Synthesis and Muscarinic Activity of Quinuclidinyl- and (1-Azanorbornyl)pyrazine Derivatives

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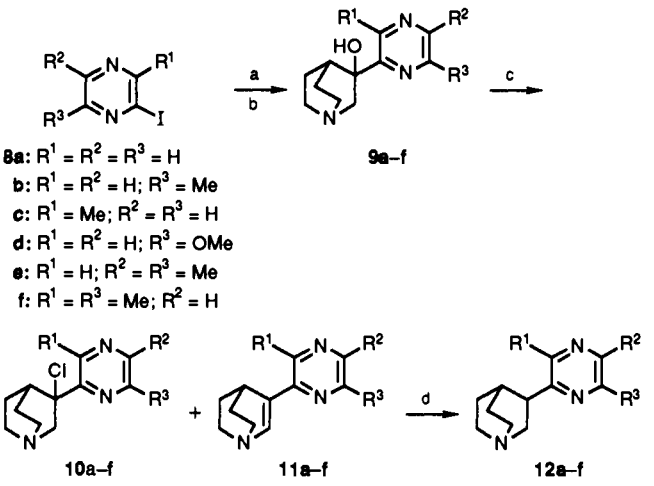
The synthesis and cortical muscarinic activity of a novel series of pyrazine-based agonists is described. Quinuclidine and azanorbornane derivatives were prepared either by reaction of lithiated pyrazines with azabicyclic ketones, followed by chlorination and reduction, or by reaction of the lithium enolate of the azabicyclic ester with 2-chloropyrazines followed by ester hydrolysis and decarboxylation. Substitution at all three positions of the heteroaromatic ring has been explored. Optimal muscarinic agonist activity was observed for unsubstituted pyrazines in the azanorbornane series. The *exo*-1-azanorbornane **18a** is one of the most efficacious and potent centrally active muscarinic agonists known. Studies on the 3-substituted derivatives have provided evidence of the preferred conformation of these ligands for optimal muscarinic activity. Substitution at C6 gave ligands with increased affinity and reduced efficacy. Moving the position of the diazine ring nitrogens to give pyrimidine and pyridazine derivatives resulted in a significant loss of muscarinic activity.

The cholinergic hypothesis[1] of Alzheimer's disease has led to several drug strategies for the potential clinical treatment of such psychiatric disorders based on improving cholinergic transmission.[2] The two most widely studied approaches to enhancing cholinergic function are by use of acetylcholinesterase inhibitors such as 9-amino-1,2,3,4-tetrahydroaminoacridine[3] and physostigmine[4] and muscarinic agonists acting directly on postsynaptic muscarinic receptors in the cerebral cortex.[2,5] Previous reports from our laboratory have described studies on the latter of these approaches. Five-membered heteroaromatic rings such as 1,2,4-oxadiazole[6-8] and thiadiazole[9] were found to be excellent, stable bioisosteres for an ester, and quinuclidinyl ligands of high affinity and efficacy for the muscarinic receptor were discovered (**1a,b**). Furthermore, it was shown that 1-azanorbornane[6,10] represents the optimum azabicyclic ring for muscarinic activity and CNS penetration which led to the discovery of some of the most potent, centrally acting, muscarinic agonists known with efficacy comparable to the endogenous ligand acetylcholine (**2a-3b**). It was concluded from these studies that high potency and efficacy requires two H-bond acceptor sites in an exact location of the heterocycle, and binding to the agonist (high-affinity) state of the receptor correlates with the magnitude of the negative potential in the vicinity of the heterocycle ring nitrogens. Oxadiazoles such as **3a** have been shown[11,12] to maximally stimulate PI turnover in cortical tissue.

Scheme I[a]



[a] Reagents: (a) ^{t}BuLi (2 equiv), ether, -45 °C, 0.25 h; (b) quinuclidin-3-one, ether, -65 °C → +25 °C; (c) $SOCl_2$, CH_2Cl_2, 0 °C; (d) H_2, 10% Pd/C, MeOH.

(1) (a) Iversen, S. The Chemistry of Dementia. *Chem. Br.* 1988, 338-342. (b) Perry, E. K. The Cholinergic Hypothesis - Ten Years On. *Br. Med. Bull.* 1986, *42*, 63-69. (c) Hirschowitz, B. I.; Hammer, R.; Giachetti, A.; Keirns, J. J.; Levine, R. R. Subtypes of Muscarinic Receptors. *Trends Pharmacol. Sci.* 1983, Supplement.

(2) (a) Moos, W. H.; Davis, R. E.; Schwarz, R. D.; Gamzu, E. R. Cognition Activators. *Med. Res. Rev.* 1988, *8*, 353-391. (b) Baker, R.; Saunders, J. Central Muscarinic Ligands and Receptors. *Annu. Rep. Med. Chem.* 1989, *24*, 31-40.

(3) Summers, W. K.; Majovski, L. V.; Marsh, G. M.; Tachiki, K.; Kling, A. Oral Tetrahydroaminoacridine in Long-Term Treatment of Senile Dementia, Alzheimer Type. *New Engl. J. Med.* 1986, *315*, 1241-1245.

(4) Christie, J. E.; Shering, A.; Ferguson, J.; Glen, A. I. M. Physostigmine and Arecoline: Effects of Intravenous Infusions in Alzheimer Presenile Dementia. *Br. J. Psychiat.* 1981, *138*, 46-50.

(5) Mouradian, M. M.; Mohr, E.; Williams, J. A.; Chase, T. N. No Response to High Dose Muscarinic Agonist Therapy in Alzheimer's Disease. *Neurology* 1988, *38*, 606-608.

(6) Saunders, J.; MacLeod, A. M.; Merchant, K.; Showell, G. A.; Snow, J.; Street, L. J.; Baker, R. Ester Bio-isosteres: Synthesis of Oxadiazolyl-1-azabicyclo[2.2.1]heptanes as Muscarinic Agonists. *J. Chem. Soc., Chem. Commun.* 1988, 1618-1619.

(7) Saunders, J.; Cassidy, M.; Freedman, S. B.; Harley, E. A.; Iversen, L. L.; Kneen, C.; MacLeod, A. M.; Merchant, K. J.; Snow, R. J.; Baker, R. Novel Quinuclidine-Based Ligands for the Muscarinic Cholinergic Receptor. *J. Med. Chem.* 1990, *33*, 1128-1138.

(8) Saunders, J.; Freedman, S. B. The Design of Full Agonists for the Cortical Muscarinic Receptor. *Trends Pharmacol. Sci., Suppl. Subtypes Muscarinic Recept. IV* 1987, 70-75.

(9) MacLeod, A. M.; Baker, R.; Freedman, S. B.; Patel, S.; Merchant, K. J.; Roe, M.; Saunders, J. Synthesis and Muscarinic Activities of 1,2,4-Thiadiazoles. *J. Med. Chem.* 1990, 2052-2059.

(10) Street, L. J.; Baker, R.; Book, T.; Kneen, C. O.; MacLeod, A. M.; Merchant, K. J.; Showell, G. A.; Saunders, J.; Herbert, R. H.; Freedman, S. B.; Harley, E. A. Synthesis and Biological Activity of 1,2,4-Oxadiazole Derivatives: Highly Potent and Efficacious Agonists for Cortical Muscarinic Receptors. *J. Med. Chem.* 1990, *33*, 2690-2697.

(11) Freedman, S. B.; Harley, E. A.; Patel, S.; Newberry, N. R.; Gilbert, M. J.; McKnight, A. T.; Tang, J. K.; Maguire, J. J.; Mudunkotuwa, N. T.; Baker, R.; Street, L. J.; MacLeod, A. M.; Saunders, J.; Iversen, L. L. A Novel Series of Non-Quaternary Oxadiazoles Acting as Full Agonists at Muscarinic Receptors. *Br. J. Pharmacol.* 1990, *101*, 575-580.

(12) Freedman, S. B.; Harley, E. A.; Marwood, R. S.; Patel, S. *In vivo* Characterisation of Novel Efficacious Muscarinic Receptor Agonists. *Eur. J. Pharmacol.* 1990, *187*, 193-199.

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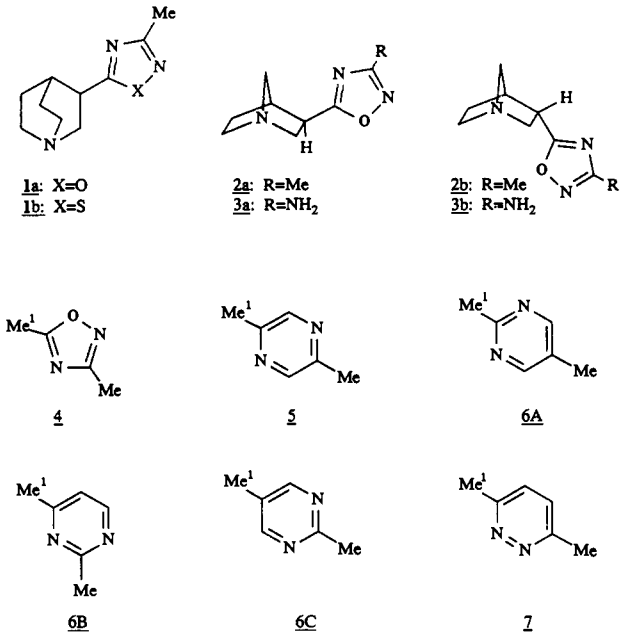


Figure 1.

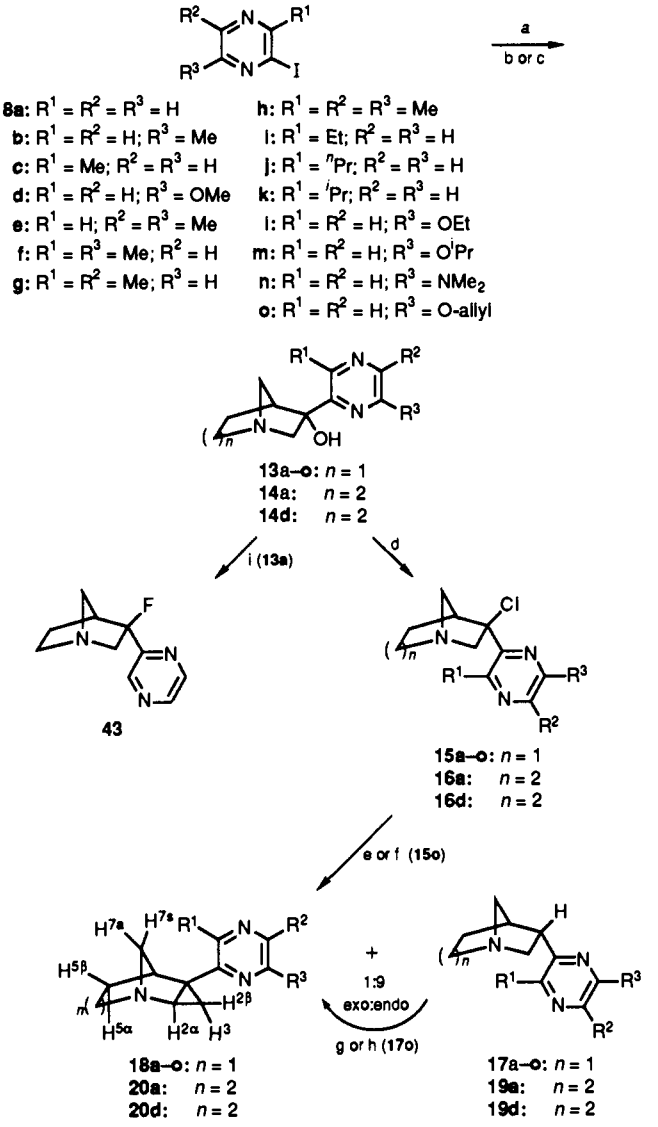
In our search for structurally diverse series of muscarinic agonists and to further map the requirements of the muscarinic receptor for effective binding in the cerebral cortex, we have examined 6-membered heteroaromatic diazine rings (**5–7**) as potential muscarinic pharmacophores. By analogy with the 5-membered rings studied,[7] it was proposed that the optimum diazine ring system, for muscarinic potency and binding to the agonist state of the receptor, would require 2-H bond acceptor sites in an exact location of space comparable to N2 and N4 of 1,2,4-oxadiazole (**4**). Examination of the two-dimensional electrostatic potential maps calculated[13] for the dimethyl-substituted diazine rings (**5–7**) (Figure 1) and comparison of the negative potentials[14,15] with oxadiazole (**4**)[7] revealed that pyrazine (**5**) has the correct disposition of H-bond acceptor sites. A different electrostatic potential distribution was found for the pyrimidine and pyridazine rings.

We describe in this paper the synthesis and biochemical evaluation of a series of pyrazine-based ligands for the cortical muscarinic receptor and report that pyrazine is a suitable, stable bioisostere for ester. Comparison of pyrazine with pyrimidine- and pyridazine-based ligands is made. Substitution at all four positions of the pyrazine ring has been studied in order to probe the receptor for central selectivity. Structure–activity has been explored in both the quinuclidine and 1-azanorbornane series. In addition, the nature of the pyrazine ring has allowed for the first time a study of the effect of di- and trisubstitution of the esteratic pharmacophore on binding and efficacy at cortical muscarinic receptors.

Synthetic Chemistry

The quinuclidinyl pyrazines[16] **12a–f** were prepared from the 2-iodopyrazines[17,18] **8a–f** (Scheme I). Addition of

Scheme II[a]



[a] Reagents: (a) tBuLi (2 equiv), ether, −45 °C, 0.25 h; (b) 1-azabicyclo[2.2.1]heptan-3-one, ether, −65 °C → +25 °C; (c) 1-azabicyclo[3.2.1]octan-6-one, ether, −65 °C → +25 °C; (d) $SOCl_2$, CH_2Cl_2, 0 °C; (e) H_2, 10% Pd/C, MeOH; (f) $^nBu_3SnH$, 2,2′-azobisisobutyronitrile (AIBN), THF; (g) NaOMe, MeOH, reflux, 2 h; (h) Na, allyl alcohol, reflux, 2 h; (i) (diethylamino)sulfur trifluoride (DAST), CH_2Cl_2, −65 °C → +25 °C.

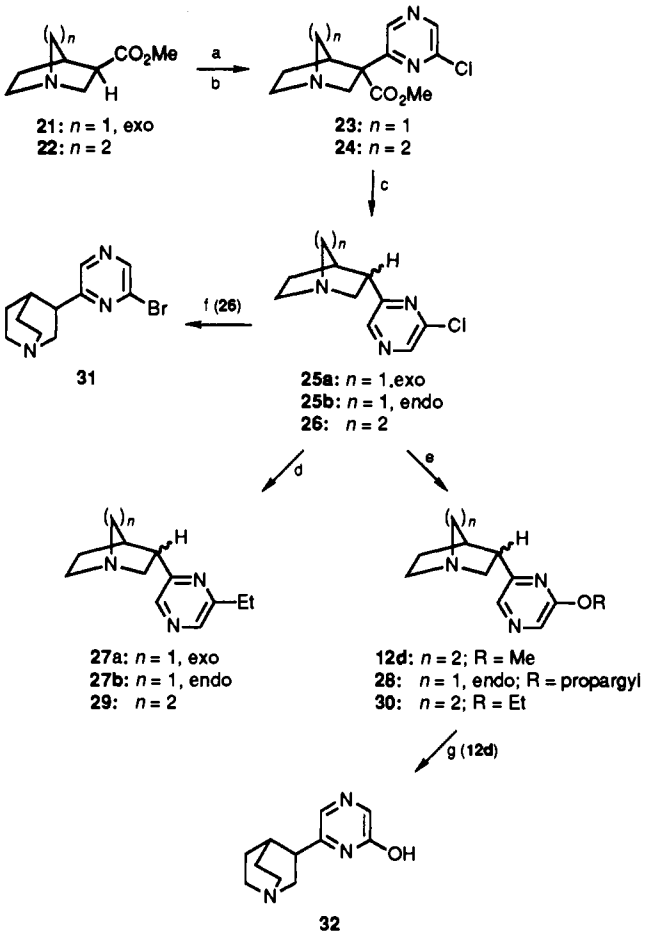
quinuclidin-3-one to an ethereal suspension of the 2-lithiopyrazines, generated from **8a–f** with tBuLi, at −50 °C, gave the crystalline alcohols **9a–f** in moderate yield. Treatment of **9a–f** with $SOCl_2$ gave an approximate equal mixture of chlorides **10a–f** and elimination products **11a–f** which could either be separated by chromatography on alumina or hydrogenated as a mixture to give **12a–f**. The (1-azanorbornyl)pyrazines **17a–b** and **18a–b** and isotropane pyrazines **19a**, **19d**, **20a**, and **20d** were prepared using similar methodology (Scheme II). 2-Iodo-6-alkoxypyrazines, **8d**, **8l**, **8m**, and **8o** were prepared by reaction of 2,6-diiodopyrazine with the appropriate sodium alkoxide. 2-Iodo-6-(dimethylamino)pyrazine (**8n**) was prepared by reaction of 2,6-diiodopyrazine with an aqueous

(13) Quantum mechanical calculations were carried out using the CHEM QM interface with the CHEMX program (Chemical Design Ltd., Oxford, U.K.).
(14) Maps were generated by the DENPOT 80 procedure; (QCPE 483) by Peeters, D.; Sana, M.
(15) Wave functions computed by GAUSSIAN 80 (QCPE 446); Singh, U. C.; Kollman, P.
(16) Baker, R.; Saunders, J.; Street, L. J. Pyrazines, Pyrimidines and Pyridazines Useful in the Treatment of Senile Dementia. European Patent Appl. 0327155, 1989.
(17) Karmas, G.; Spoerri, P. E. The Preparation of Hydroxypyrazines and Derived Chloropyrazines. *J. Am. Chem. Soc.* **1952**, *74*, 1580–1585.
(18) Hirschberg, A.; Spoerri, P. E. The Synthesis and Properties of Iodopyrazines. *J. Org. Chem.* **1961**, *26*, 1907–1912.

solution of dimethylamine. Addition of 1-azabicyclo-[2.2.1]heptan-3-one[10] to a suspension, in ether, of the 2-lithiopyrazines obtained from **8a–o** gave exclusively the *exo*-pyrazines[19] **13a–b**, resulting from addition of pyrazine to the less hindered face of the azabicycle. Chlorination of **13a–b** with $SOCl_2$ gave *endo*-pyrazines **15a–o**, arising from inversion at C-3, with only trace quantities of the *exo*-pyrazine and elimination product being isolated, in each case. Similarly, reaction of **13a** with (diethylamino)sulfur trifluoride (DAST) gave the inversion product **43**. Hydrogenation of **15a–n** gave an approximate 9:1 mixture of **17a–n** and **18a–n**, respectively, which could readily be separated by alumina chromatography. Reduction of the (allyloxy)pyrazine **15o** was achieved using $^nBu_3SnH$/AIBN to give a 9:1 mixture of **17o** and **18o**, respectively. Under thermodynamic conditions (NaOMe/MeOH for **17a–k** and **17n**, NaOEt/EtOH for **17l**, NaO^{i}Pr/Pr^{i}OH for **17m**, and NaO-allyl/allyl alcohol for **17o**) the endo isomers epimerized to the thermodynamically more stable exo isomers **18a–o**. By using the same chemistry the isotropane pyrazines **19a**, **19d**, **20a**, and **20d** (Scheme II) were prepared from 1-azabicyclo[3.2.1]-octan-6-one.[20] The stereochemical assignments for **13a–o**, **14a**, **14d**, **15a–o**, **16a**, **16d**, **17a–o**, **18a–o**, **19a**, **19d**, **20a**, **20d**, and **43** were made based on detailed analysis of the ^1H/COSY NMR spectra, by making use of four bond couplings between trans-antiperiplanar protons, as previously described for 1-azanorbornyl and isotropane 1,2,4-oxadiazoles[10] and thiadiazoles.[9] In addition to four-bond couplings, stereochemical assignments could be made based on NOE enhancement experiments. Saturation of the pyrazine proton in **13e** and **18e** gave NOE enhancements of $H2_\beta$, H4, and $H7_{syn}$, thus defining the relative stereochemistry of the pyrazine as exo. Similarly, saturation of the pyrazine proton in **15e** and **17e** gave NOE enhancements of $H2_\alpha$, H4, and $H5_\alpha$ consistent with the pyrazine moiety being endo.

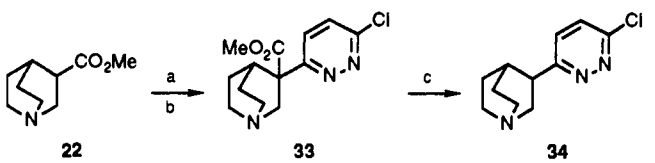
Where, either the appropriate 2-iodo-6-substituted-pyrazine was difficult to prepare, as in the case of 2-iodo-6-ethylpyrazine, or the 6-substituent was not compatible with metal–halogen exchange, e.g. chloro, bromo, hydroxy, and propargyloxy, an alternative synthesis was used (Scheme III). It was proposed that the 6-chloropyrazines **25b** and **26** could be used as intermediates to introduce a variety of substituents at the 6-position which were not accessible via the lithiated pyrazine procedure. Treatment of **21**[10] with LDA followed by 2,6-dichloropyrazine gave the 3,3-disubstituted 1-azanorbornane **23** in 35% yield and as exclusively the exo isomer, arising from preferential addition of pyrazine to the less sterically demanding face. Heating a solution of **23** in concentrated HCl resulted in both hydrolysis and decarboxylation to produce the *endo*-pyrazine **25b** in 43% yield, protonation occurring preferentially from the exo face. Only trace quantities of the less polar (alumina) exo isomer **25a** were isolated. The same methodology applied to the quinuclidine **22** gave the chloropyrazine **26**, via the 3,3-disubstituted quinuclidine **24**, in 21% overall yield. Palladium-catalyzed cross-coupling of tetraethyltin[21] with chloropyrazines **25a** and **25b** in the presence of K_2CO_3 gave a 1:6 mixture of ethyl-

Scheme III[a]



[a] Reagents: (a) lithium diisopropylamide, THF, −50 °C, 1.5 h; (b) 2,6-dichloropyrazine, THF, −50 °C → 0 °C, 16 h; (c) concentrated HCl, 130 °C, 3 h; (d) $Pd[P(Ph)_3]_4$, $SnEt_4$, K_2CO_3, DMF; (e) NaOR, ROH, reflux, 16 h; (f) concentrated HBr, CH_3CO_2H, 25 °C, 3–4 days; (g) concentrated HBr, reflux, 16 h.

Scheme IV[a]



[a] Reagents: (a) lithium diisopropylamide, THF, −50 °C, 1.5 h; (b) 3,6-dichloropyridazine, THF, −50 °C → 0 °C, 16 h; (c) concentrated HCl, 120 °C, 0.5 h.

pyrazines **27a** and **27b**, respectively, which were readily separated by alumina chromatography. Similar reaction of **26** with $Pd[P(Ph)_3]_4$ and $SnEt_4$ gave ethylpyrazine **29** in 45% yield. Chloro-displacement reaction of **26** with propargyl alcohol in the presence of NaH produced *endo*-(propargyloxy)pyrazine **28**. Displacement with NaOMe/MeOH gave an alternative route to **12d**, and reaction with NaOEt/EtOH afforded **30**. Demethylation of **12d** using concentrated HBr gave hydroxypyrazine **32**. Conversion of **26** to the bromo analogue **31** was achieved by dissolving in a solution of HBr in CH_3CO_2H and stirring for 3–4 days. As for previous derivatives, stereochemical assignments for the (1-azanorbornyl)pyrazines were made based on ^1H/COSY NMR spectra and NOE experiments.

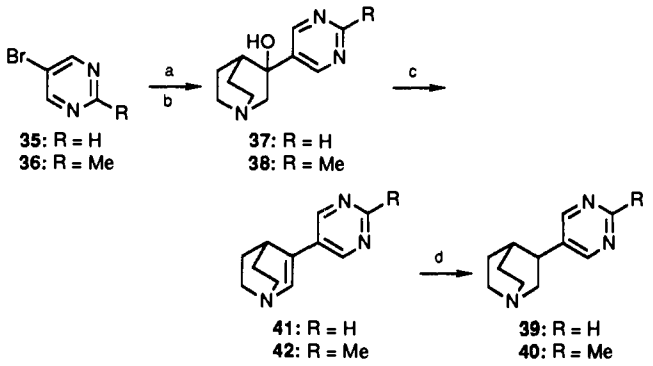
The synthetic strategy described in Scheme III was used to prepare the quinuclidinylpyridazine **34** from 3,6-dichloropyridazine (Scheme IV). Thus, reaction of 3,6-dichloropyridazine with the lithium enolate of **22** gave di-

(19) Exo is defined here as that in which the pyrazine is on the same face as the methylene bridge.

(20) Sternbach, L. H.; Kaiser, S. Antispasmodics. I. Bicyclic Basic Alcohols. *J. Am. Chem. Soc.* **1952**, *74*, 2215–2218.

(21) Watanbe, T.; Hayashi, K.; Sakurada, J.; Ohki, M.; Takamatsu, N.; Hirohata, H.; Takeuchi, K.; Yuasa, K.; Ohta, A. Alkylation and Arylation of Pyrazines by Organotin Compounds. *Heterocycles* **1989**, *29*, 123–131.

Scheme V[a]



[a] Reagents: (a) ^{n}BuLi, THF, ether, −110 °C, 1 h; (b) quinuclidin-3-one, THF, −110 °C → 25 °C, 16 h; (c) $SOCl_2$, CH_2Cl_2, 0 °C; (d) H_2, 10% Pd/C, EtOH.

substituted quinuclidine **33** in low yield. Refluxing a solution of **33** in concentrated HCl gave the desired quinuclidine **34**.

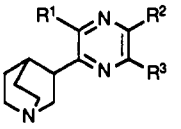
The metal–halogen exchange methodology developed for the pyrazine series was used to prepare the pyrimidines **39** and **40** (Scheme V). Reaction of 5-bromopyrimidine with ^{n}BuLi[22] at −110 °C followed by addition of quinuclidin-3-one gave **37**, albeit in low yield. Treatment of **37** with $SOCl_2$ gave the unsaturated derivative **41** which upon hydrogenation gave **39**. Similar chemistry using 2-methyl-1,3-pyrimidine[23] **36** gave **40** in higher yield. 2- and 4-Quinuclidine-substituted pyrimidines, **6A** and **6B**, respectively (Me^1 = quinuclidine), could not be prepared because the appropriate bromopyrimidines could not be lithiated.[22]

Results

The cortical muscarinic activity of the compounds of this study was assessed using the previously described NMS/OXO-M binding assay.[11,25] Thus, the dissociation constants at cortical muscarinic receptors were measured by displacement of [^{3}H]oxotremorine-M and [^{3}H]-*N*-methylscopolamine from the high- and low-affinity states of the receptor, respectively. The log of the NMS/OXO-M ratio, thus obtained, has been shown to be predictive of the ability of the ligand to stimulate cortical PI hydrolysis. The results are presented in Tables I–V.

The binding data for unsubstituted quinuclidinylpyrazine **12a** (Table I) reveals affinity and predicted cortical muscarinic efficacy comparable to quinuclidinylmethyloxadiazole **1a** and methylthiadiazole **1b** and 10-fold higher affinity than the analogous C3′-unsubstituted thiadiazole (NMS = 3.3 μM).[9] The electron-withdrawing effect[26] of the pyrazine ring on the base is reduced, compared to

Table I. In Vitro Binding Data for Quinuclidinylpyrazines Compared to Standard Muscarinic Ligands, 1,2,4-Oxadiazoles, and 1,2,4-Thiadiazoles



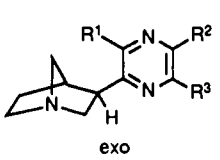
compd	R^1	R^2	R^3	binding data: K_{app}, μM[a] [^{3}H]NMS[b]	[^{3}H]OXO-M[c]	ratio[d]
arecoline	–	–	–	6.2	0.011	560
RS-86	–	–	–	5.0	0.040	130
pilocarpine	–	–	–	4.0	0.040	100
atropine	–	–	–	0.0010	0.00048	2.1
carbachol	–	–	–	22	0.0049	4500
1a	–	–	–	0.44	0.00096	460
1b	–	–	–	0.36	0.00078	460
2a	–	–	–	0.10	0.00009	1110
2b	–	–	–	3.6	0.0021	1700
3a	–	–	–	0.031	<0.000043	>1000
3b	–	–	–	1.6	0.0051	1060
12a	H	H	H	0.27	0.00068	400
12b	H	H	Me	0.066	0.0021	31
12c	Me	H	H	1.51	0.010	151
12d	H	H	OMe	0.14	0.0076	18
12e	H	Me	Me	0.078	0.0095	8
12f	Me	H	Me	0.26	0.026	10
26	H	H	Cl	0.051	0.00087	59
29	H	H	Et	0.020	0.0017	12
30	H	H	OEt	0.019	0.0021	9
31	H	H	Br	0.033	0.0010	33
32	H	H	OH	27	0.28	96

[a] Displacement of tritiated radioligand from rat cortical homogenates. Results are expressed as the geometric mean of the affinity constant (K_{app}) corrected for ligand occupancy by using the Cheng and Prusoff equation.[24] Each value is the geometric mean of three determinations performed on separate occasions. Each curve is typically four concentrations performed in triplicate. Variability in the determinations is ±10–15%. [b] Displacement of [^{3}H]-*N*-methylscopolamine. [c] Displacement of [^{3}H]oxotremorine-M. [d] The ratio of NMS/OXO-M, $K_{app,a}$.

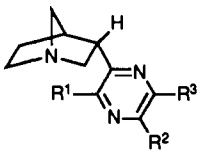
methyloxadiazole **1a** (pK_a = 8.6),[10] giving a pK_a value of 9.8 for **12a**. These compounds, however, have comparable log *P*'s (+0.6), as a result of the higher lipophilicity of pyrazine compared to C3′-H-1,2,4-oxadiazole. We have previously shown in studies on oxadiazoles that the pK_a of the ligand can be reduced, and the muscarinic activity increased, by replacing quinuclidine with 1-azanorbornane.[10] We felt that this transformation was even more justified in this series owing to the reduced electron-withdrawing effect of pyrazine on the pK_a of the base. The *exo*-1-azanorbornane **18a** (Table II) has affinity and predicted cortical muscarinic efficacy comparable to the aminooxadiazole **3a**, previously reported to be one of the most potent and efficacious, nonquaternary muscarinic agonists known.[10] The endo diastereoisomer **17a** has reduced affinity to the antagonist binding state of the receptor, compared with quinuclidine **12a**, but agonist binding is unchanged resulting in one of the highest NMS/OXO-M ratios reported to date for a nonquaternary muscarinic agonist. An accurate determination of the OXO-M binding for **18a** could not be obtained because of the high affinity of this ligand, which resulted in ligand depletion in the assay.[10] As expected, the pK_a of **18a** (9.3) is reduced compared to **12a** (9.8), resulting in higher CNS penetration[27] as measured using an ex vivo binding assay.[28] The increased conformational flexibility introduced on going

(22) Gronowitz, S.; Roe, J. The Reaction of 5-Bromo- and 2-Bromopyrimidine with Organolithium Compounds. *Acta Chem. Scand.* **1965**, *19*, 1741–1748.
(23) Kosolapoff, G. M.; Roy, C. H. Synthesis of Pyrimidylphosphonates. *J. Org. Chem.* **1961**, 1895–1897.
(24) Cheng, Y.; Prusoff, W. H. Relationship between the Inhibition Constant (K_i) and the Concentration of Inhibitor which causes 50% Inhibition (I_{50}) of an Enzymatic Reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099–3108.
(25) Freedman, S. B.; Harley, E. A.; Iversen, L. L. Relative Affinities of Drugs Acting at Cholinoceptors in Displacing Agonist and Antagonist Radioligands: The NMS/OXO-M Ratio as an Index of Efficacy at Cortical Muscarinic Receptors. *Br. J. Pharmacol.* **1988**, *93*, 437–445.
(26) Grob, C. A. Inductive Charge Dispersal in Quinuclidinium Ions: Polar Effects Part 13. *Helv. Chim. Acta* **1985**, *68*, 882–886.
(27) Freedman, S. B.; Marwood, R. S.; Patel, S. Unpublished results.
(28) Freedman, S. B.; Harley, E. A.; Patel, S. Direct Measurement of Muscarinic Agents in the Central Nervous System of Mice using *Ex Vivo* Binding. *Eur. J. Pharmacol.* **1989**, *174*, 253–260.

Table II. In Vitro Binding Data for Alkyl-Substituted Pyrazines in the 1-Azanorboranane Series



exo



endo

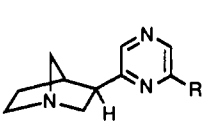
compd	R^1	R^2	R^3	stereochemistry	binding data: K_{app}, μM[a] [^{3}H]NMS[b]	[^{3}H]OXO-M[c]	ratio[d]
17a	H	H	H	endo	1.6	0.00070	2286
18a	H	H	H	exo	0.059	<0.000086	>686
17b	H	H	Me	endo	0.47	0.0015	313
18b	H	H	Me	exo	0.18	0.0014	129
17c	Me	H	H	endo	5.2	0.0016	325
18c	Me	H	H	exo	0.21[e]	0.00026[e]	800
17e	H	Me	Me	endo	0.53	0.013	41
18e	H	Me	Me	exo	0.28[e]	0.015[e]	19
17f	Me	H	Me	endo	3.0	0.13	23
18f	Me	H	Me	exo	0.19	0.011	17
17g	Me	Me	H	endo	6.2	0.66	9
18g	Me	Me	H	exo	0.75	0.017	44
17h	Me	Me	Me	endo	1.6	0.25	6
18h	Me	Me	Me	exo	0.35	0.053	7
17i	Et	H	H	endo	2.2	0.14	16
18i	Et	H	H	exo	0.69	0.020	35
18j	^{n}Pr	H	H	exo	0.35	0.015	23
18k	^{i}Pr	H	H	exo	0.48	0.022	22
27b	H	H	Et	endo	0.15[e]	0.0021[e]	71
27a	H	H	Et	exo	0.13[e]	0.0095[e]	14

[a-d] See corresponding footnotes of Table I. [e] Value derived from a single determination.

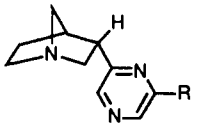
from the azanorbornane ring to isotropane results in a loss of binding to both the high- and low-affinity states of the receptor.[10] *exo*-Isotropane **20a** has comparable muscarinic activity to quinuclidine **12a**, and the endo diastereoisomer, **19a**, as in the azanorbornane series, is less active than the exo isomer. The predicted cortical efficacies of **12a** and **18a** were confirmed by measurement of their ability to stimulate phosphatidylinositol turnover in rat cortical tissue.[25] Thus, pyrazine **12a** stimulated cortical PI turnover with a maximum response of 20% (EC_{50} = 2 μM) of that seen with 1 mM carbachol (EC_{50} = 30 μM). As predicted, **18a** produced a higher maximum response (150%; EC_{50} = 0.25 μM) and like aminooxadiazole **3a** is among the most potent and efficacious, centrally active muscarinic agonists known.[27]

The 6′-methyl-substituted pyrazine **12b** has higher affinity at the NMS-labeled state of the receptor but lower affinity at the agonist binding state, compared to the unsubstituted pyrazine **12a** and, as a consequence, has reduced predicted efficacy. Methyl substitution at C3′ resulted in reduced affinity at both states of the receptor although efficacy was predicted to be higher than for 6-methylpyrazine **12b**. Although monomethyl substitution at C5′ was not possible because of the unstable nature of the precursors,[17] C5′,C6′-dimethyl-substitution was possible and gave a compound, **12e**, with affinity comparable to **12b** but with a lower NMS/OXO-M ratio. Similar activity was seen for the C3′,C6′-dimethylpyrazine **12f**. Introduction of larger substituents at C6′ e.g. ethyl, **29**, methoxy, **12d**, and ethoxy, **30**, favored low-affinity-state binding. Chloro and bromo substitution gave compounds with muscarinic activity comparable to methylpyrazine **12b** whereas the hydroxy derivative had 100-fold lower affinity than the unsubstituted pyrazine **12a**.[29]

Table III. In Vitro Binding Data for 6-Amino-, 6-Alkoxy-, and 6-Chloro-Substituted Pyrazines in the 1-Azanorbornane Series



exo



endo

compd	R	stereochemistry	binding data: K_{app}, μM[a] [^{3}H]NMS[b]	[^{3}H]OXO-M[c]	ratio[d]
17d	OMe	endo	0.46	0.0098	47
18d	OMe	exo	0.96	0.038	25
17l	OEt	endo	0.12	0.012	10
18l	OEt	exo	0.53	0.055	10
17m	O^{i}Pr	endo	0.049	0.012	4
18m	O^{i}Pr	exo	0.13	0.031	4
17o	O-allyl	endo	0.12	0.021	6
18o	O-allyl	exo	0.23	0.030	8
17n	NMe_2	endo	0.93	0.070	13
18n	NMe_2	exo	0.86	0.057	15
25b	Cl	endo	0.21	0.00056	375
28	O-propargyl	endo	0.15	0.0088	17

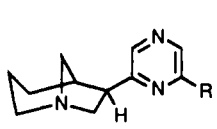
[a-d] See corresponding footnotes of Table I.

Greater bulk tolerance at C3′, C5′, and C6′ was demonstrated by the smaller azanorbornanes (Tables II and III). As seen for the unsubstituted pyrazines, **17a** and **18a**, the endo and exo isomers of the substituted derivatives showed quite different muscarinic profiles and were dependent on both of the nature of the substituent and the position of substitution. In the C5′- and C6′-substituted alkyl series (Table II), the exo isomers, e.g. **18b** and **18e**, generally have higher affinity at the antagonist state of the receptor but lower predicted efficacy than the endo isomers. Substitution at C3′ resulted in a more profound

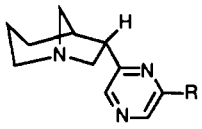
(29) The resolution of the compounds of this study and a report on the detailed pharmacological evaluation of the enantiomers shall be presented shortly.

(30) Hansch, C.; Leo, A.; Taft, R. W. A survey of Hammett Substitution Constants and Resonance and Field Parameters. *Chem. Rev.* **1991**, 165–195.

Table IV. In Vitro Binding Data for Isotropane Pyrazines



exo

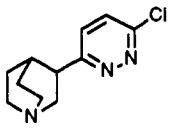


endo

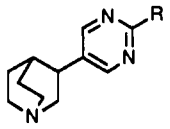
compd	R	stereochemistry	binding data: K_{app}, μM^a [^{3}H]NMS^b	[^{3}H]OXO-M^c	ratio^d
19a	H	endo	1.5^e	0.014^e	110
20a	H	exo	0.40	0.00084	476
19d	OMe	endo	0.19	0.0093	20
20d	OMe	exo	1.2	0.087	14

[a-d] See corresponding footnotes in Table I. [e] Value determined from a single determination.

Table V. In Vitro Binding Data for Quinuclidinylpyrimidines and -pyridazine



34



39, 40

compd	R	binding data: K_{app}, μM^a [^{3}H]NMS^b	[^{3}H]OXO-M^c	ratio^d
34	-	3.5	0.098	36
39	H	2.8	0.16	18
40	Me	1.5^e	0.091^e	16

[a-d] See corresponding footnotes in Table I. [e] Value determined from a single determination.

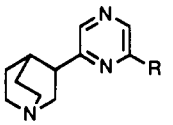
separation of activity between the diastereoisomers. Here, the exo isomers, e.g. methylpyrazines **18c** and **18g**, have both higher affinity and higher efficacy than the endo derivatives **17c** and **17g**, respectively. Increasing the size of the substituent at C6′, e.g. ethylpyrazines **27a** and **27b**, generally led to a reduction in predicted efficacy, primarily a consequence of improved displacement of NMS binding. Increasing the size of the substituent at C3′, e.g. ethyl pyrazines **17i** and **18i**, also led to a reduction in efficacy but generally was consequent on reduced displacement of OXO-M binding. In contrast to the alkyl derivatives, C6′-alkoxy substitution in both the azanorbornane and isotropane series generally lead to both higher affinity and higher efficacy for the endo diastereoisomers[29] (Tables III and IV).

The effect on muscarinic activity of changing the position of the nitrogen atoms in the diazine ring is shown in Table V. The pyrimidine **39** has 200-fold lower affinity at the agonist binding state of the receptor compared to pyrazine **12a**. Similarly, the methylpyrimidine **40** and chloropyridazine **34** have reduced activity compared with the pyrazine series.

Discussion

It was concluded from previous studies on oxadiazoles[7] that hydrogen-bond interactions, between the heterocycle ring nitrogens and the receptor, play an important role in agonist binding but contribute little to binding at the low affinity state of the receptor. In the alkyl series it was shown that the optimum substituent at C3′, for binding to both affinity states of the receptor, was methyl, with a significant loss in binding for the 3′-H analogue. It is evident from the binding data presented here, for the current series, that hydrogen represents the optimum substituent for agonist binding and efficacy. The difference in structure–activity between the oxadiazole and pyrazine series may be explained by comparison of the van der Waals volumes calculated for the oxadiazole fragment of quinuclidine **1a**[7] and the pyrazine of **12a** (Table VI). It can be proposed from this data that efficacy and high affinity binding are optimal in the pyrazine series, when the ring is unsubstituted because pyrazine occupies a larger volume of space at the receptor than methyloxadiazole and, as shown previously, antagonist binding is stabilized by hydrophobic interactions.

Table VI. Comparison of log NMS with van der Waals Volumes and Hansch Constants for 6-Substituted Pyrazines in the Quinuclidine Series and **1a**



compd	R	log NMS	V^a	π^b
1a	-	-0.36	64[7]	0.56
12a	H	-0.57	115	0.00
12b	Me	-1.18	135	0.56
29	Et	-1.70	153	1.02
12d	OMe	-0.85	141	-0.02
30	OEt	-1.72	165	0.38
26	Cl	-1.29	130	0.71

[a] van der Waals volume computed for the substituted pyrazine as a whole. [b] Approximation of the hydrophobicity for the pyrazine 6-substituent using the Hansch aromatic substituent constant.[30]

Table VII. Physical Data for Quinuclidines and Isotropanes[a]

no.	empirical formula	mp, °C
12a	$C_{11}H_{15}N_3 \cdot HCl \cdot 0.75H_2O$	203–205
12c	$C_{12}H_{17}N_3 \cdot 2HCl \cdot 1.3H_2O$	206–210
12d	$C_{12}H_{17}N_3O \cdot 2HCl \cdot 0.2H_2O$	161–163
12e	$C_{13}H_{19}N_3 \cdot 1.5(COOH)_2$	152–153
12f	$C_{13}H_{19}N_3 \cdot (COOH)_2$	235 dec
19a	$C_{11}H_{15}N_3 \cdot 2HCl \cdot 0.35H_2O$	271 dec
19d	$C_{12}H_{17}N_3O \cdot 2HCl \cdot 0.2H_2O$	168–170
20a	$C_{11}H_{15}N_3 \cdot (COOH)_2 \cdot 0.15H_2O$	157–159
20d	$C_{12}H_{17}O \cdot 1.4HCl$	193–196

[a] All compounds were crystallized from ^{i}PrOH/Et_2O and gave satisfactory microanalyses for C, H, and N.

The effect of increasing lipophicity at C6′ on binding to the NMS-labeled site is shown in Table VI by comparing antagonist binding with the hydrophobicity of the substituent. Affinity at the antagonist binding state increases and efficacy decreases with increasing bulk and hydrophobicity at C6′, suggesting that the substituent sits in a lipophilic binding pocket normally occupied by the methyl group of acetylcholine. In contrast, substitution at the 3-position results in decreased affinity at both the NMS and OXO-M labeled sites as a result of steric interaction between the substituent and $H_{8\beta}$. This result adds further credibility to the recently proposed argument that the preferred binding conformation of the pharmacophore lies close to this energy maximum.[9] The steric effect is more pronounced in the azanorbornane series in which the endo isomers **17a**, **17c**, and **17f** show between 15- and 25-fold lower affinity at the NMS binding site compared with the exo isomers, partially as a result of severe steric embarrassment between the C3′-substituent and $H_{5\alpha}$ in the endo isomers. The difference in binding between the exo and endo diastereoisomers is reduced when the 6-position is substituted, e.g. methylpyrazines **17b** and **18b**, and ethylpyrazines **27b** and **27a**, as a consequence of increased affinity at the NMS-labeled site of the endo isomers and decreased affinity of the exo isomers, relative to the unsubstituted analogues.

Table VIII. Physical Data for 1-Azanorbornanes[a]

no.	empirical formula	mp, °C	no.	empirical formula	mp, °C
17a	$C_{10}H_{13}N_3 \cdot 2HCl \cdot 0.3H_2O$	183–186	**18a**	$C_{10}H_{13}N_3 \cdot 1.5HCl$	172–175
17b	$C_{11}H_{15}N_3 \cdot 2.1HCl$	200–202	**18b**	$C_{11}H_{15}N_3 \cdot 1.5(COOH)_2$	144–147
17c	$C_{11}H_{15}N_3 \cdot 2HCl \cdot H_2O$	166–168	**18c**	$C_{11}H_{15}N_3 \cdot 1.4HCl$	214–216
17d	$C_{11}H_{15}N_3O \cdot 2.0HCl$	154–155	**18d**	$C_{11}H_{15}N_3O \cdot 1.5HCl$	205–207
17f	$C_{12}H_{17}N_3 \cdot (COOH)_2$	199–200	**18f**	$C_{12}H_{17}N_3 \cdot (COOH)_2 \cdot 0.1H_2O$	183–185
17g	$C_{12}H_{17}N_3 \cdot 2HCl \cdot H_2O$	217–220	**18g**	$C_{12}H_{17}N_3 \cdot 2.1HCl \cdot 0.7H_2O$	205 dec
17h	$C_{13}H_{19}N_3 \cdot HCl$	222 dec	**18h**	$C_{13}H_{19}N_3 \cdot 2HCl \cdot 0.6H_2O$	180 dec
17i	$C_{12}H_{17}N_3 \cdot 2(COOH)_2$	105–107	**18i**	$C_{12}H_{17}N_3 \cdot 2.1HCl$	192–195
17j	$C_{13}H_{19}N_3 \cdot 0.9HCl \cdot 0.5H_2O$	159–162	**18j**	$C_{13}H_{19}N_3 \cdot 1.1HCl \cdot 0.9H_2O$	179–182
17k	$C_{13}H_{19}N_3 \cdot HCl \cdot 1.1H_2O$	gum	**18k**	$C_{13}H_{19}N_3 \cdot HCl \cdot 0.5H_2O$	224–225
17l	$C_{12}H_{17}N_3O \cdot 1.5(COOH)_2$	136–137	**18l**	$C_{12}H_{17}N_3O \cdot HCl$	252–253
17m	$C_{13}H_{19}N_3O \cdot 1.5HCl$	132–135	**18m**	$C_{13}H_{19}N_3O \cdot 1.2HCl$	208–209
17n	$C_{12}H_{18}N_4 \cdot 2.5HCl$	215–217	**18n**	$C_{12}H_{18}N_4 \cdot 2.4HCl$	217–220

[a] All compounds were crystallized from either ^{i}PrOH or ^{i}PrOH/EtOAc or ^{i}PrOH/Et_2O and gave satisfactory microanalyses for C, H, and N except **17h**: HRMS m/z 217.1585; $C_{13}H_{19}N_3$ (free base) requires m/z 217.15790.

The data presented for the short series of pyrimidines and pyridazines suggests that the electronic distribution represented by pyrazine is optimal for high-affinity binding and agonist activity in the 6-ring heteroaromatic series. This provides further evidence that the pharmacophore requires two hydrogen bond acceptor sites in an exact location.

It can be concluded from this study that pyrazine is a suitable bioisostere for the ester group of the endogenous ligand, acetylcholine. Unlike the endogenous ligand and the oxadiazole series, hydrogen is the preferred size of substituent for binding to the agonist state of the receptor and some of the most potent and efficacious, CNS active muscarinic agonists, have been identified. Substitution at the 3-position of the heterocycle in the azanorbornane series has provided evidence of the preferred conformation for optimal binding to the muscarinic receptor. Studies at the 6-position have resulted in the identification of high affinity ligands but with reduced cortical efficacy. More detailed in vitro and in vivo evaluation of these compounds including the pharmacological selectivity of the enantiomers shall be presented in due course.

Experimental Section

Chemical Methods: General Directions. Except where otherwise stated, the following procedures were adopted: all ^{1}H NMR spectra were recorded at 360 MHz on a Bruker AM360 instrument, mass spectra with a VG 70-250 mass spectrometer, and infrared spectra on a Perkin-Elmer 782IR spectrometer. Organic solvents were purified when necessary by the methods described by D. D. Perrin, W. L. F. Armarego, and D. R. Perrin (*Purification of Laboratory Chemicals*; Pergamon: Oxford, 1966). Petroleum ether (PE) refers to that fraction having a boiling point range of 60–80 °C. All solutions were dried over sodium sulfate and evaporated on a Büchi rotary evaporator at reduced pressure. Preparative chromatography was carried out using gravity columns for both silica (Merck Art-7734) and alumina (Woelm Grade III neutral). pK_a's were determined using a Radiometer Autotitration system (PHMS4 Research pH meter ABU80 Autoburette and Hewlett Packard 858), and log P's by the shake flask method (octanol/water). Melting points were determined with a Büchi capillary melting point apparatus and are uncorrected.

2-Iodopyrazines (8a–c,e–k). 2-Iodopyrazine, **8a**, and the alkylpyrazines **8b–c** and **8e–k** were prepared by literature procedures.[17,18]

2-Iodo-6-alkoxypyrazines (8d, 8l–m, and 8o). 2-Iodo-6-methoxypyrazine (8d). 2,6-Dichloropyrazine (20 g, 0.134 mol) was added to a saturated solution of NaI in butan-2-one (800 mL), water (12 mL), and 15-crown-5 (0.5 g). A mixture of HI (18 mL) and H_2O (24 mL) was added, and the solution was refluxed for 4 days. The solvent was removed under vacuum, the residue was taken up into water (75 mL), sodium metabisulfite (0.4 g) was added, and the solution was basified with NaOH. The aqueous layer was extracted (3×) with CH_2Cl_2, and the residue remaining, after removal of solvent, was distilled under vacuum to give 2,6-diiodopyrazine (15 g, 34%), bp 120 °C (1 mmHg); ^{1}H NMR ($CDCl_3$) δ 8.70 (2 H, s, 3-CH and 5-CH).

2,6-Diiodopyrazine (6.06 g, 18.2 mmol) was added to a solution of Na (0.42 g, 18.2 mmol) in MeOH (45 mL) and heated under reflux for 3.5 h. The solvent was removed under vacuum, H_2O (150 mL) was added, and the mixture was extracted with Et_2O (3×). The crude product was chromatographed on silica in Et_2O/petroleum ether (1:1) to give 2-iodo-6-methoxypyrazine (4.2 g, 98%): ^{1}H NMR ($CDCl_3$) δ 3.95 (3 H, s, OMe), 8.18 (1 H, s, 5-CH), 8.45 (1 H, s, 3-CH).

Using the general procedure described for **8d**, the following 2-iodo-6-alkoxypyrazines were prepared from the respective alcohols.

8l: mp 36–37 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (3 H, t, J = 7.0 Hz, Me), 4.35 (2 H, q, J = 7.0 Hz, CH_2), 8.07 (1 H, s, 5-CH), 8.35 (1 H, s, 3-CH).

8m: ^{1}H NMR ($CDCl_3$) δ 1.32 (6 H, d, J = 7.0 Hz, 2 Me), 5.23 (1 H, m, CH), 8.00 (1 H, s, 5-CH), 8.30 (1 H, s, 3-CH).

8o: ^{1}H NMR ($CDCl_3$) δ 4.83–4.86 (2 H, m, CH_2O), 5.29–5.35 (1 H, m, *cis*-vinyl-CH), 5.39–5.48 (1 H, m, *trans*-vinyl-CH), 5.98–6.13 (1 H, m, vinyl-CH), 8.16 (1 H, s, 5-CH), 8.40 (1 H, s, 3-CH).

2-Iodo-6-(dimethylamino)pyrazine (8n). A solution of 2,6-diiodopyrazine (6 g, 18.1 mmol) in MeOH (50 mL) and dimethylamine (40% aqueous solution, 200 mL) was heated at reflux for 1 h. The MeOH was removed under vacuum, and the aqueous layer was saturated with K_2CO_3 and extracted (3×) with CH_2Cl_2. The crude product was chromatographed on silica in CH_2Cl_2 to give the title pyrazine (4 g, 89%): mp 46–48 °C; MS m/z 249 (M^+); ^{1}H NMR ($CDCl_3$) δ 3.10 (6 H, s, 2 Me), 7.87 (1 H, s, 5-CH), 8.01 (1 H, s, 3-CH).

General Procedure for the Preparation of (3-Hydroxyquinuclidinyl)pyrazines (9a–f). 3-Hydroxy-3-(6-methylpyrazin-2-yl)quinuclidine (9b). *tert*-Butyllithium (11.4 mL of a 1.4 M solution in hexane, 16 mmol) was added dropwise to a rapidly stirred solution of 2-iodo-6-methylpyrazine (1.78 g, 8.0 mmol) in dry Et_2O (50 mL) at −35 °C. After 0.25 h a solution of quinuclidin-3-one (1.0 g, 8.0 mmol) in dry Et_2O (20 mL) was added dropwise, and the mixture was warmed to 25 °C and stirred for 2.5 h. Water (15 mL) was added, and the mixture was extracted with CH_2Cl_2 (4×). The CH_2Cl_2 extract was dried and evaporated, and the residue was purified by column chromatography on alumina eluting with MeOH/CH_2Cl_2 (1:10). The product thus obtained was recrystallized to give **9b** (0.45 g, 26%): mp 182–184 °C (EtOAc/Et_2O); MS m/z 219 (M^+); ^{1}H NMR ($CDCl_3$) δ 1.34–1.55 (3 H, m, one of 5-CH_2 and 8-CH_2), 1.86–1.90 (1 H, m, 4-CH), 2.27–2.34 (1 H, m, one of 5-CH_2), 2.57 (3 H, s, CH_3), 2.81–3.09 (5 H, m, one of 2-CH_2, 6-CH_2, and 7-CH_2), 3.71 (1 H, dd, J = 2.1 and 14.6 Hz, one of 2-CH_2), 8.37 and 8.65 (each 1 H, each s, 3′-CH and 5′-CH). Anal. ($C_{12}H_{17}N_3O \cdot 0.25H_2O$) C, H; N: calcd, 18.77; found, 18.13.

General Procedure for the Preparation of Quinuclidinylpyrazines (12a–f). 3-(6-Methylpyrazin-2-yl)quinuclidine Sesquioxalate (12b). $SOCl_2$ (1.2 g, 10.1 mmol) was added dropwise to a rapidly stirred solution of **9b** (1.0 g, 4.6 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The mixture was warmed to 25 °C and stirred for 2 h. Water (30 mL) was added, and the aqueous layer was basified with K_2CO_3 and extracted with CH_2Cl_2 (3×). The crude product remaining after drying and removal of solvent was

chromatographed on alumina, eluting with EtOAc, to give two separated components. The less polar component was identified as 3-chloro-3-(6-methylpyrazin-2-yl)quinuclidine **10b** (0.34 g, 31%). The oil was treated with ethereal HCl and the precipitated salt was recrystallized from ^{i}PrOH/Et_2O: mp 180 °C dec; MS m/z 237 (M^+ of free base); ^{1}H NMR (D_2O) δ 1.52–1.62, 2.04–2.10, and 2.10–2.24 (each 1 H, each m, 8-CH_2, and one of 5-CH_2), 2.62 (3 H, s, CH_3), 2.68–2.80, 3.12–3.15, 3.18–3.38, and 3.46–3.88 (1 H, 1 H, 2 H, and 2 H, respectively, each m, 4-CH, one of 5-CH_2, 6-CH_2, and 7-CH_2), 3.97 (1 H, dd, J = 2.4 and 14.6 Hz, one of 2-CH_2), 5.00 (1 H, dd, J = 2.4 and 14.6 Hz, one of 2-CH_2), 8.50 and 8.83 (each 1 H, each s, 3′-CH and 5′-CH). Anal. ($C_{12}H_{16}N_3Cl$·HCl) C, H, N.

The more polar component was identified as the elimination product **11b** (0.31 g, 34%). The oil was treated with a solution of oxalic acid in Et_2O, and the salt was recrystallized from ^{i}PrOH/Et_2O: mp 185 °C dec; MS m/z 201 (M^+ of free base); ^{1}H NMR (D_2O) δ 1.87–1.93 and 2.16–2.25 (each 2 H, each m, 5-CH_2 and 8-CH_2), 2.60 (3 H, s, CH_3), 3.21–3.28, 3.65–3.75, and 3.99–4.03 (2 H, 2 H, and 1 H, each m, 4-CH, 6-CH_2, and 7-CH_2), 7.36 (1 H, d, J = 1.4 Hz, 2-CH), 8.51 and 8.67 (each 1 H, each s, 3′-CH and 5′-CH). Anal. ($C_{12}H_{15}N_3$·$(COOH)_2$·0.2H_2O) C, H, N.

A solution of either **10b** (0.35 g, 1.5 mmol) or **11b** (0.35 g, 1.7 mmol) in EtOH (25 mL) was hydrogenated over 10% Pd/C (0.3 g) in a Parr shake apparatus at 50 psi for 1.5 h. The crude product remaining after filtration and evaporation of the solvent was purified by chromatography on alumina, eluting with MeOH/CH_2Cl_2 (7:93). The oil (0.30 g) thus obtained was treated with a solution of oxalic acid in Et_2O to give **12b**: mp 136–139 °C (^{i}PrOH/Et_2O); MS m/z 203 (M^+ of free base); ^{1}H NMR (D_2O) δ 1.77–1.84, 2.08–2.23, and 2.42–2.45 (2 H, 2 H, and 1 H, respectively, each m, 4-CH, 5-CH_2, and 8-CH_2), 2.61 (3 H, s, CH_3), 3.28–3.36, 3.41–3.55, and 3.63–3.77 (1 H, 3 H, and 2 H, respectively, each m, one of 2-CH_2, 3-CH, 6-CH_2, and 7-CH_2), 4.04 (1 H, dd, J = 5.8 and 12.2 Hz, one of 2-CH_2), 8.42 and 8.46 (each 1 H, each s, 3′-CH and 5′-CH). Anal. ($C_{12}H_{17}N_3$·1.5$(COOH)_2$) C, H, N.

General Procedure for the Preparation of (3-Hydroxyazanorbornyl)pyrazines (13a–o) and (3-Hydroxyisotropanyl)pyrazines (14a and 14d). **(a) *exo*-3-(3,6-Dimethyl-1,4-diazin-2-yl)-3-hydroxy-1-azabicyclo[2.2.1]heptane (13f).** *tert*-Butyllithium (23.3 mL of a 1.7 M solution in pentane, 39.6 mmol) was added dropwise to a rapidly stirred solution of 2-iodo-3,6-dimethylpyrazine (4.64 g, 19.8 mmol) in dry Et_2O (100 mL) at −50 °C. The mixture was stirred for 0.25 h, at −50 °C, and a solution of 1-azabicyclo[2.2.1]heptan-3-one (2.2 g, 19.8 mmol) in dry Et_2O (20 mL) was then added. Stirring at room temperature for 2 h was followed by addition of H_2O (40 mL) and extraction with CH_2Cl_2 (4×). The combined extracts were dried and evaporated, and the residue was chromatographed on alumina, eluting with MeOH/CH_2Cl_2 (1:24) to give **13f** (1.86 g, 46%): mp 184–186 °C (EtOAc); MS m/z 219 (M^+); ^{1}H NMR ($CDCl_3$) δ 1.50–1.59 (1 H, m, one of 5-CH_2), 2.04 (1 H, br s, OH), 2.14–2.24 (1 H, m, one of 5-CH_2), 3.36 (1 H, dd, J = 3.5 and 9.7 Hz, one of 7-CH_2), 2.43 (3 H, s, CH_3), 2.49 (1 H, d, J = 9.7 Hz, one of 7-CH_2), 2.58 (3 H, s, CH_3), 2.59 (1 H, dd, J = 3.7 and 12.6 Hz, one of 2-CH_2), 2.65–2.71 and 2.80–2.89 (each 1 H, each m, 6-CH_2), 3.27 (1 H, dd, J = 1.9 and 12.6 Hz, one of 2-CH_2), 3.42 (1 H, d, J = 3.5 Hz, 4-CH), 8.17 (1 H, s, 5′-CH). Anal. ($C_{12}H_{17}N_3O$) C, H, N.

(b) *exo*-6-(1,4-Diazin-2-yl)-6-hydroxy-1-azabicyclo[3.2.1]octane (14a). *tert*-Butyllithium (15.5 mL of a 1.7 M solution in pentane, 26.3 mmol) was added dropwise to a rapidly stirred solution of 2-iodopyrazine (2.96 g, 14.3 mmol) in dry Et_2O (70 mL) at −50 °C. The brown suspension was stirred at −50 °C for 0.25 h, and a solution of 1-azabicyclo[3.2.1]octan-6-one (1.5 g, 11.0 mmol), in dry Et_2O (30 mL), was then added dropwise. The reaction mixture was warmed to room temperature and stirred for 7 h before adding H_2O (10 mL) and extracting with EtOAc (3×). The crude product was chromatographed through alumina, eluting with MeOH/CH_2Cl_2 (1:10) to give **14a** (0.48 g, 20%): mp 208–210 °C (EtOH); MS m/z 205 (M^+); ^{1}H NMR (D_2O) δ 1.57–2.34 (4 H, m, 3-CH_2 and 4-CH_2), 2.50–2.54 and 2.90–3.21 (1 H and 5 H, respectively, each m, 2-CH_2, 5-CH, one of 7-CH_2, and 8-CH_2), 3.72 (1 H, d, J = 14.0 Hz, one of 7-CH_2), 8.52 (1 H, d, J = 2.0 Hz, 6′-CH), 8.56 (1 H, dd, J = 1.2 and 2.0 Hz, 5′-CH), 8.91 (1 H, d, J = 1.2 Hz, 3′-CH). Anal. ($C_{11}H_{15}N_3O$) C, H, N.

General Procedure for the Preparation of Azanorbornylpyrazines (17a–n and 18a–n) and Isotropanylpyrazines (19a,d and 20a,d). **(a) *endo*-3-(5,6-Dimethyl-1,4-diazin-2-yl)-1-azabicyclo[2.2.1]heptane Hydrogen Oxalate (17e).** $SOCl_2$ (2.0 g, 9.1 mmol) was added dropwise to a rapidly stirred solution of **13e** (2.0 g, 9.1 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The reaction mixture was warmed to 35 °C and stirred for 1 h. Water (20 mL) was added, and the aqueous layer was basified with K_2CO_3 and extracted with CH_2Cl_2 (3×). The crude product was chromatographed on alumina, eluting with EtOAc to give *endo*-3-(5,6-dimethyl-1,4-diazin-2-yl)-3-chloro-1-azabicyclo-[2.2.1]heptane, **15e** (0.52 g, 24%): mp 88–89 °C; ^{1}H NMR ($CDCl_3$) δ 0.91–0.98 and 1.55–1.64 (each 1 H, each m, 5-CH_2), 2.36–2.46 (1 H, m, one of 6-CH_2), 2.53 and 2.54 (each 3 H, each s, two of CH_3), 2.66 (1 H, dd, J = 2.8 and 10.0 Hz, one of 7-CH_2), 2.74–2.83 (1 H, m, one of 6-CH_2), 3.21 (1 H, d, J = 4.5 Hz, 4-CH), 3.40 (1 H, d, J = 10.0 Hz, one of 7-CH_2), 3.45 and 4.09 (each 1 H, each dd, J = 2.1 and 13.8 Hz, and 2.8 and 13.8 Hz respectively, 2-CH_2), 8.56 (1 H, s, 3′-CH); MS m/z 237 (M^+); HRMS calcd for $C_{11}H_{16}N_3Cl$ 237.1033, found 237.1039.

A solution of **15e** (0.52 g, 2.2 mmol) in EtOH (50 mL) was hydrogenated over 10% Pd/C (0.3 g) in a Parr shake apparatus at 50 psi, for 1.5 h. The catalyst was removed by filtration through hyflo, and the crude product remaining after evaporation of solvent was chromatographed through alumina, eluting with MeOH/CH_2Cl_2 (0.5:95.5). The product (0.34 g, 76%) was treated with a solution of oxalic acid in ether to give **17e**: mp 165–168 °C (^{i}PrOH); MS m/z 203 (M^+ of free base); ^{1}H NMR (D_2O) δ 1.56–1.66 and 1.88–2.00 (each 1 H, each m, 5-CH_2), 2.54 and 2.57 (each 3 H, each s, two of CH_3), 3.33–3.50 (4 H, m, 4-CH, 6-CH_2, and one of 7-CH_2), 3.55 (1 H, d, J = 9.2 Hz, one of 7-CH_2), 3.79–3.86 (2 H, m, 2-CH_2), 3.98–4.06 (1 H, m, 3-CH), 8.28 (1 H, s, 3′-CH). Anal. ($C_{12}H_{17}N_3$·1.1$(COOH)_2$·0.1H_2O) C, H, N.

Although small quanties (5–10%) of the *exo*-pyrazines **18a–n**, **20a**, and **20d** could be obtained as a less polar component from hydrogenation of chlorides **15a–n**, **16a**, and **16d**, respectively, epimerization of the endo isomers, using NaOMe for **17a–k**, **17n**, **19a**, and **19d** and NaOEt for **17l**, provided larger quantities of the exo isomers.

(b) *exo*-3-(5,6-Dimethyl-1,4-diazin-2-yl)-1-azabicyclo-[2.2.1]heptane Hydrogen Oxalate (18e). NaOMe (0.8 g, 14.8 mmol) was added to a solution of **17e** (0.6 g, 3.0 mmol) and heated at 120 °C for 24 h. The solvent was removed under vacuum, and the crude product was chromatographed through alumina, eluting with MeOH/CH_2Cl_2 (1:99). The less polar product (0.25 g, 42%) was treated with a solution of oxalic acid in ether to give **18e**: mp 143–144 °C (^{i}PrOH/Et_2O); MS m/z 203 (M^+ of free base); ^{1}H NMR (D_2O) δ 1.94–2.04 and 2.16–2.28 (each 1 H, each m, 5-CH_2), 2.51 and 2.54 (each 3 H, each s, 2 of CH_3), 3.16 (1 H, d, J = 4.5 Hz, 4-CH), 3.17 (1 H, d, J = 8.3 Hz, one of 7-CH_2), 3.32–3.40 (1 H, m, one of 6-CH_2), 3.46–3.68 (4 H, m, 2-CH_2, one of 6-CH_2, and one of 7-CH_2), 3.87–3.92 (1 H, m, 3-CH), 8.27 (1 H, s, 3′-CH). Anal. ($C_{12}H_{17}N_3$·$(COOH)_2$·0.1H_2O) C, H, N.

***endo*-3-(6-(Allyloxy)-1,4-diazin-2-yl)-1-azabicyclo[2.2.1]-heptane Dihydrochloride (17o).** $^{n}Bu_3SnH$ (0.4 mL, 1.4 mmol) and a catalytic amount of α,α-azoisobutyronitrile (AIBN) were added to a stirred solution of *endo*-3-(6-(allyloxy)-1,4-diazin-2-yl)-3-chloro-1-azabicyclo[2.2.1]heptane, **15o** (0.26 g, 0.98 mmol), in dry THF (10 mL). The mixture was refluxed for 1.5 h and cooled to room temperature, and a further portion of $^{n}Bu_3SnH$ (0.4 mL, 1.4 mmol) and AIBN (catalytic) were added. Refluxing for 2 h was followed by cooling to room temperature and adding CH_2Cl_2 (50 mL) and 2 N HCl (10 mL). The mixture was stirred for 0.1 h before separating the aqueous phase and washing with CH_2Cl_2 (20 mL). The combined CH_2Cl_2 was extracted with 2 N HCl (2×), and the combined aqueous layer was basified with K_2CO_3 and extracted with CH_2Cl_2 (5×). The crude product was chromatographed through alumina, eluting with MeOH/CH_2Cl_2 (1:49), and the product (0.22 g, 97%) was treated with ethereal HCl to give **17o**: mp 147–149 °C (^{i}PrOH/Et_2O); MS m/z 231 (M^+ of free base); ^{1}H NMR (D_2O) δ 1.68–1.78 and 1.85–1.97 (each 1 H, each m, 5-CH_2), 3.28–3.56 (5 H, m, 4-CH, 6-CH_2 and 7-CH_2), 3.70–3.77 and 3.82–3.87 (each 1 H, each m, 2-CH_2), 4.00–4.07 (1 H, m, 3-CH), 4.97–5.02 (2 H, m, CH_2O), 5.30–5.43 (2 H, m, vinyl-CH_2), 6.07–6.18 (1 H, m, vinyl-CH), 8.17 (2 H, s, 3′-CH and 5′-CH). Anal. ($C_{13}H_{17}N_3O$·2HCl·0.1H_2O) C, H, N.

***exo*-3-(6-(Allyloxy)-1,4-diazin-2-yl)-1-azabicyclo[2.2.1]heptane Hydrochloride (18o).** A solution of 17o (0.15 g, 0.64 mmol) in allyl alcohol (1 mL) was added to a stirred solution of Na (50 mg, 2.2 mmol) in allyl alcohol (3 mL), and the mixture was refluxed for 2 h. The solvent was removed by distillation under vacuum, and the residue was purified by chromatography on alumina, eluting with $MeOH/CH_2Cl_2$ (0.5:99.5). The resultant oil (0.1 g, 67%) was treated with ethereal HCl to give 18o: mp 186–189 °C ($^iPrOH/Et_2O$); MS m/z 231 (M^+ of free base); ^1H NMR (D_2O) δ 1.96–2.04 and 2.16–2.26 (each 1 H, each m, 5-CH_2), 3.10 (1 H, d, J = 4.0 Hz, 4-CH), 3.19 (1 H, d, J = 9.2 Hz, one of 7-CH_2), 3.33–3.34, 3.50–3.60, and 3.61–3.68 (1 H, 2 H, and 1 H, respectively, each m, 2-CH_2 and 6-CH_2), 3.80 (1 H, d, J = 9.2 Hz, one of 7-CH_2), 3.87–3.94 (1 H, m, 3-CH), 4.94–4.97 (2 H, m, CH_2O), 5.32–5.45 (2 H, m, vinyl-CH_2), 6.09–6.17 (1 H, m, vinyl-CH), 8.14 and 8.15 (each 1 H, each s, 3′-CH and 5′-CH). Anal. ($C_{13}H_{17}N_3O\cdot HCl\cdot 0.2H_2O$) C, H, N.

***endo*-3-(1,4-Diazin-2-yl)-3-fluoro-1-azabicyclo[2.2.1]heptane Hydrochloride (43).** (Diethylamino)sulfur trifluoride (DAST, 0.42 g, 2.62 mmol) was added to a stirred solution of *exo*-3-(1,4-diazin-2-yl)-3-hydroxy-1-azabicyclo[2.2.1]heptane, **13a** (0.5 g, 2.62 mmol), in CH_2Cl_2 (30 mL) at −65 °C. After 24 h, H_2O (20 mL) was added, and the aqueous layer was basified with K_2CO_3 and extracted with CH_2Cl_2 (3×). Chromatography of the crude product on silica gel, eluting with $MeOH/CH_2Cl_2$ (1:9) followed by addition of ethereal HCl to the product (75 mg, 18%), gave **43**: mp 245 °C dec (^iPrOH); MS m/z 193 (M^+ of free base); ^1H NMR ($CDCl_3$) δ 1.06–1.13 and 1.44–1.55 (each 1 H, each m, 5-CH_2), 2.58 (1 H, dd, J = 3.1 and 9.7 Hz, one of 7-CH_2), 2.65–2.72, 2.83–2.91, and 3.09–3.24 (1 H, 2 H, and 2 H respectively, each m, one of 2-CH_2, 4-CH, 6-CH_2, and one of 7-CH_2), 3.59 (1 H, ddd, J = 3.1, 13.6, and 20.8 Hz, one of 2-CH_2), 8.50–8.53 (2 H, m, 5′-CH and 6′-CH), 8.91 (1 H, d, J = 1.2 Hz, 3′-CH). Anal. ($C_{10}H_{12}N_3F\cdot HCl$) C, H, N.

***exo*-3-(6-Chloro-1,4-diazin-2-yl)-3-carbomethoxy-1-azabicyclo[2.2.1]heptane (23).** A solution of LDA was prepared by addition of ^{n}BuLi (14.5 mL of a 1.6 M solution in hexane, 23.2 mmol) to a solution of diisopropylamine (2.35 g, 23.5 mmol) in dry THF (20 mL) at −50 °C. The solution was stirred for 0.5 h and then added, at −78 °C, to a solution of *exo*-3-carbomethoxy-1-azabicyclo[2.2.1]heptane (**21**; 3.0 g, 19.4 mmol) in dry THF (50 mL) at −78 °C. After 1.5 h a solution of 2,6-dichloropyrazine (3.5 g, 23.5 mmol) in dry THF (10 mL) was added, and the mixture was warmed to room temperature and stirred for 16 h. Water (40 mL) and CH_2Cl_2 (150 mL) were added, the resultant mixture stirred for 0.1 h before separating the aqueous phase and extracting with CH_2Cl_2 (3×). The combined CH_2Cl_2 extracts were dried and evaporated, and the residue was chromatographed on silica gel, eluting with $MeOH/CH_2Cl_2$ (8:92) to give **23** (1.8 g, 35%): ^1H NMR ($CDCl_3$) δ 1.28–1.37 and 1.69–1.78 (each 1 H, each m, 5-CH_2), 2.53 (1 H, dd, J = 2.7 and 10.0 Hz, one of 7-CH_2), 2.58 (1 H, d, J = 10.0 Hz, one of 7-CH_2), 2.65–2.72 and 2.89–2.97 (each 1 H, each m, 6-CH_2), 3.19 (1 H, dd, J = 2.2 and 12.8 Hz, one of 2-CH_2), 3.50 (1 H, d, J = 4.2 Hz, 4-CH), 3.67 (3 H, s, OCH_3), 3.70 (1 H, dd, J = 2.7 and 12.8 Hz, one of 2-CH_2), 8.47 and 8.49 (each 1 H, each s, 3′-CH and 5′-CH); MS m/z 267 (M^+); HRMS calcd for $C_{12}H_{14}N_3O_2Cl$ 267.07745, found 267.0763.

***endo*-3-(6-Chloro-1,4-diazin-2-yl)-1-azabicyclo[2.2.1]heptane Hydrogen Oxalate (25b).** A solution of **23** (1.8 g, 6.7 mmol) in concentrated HCl (30 mL) was refluxed for 4 h. The solution was cooled to 10 °C, CH_2Cl_2 (100 mL) was added, and the aqueous layer was basified by addition of K_2CO_3. The crude product obtained, by extracting with CH_2Cl_2 (5×), was chromatographed on alumina, eluting with $MeOH/CH_2Cl_2$ (1:49) to give the title *endo*-pyrazine (0.6 g, 43%). The hydrogen oxalate salt was prepared: mp 159–161 °C (^iPrOH); M^+ m/z 209 (M^+ of free base); ^1H NMR (free base, $CDCl_3$) δ 1.18–1.25 and 1.38–1.47 (each 1 H, each m, 5-CH_2), 2.59–2.62, 2.62–2.79, 2.85–3.10, and 3.16–3.23 (1 H, 2 H, 3 H, and 1 H, respectively, each m, 2-CH_2, 4-CH, 6-CH_2, and 7-CH_2), 3.44–3.49 (1 H, m, 3-CH), 8.38 and 8.42 (each 1 H, each s, 3′-CH and 5′-CH). Anal. ($C_{10}H_{12}N_3Cl\cdot(COOH)_2$) C, H, N.

3-(6-Chloropyrazin-2-yl)-3-carbomethoxyquinuclidine (24). A solution of LDA was prepared by addition of ^{n}BuLi (6.66 mL of a 1.6 M solution in hexane, 10.7 mmol) to a stirred solution of diisopropylamine (1.08 g, 10.7 mmol) in dry THF (30 mL) at −35 °C. The solution was stirred for 0.5 h and then added dropwise to a solution of 3-carbomethoxyquinuclidine (1.5 g, 8.88 mmol) in THF (50 mL) at −78 °C. After 2 h a solution of 2,6-dichloropyrazine (1.6 g, 10.7 mmol) in THF (15 mL) was added, and the mixture was stirred for 1 h at −78 °C and then at 0 °C for 4 h. Water (30 mL) and CH_2Cl_2 (100 mL) were added, the mixture was stirred for 0.1 h, and the aqueous phase was separated and extracted with CH_2Cl_2 (3×). The crude product obtained was chromatographed on silica gel, eluting with $MeOH/CH_2Cl_2$ (8:92) to give **24** (1.51 g, 61%); ^1H NMR ($CDCl_3$) δ 1.41–1.55 and 1.64–1.72 (each 2 H, each m, 5-CH_2 and 8-CH_2), 2.66–2.95 (5 H, m, 4-CH, 6-CH_2, and 7-CH_2), 3.64 (1 H, dd, J = 2.2 and 14.4 Hz, one of 2-CH_2), 3.67 (3 H, s, OCH_3), 3.98 (1 H, dd, J = 2.2 and 14.4 Hz, one of 2-CH_2), 8.47 and 8.57 (each 1 H, each s, 3′-CH and 5′-CH); MS m/z 281 (M^+); HRMS calcd for $C_{13}H_{16}N_3O_2Cl$ 281.09310, found 281.0920.

3-(6-Chloropyrazin-2-yl)quinuclidine Hydrochloride (26). A solution of **24** (101 g, 0.36 mol) in concentrated HCl (600 mL) was heated at 130 °C for 3 h. The solvent was concentrated to half volume, basified with Na_2CO_3, and extracted with CH_2Cl_2 (5×). The crude product was chromatographed on alumina, eluting with $MeOH/CH_2Cl_2$ (1:49) to give the title pyrazine (27.5 g, 34%). The hydrochloride salt was prepared by addition of ethereal HCl to a solution of the product in ether (300 mL): mp 149–151 °C ($^iPrOH/Et_2O$); MS m/z 223 (M^+ of free base); ^1H NMR (D_2O) δ 1.73–1.90 and 2.08–2.28 (each 2 H, each m, 5-CH_2 and 8-CH_2), 2.44–2.47, 3.29–3.38, and 3.42–3.56 (1 H, 1 H, and 3 H, respectively, each m, 4-CH, 6-CH_2, and 7-CH_2), 3.66 (1 H, ddd, J = 2.6, 10.4, and 12.7 Hz, one of 2-CH_2), 3.77–3.82 (1 H, m, 3-CH), 4.01 (1 H, dd, J = 6.3 and 12.7 Hz, one of 2-CH_2), 8.58 and 8.59 (each 1 H, each s, 3′-CH and 5′-CH). Anal. ($C_{11}H_{14}N_3Cl\cdot 1.4HCl$) C, H, N.

***exo*- and *endo*-3-(6-Ethyl-1,4-diazin-2-yl)-1-azabicyclo-[2.2.1]heptane Sesquioxalates (27a) and (27b).** To a solution of **25b** (0.5 g, 2.4 mmol) in dry DMF (10 mL) were added $Pd[P(Ph)_3]_4$ (0.14 g, 0.12 mmol), $SnEt_4$ (0.56 g, 2.4 mmol), and K_2CO_3 (0.5 g), and the mixture was refluxed for 5 h. The solvent was removed by distillation under vacuum, H_2O (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (5×). The crude product was chromatographed on alumina, eluting with $MeOH/CH_2Cl_2$ (0.5:99.5) to give two separated components. The less polar, minor component (35 mg, 7%) was identified as the exo isomer **27a**. The sesquioxalate salt was prepared: mp 82–84 °C ($^iPrOH/Et_2O$); MS m/z 203 (M^+ of free base); ^1H NMR (D_2O) δ 1.28 (3 H, t, J = 7.6 Hz, CH_3), 1.96–2.06 and 2.18–2.27 (each 1 H, each m, 5-CH_2), 2.86 (2 H, q, J = 7.6 Hz, CH_2CH_3), 2.83–2.90, 3.34–3.42, 3.47–3.70, and 3.94–4.00 (2 H, 1 H, 4 H, and 1 H, respectively, each m, 2-CH_2, 3-CH, 4-CH, 6-CH_2, and 7-CH_2), 8.41 and 8.42 (each 1 H, each s, 3′-CH and 5′-CH). Anal. ($C_{12}H_{17}N_3\cdot 1.5(COOH)_2\cdot 0.4{}^iPrOH$) C, H, N.

The more polar component (0.2 g, 41%) was identified as the endo isomer **27b**. The sesquioxalate salt was prepared: mp 102–106 °C ($^iPrOH/Et_2O$); MS m/z 203 (M^+ of free base); ^1H NMR (D_2O) δ 1.29 (3 H, t, J = 7.6 Hz, CH_3), 1.56–1.66 and 1.88–2.00 (each 1 H, each m, 5-CH_2), 2.88 (2 H, q, J = 7.6 Hz, CH_2CH_3), 3.32–3.54 (4 H, m, 4-CH, 6-CH_2, and one of 7-CH_2), 3.56 (1 H, d, J = 9.1 Hz, one of 7-CH_2), 3.75–3.92 and 4.04–4.10 (2 H and 1 H, each m, 3-CH and 2-CH_2), 8.40 and 8.41 (each 1 H, each s, 3′-CH and 5′-CH). Anal. ($C_{12}H_{17}N_3\cdot 1.3(COOH)_2$) C, H, N.

3-(6-Ethylpyrazin-2-yl)quinuclidine hydrogen oxalate (29) was prepared from **26** (0.77 g, 3.45 mmol) using the synthetic procedure described for **27a** and **27b**. The product (0.33 g, 45%) was dissolved in methanol and added to a solution of oxalic acid in ether to give the hydrogen oxalate salt: mp 136–139 °C (^iPrOH); MS m/z 217 (M^+ of free base); ^1H NMR (D_2O) δ 1.30 (3 H, t, J = 7.6 Hz, CH_3), 1.70–1.90, 2.08–2.28, and 2.40–2.42 (2 H, 2 H, and 1 H, respectively, each m, 4-CH, 5-CH_2, and 8-CH_2), 2.88 (2 H, q, J = 7.6 Hz, CH_2CH_3), 3.28–3.36, 3.40–3.45, and 3.49–3.57 (1 H, 2 H, and 1 H, respectively, each m, 6-CH_2 and 7-CH_2), 3.63–3.76 (2 H, m, one of 2-CH_2 and 3-CH), 4.06 (1 H, dd, J = 5.5 and 12.0 Hz, one of 2-CH_2), 8.39 and 8.42 (each 1 H, each s, 3′-CH and 5′-CH). Anal. ($C_{13}H_{19}N_3\cdot(COOH)_2\cdot 0.125H_2O$) C, H, N.

***endo*-3-(6-(Propargyloxy)-1,4-diazin-2-yl)-1-azabicyclo-[2.2.1]heptane Hydrochloride (28).** NaH (0.1 g of an 80% dispersion in oil, 3.33 mmol) was added to a solution of propargyl

alcohol (0.2 g, 3.6 mmol) in toluene (20 mL). A solution of **25b** (0.3 g, 1.43 mmol) in toluene (5 mL) was added, and the mixture was refluxed for 12 h. Further portions of propargyl alcohol (0.2 g, 3.6 mmol) and NaH (0.1 g) were added and refluxed for 12 h. The solvent was evaporated, H_2O (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (4×). The crude product obtained was chromatographed on alumina, eluting with $MeOH/CH_2Cl_2$ (1:99) to give the title 6-(propargyloxy)pyrazine (0.11 g, 34%). The hydrochloride salt was prepared and recrystallized from $^iPrOH/Et_2O$: mp 213–215 °C; MS m/z 229 (M^+ of free base); ^1H NMR (D_2O) δ 1.78–2.00 (2 H, m, 5-CH_2), 2.95 (1 H, t, J = 2.3 Hz, acetylenic-H), 3.27–3.34 (1 H, m, 4-CH), 3.39 (1 H, d, J = 9.1 Hz, one of 7-CH_2), 3.48–3.60 (3 H, m, 6-CH_2 and one of 7-CH_2), 3.75 (1 H, dd, J = 11.3 and 11.3 Hz, one of 2-CH_2), 3.89–3.96 and 4.04–4.10 (each 1 H, each m, one of 2-CH_2 and 3-CH), 5.04 (1 H, dd, J = 2.3 and 15.8 Hz, one of CH_2O), 5.17 (1 H, dd, J = 2.3 and 15.8 Hz, one of CH_2O), 8.18 and 8.21 (each 1 H, each s, 3′-CH and 5′-CH). Anal. ($C_{13}H_{15}N_3O$·HCl) C, H, N.

3-(6-Ethoxypyrazin-2-yl)quinuclidine Sesquioxalate (30). NaOEt (0.35 g, 5.2 mmol) was added to a solution of **26** (0.58 g, 2.59 mmol) in EtOH (10 mL), and the mixture was refluxed for 2 h. The EtOH was evaporated, and the residue was taken up into H_2O (5 mL) and extracted with CH_2Cl_2 (3×). The residue remaining after drying and removal of solvent was chromatographed on silica gel, eluting with $MeOH/CH_2Cl_2/NH_3$ (10:89:1) to give **30** (0.45 g, 75%). The sesquioxalate salt was prepared and recrystallized from ^iPrOH: mp 120–122 °C; MS m/z 233 (M^+ of free base); ^1H NMR (D_2O) δ 1.41 (3 H, t, J = 7.1 Hz, CH_3), 1.72–1.82, 1.88–2.00, 2.06–2.24, and 2.35–2.38 (1 H, 1 H, 2 H, and 1 H, respectively, each m, 4-CH, 5-CH_2, and 8-CH_2), 3.32–3.44 and 3.48–3.72 (each 3 H, each m, one of 2-CH_2, 3-CH, 6-CH_2, and 7-CH_2), 3.99 (1 H, dd, J = 5.2 and 12.2 Hz, one of 2-CH_2), 4.45–4.53 (2 H, m, CH_2O), 8.09 and 8.12 (each 1 H, each s, 3′-CH and 5′-CH). Anal. ($C_{13}H_{19}N_3O$·1.5$(COOH)_2$) C, H, N.

3-(6-Bromopyrazin-2-yl)quinuclidine Sesquioxalate (31). **26** (0.61 g, 2.74 mmol) was dissolved in a 30% solution of HBr in acetic acid (5.0 mL) and stirred at room temperature for 3.5 days, 0.5 M K_2CO_3 (75 mL) was added, and the mixture was basified with K_2CO_3 and extracted with CH_2Cl_2 (5×). The residue remaining after removal of solvent was dissolved again in a 30% solution of HBr in acetic acid (5.0 mL) and stirred at room temperature for 14 h. The crude product obtained after workup was chromatographed on silica gel, eluting with $MeOH/CH_2Cl_2/NH_3$ (10.89:1) to give **31** (0.29 g, 39%). The sesquioxalate salt was prepared: mp 173–177 °C (MeOH); MS 267, 269 (M^+ of free base); ^1H NMR (D_2O) δ 1.72–1.88, 2.06–2.26, and 2.42–2.45 (2 H, 2 H, and 1 H, respectively, each m, 4-CH, 5-CH_2, and 8-CH_2), 3.28–3.36 and 3.40–3.54 (1 H and 3 H, respectively, each m, 6-CH_2 and 7-CH_2), 3.63 (1 H, ddd, J = 2.6, 10.5, and 12.8 Hz, one of 2-CH_2), 3.74–3.78 (1 H, m, 3-CH), 3.99 (1 H, dd, J = 6.1 and 12.8 Hz, one of 2-CH_2), 8.58 and 8.64 (each 1 H, each s, 3′-CH and 5′-CH). Anal. ($C_{11}H_{14}N_3Br$·1.5$(COOH)_2$) C, H, N.

3-(6-Hydroxypyrazin-2-yl)quinuclidine Dihydrobromide (32). A solution of **12d** (0.34 g, 1.6 mmol) in concentrated HBr (10 mL) was refluxed for 20 h. The acid was removed under vacuum, and the residue taken up into MeOH (1 mL) and triturated with ether. The resultant solid was recrystallized from $MeOH/Et_2O$ to give **32** (86 mg, 15%): mp 255–258 °C dec; MS m/z 205 (M^+ of free base); ^1H NMR (D_2O) δ 1.80–1.98, 2.08–2.20, and 2.40–2.46 (2 H, 2 H, and 1 H, respectively, each m, 4-CH, 5-CH_2, and 8-CH_2), 3.30–3.58 and 3.62–3.80 (5 H and 2 H, respectively, each m, 2-CH_2, 3-CH, 6-CH_2, and 7-CH_2), 7.72 and 8.08 (each 1 H, each s, 3′-CH and 5′-CH). Anal. ($C_{11}H_{15}N_3O$·2HBr) C, H, N.

3-(6-Chloro-1,2-pyridazin-3-yl)quinuclidine Dihydrochloride (34). A solution of LDA, prepared by addition of ^nBuLi (38.7 mL of a 1.6 M solution in hexane, 62.2 mmol) to a stirred solution of diisopropylamine (6.26 g, 62.0 mmol) in THF (100 mL), at −35°C, was added to a stirred solution of **22** (10 g, 59.0 mmol) in THF (200 mL) at −78 °C. The mixture was stirred for 1 h, and a solution of 3,6-dichloropyridazine (8.8 g, 59.1 mmol) in THF (20 mL) was added dropwise. Stirring at −78 °C for 2 h, warming to room temperature, and stirring for 5 h was followed by quenching with H_2O (40 mL) and extraction with CH_2Cl_2 (5×). The crude product obtained was chromatographed on silica gel, eluting with $MeOH/CH_2Cl_2$ (8:92) to give 3-(6-chloro-1,2-pyridazin-3-yl)-3-carbomethoxyquinuclidine **33** (0.36 g, 2.8%); MS m/z 218 (M^+); ^1H NMR ($CDCl_3$) δ 1.34–1.43, 1.44–1.56, and 1.63–1.75 (1 H, 1 H, and 2 H, respectively, each m, 5-CH_2 and 8-CH_2), 2.67–3.00 (5 H, m, 4-CH, 6-CH_2, and 7-CH_2), 3.65 (3 H, s, OCH_3), 3.91 (1 H, dd, J = 1.9 and 14.0 Hz, one of 2-CH_2), 4.02 (1 H, dd, J = 1.9 and 14.0 Hz, one of 2-CH_2), 7.48 and 7.52 (each 1 H, each d, J = 9.0 Hz, 4′-CH and 5′-CH).

A solution of **33** (0.35 g, 1.2 mmol) in concentrated HCl (4 mL) was refluxed for 0.5 h. The acid was neutralized with K_2CO_3 and extracted with CH_2Cl_2 (3×). The residue obtained after evaporating the solvent was chromatographed on alumina, eluting with $MeOH/CH_2Cl_2$ (1:49), to give the title quinuclidinylpyridazine (0.15 g, 54%). The dihydrochloride salt was prepared and recrystallized from $^iPrOH/Et_2O$: mp 240 °C dec; MS m/z 223 (M^+ of free base); ^1H NMR (D_2O) δ 1.68–1.86, 2.11–2.30, and 2.45–2.48 (2 H, 2 H, and 1 H, respectively, each m, 4-CH, 5-CH_2, and 8-CH_2), 3.28–3.37 and 3.41–3.52 (1 H and 3 H, respectively, each m, 6-CH_2 and 7-CH_2), 3.69 (1 H, ddd, J = 2.6, 10.5, and 12.8 Hz, one of 2-CH_2), 3.81–3.85 (1 H, m, 3-CH), 4.20 (1 H, dd, J = 6.2 and 12.8 Hz, one of 2-CH_2), 7.79 and 7.84 (each 1 H, each d, J = 9.0 Hz, 4′-CH and 5′-CH). Anal. ($C_{11}H_{14}N_3Cl$·1.9HCl) C, H, N.

3-(1,3-Pyrimidin-5-yl)-3-hydroxyquinuclidine Hemihydrate (37). ^nBuLi (12.0 mL of a 1.6 M solution in hexane, 19.2 mmol) was added dropwise, at −110 °C, to a solution of 5-bromopyrimidine (2.0 g, 12.5 mmol) in THF (60 mL) and ether (60 mL) at −110 °C. The solution was stirred for 1.25 h before adding dropwise a solution of quinuclidin-3-one (1.72 g, 13.8 mmol), in THF (20 mL), at −110 °C. The mixture was stirred at −110 °C for 0.1 h and then warmed to room temperature and stirred for 16 h; 2 N HCl (25 mL) was added, and the mixture was stirred for 0.25 h before separating the organic phase and washing with water (2×). The combined aqueous was basified with K_2CO_3 and extracted with CH_2Cl_2 (4×). The crude product was chromatographed on alumina, eluting with $MeOH/CH_2Cl_2$ (1:9) to give **37** (0.21 g, 8%): mp 126–127 °C ($EtOAc/Et_2O$); MS m/z 205 (M^+); ^1H NMR (D_2O) δ 1.32–1.43, 1.62–1.76, 2.10–2.20, and 2.30–2.34 (1 H, 2 H, 1 H, and 1 H, respectively, 4-CH, 5-CH_2, and 8-CH_2), 2.68–2.96 (4 H, m, 6-CH_2 and 7-CH_2), 3.09 and 3.49 (each 1 H, each dd, J = 1.5 and 14.7 Hz, 2-CH_2), 8.96 and 9.08 (2 H, and 1 H, respectively, each s, 2′-CH, 4′-CH, and 6′-CH). Anal. ($C_{11}H_{15}N_3O$·0.5H_2O) C, H, N.

3-(2-Methyl-1,3-pyrimidin-5-yl)-3-hydroxyquinuclidine (38) was prepared from 2-methyl-5-bromo-1,3-pyrimidine[23] (2.04 g, 11.8 mmol) and quinuclidin-3-one (1.62 g, 12.9 mmol) using the procedure described for **37**. The product (0.57 g, 20%) was isolated as a pale yellow solid: mp 167 °C (EtOAc); MS m/z 219 (M^+); ^1H NMR (D_2O) δ 1.29–1.42, 1.60–1.74, 2.08–2.18, and 2.26–2.30 (1 H, 2 H, 1 H, and 1 H, respectively, each m, 4-CH, 5-CH_2, and 8-CH_2), 2.70 (3 H, s, CH_3), 2.70–3.00 (4 H, m, 6-CH_2 and 7-CH_2), 3.06 and 3.47 (each 1 H, each dd, J = 1.5 and 14.7 Hz, 2-CH_2), 8.83 (2 H, s, 4′-CH and 6′-CH). Anal. ($C_{12}H_{17}N_3O$) C, H, N.

3-(1,3-Pyrimidin-5-yl)quinuclidine Hydrochloride Hydrate (39). $SOCl_2$ (0.35 mL, 4.8 mmol) was added to a rapidly stirred solution of **37** (0.5 g, 2.4 mmol) in CH_2Cl_2 (15 mL), at 0 °C. The solution was warmed to room temperature, stirred for 1 h, and then refluxed for 0.25 h. Basic workup and extraction with CH_2Cl_2 (4×) gave, after drying and removal of solvent, a crude product which was chromatographed on silica gel, eluting with $MeOH/CH_2Cl_2$ (5:95) to give 3-(1,3-pyrimidin-5-yl)-1-azabicyclo[2.2.2]-oct-2-ene, **41** (0.16 g, 35%). The hydrochloride salt was prepared and recrystallized from $EtOH/Et_2O$: mp 240–242 °C dec; MS m/z 281 $(M+1)^+$; ^1H NMR (D_2O) δ 1.86–1.98, 2.15–2.26, 3.18–3.30, and 3.62–3.72 (2 H, 2 H, 2 H, and 3 H respectively, each m, 4-CH, 5-CH_2, 6-CH_2, 7-CH_2 and 8-CH_2), 7.23 (1 H, s, 2-CH), 9.00 and 9.15 (2 H and 1 H respectively, each s, 2′-CH, 4′-CH, and 6′-CH).

A solution of **41** (0.31 g, 1.66 mmol) in EtOH (40 mL) was hydrogenated over 10% Pd/C (0.12 g) in a Parr apparatus for 4 h. The catalyst was removed by filtration through hyflo, the solvent was removed under vacuum, and the residue was chromatographed on alumina, using $MeOH/CH_2Cl_2$ (5:95) as eluant, to give **39** (0.17 g, 55%). The hydrochloride salt was prepared and recrystallized from $EtOH/Et_2O$: mp 267–270 °C dec; MS m/z 189 (M^+ of free base); ^1H NMR (D_2O) δ 1.89–1.94, 2.13–2.24, and 2.38–2.46 (2 H, 2 H, and 1 H, respectively, each m, 4-CH, 5-CH_2, and 8-CH_2), 3.32–3.44 (4 H, m, 6-CH_2 and 7-CH_2), 3.56–3.72 (2 H, m, one of 2-CH_2 and 3-CH), 3.87 (1 H, ddd, J = 2.5, 9.7,

and 12.9 Hz, one of 2-CH_2), 8.85 and 9.09 (2 H and 1 H, respectively, each s, 2'-CH, 4'-CH, and 6'-CH). Anal. ($C_{11}H_{15}N_3$·HCl·0.75H_2O) C, H, N.

3-(2-Methyl-1,3-pyrimidin-5-yl)quinuclidine dihydrochloride (40) was prepared from **38** (0.57 g, 2.6 mmol) via **42** using the procedure described for the synthesis of **39**. The product obtained (0.1 g, 19%) was dissolved in MeOH (2 mL), and a solution of ethereal HCl was added to give the dihydrochloride salt: mp 256-258 °C (MeOH/Et_2O); MS m/z 203 (M^+ of free base); ^1H NMR (D_2O) δ 1.84-1.94, 2.06-2.27, and 2.32-2.44 (2 H, 2 H, and 1 H, respectively, each m, 4-CH, 5-CH_2, and 8-CH_2), 2.78 (3 H, s, CH_3), 3.32-3.54, 3.56-3.62, 3.66-3.74, and 3.82-3.90 (4 H, 1 H, 1 H, and 1 H, respectively, each m, 2-CH_2, 3-CH, 6-CH_2, and 7-CH_2), 8.90 (2 H, s, 4'-CH and 6'-CH). Anal. ($C_{12}H_{17}N_3$·2HCl) C, H; N: calcd 52.18; found, 51.58.

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Registry No. **8a**, 32111-21-0; **8b**, 58139-06-3; **8c**, 58139-08-5; **8d**, 58139-03-0; **8e**, 99968-71-5; **8f**, 59021-15-7; **8g**, 99969-02-5; **8h**, 125060-83-5; **8i**, 98140-48-8; **8j**, 137696-69-6; **8k**, 137741-99-2; **8l**, 125060-68-6; **8m**, 137696-68-5; **8n**, 125060-66-4; **8o**, 125060-75-5; **9b**, 137696-70-9; **10b**·HCl, 137696-74-3; **11b**, 137696-76-5; **12a**, 125059-50-9; **12a**·HCl, 125060-03-9; **12b**, 125059-52-1; **12b** 1.5 oxalate, 137696-85-6; **12c**, 125059-69-0; **12c**·2HCl, 125060-18-6; **12d**, 125059-53-2; **12d**·2HCl, 125060-05-1; **12e**, 137696-86-7; **12e** 1.5 oxalate, 137696-87-8; **12**, 137696-88-9; **12f** oxalate, 137696-89-0; **13a**, 135276-26-5; **13e**, 137696-73-2; **13f**, 137696-71-0; **14a**, 137696-72-1; **15e**, 137696-75-4; **15o**, 137696-77-6; **17a**, 135276-28-7; **17a**·2HCl, 137696-90-3; **17b**, 137696-91-4; **17b**·2.1HCl, 137696-92-5; **17c**, 137696-93-6; **17c**·2HCl, 125060-43-7; **17d**, 137696-94-7; **17d**·2HCl, 137696-95-8; **17e**, 125085-90-7; **17e** oxalate, 137696-96-9; **17f**, 125060-35-7; **17f** oxalate, 125060-36-8; **17g**, 137696-97-0; **17g**·2HCl, 125060-48-2; **17h**, 137696-98-1; **17h**·HCl, 137696-99-2; **17i**, 125060-88-0; **17i** 2 oxalate, 125060-89-1; **17j**, 137697-00-8; **17j**·HCl, 137697-01-9; **17k**, 137697-02-0; **17k**·HCl, 137697-03-1; **17l**, 137697-04-2; **17l** 1.5 oxalate, 137697-05-3; **17m**, 137697-06-4; **17m**·1.5HCl, 137697-07-5; **17n**, 137697-08-6; **17n**·2.5HCl, 137697-09-7; **17o**, 137697-10-0; **17o**·2HCl, 125060-39-1; **18a**, 135276-29-8; **18a**·1.5HCl, 137697-11-1; **18b**, 125060-22-2; **18b** 1.5 oxalate, 125060-23-3; **18c**, 125060-54-0; **18c**·1.4HCl, 137697-12-2; **18d**, 137697-13-3; **18d**·1.5HCl, 137697-14-4; **18e**, 125060-54-0; **18e** oxalate, 137697-15-5; **18f**, 125060-37-9; **18f** oxalate, 125060-38-0; **18g**, 137697-16-6; **18g**·2.1HCl, 137697-17-7; **18h**, 137697-18-8; **18h**·2HCl, 125060-53-9; **18i**, 125060-41-5; **18i**·2.1HCl, 137697-19-9; **18j**, 137697-20-2; **18j**·1.1HCl, 137697-21-3; **18k**, 137697-22-4; **18k**·HCl, 137697-23-5; **18l**, 137697-24-6; **18l**·HCl, 125060-29-9; **18m**, 137697-25-7; **18m**·1.2HCl, 125060-33-5; **18n**, 137697-26-8; **18n**·2.4HCl, 137697-27-9; **18o**, 137697-28-0; **18o**·HCl, 125060-40-4; **19a**, 137697-29-1; **19a**·2HCl, 137697-30-4; **19d**, 137697-31-5; **19d**·2HCl, 125060-30-2; **20a**, 137697-32-6; **20a** oxalate, 137697-33-7; **20d**, 137697-34-8; **20d**·1.4HCl, 137697-35-9; **21**, 121564-88-3; **22**, 38206-86-9; **23**, 137696-78-7; **24**, 137696-79-8; **25b**, 125076-10-0; **25b** oxalate, 125076-11-1; **26**, 125059-87-2; **26**·HCl, 125060-44-8; **27a**, 137697-38-2; **27a** oxalate, 137697-39-3; **27b**, 137697-40-6; **27b** oxalate, 137697-41-7; **28**, 137697-44-0; **28**·HCl, 125060-90-4; **29**, 137697-42-8; **29** oxalate, 137697-43-9; **30**, 137697-45-1; **30** oxalate, 137697-46-2; **31**, 137697-47-3; **31** oxalate, 137697-48-4; **32**, 125059-54-3; **32**·2HBr, 125060-06-2; **33**, 137696-84-5; **34**, 137718-39-9; **34**·2HCl, 137697-49-5; **37**, 125059-59-8; **38**, 137696-80-1; **39**, 125059-60-1; **39**·HCl, 125060-09-5; **40**, 125059-61-2; **40**·2HCl, 125060-10-8; **41**, 137696-81-2; **41**·HCl, 137696-83-4; **42**, 137696-82-3; **43**, 137697-36-0; **43**·HCl, 137697-37-1; 2,6-dichloropyrazine, 4774-14-5; 2,6-diiodopyrazine, 58138-79-7; quinuclidin-3-one, 3731-38-2; 1-azabicyclo[2.2.1]heptan-3-one, 21472-89-9; 1-azabicyclo[3.2.1]octan-6-one, 45675-76-1; 3,6-dichloropyridazine, 141-30-0; 5-bromopyridine, 4595-59-9; 2-methyl-5-bromo-1,3-pyrimidine, 7752-78-5.

Supplementary Material Available: Table of microanalytical data for novel compounds and table of HRMS data for novel compounds (4 pages). Ordering information is given on any current masthead page.

Conformational Studies of Muscarone Analogues: X-ray Analysis and Molecular Mechanics Calculations†

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The X-ray structure of muscarone analogues **3** and **4** was determined and compared with that of muscarone (**1**, iodide and picrate salts), muscarine **2**, dioxolane **5**, oxathiolane **6**, and tetrahydrofuran **7**. In order to better define the pharmacological stereoselectivity of muscarone, the conformational profiles of compounds **1**, **2**, **3**, and **5** were analyzed using Allinger's MM2(85) program or, in the case of **4**, by ^1H NMR spectroscopy. The conformation of the ring in **1** proved similar to that of the other derivatives. MM2 calculations predicted a preferred gauche arrangement of the side chain for **1** and its analogues; such an arrangement was also observed in the solid state of muscarone picrate. Thus, the antiperiplanar arrangement reported for crystalline muscarone iodide appears to be due to crystallographic packing forces. As a consequence, the rationalization of the pharmacological profile of **1** based on the antiperiplanar arrangement is now highly questionable. The lack of stereoselectivity of **4** can be attributed to the absence of a stereocenter at C-2 whereas, in our opinion, there are currently no sound explanations for the low values of eudismic ratios for the muscarone enantiomers.

There is an increasing interest in agents capable of stimulating cholinergic transmission following the evidence that the receptors of the muscarinic system consist of five molecular forms, m_1-m_5,[1,2] and three pharmacological identified subtypes, M_1, M_2, M_3,[3,4] that exhibit different structural, functional and pharmacological properties. Selective ligands are known for the three M_1/m_1-M_3/m_3

† Dedicated to Professor Paolo Grünanger on the occasion of his 65th birthday.

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(1) Buckley, N. J.; Bonner, T. I.; Buckley, C. M.; Brann, M. R. Antagonist Binding Properties of Five Cloned Muscarinic Receptors Expressed in CHO-K1 Cells. *Mol. Pharmacol.* **1989**, *35*, 469-476.

(2) Bonner, T. I. The Molecular Basis of Muscarinic Receptor Diversity. *Trends Neurosci.* **1989**, *12*, 148-151.

(3) Lavine, R. R., Birdsall, N. J. M., Eds. *Trends Pharmacol. Sci.* **1989**, *10* (Suppl. Subtypes of Muscarinic Receptors IV).

(4) Mitchelson, F. Muscarinic Receptor Differentiation. *Pharmacol. Ther.* **1988**, *37*, 357-423.

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