H), 2.82–2.94 (m, 1 H), 2.95–3.08 (m, 2 H), 3.26–3.36 (m, 1 H), 3.80 (m, 3 H), 4.48–4.70 (m, 3 H), 7.24–7.44 (m, 10 H), 7.64–7.70 (m, 2 H); IR (KBr) 3090, 3059, 2982, 2933, 1756, 1226, 1175, 1154, 707, 696 cm^{-1}.

This procedure was also employed to prepare **14** from **1** and **50** from **15**.

Method F. 4,5-Dihydro-3,3-diphenyl-5-[(2-methyl-1*H*-pyrazol-1-yl)methyl]-2(3*H*)-furanone Chloride Hydrate (65). To a solution of 0.30 g (0.94 mmol) of **61** in 3 mL of methylene chloride under argon was added dropwise 0.10 mL (0.89 mmol) of methyl trifluoromethanesulfonate. The mixture was stirred at 25 °C for 16 h. The precipitated white solid was filtered, washed with methylene chloride, and dried over P_2O_5 in vacuo. A solution of this solid quaternary methyl triflate in methanol was passed through a 10-g column of Amberlite IRA-400 (Cl) resin to afford 0.14 g of colorless crystalline solid: TLC (silica, methylene chloride/methanol 95:5) R_f = 0.10. Recrystallization from ethanol/ether gave 0.11 g (32%) of colorless crystalline **65**: NMR (CD_3OD) δ 2.82 (dd, J = 13 Hz, 1 H), 4.15 (s, 3 H), 4.74–4.81 (m, 1 H), 4.92–5.0 (m, 2 H), 6.89 (t, J = 3 Hz, 1 H), 7.21–7.45 (m, 10 H), 8.56 (d, 2 H); IR (KBr) 3443, 3389, 3119, 3080, 1758, 1643, 1445, 1306, 1172, 1093, 971, 748, 704, 645 cm^{-1}.

Method G. 4,5-Dihydro-3,3-diphenyl-5-[(3-methylimidazol-1-yl)methyl]-2(3*H*)-furanone Bromide (49). A solution of 1.35 g (4.1 mmol) of **87a** and 0.34 g (4.1 mmol) of 1-methylimidazole in 5 mL of ether was heated for 16 h at 100 °C under argon in a sealed tube. The resulting mixture was concentrated to leave an oily residue which crystallized from acetone: NMR (DMSO-d_6) δ 2.8 (dd, 1 H), 3.3 (dd, 1 H), 3.86 (s, 3 H), 4.6 (m, 3 H), 7.2–7.4 (m, 10 H), 7.7 (dd, 2 H), 9.1 (s, 1 H).

Method H. 8-Methylimidazo[1,2-*a*]pyridine (97, R = 8-CH_3). A mixture of 25.4 mL (0.2 mol) of a 50% aqueous solution of chloroacetaldehyde, 18.8 g (0.2 mol) of 2-amino-3-picoline in 150 mL of water, and 16.8 g (0.2 mol) of sodium bicarbonate was stirred at ambient temperature for 72 h. The mixture was brought to pH 1 by addition of concentrated hydrochloric acid. After the mixture was stirred for 30 min, aqueous 40% sodium hydroxide solution was added to bring the pH to 10. The solution was saturated with sodium chloride and the resulting mixture was extracted with ether. The ether extracts were dried ($MgSO_4$) and concentrated. The product was purified by distillation to give 16.3 g (62%) of a colorless liquid: bp 68–70 °C (0.1 Torr).

5,6,7,8-Tetrahydro-8-methylimidazo[1,2-*a*]pyridine (98, R = 8-CH_3). A mixture of 2.0 g (15.1 mmol) of 8-methylimidazo-[1,2-*a*]pyridine and 2 teaspoonfuls of Raney nickel 2800 in 40 mL of 1-butanol was hydrogenated at 65 °C and an initial pressure of 60 psi of hydrogen for 24 h. The mixture was filtered and the filtrate was concentrated in vacuo. Residual liquid was chromatographed (silica, 40 g, methylene chloride/methanol 98:2) to give 1.1 g of an oily product: NMR ($CDCl_3$) δ 1.32 (d, J = 7.4 Hz, 3 H), 1.42–1.58 (m, 1 H), 1.82–2.0 (m, 1 H), 2.0–2.12 (m, 2 H), 2.82–2.99 (m, 1 H), 3.80–4.02 (m, 2 H), 6.74 (d, J = 1.5 Hz, 1 H), 6.97 (d, J = 1.5 Hz, 1 H); analytical TLC (methylene chloride/methanol 95:5) R_f = 0.46.

The 5-, 6-, and 7-methyl isomers (**98**, R = 5-CH_3, 6-CH_3, and 7-CH_3) were prepared from **97**, R = 5-CH_3, 6-CH_3, and 7-CH_3, respectively, by the same general procedure.

2-(3-Chloropropyl)imidazole. Hydrogen chloride was slowly bubbled into a solution of 31 g (0.3 mol) of 3-chlorobutyronitrile and 17.4 mL (0.3 mol) of ethanol at 25 °C under argon. After the solution was saturated, it was allowed to stand at 25 °C for 5 days. Addition of ether (200 mL) precipitated 16.6 g of solid ethyl 3-chloropropanimidate. The crude imidate (16.6 g, 0.112 mol) was stirred in 20 mL of methanol, and after addition of 13.0 g (0.123 mol) of aminoacetaldehyde dimethyl acetal, the mixture was allowed to stand at 25 °C for 3 days. Concentration of the solution in vacuo at 88 °C afforded 19.6 g of a residual liquid to which were added 30 mL of concentrated hydrochloric acid and 20 mL of water. The mixture was concentrated in vacuo at 88 °C to give 14.2 g of a dark viscous liquid. A suspension of this residue in 10 mL of water was adjusted to pH 10 with solid potassium carbonate. Following removal of the water in vacuo, the residue was stirred with 200 mL of ethanol. The resulting mixture was filtered and the filtrate was concentrated in vacuo to give a hygroscopic solid that was carried on to 6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazole without purification.

2-(4-Chlorobutyl)imidazole was prepared from 4-chlorobutyl cyanide by the same procedure described for the synthesis of 2-(3-chloropropyl)imidazole. The product was obtained as a colorless liquid that was carried on to 5,6,7,8-tetrahydroimidazo-[1,2-*a*]pyridine without purification.

5,6,7,8-Tetrahydroimidazo[1,2-*a*]pyridine (98, R = H). To a solution of 11.0 g (69.3 mmol) of 2-(4-chlorobutyl)imidazole in 90 mL of 2-butanone and 10 mL of dioxane were added 12.0 g (80.0 mmol) of sodium iodide and 5.0 g (36.2 mmol) of potassium carbonate. After the mixture was stirred and refluxed for 20 h, it was cooled to 25 °C and filtered. The filtrate was concentrated

in vacuo. The residue was dissolved in 40 mL of methanol, 10 mL of propylene oxide was added, and the solution was stirred at 25 °C for 20 h. Concentration of the solution in vacuo afforded a liquid which was chromatographed (silica, 300 g, methylene chloride/methanol 98:2) to give 2.2 g of a colorless liquid which was identified by NMR but was not purified further before being alkylated.

6,7-Dihydro-5*H*-pyrrolo[1,2-*a*]imidazole was prepared from 2-(3-chloropropyl)imidazole by the same procedure described for **98** (R = H). It was sublimed at 80 °C (0.12 Torr) to provide the precursor to **77** as colorless hygroscopic crystals.

4,5-Dihydro-3,3-diphenyl-5-[(2-(hydroxymethyl)-1*H*-imidazol-1-yl)methyl]-2(3*H*)-furanone. Sodium borohydride (0.8 g, 21.1 mmol) was added in portions to a stirred solution of 1.77 g (5.1 mmol) of **38** in a mixture of 10 mL of methylene chloride and 25 mL of methanol at 0 °C. The mixture was stirred at 0 °C for 45 min and at 25 °C for 2 h, and then the reaction was quenched by addition of aqueous ammonium chloride. The layers were separated, and the aqueous part was extracted with methylene chloride. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residual solid was triturated with ethyl acetate and dried to give 1.0 g (56%) of crystals: NMR ($CDCl_3$) δ 2.51–2.59 (m, 1 H), 3.06–3.17 (m, 1 H), 4.23–4.68 (m, 5 H), 6.72 (d, J = 12 Hz, 1 H), 6.98 (d, J = 1 Hz, 1 H), 7.13–7.40 (m, 10 H).

4,5-Dihydro-3,3-diphenyl-5-[[2-(fluoromethyl)-1*H*-imidazol-1-yl]methyl]-2(3*H*)-furanone Hydrochloride (30). (Diethylamido)sulfur trifluoride (DAST) (0.45 mL, 3.41 mmol) was added dropwise to a stirred solution of 1.0 g (2.87 mmol) of 4,5-dihydro-3,3-diphenyl-5-[[2-(hydroxymethyl)-1*H*-imidazol-1-yl]-methyl]-2(3*H*)-furanone in 50 mL of methylene chloride under argon. After the reaction mixture was stirred at 25 °C for 4 h, 20 mL of water was added. The organic layer was separated, washed with brine, dried, and concentrated. The residue was chromatographed (30 g silica gel, methylene chloride/methanol 99:1) to give 0.3 g (30%) of a solid. A solution of the solid in 2-propanol/acetone was acidified with hydrogen chloride to give a colorless crystalline solid: NMR ($CDCl_3$) δ 2.50–2.58 (m, 1 H), 3.00–3.06 (m, 1 H), 4.19–4.44 (m, 2 H), 4.50–4.76 (m, 1 H), 5.40 (d, J = 2 Hz, 1 H), 5.56 (d, J = 2 Hz, 1 H), 7.09–7.40 (m, 12 H); IR (KBr) 3437, 2864, 1758, 1172, 1056 cm^{-1}; TLC (methylene chloride/methanol 98:2) R_f = 0.30.

4,5-Dihydro-3,3-diphenyl-5-[[2-(1-hydroxyethyl)-1*H*-imidazol-1-yl]methyl]-2(3*H*)-furanone Hydrochloride (32). A 3 M solution of methylmagnesium chloride in tetrahydrofuran (3.9 mL, 11.7 mmol) was added dropwise to a stirred solution of 3.84 g (11.1 mmol) of **38** in 100 mL of tetrahydrofuran under argon at 0 °C. After the addition was completed, the reaction mixture was stirred at 0 °C for 20 min and then it was stirred at ambient temperature for 5 h. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride and 5 mL of water. The organic layer was separated, washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed (silica gel, 100 g, methylene chloride/methanol 98:2 to 97:3) to give 1.5 g (39%) of a colorless liquid. A solution of this base in 2-propanol was acidified with hydrogen chloride and ether was added to afford a crystalline product which was recrystallized to give **32**: NMR ($CDCl_3$) δ 2.47–2.55 (m, 1 H), 3.14–3.20 (m, 1 H), 4.60–4.63 (m, 2 H), 4.92–4.96 (m, 1 H), 7.15–7.38 (m, 12 H).

4,5-Dihydro-3,3-diphenyl-5-[[2-(1-hydroxy-1-methylethyl)-1*H*-imidazol-1-yl]methyl]-2(3*H*)-furanone hydrochloride (**33**) was prepared from **39** by the same procedure described for conversion of **38** and **32**: NMR (DMSO-d_6) δ 1.59 (s, 3 H), 1.63 (s, 3 H), 2.82–2.89 (m, 1 H), 3.25–3.28 (m, 1 H), 4.73–4.79 (m, 3 H), 7.21–7.43 (m, 10 H), 7.61–7.70 (m, 2 H); IR (KBr) 3134, 3131, 1769, 1172, 1159, 691 cm^{-1}; TLC (methylene chloride/methanol 98:2) R_f = 0.37.

4,5-Dihydro-3,3-diphenyl-5-[[2-(1-fluoro-1-methylethyl)-1*H*-imidazol-1-yl]methyl]-2(3*H*)-furanone hydrochloride (**31**) was prepared by DAST fluorination of **33** by the same procedure described for conversion of the corresponding primary alcohol to **30**: NMR (DMSO-d_6) δ 1.84 (d, J = 4 Hz, 3 H), 1.91 (d, J = 4 Hz, 3 H), 2.85–2.93 (m, 1 H), 3.27–3.32 (m, 1 H), 4.61–4.72 (m, 3 H), 7.19–7.42 (m, 10 H, 7.68 (d, J = 1 Hz, 1 H), 7.79 (d, J = 1 Hz, 1 H); IR (KBr) 3432, 3062, 2661, 1779, 1172 cm^{-1}; TLC (methylene chloride/methanol 96:4) R_f = 0.35.

4,5-Dihydro-3,3-diphenyl-5-[[(methylsulfonyl)oxy]methyl]-2(3*H*)-furanone (88c). Triethylamine (17.6 mL, 0.126 mol) was added dropwise to a solution of 30.7 g (0.114 mol) of **88a** in 33 mL of tetrahydrofuran and 10 mL of methylene chloride under argon at 0 °C. Methanesulfonyl chloride (13.6 g, 0172 mol) was added dropwise to the vigorously stirred mixture. The mixture was stirred for 1.5 h at 0 °C and then for 16 h at 25 °C. After being diluted with 100 mL of ether and 100 mL of ethyl acetate, the mixture was poured into water. The organic layer was separated, washed with water, dried (Na_2SO_4), and concentrated. Ether was added to the residual semisolid to give 29.9 g (67%) of crystalline **88c**: NMR ($CDCl_3$) δ 3.01–3.04 (m, 1 H), 3.07 (dd, J = 4.6 Hz, J = 13.8 Hz, 1 H), 3.09 (s, 3 H), 4.38 (dd, J = 6.9 Hz, J = 15 Hz, 1 H), 4.52 (dd, J = 4.6 Hz, J = 13.8 Hz, 1 H), 4.6–4.68 (m, 1 H), 7.27–7.4 (m, 10 H).

5-(Bromomethyl)-4,5-dihydro-3,3-diphenyl-2(3*H*)-furanone (87a). A stirred mixture of 25.2 g (0.072 mol) of **88c** and 12.7 g (0.146 mol) of lithium bromide in 200 mL of dimethylformamide was heated at 80 °C for 3 h. After the mixture was allowed to cool to 25 °C, it was extracted with ether. The ether extracts were dried (Na_2SO_4) and concentrated to give 22.15 g (92%) of **87a** as colorless crystals, mp 84–85 °C.

3,3-Diphenyl-5-methyl-2(3*H*)-furanone (92) and 3,3-Diphenyl-5-methylene-2(3*H*)-furanone (93). To a stirred solution of 22.0 g (0.066 mol) of **87a** in 65 mL of benzene under argon 10.5 mL (0.07 mol) of 1,8-diazabicyclo[5.4.0]undec-7-ene was added dropwise. The stirred mixture was heated at 80 °C for 16 h. Solids were filtered from the cooled mixture, and the filtrate was added to a mixture of 150 mL of 10% hydrochloric acid and 200 mL of ether. The layers were separated, and the organic layer was washed with 10% hydrochloric acid, a saturated aqueous solution of sodium bicarbonate, and water, dried (Na_2SO_4), and concentrated to give 16.2 g (97%) of a liquid: NMR ($CDCl_3$) δ 2.02 (s), 2.08 (s), 3.54 (s), 3.64 (d), 4.41 (m), 4.78 (s), 5.69 (br s), 7.08–7.34 (m). Integration of the NMR spectrum and comparison of the resonances at δ 4.78 (=CH_2) and δ 5.69 (=CH—) indicated about 70% of **92** and 30% of **93**. The mixture had TLC (ethyl acetate) R_f = 0.64; it was employed for further reaction without purification.

5-(Bromomethyl)-3,3-diphenyl-2(3*H*)-furanone (94) and 4-Bromo-3,3-diphenyl-5-methylene-2(3*H*)-furanone (95). To a stirred solution of 4.3 g (17 mmol) of the 70:30 mixture of **92** and **93** in 40 mL of carbon tetrachloride under argon was added 4.62 g (26 mmol) of *N*-bromosuccinimide followed by 50 mg (0.3 mmol) of 2,2'-azobis(2-methylpropionitrile). After being heated at 80 °C for 16 h, the mixture was poured into water and extracted with ether. The extracts were washed with water, dried (Na_2SO_4), and concentrated to afford a liquid: NMR ($CDCl_3$) δ 1.5 (br m), 1.72 (s), 2.05 (s), 2.77 (s), 3.62 (d), 4.13 (s), 4.2–4.5 (m), 5.9 (s), 6.09 (s), 6.25 (s), 6.26 (s), 7.05–7.4 (m). Integration of the NMR signals indicated the mixture to consist of about 60% of **94** and 40% of **95**.

3,3-Diphenyl-5-[(2-isopropyl-1*H*-imidazol-1-yl)methyl]-2-(3*H*)-furanone Hydrochloride Hydrate (44). A mixture of 6.5 g (19 mmol) of approximately 60:40 **94**:**95**, 3.25 g (29 mmol) of 2-isopropylimidazole, and 1.0 g (9 mmol) of sodium carbonate in 25 mL of dimethylformamide under argon was heated at 115 °C for 10 h in a sealed tube. After the mixture was poured into 75 mL of a saturated aqueous solution of sodium bicarbonate, it was extracted with ether. The extracts were washed with water, dried (Na_2SO_4), and concentrated to leave a dark semisolid: TLC (ethyl acetate) R_f = 0.1, 0.26, 0.35, and 0.8. The product at R_f = 0.26 was isolated by column chromatography (Merck 230–400-mesh silica gel, hexane/ethyl acetate 9:1 to ethyl acetate) as 0.88 g (13%) of a viscous liquid: NMR ($CDCl_3$) δ 1.21–1.35 (m, 6 H), 2.97–3.02 (m, 1 H), 4.83 (d, 2 H), 5.71 (t, J = 1.5 Hz, 1 H), 6.89 (d, 1 H), 7.02 (d, 1 H), 7.20–7.33 (m, 10 H). A solution of this product in methanol was acidified with hydrogen chloride and ether was added to give the crystalline **44**: NMR (DMSO-d_6) δ 1.26 (d, 6 H), 3.36 (br s, H_2O), 3.44–3.56 (m, 1 H), 5.41 (s, 2 H), 6.64 (s, 1 H), 7.21–7.39 (m, 10 H), 7.69 (d, 2 H); IR (KBr) 3412, 3055, 2980, 2936, 2697, 1797, 1600, 1509, 1494, 1448, 1134, 1085, 949, 763, 699 cm^{-1}; TLC (ethyl acetate) R_f = 0.4.

3,3-Diphenyl-5-[(2-ethyl-1*H*-imidazol-1-yl)methyl]-2(3*H*)-furanone (43) was prepared from 2-ethylimidazole and approximately 60:40 94:95 by the same procedure described for 44: NMR ($CDCl_3$) δ 1.4 (t, 3 H), 2.6 (q, 2 H), 4.8 (s, 2 H), 5.7 (s, 1 H), 6.95 (d, 1 H), 7.01 (d, 1 H), 7.2–7.4 (m, 10 H); IR (KBr) 2975, 1794, 1087 cm^{-1}.

Pharmacology. Rabbit Vas Deferens (M_1 Receptor Antagonism). As described previously,[5-9] electrically stimulated isometric contractions of the prostatic portion of rabbit vas deferens were dose dependently antagonized by McN-A-343[40,41] in the absence or presence of increasing concentrations of the test compounds. The EC_{50} of McN-A-343 was defined as the concentration that inhibited electrically induced twitching by 50%. Affinity constants (K_b), i.e. the molar concentration of antagonist required to produce a 2-fold increase in the McN-A-343 ED_{50} value, are based on at least three determinations unless otherwise indicated and were calculated by Schild analysis.[5,42]

Guinea Pig Atrial Muscle (M_2 Receptor Antagonism).[5] Isolated guinea pig right atria prepared as described[43] were placed in Krebs–Henseleit buffer and cumulative concentration–rate response curves to carbachol were obtained before and after addition of increasing concentrations of test compound. Responses were expressed as a percentage of the maximum inhibition of atrial rate induced by carbachol in absence of antagonist. The molar concentration of antagonist that produced a 2-fold increase in the EC_{50} value for carbachol alone, i.e. the affinity constant (K_b) values, are based on an $n = 3$, unless otherwise indicated, and were calculated by Schild analysis.[42]

Guinea Pig Ileal Muscle (M_3 Receptor Antagonism). Longitudinal guinea pig ileum muscle strips were prepared and suspended in oxygenated Krebs buffer as previously described[5] for guinea pig bladder detrusor muscle strips. Antimuscarinic activity was determined from concentration–response curves to carbachol in the absence or presence (5-min incubation) of increasing concentrations of antagonist. Contractile responses were expressed as a percentage of the maximum contraction elicited by carbachol in the absence of antagonist. Affinity constants (K_b), based on an $n = 3$, unless otherwise indicated, were calculated by Schild analysis.[42]

In vivo cystometrogram (CMG) in urethane-anesthetized guinea pig was performed as described previously.[44] ID_{50} values, calculated by probit analysis, were defined as the dose of the test compound that inhibited peak intravesical bladder pressure (P_{ves} P) by 50%.

Guinea pig mydriasis was measured as described previously[5] in a modification of a procedure employed for rats.[45] ED_{50} values were calculated from dose–response relationships by linear regression and are defined as the dose eliciting 50% of maximal dilation.

Guinea pig salivation was measured by procedures modified[5] from previously described methods.[46] Briefly, guinea pigs were given various sc doses of the antagonist and after 30 min 0.1 mg/kg of carbachol was administered, ip. After 5–10 min the animals were evaluated for their ability to respond to the agonist. ID_{50} values, i.e. the dose of antagonist that inhibited salivation in 50% of the animals, were calculated from dose–response curves using probit analysis.

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