Articles

Aza-Tricyclic Substance P Antagonists

John A. Lowe, III,* Susan E. Drozda, Stafford McLean, Dianne K. Bryce, Rosemary T. Crawford, R. Michael Snider, Kelly P. Longo, Atsushi Nagahisa,† and Megumi Tsuchiya†

Central Research Division, Pfizer, Inc., Groton, Connecticut 06340, and Department of Medicinal Biology, Central Research Division, Pfizer Inc., 5-2 Taketoyo, Aichi 470-23, Japan

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The synthesis and structure–activity relationships of a series of aza-tricyclic analogs of the quinuclidine substance P (SP) antagonist **1** are described. The SP receptor affinity of these compounds was found to vary according to the size of the new ring fused to the quinuclidine and the mode of fusion. Correlations between receptor affinity and (1) the steric bulk of the newly introduced ring fusion and (2) the dihedral angle between the benzhydryl and benzylamino substituents of these aza-tricyclic compounds were explored.

We recently described structure–activity relationships (SAR) in a series of non-peptide substance P (SP) antagonists exemplified by compound **1**.[1] The original SAR exploration was largely confined to the portion of the molecule containing the appended aromatic rings; the opposite side, consisting of the two unsubstituted bridges of the quinuclidine system, remained unexplored. Since the model for understanding the binding interactions between **1** and the SP receptor presented initially[1] does not address interactions in this area, it seemed particularly important to obtain information with which to refine the model. A series of aza-tricyclic analogs which places bridges on the quinuclidine framework varying in position, size, and lipophilicity designed to explore this undefined region is described herein.

Chemistry

The chemistry used to prepare the aza-tricyclic quinuclidine analogs is outlined in Schemes 1–3. The basic synthetic strategy involved construction of the aza-bicyclic nucleus followed by elaboration to the core quinuclidine structure and attachment of the diphenylmethyl and benzylamine side chains. Beginning with the appropriate aza-bicyclic ketone, **2a-c**, **14a,b**, or **29**, conversion to the corresponding nitrile (as a mixture of diastereomers), **3a-c**, **15a,b**, or **30**, was accomplished by reaction with tosylmethyl isocyanide. After hydrolysis to the ester (again, as a mixture of diastereomers) and attachment of a carbethoxymethyl group, base-catalyzed ring closure[2] produced the quinuclidone ring system, **7a-c**, **19a,b**, or **33**, characterized in each case as its benzylidene derivative. This ring closure reaction failed in the case of the analog of compound **32** with a bridge one atom shorter, as indicated in Scheme 3, presumably due to ring strain. The remaining steps follow the route used to prepare **1**, including 1,4-addition of phenylmagnesium bromide and 9-BBN reduction of the imine formed from the appropriate benzylamine. It is noteworthy that the regio- and stereochemical integrity of both these steps was maintained despite the significant structural variation in the aza-tricyclic compounds. Compounds **10–13**, **22–26**, and **36** are racemic mixtures and are depicted arbitrarily in the same absolute configuration as **1**, which is the 2S,3S enantiomer. In addition, compound **36** is a mixture of diastereomers with regards to the relationship between the fused bridge and the benzhydryl and benzylamine substituents but is clearly the *cis* diastereomer regarding the relationship between the benzhydryl group and the benzylamine group, based on the coupling constant of 7.6 Hz for the protons next to these groups; it is thus depicted arbitrarily to correspond to compounds **10–13** and **22–26**.

Biology

The human IM-9 cell NK_1 receptor binding assay was carried out as described previously,[1] except that ^{125}I-labeled Bolton–Hunter SP was used as the radioligand. The capsaicin-induced plasma leakage assay was also carried out as previously described, by measuring the extent of Evans Blue dye extravasation 10 min following capsaicin challenge.[1]

Discussion

Our initial goal in this work was the determination of SAR in that portion of the quinuclidine molecule not addressed by the model presented in the description of the discovery of compound **1**.[1] Three modes of ring fusion to the quinuclidine nucleus designed to probe this region were explored: nearer to and further from the bridgehead nitrogen, compounds **10–13** and **22–26**, respectively, and the "cross-bridged" compound **36** with attachment at each position. The *in vitro* receptor binding data in Table 1 shows that receptor affinity decreases with the addition of the fused bridge. For example, the most potent compound in this series, **11a**, has only half the receptor affinity of the parent compound **1**, although this difference would be expected to diminish on resolution of **11a**. In addition, compound **11a** has significantly greater receptor affinity than compounds **11b** and **10c**, which have longer fused bridges, suggesting steric effects may play a role in receptor binding. Finally, the SAR pattern for substituents on the benzylamine side chain parallels that described for the parent series,[1] with the 2-methoxy group conferring a significantly greater receptor affinity

† Japan.

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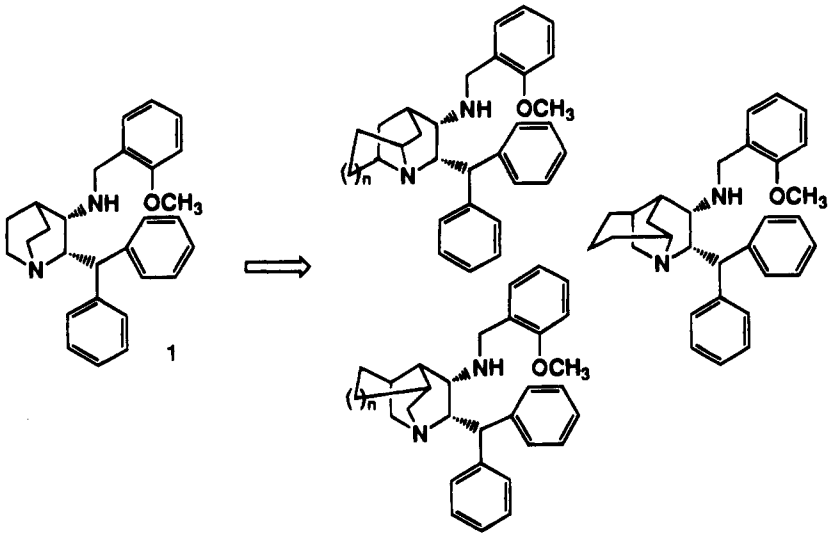
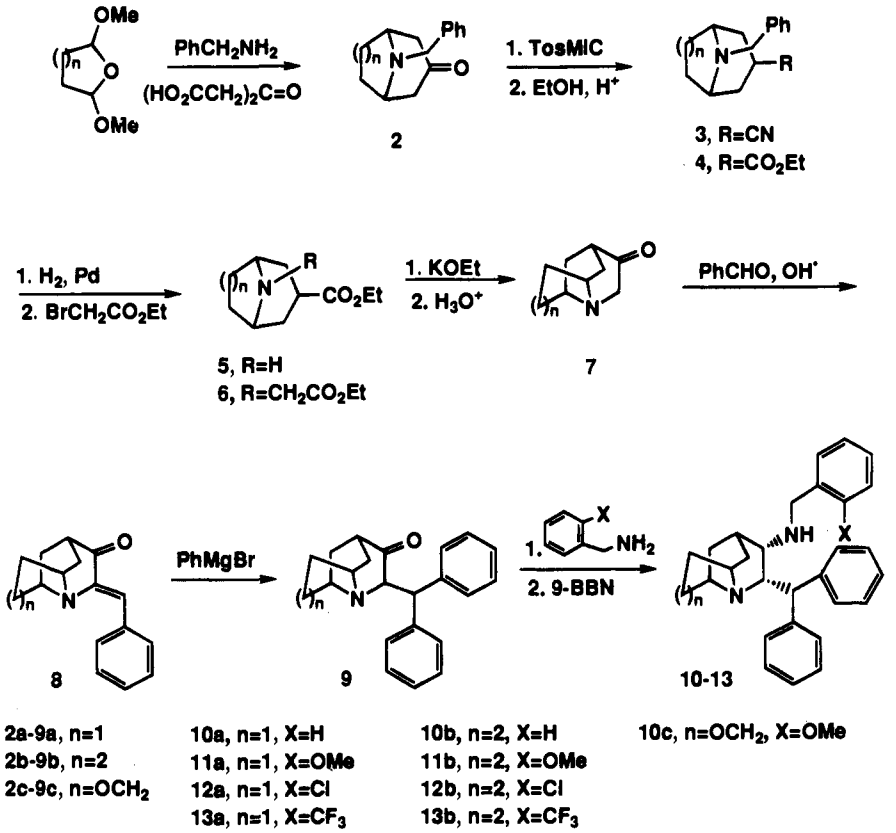


Figure 1. Aza-tricyclic analogs of quinuclidine substance P antagonist 1.

Scheme 1. Preparation of 3,7-Methanoindolizin-6-amine, 2,6-Methano-2*H*-quinolizin-3-amine, and 4,8-Methanopyrido[2,1-c][1,4]oxazin-7-amine Compounds



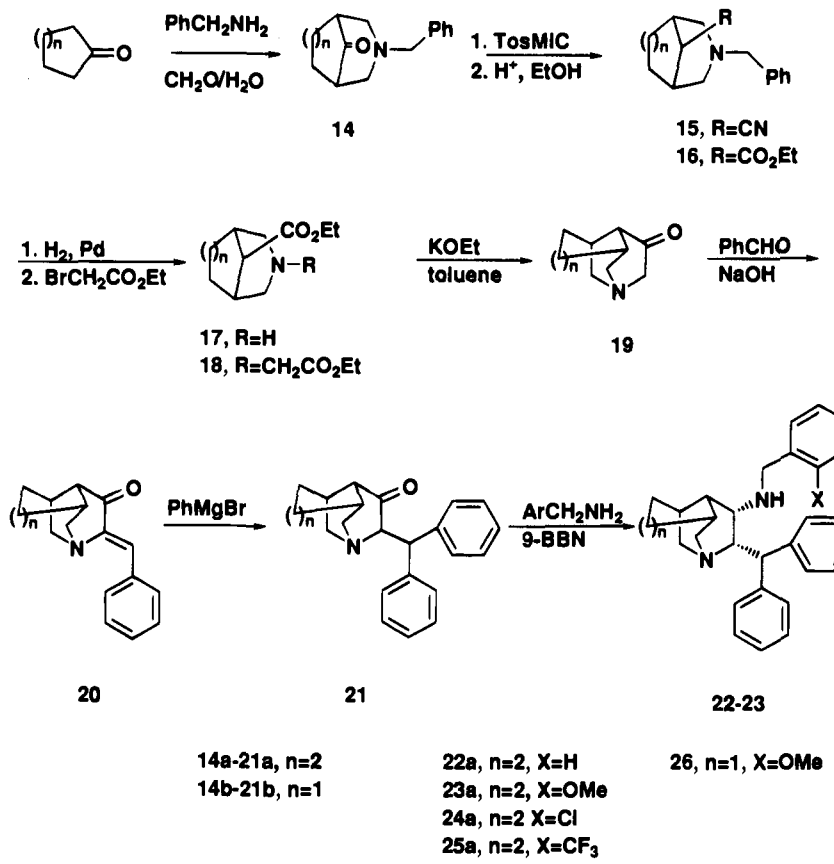
relative to the other substituents. For example, compound **11a** shows greater receptor affinity than **10a**, **12a**, or **13a**.

The *in vivo* efficacy of compounds **11a**, **23a**, and **26** is compared in the guinea pig ureter model in Table 2 with compound **1**. All the compounds showed similar ED_{50} values, consistent with their potent *in vitro* activity.

Two factors can be considered to explain the decrease in receptor affinity in the azatricyclic analogs **10**–**13**, **22**–**26**, and **36** relative to compound **1**. The first is steric interference of the newly introduced fused bridge with the receptor binding site. Steric interference with receptor binding by substitution in this area of the molecule was noted in a series of [3.2.2] analogs of **1** described recently.[3] The observation that larger fused bridges cause a greater loss of receptor affinity supports the idea that the receptor forms a particularly tight binding interaction with this portion of the quinuclidine structure.

An additional factor to consider in this series of azatricyclic compounds is the effect on the dihedral angle between the diphenylmethyl group and the benzylamine side chain due to added strain introduced by the fused bridge. The importance of this dihedral angle in maintaining receptor affinity is evidenced by the fact that the corresponding *trans* relationship at this position produces a 10-fold or greater loss of binding

Scheme 2. Preparation of 2,5-Methano-2*H*-2-pyridin-4-amine and 1*H*-2,5-Methanoisoquinolin-4-amine Compounds



potency.[1] The variation in dihedral angle at this position produced by the various bridging ring fusions, derived from MM2 calculations, is shown in Figure 2. Figure 2 also shows that the calculated dihedral angle values and the J values for $^1H-^1H$ coupling about this position correlate as expected from the Karplus equation,[4] supporting the calculated values. In addition, the calculated value for **1** agrees with the value from its published X-ray structure.[1] That this dihedral angle plays a role in determining receptor affinity is indicated by the observation that the best activity in the series is found in compound **11a**, which varies the least in its dihedral angle from compound **1**. Beyond this, the differences in both the IC_{50} values and the dihedral angle values are so small that no additional trend can be assigned. Overall, then, the receptor affinity of these compounds seems to be governed principally by steric parameters.

Conclusions

The model presented in the description of the discovery of compound **1** for understanding its interactions with the SP receptor can now be refined with the SAR from the series of aza-tricyclic compounds documented here. Figure 3 incorporates these results and depicts the unfavorable receptor interactions for additional substitution projecting from the nucleus away from the bridge bearing the diphenylmethyl and benzylamine groups. Current efforts using molecular biology techniques have succeeded in identifying the portion of the SP receptor to which **1** binds.[5] When more detailed information becomes available from these and related studies,[6] it may be possible to assign the amino acid residues within the SP receptor active site responsible for interactions with each portion of **1**, including the region of the molecule described herein.

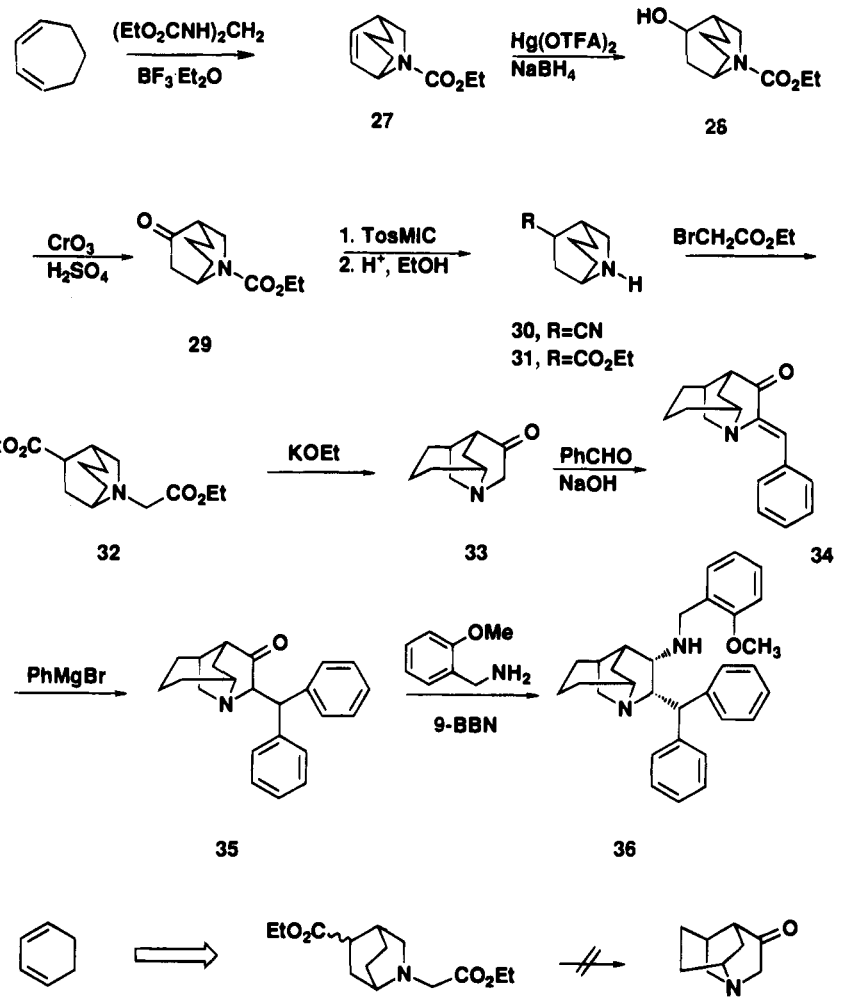
Experimental Section

Melting points were obtained on a Hoover melting point apparatus and are uncorrected. NMR spectra were obtained on a Varian XL-300 or a Bruker AM-300 spectrometer. IR spectra were obtained on Perkin-Elmer 283B or 1420 spectrometers. Mass spectra were obtained on a Finnegan 4510 mass spectrometer, and high-resolution mass spectra were obtained on an AE-9 instrument. TLC analyses were carried out on EM Kieselgel 60 F_{254} 5 × 20-cm plates. Elemental analyses were carried out by the Analytical Laboratory of Pfizer Central Research and are within ±0.4% of theory unless otherwise noted.

Method A. *N*-Benzyl-9-azabicyclo[3.3.1]nonan-3-one (2b). To a 1-L round-bottomed flask equipped with condenser and N_2 inlet were added 80 g (0.2 mol) of a 25% aqueous solution of glutaraldehyde, 29.2 g (0.2 mol) of 1,3-acetonedicarboxylic acid, and 11.4 g (0.2 mol) of benzylamine. After the initial reaction had subsided, the pH was adjusted to 5 and maintained for 14 h. The reaction mixture was then taken up in 6 N HCl, washed with ethyl acetate, and basified with 6 N sodium hydroxide solution. The aqueous layer was extracted with methylene chloride, and the organic layer filtered through Celite and evaporated. The residue was chromatographed on silica gel with ethyl acetate/methylene chloride as eluent to afford 15.034 g (33%) of a pale orange solid, mp 70–73 °C. ^1H-NMR (δ, $CDCl_3$): 1.48 (m, 4H), 1.90 (m, 2H), 2.20 (m, 2H), 2.68 (m, 2H), 3.26 (m, 2H), 3.86 (s, 2H), 7.1–7.4 (m, 5H). IR (cm^{-1}, KBr): 1690 (C=O). MS (rel intensity): 229 (27, parent). Anal. ($C_{15}H_{19}NO$) C, H, N.

Method B: *N*-Benzyl-9-azabicyclo[3.3.1]nonane-3-carbonitrile (3b). To a 500-mL round-bottomed flask equipped with condenser and N_2 inlet were added 185 mL of dimethoxyethane, 5.00 g (27.62 mmol) of *N*-benzyl-9-azabicyclo[3.3.1]-nonan-3-one, and 9.70 g (49.72 mmol) of tosylmethyl isocyanide. The solution was cooled to 0 °C, and 2.92 mL (63.53

Scheme 3. Preparation of Azatricyclo[5.4.0.0^{3,9}]undecane System



mmol) of ethanol was added, followed by 10.83 g (96.68 mmol) of potassium *tert*-butoxide in four portions. The reaction mixture was then heated at 50 °C for 10 h, poured into saturated sodium chloride solution, and extracted into ethyl acetate. The organic layer was filtered through Celite and evaporated. The residue was chromatographed on silica gel with hexane/ethyl acetate as eluent to afford an oil, 1.85 g (35%). ^{1}H-NMR (δ, $CDCl_3$): 1.45 (m, 2H), 1.68 (m, 2H), 1.84 (m, 2H), 2.03 (m, 2H), 2.25 (m, 2H), 2.87 (m, 2H), 3.33 (m, 1H), 3.83 (s, 2H), 7.2–7.4 (m, 5H). ^{13}C-NMR (δ, $CDCl_3$): 20.4, 23.6, 26.0, 30.4, 49.3, 56.6, 123.1, 127.0, 128.3, 139.5. IR (cm^{-1}, KBr): 2220 (CN). MS (rel intensity): 240 (77, parent), 172 (50), 91 (100). High-resolution mass spectrum: calcd for $C_{16}H_{20}N_2$ 240.1622, found 240.1628.

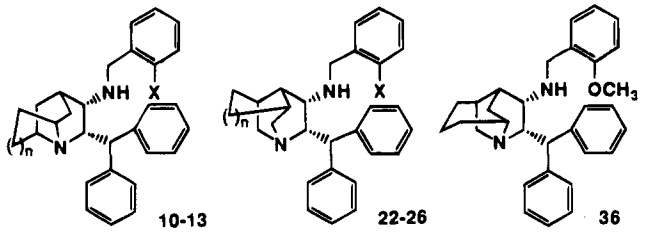
Method C: Ethyl *N*-Benzyl-9-azabicyclo[3.3.1]nonane-3-carboxylate (4b). To a 125-mL round-bottomed flask equipped with condenser and N_2 inlet were added 1.85 g (7.72 mmol) of *N*-benzyl-9-azabicyclo[3.3.1]nonane-3-carbonitrile and 51 mL of ethanol. The solution was saturated with HCl gas and heated to reflux, 0.9 mL of water was added, and refluxing was continued for 14 h. The reaction mixture was cooled, concentrated, and partitioned between methylene chloride and 1 N aqueous sodium hydroxide solution. The organic layer was separated, dried over sodium sulfate, and evaporated. The oil was used directly without further purification, yield 80.4%. ^{1}H-NMR (δ, $CDCl_3$): 1.12 (t, J = 7, 3H), 1.48 (m, 3H), 1.65 (m, 3H), 1.88 (m, 1H), 2.0–2.2 (m, 4H), 2.92 (m, 1H), 3.12 (m, 1H), 3.85 (s, 2H), 4.10 (q, J = 7, 2H), 7.1–7.5 (m, 5H). MS (rel intensity): 287 (24, parent), 229 (25), 214 (54), 186 (45), 173 (42), 172 (65), 170 (21), 92 (20), 91 (100), 65 (22).

Method D: Ethyl 9-Azabicyclo[3.3.1]nonane-3-carboxylate (5b). To a 125-mL round-bottomed flask equipped with condenser and N_2 inlet were added 8.14 g (28.36 mmol) of ethyl *N*-benzyl-9-azabicyclo[3.3.1]nonane-3-carboxylate, 60 mL of ethanol, 8.93 g (141.8 mmol) of ammonium formate, and 5 g of 10% palladium-on-carbon. The reaction mixture was refluxed, and fresh catalyst and ammonium formate were added until the starting material had disappeared (about 4 h, a total of 8 g of catalyst). The reaction mixture was cooled, filtered through Celite, and evaporated. The residue was partitioned between methylene chloride and aqueous sodium hydroxide solution, and the organic layer was separated, dried over sodium sulfate, and evaporated. The resulting oil was used directly in the next step. MS (rel intensity): 198 (92), 197 (71, parent), 168 (63), 152 (61), 140 (67), 139 (79), 124 (91), 97 (50), 96 (100), 83 (51), 82 (96), 81 (50), 80 (52), 69 (50), 68 (61), 55 (53), 54 (43).

Method E: Ethyl *N*-[(Ethoxycarbonyl)methyl]-9-azabicyclo[3.3.1]nonane-4-carboxylate (6b). To a 250-mL round-bottomed flask equipped with condenser and N_2 inlet were added 5.59 g (28.36 mmol) of ethyl 9-azabicyclo[3.3.1]-nonane-3-carboxylate, 142 mL of ethanol, and 9.47 g (56.72 mmol) of ethyl bromoacetate. The reaction mixture was refluxed 3 days, cooled, and evaporated. The residue was partitioned between methylene chloride and aqueous sodium hydroxide, and the organic layer was dried over sodium sulfate and evaporated. The residue was filtered through silica gel using ethyl acetate to afford an oil, 4.835 g (100% yield crude), a mixture of diastereomers. ^{1}H-NMR (δ, $CDCl_3$): 1.18 (triplets, 6H), 1.2–2.4 (multiplets, 7H), 2.6–3.8 (m, 6H), 3.39, 3.47, 3.75, and 3.98 (singlets, 2H), 4.0–4.2 (quartets, 4H). MS (rel intensity): 283 (15, parent), 21 (49), 210 (100), 182 (36), 168 (30), 152 (71).

Method F. 4-(Phenylmethylene)octahydro-2,6-methano-2*H*-quinolizin-3-one (8b). To a 250-mL three-neck, round-bottomed flask equipped with condenser and N_2 inlet were added 1.66 g (42.72 mmol) of potassium and 85 mL of toluene. The reaction mixture was brought to reflux, and 2.50

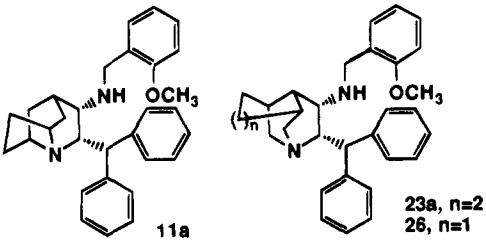
Table 1. *In Vitro* SAR of Aza-Tricyclic Substance P Antagonists



compd	X	*n*	IC_{50}[a]
10a	H	1	68 ± 1.5
11a	OCH_3	1	0.92 ± 0.09
12a	Cl	1	7.1 ± 0.66
13a	CF_3	1	1100 ± 400
10b	H	2	170 ± 20
11b	OCH_3	2	4.1 ± 1.1
12b	Cl	2	58 ± 21
13b	CF_3	2	4400 ± 150
10c	OCH_3	OCH_2	7.2 ± 4.0
22a	H	2	230 ± 67
23a	OCH_3	2	3.3 ± 0.76
24a	Cl	2	39 ± 10
25a	CF_3	2	4800 ± 1500
26	OCH_3	1	2.4 ± 1.6
36	OCH_3		1.9 ± 0.27
1			0.48 ± 0.06

[a] Binding affinity for the NK_1 receptor in human IM-9 cells using ^{125}I-labeled Bolton–Hunter substance P as ligand, given in nM units. IC_{50} values were determined from six-point concentration response curves with each concentration in duplicate. Mean ± SEM values from three separate experiments are given for each compound, except for **1** which is the result from 19 experiments.

Table 2. *In Vivo* SAR of Aza-Tricyclic Substance P Antagonists



compd	capsaicin-induced plasma leakage[a]	95% confidence limits
11a	4.13	2.67–5.58
23a	4.43	0.50–8.36
26	2.61	0.92–4.31
1	2.83	0.38–5.27

[a] ED_{50} value, in mg/kg, for inhibition of capsaicin-induced plasma leakage in guinea pig ureter. Compounds were administered 60 min prior to capsaicin challenge, at 1, 5, 10, and 15 mg/kg, except **1**, which was dosed at 0.5, 1, 5, and 10 mg/kg. 95% confidence limits are indicated in the accompanying column.

mL (42.72 mmol) of ethanol was added slowly. Once the potassium has been converted to the ethoxide, a solution of 4.836 g (17.09 mmol) of ethyl *N*-[(ethoxycarbonyl)methyl]-9-azabicyclo[3.3.1]nonane-4-carboxylate, **6b**, in 20 mL of toluene was added, and refluxing was continued overnight. The reaction mixture was then cooled, concentrated, taken up in 75 mL of 1 N hydrochloric acid, and refluxed 8 h. After cooling, it was washed with methylene chloride, the pH was adjusted to 14 with 6 N sodium hydroxide, and the aqueous layer was extracted with methylene chloride. The organic layer was dried over sodium sulfate and evaporated, and the **7b** (1.34 g, 47.5%, as a single, iodoplatinate positive spot on TLC, R_f = 0.3 in 10% methanol in methylene chloride) thus obtained was converted to its benzylidene derivative, as follows:

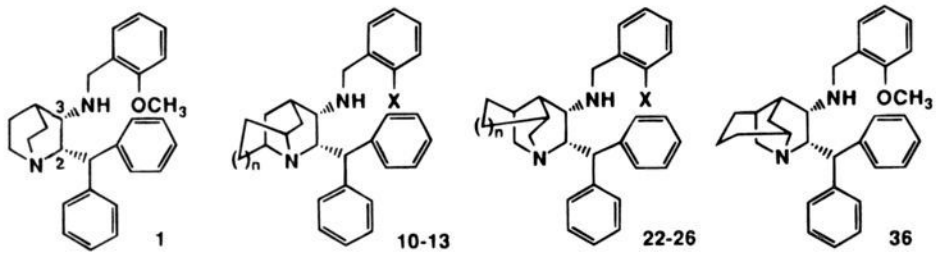
Table 3. Physical Properties of Compounds **10–13**, **22–26**, and **35**

no.	formula	mp, °C	% yield	anal.
10a	$C_{29}H_{32}N_2$	147–148	5	C, H, N
11a	$C_{30}H_{34}N_2O$	116–117	26	C, H, N
12a	$C_{29}H_{31}N_2Cl$	159–160	12	C, H, N
13a	$C_{30}H_{31}N_2F_3$	162–163.5	25	C, H, N
10b	$C_{30}H_{34}N_2$	137–140	22	C, H, N
11b	$C_{31}H_{36}N_2O{\cdot}2HCl{\cdot}3H_2O$	219–223	16	C, H, N
12b	$C_{30}H_{33}N_2Cl{\cdot}3HCl{\cdot}^5/_3H_2O$	202–210	55	C, H, N
13b	$C_{31}H_{33}N_2F_3{\cdot}2HCl{\cdot}^9/_4H_2O$	246–251	33	C, H, N
10c	$C_{30}H_{34}N_2O_2$	55–60	15	C, H, N
22a	$C_{30}H_{34}N_2{\cdot}2HCl{\cdot}^9/_4H_2O$	218–222	28	C, H, N
23a	$C_{31}H_{36}N_2O{\cdot}^1/_2H_2O$	97–102	36	C, H, N
24a	$C_{30}H_{33}N_2Cl$	115–118	67	C, H, N
25a	$C_{31}H_{33}N_2F_3$	131–135	40	C, H, N
26	$C_{30}H_{34}N_2O{\cdot}^1/_2H_2O$	147–151	33	C, H, N
36	$C_{31}H_{36}N_2O{\cdot}2HCl{\cdot}2H_2O$	200–210	19	C, H, N

The above **7b**, 1.34 g (8.12 mmol), was dissolved in 10 mL of ethanol and treated with 1.29 g (12.18 mmol) of benzaldehyde and 65 mg (1.62 mmol) of powdered sodium hydroxide. The reaction mixture was refluxed for 15 min, cooled, concentrated, and then partitioned between water and methylene chloride. The yellow organic layer was separated, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using hexane/ethyl acetate as eluent to afford **8b** as a solid, mp 109–112 °C, 1.23 g (60%). ^{1}H-NMR (δ, $CDCl_3$): 1.55 (m, 3H), 1.8–2.2 (multiplets, 7H), 2.54 (m, 1H), 3.18 (m, 2H), 6.96 (s, 1H), 7.32 (m, 3H), 8.07 (m, 2H). ^{13}C-NMR (δ, $CDCl_3$): 12.5, 29.6, 30.0, 40.8, 50.2, 124.6, 128.4, 129.5, 132.3, 134.2, 145.1, 207.2. IR (cm^{-1}, KBr): 1700 (C=O), 1625 (C=C). MS (rel intensity): 254 (12), 253 (36, parent), 224 (100), 117 (19), 116 (22), 55 (20). Anal. ($C_{17}H_{19}NO$) C, H, N.

Method G. 4-(Diphenylmethyl)octahydro-2,6-methano-2*H*-quinolizin-3-one (9b). To a 50-mL round-bottomed flask equipped with septum and N_2 inlet was added 2.54 mL (7.64 mmol) of a 3.0 M solution of phenylmagnesium bromide in ether. The solution was cooled to 0 °C, and a solution of 1.21 g (4.78 mmol) of 4-(phenylmethylene)octahydro-2,6-methano-2*H*-quinolizin-3-one, **8b**, in 10 mL of toluene was added dropwise over 3 min. The reaction mixture was allowed to warm to room temperature over 20 min, poured into aqueous ammonium chloride solution, and extracted into methylene chloride. The organic layers were combined and dried over sodium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel using hexane/ethyl acetate as eluent to afford 1.03 g (65%) of a colorless oil. ^{1}H-NMR (δ, $CDCl_3$): 1.1–2.1 (multiplets, 10H), 2.37 (m, 1H), 2.75 (m, 1H), 3.23 (m, 1H), 3.77 (d, J = 7, 1H), 4.63 (d, J = 7, 1H), 7.1–7.5 (m, 10H). ^{13}C-NMR (δ, $CDCl_3$): 13.2, 29.0, 29.7, 30.4, 30.8, 41.5, 45.0, 49.7, 53.1, 74.2, 126.2, 126.4, 128.0, 128.4, 128.7, 128.8, 142.6, 143.8. (Note: carbonyl carbon not visible in this scan.) IR (cm^{-1}, KBr): 1702 (C=O). MS (rel intensity): 331 (<1, parent), 304 (41), 303 (100), 262 (72), 212 (71), 180 (60), 165 (54), 136 (64), 117 (66), 83 (94), 67 (43). High-resolution mass spectrum: calcd for $C_{23}H_{25}NO$ 331.2064, found 331.2000.

Method H. *cis*-4-(Diphenylmethyl)octahydro-*N*-(phenylmethyl)-2,6-methano-2*H*-quinolizin-3-amine (10b). To a 50-mL round-bottomed flask equipped with a Dean–Stark trap, condenser, and N_2 inlet were added 514 mg (1.55 mmol) of 4-(diphenylmethyl)octahydro-2,6-methano-2*H*-quinolizin-3-one, **9b**, 249 mg (2.33 mmol) of benzylamine, 2 mg of camphorsulfonic acid, and 10 mL of toluene. The reaction mixture was refluxed with removal of water for 18 h, cooled, and concentrated. The residue was dissolved in 1.2 mL of dry tetrahydrofuran and treated with 6.22 mL (3.11 mmol) of a 0.5 M solution of 9-borabicyclo[3.3.1]nonane in tetrahydrofuran. The reaction mixture was stirred at room temperature for 5 days, poured slowly into 1 N hydrochloric acid, and extracted with methylene chloride. The aqueous layer was adjusted to pH 14 with aqueous sodium hydroxide and extracted into methylene chloride. The organic layer was dried over sodium sulfate and evaporated, and the residue was



CPD.	n	2,3-Dihedral Angle[a]	Δ from 1	J Value[b]	IC50, nM
11a	1	-14.7	-1.6	8.2	0.92 ± 0.09
11c	2	-12.2	-4.1	-	4.1 ± 1.1
10c	OCH_2	-12.7	-3.6	-	7.2 ± 4.0
23a	2	-19.6	+3.3	8.0	3.3 ± 0.76
26	1	-20.9	+4.6	-	2.4 ± 1.6
36		-23.7	+6.4	7.6	1.9 ± 0.27
1		-16.3		8.1	0.48 ± 0.06

Figure 2. Variation of dihedral angle between the benzhydryl and benzylamino substituents as a function of the fused ring for a series of azatricyclic analogs of **1**. (a) Dihedral angle in degrees, calculated using the MM2 program, except for **1**, for which the value is derived from the published X-ray structure.[1] (b) J value in hertz for $^1H-^1H$ coupling at the 2,3-position.

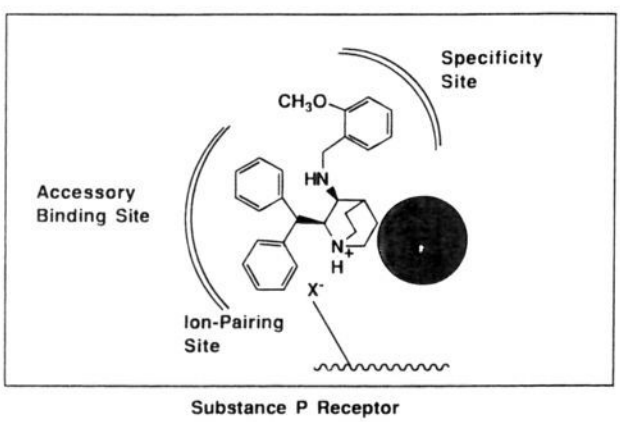


Figure 3. Model of the interactions between **1**, CP 96,345, and its analogs and the substance P receptor.

crystallized from 2-propanol to afford 144 mg (22%) of a white solid, mp 137–140 °C. ^{1}H-NMR (δ, $CDCl_3$): 1.0–1.8 (multiplets, 10H), 2.03 (m, 2H), 2.82 (m, 2H), 3.43 (AB_q, J_{AB} = 12, $\Delta\nu$ = 85, 2H), 3.55 (dd, J = 9, 12, 1H), 4.55 (d, J = 12, 1H), 6.67 (m, 2H), 7.1–7.4 (13H). ^{13}C-NMR (δ, $CDCl_3$): 13.9, 23.3, 25.8, 29.9, 30.1, 30.7, 43.7, 48.8, 52.1, 53.5, 54.2, 65.2, 125.3, 126.5, 126.6, 127.7, 127.8, 128.0, 128.2, 129.2, 140.1, 143.7, 145.5. IR (cm^{-1}, KBr): 1600 (C=C). MS (rel intensity): 421 (<1, parent − 1), 331 (13), 256 (28), 255 (100), 167 (12), 163 (11), 136 (12), 91 (90). Anal. ($C_{30}H_{34}N_2$) C, H, N.

***cis*-4-(Diphenylmethyl)octahydro-*N*-[(2-methoxyphenyl)methyl]-2,6-methano-2*H*-quinolizin-3-amine (11b). 11b** was prepared according to method H in 16% yield as an oil, after purification by chromatography on silica gel with methylene chloride/methanol as eluent. ^{1}H-NMR (δ, $CDCl_3$): 1.0–1.8 (multiplets, 10H), 2.1 (m, 2H), 2.84 (m, 2H), 3.33 (m, 2H), 3.48 (s, 3H), 3.62 (m, 1H), 4.69 (m, 1H), 6.69 (m, 2H), 6.78 (m, 1H), 7.0–7.4 (m, 11H). ^{13}C-NMR (δ, $CDCl_3$): 13.7, 23.0, 25.38, 25.42, 29.8, 29.9, 30.5, 43.7, 46.0, 48.6, 53.9, 55.3, 110.0, 120.2, 125.3, 126.5, 127.7, 128.0, 128.2, 128.3, 128.4, 129.1, 129.2, 129.5, 129.59, 129.63, 129.7, 157.5. IR (cm^{-1}, KBr): 1600 (C=C). MS (rel intensity): 452 (<1, parent), 331 (21), 286 (29), 285 (100), 167 (11), 165 (14), 136 (13), 122 (12), 121 (84), 91 (63). The hydrochloride salt was generated with HCl in ether to afford a solid, mp 219–223 °C. Anal. ($C_{31}H_{36}N_2O$·2HCl·$3H_2O$) C, H, N.

***cis*-4-(Diphenylmethyl)octahydro-*N*-[(2-chlorophenyl)methyl]-2,6-methano-2*H*-quinolizin-3-amine (12b). 12b** was prepared according to method H in 55% yield as an oil, after purification by chromatography on silica gel with methylene chloride/methanol as eluent. The hydrochloride salt was formed in ether, mp 202–210 °C. ^{1}H-NMR (δ, $CDCl_3$): 1.0–1.8 (multiplets, 10H), 2.0–2.1 (m, 1H), 2.06 (m, 1H), 2.78 (m, 1H), 3.25 (m, 1H),3.53 (AB_q, J_{AB} = 14, $\Delta\nu$ = 76, 2H), 3.56 (dd, J = 8.7, 12, 1H), 4.56 (d, J = 12, 1H), 6.66 (m, 1H), 7.0–7.4 (m, 13H). ^{13}C-NMR (δ, $CDCl_3$): 13.9, 23.2, 26.0, 30.0, 30.1, 30.7, 43.6, 48.8, 49.1, 53.5, 54.1, 65.1, 125.2, 126.5, 127.7, 127.9, 129.2, 129.8, 133.8, 137.5, 143.5, 145.7. IR (cm^{-1}, KBr): 1582 (C=C). MS (rel intensity): 455/457 (<1, parent − 1), 331 (47), 291 (49), 289 (100), 125 (48), 91 (50). Anal. ($C_{30}H_{33}N_2$-Cl·3HCl·$^5/_3H_2O$) C, H, N.

***cis*-4-(Diphenylmethyl)octahydro-*N*-[[4-(trifluoromethyl)phenyl]methyl]-2,6-methano-2*H*-quinolizin-3-amine (13b). 13b** was prepared according to method H in 33% yield as an oil, after purification by chromatography on silica gel with methylene chloride/methanol as eluent. The hydrochloride salt was formed in ether, mp 246-251 °C. ^{1}H-NMR (δ, $CDCl_3$): 1.0–1.8 (multiplets, 10H), 2.00 (m, 2H), 2.83 (m, 2H), 3.46 (ABq, J_{AB} = 14, $\Delta\nu$ = 103, 2H), 3.62 (m, 1H), 4.53 (d, J = 12, 1H), 6.75 (d, J = 8, 1H), 7.0–7.4 (m, 13H). ^{13}C-NMR (δ, $CDCl_3$): 13.7, 23.1, 25.7, 29.7, 30.0, 30.6, 43.9, 48.8, 51.4, 53.4, 54.2, 65.1, 125.1, 125.5, 126.6, 127.9, 128.1, 128.2, 128.7, 128.9, 129.1, 129.3, 143.5, 144.1, 145.0. IR (cm^{-1}, KBr): 1582 (C=C). MS (rel intensity): 489 (<1, parent − 1), 331 (34), 323 (100), 159 (59). Anal. ($C_{31}H_{33}N_2F_3$·2HCl·$^9/_4H_2O$) C, H, N.

5-(Phenylmethylene)octahydro-3,7-methanoindolizin-6-one (8a). 8a was prepared according to the last part of method F from the known octahydro-3,7-methanoindolizin-6-one, **7a**,[7] in 100% yield as an oil. ^{1}H-NMR (δ, $CDCl_3$): 1.6-1.8 (m, 4H), 2.2–2.3 (m, 4H), 2.40 (m, 1H), 3.46 (m, 2H), 7.10 (s, 1H), 7.3–7.4 (m, 3H), 8.0 (m, 2H). IR (cm^{-1}, neat): 1700, 1615 (C=O, C=C). MS (rel intensity): 239 (58, parent), 211 (72), 210 (100), 117 (43), 116 (43), 84 (49). Anal. ($C_{16}H_{17}NO$) C, H, N.

5-(Diphenylmethyl)octahydro-3,7-methanoindolizin-6-one (9a). 9a was prepared according to method G in 53% yield, mp 137–138 °C. ^{1}H-NMR: (δ, $CDCl_3$): 1.3–2.4 (multiplets, 10H), 2.23 (m, 1H, bridgehead), 3.54 (m, 1H), 4.11 (d, J = 4, 1H), 4.86 (d, J = 4, 1H), 7.1- 7.3 (m, 8H), 7.5 (m, 2H).

IR (cm^{-1}, $CDCl_3$): 1712 (C=O). MS (rel intensity): 317 (<1, parent), 289 (99), 248 (66), 198 (66), 180 (100), 179 (45), 167 (42), 165 (59), 122 (56), 91 (34), 69 (56), 54 (60). Anal. ($C_{22}H_{23}NO$) C, H, N.

***cis*-5-(Diphenylmethyl)octahydro-*N*-(phenylmethyl)-3,7-methanoindolizin-6-amine (10a).** **10a** was prepared according method H in 5% yield, mp 147–148 °C. ^{1}H-NMR (δ, $CDCl_3$): 0.76 (m, 1H), 1.1–2.0 (m, 7H), 2.17 (m, 1H), 2.67 (m, 1H), 2.99 (m, 1H), 3.32 (m, 1H), 3.34 (AB_q, J_{AB} = 13, $\Delta\nu$ = 112, 2H), 3.81 (dd, J = 8.2, 12.2, 1H), 4.38 (d, J = 12.2, 1H), 6.58 (m, 2H), 7.0–7.4 (m, 13H). MS (rel intensity): 408 (3.6, parent), 407 (5), 318 (17), 317 (70), 242 (18), 241 (100), 91 (34). Anal. ($C_{29}H_{32}N_2$) C, H, N.

***cis*-5-(Diphenylmethyl)octahydro-*N*-[(2-methoxyphenyl)methyl]-3,7-methanoindolizin-6-amine (11a).** **11a** was prepared according to method H in 26% yield, mp 116–117 °C. ^{1}H-NMR (δ, $CDCl_3$): 1.3–2.0 (series of multiplets, 8H), 2.20 (m, 1H), 2.72 (m, 1H), 3.00 (m, 1H), 3.40 (AB_q, J_{AB} = 13, $\Delta\nu$ = 96, 2H,), 3.34 (m, 1H), 3.51 (s, 3H), 3.80 (dd, J = 8.2, 12, 1H, C-8H, the 8.2-Hz coupling to the adjacent C-7 position is consistent with a *cis* stereochemical relationship), 4.46 (d, J = 12, 1H), 6.5–6.8 (m, 3H), 7.0–7.3 (m, 11H). IR (cm^{-1}, KBr): 3257 (N–H), 1600 (C=C). MS (rel intensity): 438 (<1, parent), 317 (34), 272 (33), 271 (100), 176 (19), 167 (10), 122 (24), 121 (80), 91 (59). Anal. ($C_{30}H_{34}N_2O$) C, H, N.

***cis*-5-(Diphenylmethyl)octahydro-*N*-[(2-chlorophenyl)-methyl]-3,7-methanoindolizin-6-amine (12a).** **12a** was prepared according to method H in 12% yield, mp 159–160 °C. ^{1}H-NMR (δ, $CDCl_3$): 0.76 (m, 1H), 1.1–2.0 (m, 7H), 2.17 (m, 1H), 2.67 (m, 1H), 2.99 (m, 1H), 3.3 (m, 1H), 3.43 (AB_q, J_{AB} = 13, $\Delta\nu$ = 90, 2H), 3.83 (m, 1H), 4.38 (d, J = 12.2, 1H), 6.54 (m, 1H), 7.0–7.4 (13H). MS (rel intensity): 317 (37), 277 (34), 275 (100), 127 (23), 125 (75). Anal.($C_{29}H_{31}N_2Cl$) C, H, N.

***cis*-5-(Diphenylmethyl)octahydro-*N*-[[4-(trifluoromethyl)phenyl]methyl]-3,7-methanoindolizin-6-amine (13a).** **13a** was prepared according to method H in 25% yield, mp 162–163.5 °C. ^{1}H-NMR (δ, $CDCl_3$): 0.76 (m, 1H), 1.1–2.0 (m, 7H), 2.15 (m, 1H), 2.65 (m, 1H), 3.00 (m, 1H), 3.32 (m, 1H), 3.40 (AB_q, J_{AB} = 13.5, $\Delta\nu$ = 108.7, 2H), 3.82 (dd, J = 8.2, 12.2, 1H), 4.35 (d, J = 12.2, 1H), 6.69 (d, J = 8, 2H), 7.0–7.4 (m, 12H). MS (rel intensity): 476 (2, parent), 475 (3.5), 474 (5.5), 318 (16), 317 (65), 310 (19), 309 (100), 159 (21). Anal. ($C_{30}H_{31}N_2F_3$) C, H, N.

***N*-Benzyl-7-oxa-9-azabicyclo[3.3.1]nonan-3-one (2c).** **2c** was prepared according to method A (starting from anhydroerythritol as described[8]) in 37% yield, mp 142–147 °C. ^{1}H-NMR (δ, $CDCl_3$): 2.26 (m, 2H), 2.66 (m, 2H), 3.11 (m, 2H), 3.71 (dd, J = 12, 42, 4H), 3.86 (s, 2H), 7.1–7.4 (m, 5H). ^{13}C-NMR (δ, $CDCl_3$): 40.4, 40.5, 55.4, 56.8, 71.9, 127.5, 128.6, 137.9, 207.4. IR (KBr, cm^{-1}): 1695 (C=O). MS (rel intensity): 231 (65, parent), 186 (82), 91 (100), 65 (22). Anal. ($C_{14}H_{17}NO_2$) C, H, N.

***N*-Benzyl-7-oxa-9-azabicyclo[3.3.1]nonane-3-carbonitrile (3c).** **3c** was prepared according to method B in 35% yield as an oil. ^{1}H-NMR (δ, $CDCl_3$): 1.87 (m, 2H), 2.24 (m, 2H), 2.63 (broad s, 2H), 3.82 (dd, J = 12, 48, 4H), 3.84 (s, 2H), 3.9–4.0 (m, 1H), 7.2-7.4 (m, 5H). ^{13}C-NMR (δ, $CDCl_3$): 23.4, 27.0, 50.6, 50.7, 55.9, 70.6, 122.8, 127.3, 128.5, 138.2. IR (KBr, cm^{-1}): 2165 (CN). MS (rel intensity): 243 (67), 242 (90, parent), 212 (53), 211 (84), 198 (36), 197 (96), 151 (70), 133 (45), 132 (39), 121 (37), 117 (38), 92 (46), 91 (100), 65 (56). High-resolution mass spectrum: calcd for $C_{15}H_{18}N_2O$ 242.1417, found 242.1427.

Ethyl *N*-Benzyl-7-oxa-9-azabicyclo[3.3.1]nonane-3-carboxylate (4c). **4c** was prepared according to method C in 83% yield as an oil. ^{1}H-NMR (δ, $CDCl_3$): 1.24 (t, J = 8, 3H), 1.71 (m, 2H), 2.15 (m, 2H), 2.65 (broad s, 2H), 3.65 (m, 1H), 3.84 (s, 2H), 3.85 (dd, J = 12, 42, 4H), 4.13 (q, J = 8, 2H), 7.1–7.4 (m, 5H). ^{13}C-NMR (δ, $CDCl_3$): 14.3, 25.6, 37.4, 51.5, 55.9, 60.2, 71.3, 127.0, 128.3, 128.5, 138.9, 176.0. IR (KBr, cm^{-1}): 1737 (C=O). MS (rel intensity): 289 (20), 244 (53), 186 (61), 133 (21), 94 (22), 93 (27), 91 (100), 65 (33), 57 (41). Anal. ($C_{17}H_{23}NO_3$) C, H, N.

Ethyl 7-Oxa-9-azabicyclo[3.3.1]nonane-3-carboxylate (5c). **5c** was prepared according to method D in 34% yield as an oil, which was used directly in the next step.

Ethyl *N*-[(Ethoxycarbonyl)methyl]-7-oxa-9-azabicyclo-[3.3.1]nonane-3- carboxylate (6c). **6c** was prepared according to method E in 60% yield as an oil. ^{1}H-NMR (δ, $CDCl_3$): 1.14 (overlapping triplets, 6H), 1.65 (m, 2H), 1.97 (m, 2H), 2.72 (broad s, 2H), 3.39 (s, 2H), 3.54 (m, 1H), 3.80 (dd, J = 12, 55, 4H), 4.03 (overlapping quartets, 2H). ^{13}C-NMR (δ, $CDCl_3$): 14.1, 14.2, 25.3, 36.9, 52.3, 53.4, 60.1, 60.5, 71.1, 170.7, 175.5. IR (KBr, cm^{-1}): 1725–1745 (C=O's). MS (rel intensity): 286 (39), 285 (27, parent), 240 (43), 212 (100), 182 (80), 166 (39), 129 (22), 110 (35), 108 (40), 96 (22), 94 (29), 82 (25), 81 (31), 80 (24), 70 (20), 68 (31), 67 (36), 56 (45), 55 (38), 54 (37), 53 (22). Anal. ($C_{14}H_{23}NO_5 \cdot 1/4H_2O$) C, H, N.

6-(Phenylmethylene)octahydro-4,8-methanopyrido-[2,1-*c*][1,4]oxazin-7-one (8c). **8c** was prepared according to method F in 89% yield, mp 124–128 °C. ^{1}H-NMR (δ, $CDCl_3$): 2.12 (m, 4H), 2.58 (m, 1H), 2.98 (m, 2H), 3.85 (dd, J = 12, 42, 4H), 7.00 (s, 1H), 7.2–7.4 (m, 3H), 8.0–8.1 (m, 2H). ^{13}C-NMR (δ, $CDCl_3$): 29.1, 40.6, 50.7, 71.0, 126.1, 128.5, 129.9, 132.2, 133.7, 143.3, 205.8. IR (KBr, cm^{-1}): 1710 (C=O), 1625 (C=C). MS (rel intensity): 255 (100, parent), 227 (61), 226 (95), 198 (58), 197 (92), 196 (81), 156 (67), 129 (51), 128 (64), 117 (61), 116 (73), 91 (58), 89 (64), 77 (60), 55 (61). Anal. ($C_{16}H_{17}NO_2$) C, H, N.

6-(Diphenylmethyl)octahydro-4,8-methanopyrido[2,1-*c*][1,4]oxazin-7-one (9c). **9c** was prepared according to method G in 36% yield, mp 140–147 °C. ^{1}H-NMR (δ, $CDCl_3$): 1.8–2.1 (m, 4H), 2.29 (m, 1H), 2.42 (m, 1H), 2.99 (m, 1H), 3.30 (s, 2H), 3.5–3.7 (m, 3H), 4.70 (d, J = 6, 1H), 7.0–7.5 (m, 10H). ^{13}C-NMR (δ, $CDCl_3$): 28.3, 29.9, 41.2, 46.6, 48.9, 53.1, 70.8, 71.4, 73.7, 126.5, 128.2, 128.4, 128.7, 128.8, 142.0, 143.4, 219.9. IR (KBr, cm^{-1}): 1720, 1732 (C=O). Anal. ($C_{22}H_{23}NO_2$) C, H, N.

***cis*-6-(Diphenylmethyl)octahydro-*N*-[(2-methoxyphenyl)methyl]-4,8-methanopyrido[2,1-*c*][1,4]oxazin-7-amine (10c).** **10c** was prepared according to method H in 15% yield, mp 55–60 °C. ^{1}H-NMR (δ, $CDCl_3$): 1.4 (m, 1H), 1.5–1.8 (m, 3H), 2.0–2.2 (m, 2H), 2.31 (m, 1H), 2.84 (m, 1H), 3.02 (m, 1H), 3.14 (m, 1H), 3.3–3.5 (m, 3H), 3.67 (AB_q, J_{AB} = 12, $\Delta\nu$ = 90, 2H), 3.51 (s, 3H), 4.58 (d, J = 12, 1H), 6.6–6.8 (m, 2H), 7.0–7.4 (m, 12H). ^{13}C-NMR (δ, $CDCl_3$): 22.3, 25.7, 29.4, 45.3, 46.1, 48.5, 52.3, 54.1, 55.2, 64.4, 71.3, 109.9, 120.1, 125.3, 126.5, 127.8, 127.9, 129.0, 129.4, 143.2, 145.6, 157.5. IR (KBr, cm^{-1}): 1603 (aromatic C=C). MS (rel intensity): 455 (12, parent), 333 (25), 287 (100), 167 (24), 165 (22), 122 (21), 121 (70), 91 (63), 65 (21). Anal. ($C_{30}H_{34}N_2O_2$) C, H, N.

Method I: *N*-Benzyl-3-azabicyclo[3.3.1]nonan-9-one (14a). Prepared by a modification of the literature procedure[9] as follows: To a 2-L round-bottomed flask equipped with condenser and N_2 inlet were added 69 mL (0.638 mol) of benzylamine and, dropwise, 53 mL of concentrated hydrochloric acid. To the mixture obtained on stirring were added 53 mL (0.510 mol) of cyclohexanone, 125 mL (0.620 mol) of 37% aqueous formaldehyde solution, and 730 mL of acetic acid. The solution was heated at 80 °C for 2 h and then concentrated under reduced pressure. The residue was partitioned between ether and water, the water was washed with ether, the pH was adjusted to 8 with solid sodium carbonate, and the mixture was extracted with methylene chloride. The organic layer was dried over sodium sulfate and evaporated. The residue was taken up in 150 mL of ethanol and treated with 50 mL (0.530 mol) of acetic anhydride. After 2 h of stirring, the solution was treated with 53 mL of concentrated hydrochloric acid and stirred a further 2 h. It was then concentrated, taken up in water, and extracted with methylene chloride, and the pH was adjusted to 8 with sodium carbonate. The aqueous layer was then extracted with methylene chloride and the organic layer dried over sodium sulfate and evaporated. The residue was chromatographed on silica gel using hexane/ethyl acetate as eluent to afford 8.84 g (7.6% yield) of the product as a solid, mp 47–51 °C. ^{1}H-NMR (δ, $CDCl_3$): 1.48 (m, 1H), 2.0 (m, 2H), 2.1 (m, 2H), 2.31 (broad s, 2H), 2.51 (m, 2H), 2.94 (m, 1H), 3.13 (m, 2H), 3.43 (s, 2H), 7.2–7.4 (m, 5H). ^{13}C-NMR (δ, $CDCl_3$): 21.4, 34.7, 47.8, 60.3, 62.2, 127.1, 128.4, 128.6, 138.6, 218.2. IR (KBr, cm^{-1}): 1720 (C=O). MS (rel intensity): 230 (34), 229 (80, parent), 228 (49), 138 (55), 132 (32), 120 (73), 119 (37), 106 (37), 92 (51), 91 (100), 65 (52), 55 (47). High-

resolution mass spectrum: calcd for $C_{15}H_{19}NO$ 229.1467, found 229.1465. Anal. ($C_{15}H_{19}NO$) C, H ,N.

***N*-Benzyl-3-azabicyclo[3.3.1]nonane-9-carbonitrile (15a).** **15a** was prepared according to method B in 80% yield as a low melting solid, which was a mixture of nitrile stereoisomers. ^{1}H-NMR (δ, $CDCl_3$): 1.2–1.9 (m, 5H), 2.04 (m, 2H), 2.11 (doublets, J = 2, 1H), 2.6–2.8 (m, 4H), 2.96 (doublets, J = 2, 1H), 3.38 and 3.43 (singlets, 2H), 7.2–7.4 (m, 5H). ^{13}C-NMR (δ, $CDCl_3$): 21.18, 21.22, 26.8, 30.9, 31.7, 31.8, 31.9, 34.4., 34.8, 54.9, 58.8, 63.4, 63.5, 121.5, 126.9, 127.0, 128.3, 128.7, 138.5, 138.9. IR (KBr, cm^{-1}): 2218 (CN). MS (rel intensity): 240 (48, parent), 239 (43), 163 (35), 149 (66), 120 (33), 91 (100), 65 (38). Anal. ($C_{16}H_{20}N_2$) C, H, N.

Ethyl *N*-Benzyl-3-azabicyclo[3.3.1]nonane-9-carboxylate (16a). **16a** was prepared according to method C in 33% yield as an oil, a mixture of stereoisomers. ^{1}H-NMR (δ, $CDCl_3$): 1.26 (overlapping triplets, 3H), 1.3–1.9 (m, 5H), 2.2–2.4 (m, 5H), 2.6–2.8 (m, 2H), 2.92 (m, 1H), 3.33 and 3.40 (singlets, 2H), 4.17 (overlapping quartets, 2H), 7.1–7.3 (m, 5H). ^{13}C-NMR (δ, $CDCl_3$): 14.3, 21.4, 21.6, 26.7, 30.9, 31.0, 32.5, 46.4, 46.9, 55.5, 60.0, 60.6, 63.5, 63.9, 126.6, 126.7, 128.2, 128.7, 139.4, 139.5, 173.8. IR (KBr, cm^{-1}): 1730 (C=O). MS (rel intensity): 287 (26, parent), 196 (82), 134 (30), 91 (100). High-resolution mass spectrum: calcd. for $C_{16}H_{25}NO_2$ 287.1883, found 287.1872.

Ethyl 3-Azabicyclo[3.3.1]nonane-9-carboxylate (17a). **17a** was prepared according to method D as an oil and used directly in the next step.

Ethyl *N*-[(Ethoxycarbonyl)methyl]-3-azabicyclo[3.3.1]-nonane-9-carboxylate (18a). **18a** was prepared according to method E in 88% yield as an oil. ^{1}H-NMR (δ, $CDCl_3$): 1.1 (overlapping triplets, 6H), 1.4–1.8 (m, 5H), 2.0–2.2 (m, 3H), 2.4–2.6 (m, 4H), 2.82 (m, 1H), 2.88 and 2.98 (singlets, 2H), 4.0 (overlapping quartets, 2H). ^{13}C-NMR (δ, $CDCl_3$): 14.1, 20.8, 21.0, 26.7, 30.6, 30.8, 32.4, 45.6, 46.1, 54.7, 59.2, 59.6, 59.7, 59.8, 59.9, 60.0, 60.1, 170.7, 170.8, 173.4, 173.5. IR (KBr, cm^{-1}): 1735 (C=O). MS (rel intensity): 283 (7, parent), 211 (33), 210 (100), 95 (17), 93 (17), 58 (46). High resolution mass spectrum: calcd for $C_{15}H_{25}NO_4$ 283.1785, found 283.1764.

3-(Phenylmethylene)octahydro-1*H*-2,5-methanoisoquinolin-4-one (20a). **20a** was prepared according to method F in 75% yield, mp 133–137 °C. ^{1}H-NMR (δ, $CDCl_3$): 1.3–1.6 (m, 5H), 1.9–2.0 (m, 1H), 2.25 (m, 1H), 2.34 (m, 1H), 2.8–3.1 (m, 4H), 6.99 (m, 1H), 7.2–7.4 (m, 3H), 7.99 (m, 2H). ^{13}C-NMR (δ, $CDCl_3$): 14.2, 27.8, 29.0, 49.0, 51.9, 124.9, 128.4, 129.5, 132.1, 134.0, 144.4, 206.1. IR (KBr, cm^{-1}): 1700 (C=O), 1621 (C=C). MS (rel intensity): 254 (32), 253 (100, parent), 225 (76), 224 (94), 130 (33), 103 (30), 77 (43), 67 (41). Anal. ($C_{17}H_{19}NO$) C, H, N.

3-(Diphenylmethyl)octahydro-1*H*-2,5-methanoisoquinolin-4-one (21a). **21a** was prepared according to method G in 72% yield as an oil. ^{1}H-NMR (δ, $CDCl_3$): 1.2–1.6 (m, 4H), 1.82 (m, 1H), 2.12 (m, 1H), 2.20 (m, 1H), 2.28 (m, 1H), 2.37 (dd, J = 4, 14, 1H), 2.70 (m, 1H), 2.92 (dd, J = 4,16, 1H), 3.15 (m, 1H), 3.85 (d, J = 8, 1H), 4.53 (d, J = 8, 1H), 7.1–7.5 (m, 10H). ^{13}C-NMR (δ, $CDCl_3$): 14.3, 27.6, 27.7, 28.8, 30.0, 46.1, 49.6, 50.3, 54.6, 71.5, 126.5, 126.6, 128.4, 128.5, 142.3, 143.3, 219.4. IR (KBr, cm^{-1}): 1710 (C=O). MS (rel intensity): 331 (2, parent), 304 (48), 303 (100), 302 (39), 223 (38), 222 (100), 180 (75), 179 (35), 167 (52), 165 (57), 136 (71), 91 (74), 67 (40). Anal. ($C_{23}H_{25}NO$) C, H, N.

***cis*-3-(Diphenylmethyl)octahydro-*N*-(phenylmethyl)-1*H*-2,5-methanoisoquinolin-4-amine (22a).** **22a** was prepared according to method H as the hydrochloride salt in 28% yield, mp 218–222 °C. ^{1}H-NMR (δ, $CDCl_3$): (free base) 1.3–1.9 (m, 9H), 2.2–2.4 (m, 2H), 2.76 (m, 2H), 2.92 (dd, J = 4, 10, 1H), 3.38 (AB_q, J_{AB} = 12, $\Delta\nu$ = 102, 2H), 3.64 (dd, J = 9, 12, 1H), 4.46 (d, J = 12, 1H), 6.64 (m, 2H), 7.0–7.4 (m, 13H). ^{13}C-NMR (δ, $CDCl_3$): 15.4, 15.8, 23.3, 29.3, 29.7, 29.9, 34.2, 36.4, 45.7, 49.7, 52.0, 55.2, 55.6, 62.6, 65.9, 126.0, 126.5, 126.6, 126.7, 127.5, 127.8, 127.9, 128.0, 128.2, 128.4, 129.3, 139.9, 143.8, 145.4. IR (KBr, cm^{-1}): 1561 (C=C). MS (rel intensity): 422 (<1, parent), 331 (24), 256 (29), 255 (100), 136 922), 90 (68). Anal. ($C_{30}H_{34}N_2 \cdot 2HCl \cdot {}^9/_4H_2O$) C, H, N.

***cis*-3-(Diphenylmethyl)octahydro-*N*-[(2-methoxyphenyl)methyl]-1*H*-2,5-methanoisoquinolin-4-amine (23a).** **23a** was prepared according to method H in 36% yield, mp 97–102 °C. ^{1}H-NMR (δ, $CDCl_3$): 1.3–1.8 (m, 8H), 2.30 (m, 2H), 2.55 (m, 2H), 2.93 (dd, J = 3, 10, 1H), 3.24 (m, 1H), 3.44 (AB_q, J_{AB} = 13, $\Delta\nu$ = 84, 2H), 3.54 (s, 3H), 3.65 (dd, J = 8, 12, 1H), 4.53 (d, J = 12, 1H), 6.6–6.8 (m, 3H), 7.0–7.4 (m, 11H). ^{13}C-NMR (δ, $CDCl_3$): 15.8, 23.1, 29.3, 29.7, 29.9, 34.1, 45.6, 45.9, 49.5, 55.0, 55.1, 55.2, 62.6, 109.9, 120.1, 126.0, 126.4, 127.6, 127.7, 127.8, 127.9, 128.4, 129.1, 129.3, 143.6, 145.6, 157.4. IR (KBr, cm^{-1}): 1600 (C=C). MS (rel intensity): 452 (3, parent), 331 (52), 285 (100), 136 (38), 121 (54), 91 (51). Anal. ($C_{31}H_{39}N_2O \cdot {}^1/_2H_2O$) C, H, N.

***cis*-3-(Diphenylmethyl)octahydro-*N*-[(2-chlorophenyl)-methyl]-1*H*-2,5-methanoisoquinolin-4-amine (24a).** **24a** was prepared according to method H in 67% yield, mp 115–118 °C. ^{1}H-NMR (δ, $CDCl_3$): 1.3–1.6 (m, 5H), 1.7–1.9 (m, 3H), 2.29 (m, 2H), 2.76 (m, 2H), 2.93 (dd, J = 3, 10, 1H), 3.12 (m, 1H), 3.34 (m, 1H), 3.6–3.8 (m, 2H), 4.48 (d, J = 12, 1H), 6.63 (m, 1H), 7.0–7.4 (m, 13H). ^{13}C-NMR (δ, $CDCl_3$): 15.8, 23.3, 29.5, 29.7, 29.9, 34.5, 45.6, 48.9, 55.2, 55.6, 62.6, 126.0, 126.5, 127.5, 128.0, 128.4, 129.2, 129.8, 133.8, 137.5, 143.7, 145.5. IR (cm^{-1}): 1599 and 1571 (C=C). MS (rel intensity): 456 (<1, parent Cl^{35}), 331 (31), 291 (33), 289 (100), 136 (49), 127 (32), 125 (86), 91 (63). Anal. ($C_{30}H_{33}N_2Cl$) C, H, N.

***cis*-3-(Diphenylmethyl)octahydro-*N*-[[4-(trifluoromethyl)phenyl]methyl]-1*H*-2,5-methanoisoquinolin-4-amine (25a).** **25a** was prepared according to method H in 40% yield, mp 131–135 °C. ^{1}H-NMR (δ, $CDCl_3$): 1.3–2.1 (m, 8H), 2.24 (m, 1H), 2.34 (dd, J = 2, 14, 1H), 2.76 (m, 2H), 2.91 (dd, J = 2, 10, 1H), 3.24 (m, 1H), 3.41 (AB_q, J_{AB} = 13, $\Delta\nu$ = 102, 2H), 3.73 (dd, J = 8, 12, 1H), 4.43 (d, J = 12, 1H), 6.74 (m, 2H), 7.1–7.5 (m, 12H). ^{13}C-NMR (δ, $CDCl_3$): 15.7, 23.2, 29.1, 29.5, 29.8, 34.2, 45.6, 49.7, 51.4, 55.1, 55.5, 62.6, 125.1, 126.2, 126.6, 127.5, 128.0, 128.6, 128.7, 129.4, 143.6, 144.0, 144.8. IR (KBr, cm^{-1}): 1620, 1600 (C=C). MS (rel intensity): 490 (2, parent), 332 (24), 331 (66), 324 (37), 323 (100), 180 (22), 159 (53), 136 (21). Anal. ($C_{31}H_{33}N_2F_3$) C, H, N.

***N*-Benzyl-3-azabicyclo[3.2.1]octan-8-one (14b).** **14b** was prepared by method I as an oil in 4% yield: ^{1}H-NMR (δ, $CDCl_3$): 1.82 (m, 2H), 2.04 (m, 2H), 2.13 (m, 2H), 2.51 (d, J = 12, 2H), 2.94 (dd, J = 3, 12, 2H), 3.57 (s, 2H), 7.2–7.4 (m, 5H). ^{13}C-NMR (δ, $CDCl_3$): 22.8, 45.4, 60.2, 61.7, 127.2, 128.3, 128.6, 138.8, 220.1. MS (rel intensity): 215 (30, parent), 124 (17), 91 (100), 65 (14), 55 (16), 42 (15), 41 (17). High-resolution mass spectrum: calcd for $C_{14}H_{17}NO$ 215.1254, found 215.1316.

***N*-Benzyl-3-azabicyclo[3.2.1]octane-8-carbonitrile (15b).** **15b** was prepared by method B as an oil in 99% yield: ^{1}H-NMR (δ, $CDCl_3$): 1.63 (m, 1H), 1.8–2.0 (m, 3H), 2.05 (d, J = 11, 1H), 2.35 (m, 1H), 2.4–2.8 (m, 3H), 2.71 (dd, J = 3, 11, 1H), 3.46 and 3.53 (singlets, 2H), 7.2–7.4 (m, 5H). IR (cm^{-1}, neat): 2220 (CN). MS (rel intensity): 226 (41, parent), 225 (31), 149 (37), 135 (59), 91 (100), 65 (34).

Ethyl *N*-Benzyl-3-azabicyclo[3.2.1]octane-8-carboxylate (16b). **16b** was prepared by method C as an oil in quantitative yield, as a mixture of isomers at the 8-position: ^{1}H-NMR (δ, $CDCl_3$): 1.25 (triplets, 3H), 1.6–1.8 (m, 4H), 2.02 (s, 1H), 2.10 (d, J = 8.5, 2H), 2.3–2.5 (m, 4H), 2.72 (dd, J = 4, 11, 2H), 3.43 and 3.48 (singlets, 2H), 4.17 (quartets, 2H), 7.1–7.4 (m, 5H). ^{13}C-NMR (δ, $CDCl_3$): 14.2, 14.4, 27.4, 28.5, 36.7, 38.3, 49.4, 54.4, 55.2, 59.8, 60.1, 61.9, 62.3, 126.7, 126.8, 128.1, 128.6, 139.3, 139.5, 172.7, 174.0. IR (cm^{-1}, neat): 1740 (C=O). MS (rel intensity): 273 (62, parent), 272 (43), 200 (37), 182 (91), 134 (62), 92 (31), 91 (100).

Ethyl *N*-[(Ethoxycarbonyl)methyl]-3-azabicyclo[3.2.1]-octane-8-carboxylate (18b). **18b** was prepared by method E, via intermediate **17b** (which was prepared according to method D and used directly), in 75% overall yield as an oil, as a mixture of isomers at the 8-position: ^{1}H-NMR (δ, $CDCl_3$): 1.10 (triplets, 6H), 1.5–1.7 (m, 4H), 2.19 (s, 1H), 2.3–2.5 (m, 4H), 2.6 (m, 2H), 3.00 and 3.09 (singlets, 2H), 4.0 (quartets, 4H). ^{13}C-NMR (δ, $CDCl_3$): 14.08, 14.15, 14.19, 27.0, 28.1, 36.3, 38.0, 48.6, 53.6, 54.5, 58.1, 58.7, 59.1, 59.7, 60.0, 170.6, 172.3, 173.7. IR (cm^{-1}, neat): 1737 (C=O). MS (rel intensity): 269 (15, parent), 196 (100), 81 (34), 79 (36), 58 (55), 57 (37). Anal. ($C_{14}H_{23}NO_4 \cdot {}^1/_4H_2O$) C, H, N.

3-(Phenylmethylene)octahydro-2,5-methano-2*H*-2-pyrindin-4-one (20b). **20b** was prepared by Method F *via*

octahydro-2,5-methano-2*H*-2-pyrindin-4-one, **19b**, as a solid, mp 134–140 °C, in 87% yield: ^{1}H-NMR (δ, $CDCl_3$): 1.67 (m, 2H), 1.95 (m, 2H), 2.42 (m, 1H), 2.49 (m, 2H), 2.69 (m, 2H), 3.17 (m, 2H), 6.93 (s, 1H), 7.2–7.4 (m, 3H), 7.98 (m, 2H). ^{13}C-NMR (δ, $CDCl_3$): 32.8, 38.9, 52.3, 58.5, 123.1, 128.4, 129.5, 132.3, 133.9, 144.3, 205.6. IR (cm^{-1}, KBr): 1700 (C=O), 1630 (C=C). MS (rel intensity): 239 (100, parent), 211 (75), 210 (96), 182 (32), 156 (30), 130 (33), 116 (31), 77 (33). Anal. ($C_{16}H_{17}NO$) C, H, N.

3-(Diphenylmethyl)octahydro-2,5-methano-2*H*-2-pyrindin-4-one (21b). **21b** was prepared by method G as an oil in 38% yield: ^{1}H-NMR (δ, $CDCl_3$): 1.55 (m, 1H), 1.65 (m, 1H), 1.89 (m, 2H), 2.11 (m, 1H), 2.25 (m, 1H), 2.43 (m, 1H), 2.51 (m, 1H), 2.65 (m, 1H), 2.92 (m, 1H), 3.30 (m, 1H), 3.81 (d, J = 8, 1H), 4.50 (d, J = 8, 1H), 7.1–7.5 (m, 10H). ^{13}C-NMR (δ, $CDCl_3$): 32.7, 38.5, 40.2, 50.3, 52.3, 52.6, 60.8, 71.2, 126.47, 126.52, 128.4, 128.5, 128.6, 142.2, 143.2, 219.3. IR (cm^{-1}, neat): 1715 (C=O). MS (rel intensity): 317 (6, parent), 289 (96), 222 (100), 213 (56), 184 (54), 180 (53), 167 (50), 165 (55), 152 (59), 122 (62), 91 (91), 79 (55), 67 (53), 55 (52). HRMS: calcd for $C_{22}H_{23}NO$ 317.1812, found 317.1764.

***cis*-3-(Diphenylmethyl)octahydro-*N*-[(2-methoxyphenyl)methyl]-2,5-methano-2*H*-2-pyrindin-4-amine (26).** **26** was prepared by method H, mp 147–151 °C, in 33% yield: ^{1}H-NMR (δ, $CDCl_3$): 1.3–1.6 (m, 2H), 1.6–1.8 (m, 2H), 2.02 (m, 3H), 2.1–2.4 (m, 3H), 2.98 (m, 1H), 3.13 (m, 1H), 3.5 (m, 2H), 3.57 (s, 3H), 3.6 (m, 1H), 4.52 (d, J = 12, 1H), 6.6–6.8 and 7.1–7.4 (m, 14H). ^{13}C-NMR (δ, $CDCl_3$): 30.7, 31.5, 32.7, 34.5, 38.6, 46.4, 49.4, 49.6, 53.0, 55.2, 60.4, 62.8, 110.0, 120.1, 125.8, 126.3, 127.7, 128.2, 128.3, 129.0, 129.4, 143.5, 145.7, 157.4. IR (cm^{-1}, KBr): 1602 (C=C). MS (rel intensity): 438 (1, parent), 317 (46), 272 (30), 271 (100), 121 (62), 91 (61). Anal. ($C_{30}H_{34}N_2O\cdot{}^1/_2H_2O$) C, H, N.

***N*-Carbethoxy-7-azabicyclo[3.2.1]non-8-ene (27).**[10] To a 500-mL round-bottomed flask equipped with addition funnel, condenser, and N_2 inlet were added 20.2 g (0.11 mol) of bis(carboethoxyamino)methane[10] and 175 mL of benzene. The mixture was cooled to 0 °C, and 3.78 g (0.026 mmol) of boron trifluoride etherate was added, followed by heating to reflux. To the refluxing solution was added 10 g (0.11 mol) of cycloheptadiene dropwise. Refluxing was continued for 1 h, and the reaction mixture was cooled, washed with aqueous sodium bicarbonate solution, water, and brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using hexane/ethyl acetate as eluent to afford an oil, 3.22 g (15%). ^{1}H-NMR (δ, $CDCl_3$): 1.04 (triplets, J = 7, 3H), 1.1–1.6 (multiplets, 5H), 2.32 (m, 1H), 2.95 (m, 1H), 3.27 (m, 1H), 3.91 (quartets, J = 7, 2H), 4.32 and 4.44 (multiplets, 1H), 5.85 (m, 1H), 5.96 (m, 1H). ^{13}C-NMR (δ, $CDCl_3$): 14.6, 20.8, 20.84, 28.4, 28.6, 29.2, 29.6, 31.6, 31.8, 49.0, 49.5, 49.7, 49.9, 60.7, 60.8, 128.8, 129.2, 131.6, 132.3, 155.3, 155.6. IR (neat, cm^{-1}): 1692 (C=O). MS (rel intensity): 195 (parent, 88), 166 (98), 108 (61), 94 (84), 93 (64), 81 (64), 80 (100), 79 (72). Anal. ($C_{11}H_{17}NO_2\cdot{}^1/_4H_2O$) C, H, N.

***N*-Carbethoxy-7-azabicyclo[3.2.1]nonan-9-ol (28).** To a 500-mL round-bottomed flask equipped with N_2 inlet were added 20.0 g (0.103 mol) of *N*-carbethoxy-7-azabicyclo[3.2.1]-non-8-ene and 200 mL of tetrahydrofuran. To the solution was added 52.7 g (0.124 mol) of mercuric trifluoroacetate, and the reaction mixture was stirred at room temperature for 5 days with the addition of 10 g of additional mercuric trifluoroacetate. Then 50 mL of 3 N aqueous sodium hydroxide was added followed by a solution of 17.6 g (0.463 mol) of sodium borohydride in 210 mL of aqueous 3 N sodium hydroxide with cooling. After the reaction had subsided, the layers were separated, and the aqueous layer was washed with ethyl acetate. The organic layers were dried over magnesium sulfate and filtered through Celite and then evaporated and used directly in the next step. MS (rel intensity): 213 (parent, 73), 184 (100), 152 (73), 140 (77).

***N*-Carbethoxy-7-azabicyclo[3.2.1]nonan-9-one (29).** To a 125-mL round-bottomed flask equipped with N_2 inlet were added 3.52 g (16.51 mmol) of *N*- carbethoxy-7-azabicyclo[3.2.1]-nonan-9-ol and 36 mL of acetone. The solution was cooled to 0 °C, and 6 mL of a 2.75 M solution of chromium trioxide in sulfuric acid/acetone (Jones' reagent) was added. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. It was then poured into water and diluted with ether. After the aqueous layer was washed with ether, the combined organic layers were filtered through Florosil and evaporated. The residue was chromatographed on silica gel using hexane/ethyl acetate as eluant to afford an oil, 1.57 g (45%). ^{1}H-NMR (δ, $CDCl_3$): 1.14 (triplets, 3H), 1.35 (m, 1H), 1.5–1.9 (m, 4H), 1.98 (m, 1H), 2.28 (m, 1H), 2.48 (m, 1H), 2.5–2.6 (m, 1H), 3.40 (m, 1H), 3.66 (m, 1H), 4.03 (quartets, 2H), 4.41 and 4.53 (multiplets, 1H). ^{13}C-NMR (δ, $CDCl_3$): 14.6, 19.9, 19.94, 20.1, 29.8, 30.1, 32.9, 33.3, 42.7, 42.9, 46.0, 46.7, 46.78, 46.83, 47.9, 48.0, 61.28, 61.33, 61.4, 155.6, 210.8. IR (neat, cm^{-1}): 1725 and 1690 (C=O). MS (rel intensity): 211 (parent, 53), 212 (51), 169 (57), 166 (100), 140 (72), 96 (72). HRMS: calcd for $C_{11}H_{17}NO_3$ 211.1209, found 211.1208.

9-Cyano-*N*-carboethoxy-7-azabicyclo[3.2.1]nonane (30). **30** was prepared according to method B in 63% yield as an oil. ^{1}H-NMR (δ, $CDCl_3$): 1.17 and 1.19 (triplets, 3H), 1.38 (m, 1H), 1.5–1.8 (m, 4H), 1.88 (m, 1H), 2.11 (m, 2H), 2.37 (m, 1H), 2.8-2.9 (m, 1H), 3.21 and 3.39 (multiplets, 1H), 3.57 (m, 1H), 4.08 (quartets, 2H), 4.2-4.4 (multiplets, 1H). ^{13}C-NMR (δ, $CDCl_3$): 14.7, 19.67, 19.72, 20.0, 20.1, 24.5, 24.6, 23.3, 23.4, 29.8, 30.0, 30.1, 30.3, 30.5, 32.2, 32.30, 32.34, 32.5, 33.4, 33.5, 34.0, 34.2, 34.3, 34.4, 44.7, 44.9, 46.4, 46.6, 46.9, 47.1, 47.9, 48.0, 60.3, 61.2, 121.9, 122.8, 122.9, 155.7. IR (neat, cm^{-1}): 2210 (CN), 1690 (C=O). MS (rel intensity): 222 (parent, 100), 223 (92), 149 (86), 107 (84), 82 (62). HRMS: calcd for $C_{12}H_{18}N_2O_2$ 222.1404, found 222.1371.

Ethyl 7-Azabicyclo[3.2.1]nonane-9-carboxylate (31). **31** was prepared according to method C as an oil which was used directly in the next step. MS (rel intensity): 197 (parent, 16), 183 (41), 124 (100), 96 (54), 82 (49), 80 (52).

Ethyl *N*-(Carboethoxymethyl)-7-azabicyclo[3.2.1]nonane-9-carboxylate (32). **32** was prepared according to method E as an oil in 30% overall yield. ^{1}H-NMR (δ, $CDCl_3$): 1.45 (triplets, 6H), 1.3–1.8 (m, 6H), 2.2–2.4 (m, 2H), 2.58 (m, 1H), 2.73 (m, 2H), 2.79 (m, 1H), 3.29 and 3.30 (singlets, 2H), 4.03 (quartets, 4H). ^{13}C-NMR (δ, $CDCl_3$): 14.2, 20.8, 26.2, 33.1, 33.6, 33.9, 38.9, 52.2, 54.3, 58.3, 60.26, 60.34, 171.6, 175.87, 175.92. IR (neat, cm^{-1}): 1730 (C=O). MS (rel intensity): 283 (parent, 15), 211 (39), 210 (100), 182 (20), 79 (23), 67 (25), 55 (28).

11-(Phenylmethylene)-1-azatricyclo[5.4.0.0^{3,9}]undecan-10-one (34). **34** was prepared according to method F in 73% overall yield as an oil. ^{1}H-NMR (δ, $CDCl_3$): 1.4-2.4 (m, 8H), 2.52, 2.63, and 2.80 (multiplets, 2H), 3.25, 3.44, and 3.59 (multiplets, 3H), 6.68 and 6.84 (singlets, 1H), 7.2–7.4, 7.81, and 8.00 (multiplets, 5H). ^{13}C-NMR (δ, $CDCl_3$): 19.4, 22.3, 25.5, 26.3, 27.1, 27.2, 29.3, 29.4, 31.9, 37.3, 45.3, 47.0, 51.4, 52.3, 59.1, 59.7, 116.6, 123.1, 128.4, 129.2, 129.3, 130.81, 130.87, 130.91, 131.7, 133.9, 134.1, 145.8, 149.9, 207.2, 207.5. IR (neat, cm^{-1}): 1730 and 1710 (C=O). MS (rel intensity): 253 (parent, 100), 170 (45), 117 (96), 116 (43), 109 (80), 67 (79).

11-(Diphenylmethyl)-1-azatricyclo[5.4.0.0^{3,9}]undecan-10-one (35). **35** was prepared according to method G in 18% yield as a solid from 2-propanol, mp 178–181 °C. ^{1}H-NMR (δ, $CDCl_3$): 1.5–2.7 (multiplets, 10H), 3.62 (m, 1H), 4.20 (d, J = 6, 1H), 4.67 (d, J = 6, 1H), 6.4–6.6 and 7.1–7.6 (m, 10H). ^{13}C-NMR (δ, $CDCl_3$): 19.5, 22.8, 24.2, 28.7, 28.8, 29.0, 29.5, 29.8, 36.8, 43.6, 46.5, 46.6, 47.5, 48.1, 54.7, 65.2, 70.8, 126.2, 126.3, 126.6, 126.7, 126.99, 127.05, 127.3, 127.5, 127.6, 127.7, 127.8, 127.89, 127.95, 128.0, 128.2, 128.4, 128.5, 128.7, 129.2, 129.4, 141.0, 142.3, 144.6. IR (neat, cm^{-1}): 1730 (C=O). MS (rel intensity): 332 (parent + 1, <1), 303 (45, parent − CO), 180 (40), 136 (100).

***cis*-11-(Diphenylmethyl)-*N*-[(2-methoxyphenyl)methyl]-1-azatricyclo[5.4.0.0^{3,9}]undecan-10-amine (36).** **36** was prepared according to Method H in 19% yield as an oil, which was converted to its hydrochloride salt from ether, mp 200–210 °C. ^{1}H-NMR (δ, $CDCl_3$): 1.40 (dd, J = 8, 12, 1H), 1.6–2.1 (m, 7H), 2.16 (m, 1H), 2.72 (m, 1H), 2.85 (dd, J = 5,7, 1H), 3.02 (m, 1H), 3.13 (m, 1H), 3.38 (m, 1H), 3.45 (ABq, J_{AB} = 14, $\Delta\nu$ = 98, 2H), 3.58 and 3.59 (singlets, 3H), 3.71 (dd, J = 7.6, 11.7, 1H), 4.43 (d, J = 11.7) and 4.57 (d, J = 12) (2H), 6.6–6.8 and 7.0–7.4 (m, 14H). ^{13}C-NMR (δ, $CDCl_3$): 20.0, 26.4, 26.7, 28.7, 29.5, 31.9, 44.4, 46.5, 49.2, 55.0, 55.2, 55.9, 61.5, 110.0,

120.2, 125.6, 126.3, 127.6, 127.7, 127.8, 128.0, 128.1, 128.3, 128.9, 129.0, 129.2, 143.3, 145.6, 157.4. IR (neat, cm^{-1}): 1605 (C=C). MS (rel intensity): 452 (1, parent), 285 (100), 276 (91), 121 (73), 91 (71). Anal. ($C_{31}H_{36}N_2O \cdot 2HCl \cdot 3H_2O$) C, H, N.

Biological Methods. [^{3}H]Substance P Binding in Human IM-9 Cells. The procedure was carried out as described previously[1]. Tissue was thawed, weighed, homogenized in 50 volumes (w/v) of ice-cold 50 mM Tris buffer (pH 7.7), and then centrifuged twice at 30000*g* for 20 min at 2–4 °C. The pellet was suspended in assay buffer (50 mM Tris-HCl (pH 7.7), 1 mM $MnCl_2$, 0.02% BSA, 40 mg/mL bacitracin, 4 mg/mL leupeptin, 2 mg/mL chymotrypsin, 30 mg/mL phosphoramidon), and the assay was conducted in 5 mL of polystyrene tubes with 100 μL of test compound solution, 100 μL of ligand solution (0.5 nM final concentration, 36–55 Ci/mmol), and 800 μL of tissue preparation (20 mg original wet weight/tube). After incubation in the dark at room temperature for 20 min, the assay was terminated by filtration onto GF/B filters which had been presoaked in 0.2% polyethylenimine for 1–2 h. The filters were washed (5 × 1 s) with ice-cold 50 mM Tris-HCl buffer (pH 7.7) using a Brandell harvesting system, and the filters were quantified for radioactivity by liquid scintillation counting. Standard errors are indicated following the IC_{50} values.

Capsaicin-Induced Plasma Extravasation.[1] Male Hartley guinea pigs, 300–400 g, fasted overnight, were anesthetized with sodium pentobarbitol, 25 mg/kg. Evans Blue dye was injected iv at 30 mg/kg, followed after 5 min by capsaicin [a 30 mM solution of capsaicin in 70% ethanol was diluted in 0.1% BSA buffer (Krebs bicarbonate solution: 118 mM NaCl, 4.6 mM KCl, 1.17 mM $MgSO_4$, 2.5 mM $CaCl_2$, 1.17 mM NaH_2PO_4, 25 mM $NaHCO_3$, 10 mM glucose), giving a 30 μM solution of capsaicin which was administered at 10 mL per animal]. The animals were killed 10 min later by exsanguination, and the ureter was removed and extracted with 1 mL formamide at 60 °C for 24 h. OD at 600 nm was then determined. Results are expressed as an ED_{50} with 95% confidence limits following dose–response determination. The compounds for test were administered at the doses indicated po 1 h before capsaicin challenge.

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