Identification of a Series of 3-(Benzyloxy)-1-azabicyclo[2.2.2]octane Human NK_1 Antagonists

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The synthesis and *in vitro* and *in vivo* evaluation of a series of 3-(benzyloxy)-1-azabicyclo-[2.2.2]octane NK_1 antagonists are described. While a number of 3,5-disubstituted benzyl ethers afford high affinity, the 3,5-bis(trifluoromethyl)benzyl was found to combine high *in vitro* affinity with good oral activity. Detailed structure–activity relationship studies in conjunction with data from molecular modeling and mutagenesis work have allowed the construction of a model of the pharmacophore. Specific interactions that have been identified include an interaction between His-197 and one of the rings of the benzhydryl, a lipophilic pocket containing His-265 that the benzyl ether occupies, and a possible hydrogen bond between Gln-165 and the oxygen of the benzyl ether.

The tachykinins are a family of peptides that share the common C-terminal sequence "Phe-X-Gly-Leu-Met-NH_2". There are four mammalian tachykinins: substance P (SP), neurokinin A (NKA), neurokinin B (NKB), and neuropeptide K (an N-terminally extended form of NKA). The biological actions of the tachykinins

Mammalian Tachykinins

Substance P	Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2
Neurokinin A	His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH_2
Neurokinin B	Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH_2

are mediated through specific cell-surface receptors. Three receptor subtypes, designated NK_1, NK_2, and NK_3, were identified on the basis of marked differences in the rank order of potencies of agonist peptides in different tissues, with SP being the preferred agonist for NK_1 receptors, NKA for NK_2 receptors, and NKB for NK_3 receptors. The existence of these three receptor subtypes has been confirmed by the cloning and sequencing of three distinct genes from mammalian sources.[1–4] All tachykinin receptors identified to date belong to the family of G-protein-coupled receptors and are linked to the inositol phosphate signal transduction pathway.

These receptors mediate a variety of biological effects, including vasodilation, smooth muscle contraction, and salivary secretion.[5] There is increasing evidence that SP plays a role in the transmission of pain and is involved in inflammation and the immune response.[6,7] An antagonist of SP might therefore have a role in the treatment of migraine,[8] rheumatoid arthritis,[9] asthma,[10] and inflammatory bowel disease.[11]

A number of peptide antagonists for the NK_1 receptor have been described[5]; however, the lack of potency and modest selectivity together with their poor *in vivo* stability, has limited their usefulness. A series of synthetic peptide-based spirolactams (GR 82334, **1**)[12] has been reported by Glaxo which appears to have improved *in vivo* stability (Figure 1). Fujisawa has reported a dipeptide antagonist (FK 888, **2**) designed from the tripeptide FR 113680.[13] Recently, a number of nonpeptide antagonists for peptide receptors has appeared in the literature,[14] with Pfizer reporting the discovery of the first nonpeptide SP antagonist (CP 96,-345, **3**).[15] This compound is a potent inhibitor of the actions of SP *in vitro* and *in vivo*. More recently Pfizer has reported a piperidine analogue (CP 99,994, **4**).[16] Rhone-Poulenc Rorer has developed a series of perhydroisoindolones,[17] typified by RP-67,580 (**5**). In rat brain membranes RP-67,580 competitively inhibits [^{3}H]-SP binding (K_i 4.16 nM); however, this compound has reduced affinity for the human receptor. Two series of SP antagonists have been published by Eastman Kodak. The first class, a series of imidazo[4,5-*b*]quinoxaline cyanines[18] **6**, shows modest affinity ($pA_2 = 7.23$) but also pronounced toxicity at 3 mg/kg iv. The same group has also published a series of androstano[3,2-*b*]pyrimido-[1,2-*a*]benzimidazoles[19] **7**. The most potent in this series has an affinity of 50 nM against the rat receptor but apparently has reduced affinity for the human receptor. Sanofi has reported an N-acylated 3-(3,4-dichlorophenyl)piperidine (SR 140,333, **8**) that displays high affinity for both the rat and human NK_1 receptors.[20] More recently a novel series of tryptophan esters have been described that display high affinity for the human NK_1 receptor.[21]

While CP 96,345 is a high-affinity antagonist, an Andrews analysis[22] of the structure suggests that given the functionalities involved it should have a much higher affinity for the NK_1 receptor. The observed affinity either could be due to the compound binding to the receptor in a high-energy conformation or might indicate that some of the functionality does not contri-

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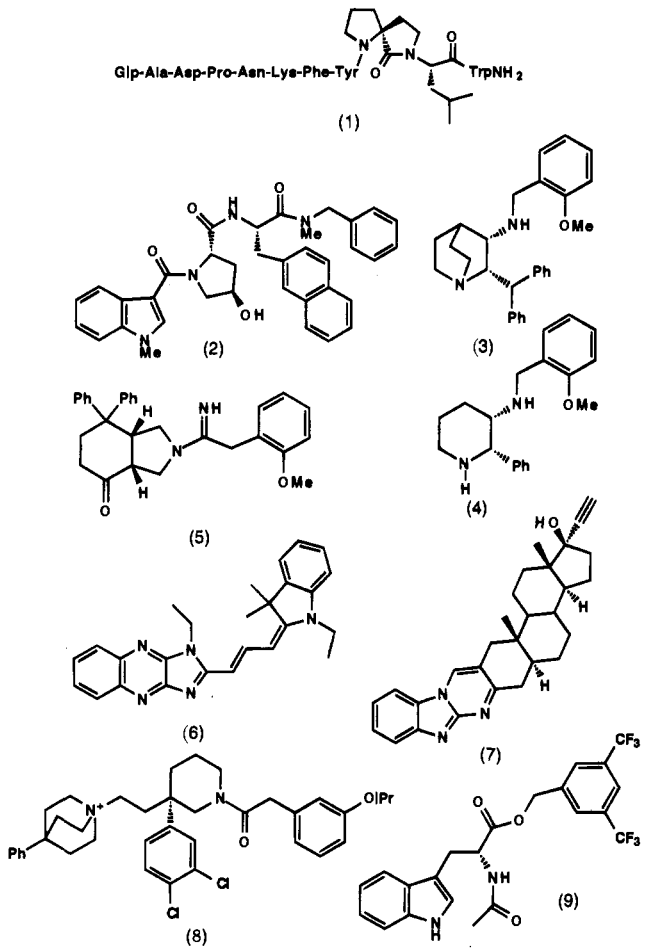
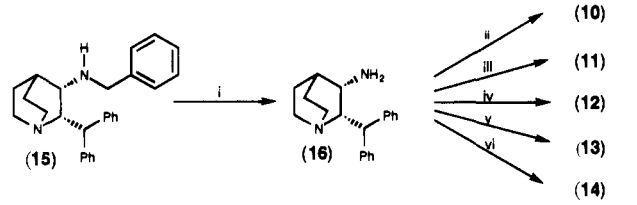


Figure 1. Structural classes of NK_1 antagonists.

Scheme 1[a]



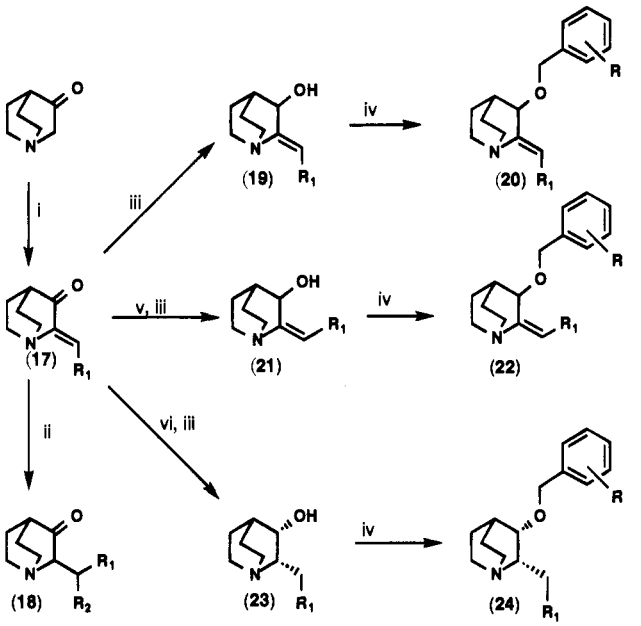
[a] Reagents: (iv) H_2, $Pd(OH)_2$; (ii) PhCOCl, DMAP, DME; (iii) PhOCOCl, Et_3N, DCM; (iv) PhNCO, Et_3N, DCM; (v) PhNCS, Et_3N, DCM; (vi) $PhSO_2Cl$, Et_3N, DCM.

bute to binding. Given that CP 96,345 is a diamine, which might compromise the *in vivo* activity, we decided to investigate replacement of either nitrogen by atoms that would be uncharged at physiological pH. Replacement of the quinuclidine bridgehead nitrogen resulted in a drop in affinity;[23] however, replacement of the benzylamine nitrogen has proved successful. This paper describes the synthesis, receptor-binding properties, and molecular modeling studies of a series of 3-(benzyloxy)-2-(diphenylmethyl)-1-azabicyclo[2.2.2]octanes.[24]

Results

Synthetic Chemistry. The key intermediate in the synthesis of compounds **10**–**14** (Scheme 1) was the benzylamine **15**;[23] the benzyl group was removed by hydrogenolysis over palladium hydroxide to give the primary amine **16**. Reaction of **16** with the appropriate acid chloride, chloroformate, isocyanate, isothiocyanate, or sulfonyl chloride afforded the amide **10**, carbamate **11**, urea **12**, thiourea **13**, or sulfonamide **14**, respectively.

Scheme 2[a]

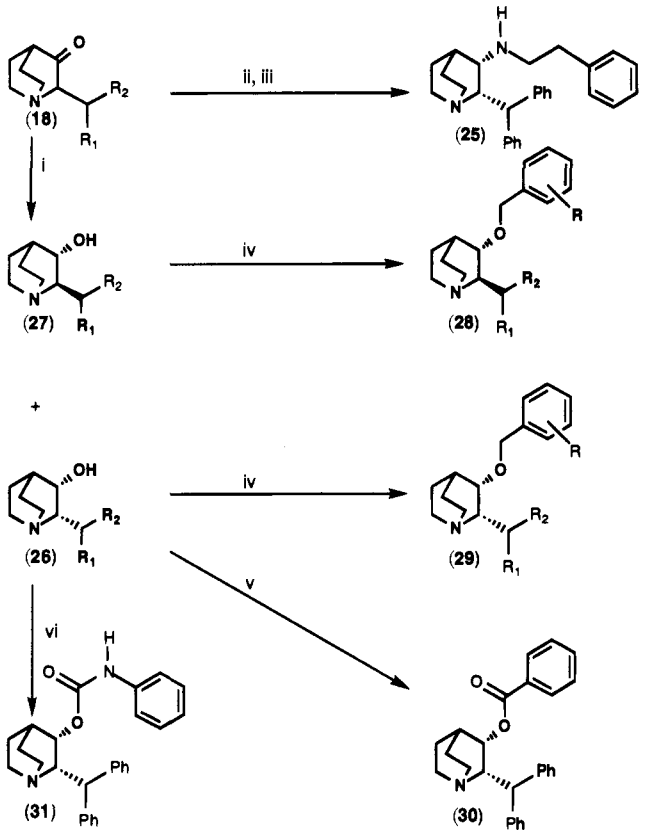


[a] Reagents: (i) R_1CHO, NaOH, EtOH; (ii) R_2MgBr; (iii) $NaBH_4$, MeOH; (iv) $KN(SiMe_3)_2$, THF, $ArCH_2Br$; (v) $CHCl_3$, HCl; (vi) H_2, Pd/C.

The key intermediate ketones **18** were prepared by aldol condensation to afford the enone **17** followed by conjugate addition using literature procedures[25] (Scheme 2). Reduction of the intermediate enone **17** afforded the unsaturated alcohol **19** which was then alkylated to give the benzyl ether **20**.[26] Alternatively, isomerization followed by reduction to **21** and alkylation yielded the corresponding *Z*-isomer **22**. Reduction of the enone **17** by catalytic hydrogenation and subsequent treatment with sodium borohydride afforded the saturated alcohol **23** which was alkylated to give ether **24**.[26] Reaction of the benzhydryl ketone **18** ($R_1 = R_2 = Ph$) with phenethylamine under reductive conditions afforded the phenethyl derivative **25** (Scheme 3). Reduction of the ketone **18** with lithium aluminum hydride afforded a mixture of the *cis* alcohol **26**, together with a small amount of the corresponding *trans* isomer **27**; subsequent alkylation using potassium hexamethyl disilazide as the base yielded the desired *trans* and *cis* ethers **28** and **29**, respectively. Reaction of the alcohol **26** with an acid chloride or isocyanate yielded the corresponding ester **30** or carbamate **31** (Scheme 3).

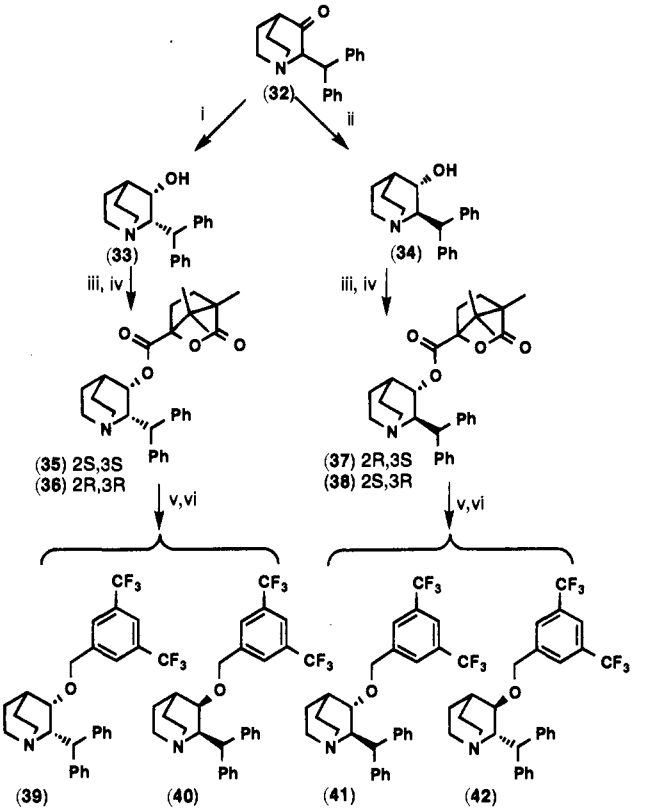
The two diastereomeric alcohols **33** and **34** could be isolated from the nonselective reduction of the benzhydryl ketone **32** as described in Scheme 3; however, they were better prepared by stereoselective reduction (Scheme 4). Reaction of **32** with the hindered reducing reagent lithium triethylborohydride afforded the *cis* alcohol **33** in 80% yield, while reduction with sodium in 2-propanol afforded the corresponding *trans* alcohol **34** in 50% yield. The isomeric alcohols were then resolved by treatment of each alcohol independently with camphanic acid chloride to afford the diastereomeric esters. Each pair of isomeric esters was then separated by recrystallization to afford the four individual diastereoisomers **35**–**38**. Hydrolysis and subsequent alkylation with 3,5-bis(trifluoromethyl)benzyl bromide afforded the four isomeric benzyl ethers **39**–**42** in yields of 50–60%.

Scheme 3[a]



[a] Reagents: (i) $LiAlH_4$, THF; (ii) $PhCH_2CH_2NH_2$, toluene, TsOH, reflux; (iii) 9-BBN; (iv) $KN(SiMe_3)_2$, THF, $ArCH_2Br$; (v) KH, PhCOCl, DMAP, DME; (vi) PhNCO, Et_3N, DCM.

Scheme 4[a]



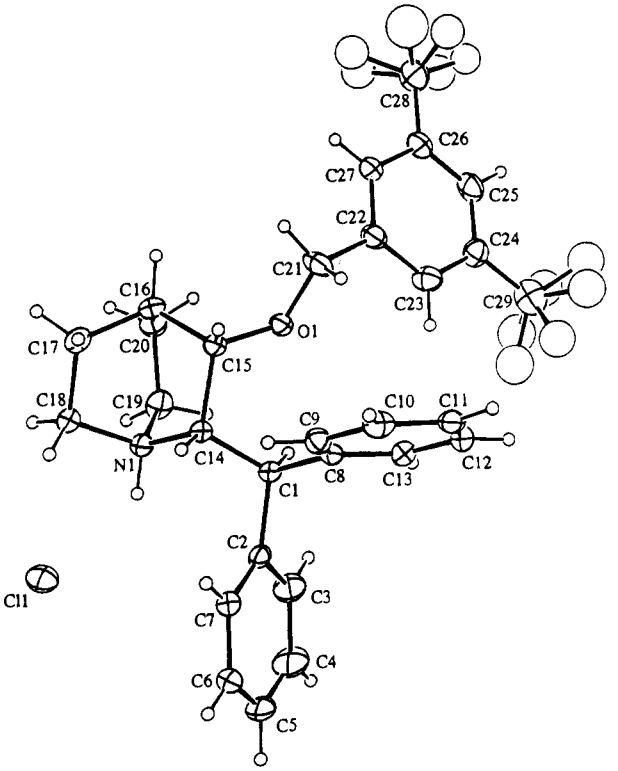
[a] Reagents: (i) $LiEt_3BH$, THF; (ii) Na, iPrOH, toluene; (iii) camphanic acid chloride, Et_3N; (iv) recrystallize (EtOAc/hexane); (v) KOH, EtOH, reflux; (vi) $KN(SiMe_3)_2$, DME, 3,5-bis(trifluoromethyl)benzyl bromide.

X-ray Crystallography. A single-crystal X-ray diffraction study was carried out on compound **69**, and the resulting model, with the crystallographic labeling, is shown in Chart 1. Although the trifluoromethyl groups are rotationally disordered, the rest of the molecule is well behaved, and the structure was refined to a conventional *R*-factor of 9.6%. The *O*-benzyl and benzhydryl groups are positioned *cis* to each other on the quinuclidine ring.

As shown (Chart 1), the substituted benzyl ring is, approximately, in an edge-to-face arrangement with one of the aromatic rings of the 2-benzhydryl group. However, the hydrogen on C23 (crystallographic numbering scheme) is not pointing at the center of the ring but is displaced to one side and is 2.54 Å above the mean plane of this ring. Thus, this arrangement is only likely to provide a modest interaction in the solid state. It is possible however that in solution the geometry is slightly altered increasing the strength of this interaction. The more important interaction in the crystal packing is probably the positioning of the CF_3 group of one benzyl ether over the center of the benzyl ring of a neighboring molecule. These rings are positioned such that the closest fluorines are *ca.* 3 Å away from the mean plane of the ring.

NMR Studies. Four related 2,3-disubstituted quinuclidines were studied by NMR to compare their solution conformations in DMSO. Proton 1D, 2D-COSY45, and phase sensitive NOESY spectra were acquired (AM500, 300 K) giving a complete assignment of the ^1H NMR. The chemical shifts of selected protons are summarized in Table 1, and the 1D ^1H NMR spectra

Chart 1 X-ray Structure of Compound **69**



of the corresponding unsubstituted benzylamines or benzyl alcohols are also included for comparison.

The NMR data indicate several stereochemical and conformational features that are common to all four

Table 1. Chemical Shifts of Selected Protons

compd	H_{10u},H_{10d}	proton[a] ortho	proton[a] para
69	4.51, 3.64	7.66 (0.34)	8.00 (0.04)
3,5-bisCF_3-benzyl alcohol	4.69	8.00	7.96
49	4.16, 3.57	6.88 (0.43)	*b*
benzyl alcohol	4.49	7.31	
15	3.49, 3.15	6.62 (0.67)	*b*
benzylamine	3.72	7.29	
3	3.45, 3.15	6.60 (0.67)	*b*
2-MeO-benzylamine	3.71	7.27	

[a] Upfield shift relative to the unsubstituted benzyl ether or benzylamine shown in parentheses. [b] *Para* proton not assigned.

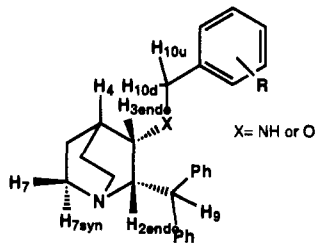


Figure 2. Protons used in NMR studies.

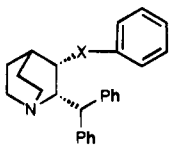
molecules. The protons H_{2endo} and H_9 (Figure 2) have a coupling constant of *ca.* 13 Hz, indicative of a dihedral angle of 180° which, together with the NOE H_9 to H_{7syn}, shows that the benzhydryl is sterically locked in a single conformation. The NOESY data confirm that the 2-benzhydryl and 3-benzyl groups are *cis* and also show that the upfield benzylic methylene proton (H_{10u}) is closer to H_{3endo} than the downfield methylene proton (H_{10d}), while H_{10d} is closer to the bridgehead proton (H_4) than is H_{10u}. Thus, the relative chemical shifts/NOEs for H_{10d}/H_{10u} are consistent with H_{10u} being shielded by the 2-benzhydryl group and near H_{3endo}, while H_{10d} is toward H_4. This limits the torsion angles around C3–X and X–C10 such that the benzyl ring is close to the 2-benzhydryl.

Comparison of the chemical shifts of the benzylic methylene protons in the corresponding unsubstituted benzylamines or benzyl alcohols with the quinuclidine amines and ethers (Table 1) shows that they are downfield from H_{10d} (0.2–0.3 ppm) but that H_{10u} is clearly more strongly shielded (0.3–0.8 ppm relative to H_{10d}). The *ortho* protons of the benzyl ring are strongly shielded (0.3–0.7 ppm) relative to the simple benzyl alcohol/amine; however, the *para* protons are unaltered, thus suggesting an aromatic–aromatic interaction between the two aryl rings.[27]

It is of interest that a larger upfield shift of the *ortho* protons is observed for the benzylamines, perhaps indicating that the geometry of the interaction between the two phenyl rings may be slightly different between the two series. In addition, comparison of the upfield shifts found for **15** and **3** suggests that the 2-methoxy does not markedly influence the solution conformation.

Biology: *In Vitro* Assays. A stable CHO cell line expressing the human NK_1 receptor was used[28] to determine binding affinity of compounds prepared in this series with [^{125}I]Tyr-8-SP as radioligand. The data in the tables are the mean of at least three determinations except where no SD is given in which case the results are the average of two determinations. Inhibition of SP-induced inositol phosphate accumulation in CHO cells expressing the human NK_1 receptor was assayed as previously described.[28]

Table 2. Binding Affinity of Antagonists Determined from Inhibition of [^{125}I]SP Binding: Variation in the Linking Group



no.	X	hNK_1, IC_{50} (μM)
15	-$NHCH_2$-	0.085 ± 0.05
25	-$NHCH_2CH_2$-	0.70
10	-NHCO-	>1
11	-NHCOO-	>1
12	-NHCONH-	>1
13	-NHCSNH-	>1
14	-$NHSO_2$-	>1
30	-OCO-	>1
31	-OCONH-	>1
44	-OCH_2-	0.11 ± 0.02

***In Vivo* Assays.** SP-induced plasma extravasation assays were performed in guinea pigs injected with SP in the dorsal skin. Inhibition of extravasation was measured by leakage of Evans blue dye after administration of the test compound.

Discussion

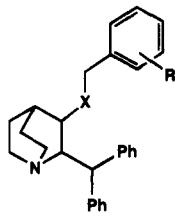
Molecular modeling studies based on CP 96,345 suggested the possibility of an offset face-to-face aromatic–aromatic interaction between the benzylamine and one of the rings of the benzhydryl group with the *ortho* proton of the benzylamine lying directly over one of the rings of the benzhydryl. Furthermore, the studies suggested the possibility that an intramolecular hydrogen bond between the 2-methoxy and the benzylamine nitrogen may have a profound influence on the conformation of the side chain. Thus, in replacing the linking nitrogen atom, it was necessary to make allowance for the possible loss of this putative hydrogen bond and investigate alternative aryl substitution.

Structure–Activity Relationships. The results in Table 2 show that homologation of the aminomethyl linkage in **15** to afford the phenethyl analogue **25** resulted in a marked reduction in affinity. A number of other derivatives, including the amide **10**, carbamate **11**, urea **12**, thiourea **13**, and sulfonamide **14**, were essentially inactive (>1 μM). Similarly, the oxygen-linked derivatives, ester **30** and carbamate **31**, had no measurable binding to the NK_1 receptor. Replacement of the unsubstituted benzylamine with an unsubstituted benzyl ether maintained affinity (**44**, IC_{50} = 110 nM; **15**, IC_{50} = 85 nM), showing that it was possible to replace the secondary nitrogen of **3** with an alternative linking group.

The poor affinity of compounds **11–13**, **25**, and **31** can be rationalized in terms of the length of the 3-atom linking group which positions the phenyl ring in a different region of space compared to **15**. Previous studies attribute the poor affinity of **10** to the nonbasic character of the amide;[29] however, the present work shows that a basic center is not essential. A more likely explanation is that the linking groups in **10–14**, **30**, and **31** all contain an sp^2-hybridized carbon atom which changes the geometry and restricts conformational flexibility of the linking group.

As had previously been reported,[23] deletion of the 2-methoxy (**15**, hNK_1 = 85 nM) in the benzylamine series (Table 3) resulted in a 100-fold drop in affinity.

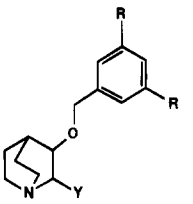
Table 3. Binding Affinity of Antagonists Determined from Inhibition of [^{125}I]SP Binding: Variation in the Benzyl Ether Substitution



no.	stereo	X	R	hNK_1 IC_{50} (nM)
3	(±)-*cis*	NH	2-OMe	0.8 ± 0.6
43	(±)-*trans*	NH	2-OMe	9.0 ± 7
15	(±)-*cis*	NH	H	85 ± 80
44	(±)-*cis*	O	H	110 ± 23
45	(±)-*cis*	O	2-Br	37 ± 16
46	(±)-*cis*	O	2-Cl	80 ± 22
47	(±)-*cis*	O	2-F	93 ± 19
48	(±)-*cis*	O	2-CF_3	67 ± 39
49	(±)-*cis*	O	2-CN	86 ± 39
50	(±)-*cis*	O	2-Me	150 ± 94
51	(±)-*cis*	O	3-Cl	62 ± 28
52	(±)-*cis*	O	3-F	37 ± 12
53	(±)-*cis*	O	3-NO_2	197 ± 45
54	(±)-*cis*	O	3-CF_3	300
55	(±)-*cis*	O	3-CN	127 ± 29
56	(±)-*cis*	O	3-Me	20 ± 4
57	(±)-*cis*	O	3-OMe	56 ± 23
58	(±)-*cis*	O	3-OPh	62 ± 2
59	(±)-*cis*	O	4-Cl	417 ± 202
60	(±)-*cis*	O	4-F	252 ± 127
61	(±)-*cis*	O	4-CF_3	370 ± 180
62	(±)-*cis*	O	4-CN	950 ± 740
63	(±)-*cis*	O	4-Me	246 ± 135
64	(±)-*cis*	O	4-OMe	1113 ± 600
65	(±)-*cis*	O	3,5-diF	33 ± 17
66	(±)-*cis*	O	2,5-diF	106 + 45
67	(±)-*cis*	O	3,5-diCl	3.5 ± 1.7
68	(±)-*trans*	O	3,5-diCl	9
69	(±)-*cis*	O	3,5-diCF_3	1.6 ± 0.3
70	(±)-*trans*	O	3,5-diCF_3	2.7 ± 1.7
71	(±)-*cis*	O	2,5-diMe	36 ± 13
72	(±)-*cis*	O	3,5-diMe	0.9 ± 0.6
73	(±)-*trans*	O	3,5-diMe	0.26 ± 0.16
74	(±)-*cis*	O	3,4-diMe	172 + 66
75	(±)-*cis*	O	3,5-diMeO	9.3 ± 2.1
76	(±)-*trans*	O	3,5-diMeO	8.3 ± 6.8
77	(±)-*cis*	O	3-Me,5-MeO	1.9 ± 1.1
78	(±)-*trans*	O	3-Me,5-MeO	1.5 ± 1.1
79	(±)-*cis*	O	3-Me,5-TMS	0.9
80	(±)-*cis*	O	3-Me,5-I	0.32 ± 0.27

However, subsequent replacement of the linking nitrogen by oxygen (**44**, hNK_1 = 110 nM) did not result in a further loss. In an effort to restore the high affinity seen with **3**, a range of substituted benzyl ethers were evaluated. All substitution at the 4-position of the benzyl ether (**59**–**64**) resulted in a loss of affinity, suggesting severe steric limitations. Substitution at the 2-position of the benzyl ether (**45**–**50**) had little effect, in contrast to the corresponding benzylamines in which *ortho* substitution is essential for high affinity.[23] A similar observation has been reported for the 2-methoxybenzyl ether.[29] Substitution at the 3-position by halogen afforded a modest 3-fold improvement (**51**, hNK_1 = 62 nM; **52**, hNK_1 = 37 nM), again in contrast to the corresponding benzylamines where 3-chloro substitution showed a 1000-fold reduction in affinity.[23] Strongly electron-withdrawing groups offered no improvement or were detrimental (**53**–**55**). Of particular note, however, is the 3-methyl analogue **56** (hNK_1 = 20 nM) which shows a 6-fold improvement over the unsubstituted compound **44** (hNK_1 = 110 nM). Using the methyl group as a probe, a range of dimethyl analogues were evaluated. The results (**71**–**74**) support the findings of the monosubstituted compounds in that substitution at the 2- and 4-positions is of no advantage. However, further *meta* substitution to afford the 3,5-dimethylbenzyl ether **72** (hNK_1 = 0.9 nM) resulted in a further 20-fold increase in affinity. This dramatic increase in affinity observed for 3,5-disubstitution was observed for a variety of substituents; both electron-withdrawing (**69**, hNK_1 = 1.6 nM) and electron-donating (**75**, hNK_1 = 9.3 nM) groups are tolerated as is the sterically demanding trimethylsilyl **79** (hNK_1 = 0.9 nM). The only exception is the 3,5-difluoro **65** (hNK_1 = 33 nM); the modest improvement in affinity is consistent with a requirement for at least one lipophilic substituent for high affinity.

Table 4. Binding Affinity of Antagonists Determined from Inhibition of [^{125}I]SP Binding: Modification at the 2-Position

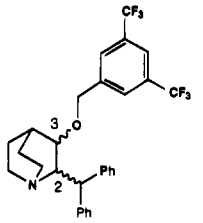


no.	stereo	Y	R	hNK_1 IC_{50} (nM)
72	(±)-*cis*	$CHPh_2$	CH_3	0.9 ± 0.6
69	(±)-*cis*	$CHPh_2$	CF_3	1.6 ± 0.3
81	(±)-*cis*	CH_2Ph	CH_3	107 ± 68
82	(±)-*cis*	CH_2Ph	CF_3	103 ± 24
83	(±)-*E*-isomer	CHPh	CH_3	120 ± 42
84	(±)-*Z*-isomer	CHPh	CH_3	2933 ± 152
85	(±)-*cis*, A	$CH(Ph)CH_2Ph$	CH_3	3.2 ± 1.3
86	(±)-*cis*, B	$CH(Ph)CH_2Ph$	CH_3	23 ± 2.5
87	(±)-*cis*, A	$CH(Ph)CH_2Ph$	CF_3	3.9 ± 2.9
88	(±)-*cis*, B	$CH(Ph)CH_2Ph$	CF_3	425 ± 25
89	(±)-*trans*, A	$CH(Ph)CH_2Ph$	CF_3	10 ± 7
90	(±)-*trans*, B	$CH(Ph)CH_2Ph$	CH_3	353 ± 143
91	(±)-*cis*, A	$CH(Ph)C_6H_{11}$	CF_3	7.5 ± 7.5

In the benzylamine series the *trans* isomer **43** showed a 10-fold reduction in affinity.[23] In contrast, in the benzyl ether series the *cis* and *trans* analogues appear to be of similar affinity: Compare the *cis* isomers **69** (hNK_1 = 1.6 nM) and **72** (hNK_1 = 0.96 nM) with the corresponding *trans* isomers **70** (hNK_1 = 2.7 nM) and **73** (hNK_1 = 0.26 nM).

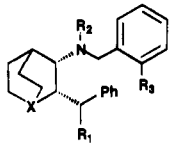
Removal of one of the phenyl rings of the benzhydryl in compounds **81** and **82** (hNK_1 = 107 and 103 nM) resulted in a 100-fold reduction in binding affinity (Table 4). In an effort to reduce the degree of conformational flexibility, a double bond was introduced between the azabicyclic skeleton and the pendant phenyl ring.[26] Interestingly, while the *Z*-isomer **84** is inactive, the *E*-isomer **83** (hNK_1 = 120 nM) maintains modest affinity. Replacement of one of the phenyl rings of the benzhydryl by benzyl results in formation of two diastereoisomers. One diastereoisomer, **85** and **87** (hNK_1 = 3.2 and 3.9 nM), maintained full activity, the other diastereoisomer displayed reduced affinity, **86** and **88** (hNK_1 = 23 and 425 nM). This observation appears also to hold true for the corresponding *trans* isomers **89** and **90**. Indeed, with the active diastereoisomer, it is possible to replace one of the phenyl rings with a fully saturated ring (**91**) and maintain affinity (hNK_1 = 7.5 nM). These results lend further support to the hypothesis that only one of the aryl rings of the benzhydryl is

Table 5. Binding Affinity of Antagonists Determined from Inhibition of [^{125}I]SP Binding: Resolved Stereoisomers



no.	stereo	hNK$_1$ IC$_{50}$ (nM)
39	2*S*,3*S*	0.2
40	2*R*,3*R*	300
41	2*R*,3*S*	0.2
42	2*S*,3*R*	125

Table 6. Influence of His-197 Mutants on Antagonist Binding



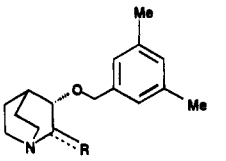
no.	X	R_1	R_2	R_3	H197A
3	N	Ph	H	OMe	large decrease
92	C	Ph	H	OMe	large decrease
93	N	Ph	Me	OMe	large decrease
15	N	Ph	H	H	large decrease
94	N	H	H	OMe	little effect

essential for high-affinity binding; the other ring probably acts as a conformational lock.

The 2*S*,3*S* stereoisomer **39** showed high affinity for the hNK$_1$ receptor, while the 2*R*,3*R* enantiomer **40** displayed a 1000-fold reduction in affinity (Table 5); this observation parallels that found for the analogous benzylamines.[23] It was of interest that the 2*R*,3*S* stereoisomer **41** (hNK$_1$ = 0.2 nM) also showed high affinity. Comparison of the active stereoisomer of both the *cis* and *trans* isomers indicates that the *S* stereochemistry at C3 is crucial for high-affinity binding, suggesting that the ether oxygen may possibly accept a hydrogen bond from the receptor. This possibility was further explored by a series of mutagenesis experiments described below. In contrast, both epimers at C2 display high-affinity binding; however, superimposition of the two active enantiomers would not allow for overlay of both rings of the benzhydryl and the benzyl ether.

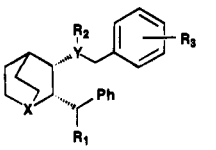
Mutagenesis. The results from the structure–activity studies have been supported by recent work using a number of mutants of the NK$_1$ receptor, in particular the interactions with histidine 197[30] and histidine 265.[31] Substitution of His-197 in helix 5 by alanine results in a large decrease in affinity for CP 96,345 (**3**) without affecting agonist binding (Table 6), suggesting that His-197 is directly involved in antagonist binding. A similar drop in affinity for the H197A mutant was observed for the all-carbon bicycle **92**,[23] the *N*-methylamine **93**,[23] and the unsubstituted benzylamine **15**. In contrast, the H197A mutation did not significantly differ from the wild-type receptor in its interactions with compounds in which the benzhydryl is replaced by a benzyl group, suggesting that it is the benzhydryl that interacts with His-197. This conclusion is also supported by a comparison of the olefins **83** and **84** (Table 7). The *E*-isomer shows a decreased affinity for the H197A mutant, while the *Z*-isomer is essentially

Table 7. Interaction of His-197 Mutants with the C2 Substituent



no.	R	H197A
69	$CHPh_2$	large decrease
83	(*E*)=CHPh	small decrease
84	(*Z*)=CHPh	no change

Table 8. Influence of His-265 Mutants on Antagonist Binding



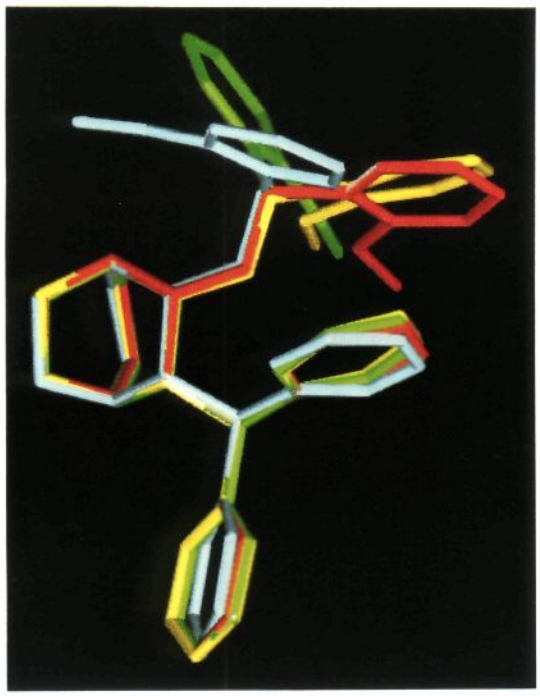
no.	X	R_1	R_2	Y	R_3	H265A
3	N	Ph	H	N	2-OMe	no effect
92	C	Ph	H	N	2-OMe	small decrease
93	N	Ph	Me	N	2-OMe	no effect
15	N	Ph	H	N	H	small decrease
44	N	Ph		O	H	small decrease
94	N	H	H	N	2-OMe	small decrease
95	N	Ph	H	N	3,5-bisCF_3	large decrease
69	N	Ph		O	3,5-bisCF_3	large decrease

unaffected by the mutation.[26] This could mean that one of the phenyl rings of the benzhydryl occupies a similar position as the phenyl ring of the *E*-isomer **75** that interacts with His-197.

Further mutations[26] have shown that His-197 can be replaced by glutamine and to a lesser extent by phenylalanine but not by lysine, tyrosine, or serine. These results suggest that the H-N on the imidazole of the histidine participates in a $\sigma-\pi$ interaction with one of the phenyl rings of the benzhydryl. A second histidine (H265) in transmembrane helix 6 also appears to be involved in the binding of some of the antagonists[31] (Table 8). A number of analogues of CP 96,345 (**3**) are unaffected by the H265A mutation; however, introduction of 3,5-disubstitution on the benzyl ring renders the series very sensitive to the H265A mutation.

Modeling Studies. Initial modeling studies[32] involved evaluation of the benzylamine series. Structure **3** was first built, and the bond angles and lengths were idealized. Sequential 30° rotations around all rotatable torsions generated a number of conformations which were then independently minimized using the Tripos force field and Gasteiger–Hückel charges. The results suggested that while the position of the benzhydryl group varies little between all the low-energy conformations, the benzylamine side chain can adopt a number of different conformations (Chart 2), some of which are stabilized by an intramolecular H-bond between the secondary amine and the methoxy group. All of the low-energy conformations appear to show an aromatic–aromatic interaction between the benzylamine ring and one of the phenyl rings of the benzhydryl in predominantly a face-to-face[33] arrangement with the *ortho* proton of the benzylamine sitting over one of the rings of the benzhydryl. The upfield shift of the *ortho* proton of the benzylamine observed in the NMR studies would also suggest that this type of interaction exists in solution. Whether the intramolecular hydrogen bond

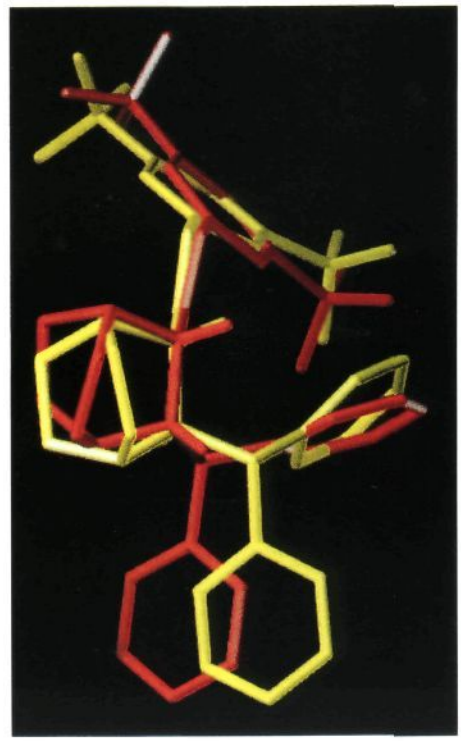
Chart 2



is present when the ligand is in solution or bound to the receptor is difficult to determine. The fact that the *N*-methyl analogue **93** only loses 10-fold in affinity might indicate that any possible intramolecular hydrogen bond does not play a major role. There is a possibility that the secondary benzylamine **93** is protonated and a hydrogen bond exists between the methoxy and the protonated nitrogen; however, the measured pK_a's (8.5 and 3.8) suggest only one nitrogen is protonated. NMR studies have confirmed that the first protonation occurs on the quinuclidine nitrogen, suggesting that the benzylamine is unlikely to be protonated at physiological pH.

Analogous modeling studies carried out on the benzyl ether **69** gave similar results, with the benzyl ether interacting with one of the phenyl rings of the benzhydryl; however, the lower energy conformations now include a number of instances in which there is an edge-to-face interaction. These results are consistent with the NMR studies and were later supported by a single-crystal X-ray determination[23] in which the benzylamine adopts a face-to-face aryl−aryl interaction,[27] while the benzyl ether adopts an edge-to-face conformation (see X-ray section). An overlay of the active enantiomer of both the *cis* and *trans* isomers (Chart 3) superimposes the benzyl ethers, the quinuclidine nitrogen, and the phenyl ring of the benzhydryl that would occupy a similar position as the phenyl ring of the *E*-isomer **83** that was shown to interact with His-197. Comparison (Chart 4) of the X-ray crystal structure of CP 96,345 (**3**) with that of the benzyl ether **69** shows that the angle between the two interacting rings is quite different, the benzylamine **3** favoring a more face-to-face relationship, while the ether tends toward an edge-to-face conformation. It is also tempting to speculate that the *ortho* methoxy of CP 96,345 occupies the same region of the receptor as one of the trifluoromethyl groups of the benzyl ether **69**.

Chart 3



Summary of Pharmacophore. Based on the structure−activity data described above and the data available for the corresponding amines,[23] four key features of the pharmacophore have been identified and depicted in Figure 3. (1) An interaction with the protonated bridgehead nitrogen: while there are a number of acidic residues within the transmembrane region, there is no evidence to suggest that any of these form an ion pair with the protonated nitrogen. However, a possible interaction with a backbone amide could not be examined by mutagenesis studies. (2) The benzhydryl forms a key element of the structure of the high-affinity NK_1 antagonists. However, only one of the phenyl rings is necessary for binding to the receptor, with the second ring probably acting as a conformational anchor. Furthermore mutagenesis studies have suggested that His-197 forms an amino−aromatic interaction with one of the phenyl rings. (3) The heteroatom of the benzyl ether probably acts as a hydrogen bond acceptor, and recent results suggest that Gln-165 may be involved[34] in this interaction. (4) The interaction of the third aromatic ring with the receptor appears to be different for the two classes of quinuclidine antagonists. It is possible that in the case of the benzyl ethers an edge-to-face aromatic−aromatic interaction stabilizes a conformation which accesses a lipophilic pocket containing His-265. In contrast, the benzylamines adopt a face-to-face conformation, perhaps allowing the *ortho* methoxy to engage in a second hydrogen-bonding interaction. While mutagenesis studies have failed to identify the residue involved, a possible interaction with the peptide backbone cannot be excluded.

***In Vivo* Studies.** While the 3,5-dimethylbenzyl ethers **72** and **73** afforded the highest *in vitro* affinity, they proved to have only modest oral activity (Table 9). However after ip administration, **73** appeared to have improved potency suggesting that there may be ex-

Chart 4

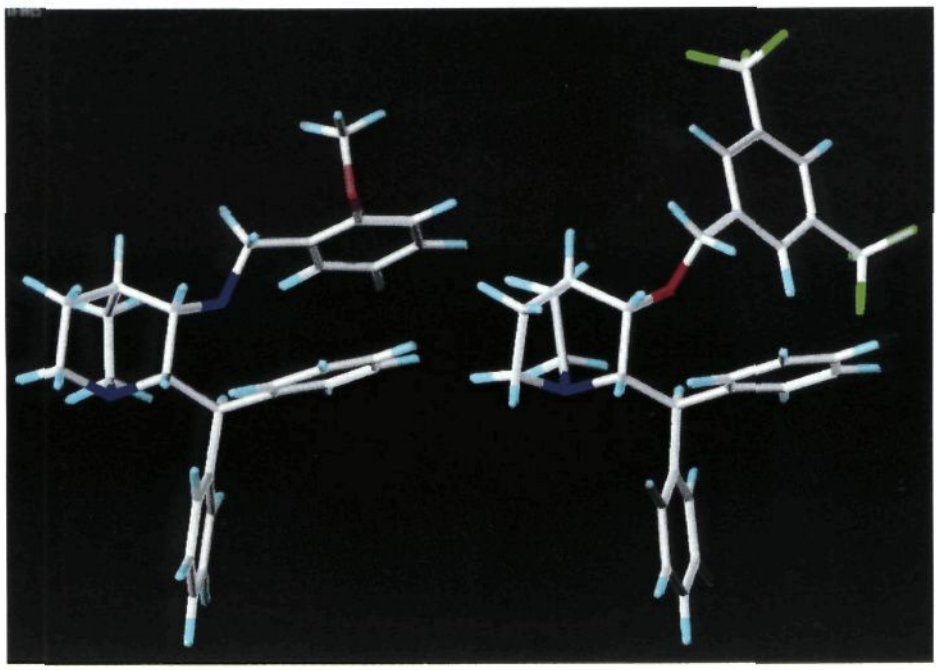


Table 9. Inhibition of SP-Induced Extravasation in the Skin of Guinea Pigs

compd	route	dose (μg/kg)	inhibition[a] (%)
72	po	10	45
73	po	10	40
73	ip	10	89
39	po	10	76
39	ip	30	100
39	ip	10	92
39	ip	3	59
39	ip	1	6
40	po	10	−17
41	po	10	70

[a] Inhibition of leakage of Evans blue from plasma.

tensive first-pass metabolism. In contrast, those compounds containing the 3,5-bis(trifluoromethyl) substitution (**39** and **41**) were found to have excellent oral activity and to be almost equipotent following ip administration with the *in vivo* potency reflecting the stereoselectivity found in the binding assay (**40**, inactive).

Conclusion

The compounds described in the paper represent a novel series of 3-(benzyloxy)quinuclidine-based NK_1 antagonists. Comparison of both the structure−activity relationships and the mutagenesis studies for the benzyl ethers and the analogous benzylamines suggests that the benzyl side chain adopts a different conformation for each series when binding to the receptor. Evidence from modeling and spectroscopic and crystallographic studies suggests that this may arise from a change in the geometry of the aryl−aryl interaction between the benzyl ring and one of the rings of the benzhydryl. *Using a combination of structure−activity and mutagenesis work, a model of the pharmacophore has been developed that should be useful in the design of novel* NK_1 antagonists. A number of 3,5-disubstituted benzyl ethers show significant *in vitro* affinity; however, the 3,5-bis(trifluoromethyl)benzyl ether has been shown to also possess excellent oral availability.

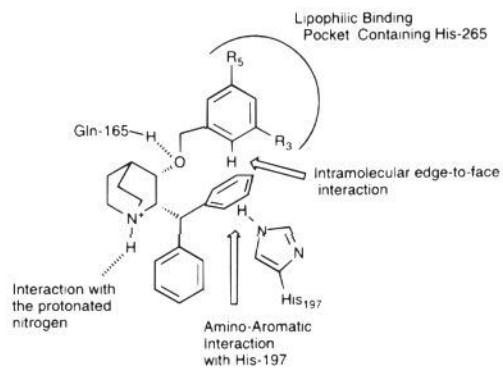


Figure 3. Proposed pharmacophore.

Experimental Section

Chemistry. General Directions. Except where otherwise stated, the following procedures were adopted. ^1H (360 MHz) and ^{13}C (90 MHz) NMR spectra were recorded on a Bruker AM360 spectrometer using a 5-mm dual probe. ^1H chemical shifts are expressed in ppm down field from tetramethylsilane; ^{13}C chemical shifts are reported relative to DMSO (δ = 39.4 ppm). Coupling constants were evaluated by first-order rules with an estimated accuracy of 0.5 Hz. Nuclear Overhauser enhancements were measured by the NOE difference method using degassed samples. Mass spectra were recorded with a VG 70-250 mass spectrometer and infrared spectra on a Perkin-Elmer 782 IR spectrophotometer. Organic solvents were purified when necessary by the methods described by Perrin *et al.*[35] All solutions were dried over anhydrous sodium sulfate and evaporated on a Buchi rotary evaporator.

***cis*-2-(Diphenylmethyl)-*N*-(phenylmethyl)-1-azabicyclo-[2.2.2]octan-3-amine (15).** 2-(Diphenylmethyl)-1-azabicyclo-[2.2.2]octan-3-one[25] (**32**) (10 g, 0.034 mol), benzylamine (5.6 mL, 0.05 mol), and *p*-toluenesulfonic acid (20 mg) were dissolved in toluene (100 mL), and the resulting solution was heated at reflux under Dean−Stark conditions for 12 h. The solution was cooled, and the solvent was removed *in vacuo* to leave a white solid. This was dissolved in tetrahydrofuran (150 mL), and the solution was cooled to 0 °C under nitrogen. 9-BBN (69 mL, 0.5 M solution in THF, 0.034 mol) was added dropwise, and the solution was allowed to stir at room

temperature for 3 days. The reaction was quenched with water and the mixture acidified with 2 N HCl (100 mL). The aqueous layer was extracted with dichloromethane (2 × 50 mL) and made basic by the addition of sodium hydroxide (2 N). This mixture was extracted with dichloromethane (4 × 50 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give a white solid which was recrystallized from 2-propanol (6.5 g, 50%). A small portion was converted to the oxalate salt for biological testing; the remainder was used in the next step as the free base: ^1H NMR ($CDCl_3$) δ 1.19–1.30 (m, H), 1.44–1.67 (m, 3H), 1.87–1.99 (m, 2H), 2.56–2.66 (t, 1H), 2.74–2.78 (t, 1H), 2.83–2.85 (m, 1H), 3.57–3.60 (d, 1H, CH_2Ph), 3.17–3.24 (d, 1H, CH_2-Ph), 3.66–3.70 (m, 1H, CHN), 4.40–4.43 (d, 1H, $CHPh_2$), 6.59–6.62 (m, 2H, ArH), 7.05–7.37 (m, 13H, ArH); MS (CI^+) *m/z* 383 ($M^+ + 1$, 100). Anal. ($C_{27}H_{30}N_2{\cdot}2C_2O_4H_2$) C, H, N.

***cis*-2-(Diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-amine (16).** Benzylamine **15** (0.8 g) was dissolved in methanolic hydrogen chloride and hydrogenated at atmospheric pressure using palladium on carbon as catalyst. The solvent was removed *in vacuo* to afford a white solid which was recrystallized from 2-propanol (0.5 g): mp 268–270 °C; ^1H NMR (D_2O) δ 2.11–2.22 (m, 4H), 2.57 (br s, 1H), 3.30–3.36 (m, 2H), 3.44–3.47 (m, 1H), 3.69–3.73 (m, 1H), 4.21–4.24 (dd, J = 9.0, 4.5 Hz, 1H), 4.66–4.69 (d, J = 13.0 Hz, 1H, $CHPh_2$), 5.08–5.14 (m, 1H, CHN), 7.36–7.79 (m, 10H, ArH); MS (FAB^+) *m/z* 293. Anal. ($C_{27}H_{30}N_2{\cdot}2C_2O_4H_2$) C, H, N.

***cis*-*N*-Benzoyl-2-(diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-amine (10).** Benzoyl chloride (0.2 mL, 1.78 mmol) was added dropwise to a solution of the amine **16** (0.5 g, 1.71 mmol), (dimethylamino)pyridine (0.22 g, 1.80 mmol), and triethylamine in dimethoxyethane (25 mL), and the resulting mixture was stirred for 12 h. The solvent was evaporated and the residue dissolved in dichloromethane. This solution was washed with water and brine; the solvent was evaporated, and the crude residue was purified on silica gel using 3% methanol in dichloromethane as eluant. The product was isolated as the oxalate salt which was recrystallized from ethanol: mp 221–223 °C; ^1H NMR ($CDCl_3$, free base) δ 1.46–1.55 (m, 1H), 1.69–1.89 (m, 3H), 2.18 (m, 1H), 2.88–2.95 (m, 3H), 3.17–3.28 (m, 1H), 4.11–4.17 (m, 1H), 4.24–4.27 (d, J = 12.5 Hz, 1H, $CHPh_2$), 4.59–4.85 (m, 1H, CHN), 6.30–6.32 (m, 1H), 6.99–7.51 (m, 13H, ArH), 7.95–7.97 (d, J = 7.5 Hz, 2H, ArH); MS (FAB^+) *m/z* 397 ($M^+ + 1$, 100). Anal. ($C_{27}H_{28}N_2O{\cdot}C_2$-$O_4H_2{\cdot}H_2O$) C, H, N.

***cis*-2-(Diphenylmethyl)-*N*-(phenoxycarbonyl)-1-azabicyclo[2.2.2]octan-3-amine (11).** Phenyl chloroformate (0.33 mL, 2.57 mmol) was added to a mixture of the amine **16** (0.75 g, 2.57 mmol) and triethylamine in dichloromethane (20 mL), and the resulting solution was stirred for 12 h. The solution was washed with water and brine and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was purified by chromatography on silica gel using 3% methanol in dichloromethane as eluant; this removed the product as a white powder which was converted to the oxalate salt by treatment with methanolic oxalic acid. The product was recrystallized from 2-propanol: mp >250 °C; ^1H NMR (DMSO-d_6, 315 K) δ 1.18–1.28 (m, 1H), 1.50–1.84 (m, 4H), 2.32–2.42 (m, 1H), 2.56–2.64 (m, 1H), 3.16–3.22 (m, 1H), 3.82–3.88 (br s, 1H), 4.04 (d, J = 10.0 Hz, 1H, CHN), 4.58 (d, J = 12.0 Hz, 1H, $CHPh_2$), 6.64–6.72 (m, 2H), 6.98–7.38 (m, 11H, ArH), 7.42–7.46 (m, 2H, ArH); MS (FAB^+) *m/z* 413 ($M^+ + 1$, 100). Anal. ($C_{29}H_{24}F_6NO{\cdot}1.4(COOH)_2{\cdot}0.6H_2O$) C, H, N.

***cis*-2-(Diphenylmethyl)-*N*-(phenylcarbamoyl)-1-azabicyclo[2.2.2]octan-3-amine (12).** Phenyl isocyanate (0.28 mL, 2.57 mmol) was added to a solution of the amine **16** (0.75 g, 2.57 mmol) in dichloromethane (15 mL). After 5 min a white solid precipitated; this was removed by filtration and converted to the oxalate salt by treatment with methanolic oxalic acid. The solid was recrystallized from a mixture of 2-propanol and methanol: mp 225–227 °C; ^1H NMR (D_2O) δ 1.95–1.97 (m, 1H), 2.11–2.21 (m, 4H), 3.17–3.34 (m, 2H), 3.44 (m, 1H), 3.65–3.66 (m, 1H), 4.52–4.56 (d, J = 13.0 Hz, 1H, $CHPh_2$), 4.57–4.61 (m, 1H, CHNH), 4.98–5.03 (m, 1H, CHN), 6.97, 7.58 (m, 15H, ArH); MS (Cl^+) *m/z* 412 ($M^+ + 1$, 50). Anal. ($C_{27}H_{29}N_3O{\cdot}$ $C_2O_4H_2{\cdot}H_2O$) C, H, N.

***cis*-2-(Diphenylmethyl)-*N*-(phenylthiocarbamoyl)-1-azabicyclo[2.2.2]octan-3-amine (13).** Phenyl isothiocyanate (0.21 mL, 1.71 mmol) was added to a solution of the amine **16** (0.5 g, 1.71 mmol) in dichloromethane (10 mL). After 12 h a white solid precipitated; this was removed by filtration and converted to the oxalate salt by treatment with methanolic oxalic acid. The solid was recrystallized from ethanol: mp 240–242 °C; ^1H NMR (pyridine-d_5) d 1.52–1.64 (m, 1H), 1.72–1.82 (m, 1H), 1.96–2.08 (m, 1H), 2.28–2.41 (m, 1H), 2.50 (br s, 1H, CH), 3.04–3.16 (m, 2H), 3.42–3.48 (m, 1H), 4.42–4.56 (m, 1H), 5.00–5.16 (m, 1H), 5.44–5.48 (m, 1H), 6.73–8.02 (m, 15H, ArH); MS (Cl^-) *m/z* 428 ($M^+ + 1$, 100). Anal. ($C_{27}H_{29}N_3S{\cdot}$ $C_2O_4H_2$) C, H, N.

***cis*-2-(Diphenylmethyl)-*N*-(phenylsulfonyl)-1-azabicyclo[2.2.2]octan-3-amine (14).** Phenylsulfonyl chloride (0.21 g, 1.13 mmol) was added to a solution of the amine **16** (0.3 g, 1.02 mmol) and triethylamine (1 mL, 7.1 mmol) in dimethoxyethane (20 mL), and the reaction mixture was stirred at room temperature for 12 h. The mixture was poured onto 5% sodium bicarbonate solution, and the precipitate was removed by filtration and converted to the oxalate salt by treatment with methanolic oxalic acid. The solid was recrystallized from 2-propanol: mp >250 °C; ^1H NMR (DMSO-d_6) δ 1.32–1.48 (m, 1H), 1.42 (br s, 1H), 1.56–1.86 (m, 3H), 2.74–2.94 (m, 2H), 3.06–3.20 (m, 1H), 3.34–3.48 (m, 1H), 3.75–3.80 (m, 1H), 4.52 (d, J = 14.5 Hz, 1H), 4.80 (br s, 1H), 7.09–7.58 (m, 13H, ArH), 7.95 (d, 2H, ArH); MS (Cl^+) *m/z* 433 ($M^+ + 1$, 100). Anal. ($C_{26}H_{28}N_2O_2S{\cdot}O_4H_2{\cdot}0.5H_2O$) C, H, N.

***cis*-2-(Diphenylmethyl)-*N*-(phenylethyl)-1-azabicyclo[2.2.2]octan-3-amine (25).** The ketone **32** (1.5 g, 0.005 mol), phenethylamine (1.0 mL, 0.077 mol), and *p*-toluenesulfonic acid (20 mg) were dissolved in toluene, and the solution was heated at reflux for 12 h under Dean–Stark conditions. The mixture was allowed to cool, and the solvent was removed *in vacuo*. The crude residue was dissolved in tetrahydrofuran (25 mL), and the solution was cooled to 0 °C. 9-BBN (10 mL, 0.5 M in THF) was added dropwise, and the resulting solution was stirred under a nitrogen atmosphere at room temperature for 3 days. The reaction was quenched with water and the mixture diluted with dichloromethane. The aqueous layer was made acidic (pH = 1, 2 N HCl) and extracted with dichloromethane (2 × 20 mL). The aqueous layer was then made basic (2 N NaOH) and extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was dissolved in ether and treated with oxalic acid; the precipitate was removed by filtration and recrystallized from 2-propanol: mp 189–190 °C; ^1H NMR ($CDCl_3$, free base) δ 1.15–1.23 (m, 1H), 1.48, 1.85 (m, 3H), 1.91 (m, 1H), 2.17–2.47 (m, 3H), 2.55–2.67 (m, 2H), 2.77–2.79 (m, 2H), 2.85–2.97 (m, 1H), 3.12–3.18 (m, 1H), 3.66–3.71 (m, 1H), 4.40 (d, J = 12 Hz, 1H, $CHPh_2$), 6.98–7.33 (m, 15H, ArH); MS (FAB^+) *m/z* 397 ($M^+ + 1$, 100), 229 (90). Anal. ($C_{28}H_{32}N_2{\cdot}1.5C_2O_4$-$H_2{\cdot}0.5H_2O$) C, H, N.

***cis*-*O*-Benzoyl-2-(diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-ol Oxalate (30).** The alcohol **26**[25] (R_1 = R_2 = Ph) (0.5 g, 1.7 mmol) and (dimethylamino)pyridine (0.2 g, 1.7 mmol) were dissolved in dimethoxyethane (50 mL); potassium hydride (0.34 g, 20% in oil, 1.7 mmol) was added, and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 30 min. Benzoyl chloride (197 mL, 1.7 mmol) was added, and the reaction mixture was heated at reflux for 1 h. The reaction was quenched by the addition of 2-propanol, and the solvent was removed *in vacuo*. The residue was partitioned between dichloromethane and water; the organic phase was washed with brine, separated, dried ($MgSO_4$), and evaporated. The crude product was purified by chromatography on silica gel using 3% methanol in dichloromethane as eluant to afford the product as a colorless oil. This was dissolved in ether and treated with ethereal oxalic acid. The solid obtained was removed by filtration and recrystallized from 2-propanol: mp 218–219 °C; ^1H NMR (pyridine-d_5) δ 1.16–1.25 (m, 1H), 1.44–1.52 (m, 1H), 1.56–1.67 (m, 1H), 1.74–1.84 (m, 1H), 2.19–2.29 (m, 1H, CH), 2.60–2.76 (m, 1H), 2.82–2.94 (m, 1H), 3.44–3.56 (m, 1H), 4.18 (dd, J = 12.0, 7.5 Hz, 1H), 4.83 (d, J = 12.0 Hz, 1H), 5.58 (m, 1H),

6.94–7.61 (m, 15H, ArH); MS (Cl^+) *m/z* 398 ($M^+ + 1$, 100), 292 (75). Anal. ($C_{27}H_{27}NO_2 \cdot 1.5C_2H_4O_2$) C, H, N.

***cis*-2-(Diphenylmethyl)-*O*-(phenylcarbamoyl)-1-azabicyclo[2.2.2]octan-3-ol (31).** The alcohol **26** (0.5 g, 1.7 mmol) and (dimethylamino)pyridine (0.2 g, 1.7 mmol) were dissolved in tetrahydrofuran (50 mL); potassium hydride (0.3 g, 25% in oil, 1.8 mmol) was added, and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 30 min. Phenyl isocyanate (184.7 mL, 1.7 mmol) was added, and the reaction mixture was heated at reflux for 1 h. The reaction was quenched by the addition of 2-propanol, and the solvent was removed *in vacuo*. The residue was partitioned between dichloromethane and water; the organic phase was washed with brine, separated, dried ($MgSO_4$), and evaporated. The crude product was purified by chromatography on silica gel using 3% methanol in dichloromethane as eluant to afford the product as a colorless oil. This was dissolved in ether and treated with ethereal oxalic acid. The solid obtained was removed by filtration and recrystallized from 2-propanol: mp 129–130 °C; ^1H NMR (pyridine-d_5) δ 1.23–1.32 (m, 1H), 1.45–1.56 (m, 1H), 1.56–1.68 (m, 1H), 1.80–1.91 (m, 1H), 2.62–2.76 (m, 2H), 2.94–3.07 (m, 1H), 3.12–3.25 (m, 1H), 4.22–4.28 (m, 1H), 4.59 (d, J = 12.0 Hz, 1H), 5.35–5.39 (m, 1H), 7.01–7.86 (m, 15H, ArH); MS (Cl^+) *m/z* 413 ($M^+ + 1$, 80), 276 (100). Anal. ($C_{27}H_{28}N_2O_2 \cdot 2C_2H_4O_2$) C, H, N.

Nonselective Reduction of the Ketone: 2-(Diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-ol (33 and 34; Mixture of *cis*/*trans* = 80:20). 2-(Diphenylmethyl)-1-azabicyclo[2.2.2]-octan-3-one (**32**) (18.9 g) was dissolved in tetrahydrofuran (350 mL, anhydrous) and cooled to 65 °C under nitrogen. Lithium aluminum hydride (1.0 M solution in THF, 40 mL) was added dropwise to the solution which was stirred at room temperature overnight. Water (2 mL) followed by sodium hydroxide (15%, 2 mL) and water (6 mL) was added dropwise to the solution resulting in precipitation of the inorganic salts. Magnesium sulfate (2 g) was added and the mixture filtered through Celite. The solvent was removed *in vacuo*, and the residue was recrystallized from 2-propanol affording the pure *cis* isomer. The mother liquors were concentrated and found to be 80:20 *cis*/*trans* by ^1H NMR; this mixture was used without further purification.

Stereoselective Reduction: (±)-*cis*-2-(Diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-ol (33). 2-(Diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-one (**32**) (50 g) was dissolved in dimethoxyethane (400 mL) and the solution stirred under nitrogen. Lithium triethylborohydride (1.0 M in THF, 200 mL) was added dropwise to the stirred solution over a period of 1 h. The excess reducing agent was destroyed by dropwise addition of hydrochloric acid (1 N). The solvent was removed *in vacuo*; the residue was made basic with sodium hydroxide (2 N) and extracted with dichloromethane (4 × 500 mL). The organic extract was dried ($MgSO_4$) and evaporated, and the residue was recrystallized from toluene: mp 192–194 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 1.25–1.4 (1H, m, CH), 1.42 (1H, d, J = 5.0 Hz, OH), 1.48–1.76 (2H, m, CH_2), 1.90–2.04 (2H, m, CH × 2), 2.64–2.9 (3H, m, CHN + CH_2N), 3.16–3.34 (1H, m, CHN), 3.68 (1H, dd, J = 14.5, 18.0 Hz, CHN), 4.00 (1H, m, CHOH), 4.54 (1H, d, J = 18.0 Hz, Ph_2CH), 7.12 (10H, m, ArH).

(2*S*,3*S*)-2-(Diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-ol ((+)-33) and (2*R*,3*R*)-2-(Diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-ol ((−)-33). (a) *cis*-2-(Diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-yl Camphanate: Diastereoisomer 1 (35) and Diastereoisomer 2 (36). A solution of *cis*-2-(diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-ol (**33**) (20 g) in dichloromethane (400 mL) was cooled in ice under N_2. (Dimethylamino)pyridine (8.3 g) and triethylamine (6.9 mL) were added to the solution followed by dropwise addition of (−)-camphanic acid chloride in dichloromethane (200 mL), and the resulting mixture was stirred at room temperature for 45 min. The mixture was washed with aqueous sodium bicarbonate, water, and brine. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 2–4% methanol in dichloromethane as eluant; this yielded the product as a 1:1 mixture of diastereoisomers. This mixture was recrystallized from ethyl acetate; the first crop was isolated and recrystallized twice from ethyl acetate to yield diastereoisomer 2 (99.5% pure, HPLC). The mother liquors from the first crystallization were evaporated and recrystallized from ethyl acetate to give diastereoisomer 1 (99.5% pure, HPLC).

Diastereomer 1: mp 231–232 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 0.88 (3H, s, CH_3), 0.90 (3H, s, CH_3), 1.08 (3H, s, CH_3), 1.24–1.36 (1H, m, CH), 1.5–2.0 (3H, m, CH + CH_2), 2.6–2.8 (3H, m, CH*H*N + CH_2N), 3.2 (1H, mc, C*H*HN), 3.82 (1H, dd, J = 14.5, 18.0 Hz, CH*H*), 4.48 (1H, d, J = 18.0 Hz, $CHPh_2$), 5.29 (1H, mc, CHOCOR), 7.0–7.38 (10H, m, ArH); $[\alpha]_D$ ($CDCl_3$, c = 1) +7.1°.

Diastereoisomer 2: mp 250–251 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 0.61 (3H, s, CH_3), 1.0 (3H, s, $C(CH_3)CH_3$), 1.06 (3H, s, $C(CH_3)CH_3$), 1.35 (1H, m, CH), 1.6–1.7 (5H, m, CH, CH_2), 1.67–1.74 (2H, m, CH*H*CH*H*N), 2.02 (1H, m, CH), 2.24 (1H, m, quinuclidine bridgehead), 2.7 (3H, m), 3.14–3.24 (1H, m, C*H*HN), 4.46 (1H, d, J = 12.2 Hz, $CHPh_2$), 5.3 (1H, m, -CHOCOR), 7.03–7.3 (10H, m, ArH); $[\alpha]_D$ ($CDCl_3$, c = 1) +1.2°.

(b) (+)- and (−)-*cis*-2-(Diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-ol. The camphanate ester (diastereoisomer 1 above) (0.25 g) was dissolved in dimethoxyethane (10 mL) and stirred under N_2. Lithium aluminum hydride (0.58 mL, 1.0 M in diethyl ether) was added to the solution dropwise. The mixture was allowed to stir for 2 h. Excess lithium aluminum hydride was destroyed by addition of water dropwise followed by sodium hydroxide and water to afford a granular precipitate. $MgSO_4$ was added to the mixture which was filtered through Celite to remove inorganic matter. The solvent was evaporated, and the residue was recrystallized from 2-propanol to afford the (−)-alcohol (99.5% enantiomer 1, HPLC): mp 174–175 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 1.20–1.30 (1H, m, CH), 1.34 (1H, d, J = 4 Hz, OH), 1.46–1.7 (2H, m, CHH), 1.86–2.0 (2H, m, CH + CH), 2.56–2.90 (3H, m, CHHN + CH*H*N), 3.10–3.20 (1H, m, C*H*HN), 3.64 (1H, dd, J = 14.5, 18.0 Hz, C*H*$CHPh_2$), 3.96 (1H, m, C*H*OH), 4.48 (1H, d, J = 18.0 Hz, Ph_2CH), 7.06–7.46 (10H, m, ArH); $[\alpha]_D$ ($CDCl_3$, c = 1) −11.2°. Anal. Calcd for $C_{20}H_{23}NO \cdot 0.25H_2O$: C, 80.63; H, 7.59; N, 4.70. Found: C, 80.89; H, 7.87; N, 4.73.

In a similar procedure, camphanate ester (diastereoisomer 2) afforded the (+)-alcohol (enantiomer 2; 99.5% optically pure, HPLC): mp 172–173 °C; $[\alpha]_D$ ($CDCl_3$, c = 1) +11.6°.

Stereoselective Reduction: *trans*-2-(Diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-ol (34). 2-(Diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-one (**32**) (50 g) was dissolved in toluene (650 mL), and the solution was heated at reflux. Sodium (19.2 g) was added portionwise followed by isopropyl alcohol (160 mL). After 1 h the mixture was cooled to ambient temperature and then the reaction quenched with methanol. Evaporation yielded a brown solid which was partitioned between water and dichloromethane. The organics were dried ($MgSO_4$) and evaporated to give a light brown solid (~50 g), which was suspended in toluene (750 mL) and then heated at reflux with benzophenone (130 g) and sodium hydride (18.9 g, 50% in oil). After 1 h the reaction was quenched with 2 N hydrochloric acid and the mixture washed with diethyl ether. The aqueous layer was basified with sodium hydroxide and the desired product extracted into dichloromethane. After evaporation, the residue was passed through a column of grade III alumina eluted with 70:30 dichloromethane:petroleum ether to yield the title compound and the starting ketone: mp 214–216 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 1.25–1.90 (5H, 3m, 2 × CH*H* α to N, CH at bridgehead), 2.53–2.60 and 2.8–3.04 (4H, 2m, 2 × CH*H* α to N), 3.35 (H, m, CHN), 3.54 (H, br s, CHOH), 3.94 (H, d, J = 12.0 Hz, $CHPh_2$), 7.1–7.4 (10H, m, ArH).

(2*S*,3*R*)-2-(Diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-ol ((+)-34) and (2*R*,3*S*)-2-(Diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-ol ((−)-34). (a) *trans*-2-(Diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-yl Camphanate: Diastereoisomers A and B (37 and 38). A solution of *trans*-2-(diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-ol (**34**) (11.3 g) in dichloromethane (150 mL) and triethylamine (4 mL) was cooled in an ice bath under an inert atmosphere. After dropwise addition of (−)-camphanic acid chloride (10.1 g) in dichloromethane (50 mL), the mixture was stirred at room temperature for 45 min. It was then washed with aqueous

sodium bicarbonate (150 mL) followed by brine (150 mL), dried (Na_2SO_4), and evaporated. The residue was purified on alumina (grade III) using 2.5% methanol in dichloromethane as eluant to yield the desired product (1:1 mixture of diastereoisomers). This 1:1 mixture of diastereoisomers was recrystallized from methanol/dichloromethane. The first crop was removed and recrystallized twice again from the same solvents to yield diastereoisomer B. The mother liquors from the first crystallization were evaporated and recrystallized from ethyl acetate/petroleum ether to give diastereoisomer A.

Diastereoisomer A: mp 206–208 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.80 (3H, s, CH_3), 0.89 (3H, s, CH_3), 1.07 (3H, s, CH_3), 1.32–2.13 (9H, m, 2 × CH*H* on camphanate bicycle, 2 × CH*H* α to N on quinuclidine, CH at bridgehead), 2.52–2.64 (H, m) and 2.87–3.05 (3H, m, 2 × CH*H* α to N), 3.68 (H, dd, J = 12.0, 4.0 Hz, CH α to N), 3.97 (H, d, J = 12.0 Hz, $CHPh_2$), 4.78–4.80 (H, m, CHO), 7.06–7.34 (10H, m, ArH); $[\alpha]_D$ ($CDCl_3$, c = 1) −58.8°.

Diastereoisomer B: mp >250 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.75 (3H, s, CH_3), 0.95 (3H, s, CH_3), 1.07 (3H, s, CH_3), 1.39–2.12 (9H, m, 2 × CH*H* on camphanate bicycle, 2 × CH*H* α to N on quinuclidine, CH at bridgehead), 2.49–2.82 (H, m) and 2.86–3.03 (3H, m, 2 × CH*H* α to N), 3.55–3.62 (H, dd, J = 12.0, 4.0 Hz, CH α to N), 3.95–3.99 (H, d, J = 12.1 Hz, $CHPh_2$), 4.82–4.85 (H, m, CHO), 7.07–7.34 (10H, m, ArH); $[\alpha]_D$ ($CDCl_3$, c = 1) +42.3°.

(b) (+)- and (−)-*trans*-2-(Diphenylmethyl)-1-azabicyclo-[2.2.2]octan-3-ol (34). Diastereoisomer A (3 g, >99.5% by HPLC) was taken up in ethanol (120 mL). A solution of potassium hydroxide (0.6 g) in ethanol (30 mL) was added and the mixture heated at reflux for 7 h. Evaporation of the solvent yielded a white residue which was partitioned between 2 N HCl and dichloromethane. The aqueous layer was separated, basified (KOH), and extracted into dichloromethane. This organic extract was washed with brine, dried (Na_2SO_4), and evaporated to give a white solid which was recrystallized from 2-propanol to afford the title compound, enantiomer A: mp 214–216 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.34–1.66 (3H, m) and 1.90 (H, m, 2 × CH*H* α to N), 1.60 (H, m, CH at bridgehead), 2.59 (H, m), 2.85 (2H, m) and 3.02 (H, m, 2 × CH*H* α to N), 3.36–3.42 (H, m, CHN), 3.56 (H, br s, CHO), 3.93–3.97 (H, d, J = 11.9 Hz, $CHPh_2$), 7.13–7.39 (10H, m, ArH); $[\alpha]_D$ (methanol, c = 1) −152.4°.

Similarly, diastereoisomer B was hydrolyzed as above to afford the alcohol, enantiomer B: $[\alpha]_D$ (methanol, c = 1) +151.5°.

***cis*-2-(Diphenylmethyl)-3-[(3-nitrobenzyl)oxy]-1-azabicyclo[2.2.2]octane Oxalate (53).** *cis*-2-(Diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-ol (**33**) (0.46 g) was dissolved in dimethoxyethane (15 mL, anhydrous) with heating. The solution was cooled to 0 °C (ice–methanol), and 18-crown-6 (10 mg) was added. Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 3.6 mL) was added dropwise. The solution was stirred at 0 °C for 15 min. A solution of 3-nitrobenzyl bromide (0.39 g) in dimethoxyethane (5 mL) as added in one portion. The mixture was stirred for 1 h, and the reaction was quenched with water. The solvent was evaporated *in vacuo*, and the residue was diluted with water and dichloromethane. The organic layer was washed with saturated sodium chloride, dried (magnesium sulfate), and evaporated *in vacuo*. The residue was purified by chromatography on alumina using ether–hexane (20:80) as the eluant and gradient elution to 50% ether. This furnished the product as a white crystalline solid (320 mg, 50%). Treatment of an ethereal solution of the free base with ethereal oxalic acid precipitated the oxalate salt; this was recrystallized from 2-propanol: mp 224–226 °C (from IPA). Anal. ($C_{27}H_{28}N_2O_3 \cdot C_2O_4H_2$) C, H, N.

The compounds **44–91** were prepared according to the method described above for **53**.

(+)-(2*S*,3*S*)-3-[[3,5-Bis(trifluoromethyl)benzyl]oxy]-2-(diphenylmethyl)-1-azabicyclo[2.2.2]octane Hydrochloride (39). (−)-*cis*-2-(Diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-ol ((+)-**33**) (5.75 g) was suspended in anhydrous dimethoxyethane (100 mL) under nitrogen. Potassium bis(trimethylsilyl)amide (46 mL, 0.5 M in toluene) was added dropwise to the stirred mixture to afford a light brown solution. After stirring for 1 h at room temperature, 3,5-bis(trifluoromethyl)-benzyl bromide (6.7 mL) was added in one portion and the mixture was stirred for 10 min, affording a deep purple mixture. The solvent was removed *in vacuo*, and the residue was purified by chromatography on alumina (grade III) using hexane/ether (70:30) as eluent. This removed the unreacted alcohol (2.7 g). The crude fractions containing the ether were purified further by medium pressure chromatography on silica gel (Lobar) using 3% methanol in dichloromethane as eluent. This afforded the ether as a white crystalline solid which was converted to the hydrochloride salt with methanolic hydrogen chloride; recrystallization from methanol/ethyl acetate afforded the title compound: mp >250 °C; ^{1}H NMR (360 MHz, $CDCl_3$, free base) δ 1.26–1.39 (1H, m, CHH), 1.5–1.60 (1H, m, CHH), 1.66–1.88 (2H, m, CH*H*), 2.16 (1H, mc, CH-bridgehead), 2.70 (1H, mc, CHHN), 2.83 (2H, mc, CH*H*N), 3.10–3.20 (1H, m, CHHN), 3.56 (1H, d, J = 11.5 Hz, OCCHPh), 3.64 (1H, mc, NCHCHO), 3.78 (1H, dd, J = 8.0, 11.0 Hz, $NCHCHPh_2$), 4.23 (1H, d, J = 11.5 Hz, OCHHPh), 4.45 (1H, d, J = 11.0 Hz, $CHPh_2$), 7.08–7.25 (10H, m, ArH), 7.46 (2H, s, ArH), 7.76 (1H, s, ArH); MS (FAB$^+$) m/z 520 (M^+ + 1, 100); $[\alpha]_D$ (methanol, c = 1) +29.1°. Anal. Calcd for $C_{29}H_{27}F_6NO \cdot HCl \cdot 0.25H_2O$: C, 62.14; H, 5.13; N, 2.50; Cl, 6.33. Found: C, 62.01; H, 5.13; N, 2.50; Cl, 6.33.

The compounds **40–42** were prepared in a similar manner using the appropriate homochiral alcohols.

***cis*-2-Benzyl-3-[(3,5-dimethylbenzyl)oxy]-1-azabicyclo-[2.2.2]octane Hydrochloride (81).** *cis*-2-Benzyl-1-azabicyclo-[2.2.2]octan-3-one (**18**, R_2 = Ph)[25] (4.3 g, 0.02 mol) was dissolved in dimethoxyethane (30 mL, anhydrous) under an inert atmosphere. Lithium triethylborohydride (24 mL, 1 M in tetrahydrofuran, 0.024 mol) was added dropwise to the resulting solution, and stirring was continued for 2 h. The reaction was quenched with hydrochloric acid (100 mL, 2 N), the solvent was removed *in vacuo*, and the aqueous residue was extracted with dichloromethane. The aqueous phase was made basic with potassium hydroxide and back-extracted with dichloromethane (4 × 50 mL). The organic phase was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was recrystallized from toluene to afford the *cis* alcohol (2.5 g, 57%): MS (CI$^+$) m/z 218 (M^+ + 1).

The resulting alcohol (**23**, R_2 = Ph) (0.9 g, 0.004 mol) was dissolved in dimethoxyethane (20 mL) under an inert atmosphere. Potassium bis(trimethylsilyl)amide (10 mL, 0.5 M in toluene, 0.005 mol) was added dropwise to the stirred solution. After 1 h 3,5-dimethylbenzyl bromide was added, and the mixture was stirred for 1 h. The mixture was partitioned between ethyl acetate and water, and the organic layer was washed with brine and dried and the solvent removed *in vacuo*. The residue was purified by medium pressure chromatography on silica gel using 6–10% methanol in dichloromethane as eluant to afford the product (0.67 g, 50%). Formation of the hydrochloride salt in ether followed by recrystallization from 2-propanol afforded the desired product. Anal. ($C_{29}H_{34}NO \cdot HCl$) C, H, N.

2-Benzylidene-3-[(3,5-dimethylbenzyl)oxy]-1-azabicyclo-[2.2.2]octane Hydrochloride, *E*-Isomer (83). 2-Benzylidene-1-azabicyclo[2.2.2]octan-3-one, *Z*-isomer[25] (**17**, R_1 = Ph) (3 g, 0.014 mol), was dissolved in chloroform (200 mL). Hydrogen chloride gas (anhydrous) was bubbled through the solution for 2 h. The reaction mixture was evaporated *in vacuo*, and the residue was suspended in diethyl ether and made basic with aqueous potassium hydroxide. The ethereal extract was washed with water and brine, dried ($MgSO_4$), and evaporated *in vacuo*. Crude ^{1}H NMR indicated an *E*:*Z* ratio of 2:1. The isomers were separated by chromatography on silica gel using dichloromethane as eluant to remove the residual *Z*-isomer; gradient elution using 1–6% methanol in dichloromethane afforded the desired *E*-isomer: ^{1}H NMR δ 1.89–2.04 (4H, m, NCH_2CH_2), 2.60–2.66 (1H, q, J = 3.0 Hz, CH), 3.03–3.20 (4H, m, 2 × NCH_2), 6.62 (1H, s, C=CH), 7.34–7.38 (3H, m, ArH), 7.87–7.91 (2H, m, ArH).

The ketone (1.84 g, 0.009 mol) was dissolved in a solution of dichloromethane (10 mL) and methanol (50 mL), and sodium borohydride (1.64 g, 0.043 mol) was added to the solution portionwise. After 30 min the reaction was quenched by the

addition of water and the solvents were removed *in vacuo* to afford the product (**21**, R_1 = Ph) as a white solid (1.89 g): ^{1}H NMR δ 1.36–1.56 (1H, m, CHH), 1.57–1.76 (1H, m, CH_2), 2.0 (5H, mc), 2.8–3.18 (4H, m), 4.54–4.58 (1H, d, J = 5.0 Hz, C*H*OH), 6.58 (1H, s, C=CH), 7.20–7.46 (3H, m, ArH), 7.52–7.60 (2H, m, ArH). The alcohol was reacted with 3,5-dimethylbenzyl bromide according to the procedure described for **81** above to afford the product as a white crystalline solid. Anal. ($C_{23}H_{27}NO$·HCl) C, H, N.

3-[[(3,5-Dimethylphenyl)methyl]oxy]-2-(1,2-diphenylethyl)-1-azabicyclo[2.2.2]octane (85 and 86). (a) 2-(1,2-Diphenylethyl)-3-oxo-1-azabicyclo[2.2.2]octane. To a stirred solution of 2-benzylidene-3-oxo-1-azabicyclo[2.2.2]-octane (10 g) in diethyl ether (200 mL) at −10 °C under a nitrogen atmosphere was added a solution of benzylmagnesium chloride (30 mL, 2 M in tetrahydrofuran, 60 mmol) and diethyl ether (100 mL). The solution was stirred at −10 °C for 30 min and at ambient temperature for 16 h. A saturated solution of aqueous ammonium chloride (200 mL) was carefully added and the product extracted into ethyl acetate. The organic phase was dried ($MgSO_4$) and evaporated to dryness. The residue was chromatographed on a column containing silica gel 60 (220–440 mesh ASTM) eluting with mixtures of 30%, 50%, and 70% ethyl acetate in petroleum ether (bp 60–80 °C). 2-(1,2-Diphenylethyl)-3-oxo-1-azabicyclo[2.2.2]octane was obtained as a 1:1 mixture of stereoisomers by evaporating the appropriate fractions.

(b)2-(1,2-Diphenylethyl)-3-hydroxy-1-azabicyclo[2.2.2]-octane. To a solution of the product of step a above (3.1 g, 1:1 mixture of diastereomers), in tetrahydrofuran (50 mL) at −78 °C, was added a solution of lithium aluminum hydride (10.16 mL, 1 M in diethyl ether). After the solution had stirred at −78 °C for 2 h, water (3 mL) was added followed by aqueous sodium hydroxide (3 mL, 2 M) and water (6 mL). When at room temperature, diethyl ether was added and the mixture filtered through Hyflo supercel. The ethereal phase of the filtrate was washed with water (2 × 30 mL) and brine (30 mL) and dried ($MgSO_4$). After removal of the solvent *in vacuo*, the residue was chromatographed on silica gel eluting with ethyl acetate/petroleum ether (bp 60–80 °C) (1:1) followed by methanol/ethyl acetate (1:50) to give the title compound as a mixture of stereoisomers.

(c) 3-[[(3,5-Dimethylphenyl)methyl]oxy]-2-(1,2-diphenylethyl)-1-azabicyclo[2.2.2]octane Hydrogen Oxalate Salt. To a solution of the alcohol of step b above (0.78 g, 1:1 mixture of stereoisomers) was added potassium hexamethyl disilazide (5.84 mL, 0.5 M in toluene). After 1 h, 3,5-dimethylbenzyl bromide (0.58 g) was added and the resulting solution stirred for 3 h. The solution was evaporated to dryness and the residue partitioned between dichloromethane and water. The organic phase was dried ($MgSO_4$), evaporated, and purified by column chromatography on silica gel eluting with petroleum ether (bp 60–80 °C) containing increasing amounts of ethyl acetate (50–100%) and then with methanol/ethyl acetate (15:85) to give a single diastereomer of the title compound. This was crystallized by addition of oxalic acid (72 mg) in propan-2-ol and diethyl ether to give 3-[[(3,5-dimethylphenyl)methyl]-oxy]-2-(1,2-diphenylethyl)-1-azabicyclo[2.2.2]octane hydrogen oxalate salt, isomer A: mp 64–66 °C; ^{1}H NMR (DMSO, 360 MHz) δ 7.2–6.6 (13H, m, aryl), 4.6 (1H, d, J = 16.0 Hz, OC*H*H), 4.4 (1H, d, J = 16.0 Hz, OCH*H*), 3.5 (1H, m, OCHCH), 3.3 (1H, m, NC*H*H), 2.99 (1H, dd, NCHC*H*), 2.8–2.60 (5H, m, NCHH, NCH*H*, PhC*H*H), 2.4 (1H, m, PhCHCH*H*), 2.3 (6H, s, CH_3, CH_3), 2.25 (1H, m, bridgehead CH), 1.9 (1H, m, NCH*H*-CHH), 1.65 (1H, m, NCH*H*CHH), 1.46–1.22 (2H, m, NCH*H*-CH*H*); MS *m/z* (EI) 425 (M^+), (Cl^+), 426 (M + H), (Cl^-) 424 (M − H). Anal. Calcd for $C_{30}H_{35}NO{\cdot}C_2H_2O_4{\cdot}0.3H_2O$: C, 71.19; H, 6.86; N, 2.67. Found: C, 71.09; H, 6.84; N, 2.51.

Chromatographic separation performed above (step c) also yielded isomer B, which was recrystallized as an oxalate salt from ethanol/diethyl ether to give 3-[[(3,5-dimethylphenyl)-methyl]oxy]-2-(1,2-diphenylethyl)-1-azabicyclo[2.2.2]octane hydrogen oxalate salt, isomer B: mp 128–130 °C. Anal. ($C_{30}H_{35}NO{\cdot}C_2H_2O_4{\cdot}H_2O$) C, H, N.

The product of step a was crystallized from diethyl ether. The mother liquor (enriched in one diastereomer) was reduced according to the procedure described in step b and alkylated (step c) to give 3-[[(3,5-dimethylphenyl)methyl]oxy]-2-(1,2-diphenylethyl)-1-azabicyclo[2.2.2]octane hydrogen oxalate, isomer C: mp 55–58 °C. Anal. ($C_{30}H_{35}NO{\cdot}1.5C_2H_2O_4{\cdot}2H_2O$) C, H, N.

X-ray Experimental Data. Compound **69**: $C_{29}H_{28}ClF_6NO$, M_r = 555.996, triclinic, $P1$; a = 10.158(2), b = 15.448(2), and c = 8.764(1) Å, α = 91.84(1)°, β = 100.80(1)°, γ = 89.42(1)°, V = 1350.2(7) Å^3, Z = 2, D_x = 1.368 g cm^{-3}; monochromatized radiation λ (Cu Kα) = 1.541 838 Å, μ = 1.83 mm^{-1}; $F(000)$ = 576, T = 294 K. Data were collected on a Rigaku AFC5 diffractometer to a θ limit of 71.15° which yielded 4993 unique reflections, of which nine were suppressed as being unsuitable (too negative) for inclusion during refinement. The structure was solved by direct methods (SHELXS-86)[36] and refined using full-matrix least-squares on F_2 (SHELXL-93). The final model was refined using 339 parameters and all 4984 data. All atoms other than H and F were assigned with anisotropic thermal displacements. The fluorine atoms were refined isotropically, while the hydrogens were assigned fixed thermal parameters 1.2 times that of their attached atom. The final agreement statistics are R = 0.096 (based on 2875 reflections with $I \geq 2\sigma(I)$), R_w = 0.262, S = 1.18 with $(\Delta/\sigma)_{max}$ = 0.70. The maximum peak height in a final difference Fourier map was 0.657 eÅ^{-3} and located near one of the disordered CF_3 groups. The atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, U.K.

SP-Induced Dermal Inflammation in the Guinea Pig. Male Dunkin Hartley guinea pigs were anesthetized with ketamine (25 mg/kg) and acepromazine (2.5 mg/kg). The dorsal hair was shaved and Evans blue dye (0.5 mL, 2.5 g/100 mL in saline) was injected iv. After 10 min, SP (0.5 pmol in 0.1% HSA saline) was injected intradermally, and exposure to the agonist continued for 1 h before sacrificing the animals by exposure to CO_2 gas. The injection sites on the dorsal surface were removed using 6-mm punch biopsies, and the Evans blue dye was extracted by incubation overnight at 45 °C in formamide (0.5 mL). The extent of plasma extravasation was assessed by comparing the O.D. (at 650 nm) of the tissue extract to that of a known volume of plasma from the same animal. Test compounds were administered either ip or po 1 h before SP challenge.

Supporting Information Available: Combustion analyses and melting points for all new compounds referred to in the text, ^{1}H NMR and mass spectral data for selected representative compounds, and tables of atomic coordinates, bond lengths, and bond angles for compound **69** (21 pages). Ordering information is given on any current masthead page.

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