Journal of Medicinal Chemistry Article

J. Med. Chem. **2009,** *52,* 5241–5252 **5241**
DOI: 10.1021/jm900736e

Design, Synthesis, and Structure−Activity Relationship of Tropane Muscarinic Acetylcholine Receptor Antagonists

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Received May 18, 2009

Novel tropane derivatives were characterized as muscarinic acetylcholine receptor antagonists (mAChRs). Through optimization of the structure−activity relationship around the tropane scaffold, the quaternary ammonium salt **34** was identified as a very potent M_3 mAChR antagonist. The compound was functionally active and displayed greater than 24 h duration of action in a mouse model of bronchoconstriction.

Introduction

Muscarinic acetylcholine receptors (mAChRs[a]) belong to the superfamily of G-protein-coupled seven-transmembrane (TM) receptors. Five subtypes of mAChRs, termed M_1-M_5, have been identified to-date.[1,2] The mAChRs are widely distributed in mammalian organs where they mediate many of the vital functions.[1−3] In the lungs, mAChRs have been localized to smooth muscle in the trachea and bronchi, the submucosal glands, and the parasympathetic ganglia.[4] The three subtypes of mAChRs that are known to exert their physiological effect in the lungs through the action of the native ligand, acetylcholine, are the M_1, M_2, and M_3 receptors.[4] The M_3 mAChRs are located on the airway smooth muscle and also on the pulmonary submucosal glands where they mediate muscle contraction and mucus secretion respectively.[5,6] The M_2 mAChRs, which make up the majority of the cholinergic receptor population on airway smooth muscle, are also located on postganglionic parasympathetic nerves,[7] where their role is autoinhibitory, to provide tightly regulated control of acetylcholine release. M_1 mAChRs are found in the pulmonary parasympathetic ganglia where they function to facilitate neurotransmission.[8]

mAChR dysfunction in the lungs has been noted in a variety of different pathophysiological states.[9] In particular, in asthma and chronic obstructive pulmonary disease (COPD), inflammatory conditions lead to loss of inhibitory M_2 mAChR autoreceptor function on parasympathetic nerves supplying the pulmonary smooth muscle, causing increased acetylcholine release following vagal nerve stimulation.[10] This mAChR dysfunction results in airway hyperreactivity and hyperresponsiveness mediated by increased stimulation of M_3 mAChRs. Thus, mAChR antagonists are useful therapeutics in mAChR-mediated disease states and particularly COPD. Inhaled anticholinergic agents approved for the treatment of COPD include ipratropium bromide, oxitropium bromide, and more recently tiotropium bromide.[11] Ipratropium and oxitropium have relatively short durations of action (4−8 h), whereas tiotropium has a duration of action of over 24 h, making it suitable for once-daily treatment.[12] As part of a general strategy to develop new respiratory products, our goal was to discover novel long-acting muscarinic antagonists.

The topography of the binding site of the muscarinic receptors has been extensively studied over the years.[13,14] In particular, it has been established that two important structural features for an antimuscarinic agent are a positively charged center (generally a protonated or quaternized nitrogen) and an aromatic group attached to an ester moiety, as exemplified by the belladonna alkaloids atropine and scopolamine.[15] The optimum distance between the nitrogen and the carbonyl oxygen of 2,2-diphenylpropionate antimuscarinics has been estimated to be between 4.4 and 5.9 Å.[16] On the basis of that knowledge, we explored our compound collection for molecules incorporating various nitrogen containing rings (e.g., piperidine, pyrrolidine, or tropane) and an aromatic moiety (e.g., phenyl, thiophene, or biphenyl) separated by four to six carbon−carbon bonds. Through this exercise, we uncovered the tropane derivative **1a**, which had been previously discovered by our predecessor Charles L. Zirkle and his team during their research on antispasmotic agents possessing parasympathetic activity.[17] The general strategy to further explore this template is depicted in Figure 1. From a pool of analogues of **1a**, we gained useful information on the attachment point stereochemistry and nature of the linker. To further build upon this knowledge, our plan was to

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[a] Abbreviations: mAChR, muscarinic acetycholine receptor; TM, transmembrane; COPD, chronic obstructive pulmonary disease; SAR, structure−activity relationship; HWE, Horner−Wadsworth−Emmons; ACh, acetylcholine; CHO, Chinese hamster ovary; SPA, scintillation proximity assay; MCh, metacholine; Penh, enhanced pause; i.n., intranasal; HPLC, high pressure liquid chromatography; NQ, not quantifiable; ESI, electrospray ionization; HRMS, high resolution mass spectrum; LC, liquid chromatography; FLIPR, fluorometric imaging plate reader.

Published on Web 07/24/2009

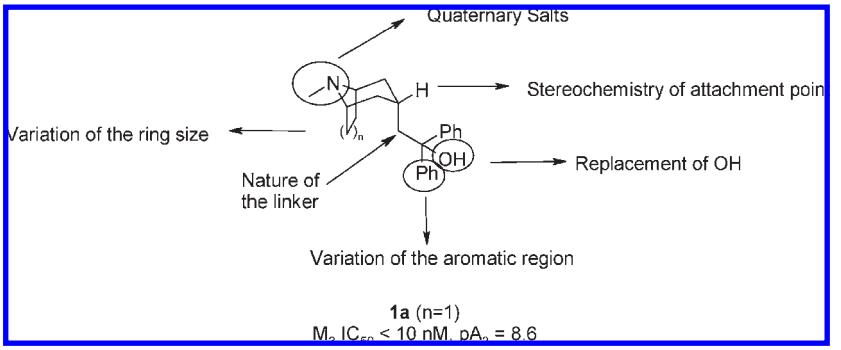
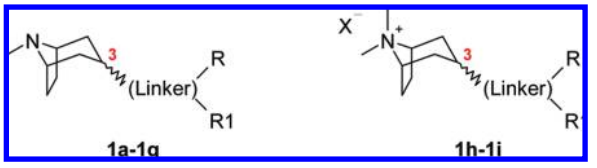


Figure 1. General strategy.

Table 1. Selection of Analogues of **1a**[a]



compd	R	R1	linker	C-3 configuration	X	M_3 IC_{50}[a] (nM)	M_3 pA_2[a]	% I[b] at 24 h (50 μg)
1a	Ph	Ph	$-CH_2C(OH)$	endo		< 10	8.6 ± 0.1	> 10
1b	Ph	Ph	$-CH_2C(OH)$	exo		973 ± 110		
1c	Ph	Ph	$-C(OH)$	endo		1498 ± 140		
1d	Ph	Ph	$-(CH_2)_2C(OH)$	endo		134 ± 12		
1e	Ph	2-Pyr	$-CH_2C(OH)$	endo		19 ± 4		
1f	2-Th	2-Th	$-CH_2C(OH)$	endo		< 10	8.6 ± 0.1	> 10
1g	Ph	Et	$-CH_2C(OH)$	endo		135 ± 23		
1h	Ph	Ph	$-CH_2C(OH)$	endo	Br	< 10	9.3 ± 0.2	62
1i	Ph	Ph	$-CH{=}C$	endo	Br	< 10	8.3 ± 0.1	76

[a] Values are the mean of two or more independent assays. [b] % I = percent inhibition of MCh-induced bronchoconstriction in conscious mice.

further explore the substitution at the β-position of the side chain and the structure−activity relationship (SAR) of the aromatic region. In this paper, we report the key points of the synthesis, structure−activity relationships, and pharmacological evaluation of this series of mAChR antagonists.

Chemistry

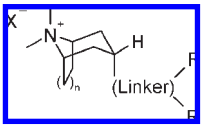
The general preparation methods for the alcohol and alkene derivatives from Table 2 are depicted in Scheme 1. Tropinone **2a** was converted to the corresponding α,β unsaturated ester **3a** via a Horner−Wadsworth−Emmons (HWE) reaction with trimethyl phosphonacetate.[18−20] Catalytic hydrogenation of **3a** gave the C-3 endo isomer **4a** as the main product.[19,21] Alternatively, the Knoevenagel condensation of **2a** with ethyl cyanoacetate gave an intermediate alkene,[22] which was hydrogenated to afford the saturated nitrile derivative **3b**.[23] The subsequent combined hydrolysis/decarboxylation of **3b** followed by treatment with acidic ethanol gave the ester **4b**.[23] In a sequence similar to that for **2a**, the HWE reaction of the [3.3.1] bicyclic ketone **2b** using diethyl (cyanomethyl)phosphonate provided the alkane **3c**, which was then hydrolyzed and esterified in situ to give the ester **4c**. Subsequent reaction of **4a**, **4b**, or **4c** with an excess of an appropriate organometallic reagent gave tertiary alcohol intermediates, which were subsequently treated with a methylating agent to generate the corresponding quaternary dimethyl ammonium salts **5**−**17** and **20**−**22**. Alternatively, the tertiary alcohol intermediates could undergo an acid catalyzed dehydration followed by treatment with a methylating agent to yield the alkenes **18**, **19**, and **23**.

Scheme 2 illustrates the synthetic approaches for the installation of various substituents at the β-position of the C-3 side chain. Iodination of the known primary alcohol **24**[24] followed by alkylation of the resultant iodide **25** with diphenylacetonitrile in the presence of NaH provided the nitrile **26**. Further reduction of **26** with borane furnished the primary amine **27**, which was reacted with a variety of electrophiles (isocyanates, acylating and sulfonaylating agents) to prepare a small array of ureas (**28a**−**c**), amide (**28d**), and sulfonamides **28e**−**f**. Compound **26** could also be converted to the amide **29** upon treatment with sulfuric acid. The preparation of the triphenyl derivative **30** proved more challenging. The best method identified after exploring various conditions afforded **30** in about 17% yield by coupling **25** with triphenylmethane in the presence of *n*-BuLi. The carboxylic acid **31** was prepared by treating **1a** with formic acid and concentrated sulfuric acid at −20 °C for 1 week.[25] Subsequent coupling of **31** with benzylamine afforded the amide **33**, whereas microwave assisted reduction of **32** with $LiAlH_4$ gave the primary alcohol 32. Quaternization of the tertiary amines **26**, **29**, and **32** with an appropriate methylating agent then afforded the corresponding quaternary salts **34**−**36**.

Pharmacology

The functional activities and potencies of the synthesized compounds were first evaluated by calcium mobilization

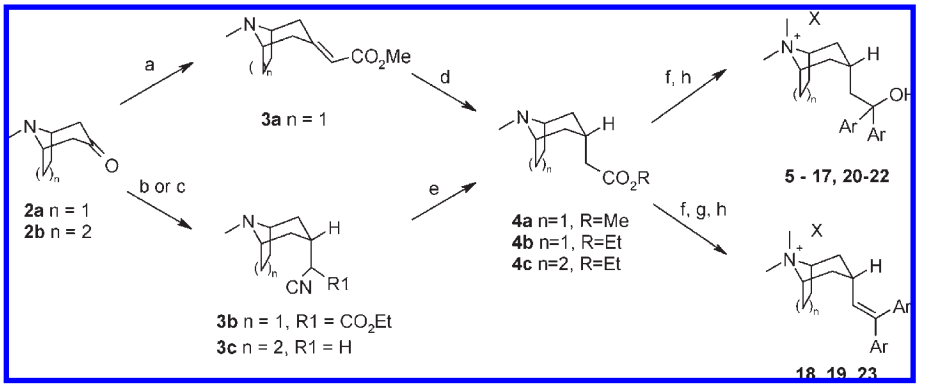
Table 2. Structure−Activity Relationship Studies of Analogues of **1h**



compd	*n*	R	linker	X	M_3 IC_{50} [a] (nM)	M_3 pA_2	% I [b] at 24 h (5 μg)
1h	1	Ph	$-CH_2C(OH)$	Br	< 10	9.3 ± 0.2	34
5	1	2-Me-Ph	$-CH_2C(OH)$	Br	10 ± 5	8.3 ± 0.2	
6	1	2-OMe-Ph	$-CH_2C(OH)$	Br	> 10000		
7	1	3-F-Ph	$-CH_2C(OH)$	I	11 ± 7	8.0 ± 0.1	
8	1	3-Cl-Ph	$-CH_2C(OH)$	I	25 ± 8		
9	1	4-OMe-Ph	$-CH_2C(OH)$	Br	> 10000		
10	1	4-Cl-Ph	$-CH_2C(OH)$	I	74 ± 20		
11	1	2-Me-3-F-Ph	$-CH_2C(OH)$	Br	65 ± 57		
12	1	2-Me-5-F-Ph	$-CH_2C(OH)$	Br	37 ± 13		
13	1	3,5-di-F-Ph	$-CH_2C(OH)$	Br	112 ± 74		
14	1	3,4-di-F-Ph	$-CH_2C(OH)$	Br	290 ± 240		
15	1	2-Th	$-CH_2C(OH)$	Br	< 10	8.6 ± 0.1	19
16	1	3-Th	$-CH_2C(OH)$	I	17 ± 1		
17	1	5-Me-3-Th	$-CH_2C(OH)$	Br	65 ± 36		
18	1	2-Th	$-CH{=}C$	Br	< 10	10.0 ± 0.3	72
19	1	2-Me-Ph	$-CH{=}C$	Br	< 10	10.0 ± 0.4	91
20	2	2-Th	$-CH_2C(OH)$	I	< 10	8.7 ± 0.2	44
21	2	2-Me-Ph	$-CH_2C(OH)$	I	23 ± 2		
22	2	Ph	$-CH_2C(OH)$	Br	< 10	8.8 ± 0.1	34
23	2	2-Th	$-CH{=}C$	Br	< 10	9.0 ± 0.1	49

[a] Values are the mean of two or more independent assays. [b] % I = percent inhibition of MCh-induced bronchoconstriction in conscious mice.

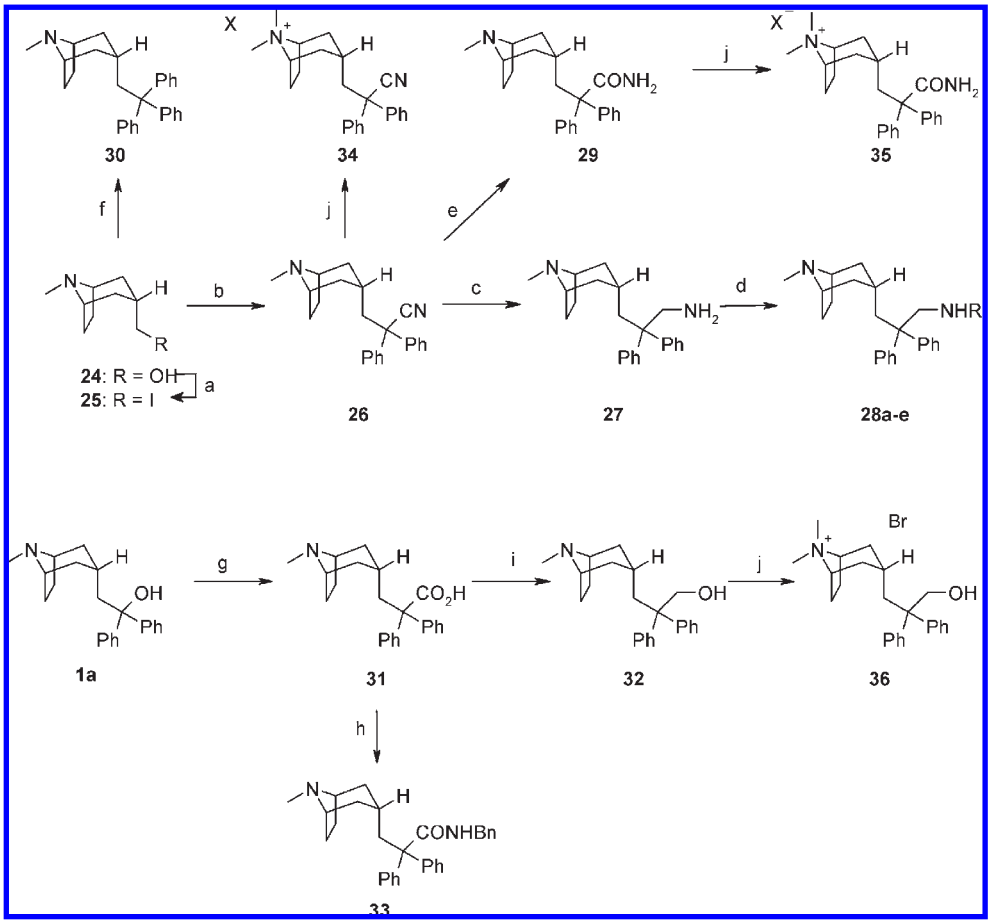
Scheme 1. General Methods of Preparation for the Compounds from Table 2[a]



[a] Reagents and conditions: (a) $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF, −45 °C to room temp, then reflux; (b) $NCCH_2CO_2Et$, $NH_4^+AcO^-$, AcOH, H_2, Pd/C, EtOH (**2a**−**3b**); (c) (i) $(MeO)_2P(O)CH_2CN$, NaH, room temp, (ii) H_2, AcCl, 10% Pd/C, MeOH (**2b**−**3c**); (d) H_2, Pd/C, EtOH; (e) (i) conc HCl, reflux; (ii) HCl, EtOH; (f) ArLi or ArMgX (see Table 2 for scope of Ar), THF or Et_2O; (g) HCl or oxalic acid, reflux; (h) MeBr or MeI, acetone.

assays to determine inhibition of acetylcholine (ACh) induced receptor activation at cloned human M_3 receptors expressed in CHO cells. The inhibitory potency of a compound was first evaluated at a single ACh concentration to determine its IC_{50}. When a compound IC_{50} was lower than 10 nM, antagonist potency was further quantified with a pA_2, by measuring the ratio of the EC_{50} of ACh in the presence and absence of the compound.[26] Antagonist binding was also assessed in radioligand binding assays conducted using cell membrane preparations from CHO cells expressing human M_1, M_2, or M_3 receptors in a scintillation proximity assay (SPA) with 0.5 nM [^{3}H]-*N*-methylscopolamine as the ligand. The binding potency was determined as a K_i. Functional activity of antagonists was determined in human bronchial tissues from primary, secondary, or tertiary airways obtained at autopsy, cut into strips, then connected to force-displacement transducers suspended in standard organ baths. Tissue strips were preincubated with the test compound for 2 h and then incubated with increasing concentrations of carbachol. The mechanical responses were recorded isometrically, and the potencies of the compounds were determined as pA_2 values. To assess reversibility and to calculate the off-rate, the antagonists were allowed to equilibrate with the bronchial strips until they reached maximum inhibition of carbachol-induced contraction. At this point antagonists were removed from the perfusate and tissues were superfused with buffer containing carbachol with tension recovery measured over time. The results are expressed as the time in minutes for 50% reversal of antagonist blockade of carbachol-induced contraction (Off t_{50}). The in vivo efficacy of the compounds was determined by their blockade of airway

Scheme 2. Preparation of the Compounds from Table 3[a]



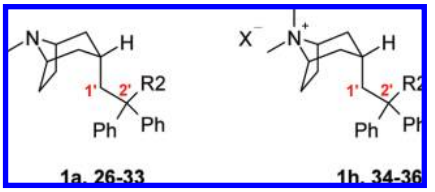
[a] Reagents and conditions: (a) I_2, PS-PPh_3, DCM; (b) Ph_2CHCN, NaH, DMF; (c) BH_3.THF, THF; (d) addition of an electrophile such as (i) $PhCH_2NCO$, (ii) EtNCO, (iii) Ac_2O, (iv) $PhSO_2Cl$, or (v) $MeSO_2Cl$; (e) H_2SO_4, DCM; (f) Ph_3CH, *n*-BuLi; (g) HCO_2H, H_2SO_4; (h) $BnNH_2$, EDC, HOBt; (i) $LiAlH_4$, THF, microwave, 100 °C; (j) MeBr, *t*-BuOMe or MeI, acetone.

responsiveness to methacholine (MCh) induced contraction in a mouse plethysmography model. Barometric plethysmography was used to measure enhanced pause (Penh), a unitless measure that has been shown to correlate with the changes in airway resistance that occur during bronchial challenge with methacholine.[27] Mice were pretreated intranasally (i.n.) with a solution of the compound in 50 μL of vehicle (10% DMSO) and were then placed in the plethysmography chamber for a given amount of time following drug administration. For potency determination, a dose−response experiment was performed, and all Penh measurements were carried out 15 min following i.n. drug administration. For duration of action determination, repeated Penh measurements were taken from 15 min up to 96 h following drug administration.

Results and Discussion

The identification of **1a** was a good starting point for our program, as the compound exhibited a high intrinsic level of potency at the M_3 receptor. However, improvement was still needed, as the compound did not exhibit significant bronchoprotection after 24 h in our in vivo mouse model at a relatively high screening dose (50 μg/mouse) as shown in Table 1. Further examination of our compound collection uncovered a series of analogues of **1a** possessing the same hydroxyethyl group linking the tropane and the aromatic region. Other related compounds were also found that possessed either an alkyl or an alkylene linker. All these compounds originated from the work of Zirkle et al.[17] Subsequently, the SAR of the compounds containing the alkane linker was found to mirror very closely that of the alkenes and therefore will not be reported in this article. From the representative set shown in Table 1, it can be seen that the endo configuration at C-3 is preferred as exemplified by the marked decrease of potency at the M_3 receptor of the exo derivative **1b** compared to its epimer **1a**. The effect of the length of the linker between the tropane ring and the diphenyl moiety was assessed with compounds **1c** and **1d**. The substantial loss of affinities of these two molecules suggested that a two-bond length linker, as in **1a**, was probably optimal. Replacement of one of the phenyl rings of **1a** with a pyridine ring as in **1e** or with an ethyl chain as in **1g** also resulted in a loss of potency. However, the incorporation of thiophene rings was tolerated and gave the equipotent analogue **1f**, which also exhibited a similar in vivo duration of action to **1a**. Compound **1h**, which is the dimethyl quaternary ammonium derivative of **1a**, displayed a slightly increased potency at M_3 but a significant longer duration of action than **1a**. A similar in vivo efficacy to **1h** was found with compound **1i**, which indicated that an ethylene group could be used as a surrogate to the hydroxylethyl linker. This initial set of results showed that the C-3 endo configuration, a quaternary ammonium salt, and a two-carbon linker were all preferred features around the tropane template.

Table 3. C-3 Side Chain β-Substitution



compd	R2	X	M_3 IC_{50} (nM)[a]	M_3 pA_2[a]	% I[b] at 24 h (5 μg)
1a	−OH		< 10	8.6 ± 0.1	
1h	−OH	Br	< 10	9.3 ± 0.2	34
26	−CN		< 10	9.5 ± 0.3	11
28a	$-CH_2NHC(O)NHBn$		1338 ± 320		
28b	$-CH_2NHC(O)NHEt$		1939 ± 410		
28c	$-CH_2NHC(O)CH_3$		2895 ± 1300		
28d	$-CH_2NHS(O_2)Ph$		1059 ± 81		
28e	$-CH_2NHS(O_2)CH_3$		2732 ± 1100		
29	$-CONH_2$		< 10	10.0 ± 0.1	> 10
30	−Ph		206 ± 84		
31	$-CO_2H$		687 ± 250		
32	−CH2OH		< 10	8.4 ± 0.2	15
33	−C(O)NHBn		839 ± 450		
34	−CN	Br	< 10	10.7 ± 0.2	> 95
35	$-CONH_2$	I	< 10	9.9 ± 0.2	90
36	$-CH_2OH$	Br	< 10	8.4 (n = 1)	23

[a] Unless specified, values are the mean of two or more independent assays. [b] % I = percent inhibition of MCh-induced bronchoconstriction in conscious mice.

Taking these findings into consideration, SAR studies to probe the aromatic region and the ring size were pursued by preparing a series of quaternary ammonium salts derived from **1h**. The compounds with an IC_{50} below 10 nM were screened in our high-throughput mouse model at a fixed dose (5 μg/mouse) to establish a SAR for duration of bronchoprotection. As reported in Table 2, the 2-methyl analogue **5** showed high affinity (10 nM) against the M_3 receptor, whereas methoxy substitution as in **6** resulted in a significant decrease in activity. The introduction of a fluoro (**7**) or a chloro (**8**) at the meta position was well tolerated. Para-substitution, however, was detrimental for activity in the case of the chloro derivative **10** and led to a sharp drop in potency for the methoxy analogue **9**. The addition of a second substituent of small size on the aromatic rings, such as a fluorine atom, was also detrimental to activity (compare **11**, **12** with **5** and **13**, **14** with **7**). As previously observed with **1a** and **1f**, the -thiophene group was a good bioisostere replacement for the phenyl, as compound **15** displayed an in vivo duration of action almost comparable to **1h**, albeit with a slightly lower potency at M_3. Unlike the 2-thiophene derivatives, the 3-thiophenes **16** and **17** did not meet our criteria for in vivo testing and were not further investigated. The alkene derivatives **18** and **19** displayed greater potencies than the corresponding alcohols **15** and **5**. More interestingly, these compounds exhibited 72% and 91% in vivo bronchoprotection after 24 h, respectively. The introduction of an extra methylene into the bicyclic scaffold produced potent compounds but did not bring any significant advantage over the tropanes. For example, the [3.3.1] derivatives **21**, **22**, and **23** proved to be less potent at the M_3 receptor and less efficacious than compounds **5**, **1h**, and **18**, respectively. However, the duration of action of **20** was improved compared to **15** but far shorter than that of **18** or **19**.

The previous set of results indicated that the nature of the linker between the tropane ring and the aromatic rings was important for potency and in vivo efficacy. On that basis, the effect of substituting the linker at the C-2′ position was explored for further optimization.

As shown in Table 3, the nitrile **26** and the amide **29** were more potent M_3 antagonists than **1a**, initially suggesting that relatively small polar groups with hydrogen bond accepting capabilities were preferred at the C-2′ position. This assumption was supported by the marked decrease in potency of the phenyl **30**, devoid of such potential. Carboxylic moieties, however, were not preferred at this position as shown by compound **31**. The homoalcohol **32** was almost equipotent to **1a**, suggesting that a moiety with more rotational freedom could be tolerated. The R2 group could not, however, be too large as it would clash with other residues in the receptor. Thus, the clear drop in potency seen in **28a**−**e** and **33** prompted us to stop any further investigation of this region of our template. As was previously observed in the case of **1h** and related analogues, formation of the quaternary salts derived from **26**, **29**, and **32** (**34**−**36**, respectively) led to some significant improvement in the duration of action in our screening model. This was particularly striking in the case of **34** and **35**, which both exhibited near maximal protection of bronchoconstriction at our screening dose (5 μg/mouse). The lower efficacy in inhibiting bronchoconstriction of compound **36** correlated with its lower potency at the M_3 receptor, when compared with **34** and **35**.

On the basis of the data reported above, compounds **18** and **34** were selected for further pharmacological evaluation (Table 4). Radioligand binding studies showed that both compounds potently competed with [^{3}H]-*N*-methylscopolamine binding to any of the three mAChR subtypes (M_1−M_3). At M_3 mAChRs, **34** had an affinity about 8-fold higher than **18**. No clear selectivity for M_3 over the two other receptors subtypes was observed. Compound **34** was also more potent than **18** at endogenously expressed M_3 mAChRs, as

Table 4. Additional Data on Selected Compounds

	binding affinity (K_i)[a]			in vitro tissue studies		mouse in vivo studies		rat PK properties	
compd	M_1 (nM)	M_2 (nM)	M_3 (nM)	pA_2[b]	off t_{50} (min)[c]	ED_{50}[d] (μg/mouse)	duration (h)[e]	Cl[f] ((mL/min)/kg)	oral F[g] (%)
18	0.38 ± 0.07	0.73 ± 0.13	0.45 ± 0.04	9.0 ± 0.2	59 ± 9	0.2	24 (5 μg)	85 ± 7	6.5, 2.4, NQ[h,i]
34	0.05 ± 0.01	0.17 ± 0.01	0.06 ± 0.02	10.0 ± 0.2	85 ± 5	0.01	>24 (0.5 μg)	74 ± 21	NQ[h]

[a] Radioligand binding assays were conducted using CHO cell membrane preparations in SPA format vs 0.5 nM [^{3}H]-*N*-methylscopolamine. Values are the mean of two or more independent assays. [b] Potency against carbachol-induced contraction in human bronchus. [c] Reversal time for 50% of carbachol-induced contraction to return to maximum relaxation in human bronchus after incubation at 10 nM antagonist. [d] Potency in conscious mice against MCh-induced bronchoconstriction (n = 1). [e] Duration of bronchoprotection in conscious mice against MCh-induced bronchoconstriction. Time to 50% loss of maximum protection (dose). [f] Cl: systemic plasma clearance. iv doses: 2.8 mg/kg (**18**), 2.5 mg/kg (**34**). [g] F: percent bioavailability. po doses: 5.8 mg/kg (**18**), 5.7 mg/kg (**34**). [h] NQ: no quantifiable plasma levels following oral administration. [i] Individual doses listed because of variability.

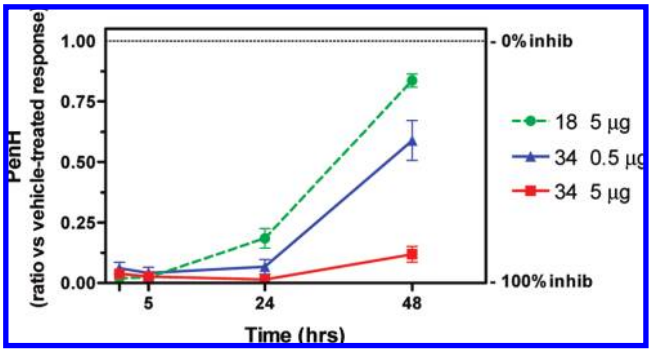


Figure 2. Duration of action−inhibition of MCh-induced bronchoconstriction in conscious mice. Balb/C mice (n = 4 for each) were dosed with the test compound intranasally (i.n.) and then challenged after 0.25−48 h with 30 mg/mL MCh aerosolized for 2 min. The magnitude of bronchoconstriction was measured as Penh over the next 5 min. The data are expressed as a ratio of the Penh achieved with MCh after drug was given to that achieved before drug. A ratio of 1.0 (dotted line) indicates that there was no change in the Penh in response to aerosolized MCh (i.e., 0% inhibition), and a ratio of 0.0 means that there was no bronchoconstriction in response to MCh challenge (i.e., 100% inhibition).

determined by tissue bath studies using human bronchus. In additional kinetic studies, **34** was found to have an off rate of 85 min, which was longer than **18** (59 min).

The pharmacokinetic profiles of both compounds in the rat were characterized by low oral bioavailability and high plasma clearance (Table 4). These properties are preferred to optimize the topical efficacy of these agents in the lungs[28,29] and to minimize systemic exposure and thus potential mAChR-mediated side effects. The compounds were also further characterized in the mouse plesthymography model. Compound **34** had excellent potency when dosed intranasally with an ED_{50} of 0.01 μg. At a dose of 0.5 μg, **34** displayed 24−48 h of bronchoprotection (Figure 2). Elevation of the dose to 5 μg showed greater than 48 h bronchoprotection, indicating that the duration of action of **34** could be dose-related. Compared to **34**, the in vivo potency of **18** was lower (ED_{50} = 0.2 μg/mouse) and its duration of action was shorter. Taken together, these data suggest that the longer duration of action of **34** than **18** may be a function of its higher potency and lower reversibility at M_3 mAChRs.

Conclusion

In conclusion, a novel series of tropane derivatives was characterized as mAChR antagonists. Through optimization of the structure−activity relationship around the tropane scaffold, compounds **18** and **34** were identified as very potent M_3 mAChR antagonists. Kinetic washout studies in human bronchus showed that **34** had a slower reversibility profile than **18**. Compared to **34**, the in vivo potency of **18** was lower and its duration of action was shorter. Taken together, these results suggest that **34** has a better likelihood than **18** of achieving long duration of bronchodilation in humans. Further pharmacological studies of these compounds will be reported elsewhere.

Experimental Section

Chemistry. All materials and reagents were used as is unless otherwise indicated. Air- or moisture-sensitive reactions were carried out under a nitrogen atmosphere. Flash chromatography was performed using silica gel (EM Science, 230−400 mesh) under standard techniques or using silica gel cartridges (RediSep normal phase disposable flash columns) on an Isco CombiFlash. Preparative and analytical HPLC were carried out on a Gilson 306 HPLC system. Unless otherwise stated, the conditions for the preparative reverse phase HPLC purifications used YMC Combiscreen ODS-A 75 mm × 30 mm (30 mL/min; gradient, (A) acetonitrile, (B) water, 10−80% A during 10 min) with UV detection at 214. The ^{1}H NMR spectra were recorded at 400 MHz using a Bruker Avance 400 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield of tetramethylsilane (δ scale). Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants (J) are reported in hertz and refer to apparent multiplicities. Mass spectra were recorded on an Applied Biosystems MDS Sciex API 150EX single quadrupole mass spectrometer with an electrospray ionization (ESI) source. Elemental analyses for compounds **18** and **34** were performed by Quantitative Technologies, Inc., Whitehouse, NJ. High-resolution mass spectral (HRMS) data were determined on a Bruker Daltonics 7T FTICR-MS, equipped with an Apollo ESI interface. The purity of the tested compounds was determined by liquid chromatography (LC) on a Schimadzu LC system. Unless stated otherwise, the conditions for the LC used an Aquasil C18 40 mm × 1 mm column (flow rate, 300 μL/min, 10% solution A, 90% solution B; A = water with 0.02% TFA; B = acetonitrile with 0.018% TFA, duration 4.2 min) with UV detection at 214 nm. All reported compounds, with the exception of **5** and **13**, possess a purity of at least 95%.

Methyl (8-Methyl-8-azabicyclo[3.2.1]oct-3-ylidene)acetate (3a). Trimethylphosphonacetate (19.6 mL, 0.121 mol) was added to a slurry of sodium hydride (95%, 3.15 g, 0.125 mol) in THF (150 mL) at −45 °C. The resulting mixture was stirred between −45 and −35 °C for 1 h. A solution of tropinone (15 g, 0.108 mol) in THF (100 mL) was added, and the resulting mixture was stirred from −30 °C to room temperature over 2 h. The reaction mixture was then heated at reflux for 24 h. After cooling to room temperature, the reaction mixture was quenched with water (50 mL) and then concentrated under vacuum to give a residue which was partitioned between 2 M HCl (150 mL) and ether (400 mL). The aqueous phase was separated, washed with ether (2 × 200 mL), then basified to pH 12 with 2.5 M NaOH (150 mL). The aqueous layer was then extracted with ethyl acetate (4 × 100 mL). The combined organics were dried over $MgSO_4$ and concentrated to give

methyl (8-methyl-8-azabicyclo[3.2.1]oct-3-ylidene)acetate as a crude oil (16 g, 76%). LC/MS (ES) m/z 196 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.71 (t, J = 2.15 Hz, 1 H), 3.70 (s, 3 H), 3.52 (d, J = 15.16 Hz, 1 H), 3.27 (br s, 2 H), 2.71 (d, J = 13.64 Hz, 1 H), 2.43 (d, J = 15.41 Hz, 1 H), 2.39 (s, 3 H), 2.08−1.91 (m, 3 H), 1.52 (dd, J = 8.08, 1.52 Hz, 2 H).

Methyl (3-*endo*)-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl]acetate (4a). A sample of 10% Pd/C (1 g) was added to a solution of crude **3a** (16 g) in MeOH (400 mL). The resulting mixture was allowed to hydrogenate at room temperature under a 40−56 psi pressure of H_2. After 43 h no H_2 intake was observed. After filtration of the catalyst over Celite, the solvent was evaporated under vacuum to give a crude oil which was purified by distillation to give a colorless oil (11.2 g, 69%), bp 122−125 °C (0.3 mmHg). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.68 (s, 3 H), 3.15−3.08 (m, 2 H), 2.49 (d, J = 8.34 Hz, 2 H), 2.27 (s, 3 H), 2.30−2.25 (m, 1 H), 2.17 (ddd, J = 18.19, 4.29, 4.04 Hz, 2 H), 2.07 (dd, J = 8.34, 3.79 Hz, 2 H), 1.63 (d, J = 8.34 Hz, 2 H), 1.30 (d, J = 14.91 Hz, 2 H).

Ethyl Cyano[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]acetate (3b). A mixture of tropinone (13.9 g, 0.1 mol), ethyl cyanoacetate (11.3 g, 0.1 mol), ammonium acetate (1.6 g, 0.021 mol), acetic acid (7.3 g, 0.12 mol), and 10% Pd/C (0.6 g) in absolute ethanol (20 mL) was hydrogenated under 60 psi at 50 °C for 18 h. After the catalyst was filtered off, the filtrate was evaporated under vacuum. The amber oily residue was dissolved in 1 N HCl (200 mL), and the solution was extracted with ether (200 mL). The acid solution was neutralized and saturated with K_2CO_3. The product was extracted with ether (6 × 200 mL). Distillation of the ether solution gave **3b** as a yellow oil (8.0 g, 34%), bp 139−140 °C (2 mmHg). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.28 (q, J = 7.20 Hz, 2 H), 3.55 (d, J = 9.6 Hz, 1 H), 3.23−3.15 (m, 2 H), 2.52−2.42 (m, 1 H), 2.35−2.12 (m, 4 H), 2.24 (s, 3 H), 1.60−1.40 (m, 3 H), 1.30−1.20 (m, 1 H), 1.33 (t, J = 7.20 Hz, 3 H).

(3-*endo*)-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)acetic Acid Ethyl Ester (4b). A solution of **3b** (5.6 g) in 37% hydrochloric acid (25 mL) was heated at reflux for 13 h. The solution was evaporated under vacuum. The residual water was removed with successive addition and removal by distillation of absolute ethanol. The crude was treated with a solution of absolute ethanol (40 mL) saturated with hydrogen chloride and allowed to stand overnight at room temperature. Most of the alcohol was removed under vacuum. Then a cold 5 N NaOH solution (20 mL) was added to the residue and the product was extracted with ether (6 × 50 mL). Removal of ether gave the desired product as a pale-yellow oil (5.0 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.12 (q, J = 7.20 Hz, 2 H), 3.09 (br s, 2 H), 2.46−2.42 (m, 1 H), 2.45 (d, J = 8.40 Hz, 2 H), 2.24 (s, 3 H), 2.15−2.10 (m, 2 H), 2.07−2.02 (m, 2 H), 1.64 (m, 2 H), 1.31−1.21 (m, 2 H), 1.24 (t, J = 7.20 Hz, 3 H).

[(3-*endo*)-9-Methyl-9-azabicyclo[3.3.1]non-3-yl]acetonitrile (3c). Step 1. Diethyl (cyanomethyl)phosphonate (5.12 mL, 31.7 mmol) was added dropwise over 6 min to a stirred slurry of 95% NaH (800 mg, 31.7 mmol) in anhydrous THF (32 mL) under argon at room temperature. This mixture was stirred for 40 min, and a solution of 9-methyl-9-azabicyclo[3.3.1]nonan-3-one (970 mg, 6.33 mmol) in THF (10 mL) was added in one portion. Stirring was continued for 70 h, whereupon MeOH (5 mL) was added in one portion. The mixture was concentrated under reduced pressure, and the residue was taken up in a 1:1 mixture of H_2O/EtOAc (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography, giving 886 mg (79%) of (9-methyl-9-azabicyclo[3.3.1]non-3-ylidene)ethanenitrile as a yellow oil. LC/MS (ES) m/z 177 $(M)^+$.

Step 2. Acetyl chloride (0.57 mL, 7.49 mmol) was added dropwise with stirring to MeOH (3.2 mL) at room temperature. (9-Methyl-9-azabicyclo[3.3.1]non-3-ylidene)ethanenitrile (880 mg, 4.99 mmol) was dissolved in this solution and then concentrated under reduced pressure. S sample of 10% Pd−C (266 mg, 0.25 mmol) and then MeOH (10 mL) were added, and the mixture was stirred at room temperature under an atmosphere of hydrogen for 22 h. The reaction mixture was filtered through Celite 521, and the filtrate was concentrated under reduced pressure. The residue was taken up in saturated K_2CO_3 (10 mL) and EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography, giving 517 mg (58%) of [(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]acetonitrile. LC/MS (ES) m/z 179 $(M)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.03 (d, J = 10.9 Hz, 2 H), 2.51 (s, 3 H), 2.31−2.18 (m, 5 H), 2.00−1.84 (m, 3 H), 1.49−1.46 (m, 1 H), 1.27−1.21 (m, 2 H), 0.98 (d, J = 12.1 Hz, 2 H).

Ethyl [(3-*endo*)-9-Methyl-9-azabicyclo[3.3.1]non-3-yl]acetate (4c). A solution of [(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]acetonitrile (515 mg, 2.89 mmol) in concentrated HCl (10 mL) was heated at reflux for 2 h and then concentrated under reduced pressure. In a separate flask, a solution of 2 M HCl/EtOH (5 mL) was prepared by dropwise addition of acetyl chloride (0.7 mL, 9.8 mmol) to EtOH (4.3 mL) with stirring (caution: exothermic). This solution was then added to the crude product previously obtained, and the mixture was stirred at room temperature for 24 h and then concentrated under reduced pressure. The residue was taken up in a 2:1 mixture of saturated K_2CO_3/EtOAc (15 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure, giving 516 mg (79%) of the title compound. LC/MS (ES) m/z 226.2 $(M)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.13 (m, 2 H), 3.00 (d, J = 9.9 Hz, 2 H), 2.51 (s, 3 H), 2.40−2.33 (m, 1 H), 2.24−2.12 (m, 4 H), 1.98−1.84 (m, 3 H), 1.46−1.42 (m, 1 H), 1.29−1.24 (m, 3 H), 1.14−1.07 (m, 2 H), 0.95 (d, J = 10.9 Hz, 2 H).

Method A: Preparation of the Tertiary Alcohol Derivatives 5−15 and 17. To a solution of an organometallic reagent (6−8 equiv) in ether or THF at 0 °C, methyl (3-*endo*)-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl]acetate (1 equiv) in anhydrous THF (4 mL/mmol) was added dropwise. After warming up to room temperature and stirring at room temperature for half an hour, the reaction mixture was heated at reflux for 2 h. The reaction mixture was quenched with aqueous saturated ammonium chloride and then extracted with ethyl acetate. The organic phase was concentrated and purified by reverse-phase HPLC to afford the tertiary alcohol intermediate, which was redissolved in acetone and treated with bromomethane or iodomethane (20 equiv) at room temperature. The resulting solution was stirred at room temperature for 12 h. The reaction mixture was filtered off and washed with cold ether to give the quaternary salts as solids.

Method B: Preparation of the Alkenes Derivatives 18 and 19. To a solution of an organometallic reagent (6−8 equiv) in ether or THF at 0 °C, methyl (3-*endo*)-(8-methyl-8-azabicyclo-[3.2.1]oct-3-yl]acetate (1 equiv) in anhydrous THF (4 mL/mmol) was added dropwise. After warming to room temperature and being stirred at room temperature for half an hour, the reaction mixture was heated at reflux for 2 h. The reaction mixture was quenched with aqueous saturated ammonium chloride and then extracted with ethyl acetate. The organic phase was concentrated and purified by reverse-phase HPLC to afford the tertiary alcohol intermediate, which was redissolved in 6 N HCl (5 mL/mmol) or 2 M aqueous oxalic acid (5 equiv). The mixture was heated at reflux for 1 h, then cooled down and rendered alkaline by addition of 10% NaOH. The aqueous mixture was extracted three times with ether. After evaporation of the ether, a residue was obtained, which was redissolved in acetone and treated with bromomethane or iodomethane (20 equiv) at room temperature. The resulting solution was stirred at room temperature for

12 h. The reaction mixture was filtered off and washed with cold ether to give the quaternary salts as solids.

(3-*endo*)-3-[2-Hydroxy-2,2-bis(2-methylphenyl)ethyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane Bromide (5). The title compound was prepared by method A in 38% yield. LC/MS (ES) *m/z* 364 $(M)^+$. Purity by LC: 86%. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 7.81 (d, J = 7.83 Hz, 2 H), 7.26−7.19 (m, 2 H), 7.16 (t, J = 7.45 Hz, 2 H), 7.03 (d, J = 7.33 Hz, 2 H), 4.87 (s, 1 H), 3.72 (br s, 2 H), 3.07 (s, 3 H), 3.05 (s, 3 H), 2.85 (d, J = 5.81 Hz, 2 H), 2.51−2.39 (m, 2 H), 2.38−2.14 (m, 5 H), 1.85 (s, 6 H), 1.60 (d, J = 15.66 Hz, 2 H). HRMS calcd for ($C_{25}H_{34}N_2O^+$) 364.2635, found 364.2635.

(3-*endo*)-3-{2-Hydroxy-2,2-bis[2-(methyloxy)phenyl]ethyl}-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane Bromide (6). The title compound was prepared by method A in 10% yield. LC/MS (ES) *m/z* 396$(M)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.52 (dd, J = 7.83, 1.77 Hz, 2 H), 7.20 (s, 1 H), 7.20 (dd, J = 15.41, 1.52 Hz, 1 H), 6.95 (t, J = 7.58 Hz, 2 H), 6.89 (d, J = 8.08 Hz, 2 H), 5.20 (s, 1 H), 3.72−3.65 (m, 2 H), 3.48 (s, 6 H), 2.95 (s, 3 H), 2.93 (s, 3 H), 2.80 (d, J = 6.06 Hz, 2 H), 2.35−2.28 (m, 2 H), 2.21−2.09 (m, 4 H), 1.96−1.84 (m, 1 H), 1.58 (d, J = 15.92 Hz, 2 H). HRMS calcd for ($C_{25}H_{34}NO_3^+$) 396.2533, found 396.2530.

(3-*endo*)-1,1-Bis-(3-fluorophenyl)-2-(8,8-dimethyl-8-azoniabicyclo[3.2.1]oct-3-yl)ethanol Iodide (7). The title compound was prepared by method A in 10% yield. LC/MS (ES) *m/z* 372 $(M)^+$. LC/MS (ES) *m/z* 372 (M^+). Purity by LC: 100%. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 7.36 (m, 2 H), 7.26 (m, 4 H), 6.96 (m, 2 H), 3.74 (br. s, 2 H), 3.07 (s, 3 H), 3.03 (s, 3 H), 2.77 (d, J = 6.00 Hz, 2 H), 2.47−2.40 (m, 6 H), 2.12 (br s, 1 H), 1.89 (d, J = 14.8 Hz, 2 H). HRMS calcd for ($C_{23}H_{28}F_2NO^+$) 372.2134, found 372.2131.

(3-*endo*)-3-[2,2-Bis(3-chlorophenyl)-2-hydroxyethyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane Iodide (8). The title compound was prepared by method A in 10% yield. LC/MS (ES) m/*z* 404 $(M)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.56 (d, J = 1.60 Hz, 2 H), 7.46 (d, J = 8.00 Hz, 2 H), 7.34 (d, J = 7.60 Hz, 2 H), 7.27 (d, J = 7.20 Hz, 2 H), 3.74 (br, 2 H), 2.99 (s, 3 H), 2.93 (s, 3 H), 2.73 (d, J = 5.60 Hz, 2 H), 2.32−2.18 (m, 6 H), 1.89 (br s, 1 H), 1.76 (d, J = 4.80 Hz, 2 H), 1.71 (s, 1 H). HRMS calcd for ($C_{23}H_{28}Cl_2NO^+$) 404.1543, found 404.1541.

(3-*endo*)-3-{2-Hydroxy-2,2-bis[4-(methyloxy)phenyl]ethyl}-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane Iodide (9). The title compound was prepared by method A in 10% yield. LC/MS (ES) *m/z* 396 $(M)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.33 (d, J = 9.09 Hz, 4 H), 6.83 (d, J = 14.91 Hz, 4 H), 5.42 (s, 1 H), 3.71 (s, 6 H), 3.73−3.67 (m, 2 H), 2.96 (s, 3 H), 2.93 (s, 3 H), 2.61 (d, J = 6.06 Hz, 2 H), 2.35−2.13 (m, 6 H), 1.95−1.88 (m, 1 H), 1.72 (d, J = 15.66 Hz, 2 H). HRMS calcd for ($C_{25}H_{34}NO_3^+$) 396.2533, found 396.2530.

(3-*endo*)-1,1-Bis-(4-chlorophenyl)-2-(8,8-dimethyl-8-azoniabicyclo[3.2.1]oct-3-yl)ethanol Iodide (10). The title compound was prepared by method A in 10% yield. LC/MS (ES) *m/z* 404 $(M)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 7.46 (d, J = 13.60 Hz, 4 H), 7.34 (d, J = 14.00 Hz, 4 H), 3.74 (br s, 2 H), 3.07 (s, 3 H), 3.05 (s, 3 H), 2.75 (d, J = 13.60 Hz, 2 H), 2.47−2.34 (m, 6 H), 2.08 (br s, 1 H), 1.85(d, J = 15.66 Hz, 2 H). HRMS calcd for ($C_{23}H_{28}Cl_2NO^+$) 404.1543, found 404.1542.

(3-*endo*)-1,1-Bis(3-fluoro-2-methylphenyl)-2-(8,8-dimethyl-8-azoniabicyclo[3.2.1]oct-3-yl)ethanol Bromide (11). The title compound was prepared by method A in 10% yield. LC/MS (ES) *m/z* 400 (M^+). Purity by LC: 100%. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 7.64 (d, J = 7.93 Hz, 2 H), 7.29−7.22 (m, 2 H), 7.00 (t, J = 8.92 Hz, 2 H), 3.72 (br s, 2 H), 3.07 (s, 3 H), 3.05 (s, 3 H), 2.83 (d, J = 6.04 Hz, 2 H), 2.51−2.25 (m, 6 H), 2.20−2.00 (m, 1 H), 1.80 (s, 6 H), 1.63 (d, J = 16.03 Hz, 2 H). HRMS calcd for ($C_{25}H_{32}F_2NO^+$) 400.2447, found 400.2448.

(3-*endo*)-1,1-Bis(5-fluoro-2-methylphenyl)-2-(8,8-dimethyl-8-azoniabicyclo[3.2.1]oct-3-yl)ethanol Bromide (12). The title compound was prepared by method A in 9.6% yield. LC/MS (ES) *m/z* 400 $(M)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 7.64 (dd, J = 11.39 Hz, J = 2.74 Hz, 2 H), 7.08−7.03 (m, 2 H), 6.95−6.89 (m, 2 H), 3.72 (br s, 2 H), 3.07 (s, 3 H), 3.05 (s, 3 H), 2.79 (d, J = 6.11 Hz, 2 H), 2.55−2.30 (m, 6 H), 2.22−2.10 (m, 1 H), 1.83 (s, 6 H), 1.70−1.63 (m, 2 H). HRMS calcd for ($C_{25}H_{32}F_2NO^+$) 400.2447, found 400.2443.

(3-*endo*)-3-[2,2-Bis(3,5-difluorophenyl)-2-hydroxyethyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane Bromide (13). The title compound was prepared by method A in 10% yield. LC/MS (ES) *m/z* 408 $(M)^+$. Purity by LC: 93%. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 7.20−7.11 (m, 4 H), 6.89−6.82 (m, 2 H), 3.77 (br s, 2 H), 3.09 (s, 3 H), 3.07 (s, 3 H), 2.78−2.70 (m, 2 H), 2.65−2.40 (m, 6 H), 2.15−2.01 (m, 1 H), 1.87 (d, J = 16.39 Hz, 2 H). HRMS calcd for ($C_{23}H_{26}F_4NO^+$) 408.1945, found 408.1944.

(3-*endo*)-1,1-Bis(3,4-difluorophenyl)-2-(8,8-dimethyl-8-azoniabicyclo[3.2.1]oct-3-yl)ethanol Bromide (14). The title compound was prepared by method A in 38% yield. LC/MS (ES) *m/z* 408 (M^+). Purity by LC: 100%. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 7.45−7.39 (m, 2 H), 7.30−7.19 (m, 4 H), 3.76 (br s, 2 H), 3.08 (s, 3 H), 3.06 (s, 3 H), 2.74 (d, J = 6.14 Hz, 2 H), 2.50−2.35 (m, 6 H), 2.15−2.02 (m, 1 H), 1.83 (d, J = 16.44 Hz, 2 H). HRMS calcd for ($C_{23}H_{26}F_4NO^+$) 408.1945, found 408.1944.

(3-*endo*)-3-(2-Hydroxy-2,2-di-2-thienylethyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane Iodide (15). The title compound was prepared by method A in 61% yield. LC/MS (ES) *m/z* 348 (M^+). Purity by LC: 100%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.38 (dd, J = 5.05, 1.26 Hz, 2 H), 7.05 (dd, J = 3.54, 1.26 Hz, 2 H), 6.96 (dd, J = 5.05, 3.79 Hz, 2 H), 6.39 (s, 1 H), 3.72 (br s, 2 H), 2.99 (s, 3 H), 2.94 (s, 3 H), 2.68 (d, J = 6.06 Hz, 2 H), 2.12−2.37 (m, 6 H), 1.96−2.11 (m, 1 H), 1.67 (d, J = 15.92 Hz, 2 H). HRMS calcd for ($C_{19}H_{26}NOS_2^+$) 348.1450, found 348.1447.

(3-*endo*)-1,1-Bis-(3-thienyl)-2-(8,8-dimethyl-8-azoniabicyclo-[3.2.1]oct-3-yl)ethanol Iodide (16). A solution of 3-bromothiophene (1.93 g, 11.8 mmol) in ether (6 mL) was cooled to −70 °C and added with stirring to a solution of *n*-butyllithium (2.5 M in hexane, 4.8 mL) at −70 °C under Ar. The reaction mixture was stirred at −70 °C for 30 min. (3-*endo*)-(8-Methyl-8-azabicyclo-[3.2.1]oct-3-yl)acetic acid ethyl ester (1.00 g, 4.74 mmol) in ether was added via cannula, and the solution was kept stirring at −70 °C for 1 h. Water (10 mL) was added and the reaction mixture allowed warmed to room temperature. The reaction mixture was then extracted with ether and washed with saturated NaCl. The ether layer was dried over Na_2SO_4 and evaporated to give a crude product, which was purified by reverse-phase HPLC to afford (3-*endo*)-1,1-bis-(3-thienyl)-2-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)ethanol as white solid (460 mg, 29%). LC/MS (ES) *m/z* 334 $(M + H)^+$. A solution of (3-*endo*)-1,1-bis-(3-thienyl)-2-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)ethanol (100 mg, 0.30 mmol) in dichloromethane/acetonitrile (2:1,12 mL) was mixed with iodomethane (852 mg, 6 mmol) at room temperature. The resulting mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated to afford the title compound as a white solid (130 mg, 91%). LC/MS (ES) *m/z* 348 $(M)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 7.39−7.32 (m, 4 H), 7.06 (dd, J = 5.20, 1.40 Hz, 2 H), 3.75 (br s, 2 H), 3.09 (s, 3 H), 3.06 (s, 3 H), 2.68 (d, J = 6.40 Hz, 2 H), 2.50−2.31 (m, 6 H), 2.22−2.12 (m, 1 H), 1.82 (d, J = 16.00 Hz, 2 H). HRMS calcd for ($C_{19}H_{26}NOS_2^+$) 348.1450, found 348.1448.

(3-*endo*)-3-[2-Hydroxy-2,2-bis(4-methyl-3-thienyl)ethyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane Bromide (17). The title compound was prepared by method A in 12% yield. LC/MS (ES) *m/z* 376 $(M)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.53 (s, 2 H), 7.03 (s, 2 H), 5.33 (s, 1H), 3.70 (br s, 2 H), 2.99 (s, 3 H), 2.94 (s, 3 H), 2.66−2.62 (m, 2 H), 2.35−2.15 (m, 6 H), 2.15−2.00 (m, 1 H), 1.70 (s, 6 H), 1.46 (d, J = 15.75 Hz, 2 H). HRMS calcd for ($C_{21}H_{30}NO\,S_2^+$) 376.1763, found 376.1761.

(3-*endo*)-3-(2,2-Di-2-thienylethenyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane Bromide (18). The title compound was

prepared by method B in 79%. LC/MS (ES) m/z 346 $(M)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.73 (dd, J = 5.18, 1.14 Hz, 1 H), 6.51 (dd, J = 5.05, 1.01 Hz, 1 H), 6.33 (dd, J = 5.05, 3.54 Hz, 1 H), 6.25 (dd, J = 3.41, 1.14 Hz, 1 H), 6.17 (dd, J = 5.18, 3.66 Hz, 1 H), 6.09 (dd, J = 3.54, 1.26 Hz, 1 H), 5.83 (d, J = 9.85 Hz, 1 H), 3.07 (br s, 2 H), 2.35 (s, 3 H), 2.31 (s, 3 H), 2.31−2.23 (m, 1 H), 1.87−1.68 (m, 4 H), 1.60−1.52 (m, 2 H), 1.11 (d, J = 16.17 Hz, 2 H). Anal. ($C_{19}H_{24}NS_2Br$) C, H, N.

(3-*endo*)-3-[2,2-Bis(2-methylphenyl)ethenyl]-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane Bromide (19). The title compound was prepared by method B in 19% yield. LC/MS (ES) m/z 346 $(M)^+$.)$^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 7.30−7.05 (m, 8 H), 6.23 (d, J = 10.51 Hz, 1 H), 3.87 (br s, 2 H), 3.12 (s, 3 H), 3.11 (s, 3 H), 2.95−2.82 (m, 1 H), 2.75−2.55 (m, 4 H), 2.40−2.30 (m, 2 H), 2.34 (s, 3 H), 2.08 (s, 3 H), 1.89 (d, J = 16.14 Hz, 2 H). HRMS calcd for ($C_{25}H_{32}N^+$) 346.2527, found 346.2529.

(3-*endo*)-3-(2-Hydroxy-2,2-di-2-thienylethyl)-9,9-dimethyl-9-azoniabicyclo[3.3.1]nonane Iodide (20). Step 1. A solution of ethyl [(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]acetate (**4c**) (273 mg, 1.21 mmol) in THF (3 mL) was added dropwise to a 1 M solution of 2-thienyllithium in THF (4.8 mL, 4.8 mmol) at −30 °C under argon. The cooling bath was removed, and stirring was continued for another 5 h, whereupon H_2O (3 mL) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were combined and washed with saturated NaCl, then dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (20 g), eluting with 5% MeOH/CH_2Cl_2 (600 mL) followed by 10% MeOH/CH_2Cl_2 (300 mL) to give 145 mg (48%) of 2-[(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1,1-di-2-thienylethanol. LC/MS (ES) m/z 226 $(M)^+$.

Step 2. MeI (0.034 mL, 0.547 mmol) was added to a solution of 2-[(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1,1-di-2-thienylethanol (19 mg, 0.0547 mmol) in acetone (1 mL). The mixture was stirred at room temperature for 20 h, and the solvent was removed under reduced pressure to give a crude product, which was rinsed with Et_2O (5 × 1 mL). The washings were filtered, and the combined solid residue was dried under high vacuum to give the title compound (17 mg, 88%). LC/MS (ES) m/z 362.2 $(M)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.39−7.37 (m, 2 H), 7.05−7.04 (m, 2 H), 6.99−6.95 (m, 2 H), 6.37 (s, 1 H), 3.44 (m, 2 H), 3.09 (s, 3 H), 2.98 (s, 3 H), 2.61 (d, J = 5.05 Hz, 2 H), 2.44−2.39 (m, 2 H), 2.27−2.13 (m, 3 H), 1.91−1.77 (m, 1 H), 1.64−1.54 (d, J = 15.92 Hz, 5 H).

(3-*endo*)-3-[2-Hydroxy-2,2-bis(2-methylphenyl)ethyl]-9,9-dimethyl-9-azoniabicyclo[3.3.1]nonane Iodide (21). Step 1. To a solution of ethyl [(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]acetate (**4c**) (300 mg,1.33 mmol) in THF (15 mL) was added a 2 M solution of 2-methylphenylmagnesium bromide in THF (4 mL, 7.9646 mmol). The reaction mixture was heated at 70 °C for 2 h. Water (5 mL) was added to quench the reaction. The reaction mixture was extracted with ethyl acetate (3 × 10 mL), dried ($MgSO_4$), and concentrated. The tertiary amine intermediate (130 mg, 27%) was obtained after purification with CombiFlash, eluting with 9:1 MeOH/CH_2Cl_2. LC/MS (ES) m/z 364.8 $(M)^+$.

Step 2. To a solution of 2-[(3-*endo*)-9-methyl-9-azabicyclo-[3.3.1]non-3-yl)-1,1-bis(2-methylphenyl)ethanol (25 mg, 0.068 mmol) in acetone (5 mL) was added methyl iodide (0.5 mL, 8.03 mmol). The reaction mixture was stirred overnight. The title compound (20 mg, 77%) was obtained after concentration. LC/MS (ES) m/z 378.4 (M^+). Purity by LC: 100%. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 7.86 (d, J = 7.60 Hz, 2 H), 7.24 (t, J = 7.20 Hz, 2 H), 7.18 (d, J = 7.20 Hz, 2 H), 7.04 (d, J = 7.20 Hz, 2 H), 3.17 (s, 3 H), 3.06 (s, 3 H), 2.76 (d, J = 4.80 Hz, 2 H), 2.56 (s, 1 H), 2.45−2.36 (m, 5 H), 2.32 (s, 1 H), 2.07 (br s, 1 H), 1.85 (s, 6 H), 1.70−1.68 (m, 4 H), 1.53−1.51 (m, 2 H). HRMS calcd for ($C_{26}H_{36}NO^+$) 378.2791, found 378.2790.

(3-*endo*)-3-(2-Hydroxy-2,2-diphenylethyl)-9,9-dimethyl-9-azoniabicyclo[3.3.1]nonane Bromide (22). Step 1. A solution of ethyl [(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]acetate (315 mg, 1.40 mmol) in THF (7 mL) was added to a 1.5 M solution of PhLi in 70:30 cyclohexane/Et_2O (3.73 mL, 5.6 mmol) at −30 °C (bath temp) under argon. The ice bath was removed, and the mixture was stirred for 3 h, whereupon H_2O (5 mL) was added, followed by EtOAc (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 2 mL). The combined organic layers were washed with saturated NaCl (1 × 5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified on a Biotage 25+S cartridge (20 g silica gel) at 5 psi, eluting with 0.5% aqueous NH_4OH/10% MeOH/CH_2Cl_2 (2 L) to give 295 mg (63%) of 2-[(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1,1-diphenylethanol. LC/MS (ES) m/z 336.2 $(M)^+$.

Step 2. A 2 M solution of MeBr in *tert*-butyl methyl ether (1.19 mL, 2.38 mmol) was added to a solution of 2-[(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1,1-diphenylethanol (40 mg, 0.119 mmol) in acetone (1 mL). The mixture was stirred at room temperature for 43 h. The precipitate was filtered off, rinsed with Et_2O (1 mL), and dried under high vacuum to give 43.5 mg (85%) of title compound. LC/MS (ES) m/z 350 $(M)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.48 (d, J = 7.33 Hz, 4 H), 7.29 (t, J = 7.58 Hz, 4 H), 7.17 (t, J = 7.20 Hz, 2 H), 5.59 (s, 1 H), 3.42 (br s, 2 H), 3.08 (s, 3 H), 2.95 (s, 3 H), 2.63 (d, J = 5.05 Hz, 2 H), 2.41−2.32 (m, 2 H), 2.25−2.18 (m, 2 H), 2.12−2.02 (m, 1 H), 1.96−1.84 (m, 1 H), 1.60−1.54 (m, 5 H). HRMS calcd for ($C_{24}H_{32}NO^+$) 350.2478, found 350.2477.

(3-*endo*)-3-(2,2-Di-2-thienylethenyl)-9,9-dimethyl-9-azoniabicyclo[3.3.1]nonane Bromide (23). A solution of ethyl [(3-*endo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]acetate (200 mg, 0.888 mmol) in THF (4.4 mL) was added to a solution of 1 M 2-thienyllithium (3.55 mL, 3.55 mmol) at −30 °C (bath temp). The ice bath was removed, and the mixture was stirred at room temperature for 3 h. Water (5 mL) and EtOAc (5 mL) were added, the layers were separated, and the aqueous layer was extracted with EtOAc (4 × 2 mL). The combined organic layers were washed with saturated NaCl (1 × 5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel, giving 305 mg (99%) of the title compound 2-(9-methyl-9-azabicyclo-[3.3.1]non-3-yl)-1,1-di-2-thienylethanol.

Step 2. To a suspension of the compound previously prepared (200 mg, 0.58 mmol) in water (2 mL) was added oxalic acid (207 mg, 2.3 mmol) in vial, which was sealed. The mixture was heated at 110 °C for 1 h. Then a solution of 6 M NaOH (1 mL) was added, and the mixture was extracted with EtOAc (4 × 2 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel, giving 135 mg (71%) of 3-(2,2-di-2-thienylethenyl)-9-methyl-9-azabicyclo[3.3.1]nonane.

Step 3. To a solution of the compound previously prepared (74 mg, 0.225 mmol) in acetone (1 mL) was added methyl bromide (2.25 mL, 4.5 mmol). The reaction mixture was stirred at room temperature for 80 h. The resulting precipitate was filtered and washed with Et_2O (3 × 1 mL). The filter cake was dried under high vacuum, giving 61 mg (64%) of the title compound. LC/MS (ES) m/z 344 $(M)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 7.54 (d, J = 5.05 Hz, 1 H), 7.31 (d, J = 5.05 Hz, 1 H), 7.15−7.12 (m, 1 H), 7.09−7.06 (m, 1 H), 6.96 (t, J = 3.54 Hz, 1 H), 6.89−6.86 (m, 1 H), 6.46 (d, J = 8.59 Hz, 1 H), 3.55 (br s, 2 H), 3.26−3.15 (m, 1 H), 3.23 (s, 3 H), 3.12 (s, 3H), 2.76−2.68 (m, 2 H), 2.47−2.35 (m, 2 H), 2.20−2.06 (m, 1 H), 1.87−1.74 (m, 5 H). HRMS calcd for ($C_{20}H_{26}NS_2^+$) 344.15012, found 344.14982.

(3-*endo*)-3-Iodomethyl-8-methyl-8-azabicyclo[3.2.1]octane (25). A solution of iodine (6.67 g, 25.8 mmol) and ((*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)methanol (2.0 g, 12.9 mmol)

in CH_2Cl_2 (120 mL) was mixed with PS-PPh_3 (8.6 g, 3 mmol/g, 25.8 mmol). The resultant mixture was stirred for 17 h, filtered, and concentrated to afford the title compound (2.63 g, 77%). LC/MS (ES) m/z 266 $(M + H)^+$. ^{1}H NMR ($CDCl_3$) δ ppm 3.81 (s, 2H), 3.45 (d, 2H), 2.98 (m, 2H), 2.79 (d, 3H), 2.39 (m, 3H), 2.05 (m, 4H).

3-[(3-*endo*)-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl]-2,2-diphenylpropanenitrile Trifluoroacetate (26). A solution of (3-*endo*)-iodomethyl-8-methyl-8-azabicyclo[3.2.1]octane (1.06 g, 4.0 mmol) and Ph_2CHCN (2.32 g, 12.0 mmol) in DMF (20 mL) was mixed with NaH (0.288 g, 12.0 mmol). The resultant mixture was stirred at room temperature for 60 min. Filtration and purification by reverse phase HPLC then afforded the title compound (1.16 g, 93%). LC/MS (ES) m/z 331 $(M + H)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.43−7.30 (m, 10 H), 3.83 (br s, 2 H), 2.82−2.66 (m, 5 H), 2.59−2.40 (m, 2 H), 2.38−2.05 (m, 5 H), 1.78 (d, J = 15.66 Hz, 2 H).

3-[(3-*endo*)-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl]-2,2-diphenyl-1-propanamine Trifluoroacetate (27). A solution of 3-[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-2,2-diphenylpropionitrile (250 mg, 0.758 mmol) in THF (2.5 mL) was mixed with BH_3 (2.53 mL, 1.5 M in THF, 3.79 mmol) at 0 °C. The mixture was stirred at room temperature for 20 h and diluted with H_2O (1.0 mL). The solution was then mixed with K_2CO_3 (0.1 g) and stirred at room temperature for 1 h. Organic layers were separated, and the aqueous part was extracted with EtOAc (2 × 3 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. Purification via a reverse phase HPLC afforded the title compound (159 mg, 56%). LC/MS (ES) m/z 335 $(M + H)^+$. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 7.45−7.37 (m, 4 H), 7.36−7.30 (m, 2 H), 7.29−7.20 (m, 4 H), 3.77−3.65 (m, 5 H), 2.68 (s, 3 H), 2.55 (s, 2 H), 2.34 (s, 4 H), 2.13−1.80 (m, 3 H), 1.37−1.33 (d, J = 15.40 Hz, 2 H).

***N*-{3-[(3-*endo*)-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl]-2,2-diphenylpropyl}-*N'*-(phenylmethyl)urea Trifluoroacetate (28a).** A solution of 3-((*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,2-diphenylpropylamine (50.0 mg, 0.149 mmol) in CH_2Cl_2 (2.0 mL) was mixed with $PhCH_2NCO$ (20.4 μL, 0.164 mmol) and Et_3N (62.8 μL, 0.447 mmol). The resulting mixture was stirred at room temperature for 1 h and concentrated. Purification by reverse phase HPLC afforded the title compound (13.0 mg, 19%). LC/MS (ES) m/z 468 $(M + H)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 7.36−7.29 (m, 6 H), 7.27−7.20 (m, 9 H), 4.24 (s, 2 H), 3.97 (s, 2 H), 3.62 (br s, 2 H), 2.67 (s, 3 H), 2.49 (d, J = 4.04 Hz, 2 H), 2.31−2.14 (m, 4 H), 1.99−1.80 (m, 3 H), 1.25 (d, J = 14.15 Hz, 2 H). HRMS calcd for ($C_{31}H_{37}N_3O^+$) 468.3009, found 468.3013.

***N*-Ethyl-*N'*-{3-[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-2,2-diphenylpropyl}urea Trifluoroacetate (28b).** The title compound was prepared from 3-[(3-*endo*)-8-methyl-8-azabicyclo-[3.2.1]oct-3-yl]-2,2-diphenylpropylamine and CH_3CH_2NCO by following the procedure for compound **28b** (45% yield). LC/MS (ES) m/z 406 $(M + H)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 7.34 (t, J = 7.45 Hz, 4 H), 7.28−7.17 (m, 6 H), 3.94 (s, 2 H), 3.68 (br s, 2 H), 3.08 (q, J = 7.07 Hz, 2 H), 2.68 (s, 3 H), 2.59−2.52 (m, 2 H), 2.33−2.26 (m, 4 H), 2.07−1.84 (m, 3 H), 1.33 (d, J = 15.16 Hz, 2 H), 1.03 (t, J = 7.20 Hz, 3 H).

***N*-{3-[(3-*endo*)-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl]-2,2-diphenylpropyl}acetamide Trifluoroacetate (28c).** A solution of 3-[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-2,2-diphenylpropylamine (33.4 mg, 0.10 mmol) in CH_2Cl_2 (0.5 mL) was mixed with Ac_2O (18.9 μL, 0.20 mmol) and pyridine (16.2 μL, 0.20 mmol). The mixture was stirred at room temperature for 1 h and concentrated. Purification via a reverse phase HPLC afforded the title compound (10.7 mg, 29%). LC/MS (ES) m/z 377 $(M + H)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 7.35−7.31 (m, 4 H), 7.27−7.21 (m, 6 H), 4.00 (s, 2 H), 3.66 (s, 2 H), 2.67 (s, 3H), 2.53−2.52 (d, J = 3.80 Hz, 2 H), 2.26 (s, 4 H), 1.97−1.95 (m, 3 H), 1.82 (s, 3 H), 1.28−1.24 (d, J = 15.7 Hz, 2 H).

***N*-{3-[(3-*endo*)-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl]-2,2-diphenylpropyl}benzenesulfonamide Trifluoroacetate (28d).** A solution of 3-[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-2,2-diphenylpropylamine (67.0 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL) was mixed with $PhSO_2Cl$ (28.2 μL, 0.22 mmol) and Et_3N (84.3 μL, 0.60 mmol). The result mixture was stirred at room temperature for 1 h and concentrated. Purification of the residue by reverse phase HPLC then afforded the title compound (51.5 mg, 54%) as a TFA salt. LC/MS (ES) m/z 475 $(M + H)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 7.80 (d, J = 8.34 Hz, 2 H), 7.67−7.60 (m, 1 H), 7.55 (t, J = 7.58 Hz, 2 H), 7.29 (t, J = 7.20 Hz, 4 H), 7.23 (d, J = 7.07 Hz, 2 H), 7.12 (d, J = 8.08 Hz, 4 H), 3.69 (br s, 2 H), 3.61 (s, 2 H), 2.69 (s, 5H), 2.30 (br s, 4 H), 2.05 (s, 1 H), 2.03−1.95 (m, 2 H), 1.94−1.87 (m, 1 H), 1.39 (d, J = 15.41 Hz, 2 H). HRMS calcd for ($C_{29}H_{34}N_2O_2S^+$) 475.2414, found 475.2415.

***N*-{3-[(3-*endo*)-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl]-2,2-diphenylpropyl}methanesulfonamide Trifluoroacetate (28e).** The title compound was prepared from 3-[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-2,2-diphenylpropylamine and $MeSO_2Cl$ by following the procedure for compound **28e** (28% yield). LC/MS (ES) m/z 413 $(M + H)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 7.34 (br s, 4 H), 7.21−7.28 (m, 6 H), 3.84 (br s, 2 H), 3.68 (br s, 2 H), 2.76 (s, 3 H), 2.68 (br s, 5 H), 2.30 (br s, 4 H), 2.05−1.84 (m, 3 H), 1.39 (d, J = 14.40 Hz, 2 H).

3-[(3-*endo*)-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl]-2,2-diphenylpropanamide Trifluoroacetate (29). A solution of 3-[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-2,2-diphenylpropionitrile (53 mg, 0.16 mmol) in CH_2Cl_2 (0. 25 mL) was mixed with H_2SO_4 (0.28 mL, 96%) and stirred at 40 °C for 30 h. The mixture was then poured onto ice, neutralized with $NH_3 \cdot H_2O$, extracted with EtOAc, and concentrated. The resultant residue was dissolved in DMSO and filtered. Purification by reverse phase HPLC provided the title compound (17.2 mg, 30%). LC/MS (ES) m/z 347 $(M + H)^+$. Purity by LC: 100%. ^{1}H NMR ($CDCl_3$) δ ppm 7.45−7.32 (m, 10 H), 6.89 (br s, 1 H), 5.82 (br s, 1 H), 3.67 (br s, 2 H), 2.79 (d, J = 5.05 Hz, 2 H), 2.67 (d, J = 4.80 Hz, 3 H), 2.45−2.34 (m, 2 H), 2.34−2.13 (m, 4 H), 2.02−1.94 (m, 1 H), 1.31 (d, J = 15.16 Hz, 2 H).

(3-*endo*)-8-Methyl-3-(2,2,2-triphenylethyl)-8-azabicyclo[3.2.1]-octane Trifluoroacetate (30). A solution of triphenylmethane (0.276 g, 1.13 mmol) in THF (0.5 mL) was mixed with *n*-BuLi (0.706 mL, 1.6 M in hexane, 1.13 mmol). The solution was stirred for 10 min, and a solution of (*endo*)-3-iodomethyl-8-methyl-8-azabicyclo[3.2.1]octane (100 mg, 0.377 mmol) in DMF (1.0 mL) was added. The mixture was stirred at room temperature for 60 min, mixed with H_2O (0.1 mL), concentrated, and filtered. Purification by reverse phase HPLC afforded the title compound (23.8 mg, 17%). LC/MS (ES) m/z 382 $(M + H)^+$. Purity by LC: 100%. ^{1}H NMR($CDCl_3$) δ ppm 7.36−7.28 (m, 12 H), 7.26−7.18 (m, 3 H), 3.64 (br s, 2 H), 2.97 (d, J = 5.05 Hz, 2 H), 2.65 (d, J = 4.80 Hz, 3 H), 2.50−1.87 (m, 7 H), 1.08 (d, J = 15.41 Hz, 2 H).

3-[(3-*endo*)-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl]-2,2-diphenylpropanoic Acid Trifluoroacetate (31). To a solution of 2-[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-1,1-diphenylethanol (100 mg, 1.56 mmol) in HCOOH (0.25 mL) was quickly added H_2SO_4 (2.73 mL, 90%) at 0 °C. The reaction vial was capped immediately and stored in a refrigerator at −20 °C for 7 days. The solution was poured into ice, neutralized with $NH_3 \cdot H_2O$, extracted with EtOAc, and concentrated. The resultant residue was dissolved in DMSO and filtered. Purification by reverse phase HPLC then afforded the title compound (52 mg, 48%). LC/MS (ES) m/z 350 $(M + H)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 7.46−7.20 (m, 10 H), 3.69 (br s, 2 H), 2.84 (d, J = 5.31 Hz, 2 H), 2.69 (s, 3 H), 2.34−2.27 (m, 4 H), 2.02−1.94 (m, 2 H), 1.90−1.80 (m, 1 H), 1.40 (d, J = 15.41 Hz, 2 H).

3-[(3-*endo*)-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl]-2,2-diphenyl-1-propanol Trifluoroacetate (32). A mixture of 3-[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-2,2-diphenylpropionic acid

(42.5 mg, 0.122 mmol) and $LiAlH_4$ (0.488 mL, 1.0 M in THF, 0.488 mmol) was heated with a microwave reactor at 100 °C for 1 h. It was diluted with saturated Na_2SO_4 solution, filtered through Celite, and concentrated. The resultant residue was dissolved in DMSO and filtered. Purification by reverse phase HPLC then afforded the title compound (29.1 mg, 71%). LC/MS (ES) m/z 336 $(M + H)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.39−7.21 (m, 7 H), 7.17−7.08 (m, 3 H), 4.17 (s, 2 H), 3.73 (br s, 2 H), 2.70 (d, J = 4.80 Hz, 3 H), 2.62−2.56 (m, 2 H), 2.44−2.19 (m, 6 H), 1.98−1.87 (m, 1 H), 1.41 (d, J = 15.41 Hz, 2 H).

3-[(3-*endo*)-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl]-2,2-diphenyl-*N*-(phenylmethyl)propanamide Trifluoroacetate (33). A solution of 3-[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-2,2-diphenylpropionic acid (82.0 mg, 0.235 mmol) in CH_2Cl_2 (3.0 mL) was mixed with $PhCH_2NH_2$ (28.2 μL, 0.258 mmol), EDC (49.5 mg, 0.258 mmol), HOBt (3.2 mg, 0.024 mmol), and Et_3N (0.232 mL, 1.65 mmol). The mixture was stirred at room temperature for 60 h and concentrated. The resultant residue was dissolved in DMSO and filtered. Purification by reverse phase HPLC afforded the title compound (29.8 mg, 30%) as a TFA salt. LC/MS (ES) m/z 439 $(M + H)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.06 (br s, 1 H), 7.31−7.22 (m, 10 H), 7.23 (dd, J = 3.79, 2.53 Hz, 3 H), 6.98−6.86 (m, 2 H), 4.41 (d, J = 5.81 Hz, 3 H), 3.66 (br s, 2 H), 2.83 (d, J = 5.31 Hz, 2 H), 2.67 (d, J = 5.05 Hz, 3 H), 2.43−2.28 (m, 4 H), 2.24−2.14 (m, 2 H), 1.99−1.91 (m, 1 H), 1.32 (d, J = 15.41 Hz, 2 H).

(3-*endo*)-3-(2-Cyano-2,2-diphenylethyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane Bromide (34). A solution of 3-[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-2,2-diphenylpropionitrile (310 mg, 0.938 mmol) in acetone (6.0 mL) was mixed with MeBr (4.69 mL, 2.0 M in *t*-BuOMe, 9.38 mmol). The resultant mixture was stirred at room temperature for 60 min and filtered. The solid was washed with acetone (2 × 3 mL) to afford the title compound (333 mg, 83%). LC/MS (ES) m/z 345 $(M)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 7.50 (d, J = 7.33 Hz, 4 H), 7.43 (t, J = 7.96 Hz, 4 H), 7.40−7.32 (m, 2 H), 3.79 (br s, 2 H), 3.10 (s, 3 H), 3.07 (s, 3 H), 3.01 (d, J = 5.81 Hz, 2 H), 2.58−2.43 (m, 4 H), 2.40−2.33 (m, 2 H), 2.23−2.09 (m, 1 H), 1.83 (d, J = 16.42 Hz, 2 H). HRMS calcd for $(C_{24}H_{29}N_2^+)$ 345.232 53, found 345.232 22. Anal. ($C_{24}H_{29}N_2Br$) C, H, N.

(3-*endo*)-3-(2-Carbamoyl-2,2-diphenylethyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane Iodide (35). The title compound was prepared from 3-[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-2,2-diphenylpropionamide and methyl iodide by following the procedure for compound **34** (33% yield). LC/MS (ES) m/z 363 $(M)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.44−7.32 (m, 10 H), 5.91 (br s, 1 H), 5.65 (br s, 1 H), 3.94 (br s, 2 H), 3.23 (s, 3 H), 3.17 (s, 3 H), 2.84 (d, J = 5.31 Hz, 2 H), 2.31−2.49 (m, 4 H), 2.29−2.17 (m, 2 H), 1.98−1.91 (m, 1 H), 1.49 (d, J = 16.42 Hz, 2 H).

(3-*endo*)-3-(3-Hydroxy-2,2-diphenylpropyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane Bromide (36). The title compound was prepared from 3-[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-2,2-diphenyl-1-propanol following the procedure for compound **34** (38% yield). LC/MS (ES) m/z 363 $(M)^+$. Purity by LC: 100%. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 7.50 (d, J = 7.33 Hz, 4 H), 7.43 (t, J = 7.96 Hz, 4 H), 7.32−7.40 (m, 2 H), 4.87 (s, 2 H), 3.79 (br s, 2 H), 3.10 (s, 3 H), 3.07 (s, 3 H), 3.01 (d, J = 5.81 Hz, 2 H), 2.43−2.58 (m, 4 H), 2.36 (d, J = 8.84 Hz, 2 H), 2.14−2.21 (m, 1 H), 1.83 (d, J = 16.42 Hz, 2 H).

Acknowledgment. The authors thank Len Azzarano, Gary Stelman, and Sandra Umbrecht for providing the PK data. The authors also thank Dulcie Schmidt for excellent technical assistance with the fluorometric imaging plate reader (FLIPR) assays.

Supporting Information Available: Elemental analysis data for compounds **18** and **34** and general methods for the in vitro and in vivo assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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