Antimuscarinic 3-(2-Furanyl)quinuclidin-2-ene Derivatives: Synthesis and Structure−Activity Relationships

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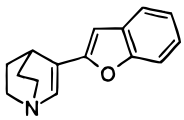
A series of 25 derivatives of the muscarinic antagonist 3-(2-furanyl)quinuclidin-2-ene (**4**) was synthesized and evaluated for muscarinic and antimuscarinic properties. Substitution at all three positions of the furan ring has been investigated. The affinities of the new compounds were determined by competition experiments in homogenates of cerebral cortex, heart, parotid gland, and urinary bladder from guinea pigs using (−)-[^{3}H]-3-quinuclidinyl benzilate as the radioligand, and the antimuscarinic potency was determined in a functional assay on isolated guinea pig urinary bladder using carbachol as the agonist. Several of the novel derivatives displayed high muscarinic affinities. Whereas the affinity of lead compound **4** for cortical muscarinic receptors is moderate (K_i = 300 nM), it is much higher for the 5-methyl (**48**; K_i = 12 nM), 5-ethyl (**52**; K_i = 7.4 nM), 5-bromo (**33**; K_i = 6.4 nM), and 3-phenyl (**49**; K_i = 2.8 nM) substituted derivatives. The substituent-induced increases in affinity do not appear to be additive as a 5-bromo-3-phenyl (**54**), and a 5-methyl-3-phenyl (**55**) substitution pattern only slightly increases affinity (K_i = 1.55 and 2.39 nM, respectively). The conformational preferences of the 3-phenyl (**49**) and 5-phenyl (**51**) derivatives were studied by X-ray crystallography and molecular mechanics calculations. Because of the observed high affinity of **49**, a series of 16 meta- and para-substituted analogues of **49** was synthesized and tested. The *m*-hydroxy derivative (**68**) exhibited more than 10-fold improvement in affinity as compared to **49**. The structure−activity relationships of the new series are well described with QSAR and CoMFA models.

Introduction

Recently, we explored the ability of achiral quinuclidin-2-ene derivatives, substituted with various mono- and bicyclic aromatic rings, to bind to muscarinic receptors.[1,2] In this series, 3-(benzofuran-2-yl)quinuclidin-2-ene (**1**) is the most potent muscarinic antagonist, having affinities (K_i values) for muscarinic receptors ranging from 9.6 nM (cortex) to 67 nM (urinary bladder) in the various tissue preparations studied.[1] The most potent analogue with a monocyclic heteroaromatic ring was the 2-thienyl-substituted derivative **2** (K_i = 290 nM), but the 2-furanyl derivative **4** also had a similar affinity for cortical muscarinic receptors (K_i = 300 nM).



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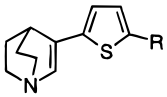
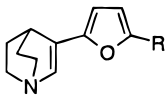


2: R = H
3: R = Me



4: R = H
48: R = Me

Attempts to increase the affinity of **1** by introduction of various substituents in the benzofuranyl ring did not improve the affinity for muscarinic receptors.[2] In order to investigate if substitution in the heteroaromatic ring might enhance the affinity of the 2-thienyl (**2**) and 2-furanyl (**4**) derivatives, we prepared the 5-methyl-substituted analogues **3** and **48**. The introduction of a 5-methyl substituent in **4**, producing **48**, led to a 25-fold increase in affinity, whereas a 5-methyl substituent (producing **3**) caused only a 4-fold enhancement of the muscarinic affinity in the 2-thienyl derivative **2** (Table 3). These findings led to the present study of structure−activity relationships (SAR) of substituted derivatives of **4**. An additional aim of this study was to extend the SAR derived from a series of substituted benzofuranyl derivatives[2] by exploring areas in space not previously studied.

The new compounds were investigated for their ability to displace (−)-[^{3}H]-3-quinuclidinyl benzilate [(−)-[^{3}H]-QNB] from muscarinic receptors in the cerebral cortex, heart, parotid gland, and urinary bladder from guinea pigs. In addition, the antimuscarinic potencies were evaluated in a functional assay on the isolated guinea pig bladder.

Chemistry

Synthesis. The syntheses of the substituted 3-(2-furanyl)quinuclidin-2-ene derivatives required access to a number of different 2-bromofuran derivatives (**5**−**17**, Table 1). The preparations of furan derivatives **5**,[3] **6**,[4] **9**,[3,4] **14**,[5] **15**,[6] **16**,[7] and **17**[8] have been described previously.

2-Bromo-3-furoic acid (**6**) was prepared by treating 3-furoic acid with LDA[9] and 1,2-dibromotetrafluoroethane[10] (Scheme 1). The ester derivatives **7** and **14** were obtained by esterification of the corresponding acids, using dimethyl sulfate in the presence of K_2CO_3 (**7**;

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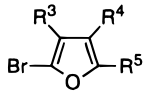
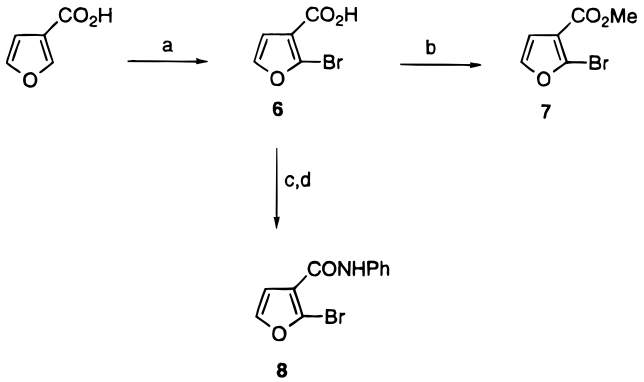
Table 1. Yields and Physical Data of Some Bromofuran Derivatives



compd	R^3	R^4	R^5	prepn method[a]	% yield	mp, °C	recrystn solvents[b]	formula
5	H	H	H	*c*	66	oil		C_4H_3BrO
6	CO_2H	H	H	*a*	32	160−162[d]	A	$C_5H_3BrO_3$
7	CO_2Me	H	H	*a*	92	46−48		$C_6H_5BrO_3$
8	CONHPh	H	H	IA	84	127−128		$C_{11}H_8BrNO_2$
9	H	CO_2H	H	*e*	59	130−133[f]	B	$C_5H_3BrO_3$
10	H	CO_2Me	H	*a*	24	37−38		$C_6H_5BrO_3$
11	H	CONHPh	H	IA	78	150−152		$C_{11}H_8BrNO_2$
12	H	$CONH_2$	H	IB	44	167−169	B	$C_5H_4BrNO_2 \cdot {}^1/_2H_2O$
13	H	CN	H	II	83	50−52		C_5H_2BrNO
14	H	H	CO_2Me	*a*	84	62−64[g]		$C_6H_5BrO_3$
15	H	H	CONHPh	IA	59	143−144[h]	C	$C_{11}H_8BrNO_2$
16	H	H	$CONH_2$	IB[i]	82	144−146[j]	B	$C_5H_4BrNO_2$
17	H	H	CN	II[k]	65	oil		C_5H_2BrNO

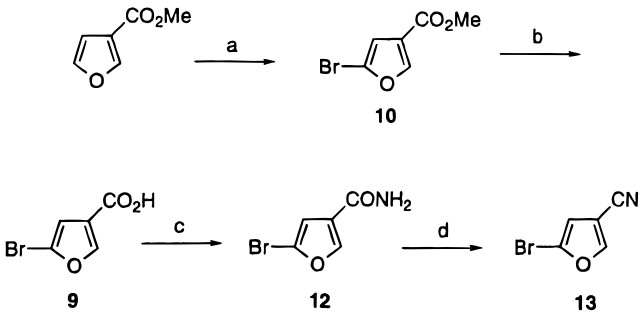
[a] See the Experimental Section. [b] A: MeOH/H_2O. B: H_2O/EtOH. C: MeOH. [c] Prepared according the literature procedure, ref 3. [d] Lit.[4] mp 158 °C. [e] Prepared according the literature procedure, ref 3a. [f] Lit.[4] mp 130 °C. [g] Lit.[5b] mp 62.5−63.5 °C. [h] Lit.[6] mp 143−144 °C. [i] Prepared according the literature procedure, ref 7. [j] Lit.[7] mp °C 145−146.5. [k] Prepared according the literature procedure, ref 8.

Scheme 1[a]



[a] Reagents: (a) (i) 2.2 equiv of LDA, THF, −78 °C, (ii) 1,2-dibromotetrafluoroethane; (b) Me_2SO_4, K_2CO_3, acetone; (c) $SOCl_2$, benzene, reflux; (d) aniline, Et_3N.

Scheme 2[a]



[a] Reagents: (a) Br_2, 1,2-dichloroethane, reflux; (b) (i) 20% aqueous NaOH/MeOH, (ii) concentrated HCl; (c) (i) $SOCl_2$, benzene, reflux, (ii) NH_4OH; (d) $POCl_3$, 1,2-dichloroethane, NaCl.

Scheme 1) or iodomethane in the presence of Cs_2CO_3 (**14**),[11] respectively. The amide derivatives **8**, **11**, **12**, **15**, and **16** were prepared by treatment of the appropriate carboxylic acid derivative with thionyl chloride, followed by addition of aniline (method IA)[6] or ammonium hydroxide (method IB).[7]

Bromination of methyl furan-3-carboxylate gave a mixture of mono- and dibromo derivatives[3a] from which the monobromo derivative **10** was obtained by distillation (Scheme 2). Dehydration of the primary amides **12** and **16**, using phosphorus oxychloride (method II), provided the cyano derivatives **13** (Scheme 2) and **17**.[8]

The syntheses of the novel 3-(2-furanyl)quinuclidin-2-ene derivatives (Table 2) are outlined in Schemes 3−9. 3-Hydroxyquinuclidine derivatives **20**, **21**, and **23**−**29** were synthesized by addition of quinuclidin-3-one to the appropriate 2-lithiofuranyl derivative, generated by deprotonation with LDA (method IIIA) or *n*-BuLi (method IIIB; Scheme 3).[12] Most of the alcohols (**20**, **22**, **24**−**27**, and **30**) were dehydrated to the corresponding quinuclidin-2-ene analogues (**31**, **32**, **34**, **48**, and **51**−**53**) by heating in concentrated formic acid (method IVA; Scheme 3).[1] The 5-bromo (**23**), 3-cyano (**28**), and 5-cyano (**29**) derivatives were unstable under acidic conditions. Therefore, these derivatives were dehydrated by heating in the presence of Burgess' reagent[13] in THF or benzene (method IVB), giving **33**, **43**, and **45** (Scheme 3).

The 4-bromofuranyl derivative **22** was prepared from the TMS-protected intermediate **21** (Scheme 4); 3-bromo-2-lithiofuran, formed by treatment of 3-bromofuran with LDA,[14] was treated with chlorotrimethylsilane to give 3-bromo-2-(trimethylsilyl)furan which was, without purification, treated with LDA and quenched with quinuclidin-3-one to afford **21**. Desilylation of **21**, using *p*-toluenesulfonic acid in methanol, gave **22**.[15] However, both desilylation and dehydration of **21**, producing **32**, occurred on heating in concentrated formic acid (method IVA).

Treatment of 3-(2-methyl-1,3-dioxolan-2-yl)furan (**18**)[16] with *n*-BuLi and subsequent reaction with quinuclidin-3-one afforded **24**, which was both dehydrated and deprotected in concentrated formic acid (method IVA) to give **34**. More direct approaches to **34**, such as metal−halogen exchange of **31** with *n*-BuLi and further reaction with acetyl chloride, Heck coupling of **31** with butylvinyl ether,[17] or Stille-type coupling with (α-ethoxyvinyl)tributyltin (*vide infra*) produced mainly debrominated product.

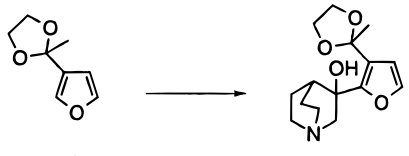
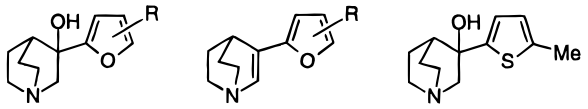


Table 2. Yields and Physical Data of Some Novel Quinuclidine Derivatives



A B C

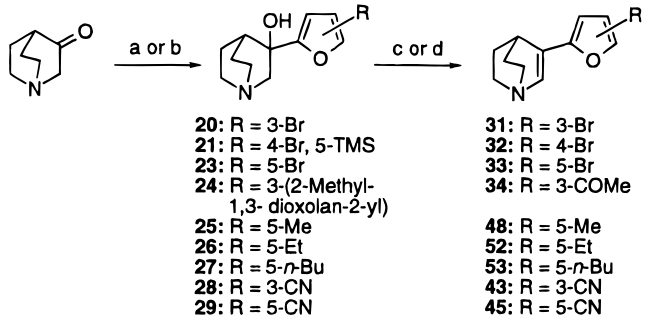
compd	general structure	R	prepn method[a]	% yield	mp, °C	recrystn solvents[b]	formula
3			IVA	96	196−198	A	$C_{12}H_{15}NS\cdot0.5C_4H_4O_4$
20	A	3-Br	IIIA	82	225−226	B	$C_{11}H_{14}BrNO_2\cdot0.5(COOH)_2\cdot0.25H_2O$
21	A	4-Br,5-TMS	*a*	54	118−119	A	$C_{14}H_{22}BrNO_2Si$
22	A	4-Br	*a*	61	156−158	C	$C_{11}H_{14}BrNO_2\cdot(COOH)_2\cdot0.25H_2O$
23	A	5-Br	IIIA	78	238−239	A	$C_{11}H_{14}BrNO_2\cdot0.5(COOH)_2\cdot0.25H_2O$
24	A	*c*	IIIB	29	218−219	D	$C_{15}H_{21}NO_4\cdot0.5(COOH)_2\cdot0.25H_2O$
25	A	5-Me	IIIB	82	177−178	A	$C_{12}H_{17}NO_2\cdot0.5C_4H_4O_4$
26	A	5-Et	IIIB	62	159−160	A	$C_{13}H_{19}NO_2\cdot0.5C_4H_4O_4$
27	A	5-*n*-Bu	IIIB	91	94−96	D	$C_{15}H_{23}NO_2$
28	A	3-CN	IIIA	62	215−217	F	$C_{12}H_{14}N_2O_2$
29	A	5-CN	IIIA	33	173−175	E	$C_{12}H_{14}N_2O_2$
30	A	5-Ph	VII	64	186−187		$C_{17}H_{19}NO_2\cdot0.25H_2O$
31	B	3-Br	IVA	86	148−149	A	$C_{11}H_{12}BrNO\cdot(COOH)_2\cdot0.75H_2O$
32	B	4-Br	IVA	88 (47)[d]	150−152	A	$C_{11}H_{12}BrNO\cdot(COOH)_2$
33	B	5-Br	VIII (IVB)[e]	40 (27)	125−128	E	$C_{11}H_{12}BrNO\cdot(COOH)_2\cdot0.25H_2O$
34	B	3-COMe	IVA	53	150−151	A	$C_{13}H_{15}NO_2\cdot(COOH)_2$
35	B	4-COMe	*a*	47	175−176	A	$C_{13}H_{15}NO_2\cdot(COOH)_2$
36	B	5-COMe	*a*	41	166−167	A	$C_{13}H_{15}NO_2\cdot(COOH)_2$
37	B	3-CONHPh	VA(VB)	10 (18)	264 dec	E	$C_{18}H_{18}N_2O_2\cdot HCl$
38	B	4-CONHPh	VA(VB)	45 (59)	270 dec	A	$C_{18}H_{18}N_2O_2\cdot HCl\cdot0.25H_2O$
39	B	5-CONHPh	VC	41	238−239	A	$C_{18}H_{18}N_2O_2\cdot(COOH)_2$
40	B	3-CO_2Me	VA	9 (16)[f]	122 dec	E	$C_{13}H_{15}NO_3\cdot1.5(COOH)_2$
41	B	4-CO_2Me	VA	19	167−168	A	$C_{13}H_{15}NO_3\cdot(COOH)_2$
42	B	5-CO_2Me	VC	37	162−163	A	$C_{13}H_{15}NO_3\cdot(COOH)_2$
43	B	3-CN	IVB	36	206−208	A	$C_{12}H_{12}N_2O\cdot HCl$
44	B	4-CN	VA	31	186−188	A	$C_{12}H_{12}N_2O\cdot(COOH)_2$
45	B	5-CN	IVB (VC)	58 (40)	152−154	E	$C_{12}H_{12}N_2O\cdot(COOH)_2$
46	B	3-Me	VI	88	222−224 dec	A	$C_{12}H_{15}NO\cdot(COOH)_2\cdot0.25H_2O$
47	B	4-Me	*g*	40	141−143	A	$C_{12}H_{15}NO\cdot(COOH)_2$
48	B	5-Me	IVA	93	159−160		$C_{12}H_{15}NO\cdot0.5C_4H_4O_4$
49	B	3-Ph	VII	72	185−187	A	$C_{17}H_{17}NO\cdot(COOH)_2$
50	B	4-Ph	VII	55	177−179	A	$C_{17}H_{17}NO\cdot(COOH)_2\cdot0.5H_2O$
51	B	5-Ph	IVA	78	201−202	A	$C_{17}H_{17}NO\cdot C_4H_4O_4$
52	B	5-Et	IVA[h]	96	81−83	A	$C_{13}H_{17}NO\cdot C_4H_40_4\cdot0.25H_2O$
53	B	5-*n*-Bu	IVA[h]	73	163−164	A	$C_{15}H_{21}NO\cdot(COOH)_2\cdot0.25H_2O$
54	B	3-Ph, 5-Br	VIII	52	183−184	E	$C_{17}H_{16}BrNO\cdot1.5(COOH)_2$
55	B	3-Ph, 5-Me	VI	61	180−182	E	$C_{18}H_{19}NO\cdot1.5(COOH)_2\cdot0.25H_2O$
56	B	3-(*m*-F_3CPh)	VII	83	140−141	E	$C_{18}H_{16}F_3NO\cdot(COOH)_2$
57	B	3-(*p*-F_3CPh)	VII	80	158−159	E	$C_{18}H_{16}F_3NO\cdot(COOH)_2$
58	B	3-(*m*-BuOPh)	IX	35	138−139	E	$C_{21}H_{25}NO_2\cdot(COOH)_2$
59	B	3-(*p*-BuOPh)	IX	57	138−140	E	$C_{21}H_{25}NO_2\cdot(COOH)_2$
60	B	3-(*m*-EtPh)	IX	19	141−145	E	$C_{19}H_{21}NO\cdot(COOH)_2$
61	B	3-(*p*-EtPh)	IX	41	122−124	E	$C_{19}H_{21}NO\cdot1.5(COOH)_2$
62	B	3-(*m*-morpholinoPh)	IX	34	223−224	H	$C_{21}H_{24}N_2O_2\cdot2HCl$
63	B	3-(*p*-morpholinoPh)	IX	28	dec	E	$C_{21}H_{24}N_2O_2\cdot HCl\cdot0.25H_2O$
64	B	3-(*m*-NCPh)	XA	46	175−176	E	$C_{18}H_{16}NO_2\cdot(COOH)_2$
65	B	3-(*p*-NCPh)	XA	46	178−179	E	$C_{18}H_{16}N_2O\cdot1.5(COOH)_2$
66	B	3-(*m*-$MeCO_2$Ph)	XB	28	161−163	F	$C_{19}H_{19}NO_3\cdot1.5(COOH)_2$
67	B	3-(*p*-$MeCO_2$Ph)	XB	23	180−182	F	$C_{19}H_{19}NO_3\cdot(COOH)_2\cdot0.4H_2O$
68	B	3-(*m*-HOPh)	XI	38	220−222	A	$C_{17}H_{17}NO_2\cdot HCl$
69	B	3-(*p*-HOPh)	XI	35	163−164	F	$C_{17}H_{17}NO_2\cdot1.5(COOH)_2$
70	B	3-(*m*-F_3CSO_3Ph)	*a*	65	186−187	A	$C_{18}H_{16}F_3NO_4S\cdot HCl$
71	B	3-(*m*-$MeSO_3$Ph)	*a*	88	188−190	A	$C_{18}H_{19}NO_4S\cdot HCl\cdot0.25H_2O$
73	C		IIIB	81	206−207	A	$C_{12}H_{17}NOS\cdot0.5C_4H_4O_4\cdot0.5H_2O$

[a] See the Experimental Section. [b] A: Methanol/ether. B: Methanol/chloroform. C: Acetonitrile/methanol. D: Acetonitrile. E: Ethylacetate/methanol. F: Acetonitrile/ether. [c] 3-(2-Methyl-1,3-dioxolan-2-yl). [d] Overall yield calculated from **21** using method IVA. [e] THF was substituted with benzene as the solvent. [f] Addition of 1 equiv of silver(I) oxide to the reaction mixture improved the yield. [g] The synthesis of **47** has been described previously.[23] However, no pharmacological data on muscarinic properties were reported for this compound. [h] The corresponding hydroxy compound was stirred in concentrated formic acid at room temperature.

Palladium-catalyzed Stille-type coupling reactions between 3-(tributylstannyl)quinuclidin-2-ene (**19**)[18] and the appropriate bromofuran derivatives produced amides (**37**−**39**), esters (**40**−**42**), and nitriles (**44** and **45**) (method VA−C; Scheme 5). In certain reactions, addition of silver(I) oxide (**40**)[19,20] or cupric oxide[20] (method VB) increased the yields and slightly reduced the reaction times of the cross-coupling reactions. Attempts to prepare **37**, **38**, **40**, and **41** by a palladium-catalyzed carbonylation of **31** and **32** was impractical because of a low yields (GLC−MS).

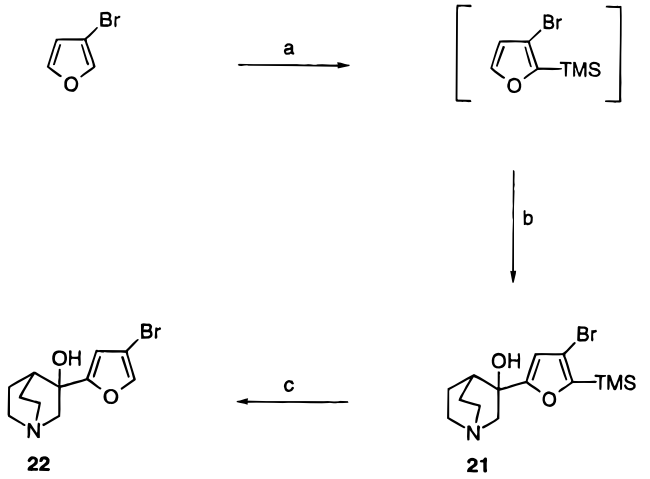
The 3-methyl (**46**) and 3- and 4-phenyl (**49** and **50**) substituted derivatives were synthesized by palladium-catalyzed coupling reactions of the corresponding bromo-substituted derivatives **31** and **32** with tetramethyltin[21] or phenylboronic acids,[22] respectively (methods VI and

Scheme 3[a]



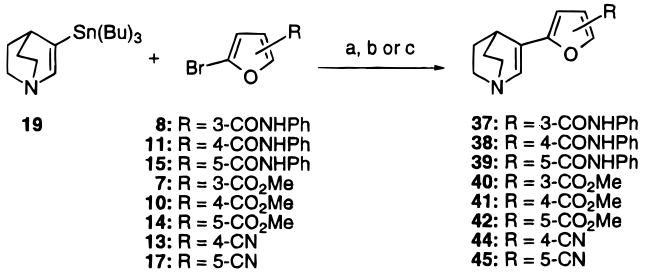
[a] Reagents: (a) heterocycle, LDA, THF; (b) heterocycle, *n*-BuLi, ether; (c) HCOOH, 100 °C; (d) $MeO_2CNSO_2NEt_3$ (Burgess' reagent), THF or benzene.

Scheme 4[a]



[a] Reagents: (a) (i) LDA, THF, (ii) chlorotrimethylsilane; (b) (i) LDA, THF, (ii) quinuclidin-3-one; (c) *p*-toluenesulfonic acid, MeOH/H_2O.

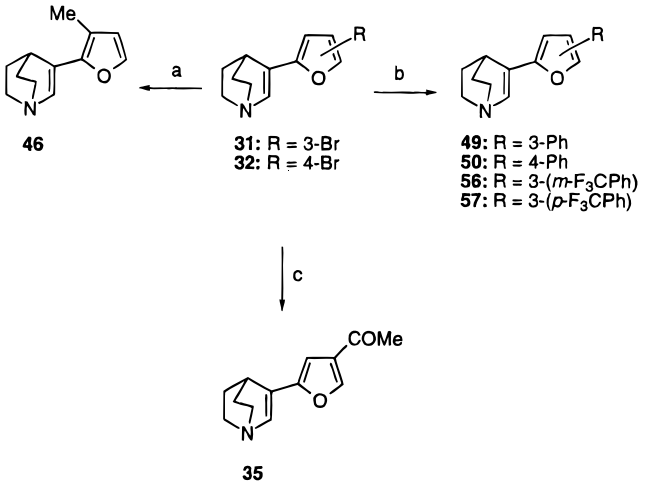
Scheme 5[a]



[a] Reagents: (a) $Pd(PPh_3)_4$, DMF; (b) $Pd(PPh_3)_4$, CuO, DMF; (c) $PdCl_2(PPh_3)_2$, dioxane.

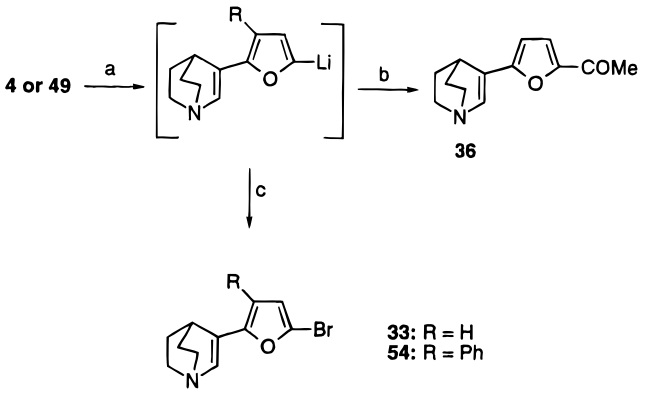
VII; Scheme 6). The 5-methyl-substituted derivative **55** was synthesized from **54** using the conditions described above (method VI; Table 2). However, attempts to synthesize the 4-methyl-substituted derivative **47** from **32** using these conditions were unsuccessful because of competitive debromination; the resulting crude mixture could be purified neither by crystallization nor by column chromatography. Instead, **47** was prepared by using a procedure described by Saunders *et al.*[23] The 5-phenyl-substituted derivative **51** was prepared by a palladium-catalyzed coupling reaction of alcohol **23** with phenylboronic acid to give the corresponding alcohol **30**, which was dehydrated in concentrated formic acid (method IVA) to afford **51**. Methyl ketone **35** was produced by a Stille-type coupling reaction of **32** with

Scheme 6[a]



[a] Reagents: (a) $(CH_3)_4Sn$, $Pd(OAc)_2$, tri-*o*-tolylphosphine, DMF; (b) $ArB(OH)_2$, $Pd(PPh_3)_4$, 2 M aqueous Na_2CO_3, DME; (c) (i) (α-ethoxyvinyl)tributyltin, $Pd(OAc)_2$, tri-*o*-tolylphosphine, DMF, (ii) 1 M aqueous HCl.

Scheme 7[a]



[a] Reagents: (a) *n*-BuLi, ether; (b) (i) *N*,*N*-dimethylacetamide, (ii) 2.5 M aqueous HCl; (c) 1,2-dibromotetrafluoroethane.

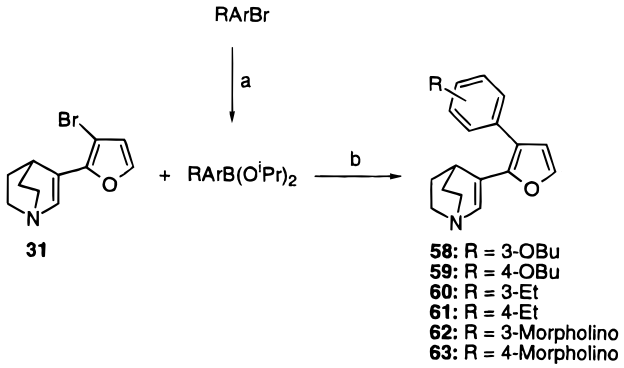
(α-ethoxyvinyl)tributyltin[24] followed by acid-catalyzed hydrolysis of the resulting enol ether (Scheme 6).

Treatment of **4** with *n*-BuLi in ether followed by reaction with *N*,*N*-dimethylacetamide[16] produced acetyl derivative **36** (Scheme 7). Similarly, reactions of the 5-lithio derivatives of **4** and **49** with 1,2-dibromotetrafluoroethane[10] produced the 5-bromo-substituted derivatives **33** and **54**, respectively (method VIII; Scheme 7).

Compounds **56**−**63** were prepared by palladium-catalyzed Suzuki-type coupling reactions between the 3-bromo derivative **31** and *in situ* generated aryl borates (method IX; Scheme 8) or commercially available arylboronic acids (method VII; Scheme 6). Treatment of the appropriate aryl halide with *n*-BuLi followed by addition of triisopropyl borate produced the aryl borates.[25]

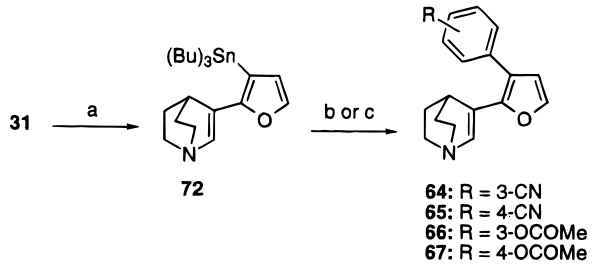
An alternative approach was used to introduce a phenyl ring substituted with a base-sensitive functional group (Scheme 9); lithiation of **31** with *n*-BuLi followed by treatment with tributyltin chloride produced tin derivative **72**. Palladium-catalyzed cross-coupling reactions of **72** with the appropriate aryl halide produced the cyano-substituted derivatives **64** and **65** (method XA) and esters **66** and **67** (method XB). The presence of CuI as a cocatalyst was essential in the reactions affording **66** and **67**.[26]

Scheme 8[a]



[a] Reagents: (a) (i) *n*-BuLi, THF, (ii) $B(O^iPr)_3$; (b) $Pd(PPh_3)_4$, 2 M aqueous Na_2CO_3, DME, reflux.

Scheme 9[a]



[a] Reagents: (a) (i) *n*-BuLi, ether, (ii) tributyltin chloride; (b) *m*- or *p*-bromobenzonitrile, $Pd(PPh_3)_4$, DMF, 100 °C; (c) *m*- or *p*-iodophenyl acetate, Pd_2dba_3, $AsPh_3$, CuI, DMF, 50 °C.

Hydrolysis of **66** and **67** gave phenols **68** and **69**, respectively (method XI). Treatment of **68** with *N*-phenyltrifluoromethanesulfonimide[27] or methanesulfonyl chloride[28] in the presence of Et_3N produced triflate **70** and mesylate **71**, respectively.

Conformational Analysis. Certain substitutions in the 3- and/or 5-positions of the furan ring of **4** led to particularly high muscarinic affinities (*vide infra*). Introduction of a bulky substituent in the 3-position of the furan ring in **4** might change the conformational preferences, whereas substitutions in the 4- and 5-positions of the furan ring should not. Such potential differences in conformational preferences would have to be considered in the subsequent CoMFA studies. Therefore, we decided to study the conformational preferences of the 3-phenyl (**49**, oxalate) and 5-phenyl (**51**, fumarate) substituted derivatives in some detail using experimental (X-ray crystallography) and theoretical (molecular mechanics calculations) methods.

The crystal structure of **49** contains two crystallographically independent complexes (Figure 1). A fitting of the non-hydrogen atoms of the two protonated 3-(3′-phenylfuran-2-yl)quinuclidin-2-ene molecules gave a root mean square (rms) deviation of only 0.08 Å but 1.1 Å for the two oxalate anions, thus indicating analogous geometry for the cations but slightly different conformations for the oxalate counterions. The crystal structure of **51** contains a protonated 3-(5′-phenylfuran-2-yl)-quinuclidin-2-ene molecule with a fumarate as the counterion (Figure 2). Bond lengths and torsion angles indicate a partly conjugated system from the C2−C3 double bond over the furan ring to the phenyl ring for the protonated cations in both **49** and **51** (Supporting Information). The angle between the normals of the least-squares planes of the furan and the phenyl moieties are 38.1(1)° and 40.0(1)° for molecules **a** and **b** in **49**, respectively, but only 6.8(2)° in **51**. The deviation from the planarity of the conjugated part in **49** is predominantely due to the steric interactions between H2 in the quinuclidin-2-ene moiety and H11′ in the phenyl group.

The steric interactions between H11′ and H2 is not present in **51**, in which the conjugated part adopts a nearly planar arrangement. The atoms in **51** that deviate most from a least-squares plane through the conjugated system (the phenyl group, the furan moiety, C2 and C3) of the non-hydrogen atoms are C2, 0.144(1) Å, and C11′, 0.141(2) Å, located on opposite sides of the plane.

The crystal structures are held together by hydrogen bonds between the quinuclidin-2-ene moiety and the oxalate/fumarate anions on one hand, and between either the oxalate or the fumarate anions, on the other. In addition to the these strong hydrogen bonds, both

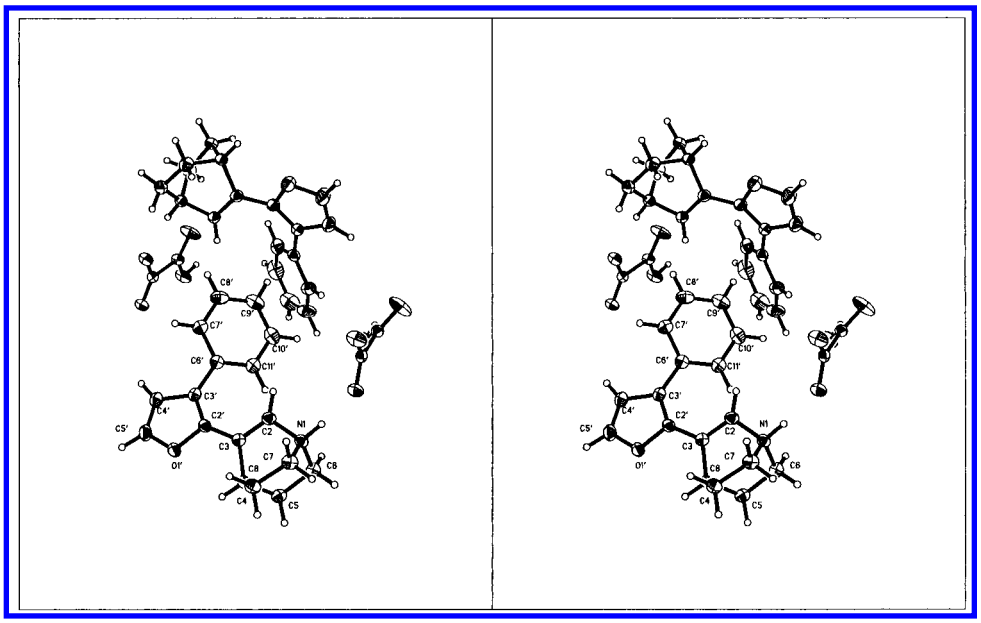


Figure 1. Stereoscopic representation of the solid state conformers of **49**, **a** and **b**. The atom labeling is shown in **a**. The displacement ellipsoids are represented at 50% probability level.

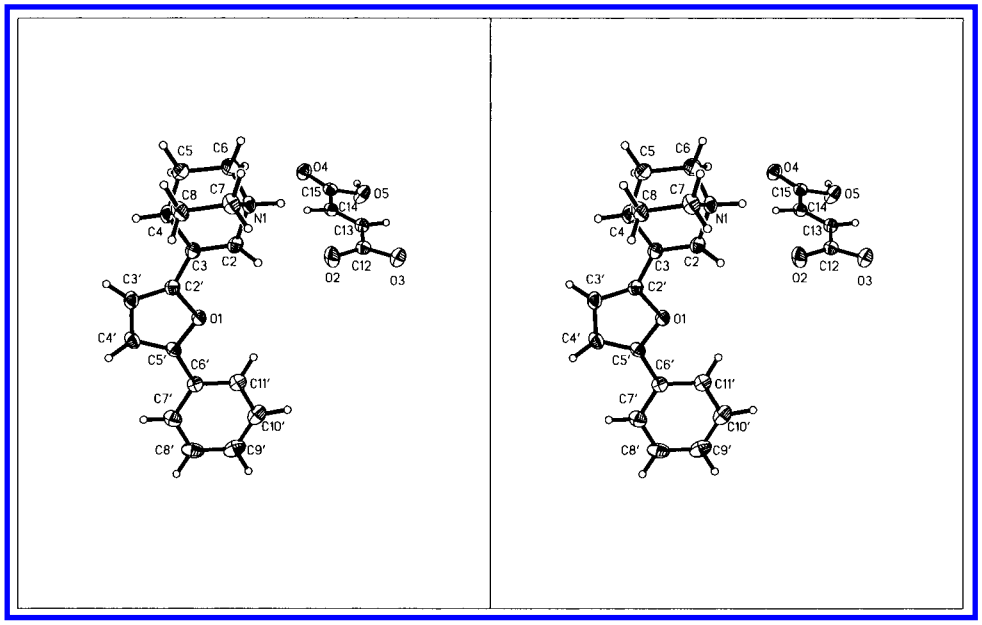


Figure 2. Stereoscopic representation of **51**. The displacement ellipsoids are drawn at 50% probability level.

49 and **51** have several potential C−H···O interactions (Supporting Information).

We calculated energy contour maps of the torsion angle C2−C3−C2′−C3′ versus C2′−C3′−C6′−C11′ or C4′−C5′−C6′−C11′ for **49** and **51**, respectively. The calculations were performed on the free bases of **49** and **51** with the MM2* force field as implemented in the MacroModel program[29] using a dielectric constant of 1. The largest difference between the crystal structure conformations and the computationally derived conformations with the lowest calculated energies was found in **49**. In the crystal structure of **49** the furan oxygen atom is located opposite to the protonated quinuclidin-2-ene nitrogen, but in the conformation with the lowest calculated energy the oxygen atom is close to the nitrogen atom. The energy difference between the minimized crystal structure and the global energy minimum is 4.5 kJ/mol. According to the MM2* calculations, an energy increase of approximately 3 kJ/mol is necessary to force the furan ring to become coplanar with the C2−C3 double bond in the quinuclidin-2-ene ring in **49**. In contrast, the lowest energy conformation derived from the calculations is almost identical to the solid state conformation observed in the crystal structure of **51**, but the molecular mechanics calculations predict a planar arrangement of the conjugated system whereas it was found to be slightly twisted in the solid state conformation.

In conclusion, the above studies demonstrate that both **49** and **51** are able to adopt a conformation in which the furan ring is coplanar with the double bond in the quinuclidin-2-ene ring and with the furan oxygen close to the quinuclidin-2-ene nitrogen. However, such a conformation of **49** is about 3 kJ/mol above the calculated (MM2*) global energy minimum.

Results and Discussion

Pharmacological Results. Affinities of the compounds (expressed as K_i values; Table 3) for muscarinic receptors in the cerebral cortex, heart, parotid gland, and urinary bladder were determined by competition experiments with (−)-[^{3}H]QNB.[30−33] Cerebral cortex in rat expresses a mixture of muscarinic receptor subtypes (m1 40%, m2 30%, m3 5%, m4 20%) as found with immunoprecipitation.[34,35] The heart expresses a homogeneous population of the m2 subtype, in rat and rabbit.[36,37] Parotid gland contains 93% of m3, determined with specific antibodies for m1−m5, in rat.[38] In the urinary bladder the predominant subtype is m2. However, a smaller population of m3 is present, in rat, rabbit, guinea pig, and human bladder.[39]

Antimuscarinic potencies (expressed as K_B values; Table 3) were evaluated by functional *in vitro* studies on isolated guinea pig bladder, using carbachol as the agonist. In the presence of antagonist, the concentration−response curves to carbachol were shifted in parallel toward higher concentrations, but the maximal responses remained unaffected. Thus, the inhibition seemed to be competitive since it could always be overcome by an increase in the carbachol concentration. None of the compounds exhibited any muscarinic agonist activity in the isolated urinary bladder when tested in concentrations of 0.5−1000 μM. For comparison, reference data for **2**−**4**, racemic QNB, and atropine are included in Table 3.

The present series of quinuclidine derivatives displayed a wide range of affinities. The least potent derivative (**39**) exhibited an 11-fold decrease in affinity for cortical muscarinic receptors as compared to lead compound **4**. In contrast, introduction of a 3-(3-hydroxyphenyl) substituent in **4**, producing **68**, the most potent analogue in the present series, increased the affinity for cortical muscarinic receptors more than 1100-fold. The effect of multiple substituents on the furan ring was briefly examined. 5-Methyl (**48**), 5-bromo (**33**), and 3-phenyl (**49**) substitution in **4** led to potent antagonists. However, the 5-bromo-3-phenyl (**54**) and 5-methyl-3-phenyl (**55**) derivatives were only slightly more potent than **49** (Table 3). Thus, the effects of 3- and 5-substituents on affinity do not seem to be additive.

In general, there was a good agreement between receptor binding data (K_i) and functional data (K_B) in the urinary bladder. The binding data show that the new compounds exhibited low tissue selectivity. The most selective muscarinic antagonist in this series, the 4-amide-substituted derivative **38**, displayed about 12-

Table 3. Affinities (K_i)[a] for Muscarinic Receptors, Determined by Competition Experiments with (−)-[^{3}H]QNB and Functional *in Vitro* Data (K_B), Determined on Isolated Urinary Bladder Strips from Guinea Pig vs Carbachol

	K_i (nM)				K_B (nM)
compd	cerebral cortex	heart	parotid gland	urinary bladder	urinary bladder
2	290 ± 10	620 ± 110	1200 ± 200	1500 ± 300	1100[b] ± 200
3	73 ± 2	230 ± 30	264 ± 0.5	500 ± 90	330[b] ± 40
4	300 ± 70	390 ± 60	1100 ± 90	850 ± 130	550[c] ± 30
31	140 ± 20	210 ± 20	420 ± 70	390 ± 110	215[d] ± 25
32	130 ± 0.4	320 ± 10	460 ± 80	540 ± 20	260[d] ± 50
33	6.4 ± 0.2	15 ± 3	28 ± 4	29 ± 2	nd[e]
34	570 ± 40	1200 ± 100	2300 ± 20	2500 ± 600	nd
35	1300 ± 200	3200 ± 300	2400 ± 900	4100 ± 700	3100[f] ± 500
36	1100 ± 90	2460 ± 50	4600 ± 700	3900 ± 500	nd
37	800 ± 70	1900 ± 400	1200 ± 100	nd	nd
38	580 ± 110	220 ± 8	2600 ± 300	nd	nd
39	3320 ± 90	3600 ± 700	>20000	5100 ± 800	nd
40	60 ± 2	120 ± 20	240 ± 40	nd	nd
41	1100 ± 100	2840 ± 30	2900 ± 900	nd	nd
42	810 ± 60	2530 ± 40	3900 ± 100	2500 ± 200	2600[b] ± 300
43	400 ± 80	460 ± 80	1200 ± 200	nd	nd
44	710 ± 0.7	2000 ± 400	3400 ± 700	nd	nd
45	93 ± 7	230 ± 80	720 ± 120	nd	nd
46	520 ± 20	575 ± 20	1300 ± 200	1300 ± 20	1100[g] ± 200
47	99 ± 8	400 ± 80	680 ± 230	670 ± 120	nd
48	12 ± 1	35 ± 2	64 ± 5	64 ± 16	61[d] ± 13
49	2.8 ± 0.5	6.9 ± 1.6	8.6 ± 0.9	13 ± 2	2.7[h] ± 1.0
50	730 ± 40	1600 ± 100	1900 ± 100	1765 ± 1	1300[i] ± 400
51	330 ± 30	547 ± 5	970 ± 50	1800 ± 200	1000[j] ± 480
52	7.4 ± 0.5	24 ± 4	40 ± 1	47 ± 5	31 ± 2
53	17.1 ± 0.7	48 ± 3	58 ± 2	80 ± 3	nd
54	1.55 ± 0.02	2.4 ± 0.3	7.7 ± 1.1	nd	18[k] ± 4
55	2.39 + 0.07	3.1 ± 0.1	4.4 ± 0.2	nd	nd
56	5.7 ± 1.4	10.7 ± 0.7	25 ± 9	nd	nd
57	180 ± 60	130 ± 20	830 ± 160	nd	nd
58	8.4 ± 2.1	9.5 ± 2.5	33 ± 6	nd	nd
59	370 ± 50	280 ± 50	940 ± 10	nd	nd
60	2.1 ± 0.03	1.9 ± 0.4	6.9 ± 1.3	nd	nd
61	59 ± 12	38 ± 6	124 ± 9	nd	nd
62	5.0 ± 0.5	2.3 ± 0.6	10.3 ± 0.8	nd	nd
63	780 ± 140	420 ± 110	2760 ± 600	nd	nd
64	7.8 ± 1.8	11 ± 4	58 ± 3	nd	nd
65	230 ± 70	190 ± 40	320 ± 130	nd	nd
66	0.95 ± 0.23	2.2 ± 0.5	0.80 ± 0.08	nd	nd
67	4.2 ± 0.3	3.3 ± 1.0	2.20 ± 0.02	nd	nd
68	0.27 ± 0.06	0.72 ± 0.20	0.61 ± 0.01	nd	nd
69	0.79 ± 0.13	1.12 ± 0.06	3.9 ± 0.5	nd	nd
70	16 ± 1	25 ± 5	38 ± 10	nd	nd
71	8.2 ± 0.1	11 ± 3	16 ± 4	nd	nd
(±)-QNB	0.051 ± 0.003[l]	0.045 ± 0.003[l]	0.24 ± 0.01[m]	0.20 ± 0.02[m]	
atropine	0.32 ± 0.02[l]	0.89 ± 0.06[l]	0.85 ± 0.005[m]	1.6 ± 0.1[m]	

[a] Values are means ± SEM of two to five experiments performed in triplicate. [b] Concentration of antagonists: 100 μM. [c] Concentration of antagonists: 100, 1000 μM. [d] Concentration of antagonists: 50, 100 μM. [e] nd = not determined. [f] Concentration of antagonists: 30, 100 μM. [g] Concentration of antagonists: 10, 100 μM. [h] Concentration of antagonists: 1 μM. [i] Concentration of antagonists: 10, 30 μM. [j] Concentration of antagonists: 30 μM. [k] Concentration of antagonists: 0.5, 1.0 μM. [l] Value is from ref 31. [m] Value is from ref 32.

fold selectivity for muscarinic receptors in heart versus parotid gland. Since all compounds except **38** showed limited tissue selectivity, we used only receptor affinities for cortex in the SAR analysis.

Structure−Activity Relationships. In order to describe the structure−activity relationships (SAR) within the present series, both traditional QSAR and 3D-QSAR methods were used. The compounds substituted in the 3- and 4-positions of the 3-phenyl ring (**56**, **58**, **60**, **62**, **64**, **68**, **70**, **71** and **57**, **59**, **61**, **63**, **65**, **69**) were analyzed using traditional QSAR. These compounds were part of an experimental design set; the substituents that were introduced in the 3- or 4-position of the 3-phenyl group were selected by factorial design based on three factors (π, σ-para and molar refractivity [MR]). The final selection of substituents was also based on the synthetic accessibility. The 3- and the 4-substituted 3-phenyl derivatives were analyzed separately. The QSAR analyses of the eight 3-substituted 3-phenylfuranyl derivatives (**56**, **58**, **60**, **62**, **64**, **68**, **70**, and **71**) were performed using a partial least-squares (PLS) analysis.[40] The three descriptors used in the experimental design were also used in the analysis. This resulted in a model[41] explaining 96% of the variance in affinity and with a cross-validated r^2 (q^2) of 0.795 using two principal components (see Figure 3).

The analysis of the 4-substituted compounds (including the unsubstituted **49**) using PLS resulted in a model explaining 96% of the variance with a cross-validated r^2 (q^2) of 0.753 using two principal components (see Figure 4).[42]

These analyses show that both 3- and 4-substituted phenyl derivatives exhibit similar SAR, a small, electron-donating, and hydrophilic substituent providing optimum affinity. A substituent in the 4-position of the 3-phenyl substituent appears to be less favorable than in the 3-position since all of these compounds have lower affinity than the corresponding 3-substituted deriva-

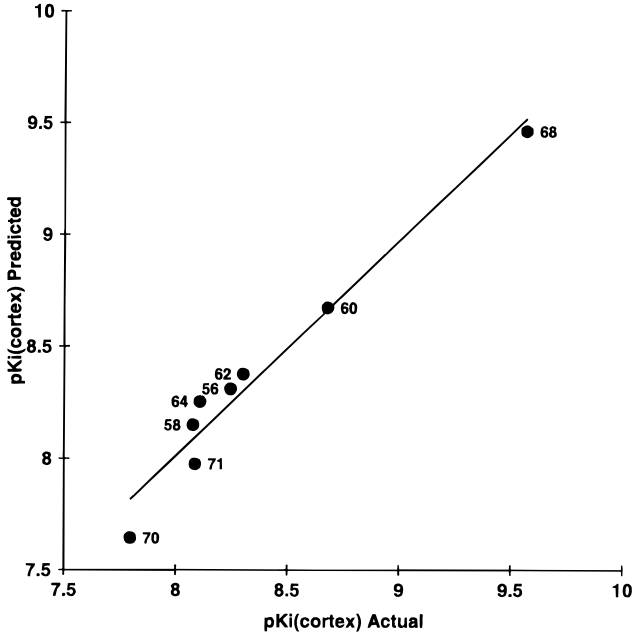


Figure 3. Plot of actual versus predicted affinities for the 3-substituted 3-phenylfuran derivatives derived from the QSAR model 1.

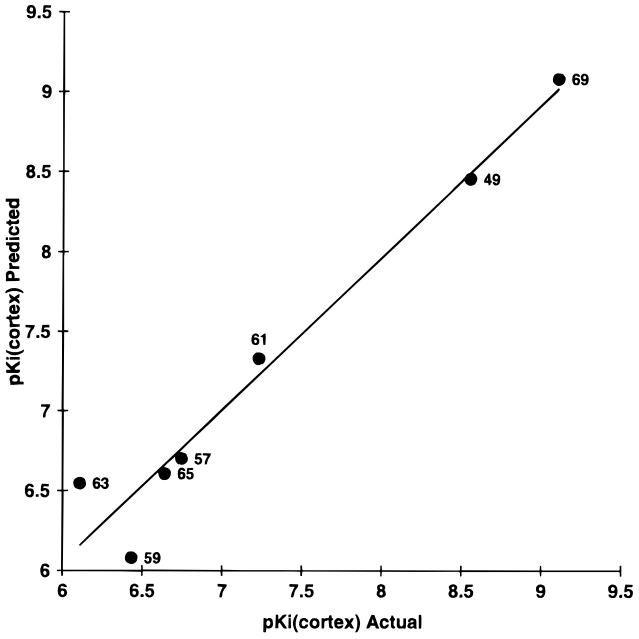


Figure 4. Plot of actual versus predicted affinities for the 4-substituted 3-phenylfuran derivatives derived from the QSAR model 2.

tives. A large 4-substituent also reduces the affinity significantly more than the corresponding substituent in the 3-position (cf. refs 41 and 42). This indicates that the environment around the phenyl group in the two series is relatively similar, but the receptor region close to the 4-position of the phenyl group seems to be sterically crowded.

Substituting the phenyl group with a 3- or 4-hydroxyl group, that is, a small, electron-donating, and hydrophilic group, produced compounds (**68** and **69**) with high affinity, possibly because the hydroxyl group participates in a hydrogen bond interaction with the receptor protein.[43,44]

We also included the ^{13}C NMR chemical shifts for the furan ring carbons of 3-, 4-, and 5-substituted furan derivatives as descriptors in the QSAR analysis. However, no improved correlation was found by including the ^{13}C NMR shift values.

Comparative molecular field analysis (CoMFA)[45] was performed in an attempt to describe the SAR of all tested compounds.[46] The compounds were aligned by fitting all heavy atoms in the quinuclidin-2-ene ring using **4** as a template. They were superimposed in the same energetically accessible rotameric form, the furan ring being coplanar with the double bond in the quinuclidin-2-ene ring and the furan oxygen located close to the quinuclidin-2-ene nitrogen. This particular conformation was used because it produced the best fit with our model of the m1 receptor.[44] Semiempirical PM3 charges and geometries were used in the study. Conformational preferences of the substituents were taken from dihedral drives using Macromodel[29] with subsequent minimization using Macromodel and the PM3 Hamiltonian. The compounds were included in a box, and the steric and electrostatic interactions were evaluated at grid points in the box. The CoMFA analysis was performed with a grid size of 2 Å using a positively charged carbon as the probe atom. CoMFA standard scaling and no column filtering was used in the analysis. The steric and electrostatic cutoff values were set to +30 kcal/mol. The electrostatic interaction was dropped for each compound within the steric cutoff values. The analysis was made with cross-validation using the "leave one out" procedure. The g^2, which is a measure of the predictive power of a model, was used to evaluate the models. This value is always lower than the conventional r^2, and a $g^2 > 0.5$ is considered to indicate a good predictive ability.

The derived CoMFA model gave a $g^2 = 0.63$ (CoMFA model 1, Table 4). A correlation coefficient (r^2) of 0.92 was found for a plot of actual versus predicted affinity (Figure 5). Steric and electrostatic factors have similar contributions to the model (Table 4). Compounds **68** and **69** were among those that were most poorly predicted. One possible explanation may be that the CoMFA method underestimates possible hydrogen bond interactions. It is noteworthy that the QSAR equation (*vide supra*) gives a good model and predicts compounds **68** and **69** well without explicity taking into account hydrogen bonds (no specific hydrogen bond descriptors are used). However, log P, which is present in the QSAR equation, is a complex descriptor and is affected by the hydrogen bond donating/accepting ability of a substituent.

Table 4. Summary of CoMFA Results for Models 1−3[a]

model	g^2	principal components	r^2	standard error of estimate	F value	relative contribution	
						steric	electrostatic
1	0.63	4	0.92	0.32	98.7	0.59	0.41
2	0.61	2	0.86	0.38	68.4	0.52	0.48
3	0.48	2	0.87	0.40	36.8	0.52	0.48

[a] See Figure 5 for a graphical representation of model 1.

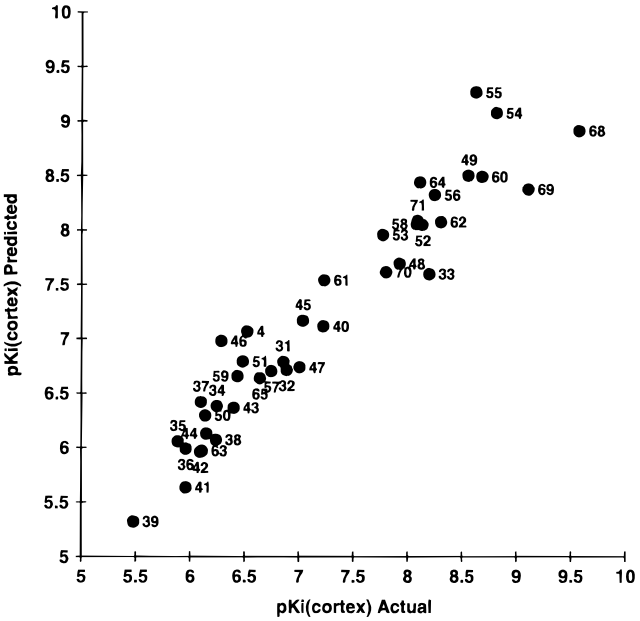


Figure 5. Plot of actual versus predicted affinities for all compounds derived from CoMFA model 1.

The CoMFA contour values were chosen from a steric field distribution histogram to identify contour values with sufficient data points at a location where the influence of field properties on affinity is the greatest. Figure 6 shows that a small or flexible group (such as an ethyl group) at the 5-position of the furan ring (green contours) is beneficial for affinity to cortical muscarinic receptors. Small groups in the 3- and 4-position of the 3-phenyl ring also increase the affinity (the hydroxy groups). Steric bulk in the 4-position of the furan ring is detrimental to the affinity (yellow contours). Large groups in the 4-position of the 3-phenyl ring also decrease the affinity (yellow contours). The red contours located around both the furan ring and the 3-phenyl group indicate that these aromatic rings should be electron rich for optimal affinity.

Two additional CoMFA models were also produced. CoMFA model 2 (Table 4) includes only the 3-, 4-, and 5-substituted furan derivatives, but the substituted 3-phenyl derivatives are not included. This also produced a good model ($g^2 = 0.61$ and $r^2 = 0.86$). A model of only the substituted 3-phenyl derivatives (CoMFA model 3, Table 4) produced a model with reduced g^2 (0.48).

Conclusion. Our studies of antimuscarinic quinuclidin-2-ene derivatives substituted in the 3-position with a heteroaromatic ring[1,2] have now been extended to substituted furan derivatives. In a previous study of 3-(2-benzofuranyl)quinuclidin-2-ene derivatives,[2] substitutions in the benzofuranyl moiety decreased or did not affect the affinity for muscarinic receptors. In contrast, the present study demonstrates that the affinity of furan derivative **4** for muscarinic receptors can be enhanced more than 1000-fold by an appropriate [a 3-(3-OH-phenyl)] substitution in the furan ring. Furthermore, the SAR of the 41 derivatives described herein are well described by a CoMFA model (model 1). This may allow for the design of novel potent antimuscarinic agents which exhibit receptor-subtype selectivity, a missing property in the present series of compounds.

Experimental Section

Chemistry. General Comments. Reactions were carried out under nitrogen. Tetrahydrofuran (THF) was distilled from Na/benzophenone ketyl. Melting points were determined in open glass capillaries on a Thomas-Hoover apparatus. IR spectra were recorded on a Perkin-Elmer 298 infrared spec-

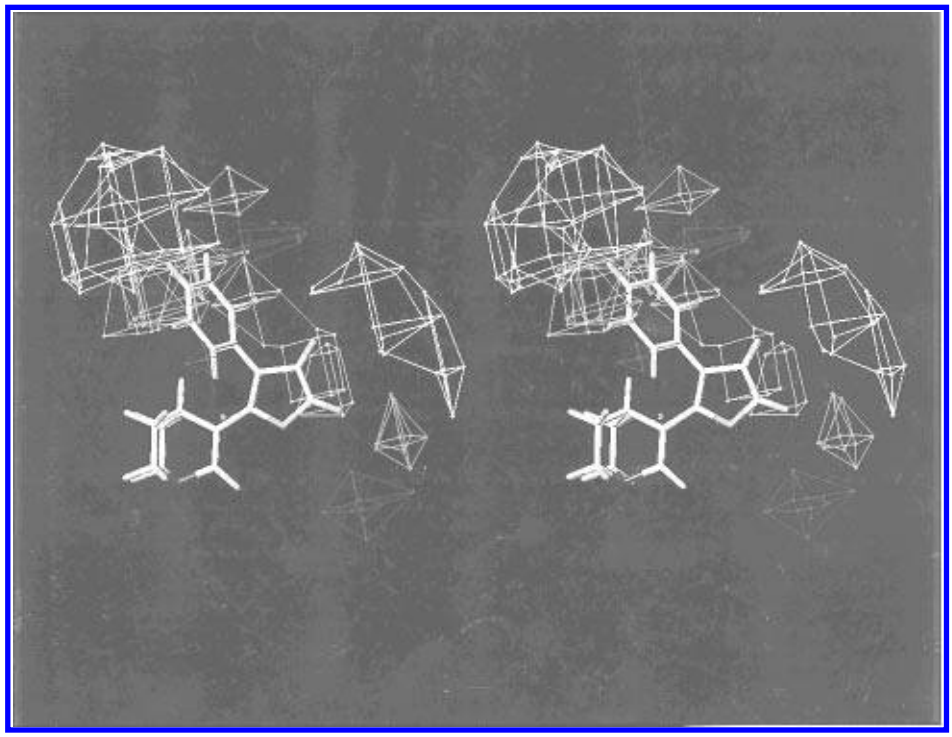


Figure 6. Stereoscopic representation of CoMFA model 1. Included within the CoMFA contours is compound **49**. The contour levels are made using actual STDEV*COEFF values. The red electrostatic contours (−0.010) indicate areas where negative groups are beneficial for activity, i.e., where they lower the K_i value. Blue contours (0.040) indicate areas where positive groups increase the affinity. The green contours (0.050) indicate areas where an increase in bulk would increase the activity. Yellow contours (−0.020) indicate areas where steric bulk is detrimental to the biological activity.

trophotometer or on a Perkin-Elmer 1600 series FTIR. Most ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX 270 spectrometer at 270.2 and 67.9 MHz, respectively. Some NMR spectra were also recorded on a JEOL FX 90Q spectrometer at 22.5 MHz, or on a JEOL JNM-EX 400 spectrometer at 399.95 and 100.5 MHz, respectively. ^{1}H and ^{13}C NMR spectra were referenced to internal tetramethylsilane. Dioxane was used as internal reference for ^{1}H and ^{13}C NMR spectra (3.60 and 68.0 ppm, respectively) recorded in D_2O. All spectra were in accordance with the assigned structures. Low-resolution electron-impact mass spectral data (70 eV) were obtained on a Hewlett-Packard mass spectrometer HP5971A MSD connected to a gas chromatograph HP GC5890 series 2, equipped with a HP-1 (25 m × 0.2 mm i.d.) column. Thin-layer chromatography was carried out on aluminum sheets precoated with silica gel 60 F_{254} (0.2 mm) or aluminum oxide 60 F_{254} neutral (type E) (E. Merck). Column chromatography was performed on silica using Kiselgel 60 (230−400 mesh), E. Merck, or on alumina: aluminum oxide 90, E. Merck. Chromatographic spots were visualized by UV and/or I_2 vapor. The elemental analyses were performed by Mikro Kemi AB, Uppsala, Sweden, or Analytische Laboratorien, Lindlar, Germany, and were within 0.4% of the calculated values unless otherwise stated. The following heteroaryl and aryl halides were prepared according to literature procedures: 5-Bromo-3-furoic acid,[4] 5-bromo-2-furancarbonitrile,[8] 5-bromo-2-furancarboxamide,[7] 4-(4-bromophenyl)morpholine.[47] *m*-Bromobutoxybenzene was obtained by alkylation of 3-bromophenol with 1-bromobutane in the presence of K_2CO_3. *p*-Iodophenyl acetate and *m*-iodophenyl acetate were prepared from the corresponding phenols by acylation with acetyl chloride in the presence of Et_3N.[48]

Synthesis. Below are given representative examples of the general methods presented in Table 1 and 2.

Method IA. 2-Bromo-3-furancarboxanilide (8). Thionyl chloride (2 mL, 27.4 mmol) was added to a solution of **6** (1.02 g, 5.34 mmol) in dry benzene (10 mL). The solution was stirred under reflux for 4 h. The solution was concentrated under reduced pressure. The residue was dissolved in dry benzene (10 mL), and a solution of freshly distilled aniline (1.45 g, 15.6 mmol) and Et_3N (1.58 g, 15.6 mmol) in dry benzene (5 mL) was added dropwise at 0 °C. The resulting solution was stirred at room temperature for 5 h and was poured into 1 M aqueous HCl (20 mL). The aqueous phase was extracted with ether (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography on SiO_2 using ether/petroleum ether (1:1) as eluent gave 1.20 g (84%) of **8** as a pale yellow solid: TLC R_f = 0.5 [SiO_2, ether/petroleum ether (1:1)]; MS (free base), *m*/*z* 267 (M^+ ^{81}Br), 265 (M^+ ^{79}Br); IR (KBr disk) 3320, 1648 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.00 (br s, 1 H), 7.62−7.57 (m, 2 H), 7.49 (d, J = 2.1 Hz, 1 H), 7.42−7.31 (m, 2 H), 7.21−7.12 (m, 1 H), 6.91 (d, J = 2.1 Hz, 1 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 159.19, 144.83, 137.53, 129.27 (2C), 124.94, 123.21, 121.29, 120.41 (2C), 112.95. Anal. ($C_{11}H_8BrNO_2$) C, H, N.

Method IB. 5-Bromo-3-furancarboxamide (12). Compound **12** was prepared from **9** by slow addition of 5-bromo-3-furoyl chloride to an excess of cold ammonium hydroxide which resulted in the immediate formation of a white precipitate. The reaction mixture was concentrated, and the residue was crystallized from aqueous EtOH to give 495 mg (44%) of **12** as a pale yellow solid: TLC R_f = 0.2 [Al_2O_3, ether]; MS (free base), *m*/*z* 191 (M^+ ^{81}Br), 189 (M^+ ^{79}Br); IR (KBr disk) 3395, 3197, 1652, 1621 cm^{-1}; ^{1}H NMR (270 MHz, CD_3OD) δ 8.07 (br s, 1 H), 6.76 (br s, 1 H); ^{13}C NMR (67.9 MHz, CD_3OD) δ 166.05, 148.43, 126.00, 124.85, 111.70. Anal. Found: C, 30.15; H, 2.15; N, 6.6. $C_5H_4BrNO_2 \cdot {}^1/_2H_2O$ requires: C, 30.18; H, 2.41; N, 7.04.

Method II. 5-Bromo-3-furancarbonitrile (13). Compound **13** was prepared by the procedure previously used for the synthesis of 5-bromo-2-furancarbonitrile (**17**). A mixture of 5-bromo-3-furancarboxamide (**12**; 417 mg, 2.19 mmol), NaCl (155 mg, 2.66 mmol), and 1,2-dichloroethane (15 mL) was refluxed for 15 min. Phosphorus oxychloride (1.0 mL, 10.7 mmol) was added, and the reaction mixture was stirred under reflux for 3.5 h. The solution was filtered and concentrated under reduced pressure. Bulb-to-bulb distillation (bp 78−82 °C/∼17 mm) gave 313 mg (83%) of **13** as an oil which solidified in the freezer: TLC R_f = 0.82 [SiO_2, *n*-pentane/ether (9:1)]; MS (free base), *m*/*z* 173 (M^+ ^{81}Br), 171 (M^+ ^{79}Br); IR (KBr disk) 2244 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.92 (d, J = 1 Hz, 1 H), 6.56 (d, J = 1 Hz, 1 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 150.82, 125.12, 112.18, 111.70, 100.64. Anal. (C_5H_2BrNO) C, H, N.

Method IIIA. 3-(3-Bromofuran-2-yl)quinuclidin-3-ol Oxalate (20). A solution of LDA in THF/*n*-heptane (1.5 M; 19.5 mL, 29.3 mmol) was added to a stirred solution of 3-bromofuran (4.00 g, 27.3 mmol) in dry THF (50 mL) at −80 °C. After 2.5 h, a solution of quinuclidin-3-one (3.41 g, 27.3 mmol) in dry THF (20 mL) was added. The reaction mixture was slowly warmed to room temperature. After 10 h, a solution of saturated aqueous ammonium chloride (3 mL) was added dropwise, and the mixture was filtered through a pad of Celite and concentrated under reduced pressure. Column chromatography of the crude product on Al_2O_3 with gradient elution using EtOAc → EtOAc/MeOH (9:1) yielded 6.09 g (82%) of the pure base which was converted into its oxalate salt and recrystallized: TLC R_f (free base) = 0.27 [Al_2O_3, $CHCl_3$/MeOH (95:5)]; MS (free base), *m*/*z* 273 (M^+ ^{81}Br), 271 (M^+ ^{79}Br); ^{1}H NMR (270 MHz, CD_3OD) δ 7.53 (d, J = 2.0 Hz, 1 H), 6.56 (d, J = 2.0 Hz, 1 H), 4.09 (d, J = 13.9 Hz, 1 H), 3.48−3.10 (m, partly obscured, 5 H), 2.85−2.82 (m, 1 H), 2.48−2.31 (m, 1 H), 2.04−1.76 (m, 2 H), 1.70−1.53 (m, 1 H); ^{13}C NMR (67.9 MHz, CD_3OD) δ 172.38, 152.58, 143.54, 117.09, 98.09, 70.35, 66.94, 47.33, 46.59, 30.89, 21.20, 19.23. Anal. ($C_{11}H_{14}BrNO_2 \cdot 0.5(COOH)_2 \cdot {}^1/_4H_2O$) C, H, N.

Method IIIB. 3-(5-Methylfuran-2-yl)quinuclidin-3-ol Fumarate (25). A solution of *n*-BuLi in hexane (1.4 M; 16.5 mL, 23.1 mmol) was added dropwise to a stirred solution of 2-methylfuran (2.85 mL, 31.3 mmol) in dry ether (45 mL) at 0 °C. The cooling bath was removed, and the solution was stirred at room temperature for 4 h. The reaction mixture was cooled to 0 °C, a solution of quinuclidin-3-one (2.53 g, 20.2 mmol) in ether (25 mL) was added, and the mixture was stirred at room temperature for 10 h. A solution of saturated ammonium chloride (15 mL) was added dropwise. The mixture was poured into 2 M aqueous HCl (40 mL) and was washed with ether (3 × 125 mL). The aqueous layer was made basic with 5 M aqueous NaOH and was extracted with ether (5 × 175 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on Al_2O_3 with gradient elution [$CHCl_3$ → $CHCl_3$/MeOH (95:5)] to yield 3.45 g (82%) of the pure base, which was converted into its fumarate salt and recrystallized: TLC R_f (free base) = 0.32 [Al_2O_3, $CHCl_3$/MeOH (95:5)]; MS (free base), *m*/*z* 207 (M^+); ^{1}H NMR (270 MHz,CD_3OD) δ 6.65 (s, 1 H), 6.34 (d, J = 3.1 Hz, 1 H), 6.01−5.98 (m, 1 H), 3.75 (dd, J = 2.0 and 13.7 Hz, 1 H) 3.40−3.00 (m, partly obscured, 5 H), 2.48−2.30 (m, 2 H), 2.28 (d, J = 0.9 Hz, 3 H), 1.93−1.60 (m, 3 H); ^{13}C NMR (22.5 MHz, CD_3OD) δ 174.62, 155.07, 153.62, 137.00, 108.68, 107.32, 69.18, 59.08, 47.16, 46.33, 31.96, 21.19, 19.30, 13.47. Anal. ($C_{12}H_{17}NO_2 \cdot 0.5C_4H_4O_4$) C, H, N.

Method IVA. 3-(3-Bromofuran-2-yl)quinuclidin-2-ene Oxalate (31). The free base of **20** (507 mg, 1.86 mmol) was dissolved in concentrated formic acid and stirred under reflux for 4 h. The solution was made basic with 5 M aqueous NaOH and was extracted with ether (4 × 150 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated *in vacuo* to yield 407 mg (86%) of the pure base as an oil which solidified in the freezer. The base was converted into the oxalate salt and recrystallized: TLC R_f (free base) = 0.7 [Al_2O_3, EtOAc/MeOH (95:5)]; MS (free base), *m*/*z* 255 (M^+ ^{81}Br), 253 (M^+ ^{79}Br); ^{1}H NMR (270 MHz, CD_3OD) δ 7.67 (d, J = 2.0 Hz, 1 H), 7.32 (app d, 1 H), 6.71 (d, J = 2.0 Hz, 1 H), 3.96−3.88 (m, 1 H), 3.73−3.58 (m, 2 H), 3.27−3.12 (m, partly obscured, 2 H), 2.24−2.08 (m, 2 H), 1.94−1.77 (m, 2 H); ^{13}C NMR (67.9 MHz, CD_3OD) δ 166.50, 145.89, 144.40, 138.16, 125.05, 117.84, 101.76, 51.43 (2C), 27.79, 24.11 (2C). Anal. ($C_{11}H_{12}BrNO \cdot (COOH)_2 \cdot {}^3/_4H_2O$) C, H, N.

Method IVB. 3-(3-Cyanofuran-2-yl)quinuclidin-2-ene Hydrochloride (43). The free base of 3-(3-cyanofuran-2-yl)-quinuclidin-3-ol (**28**) (428 mg, 1.96 mmol) in dry THF (30 mL) was added dropwise to a solution of Burgess' reagent[13] (1.0 g, 4.2 mmol) in dry THF (40 mL). The solution was stirred at room temperature for 1 h and then under reflux for 6 h. The crude mixture was concentrated, and the residue was partitioned between 1 M aqueous NaOH and $CHCl_3$. The combined organic extracts were dried (K_2CO_3), filtered, and concentrated. Column chromatography of the crude product on SiO_2 using $CHCl_3$/MeOH (95:5) as eluent gave 141 mg (36%) of the pure base. The product was converted into its hydrochloride salt and recrystallized: TLC R_f (free base) = 0.32 [Al_2O_3, $CHCl_3$/MeOH (95:5)]; MS (free base), m/z 200 (M^+); IR (KBr disk) 2235 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 7.83 (d, J = 2.0 Hz, 1 H), 7.33 (app d, 1 H), 6.92 (d, J = 2.0 Hz, 1 H), 3.92−3.85, (m, 1 H), 3.81−3.66 (m, 2 H), 3.33−3.17 (m, partly obscured, 2 H), 2.30−2.14 (m, 2 H), 1.99−1.82 (m, 2 H); ^{13}C NMR (67.9 MHz, CD_3OD) δ 154.09, 146.70, 137.21, 127.71, 114.90, 114.41, 97.02, 51.64 (2C), 27.85, 24.03 (2C). Anal. ($C_{12}H_{12}N_2O$·HCl) C, H, N.

Method VA. 3-(4-Cyanofuran-2-yl)quinuclidin-2-ene Oxalate (44). A mixture of 5-bromo-3-furancarbonitrile (**13**) (105 mg, 0.61 mmol) and $Pd(PPh_3)_4$ (70 mg, 0.061 mmol) in DMF (3 mL) was stirred at 100 °C. A solution of 3-(tributylstannyl)quinuclidin-2-ene (**19**)[18] (403 mg, 1.01 mmol) in DMF (1 mL) was added to the reaction mixture after 5 min. The mixture was heated at 100 °C for 48 h in a sealed flask, diluted with dioxane, filtered through a pad of Celite, and concentrated *in vacuo*. The residue was purified by repetitive chromatography on SiO_2 using $CHCl_3$/MeOH (9:1) as eluent. The crude base was converted into the oxalate salt and recrystallized. This afforded 61.9 mg (31%) of **44**: TLC R_f (free base) = 0.44 [SiO_2, $CHCl_3$/MeOH (9:1)]; MS (free base), m/z 200 (M^+); IR (KBr disk) 2241 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 8.39 (s, 1 H), 7.20 (s, 1 H), 7.11 (s, 1 H), 3.75−3.40 (m, 3 H), 3.35−3.20 (m, partly obscured, 2 H), 2.23−2.06 (m, 2 H), 1.91−1.73 (m, 2 H); ^{13}C NMR (67.9 MHz, CD_3OD) δ 166.72, 153.39, 150.58, 137.30, 125.12, 113.31, 112.02, 100.90, 51.84 (2C), 28.57, 24.28 (2C). Anal. ($C_{12}H_{12}N_2O$·$(COOH)_2$) C, H, N.

Method VB. 3-[4-(*N*-Phenylcarbamoyl)furan-2-yl]quinuclidin-2-ene Hydrochloride (38). A mixture of 5-bromo-3-furancarboxanilide (**11**) (435 mg, 1.64 mmol), $Pd(PPh_3)_4$ (189 mg, 0.164 mmol), and CuO (130 mg, 1.64 mmol) in DMF (8 mL) was stirred at 100 °C in a sealed flask. After 5 min, a solution of **19** (781 mg, 1.96 mmol) in DMF (1 mL) was added. The reaction mixture was heated at 100 °C for 7 h. The mixture was diluted with dioxane, filtered through Celite, and concentrated *in vacuo*. The residue was purified by repetitive column chromatography on SiO_2 with gradient elution using $CHCl_3$ → $CHCl_3$/MeOH (9:1) as eluent and then on Al_2O_3 with EtOAc as eluent. This provided 283 mg (59%) of the pure base as a white solid. The base was converted into the hydrochloride salt and recrystallized: TLC R_f (free base) = 0.20 [SiO_2, $CHCl_3$/MeOH (9:1)]; MS (free base), m/z 294 (M^+); IR (KBr disk) 3255, 1640 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 8.33 (s, 1 H), 7.72−7.60 (m, 2 H), 7.43−7.27 (m, 3 H), 7.20−7.09 (m, 1 H), 7.02 (s, 1 H), 3.78−3.46 (m, 3 H), 3.35−3.12 (m, partly obscured, 2 H), 2.28−2.08 (m, 2 H), 1.94−1.76 (m, 2 H); ^{13}C NMR (67.9 MHz, CD_3OD) δ 162.42, 149.68, 148.34, 139.48, 138.22, 129.88 (2C), 126.25, 125.73, 122.91, 122.15 (2C), 110.89, 52.15 (2C), 28.63, 24.20 (2C). Anal. ($C_{18}H_{18}N_2O_2$·HCl·$^1/_4H_2O$) C, H, N.

Method VC. 3-(5-(Methoxycarbonyl)furan-2-yl)quinuclidin-2-ene Oxalate (42). To a stirred solution of **19** (3.43 g, 8.61 mmol) in dioxane (50 mL) were added methyl 5-bromofuran-2-carboxylate (**14**; 1.76 g, 8.61 mmol) and $PdCl_2(PPh_3)_2$ (0.18 g, 0.26 mmol). The reaction mixture was refluxed for 5 days. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography on Al_2O_3 with $CHCl_3$ as eluent and then on SiO_2 using $CHCl_3$/MeOH (9:1) as eluent. This provided 0.74 g (37%) of the pure base as an oil which was converted into the oxalate salt and recrystallized: TLC R_f (free base) = 0.42 (Al_2O_3, $CHCl_3$); MS (free base), m/z 233 (M^+); IR (KBr disk) 1727 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6) δ 7.41 (d, J = 3.6 Hz, 1 H), 7.12 (d, partly obscured, J = 3.6 Hz, 1 H), 7.10 (br s, 1 H), 3.83 (s, 3 H), 3.53−3.36 (m, 3 H), 3.05−2.82 (m, 2 H), 2.05−1.89 (m, 2 H), 1.72−1.55 (m, 2 H); ^{13}C NMR (22.5 MHz, CD_3OD) δ 166.53, 160.19, 151.98, 146.45, 137.90, 125.39, 120.48, 113.22, 52.69, 51.73 (2C), 28.47, 24.31 (2C). Anal. ($C_{13}H_{15}NO_3$·$(COOH)_2$) C, H, N.

Method VI. 3-(3-Methylfuran-2-yl)quinuclidin-2-ene Oxalate (46). A mixture of the free base of **31** (930 mg, 3.66 mmol), $Pd(OAc)_2$ (16 mg, 0.071 mmol), P(*o*-tolyl)$_3$ (89 mg, 0.29 mmol), Et_3N (509 μL, 3.66 mmol), and Me_4Sn (1.3 g, 7.32 mmol) in DMF (5 mL) was heated at 100 °C for 36 h in a sealed flask. The mixture was diluted with dioxane, filtered through Celite, and concentrated under reduced pressure. The residue was purified by repetitive column chromatography on SiO_2 with gradient elution using $CHCl_3$ → $CHCl_3$/MeOH (9:1) to yield 612 mg (88%) of pure base as a pale yellow solid. The product was converted into the oxalate salt and recrystallized: TLC R_f (free base) = 0.45 [SiO_2, $CHCl_3$/MeOH (85:15)]; MS (free base), m/z 189 (M^+); ^1H NMR (270 MHz, CD_3OD) δ 7.53 (d, J = 1.7 Hz, 1 H), 6.81 (br s, 1 H), 6.44 (d, J = 1.7 Hz, 1 H), 3.78−3.56 (m, 3 H), 3.34−3.16 (m, partly obscured, 2 H), 2.28−2.10 (m, 5 H), 1.94−1.76 (m, 2 H); ^{13}C NMR (67.9 MHz, CD_3OD) δ 166.15, 144.40, 143.66, 139.84, 123.29, 121.72, 116.75, 51.86 (2C), 28.07, 24.03 (2C), 11.86. Anal. ($C_{12}H_{15}NO$·$(COOH)_2$·$^1/_4H_2O$) C, H, N.

Method VII. 3-[3-(4-(Trifluoromethyl)phenyl)furan-2-yl]quinuclidin-2-ene Oxalate (57). $Pd(PPh_3)_4$ (332 mg 0.29 mmol) was added to a stirred solution of the free base of **31** (1.22 g, 4.80 mmol) in 1,2-dimethoxyethane (15 mL). After 10 min, 4-(trifluoromethyl)benzeneboronic acid (1.00 g, 5.26 mmol) and 2 M aqueous Na_2CO_3 (10 mL) were added, and the reaction mixture was stirred under reflux for 3 h. The mixture was concentrated and partitioned between 1 M aqueous HCl (50 mL) and ether (50 mL). The aqueous layer was made basic with K_2CO_3 and extracted with $CHCl_3$ (3 × 150 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated. The residue was purified by column chromatography, first on SiO_2 using EtOAc/MeOH (9:1) as eluent and then on Al_2O_3 using ether as eluent, to yield 1.22 g (80%) of the base which was converted into the oxalate and recrystallized: TLC R_f (free base) = 0.51 [SiO_2, $CHCl_3$/MeOH (9:1)]; MS (free base), m/z 319 (M^+); ^1H NMR (270 MHz, CD_3OD) δ 7.80−7.72 (m, 2 H), 7.70 (d, J = 1.9 Hz, 1 H), 7.66−7.60 (m, 2 H), 6.93 (app d, 1 H), 6.69 (d, J = 1.9 Hz, 1 H), 3.70−3.52 (m, 2 H), 3.26−3.06 (m, 3 H), 2.10−1.70 (m, 4 H); ^{13}C NMR (67.9 MHz, CD_3OD) δ 166.50, 145.24, 143.82, 138.85, 138.63, 131.20 (q, $J_{C,F}$ = 33 Hz), 130.63 (2C), 127.38, 126.82 (q, $J_{C,F}$ = 4.2 Hz, 2C), 125.57 (q, $J_{C,F}$ = 271 Hz, CF_3), 124.83, 115.50, 51.62 (2C), 28.41, 24.20 (2C). Anal. ($C_{18}H_{16}F_3NO$·$(COOH)_2$) C, H, N.

Method VIII. 3-(5-Bromo-3-phenylfuran-2-yl)quinuclidin-2-ene Sesquioxalate (54). A solution of *n*-BuLi in hexane (1.6 M; 1.61 mL, 2.58 mmol) was added dropwise to a stirred solution of **49** (500 mg, 1.99 mmol) in dry ether (50 mL) at −70 °C. The cooling bath was removed, and the solution was stirred at room temperature for 4 h. The reaction mixture was cooled to −70 °C, and 1,2-dibromotetrafluoroethane (0.38 mL, 3.97 mmol) was added dropwise. The mixture was allowed to slowly reach room temperature over 10 h. The reaction was quenched by addition of water (5 mL) and concentrated under reduced pressure. The residue was purified by column chromatography on SiO_2 using gradient elution [$CHCl_3$ → $CHCl_3$/MeOH (9:1)] to give 342 mg (52%) of the pure base of **54**. The product was converted into the oxalate and recrystallized: TLC R_f (free base) = 0.37 [SiO_2, $CHCl_3$/MeOH (95:5)]; MS (free base), m/z 331 (M^+ ^{81}Br), 329 (M^+ ^{79}Br); ^1H NMR (270 MHz, CD_3OD) δ 7.51−7.38(m, 5 H), 6.87 (app d, 1 H), 6.66 (s, 1 H), 3.67−3.52 (m, 2 H), 3.26−3.04 (m, 3 H), 2.02−1.71 (m, 4 H); ^{13}C NMR (67.9 MHz, CD_3OD) δ 165.01, 145.30, 138.29, 133.26, 131.44, 130.04 (2C), 129.95 (2C), 125.50, 124.29, 117.43, 51.75 (2C), 28.05, 24.15 (2C). Anal. ($C_{17}H_{16}BrNO$·1.5$(COOH)_2$) C, H, N.

Method IX. 3-[3-(4-Butoxyphenyl)furan-2-yl]quinuclidin-2-ene Oxalate (59). A solution of *n*-BuLi in hexane (1.6 M; 15 mL, 24 mmol) was added over 5 min to a stirred solution of *p*-bromobutoxybenzene (5.0 g, 21.8 mmol) in dry THF (100 mL) at −78 °C. After 20 min, triisopropyl borate (6.67 mL, 28.3 mmol) was added, and the mixture was stirred at −78

°C for 3 h. The reaction was quenched by addition of water (2 mL) and concentrated. The residue was dissolved in 1,2-dimethoxyethane (30 mL), and the free base of **31** (5.03 g, 19.8 mmol), $Pd(PPh_3)_4$ (1.38 g, 1.19 mmol), and 2 M aqueous Na_2CO_3 (15 mL) were added. The reaction mixture was refluxed for 3 h, concentrated, and extracted with $CHCl_3$ (3 × 150 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated. The residue was purified by repetitive column chromatography, first on SiO_2 using $CHCl_3$/MeOH (9:1) as eluent and then on Al_2O_3 using EtOAc as eluent, to yield 3.64 g (57%) of pure base. The product was converted into the oxalate and recrystallized: TLC (free base) $R_f = 0.59$ [SiO_2, $CHCl_3$/MeOH (9:1)]; MS (free base), m/z 323 (M^+); IR (KBr disk) 1245 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 7.60 (d, J = 1.9 Hz, 1 H), 7.25−7.20 (m, 2 H), 7.05−6.80 (m, 2 H), 6.56 (d, J = 1.9 Hz, 1 H), 4.00 (t, J = 6.3 Hz, 2 H), 3.67−3.50 (m, 2 H), 3.25−3.05 (m, 3 H), 2.04−1.42 (m, 8 H), 0.99 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (67.9 MHz, CD_3OD) δ 166.52, 160.72, 144.66, 142.91, 139.30, 131.13, 128.97, 126.31, 123.44, 115.89, 115.80, 68.82, 51.73(2C), 32.49, 27.96, 24.20(2C), 20.32, 14.21. Anal. ($C_{21}H_{25}NO_2 \cdot (COOH)_2$) C, H, N.

Method XA. 3-[3-(4-Cyanophenyl)furan-2-yl]quinuclidin-2-ene Sesquioxalate (65). A mixture of stannane derivative **72** (803 mg, 1.73 mmol), $Pd(PPh_3)_4$ (200 mg, 0.173 mmol), *p*-bromobenzonitrile (314 mg, 1.73 mmol), and DMF (4 mL) was stirred in a sealed flask for 24 h at 100 °C. The reaction mixture was concentrated, and the residue was purified by repetitive column chromatography on SiO_2 using $CHCl_3$/MeOH (9:1) as eluent to yield 219 mg (46%) of the base which was converted into its oxalate salt and recrystallized: TLC (free base) $R_f = 0.40$ [SiO_2, $CHCl_3$/MeOH (9:1)]; MS (free base), m/z 276 (M^+); IR (KBr disk) 2228 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 7.86−7.78 (m, 2 H), 7.71 (d, J = 1.9 Hz, 1 H), 7.67−7.59 (m, 2 H), 6.90 (app d, 1 H), 6.70 (d, J = 1.9 Hz, 1 H), 3.70−3.54 (m, 2 H), 3.27−3.10 (m, 3 H), 2.10−1.94 (m, 2 H), 1.92−1.74 (m, 2 H); ^{13}C NMR (67.9 MHz, CD_3OD) δ 165.80, 146.30, 144.83, 140.34, 139.63, 134.67 (2C), 131.75 (2C), 127.99, 125.85, 120.30, 116.15, 113.79, 52.52 (2C), 29.34, 25.05 (2C). Anal. ($C_{18}H_{16}N_2O \cdot 1.5(COOH)_2$) C, H, N.

Method XB. 3-[3-(3-Acetoxyphenyl)furan-2-yl]quinuclidin-2-ene Sesquioxalate (66). A mixture of stannane derivative **72** (3.19 g, 6.87 mmol), Pd_2dba_3 (252 mg, 0.28 mmol), $AsPh_3$ (337 mg, 1.10 mmol), and *m*-iodophenyl acetate (1.80 g, 6.87 mmol) in degassed DMF (15 mL) was stirred at room temperature. After 5 min, CuI[49] (105 mg, 0.55 mmol) was added, and the mixture was stirred at 50 °C for 60 h. The reaction mixture was filtered, and the solvent was removed under reduced pressure. The residue was purified by repetitive column chromatography on SiO_2 with gradient elution using $CHCl_3$ → $CHCl_3$/MeOH (9:1) as eluents to yield 597 mg (28%) of the base which was converted into the oxalate and recrystallized: TLC (free base) $R_f = 0.41$ [SiO_2, $CHCl_3$/MeOH (9:1)]; MS (free base), m/z 309 (M^+); IR (KBr disk) 1761 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 7.67 (d, J = 2.0 Hz, 1 H), 7.55−7.45 (m, 1 H), 7.35−7.08 (m, 3 H), 6.85 (br s, 1 H), 6.65 (d, J = 2.0 Hz, 1 H), 3.70−3.42 (m, 2 H), 3.38−3.06 (m, partly obscured, 3 H), 2.29 (s, 3 H), 2.10−1.68 (m, 4 H); ^{13}C NMR (100.5 MHz, CD_3OD) δ 171.29, 165.27, 152.49, 145.13, 143.52, 139.04, 135.77, 131.20, 128.07, 127.41, 124.12, 123.74, 122.49, 115.60, 51.77 (2C) 28.11, 24.23 (2C), 20.96. Anal. ($C_{19}H_{19}NO_3 \cdot 1.5(COOH)_2$) C, H, N.

Method XI. 3-[3-(3-Hydroxyphenyl)furan-2-yl]quinuclidin-2-ene Hydrochloride (68). A mixture of the free base of **66** (597 mg, 1.93 mmol), MeOH (10 mL), and 10% aqueous NaOH (10 mL) was stirred under reflux for 1 h. The MeOH was evaporated, and the residue was washed with ether (10 mL). The pH of the aqueous layer was adjusted to ∼8.5 with 5 M aqueous HCl and extracted with CH_2Cl_2 (6 × 75 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give an amorphous residue. Addition of ethereal HCl produced the hydrochloride of **68** which was recrystallized: TLC (free base) $R_f = 0.19$ [SiO_2, $CHCl_3$/MeOH (9:1)]; MS (free base) m/z 267 (M^+); ^1H NMR (270 MHz, CD_3OD) δ 7.63 (d, J = 2.0 Hz, 1 H), 7.30−7.20 (m, 1 H), 6.90−6.65 (m, 4 H), 6.58 (d, J = 2.0 Hz, 1 H), 3.70−3.54 (m, 2 H), 3.28−3.08 (m, partly obscured, 3 H), 2.08−1.70 (m, 4 H); (67.9 MHz, CD_3OD) δ 159.80, 145.67, 143.84, 140.35, 136.51, 131.84, 130.25, 124.05, 121.86, 117.53, 117.12, 116.58, 52.81 (2C), 29.82, 24.96 (2C). Anal. ($C_{17}H_{17}NO_2 \cdot HCl$) C, H, N.

Synthetic Procedure for Compounds Not Prepared by General Methods: 4-(3-Bromophenyl)morpholine. This compound was prepared using a slight modification of a procedure reported for the synthesis of 4-(4-bromophenyl)-morpholine. A mixture of 3-bromoaniline (17.2 g, 0.1 mol), 2,2′-dichlorodiethyl ether (14.4 g, 0.1 mol), and 2 M aqueous NaOH (80 mL) was heated under reflux for 5 days. The cooled mixture was extracted with ether (4 × 100 mL). The combined ether layers were dried (M_gSO_4), filtered, and concentrated. The residue was purified by repeated column chromatography on SiO_2 using *n*-pentane/ether (75:25) as eluent to give an oil. The crude product was converted into the hydrochloride salt and recrystallized from MeCN/MeOH. The crystals were treated with 1 M aqueous NaOH, and the free base was extracted with ether. The organic layer was dried (K_2CO_3), filtered, and concentrated to give 5.8 g (24%) of pure 4-(3-bromophenyl)morpholine as an oil: TLC R_f (free base) = 0.50 [SiO_2, $CHCl_3$/MeOH (9:1)]; MS (free base), m/z 243 (M^+ ^{81}Br), 241 (M^+ ^{79}Br); ^1H NMR (free base; 270 MHz, $CDCl_3$) δ 7.12 (dd, J = 8.0 Hz, 1 H), 7.04−6.92 (m, 2 H), 6.88−6.86 (m, 1 H), 3.88−3.79 (m, 2 H), 3.18−3.09 (m, 2 H); ^{13}C NMR (free base; 67.9 MHz, $CDCl_3$) δ 152.40, 130.29, 123.19, 122.46, 118.27, 113.96, 67.57 (2C), 49.71 (2C). Anal. ($C_{10}H_{12}BrNO$) C, H, N.

2-Bromo-3-furoic Acid (6). A solution of LDA in THF/*n*-heptane (2 M; 89.7 mL, 179.3 mmol) was added over 0.5 h to a stirred solution of 3-furoic acid (9.14 g, 81.5 mmol) in THF (250 mL) at −78 °C. After 3 h, 1,2-dibromotetrafluoroethane was added dropwise, and the mixture was allowed to slowly reach room temperature over 10 h. The reaction was quenched by addition of water (2 mL) and concentrated. The residue was dissolved in water, filtered, and washed with ether (2 × 10 mL). The aqueous portion was acidified with concentrated HCl and extracted with ether (4 × 150 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was dissolved in methanol, decolorized with charcoal, and then crystallized from aqueous methanol. This gave 4.93 g (32%) of the acid as white needles: IR (KBr disk) 1689 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 7.63 (d, J = 2.1 Hz, 1 H), 6.79 (d, J = 2.1 Hz, 1 H); ^{13}C NMR (67.9 MHz, CD_3OD) δ 164.96, 146.29, 130.12, 119.08, 113.96. Anal. ($C_5H_3BrO_3$) C, H.

Methyl 2-Bromofuran-3-carboxylate (7). Dimethyl sulfate (1.46 g, 11.6 mmol) was added to a suspension of **6** (2.01 g, 10.5 mmol) and K_2CO_3 (2.9 g, 21.0 mmol) in acetone (50 mL). The reaction mixture was stirred at room temperature overnight. A solution of ethanol saturated with ammonia (0.5 mL) was added to quench the reaction. Insoluble material was filtered off, and the acetone was removed under reduced pressure. Purification by flash chromatography on SiO_2 using *n*-pentane/ether (9:1) as eluent gave 1.98 g (92%) of **7** as a pale yellow solid: TLC $R_f = 0.89$ [SiO_2, *n*-pentane/ether (9:1)]; MS (free base), m/z 206 (M^+ ^{81}Br), 204 (M^+ ^{79}Br); IR (KBr disk) 1733 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.43 (d, J = 2.1 Hz, 1 H), 6.77 (d, J = 2.1 Hz, 1 H), 3.86 (s, 3 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 162.37, 144.35, 129.05, 117.25, 112.68, 51.82. Anal. ($C_6H_5BrO_3$) C, H.

Methyl 5-Bromofuran-3-carboxylate (10). A solution of Br_2 (4.06 g, 25.4 mmol) in 1,2-dichloroethane (10 mL) was added during 15 min to a boiling solution of methyl furan-3-carboxylate (3.20 g, 25.4 mmol) in 1,2-dichloroethane (50 mL). The solution was refluxed for 24 h and then allowed to reach room temperature. The organic solution was washed with cold saturated aqueous $NaHCO_3$ and water, then dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash chromatography on SiO_2 using *n*-pentane/ether (9:1) as eluent. Repeated distillation in a Kugelrohr apparatus gave 1.25 g (24%) of pure **10** as a pale yellow solid: TLC $R_f = 0.48$ [SiO_2, ether/petroleum ether (9:1)]; MS (free base), m/z 206 (M^+ ^{81}Br), 204 (M^+ ^{79}Br); IR (KBr disk) 1727 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.96 (d, J = 1.0 Hz, 1 H), 6.67 (d, J = 1.0 Hz, 1 H), 3.84 (s, 3 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 162.33, 148.64, 123.92, 121.65, 111.36, 52.04. Anal. ($C_6H_5BrO_3$) C, H.

Methyl 5-Bromofuran-2-carboxylate (14). Iodomethane (475 mL, 7.86 mmol) was added to a solution of 5-bromofuroic acid (1.0 g, 5.2 mmol) and Cs_2CO_3 (2.05 g, 6.29 mmol) in DMF (15 mL). The reaction mixture was stirred at room temperature overnight. The solution was concentrated under reduced pressure. The residue was purified by column chromatography on Al_2O_3 using ether as eluent to give 0.90 g (84%) of **14** as a white solid: TLC R_f = 0.9 [SiO_2, *n*-pentane/ether (9:1)]; MS (free base), *m*/*z* 206 ($M^{+\ 81}Br$), 204 ($M^{+\ 79}Br$); IR (KBr disk) 1710 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.10 (d, *J* = 3.5 Hz, 1 H), 6.43 (d, *J* = 3.5 Hz, 1 H), 3.86 (s, 3 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 158.03, 146.21, 127.52, 120.18, 113.94, 52.11. Anal. ($C_6H_5BrO_3$) C, H.

3-(4-Bromo-5-(trimethylsilyl)furan-2-yl)quinuclidin-3-ol (21). A solution of LDA (13.6 mL, 2 M, 27.2 mmol) in THF/*n*-heptane was added dropwise to a stirred solution of 3-bromofuran (4.0 g, 27.2 mmol) in dry THF (50 mL) at −78 °C. After being stirred for 3 h, chlorotrimethylsilane (3.43 mL, 27.2 mmol) was added. The mixture was allowed to reach room temperature over 10 h. The reaction mixture was quenched by addition of water (2 mL), filtered, and concentrated. The resulting solution (∼15 mL) was diluted with petroleum ether (400 mL) and washed with water until neutral. The organic layer was dried (M_gSO_4), filtered, and concentrated. The resulting oil (5.89 g) was dissolved in dry THF (100 mL), the mixture was cooled down to −78 °C, and a solution of LDA (14.8 mL, 2 M, 29.6 mmol) in THF/*n*-heptane was added dropwise. After 3.5 h, a solution of quinuclidin-3-one (3.36 g, 26.8 mmol) in dry THF (15 mL) was added. The mixture was allowed to reach room temperature over 10 h. The reaction mixture was quenched by addition of water (2 mL), filtered, and concentrated. Column chromatography of the crude product on Al_2O_3 using $CHCl_3$ as eluent gave 5.1 g (54%) of the pure base: TLC R_f (free base) = 0.57 [Al_2O_3, $CHCl_3$/MeOH (95:5)]; MS (free base), *m*/*z* 345 ($M^{+\ 81}Br$), 343 ($M^{+\ 79}Br$); ^1H NMR (free base; 270 MHz, $CDCl_3$) δ 6.31 (s, 1 H), 3.33 (dd, *J* = 2.0 Hz and 14.4 Hz, 1 H), 3.02−2.05 (m, 8 H), 1.57−1.27 (m, 3 H), 0.33 (s, 9 H,); ^{13}C NMR (free base, 67.9 MHz, $CDCl_3$) δ 163.28, 155.99, 110.79, 110.28, 70.24, 61.08, 46.93, 46.22, 32.42, 23.50, 20.99, −1.39 (3C). Anal. ($C_{14}H_{22}BrNO_2Si$) C, H, N.

3-(4-Bromofuran-2-yl)quinuclidin-3-ol Oxalate (22). A solution of the free base of **21** (4.96 g, 14.4 mmol), *p*-toluenesulfonic acid (10 g 52.6 mmol), MeOH (150 mL), and water (15 mL) was stirred at room temperature for 6 days. The MeOH was evaporated, and the mixture was made basic with 5 M aqueous NaOH and extracted with $CHCl_3$ (5 × 150 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated under reduced pressure. The crude product was triturated with ether/*n*-hexane (1:1) and then recrystallized from EtOAc/MeOH. This gave 2.4 g (61%) of the pure base which was converted into the oxalate salt and recrystallized: TLC R_f (free base) = 0.52 [Al_2O_3, $CHCl_3$/MeOH (95:5)]; MS (free base), *m*/*z* 273 ($M^{+\ 81}Br$), 271 ($M^{+\ 79}Br$); ^1H NMR (270 MHz, CD_3OD) δ 7.65 (s, 1 H), 6.66 (s, 1 H), 3.85−3.75 (m, 1 H), 3.42−3.24 (m, partly obscured, 5 H), 2.49−2.42 (m, 2 H), 1.99−1.63 (m, 3 H); ^{13}C NMR (67.9 MHz, CD_3OD) δ 166.79, 158.33, 142.66, 111.64, 101.40, 69.33, 58.98, 47.53, 46.72, 32.02, 20.86, 19.16. Anal. ($C_{11}H_{14}BrNO_2 \cdot (COOH)_2 \cdot {}^1/_4H_2O$) C, H, N.

3-(4-Acetylfuran-2-yl)quinuclidin-2-ene Oxalate (35). A mixture of the free base of **32** (117 mg, 0.46 mmol), $Pd(OAc)_2$ (2.0 mg, 0.0089 mmol), P(*o*-tolyl)$_3$ (11.0 mg 0.036 mmol), K_2CO_3 (128 mg, 0.93 mmol), and (α-ethoxyvinyl)tributyltin (312 μL, 0.92 mmol) in dry DMF (2.5 mL) was heated at 100 °C for 24 h in a sealed flask. The DMF was evaporated, and 1 M aqueous HCl (5 mL) was added. The mixture was stirred at room temperature for 1 h, made basic with 5 M aqueous NaOH, and extracted with CH_2Cl_2. The combined organic layers were dried (K_2CO_3), filtered, and concentrated. The residue was purified by column chromatography on SiO_2 using $CHCl_3$/MeOH (9:1) as eluent to yield 47 mg (47%) of the pure base which was converted into the oxalate and recrystallized: TLC R_f (free base) = 0.36 [SiO_2, $CHCl_3$/MeOH (9:1)]; MS (free base), *m*/*z* 217 (M^+); IR (KBr disk) 1670 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 8.43 (s, 1 H), 7.18 (s, 1 H), 7.05 (s, 1 H), 3.73−3.45 (m, 3 H), 3.37−3.10 (m, partly obscured, 2 H), 2.46 (s, 3 H), 2.24−2.05 (m, 2 H), 1.90−1.74 (m, 2 H); ^{13}C NMR (67.9 MHz, CD_3OD) δ 194.34, 167.15, 151.44, 150.51, 138.02, 130.82, 124.04, 109.70, 51.90 (2C), 28.63, 27.76, 24.37 (2C). Anal. ($C_{13}H_{15}NO_2 \cdot (COOH)_2$) C, H, N.

3-(5-Acetylfuran-2-yl)quinuclidin-2-ene Oxalate (36). A solution of *n*-BuLi in hexane (1.6 M; 4.7 mL, 7.52 mmol) was added dropwise to a stirred solution of the free base of **4** (1.14 g, 6.50 mmol) in dry ether (50 mL) at −30 °C. The cooling bath was removed, and the solution was stirred at room temperature for 4 h. The reaction mixture was cooled to −70 °C, and *N*,*N*-dimethylacetamide (0.70 mL, 7.55 mmol) was added. The mixture was allowed to slowly reach room temperature over 10 h. The reaction was quenched by addition of water (5 mL) and concentrated under reduced pressure. The residue was stirred with 2.5 M aqueous HCl (15 mL) at room temperature for 1 h. The solution was made basic by addition of 5 M aqueous NaOH and extracted with $CHCl_3$ (4 × 50 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated *in vacuo*. Column chromatography of the crude product on SiO_2 using $CHCl_3$/MeOH (9:1) as eluent gave 580 mg (41%) of the pure base. The product was converted into the oxalate and recrystallized: TLC R_f (free base) = 0.37 [SiO_2, $CHCl_3$/MeOH (9:1)]; MS (free base), *m*/*z* 217 (M^+); IR (KBr disk) 1675 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 7.41 (d, *J* = 3.7 Hz, 1 H), 7.26 (br s, 1 H), 7.04 (d, *J* = 3.7 Hz, 1 H) 3.78−3.52 (m, 3 H), 3.38−3.14 (m, partly obscured, 2 H), 2.48 (s, 3 H), 2.29−2.04 (m, 2 H), 1.94−1.75 (m, 2 H); ^{13}C NMR (67.9 MHz, CD_3OD) δ 188.50, 166.56, 154.03, 152.18, 137.97, 125.95, 120.75, 113.60, 51.72 (2C), 28.50, 26.09, 24.31 (2C). Anal. ($C_{13}H_{15}NO_2 \cdot (COOH)_2$) C, H, N.

3-{3-[3-[[(Trifluoromethyl)sulfonyl]oxy]phenyl]furan-2-yl}quinuclidin-2-ene Hydrochloride (70). A slurry of **68**·HCl (80 mg, 0.26 mmol), Et_3N (1 mL), and CH_2Cl_2 (10 mL) was stirred for 1 h at room temperature. *N*-Phenyltrifluoromethanesulfonimide (160 mg, 0.45 mmol) was added, and the mixture was stirred under reflux for 2.5 h and then at room temperature for 20 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with 10% aqueous K_2CO_3 (10 mL). The organic layer was dried (K_2CO_3), filtered, and concentrated under reduced pressure. The residue was purified by repetitive column chromatography on SiO_2 using gradient elution [$CHCl_3$ → $CHCl_3$/MeOH (9:1)] to give 68 mg (65%) of the pure base of **70** which was converted into the hydrochloride and recrystallized: TLC (free base) R_f = 0.50 [SiO_2, $CHCl_3$/MeOH (9:1)]; MS (free base), *m*/*z* 399 (M^+); IR (HCl salt, KBr disk) 1212, 1140 cm^{-1}; ^1H NMR (399 MHz, CD_3OD) δ 7.71 (d, *J* = 2.0 Hz, 1 H), 7.68−7.62 (m, 1 H), 7.58−7.49 (m, 2 H), 7.46−7.40 (m, 1 H), 6.78 (app d, 1 H), 6.68 (d, *J* = 2.0 Hz, 1 H), 3.70−3.54 (m, 2 H), 3.40−3.10 (m, partly obscured, 3 H), 2.10−1.97 (m, 2 H), 1.91−1.77 (m, 2 H); ^{13}C NMR (67.9 MHz, CD_3OD) δ 151.16, 145.42, 143.88, 139.12, 137.36, 132.38, 130.53, 126.81, 124.63, 123.14, 122.10, 120.23 (q, $J_{C,F}$ = 320 Hz, CF_3), 115.63, 51.82 (2C), 28.23, 24.29 (2C). Anal. ($C_{18}H_{16}F_3NO_4S$·HCl) C, H, N.

3-{3-[3-[(Methylsulfonyl)oxy]phenyl]furan-2-yl}quinuclidin-2-ene Hydrochloride (71). A slurry of **68**·HCl (51 mg, 0.168 mmol), Et_3N (117 μL, 0.84 mmol), and CH_2Cl_2 (5 mL) was stirred for 1 h at room temperature. A solution of methanesulfonyl chloride (22 μL, 0.28 mmol) in CH_2Cl_2 (1 mL) was added dropwise at −40 °C. The cooling bath was removed and the reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with 10% aqueous K_2CO_3 (10 mL). The organic layer was dried (K_2CO_3), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on SiO_2 using gradient elution [$CHCl_3$ → $CHCl_3$/MeOH (9:1)] to give 51 mg (88%) of the pure base of **71** which was converted into the hydrochloride and recrystallized: TLC (free base) R_f = 0.50 [SiO_2, $CHCl_3$/MeOH (9:1)]; MS (free base), *m*/*z* 345 (M^+); IR (HCl salt, KBr disk) 1358, 1150 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 7.70 (d, *J* = 1.9 Hz, 1 H), 7.61−7.53 (m, 1 H), 7.47−7.41 (m, 2 H), 7.37−7.31 (m, 1 H), 6.77 (br s, 1 H), 6.69 (d, *J* = 1.9 Hz, 1 H), 3.66−3.51 (m, 2 H), 3.40−3.10 (m, partly obscured, 3 H), 2.12−1.76 (m, 4 H); ^{13}C NMR δ (100.5 MHz, CD_3OD) δ 150.84, 145.39, 143.65, 139.01,

136.48, 131.91, 128.93, 127.34, 124.38, 123.96, 122.91, 115.53, 51.81 (2C), 37.97, 28.26, 24.25 (2C). Anal. ($C_{18}H_{19}NO_4S \cdot HCl \cdot {}^1/_4H_2O$) C, H, N.

3-(3-(Tributylstannyl)furan-2-yl)quinuclidin-2-ene (72). A solution of *n*-BuLi in hexane (1.6 M; 3.20 mL, 5.12 mmol) was added over 5 min to a stirred solution of **31** (1.17 g, 4.60 mmol) in dry THF (50 mL) at −78 °C. After 10 min, tributyltin chloride (1.38 mL, 5.13 mmol) was added, and the mixture was stirred at −78 °C for 2 h. The cooling bath was removed, and the reaction was quenched by addition of water (2 mL). The mixture was concentrated and partitioned between water (30 mL) and ether (3 × 100 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated. The residue was purified by repetitive column chromatography on SiO_2 using ammonia-saturated ether as eluent to give 1.42 g (66%) of **72** as an oil. An aliquot was subjected to bulb-to-bulb distillation (bp 200−210 °C/∼0.5 mm) to give the analytical sample: TLC (free base) $R_f = 0.55$ [SiO_2, $CHCl_3$/MeOH (9:1)]; ^{1}H NMR (free base; 270 MHz, $CDCl_3$) δ 7.51 (d, $J = 1.7$ Hz, 1 H), 6.75 (d, $J = 1.7$ Hz, 1 H), 6.37 (d, $J = 1.7$ Hz, 1 H), 3.17−2.91 (m, 3 H), 2.72−2.57 (m, 2 H), 1.80−0.80 (m, 31 H); ^{13}C NMR (free base; 67.9 MHz, $CDCl_3$) δ 155.69, 141.54, 139.96, 136.85, 117.48, 111.25, 49.27 (2C), 29.07 (3C), 28.55, 28.14 (2C), 27.31 (3C), 13.68 (3C), 10.23 (3C). Signals due to C−Sn couplings were observed but are not indicated. Anal. ($C_{23}H_{39}NOSn$) C, H, N.

Computational Methods. The PLS analyses were performed in Simca-S for Windows version 6.0.[50] Dihedral drives and energy minimizations were performed in Macromodel 5.0.[29] The PM3 calculations were performed in SPARTAN 4.1.1.[51] Sybyl 6.2 was used for the CoMFA analysis. The docking was made manually using Sybyl 6.2.

Pharmacology. Muscarinic Receptor Binding Studies. The tissue preparations and the general methods used have been described in detail elsewhere for the parotid gland,[30] urinary bladder,[31] heart,[32] and cerebral cortex.[32] Male guinea pigs (250−400 g of body weight) were killed by a blow to the neck and exsanguinated. The brain was placed on ice for dissection of the cerebral cortex (gray matter only). Urinary bladders, hearts, and parotid glands were dissected in a Krebs-Henseleit buffer (pH 7.4) containing 1 mM phenylmethanesulfonyl fluoride (PMSF; Sigma), a protease inhibitor. The Krebs-Henseleit buffer was composed of (mM) the following: NaCl 118.0, KCl 5.36, $CaCl_2$ 2.52, $MgSO_4$ 0.57, NaH_2PO_4 1.17, $NaHCO_3$ 25.0, and glucose 11.1. Dissected tissues were homogenized in an ice-cold sodium−potassium phosphate buffer (50 mM, pH 7.4) containing 1 mM PMSF, using a Polytron PT-10 instrument (bladder, heart, parotid) and a Potter-Elvehjem Teflon glass homogenizer (cortex). All homogenates were diluted with ice-cold phosphate/PMSF buffer to a final protein concentration of ≤0.3 mg/mL and were immediately used in the receptor-binding assays. Protein was determined by the method of Lowry *et al.*[52] using bovine serum albumin as the standard.

The muscarinic receptor affinities of the unlabeled compounds were derived from competition experiments in which the ability to inhibit the receptor specific binding of (−)-[^{3}H]-QNB (3-quinuclidinyl [*phenyl*-4-^{3}H]benzilate, 32.9−45.4 Ci/mmol) was monitored as previously described.[32,33] Each sample contained 10 μL of (−)-[^{3}H]QNB solution (final concentration 2 nM), 10 μL of a solution of test compound, and 1.0 mL of tissue homogenate. Triplicate samples were mixed and incubated in a water bath or in a cool incubator under conditions of equilibrium (times in cool incubator are noted in parentheses), i.e., at 25 °C for 60 (80) (urinary bladder), 80 (100) (heart and cerebral cortex), or 210 (240) (parotid gland) min. Nonspecific binding was determined in the presence of 10 μM unlabeled atropine. Incubations were terminated by centrifugation[31] or rapid filtration onto GF/B filter plates. The radioactivity in the pellets, respective in the filter plates, was determined by liquid scintillation spectrometry.[31]

IC_{50} values (concentration of unlabeled compound producing 50% inhibition of the receptor specific (−)-[^{3}H]QNB binding) were determined graphically from the experimental concentration−inhibition curves. Affinities, expressed as the dissociation constants, K_i, were calculated by correcting the IC_{50} for the radioligand-induced parallel shift and differences in receptor concentration, using the method of Jacobs *et al.*[53] The binding parameters for (−)-[^{3}H]QNB (K_D and receptor densities) used in these calculations have been determined in separate series of experiments.[30−32]

Functional *in Vitro* Studies. Male guinea pigs, weighing about 300 g, were killed by a blow to the neck and exsanguinated. Smooth muscle strips of the urinary bladder were dissected in a Krebs-Henseleit solution (pH 7.4). The strip preparations were mounted vertically between two hooks in thermostatically controlled (37 °C) organ baths (5 mL). One of the hooks was adjustable and connected to a force transducer (FT 03, Grass Instruments). The Krebs-Henseleit solution was continuously bubbled with carbogen gas (93.5% O_2/6.5% CO_2) to maintain the pH at 7.4. Isometric tension was recorded by a Grass Polygraph (Model 79D). A resting tension of approximately 5 mN was initially applied on each muscle strip, and the preparations were allowed to stabilize for at least 45 min. The resting tension was adjusted, and the preparations were washed several times during the stabilization. The urinary bladder strips were used for evaluation of antimuscarinic activity (see Pharmacological Results). Carbachol (carbamylcholine chloride) was used as the agonist. Concentration−response curves to carbachol were generated by cumulative dose−response technique.

In studies of antagonism, a control concentration−response curve to carbachol was generated by cumulative addition of carbachol to the bladder strip (i.e., stepwise increase of the agonist concentration until the maximal contractile response was reached), followed by washing out and a resting period of at least 15 min prior to addition of a fixed concentration of the test compound (antagonist) to the organ bath. After 60 min of incubation with antagonist, a second cumulative concentration−response curve to carbachol was generated. Responses were expressed as percent of the maximal response to carbachol. EC_{50} values for carbachol in the absence (control) and presence of antagonist were graphically derived, and dose ratios (r) were calculated. Dissociation constants, K_B, for the antagonists were then calculated by $K_B = [A]/(r - 1)$, where [A] is the concentration of the test compound.[54]

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Supporting Information Available: Tables 1−9 showing data collected by X-ray crystallographic analysis of compounds **49** and **51**; fractional atomic coordinates and equivalent isotropic displacement parameters of the non-hydrogen atoms, bond lengths and angles, anisotropic displacement parameters for the non-hydrogen atoms, and fractional atomic coordinates of the hydrogen atoms; bond distances (Å) and angles (deg) for possible hydrogen bonds with esd's; and ^{1}H NMR and ^{13}C NMR spectral data for **3**, **11**, **23**, **24**, **26**−**30**, **32**−**34**, **37**, **39**−**41**, **45**, **47**−**53**, **55**, **56**, **58**, **60**−**64**, **67**, **69**, and **73** (19 pages). Ordering information is given on any current masthead page.

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(43) In order to explore this possibility, we docked **68** into a homology-based model of the muscarinic m1 receptor (see ref 44). During the docking the protonated quinuclidin-2-ene nitrogen was kept interacting via a hydrogen bond reinforced ionic interaction with Asp105 in transmembrane region (TM) 3. The 3-phenyl group could interact with Trp164. We also identified a possible hydrogen bond interaction with Ser388 in TM6. This is a variable residue between the subtypes (Ser in m1 and m5, Asn in m2, m3 and m4). The lack of subtype selectivity exhibited by **68** may be rationalized as both serine and aspargine residues can accept and donate hydrogen bonds to the ligand.

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