Substituent Variation in Azabicyclic Triazole- and Tetrazole-Based Muscarinic Receptor Ligands

Sarah M. Jenkins,* Harry J. Wadsworth,* Steven Bromidge, Barry S. Orlek, Paul A. Wyman, Graham J. Riley, and Julie Hawkins

SmithKline Beecham Pharmaceuticals, Medicinal Research Centre, Coldharbour Road, The Pinnacles, Harlow, Essex, CM19 5AD, U.K. *Received November 26, 1991*

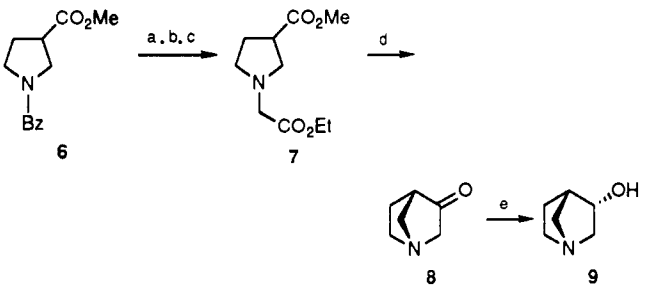
The effect of variation of the 1-azabicyclic substituent on the novel 1,2,3-triazol-4-yl-, 1,2,4-triazol-1-yl-, tetrazol-5-yl-, and tetrazol-2-yl-based muscarinic receptor ligands has been studied, and the *exo*-azabicyclic[2.2.1]hept-3-yl substituent was found to give the most potent and efficacious compounds. In addition, variation of the second substituent on 1,2,4-triazol-1-yl- and tetrazol-2-yl-based muscarinic receptor ligands has yielded a series of novel compounds with high potencies and efficacies, ranging from full agonists to antagonists. Small lipophilic electron withdrawing substituents give potent but low efficacy compounds, while small polar electron donating substituents give potent and efficacious compounds. The activity of these compounds is described in terms of a model of the receptor involving lipophilic and hydrogen bonding interactions. These compounds provide muscarinic ligands with high potency and a range of efficacies suitable for testing as candidate drugs in the treatment of Alzheimer's disease.

Introduction

Senile dementia of the Alzheimer type is associated with the loss of cholinergic function in the brain. We have been developing selective muscarinic agonists as cholinergic agents with potential for the treatment of Alzheimer's disease (AD).[1] A study of a range of 1-azabicyclo-[2.2.2]oct-3-yl-substituted triazoles and tetrazoles has identified four azoles which afford potent muscarinic agonists[2] (Figure 1). We have described the effects of variation of the 1-azabicyclic ring in ester and oxadiazole-based muscarinic agonists.[1] The requirements identified for potency and efficacy at the muscarinic receptor of a 1-azabicyclic system were a two-carbon link between the tertiary nitrogen atom and the azole, and a size constraint for which 1-azabicyclo[2.2.2]octane represented the preferred maximum. Within these constraints, five azabicyclic substituents were identified as yielding novel, potent, and efficacious muscarinic agonists (Figure 2). We wished to investigate the effect of variation of the 1-azabicyclic ring on potency and efficacy at the muscarinic receptor of the four azoles previously identified. Synthetic routes to these compounds were devised.

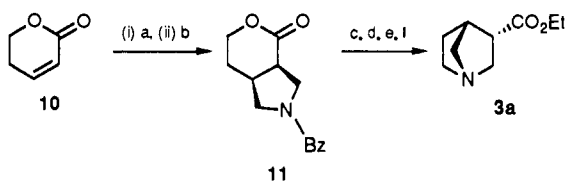
We also wished to study the effect of variation of a second substituent on the azole ring on the potency and efficacy at muscarinic receptors. The effect of variation of the corresponding substituent in an oxadiazole-based series of muscarinic agonists has been described.[3] The anticipated range of efficacies thus afforded would enable the selection of compounds with partial agonist properties, which we believe are most appropriate for the treatment of AD.[4]

Scheme I[a]



[a] Reagents: (a) $BrCH_2CO_2Et$; (b) H_2/Pd; (c) K_2CO_3; (d) KO^{t}Bu/toluene; (e) H_2/Pt.

Scheme II[a]



[a] Reagents: (a) *N*-benzyl-*N*-(methoxymethyl)-*N*-[(trimethylsilyl)methyl]amine; (b) TFA; (c) HBr/EtOH; (d) aqueous K_2CO_3; (e) H_2/Pd; (f) aqueous K_2CO_3

The abundance in the cortex of the postsynaptic M_1 receptor makes it a logical target for cholinergic drug treatment of Alzheimer's disease. Within the structural variation described above we therefore also wished to discover compounds which were selective for this receptor.

Synthetic Chemistry

[*We have used a numbering system where the azabicycle is given a standard number (see Figure 2) and the substituent is given a standard letter. Compounds not conveniently falling into this system are numbered sequentially.*]

In order to achieve the efficient synthesis of the 1-azabicyclic triazoles and tetrazoles identified previously we required ready access to the appropriately substituted 1-azabicycles. Ethoxycarbonyl substituents can be converted to 1,2,3-triazole-4-yl or tetrazol-5-yl groups, while hydroxy substituents can be converted via mesylates to 1,2,4-triazol-1-yl or tetrazol-2-yl groups.[2]

Routes to 3-*endo*- and 3-*exo*-hydroxy-1-azabicyclo-[2.2.1]heptane are known,[5] but in our hands conversion of

(1) Orlek, B. S.; Blaney, F. E.; Brown, F.; Clark, M. S. G.; Hadley, M. S.; Hatcher, J.; Riley, G. J.; Rosenberg, H. E.; Wadsworth, H. J.; Wyman, P. A. Comparison of Azabicyclic Esters and Oxadiazoles as ligands for the Muscarinic Receptor. *J. Med. Chem.* **1991**, *34*, 2726-2735.

(2) Wadsworth, H. J.; Jenkins, S. M.; Orlek, B. S.; Cassidy, F. C.; Clark, M. S. G.; Brown, F.; Riley, G. J.; Graves, D.; Naylor, C. B. Synthesis and Muscarinic Activity of Quinuclidin-3-yl Triazole and Tetrazole Derivatives. *J. Med. Chem.* **1992**, *35*, 1280-1290.

(3) 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.

(4) Loudon, J.; Brown, F.; Clark, M.; Riley, G. Hippocampal and cardiovascular effects of muscarinic agents in Alzheimer's Disease. *Epidemiology, Neuropathology, Neurochemistry and Clinical Studies*; Springer-Verlag: New York, 1990, pp 229-233.

(5) Spry, D. O.; Aaron, H. S. Azabicyclic Alcohols. VI. Stereospecific Synthesis of the 1-Azabicyclo[2.2.1]heptan-3-ol Epimers. *J. Org. Chem.* **1969**, *34*, 3674-3676.

0022-2623/92/1835-2392$03.00/0

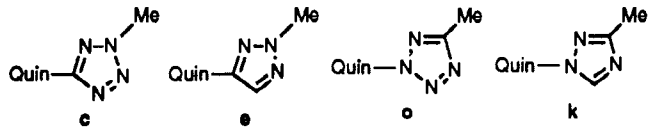


Figure 1. Potent ester isosteres in muscarinic agonists[2] (lettering as used in this article). Quin = quinuclidin-3-yl (1-azabicyclo-[2.2.2]octan-3-yl).

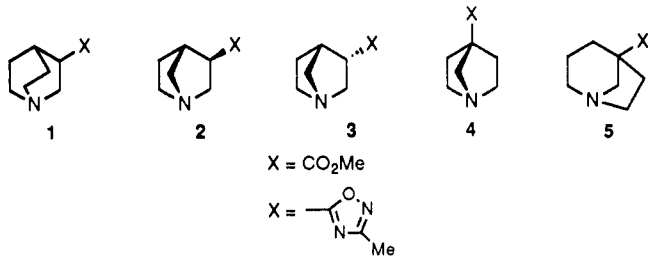
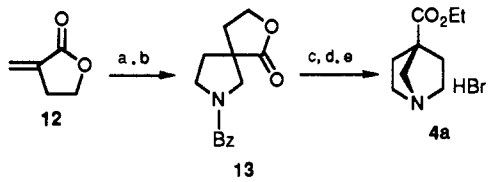


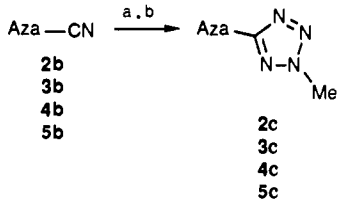
Figure 2. Potent azabicyclic tertiary amine mimics in muscarinic agonists[1] (numbering as used in this article).

Scheme III[a]



[a] Reagents: (a) *N*-benzyl-*N*-(methoxymethyl)-*N*-[(trimethylsilyl)methyl]amine; (b) TFA; (c) HBr; (d) K_2CO_3; (e) H_2/Pd.

Scheme IV[a]

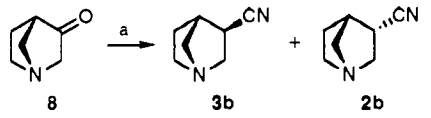


[a] Reagents: (a) TMS-N_3; (b) CH_2N_2.

the exo alcohol to the endo alcohol by chromic acid oxidation and hydrogenation were unreliable. An alternative route to 3-oxo-1-azabicyclo[2.2.1]heptane (**8**) has been described.[6] We used a modification of this procedure starting with methyl *N*-benzylpyrrolidine-3-carboxylate (**6**), readily prepared by cycloaddition of N-benzylazamethine ylide to methyl acrylate (Scheme I).[7] Quaternization with ethyl bromoacetate followed by hydrogenation gave the diester **7**. Dieckmann cyclization, hydrolysis and decarboxylation afforded the ketone **8**. Hydrogenation of **8** was stereospecific with addition of hydrogen from the least hindered side, to give the endo alcohol **9**.[5]

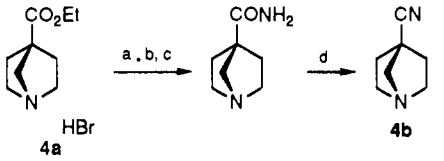
Routes to 3-*exo*-, 3-*endo*-, and 4-carboxyethyl-substituted 1-azabicyclo[2.2.1]heptanes have been described.[8,9]

Scheme V[a]



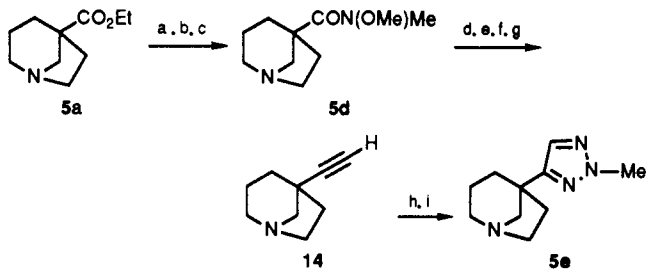
[a] Reagents: (a) TosMIC, ^{t}BuOK, EtOH.

Scheme VI[a]



[a] Reagents: (a) concentrated HCl; (b) $SOCl_2$; (c) NH_3/DCM; (d) TFA, pyridine, <30 °C.

Scheme VII[a]



[a] Reagents: (a) H^+; (b) $SOCl_2$; (c) NH(Me)OMe; (d) DIBAL; (e) $Ph_3P{=}CBr_2$; (f) BuLi; (g) H^+; (h) TMS-N_3; (i) CH_2N_2.

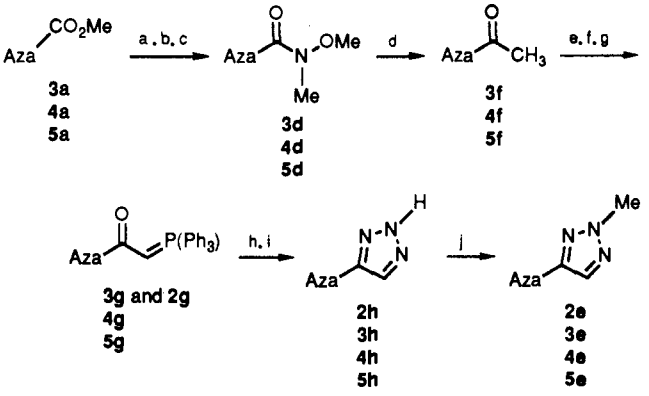
An identical route to chiral **3a** was described during the preparation of this manuscript.[10] This is based on hydrogen bromide cleavage of suitable lactones **11** and **13** followed by recyclization of the resulting bromo esters on basification (Schemes II and III). These lactones are conveniently prepared by dipolar cycloadditions of *N*-benzylazamethine ylide to the α,β-unsaturated lactones **10** and **12**. Full experimental details are now presented.

The 1-azabicyclotetrazol-5-yl compounds were prepared by standard procedures[11] (Scheme IV). Cycloaddition of trimethylsilyl azide to the appropriate nitriles (**2b–5b**) under forcing conditions gave the trimethylsilyltetrazoles, which on deprotection with methanol and methylation with diazomethane gave mainly the 2-*N*-methyl isomers[2] (**2c–5c**), which could be readily purified by column chromatography. The regiochemistry was confirmed by NOE experiments as described previously.[2] The required nitriles **2b** and **3b** were prepared by treatment of the ketone **8** with TosMIC and potassium *tert*-butoxide[12] followed by chromatographic separation of the isomers (Scheme V). By contrast, the bridgehead azabicyclic nitrile **4b** was prepared from the ester **4a** by conversion to the amide and dehydration (Scheme VI). **1b** and **5b** were prepared by literature procedures.[1]

Two routes to 4-substituted 2-methyl-1,2,3-triazoles were used. Cycloaddition of trimethylsilyl azide to acetylenes

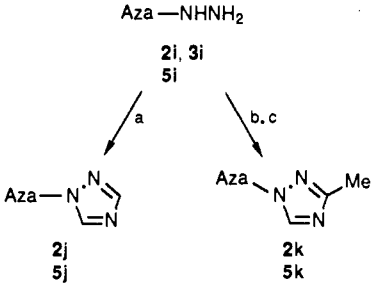
(6) Saunders, J.; MacLeod, A. M.; Merchant, K. J.; Showell, G. A.; Snow, R. J.; Street, L. J.; Baker, R. J. Ester Bioisosteres: Synthesis of Oxadiazolyl-1-azabicyclo[2.2.1]heptanes as Muscarinic Agonists. *J. Chem. Soc., Chem. Commun.* **1988**, 1618–1619.
(7) Terao, Y.; Kotake, H.; Imai, N.; Achiwa, K. Trifluoroacetic Acid-Catalysed 1,3-Cycloaddition of the Simplest Iminium Ylide leading to 3- or 3,4-Substituted Pyrrolidines or 2,5-Dihydropyrroles. *Chem. Pharm. Bull.* **1985**, *33*, 2762–2766.
(8) Orlek, B. S.; Wadsworth, H. J.; Wyman, P. A.; Hadley, M. S. Diastereoselective Routes to *endo* and *exo* Ethyl-1-azabicyclo[2.2.1]hept-3-yl Carboxylates. *Tetrahedron Lett.* **1990**, *32*, 1241–1244.
(9) Orlek, B. S.; Wadsworth, H. J.; Wyman, P. A.; King, F. D. Synthesis of Ethyl-1-azabicyclo[2.2.1]hept-4-yl Carboxylate. *Tetrahedron Lett.* **1990**, *32*, 1245–1246.
(10) Cottrell, I. F.; Hands, D.; Kennedy, D. J.; Kerensa, J. P.; Wright, S. H. B.; Hoogsteen, K. A synthesis of 1-azabicyclo-[2.2.1]heptane-3-carboxylic acid ester in enantiomerically pure form. *J. Chem. Soc. Perkin Trans. I* **1991**, 1091–1097.
(11) Birkofer, L.; Wegner, P. *Chem. Ber.* **1966**, *99*, 2512–2517.
(12) Nahm, S.; Weinreb, S. M. N-Methoxy-N-methylamides as effective acylating agents. *Tetrahedron Lett.* **1981**, *22* (39), 3815–3818.

Scheme VIII[a]



[a] Reagents: (a) H^+; (b) $SOCl_2$; (c) NH(Me)OMe; (d) MeLi; (e) HCl, Cl_2; (f) $(Ph_3)P$; (g) K_2CO_3; (h) *m*-nitrobenzoyl azide, CH_3CN; (i) Al_2O_3; (j) CH_2N_2.

Scheme IX[a]

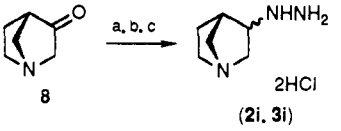


[a] Reagents: (a) Gold's reagent; (b) *O*-methyl acetimidate; (c) $(EtO)_3CH$.

under forcing conditions is known to yield 1-trimethylsilyl-substituted 1,2,3-triazoles,[11] which can be hydrolyzed to the free triazoles. This route was successfully applied to the synthesis of **5e** (Scheme VII). The ester **5a**[1] was converted to the *N*-methyl-*N*-methoxyamide **5d** and reduced with DIBAL to afford the aldehyde.[12] Direct reduction of the ester with DIBAL gave impure aldehyde as product. The aldehyde was converted to the acetylene **14** using the method of Corey.[13] Heating **14** in TMS azide followed by hydrolysis and methylation with diazomethane gave a poor yield of triazole **5e**. The major 2-*N*-methyl isomer[14] was separated from minor regioisomers by chromatography, and the regiochemistry was assigned by NOE experiments as described previously.[2] Attempts to prepare **1e** and **4e** by this route failed. The corresponding acetylenes were prepared by an analogous route but no triazole could be isolated after heating with TMS azide and methylating with diazomethane.

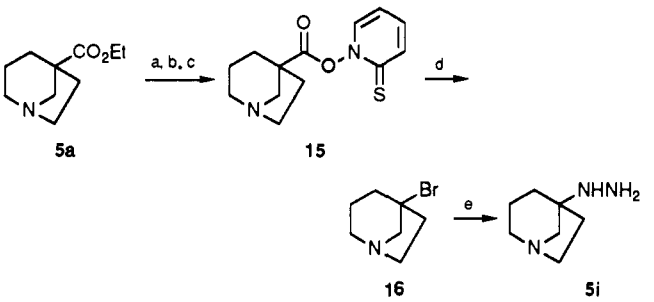
An alternative route that has been described previously[2] was used to prepare **2e**, **3e**, **4e**, and **5e** (Scheme VIII). The strongly acidic conditions used in the conversion of the methyl ketone **3f** to the α-keto phosphorus ylides caused equilibration to a mixture of the exo isomer **2g** and the endo isomer **3g**. This mixture was readily separated by column chromatography and this enabled the endo ester **2a**, which is significantly more accessible, to be used in the preparation of the exo triazole **2e**. The stereochemistry of the isomers was assigned using the difference in chemical shift of the signal due to the C-5 carbon in the ^{13}C

Scheme X[a]



[a] Reagents: (a) NH_2NH-^{t}Boc; (b) H_2; (c) HCl/MeOH.

Scheme XI[a]



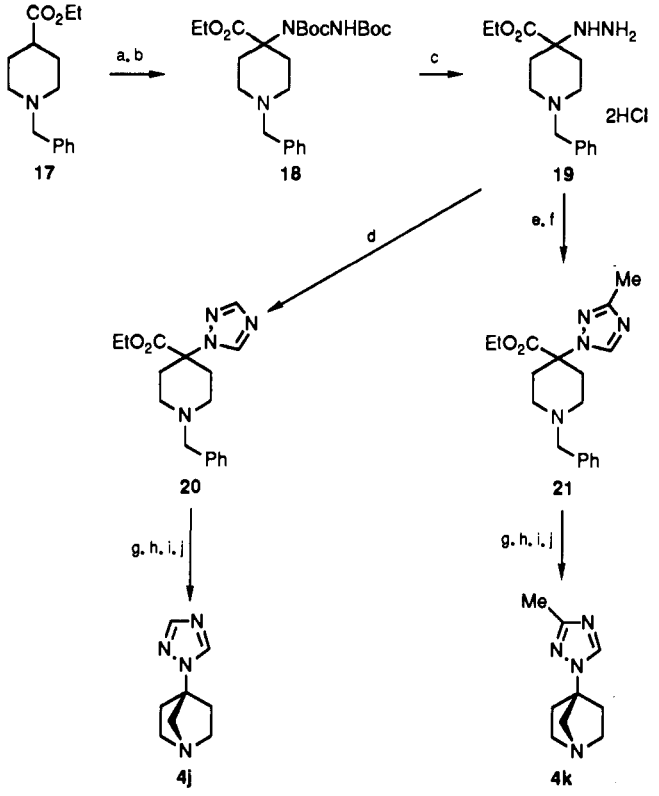
[a] Reagents: (a) H^+, H_2O; (b) $SOCl_2$; (c) 1-hydroxypyridine-2-(1*H*)-thione, sodium salt; (d) CCl_3Br, Δ; (e) NH_2NH_2.

NMR spectra, i.e. [C-5 exo δ 30.6] − [C-5 endo δ 25.11] = δ 5.49 consistent with previous findings.[8] The α-keto ylides reacted readily with *m*-nitrobenzoyl azide[15] to give, after hydrolysis and methylation with diazomethane, mainly the 2-*N*-methyl isomer.[14] After purification by chromatography, the regiochemistry was confirmed by NOE experiments, as described previously.[2]

Three routes to 1,2,4-triazol-1-yl moieties were used. Stepwise assembly of the 1,2,4-triazole following a previously described procedure[2] (Scheme IX) gave access to the unsubstituted-(**2j** and **5j**) and 3-methyl-(**2k** and **5k**)-1,2,4-triazoles, the regiochemistry of which was confirmed by irradiation of H-5 of the triazole at δ 8.90 which gave an NOE to the azabicyclic ring proton (H-3) at δ 4.92, and the lack of NOE on irradiation of the methyl group at δ 2.31 to the azabicyclic ring protons. The stereochemistry of **2j** and **2k** was identified as described previously. The hydrazines **2i** and **3i** were prepared from the ketone **8** by conversion to the hydrazone and hydrogenation (Scheme X), resulting in a 2:1 mixture of endo–exo isomers. 1-Azabicyclo[3.2.1]oct-5-ylhydrazine (**5i**) was prepared via a displacement reaction (Scheme XI). Bridgehead-substituted adamantane hydrazines have been prepared from the corresponding bromides by displacement with hydrazine under vigorous conditions.[16] The bromide required for an analogous synthesis was available by oxidative decarboxylation of the ester **5a** using the method of Barton.[17] Heating with anhydrous hydrazine gave the required alkylhydrazine **5i**. Attempts to prepare the corresponding 1-azabicyclo[2.2.1]hept-4-ylhydrazine (**4i**) by this route failed. Although the corresponding bromide could be prepared by an analogous route, all attempts to achieve reaction with hydrazine or equivalents, even under severely forcing conditions (150 °C, autoclave) gave only starting material. This is consistent with the highly strained carbonium ion transition state required not being accessible as reported previously.[18] An alternative route to **4j**

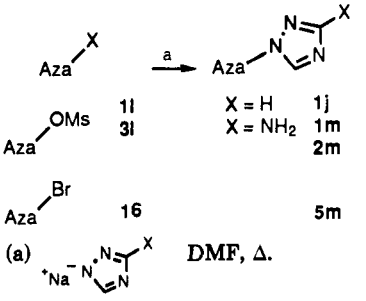
(13) Corey, E. J.; Fuchs, P. L. A Synthetic Method for Formyl-Ethynyl Conversion (RCHO—RC≡CH or RC≡CR'). *Tetrahedron Lett.* **1972**, *36*, 3769–3772.
(14) Wamhoff, H. 1,2,3-Triazoles and their Benzo Derivatives. In *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon Press: New York, 1984, *5*, p 698.
(15) Munch-Petersen, J. *m*-Nitrobenzazide. *Organic Syntheses*; Wiley: New York, 1963; Collect Vol. IV, p 715–717.
(16) Thomas, T. L.; Shetty, B. V. Preparation of Hydrazinoadamantane Compounds. U.S. Patent 3719710, Sept 20, 1968.
(17) Barton, D. H. R.; Crich, D.; Motherwell, W. B. The Intervention of New Radical Chain Reactions. Part VIII. Radical Chemistry of Thiohydroxamic Esters: A New Method for the Generation of Carbon Radicals from Carboxylic Acids. *Tetrahedron* **1985**, *41* (19), 3901–3924.

Scheme XII[a]



[a] Reagents: (a) LDA; (b) Boc-N=N-Boc; (c) MeOH/HCl/Δ; (d) Gold's reagent; (e) MeC(=NH)OMe/Et_3N; (f) $HC(OEt)_3$; (g) $LiAlH_4/Et_2O$/0 °C; (h) TosCl, pyridine; (i) Δ; (j) H_2/Pd–C.

Scheme XIII[a]

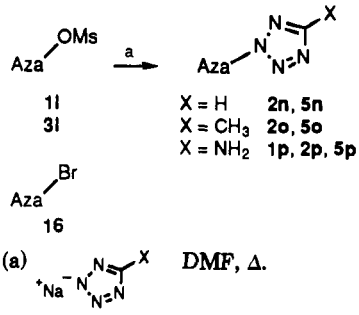


[a] Reagents: (a) DMF, Δ.

and **4k** was devised which introduced the 1,2,4-triazole prior to formation of the strained 1-azabicyclo[2.2.1]heptane (Scheme XII). The carbanion derived from ethyl *N*-benzylisonipecotate added to di-*tert*-butyl carbazate in a Michael type reaction.[19] Having made the key C–N bond, the protected hydrazine was converted to the required 1,2,4-triazoles using standard conditions. The ester was then reduced and the resulting alcohol cyclized to the 1-azabicyclo[2.2.1]heptane.

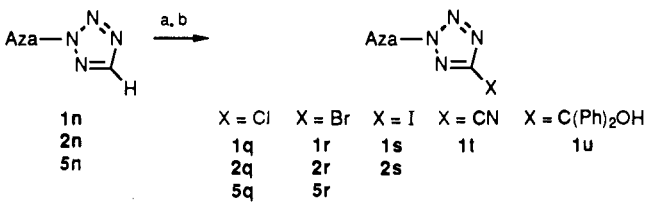
A direct displacement route to 1,2,4-triazol-1-yl groups was also used analogous to the synthesis of 1,2,4-triazol-1-yl-1-azabicyclo[2.2.2]octane[2] (Scheme XIII). The major isomer was purified by chromatography and the regiochemistry assigned as the 1-substituted isomer by NOE experiments as described previously.[2] The mesylates derived from the *exo*[5]- and *endo*-3-hydroxy-1-azabicyclo-[2.2.1]heptane (**9**) reacted with the triazolate anions via an S_n2 reaction stereospecifically with inversion of stereochemistry to give the endo and exo products respectively. This route was used to prepare the unsubstituted and 3-amino-1,2,4-triazoles. The stereochemistry was identified by comparison of the ^{13}C NMR spectra wherein the chemical shifts of the C-5 carbon atom in the azabicycle were δ C-5 exo – δ C-5 endo = 5 ppm.[8] The reaction was extended to utilize the bridgehead bromide **16** as a precursor for the triazoles **5j**, **5k**, and **5m**. Attempts to use this method of direct displacement for the synthesis of **4j** using the corresponding bromide also failed, even under extremely forcing conditions. Use of ethyl 4-bromo-*N*-benzylisonipecotate or the corresponding 4-mesylate under similar conditions also failed, yielding only elimination products.

Scheme XIV[a]



[a] Reagents: (a) DMF, Δ.

Scheme XV[a]



[a] Reagents: (a) ^tBuLi, THF, <–50 °C; for **q**, **r**, **s**: (b) X_2 where X is Cl, Br, I; for **t**: (b) (i) *N*-methylformanilide; (ii) HCl; (iii) NH_2OH; (iv) Ac_2O; for **u**: (b) $Ph_2C{=}O$.

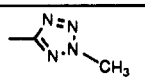
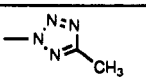
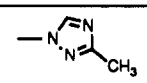
The 5-H, 5-methyl, and 5-aminotetrazoles **1p**, **2n–p**, and **5n–p** were also prepared by this method of direct displacement by analogy with the preparation of (2-methyltetrazol-5-yl)-1-azabicyclo[2.2.2]octane (Scheme XIV).[2] The same inversion of stereochemistry was noted on transformation of **3l** to **2j**, **2k**, and **2m**.

The range of substituents on the 1,2,4-triazol-1-yls and tetrazol-5-yls was extended by modification of a preformed 1-azabicyclic triazole or tetrazole as described.

The literature reports that 1-alkyltetrazoles on treatment with butyllithium at –60 °C are deprotonated and the resulting anion, although rather unstable, can be reacted with a range of electrophiles at low temperature.[20] We attempted to repeat this procedure with tetrazol-2-yl-1-azabicyclo[2.2.2]octane[2] (**1n**) but no deprotonation was observed even using 5 equiv of *n*-butyllithium at 0 °C. However, the reaction proceeded in good yield when the more reactive *tert*-butyllithium was used (Scheme XV). The anion was also found to be more stable than that derived from 1-alkyltetrazoles.[20] Treatment with the elemental halogens (excluding fluorine) afforded the 5-halotetrazoles. The pseudo-halogen C≡N could not directly be introduced by this route as cyanogen bromide reacted exclusively at the bromine residue.[21] The nitrile

(18) Bartlett, P. D.; Knox, L. H. Bicyclic Structures Prohibiting the Walden Inversion. Replacement Reactions in 1-Substituted 1-apocamphanes. *J. Am. Chem. Soc.* **1939**, *61*, 3184–3192.
(19) Genet, J. P.; Juge, S.; Mallart, S. Electrophilic Amination: Enantioselective Synthesis of D-Allothreonine and L-Threonine. *Tetrahedron Lett.* **1988**, *29*, 6765–6768.
(20) Raap, R. Reactions of 1-Substituted 5-Tetrazolyllithium Compounds. Preparation of 5-Substituted 1-Methyltetrazoles. *Can. J. Chem.* **1971**, *49*, 2139–2142.
(21) Freidrich, K.; Wallenfels, K. Introduction of a cyano group into a molecule. In *The Chemistry of Functional Groups. The Cyano Group*; Patai, S., Ed.; Wiley Interscience: 1979, p 89.

Table I. In Vitro Affinities for Muscarinic Receptors[a]

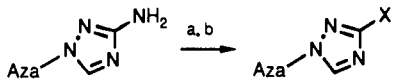
X	e	 c	 o	 k
 1	48[b] (41–56) 4523[c] (3100–6600) 94[d]	143[b] (95–200) 5100[c] (3300–6500) 36[d]	31[b] (13.5–62.5) 2800[c] (2600–3100) 92[d]	75[b] (68–83) 4500[c] (3600–5600) 60[d]
 2	5.4[b] (3.6–8.9) 2800[c] (1400–5800) 532[d]	11[b] (11–12) 2900[c] (2250–3700) 251[d]	4.2[b] (3.0–6.9) 1900[c] (1250–3000) 456[d]	17[b] (13–22) 4300[c] (2900–6300) 253[d]
 3	16[b] (10.5–25.5) 13500[c] (10300–18500) 844[d]	325[b] (310–340) 30600[c] (23500–40000) 94[d]		
 4	35[b] (30–43) 14400[c] (10300–20000) 407[d]	250[b] (245–255) 46700[c] (39000–56000) 187[d]		86[b] (63–118) 14900[c] (13000–17000) 173[d]
 5	14[b] (10.5–20.5) 3100[c] (2750–3500) 217[d]	100[b] (80–125) 5700[c] (4000–8200) 57[d]	14[b] (11.5–17) 1925[c] (1300–2850) 138[d]	12[b] (10.5–17) 2100[c] (1500–2600) 174[d]

[a] Displacement of tritiated radioligand from rat cortical homogenates. Each value represents the geometric mean of at least two determinations performed in separate experiments, using seven concentrations. [b] This represents the IC_{50} (nM) for displacement of [^{3}H]OXO-M, with the range of values obtained shown in parentheses. [c] This represents the IC_{50} (nM) for displacement of [^{3}H]QNB, with the range of values obtained shown in parentheses. [d] The ratio of QNB/OXO-M.

was subsequently prepared via the aldehyde, followed by condensation with hydroxylamine and dehydration to give the required nitrile **1t**. The anion also reacted with benzophenone to give the tertiary alcohol **1u**.

We attempted to use the same strategy to prepare 3-substituted 1,2,4-triazol-1-yl rings. However, deprotonation of 3-(1,2,4-triazol-1-yl)-1-azabicyclo[2.2.2]octane with *tert*-butyllithium followed by quenching with bromine gave exclusively the 5-bromo derivative as indicated by the chemical shift of the remaining 3-H, which is consistent with previous reports.[22] Introduction of a variety of 3-substituents was achieved by the Sandmeyer reaction on the 3-diazonium salt,[23] derived from the 3-aminotriazole **2m** by aqueous diazotization. This route afforded the 3-bromo (**2v**), 3-chloro (**2w**), 3-azido (**2x**), and 3-nitro (**2y**) triazoles (Scheme XVI).

Scheme XVI[a]



2m

X = Br **2v**
X = Cl **2w**
X = N_3 **2x**
X = NO_2 **2y**

[a] Reagents: (a) HNO_2; (b) for X = Br, Cl use Cu(I)X; for X = N_3, NO_2 use NaX.

Results and Discussion

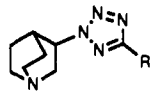
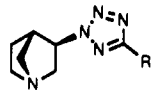
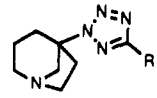
The IC_{50} values for inhibition of tritiated muscarinic ligand binding by the compounds in this study, at rat cerebral cortex muscarinic receptor, were determined as described previously.[24] We have shown that [^{3}H]oxotremorine-M ([^{3}H]OXO-M) binding is inhibited by both muscarinic agonists and antagonists with high potency. Conversely, [^{3}H]quinuclidinyl benzilate ([^{3}H]QNB) binding is inhibited by muscarinic antagonists with high potency, whereas agonists are always much less potent. In consequence, the ratio of the (IC_{50} [^{3}H]QNB/IC_{50} [^{3}H]OXO-M) values is correlated with the potential efficacy of muscarinic compounds as agonists. A ratio of greater than 100 is usually associated with a full agonist, and antagonists have ratios close to unity. Intermediate ratios are suggestive of partial agonism. The results are shown in Tables I, II, and IV. Table VI contains a range of accepted M_1 ligands for comparison.

The effect on IC_{50} OXO-M and IC_{50} QNB values of varying the azabicyclic ring in the four triazole and tetrazole series in Table I is consistent with results from a previous study[1] in a series of 1,2,4-oxadiazoles. Considering first the affinity for the OXO-M-labeled agonist binding site, within each column of Table I it can be seen that generally the most potent compounds are those substituted with *exo*-azabicyclo[2.2.1]heptan-3-yl moiety (row **2**). Compounds substituted with azabicyclo[3.2.1]octan-3-yl group (row **5**) are of slightly lower affinity while the other three azabicyclic substituents (rows **1**, **3**, and **4**), within each azole series, are generally less potent. This pattern of activity reflects a size constraint at the receptor supporting previous conclusions[1] together with geometric and electronic factors which we have not characterized.

The triazoles and tetrazoles series (columns **e**, **o**, and **k** in Table I), when compared across the series of azabicyclic rings, are of similar potency against (OXO-M-labeled re-

(22) Kauffman, T.; Legler, J.; Ludorff, E.; Fischer, H. Synthesis and Properties of Azole-Pyridine Combinations: Problem of the Hydrolytic Cleavage of Hetarene Combinations. *Angew. Chem. Int. Ed. Engl.* **1972**, *11* (9), 846–847.
(23) Temple, C. *Heterocyclic Compounds*; Montgomery, J. A., Ed.; John Wiley and Sons: New York, 1981; Vol. 37, 225–238.
(24) Brown, F.; Clark, M.; Graves, D.; Hadley, M.; Hatcher, J.; McArthur, R.; Riley, G.; Semple, J. Variation of Muscarinic Activities of Oxotremorine Analogues. *Drug Dev. Res.* **1988**, *14*, 343–347.

Table II. Variation of Substituent on Tetrazoles[a]

R	 1	 2	 5
H	242[b] (195–300)	30[b] (22–40)	19[b] (16.5–22)
n	15900[c] (9000–28000) 66[d]	14300[c] (9250–22000) 481[d]	7200[c] (4000–12800) 376[d]
CH_3	31[b] (13.5–62.5) 2800[c]	4.2[b] (3.0–6.9) 1900[c]	14[b] (11.5–17) 1900[c]
o	(2600–3100) 92[d]	(1250–3000) 456[d]	(1300–2850) 138[d]
NH_2	38[b] (35–42) 4400[c]	2.6[b] (2.2–3.2) 4360[c]	5.9[b] (4.6–7.5) 2670[c]
p	(3000–6500) 115[d]	(3400–5600) 1663[d]	(925–3300) 455[d]
Cl	27[b] (22–46) 578[c]	7.6[b] (7.3–8.0) 630[c]	3.5[b] (3.2–3.8) 332[c]
q	(460–725) 21[d]	(570–770) 83[d]	(220–500) 95[d]
Br	20[b] (18–21.5) 488[c]	7.4[b] (6.5–8.5) 822[c]	5.5[b] (4.6–6.5) 279[c]
r	(305–780) 25[d]	(430–1500) 111[d]	(190–410) 51[d]
I	43[b] (36–52) 216[c]	48[b] (42–57) 372[c]	
s	(130–360) 5[d]	(330–420) 8[d]	
CN	1400[b] (1400–1400) 5200[c]		
t	(3500–7750) 3.7[d]		
CPh_2OH	3.6[b] (3.2–4.1) 2.8[c]		
u	(2.5–3.2) 0.8[d]		

[a] See footnote *a* in Table I. [b] See footnote *b* in Table I. [c] See footnote *c* in Table I. [d] See footnote *d* in Table I.

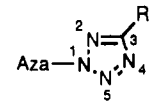
ceptor binding. The tetrazole series (column **c**) is generally less active, though **2c** is more potent than **2k**. We have previously shown[2] that the potency against OXO-M binding in a series of quinuclidin-3-yl azoles is given by the equation:

$$\log (IC_{50}\ \text{OXO-M}) = 0.27\nu_2 + 0.18\nu_4 + 4.9$$

where ν_2 and ν_4 represent the electrostatic minima adjacent to positions corresponding to the 1- and 3-positions in the triazole (**e**). We have calculated the electrostatic potentials around the four azole systems in Table I as described previously.[2] The azabicyclic ring was replaced with a methyl substituent to simplify the calculation. We have shown that smaller electrostatic minima adjacent to the comparable positions in the quinuclidin-3-yl tetrazole (**1c**)[2] predict the lower activity of this series. This effect is now shown to be generally consistent over a range of azabicyclic systems.

The affinity of the compounds in Table I for the antagonist binding site labeled by QNB is broadly independent of the azole series but is affected by variation of the azabicycle. It has previously been shown[2,3] that affinity for the antagonist binding site in a closely related series

Table III.[a] Electrostatic Minima (ν_2 and ν_4) and Lipophilicity of the Tetrazole Substituent (R)



R	π[b]	ν_2[c]	ν_4[c]
H	0	−75.6	−58.3
CH_3	0.56	−77.3	−61.7
NH_2	−0.5[d]	−73.6	−62.8
Cl	0.71	−67.9	−51.4
Br	0.86		
I	1.12		
CN	−0.57	−58.8	−40.0

[a] Numbering system used corresponds with that used in the discussion (in order to be consistent between various triazole and tetrazole series). [b] Reference 31. [c] The depth of the electrostatic minima in kcal mol^{-1} (calculated as described in the Experimental Section) in the plane of the aromatic ring adjacent to position 2 for ν_2 and position 4 for ν_4. [d] Taken from measurement of amino substituent in *p*-nitrobenzene as an approximation to an electron-deficient aromatic ring (e.g. tetrazole), ref 31.

of compounds is dependent on the magnitude of the lipophilic interaction at position 3 of the azole substituted by a methyl group in Table I. However, affinity is independent of the electrostatic minima around the azole. Thus, there is little variability across the rows in Table I of azoles. Variation down the columns in Table I is a result of changes in the strength of the charge-reinforced hydrogen bond from the nitrogen atom of the azabicycle to the receptor. This is dependent on how azabicyclic structure affects the basicity of the nitrogen atom[25] and will be the subject of a future publication.

The IC_{50} QNB/IC_{50} OXO-M ratios in Table I, which are a product of the factors discussed above, vary from 36 for **1c**, suggesting partial agonism, to 844 for **3e**, suggesting full agonism. This value is higher than previously seen in this class of muscarinic agonists, and provides a suitable candidate with which to test the theory that only full agonists are of use in the treatment of AD.[26]

Substituent Variation

The effect of a range of sizes of substituents on muscarinic activity at the 3-position in a quinuclidin-3-yl-1,2,4-oxadiazol-5-yl series[3,25] has been described. Only small substituents of the size of methyl and ethyl were compatible with (IC_{50} QNB/IC_{50} OXO-M) ratios predictive of partial to full agonist character and high affinity for the OXO-M-labeled binding site.

Substituents **n** to **t** in Table II were selected as potentially demonstrating full to partial agonist character in this series of muscarinic ligands. The N-linked tetrazoles in Table II represent a potent series in which to investigate the effect of substitution.

We have previously shown[2] that the affinity at the agonist OXO-M-labeled binding site is related to a lipophilic interaction at position 3 as defined in Table III as well as the electrostatic potentials at ν_2 and ν_4. The electrostatic potentials at these positions and the lipophilicity of the 3-substituent for the compounds in Table II are shown in Table III. Again, the electrostatic potentials were calculated for molecules where the azabicycle was replaced by a methyl group to simplify the calculation. The lipophilicity of the substituents is included to enable

(25) Wyman, P. A. Unpublished results.
(26) Hansch, C.; Leo, A. Substituent Constants for Correlation Analysis in Chemistry and Biology; Wiley Interscience: New York, 1979, Vol. III, p 15 and Vol. IV, p 49.

the contribution to binding made by the lipophilic interaction at position 3 to be assessed.

The increase in affinity for the agonist OXO-M-labeled receptor on replacement of a hydrogen substituent with a methyl substituent (**n** to **o**) was consistent across all three series. A comparable increase in affinity for the antagonist QNB-labeled receptor was also observed, with the result that the (IC_{50} QNB/IC_{50} OXO-M) ratios were only marginally reduced. These changes are consistent with IC_{50} OXO-M binding being determined by ν_2 and ν_4 (which are not significantly affected by methyl substitution) and a lipophilic interaction at position 3. The IC_{50} QNB binding which is primarily affected by changes in the lipophilic interaction at position 3[3] is also equally increased.

Interestingly, substitution of methyl (**o**) by amino (**p**) (Table II) gave either small increases or decreases in affinity at the agonist OXO-M-labeled binding site, while affinity at the antagonist QNB-labeled site was decreased. This suggests more agonistic character in these compounds. We suspect that delocalization of the amino nitrogen atom lone pair onto N-2 is a major factor contributing to the high affinity of these compounds at the OXO-M-labeled site. The electrostatic potentials ν_2 and ν_4 should become more negative upon amino substitution due to electron release by the amino substituent, thus increasing affinity at the OXO-M-labeled site. This is not seen in Table III but is apparent in Table V. We suspect the figures for ν_2 and ν_4 with amino substitution shown in Table II are incorrect. We have taken a value of π for an amino substituent in *p*-nitrobenzene as an equivalent to the electron-deficient tetrazole ring.[26] Binding to the antagonist QNB-labeled site is mainly dependent on the lipophilic interaction at position 3 and is therefore decreased as $\Delta\pi$ on methyl to amino substitution is negative.

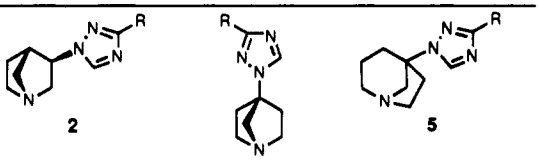
Halogen substitution at position 3 in series **q**, **r**, and **s** (Table II) afforded compounds which had either increased or decreased potencies at the OXO-M-labeled agonist binding site compared to the methyl-substituted series **o** (within each azabicyclic series). By comparison, the affinities at the antagonist QNB-labeled site were all increased. These changes are opposite to those seen in the amino-substituted compounds **p**, and the resulting (IC_{50} QNB/IC_{50} OXO-M) ratios are predictive of these compounds having lower efficacy than the methyl-substituted series. These results can be rationalized by inspection of the changes in π, ν_2, and ν_4 in Table III. The increase in lipophilicity at the 3 position compensates for the reduced electrostatic potentials at ν_2 and ν_4 when considering binding at the OXO-M-labeled site. Binding at the QNB-labeled site determined primarily by the lipophilicity of the substituent at position 3 is increased.

The cyanotetrazole (**1t**) (Table II) has both low potency and efficacy. The electron withdrawing cyano group reduces the electrostatic potentials at ν_2 and ν_4, and is itself hydrophilic, and therefore reduces both QNB and OXO-M binding.

The diphenyl hydroxy tetrazole (**1u**) (Table II) has high affinity for both the agonist site and the antagonist site as it has both a large lipophilic group at position 3 together with predicted similar electrostatic potentials at ν_2 and ν_4 (not calculated) to the methyl-substituted analogue. This compound is consequently a highly potent antagonist, as is the oxadiazole analogue prepared previously.[3]

The results of a substituent variation study on the N-linked triazole series are presented in Table IV. The electrostatic potentials at ν_2 and ν_4 and the π values of these substituents are presented in Table V. While an increase in affinity at the agonist-labeled OXO-M binding

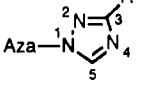
Table IV. Variation of Substituent on Triazoles[a]



R	2	4	5
H	79[b] (48–130) 38200[c]	79[b] (63–100) 39900[c]	12[b] (6.3–22) 3600[c]
j	(34000–43000) 484[d]	(24500–65000) 503[d]	(3300–3950) 290[d]
CH_3	17[b] (13–22) 4270[c]	86[b] (63–117) 14900[c]	12[b] (10.5–36) 2100[c]
k	(2900–6300) 253[d]	(13000–17000) 173[d]	(1800–2600) 174[d]
NH_2	18[b] (17.5–19.5) 3600[c]		13[b] (8.5–19.5) 3900[c]
m	(1600–8200) 196[d]		(2200–6750) 304[d]
Cl	14[b] (6.6–29)		
w	1290[c] (900–1850) 93[d]		
Br	31[b] (30.5–32)		
v	3040[c] (2100–4400) 97[d]		
N_3	1017[b] (900–1150) 26200[c]		
y	(24500–28000) 26[d]		
NO_2	4100[b] (3900–4500) 35600[c]		
y	(27000–47000) 8.5[d]		

[a] See footnote *a* in Table I. [b] See footnote *b* in Table I. [c] See footnote *c* in Table I. [d] See footnote *d* in Table I.

Table V.[a] Electrostatic Minima (ν_2 and ν_4) and Lipophilicity of the Triazole Substituent (R)



R	π[b]	ν_2[c]	ν_4[c]
H	0	−73.2	−84.9
CH_3	0.56	−76.3	−85.1
NH_2	−0.5[d]	−92.4	−90.7
Cl	0.71	−65.5	−76.6
N_3	0.46	−66.6	−74.4
NO_2	−0.28	−49.2	−64.5

[a] See footnote *a* in Table III. [b] See footnote *b* in Table III. [c] See footnote *c* in Table III. [d] See footnote *d* in Table III.

site is seen on introduction of methyl substitution in **2k**, no similar increase is seen for **4k** and **5k**, probably reflecting the different position adopted by the azole when attached to a bridgehead-substituted azabicycle. Introduction of amino substitution (**m**) gives compounds with both similar affinity at the OXO-M-labeled agonist site and at the antagonist QNB-labeled site as the methyl analogues.

Introduction of a halo substituent (rows **v**, **w** in Table IV) gives compounds with potencies at the agonist OXO-

Table VI. In Vitro Affinities of Muscarinic Receptors for Standard Muscarinic Ligands[a]

compound	[^{3}H]OXO-M IC_{50} (nM)	[^{3}H]QNB IC_{50} (nM)	IC_{50} QNB/ IC_{50} OXO-M
acetylcholine[b]	12 (7–20) $n = 3$	24000 (12000–50000) $n = 3$	2000
arecoline	115 (75–170) $n = 16$	25400 (10000–110000) $n = 8$	222
oxotremorine	17 (7.5–33) $n = 18$	3300 (1750–4400) $n = 11$	190
oxotremorine-M	13 (9–33) $n = 10$	23000 (12000–62000) $n = 12$	1820
pirenzepine	322 (80–1400) $n = 30$	213 (145–1450) $n = 31$	0.7

[a] Displacement of tritiated radioligand from rat cortical homogenates. Each value represents the geometric mean of n determinations performed in separate experiments using seven concentrations. The ranges of values are given in parentheses. [b] Assays carried out in the presence of eserine.

M-labeled receptor similar to the methyl-substituted analogues as seen previously but with higher affinity for the antagonist QNB-labeled site. The resulting (IC_{50} QNB/IC_{50} OXO-M) ratios are suggestive of compounds of lower efficacy compared to the methyl-substituted analogues.

The azido- and nitro-substituted triazoles manifest lower affinity both at the OXO-M- and QNB-labeled site. The additional size of the substituents probably cannot be tolerated at the OXO-M receptor and the electron withdrawing character of both functional groups reduces the electrostatic potentials at ν_2 and ν_4. In addition the nitro group is incompatible with the requirement for a lipophilic substituent at position 3.

Conclusion

Within the four azole series studied in this work, the *exo*-3-azabicyclo[2.2.1]heptane substituent gave the most potent and efficacious muscarinic agonists, consistent with results found in other related azole series.[2]

The effect of substituent variation on the azole moiety has been rationalized in terms of a previously described model,[1,3] though the potency and efficacy of the amino-substituted compounds remains somewhat anomalous, possibly due to difficulties in calculating their electrostatic potentials and π values correctly. Binding at the agonist binding site is mainly dependent on the magnitude of the electrostatic potentials at ν_2 and ν_4, and also on a lipophilic interaction at position 3. Binding at the antagonist QNB-labeled site is more dependent upon a lipophilic interaction at position 3 than on the electrostatic potentials at ν_2 and ν_4.

Substituent variation has afforded muscarinic ligands with high potencies and a range of efficacies. The compounds **2o**, **2e**, and **2p** have the properties predictive of a full agonist of high potency, while compounds such as **1q**, **1r**, and **1s**, have the characteristics predictive of partial agonists. There has been a debate in the literature concerning whether a full muscarinic agonist[27] or a partial muscarinic agonist[4] is required in the treatment of AD. This series provides suitable candidate drugs for both approaches.

Experimental Section

Chemistry. Melting points and boiling points are uncorrected. The elemental analyses were within 0.4% of the theoretical values. NMR spectra were recorded on a Bruker AM-400, Bruker AC-250 or a JEOL GX-270 spectrometer using Me_4Si as internal standard. UV spectra were recorded on a Perkin-Elmer SP800 spectrometer. All evaporations of solvents were carried out under reduced pressure, and organic solutions were dried over $NaSO_4$. For column chromatography, the silica gel used was Merck Kieselgel 60, and the alumina, Camag Brockmann type II alkaline or BDH Brockmann type I neutral. Petroleum ether refers to the fraction with bp 60–80 °C.

1-[(Ethoxycarbonyl)methyl]-3-(methoxycarbonyl)-pyrrolidine (7).[6] 1-Benzyl-3-(methoxycarbonyl)pyrrolidine (**6**)[7] (232 g, 1.05 mol) was dissolved in EtOH (1 L) and treated with ethyl bromoacetate (184 g, 1.1 mol) and K_2CO_3 (27 g, 0.2 mol) with stirring and the solution heated under reflux for 6 h. The reaction was then allowed to cool and was filtered. The filtrate was evaporated to dryness and the residual oil washed with Et_2O to remove any unreacted ethyl bromoacetate. After separation from Et_2O, the oil was redissolved in EtOH (500 mL) and treated with acetic acid (30 mL). To this was added 10% Pd–C (20 g), and the mixture was stirred under an atmosphere of H_2 until H_2 uptake was complete. The solution was filtered through Celite and evaporated to dryness, and the residue partitioned between saturated aqueous K_2CO_3 and $CHCl_3$ (2 × 500 mL). The organic extracts were dried, evaporated to dryness, and purified by vacuum distillation to afford **7** as the main fraction (132.5 g, 59%): bp 110–120 °C at 0.5 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.3 (3 H, *t*, J = 8 Hz, CH_3), 2.1–2.2 (2 H, m), 2.5 (1 H, q, J = 8 Hz), 2.75 (1 H, br s), 2.85–3.0 (1 H, m), 2.05–3.2 (2 H, m), 3.3 and 3.4 each (1 H, d, J = 16 Hz), 3.7 (3 H, s, CH_3), 4.2 (2 H, q, J = 8 Hz).

3-Oxo-1-azabicyclo[2.2.1]heptane (8).[5] Potassium *tert*-butoxide (165 g, 1.35 mol) in dry toluene (2 L) was heated to reflux under N_2. **7** (132 g, 0.62 mol) was added dropwise over a period of 1 h, and the reaction was heated under reflux for 2 h. The mixture was then cooled on an ice/methanol bath to −10 °C and acetic acid (80 mL) added with continuous stirring. The toluene solution was repeatedly extracted with 5 N HCl (4 × 500 mL), and the combined aqueous extracts were heated under reflux for 10 h. The solution was evaporated to ca. 1 L and neutralized with saturated aqueous K_2CO_3. Extraction with CH_2Cl_2 (4 × 200 mL) afforded a yellow oil which was purified by vacuum distillation to afford **8** (24.9 g, 36%): bp 80–82 °C at 0.4 mmHg; mp 40–50 °C (hygroscopic); ^{1}H NMR ($CDCl_3$) δ 1.73–1.85 (1 H, m), 2.0–2.2 (1 H, m), 2.65–2.85 (4 H, m), 3.3–3.5 (3 H, m). **8** crystallized from acetone as an oxalate salt: mp 144–145 °C; ^{1}H NMR (DMSO) δ 1.89–2.04 (1 H, m), 2.4–2.58 (1 H, m), 3.30 (1 H, d, J = 4 Hz), 3.40–3.90 (5 H, m), 3.85–4.07 (1 H, m), ^{13}C NMR (DMSO) δ 22.6 (C-5), 46.7 (C-4), 50.6, 57.5, 60.6 (C-2,6,7), 164.6 (oxalate), 206 (C=O). Anal. ($C_6H_9NO \cdot C_2H_2O_4 \cdot 0.2H_2O$) C, H, N.

***endo*-3-Hydroxy-1-azabicyclo[2.2.1]heptane (9).**[5] **8** (10 g, 0.088 mol) in EtOH (50 mL) was treated with Adam's catalyst (PtO_2) (1 g) and hydrogenated at room temperature for 5 h. The suspension was filtered through Celite and evaporated to dryness and the residue crystallized from Et_2O to afford **9** (8.72 g, 85%): mp 132–135 °C [lit.[5] mp 140–142 °C]; ^{1}H NMR ($CDCl_3$) δ 1.30–1.52 (1 H, m), 2.0–2.15 (2 H, m), 2.35–2.45 (1 H, m), 2.50–2.72 (3 H, m), 2.80–2.95 (1 H, m), 2.95–3.10 (1 H, m), 4.25–4.37 (1 H, m), 4.90 (1 H, s, OH). The oxalate salt was crystallized from acetone, mp 168–170 °C.

***cis*-2-Benzylhexahydropyrano[3,4-*c*]pyrrol-4(3a*H*)-one (11).**[8] To a stirred solution of 5,6-dihydro-2*H*-pyran-2-one[28] (**10**) (136 g, 1.39 mol) in CH_2Cl_2 (2 L) at −20 °C was added *N*-benzyl-*N*-(methoxymethyl)-*N*-[(trimethylsilyl)methyl]amine[7] (80% pure) (450 g, 1.5 mol). Trifluoroacetic acid in CH_2Cl_2 (140 mL, 1 M solution) at −20 °C was added and the reaction mixture

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

(28) Nakagawa, M.; Saegusa, J. 5,6-Dihydro-2H-pyran-2-one and 2H-Pyran-2-one. *Organic Syntheses*, Wiley: New York, 1977; Vol. 56, 49–52.

then transferred at −20 °C under a small positive pressure of N_2 via a double-ended needle to a second flask on a water bath at 30 °C. As the cold mixture warmed, an exothermic reaction occurred and the rate of addition was controlled to maintain a gentle reflux. When the addition was complete, the reaction was allowed to stand at room temperature for 2 h. The reaction was then washed with saturated aqueous K_2CO_3, dried, and evaporated to dryness. Purification by vacuum distillation afforded 11 as a single main fraction (180.9 g, 56%): bp 180–190 °C at 0.5 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.55–1.75 (1 H, m), 1.95–2.10 (1 H, m), 2.23–2.34 (1 H, m), 2.63–3.0 (4 H, m), 3.05–3.2 (1 H, m), 3.55 and 3.65 each (1 H, d, J = 12 Hz), 4.22 (1 H, t, J = 2 Hz), 4.35–4.48 (1 H, m), 7.30 (5 H, br s); ^{13}C NMR ($CDCl_3$) δ 28.4, 35.1, 42.1, 57.5, 59.6, 60.2, 67.2, 127.2, 128.4, 128.7, 138.6, 173.3. Anal. ($C_{14}H_{17}NO_2 \cdot C_2H_2O_4$) C, H, N.

***endo*-Ethyl 1-Azabicyclo[2.2.1]heptane-3-carboxylate (3a).**[8] Compound 11 (180 g, 0.78 mol) in EtOH (400 mL) was stirred and cooled to 0 °C, and HBr gas was introduced at such a rate that the temperature did not exceed 20 °C until saturation. The mixture was allowed to stand at room temperature for 6 h and then poured into a well-stirred mixture of $CHCl_3$ (2 L) and saturated aqueous K_2CO_3 (1.5 L) which was cooled by the addition of solid CO_2. The organic phase was separated and the aqueous phase extracted with $CHCl_3$ (4 × 500 mL). The combined organic extracts were dried and evaporated to dryness, and the residue was stirred with Et_2O (3 × 750 mL) to remove unreacted starting material. The Et_2O-insoluble residue was dissolved in EtOH (1 L) and 10% Pd–C (20 g) was added. The mixture was stirred under H_2 at 50 °C for 6 h, filtered through Celite, and evaporated to dryness. The residue was partitioned between saturated aqueous K_2CO_3 (500 mL) and $CHCl_3$ (3 × 500 mL), and the organic extracts were dried and evaporated to dryness to afford **3a** (75 g, 56%): bp 90–95 °C at 0.5 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.28 (3 H, t, J = 8 Hz), 1.3–1.45 (1 H, m), 1.5–1.65 (1 H, m), 2.5–2.7 (3 H, m), 2.85–3.05 (5 H, m), 4.15 (2 H, q, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 25.3, 40.9, 46.3, 53.2, 55.7, 60.5, 61.2, 173.2 (C=O). The oxalate salt crystallized from acetone, mp 130–132 °C. Anal. ($C_9H_{15}NO_2 \cdot C_2H_2O_4$) C, H, N.

α-Methylene-γ-butyrolactone (12).[29] A stirred suspension of sodium hydride (300 g of 80% oil dispersion, 10 mol) in dry Et_2O (8 L) under N_2 was treated slowly with absolute EtOH (60 mL, 1.1 mol), followed immediately by a mixture of ethyl formate (808 mL, 10 mol) and γ-butyrolactone (770 mL, 10 mol) over 1.25 h. The rate of addition was controlled to give a steady reflux and evolution of H_2 (about 220 L). After completing the addition, the mixture was stirred for a further 30 min and the solid filtered, washed with Et_2O, and dried in vacuo to give α-formyl-γ-butyrolactone sodium salt (1.32 kg, 97%). A stirred suspension of paraformaldehyde (270 g, 9.0 mol) in THF (3.5 L) at room temperature in a 20-L flask under N_2 was treated with this product (270 g, 2.0 mol) and the mixture immediately heated to reflux for 1 h. Evolution of a small quantity of gas was observed. The mixture was cooled to 10 °C and treated with saturated aqueous K_2CO_3 (500 mL) and Et_2O (1.5 L), and the organic layer was separated, dried, and evaporated to dryness to afford a pale yellow oil. Purification by vacuum distillation yielded 12 (125 g, 64%): bp 76–80 °C at 8 mmHg; ^{1}H NMR ($CDCl_3$) δ 2.95–3.03 (2 H, m), 4.40 (2 H, t, J = 7 Hz), 5.69 (1 H, t, J = 3 Hz), 6.5 (1 H, t, J = 3 Hz).

7-Benzyl-7-aza-2-oxaspiro[4.4]nonan-1-one (13).[1] A stirred solution of *N*-benzyl-*N*-(methoxymethyl)-*N*-[(trimethylsilyl)-methyl]amine[7] (75% pure) (160 g, 0.51 mol) and 12 (50 g, 0.51 mol) in CH_2Cl_2 (1 L) under N_2 was cooled to 0 °C and treated with trifluoroacetic acid in CH_2Cl_2 (50 mL, 1 M solution) below 5 °C, and the reaction was allowed to stand at room temperature for 2 h. The reaction was then washed with saturated $NaHCO_3$ solution, washed with brine, dried, and evaporated to dryness. Purification by vacuum distillation afforded 13 as a single main fraction (96 g, 81%): bp 160–170 °C 1 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.77–1.92 (1 H, m), 2.15–2.40 (3 H, m), 2.48–2.78 (3 H, m), 2.85–2.98 (1 H, m), 3.55–3.70 (2 H, m), 4.10–4.30 (2 H, m), 7.15–7.35 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 35.6, 37.6, 47.8, 53.7, 59.7, 62.5, 65.7, 127.1, 128.3, 128.6, 138.6, 181.3.

Ethyl 1-Azabicyclo[2.2.1]heptane-4-carboxylate Hydrobromide (4a). A stirred solution of 13 (96 g, 0.42 mol) in EtOH (150 mL) was saturated with HBr gas at 0 °C and allowed to stand at room temperature for 18 h. The solution was evaporated to dryness and the residue partitioned between saturated aqueous K_2CO_3 and $CHCl_3$. The organic extracts were dried and evaporated to dryness, and the residue was treated with Et_2O. The resulting solid was filtered off, washed with Et_2O, and dried to give a white solid (130 g). This was suspended in EtOH (500 mL) and hydrogenated over 10% Pd–C (8 g) at atmospheric temperature and pressure for 18 h. The mixture was filtered through Celite, the solid washed several times with hot EtOH, and the combined filtrate evaporated to dryness to give **4a** (80.1 g, 76%): mp 203–205 °C; ^{1}H NMR (HBr salt) (CD_3OD) δ 1.3 (3 H, t, J = 7 Hz), 2.0–2.18 (2 H, m), 2.3–2.5 (2 H, m), 3.35–3.5 (2 H, m), 3.45 (2 H, s), 3.5–3.7 (2 H, m), 4.25 (2 H, q, J = 7 Hz); ^{13}C NMR (free base) ($CDCl_3$) δ 14.2 (CH_3), 34.2 (C-3,5), 53.9 (C-4), 55.2 (C-2,6), 60.2 and 63.3, 174.5 (C=O). Anal. ($C_9H_{15}NO_2 \cdot HBr$) C, H, N.

***exo*-3-Cyano-1-azabicyclo[2.2.1]heptane (2b) and *endo*-3-Cyano-1-azabicyclo[2.2.1]heptane (3b).** Compound 8 (5.0 g, 0.045 mol) was dissolved in Na-dried DME (200 mL) and tosylmethyl isocyanide (TosMIC) (9.67 g) added under N_2 at 0 °C. Dry EtOH (2.64 mL) was added and the solution cooled under N_2 to −40 °C. KO^{t}Bu (12.28 g) was added portionwise under N_2, maintaining the temperature below −20 °C. The solution was then stirred at −8 °C for 2 h, allowed to warm to room temperature, and stirred for 1 h. The suspension was quenched with sufficient AcOH to dissolve the precipitate and the solution evaporated to dryness. The residue was basified with saturated aqueous K_2CO_3 and extracted with $CHCl_3$, and the organic extracts were dried and evaporated to dryness. The resulting red oil was purified by Kugelröhr distillation (bp 160 °C oven temperature at 10 mmHg) to afford **2b** and **3b** (2.79 g, 56%). The exo and endo isomers were separated by column chromatography on neutral alumina, eluting with Et_2O to EtOAc to afford in order of elution **2b** (1.5 g): ^{1}H NMR ($CDCl_3$) δ 1.14 (1 H, m), 1.67 (1 H, m), 2.22 (1 H, m), 2.47 (2 H, bm), 2.69 (1 H, dm), 2.94 (4 H, complex m); ^{13}C NMR ($CDCl_3$), δ 29.58 (CH_2), 32.29 (CH), 42.92 (CH), 53.80 (CH_2), 59.59 (CH_2), 60.37 (CH_2), 122.23 (CN), which was crystallized from MeOH/Et_2O as an oxalate salt: mp 151–153 °C. Anal. ($C_7H_{10}N_2 \cdot C_2H_2O_4$) C, H, N. Also isolated was **3b** (1.2 g) ^{1}H NMR ($CDCl_3$) δ 1.63 (1 H, m), 1.80 (1 H, m), 2.56 (4 H, complex m), 2.78 (1 H, m), 2.91 (2 H, complex m), 3.18 (1 H, tm); ^{13}C NMR ($CDCl_3$) δ 25.68 (CH_2), 31.08 (CH), 40.72 (CH), 54.05 (CH_2), 59.16 (CH_2), 60.48 (CH_2), 121.61 (CN) (which was crystallized from MeOH/Et_2O as an oxalate salt, mp 139–141 °C). Anal. ($C_7H_{10}N_2 \cdot C_2H_2O_4$) C, H, N.

4-Cyano-1-azabicyclo[2.2.1]heptane (4b). Compound **4a** (7.4 g, 0.03 mol) was dissolved in concentrated HCl (55 mL), water (20 mL) added, and the solution heated under reflux for 17 h. The solution was evaporated to dryness and the residue azeotroped with dry toluene to afford the acid hydrochloride. $SOCl_2$ (100 mL) was added and the reaction heated under reflux for 4.25 h until the solution was homogeneous and then evaporated to dryness and azeotroped with three portions of dry toluene to afford the acid chloride hydrochloride. This was suspended in dry CH_2Cl_2 (100 mL) and cooled to −40 °C and a saturated solution of ammonia in CH_2Cl_2 (400 mL) added. The solution was warmed to room temperature overnight, and saturated aqueous K_2CO_3 was added. The organic extract was dried and evaporated to dryness to afford the amide (2.63 g, 66%): ^{1}H NMR (CD_3OD) δ 1.50–1.67 (2 H, m), 1.9–2.08 (2 H, m), 2.62–2.78 (2 H, m), 2.65 (2 H, s), 2.95–3.10 (2 H, m), 5.00 (NH_2). The amide (2.63 g, 0.02 mol) was suspended in dry THF (100 mL) and pyridine (3.2 mL, 0.04 mol) added. The mixture was treated with TFAA (3.5 mL, 0.024 mol) with stirring, maintaining an internal temperature of <30 °C. After 15 min, the reaction was quenched with water (5 mL), evaporated to dryness, and partitioned between saturated aqueous K_2CO_3 and $CHCl_3$. The organic extracts were dried, evaporated to dryness, and purified by Kugelröhr distillation (bp 125 °C oven temperature at 1.5 mmHg) which slowly crystallized on standing to afford **4b** (2.0 g, 82%): mp 30–33 °C; ^{1}H NMR ($CDCl_3$) δ 1.58–1.62 (2 H, m), 1.95–2.10 (2 H, m), 2.58–2.70 (2 H, m), 2.75 (2 H, s), 2.95–3.10 (2 H, m). The oxalate salt crystallized

(29) Murray, A. W.; Reid, R. G. Convenient Synthesis of α-Epoxylactones (4-Oxo-1,5-dioxaspiro[2,4]heptanes and -[2,5]octanes). *Synthesis* **1985**, 35–38.

from acetone: mp 143–145 °C; ^{13}C NMR [oxalate] (CD_3OD) δ 32.9 (C-3,5), 38.5 (C-4), 53.7 (C-2,6), 61.5 (C-7), 118.1 (C≡N), 166.1 (oxalate). Anal. ($C_7H_{10}N_2 \cdot C_2H_2O_4$) C, H, N.

***exo*-3-(2-Methyltetrazol-5-yl)-1-azabicyclo[2.2.1]heptane (2c).** Compound **2b** (515 mg, 4.22 mmol) was dissolved in dry THF (5 mL), azidotrimethylsilane (2.0 mL, 15.1 mmol) was added, and the mixture was placed in a PTFE-lined autoclave. The solution was heated to 110 °C for 20 h, and the resulting mixture was transferred to a flask using MeOH. Excess solvent was evaporated, and an ethereal solution of diazomethane (10 mmol) was added at 0 °C. The mixture was stirred for 1.5 h, evaporated to dryness, and dissolved in saturated aqueous K_2CO_3. The solution was extracted with EtOAc, and the organic extracts were dried and evaporated to dryness. The residue was purified by column chromatography on neutral alumina eluting with EtOAc/MeOH (36:1). The fraction first eluted (**2c**) was crystallized from MeOH/Et_2O as a hydrochloride salt (143 mg, 19%): mp 185–187 °C; ^{1}H NMR (DMSO) δ 1.86 (1 H, m), 2.06 (1 H, m), 3.05 (1 H, d), 3.20 (2 H, m), 3.33 (2 H, m), 3.58 (1 H, m), 3.76 (1 H, m), 4.33 (3 H, s, Me); ^{13}C NMR (DMSO) δ 26.51, 36.36, 41.13, 51.23, 56.42, 56.79, 166.12. Anal. ($C_8H_{13}N_5 \cdot 0.7HCl \cdot H_2O$) C, H, N. Further elution gave the 1-methyl isomer.

***endo*-3-(2-Methyltetrazol-5-yl)-1-azabicyclo[2.2.1]heptane (3c).** Compound **3c** was prepared from **3b**, as for **2c** to afford **3c**, which was crystallized from acetone/Et_2O as a hydrochloride salt in 7% yield: mp 197–200 °C; ^{1}H NMR (DMSO) δ 1.42 (1 H, m), 1.84 (1 H, m), 3.19 (4 H, complex m), 3.81 (1 H, dt), 4.01 (1 H, m), 4.36 (3 H, s, Me); ^{13}C NMR (DMSO) δ 21.92, 35.09, 35.10, 40.01, 51.91, 54.49, 59.18, 163.92. Anal. ($C_8H_{13}N_5 \cdot HCl$) C, H, N.

4-(2-Methyltetrazol-5-yl)-1-azabicyclo[2.2.1]octane (4c). Compound **4c** was prepared from **4b**, as for **2c** to afford **4c**, which was crystallized from MeOH/Et_2O as an oxalate salt in 17% yield: mp 139–144 °C; ^{1}H NMR (CD_3OD) δ 2.23–2.37 (2 H, m), 2.46–2.64 (2 H, m), 3.4–3.58 (2 H, m), 3.62 (2 H, s), 3.67–3.80 (2 H, m), 4.38 (3 H, s); ^{13}C NMR (DMSO) δ 32.2 (C-3,5), 40.1 (CH_3), 44.4 (C-4), 52.3 (C-2,6), 60.6 (C-7), 163.9 (oxalate), 164.6 (C-5′). Anal. ($C_8H_{13}N_5 \cdot C_2H_2O_4$) C, H, N.

5-(2-Methyltetrazol-5-yl)-1-azabicyclo[3.2.1]octane (5c). Compound **5c** was prepared from **5b** as for **2c**, using dioxane instead of THF, in 7% yield, which was crystallized from MeOH/Et_2O as an oxalate salt: mp 126–128 °C; ^{1}H NMR (CD_3OD) δ 1.98–2.30 (6 H, m), 3.37–3.50 (2 H, m), 3.53–3.68 (2 H, m), 3.70–3.85 (2 H, m), 4.35 (3 H, s, Me); ^{13}C NMR (CD_3OD) δ 18.0, 33.7 and 34.9 (all CH_2), 40.2 (CH_3), 43.2 (C-5), 52.0, 53.9 and 61.9 (all CH_2), 166.7 (oxalate), 168.8 (C-5′). Anal. ($C_9H_{15}N_5 \cdot C_2H_2O_4 \cdot 0.3H_2O$) C, H, N.

***N*-Methoxy-*N*-methyl-1-azabicyclo[3.2.1]octane-4-carboxamide (5d).** Compound **5a** (10 g, 0.059 mol) was dissolved in 5 N HCl (100 mL), heated under reflux for 1.5 h, and evaporated to dryness. The residue was dissolved in $SOCl_2$ (50 mL) and heated under reflux for 15 min until the evolution of gas had ceased. The solution was evaporated to dryness, azeotroped with dry toluene, and then redissolved in absolute $CHCl_3$ (100 mL) and treated with *N,O*-dimethylhydroxylamine hydrochloride (5.72 g, 0.065 mol) at −20 °C and pyridine (23 g, 0.3 mol), added slowly with stirring, maintaining the temperature below −20 °C. The solution was allowed to warm to 20 °C, stirred for 3 h, and then evaporated to dryness. The residue was partitioned between $CHCl_3$ and saturated aqueous K_2CO_3, and the organic extracts were dried and evaporated to dryness. The residue was purified by Kugelröhr distillation (bp 160 °C oven temperature at 0.5 mmHg) which crystallized on standing to afford **5d** (69%): mp 38–40 °C; ^{1}H NMR ($CDCl_3$) δ 1.47 (1 H, m), 1.68–2.13 (7 H, m), 2.78–3.15 (6 H, m), 3.17 (3 H, s), 3.67 (3 H, s); ^{13}C NMR (CD_3OD) δ 18.0 (C-4), 30.4, 32.1 (C-3,6), 33.1 (NMe), 51.7, 51.9, 53.6, 60.6 (C-2,7,8), 61.9 (OMe), 166.5 (oxalate), 174.4 (C=O). The oxalate salt crystallized from acetone, mp 145–146 °C. Anal. ($C_{10}H_{18}N_2O_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

***endo*-*N*-Methyl-*N*-methoxy-1-azabicyclo[2.2.1]heptane-3-carboxamide (3d).** Compound **3d** was prepared from **3a** as for **5d**, heating in 5 N HCl for 4 h, in $SOCl_2$ for 15 min, and using dry MeCN instead of absolute $CHCl_3$, in 35% yield of an oil **3d**: bp 150 °C at 0.5 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.35–1.45 (2 H, m), 2.40–2.50 (1 H, m), 2.55–3.15 (7 H, m), 3.20 (3 H, s), 3.73 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 25.2, 32.3, 40.9 (NMe), 44.1 (OMe), 53.7, 56.3, 61.2, 62.3, 128.3 (C=O). The oxalate salt crystallized from acetone, mp 90–97 °C. Anal. ($C_9H_{16}N_2O_2 \cdot C_2H_2O_4 \cdot 0.3H_2O$) C, H, N.

***N*-Methoxy-*N*-methyl-1-azabicyclo[2.2.1]heptane-4-carboxamide (4d).** Compound **4d** was prepared from **4a** as for **3d**, heating in 5 N HCl for 17 h, in $SOCl_2$ for 4 h, and purifying **4d** by decolorization with charcoal in CH_2Cl_2 and recrystallization from Et_2O instead of Kugelröhr distillation, in 84% yield: mp 108–110 °C; ^{1}H NMR ($CDCl_3$) δ 1.60–1.75 (2 H, m), 1.85–1.95 (2 H, m), 2.57–2.70 (2 H, m), 2.75 (2 H, s), 2.95–3.10 (2 H, m), 3.25 (3 H, s, NMe), 3.75 (3 H, s, OMe); ^{13}C NMR ($CDCl_3$) δ 33.1 (C-4), 34.0 (C-3,C-5), 55.5 (C-2,C-6), 55.7 (C-7), 61.4 (NMe), 63.1 (OMe), 175 (C=O). The oxalate salt crystallized from acetone, mp 174–175 °C. Anal. ($C_9H_{16}N_2O_2 \cdot C_2H_2O_4 \cdot 0.1H_2O$) C, H, N.

5-Ethynyl-1-azabicyclo[3.2.1]octane (14). Compound **5d** (10 g, 0.05 mol) in dry THF (250 mL) was treated with DIBAL (43 mL of a 1.5 M solution in toluene, 0.065 mol) at −60 °C, and warmed to room temperature over 1.5 h. The mixture was cooled to −60 °C and poured into 5 N HCl at −20 °C, and the solution was evaporated to remove THF and partitioned between saturated aqueous K_2CO_3 and $CHCl_3$. The organic extracts were dried and evaporated to dryness, and the residue was purified by Kugelröhr distillation to afford the aldehyde (5.5 g, 80%): bp 140–150 °C at 0.5 mmHg; ^{1}H NMR ($CDCl_3$) δ 9.55 (1 H, s). A solution of the aldehyde (5.0 g, 0.036 mol) in CH_2Cl_2 (25 mL) was added at room temperature to a mixture prepared by stirring together Ph_3P (18.8 g, 0.072 mol), CBr_4 (23.6 g, 0.072 mol), and Zn powder (4.68 g, 0.072 mol) in CH_2Cl_2 (150 mL) for 24 h at room temperature. The solution was then stirred for 2 h, and saturated aqueous K_2CO_3 was added. The solution was then filtered through Kieselguhr and the organic layer separated. The aqueous layer was reextracted, and the combined organic extracts were dried and evaporated to dryness to afford a gum which was triturated with Et_2O to afford the dibromoethenyl derivative contaminated with a little Ph_3P (10 g, 95%). A solution of this compound (10 g, 34 mmol) in dry THF (200 mL) was cooled to −78 °C under N_2 and treated with ^{n}BuLi in hexane (49 mL of a 1.6 M solution, 0.078 mol). After stirring for 1 h, the solution was warmed to room temperature for 1 h. The mixture was then cooled to −78 °C and acetic acid (10 mL) added. The solution was evaporated to dryness and the residue partitioned between saturated aqueous K_2CO_3 and $CHCl_3$. The combined organic extracts were dried, evaporated to dryness, and purified by vacuum distillation to afford 14 (2.5 g, 51%): bp 110–120 °C at 0.5 mmHg, mp 41–42 °C, ^{1}H NMR ($CDCl_3$) δ 1.35–1.50 (1 H, m), 1.6–2.1 (5 H, m), 2.15 (1 H, s), 2.7–2.95 (5 H, m), 3.00–3.15 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 19.4, 36.9, 37.1, 38.3, 52.5, 54.5, 66.1, 68.9, 89.2. The oxalate salt was crystallized from acetone, mp 116–119 °C. Anal. ($C_9H_{13}N \cdot C_2H_2O_4 \cdot 0.4H_2O$) C, H, N.

5-(2-Methyl-1,2,3-triazol-4-yl)-1-azabicyclo[3.2.1]octane (5e). A solution of 14 (1.0 g, 0.0074 mol) in THF (5 mL) was treated with azidotrimethylsilane (1.27 g, 0.011 mol) at 140 °C for 8 h in a PTFE-lined autoclave. The reaction was then cooled, treated with MeOH (30 mL), and evaporated to dryness. The residue was dissolved in MeOH (30 mL), treated with diazomethane in Et_2O (excess), and allowed to stand for 15 min at room temperature. The reaction mixture was then evaporated to dryness and purified by column chromatography on neutral alumina eluting with EtOAc/MeOH (7:1) to afford **5e**, which was crystallized from petroleum ether (99 mg, 7%): mp 65–70 °C; ^{1}H NMR ($CDCl_3$) δ 1.4–1.55 (1 H, m), 1.70–2.05 (5 H, m), 2.70–3.20 (6 H, m), 4.10 (3 H, s, NMe), 7.3 (1 H, s, CH); ^{13}C NMR ($CDCl_3$) δ 19.8, 36.5, 37.0, 41.5 (CH_3), 52.2, 54.4, 65.5, 130.9, 153.4. The oxalate salt was crystallized from acetone, mp 105–107 °C. Anal. ($C_{10}H_{16}N_4 \cdot 1.5C_2H_2O_4$) C, H, N.

***endo*-3-Acetyl-1-azabicyclo[2.2.1]heptane (3f).** Compound **3d** (3.6 g, 0.0195 mol) in dry THF (100 mL) under N_2 was cooled to −50 °C and treated dropwise with MeLi in Et_2O (20 mL of a 1 M solution, 0.02 mol) and the reaction allowed to warm to −20 °C over 30 min. The solution was then recooled to −50 °C, AcOH added, and the solution evaporated to dryness. The residue was partitioned between saturated aqueous K_2CO_3 and $CHCl_3$, and the organic phases were dried and evaporated to dryness to afford an oil which was purified by Kugelröhr distillation to afford **3c** (2.8 g, 100%): bp 140 °C oven temperature at 1.0 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.08–1.22 (1 H, m), 1.38–1.54 (1 H, m), 2.19 (3 H, s, Me), 2.44–3.05 (8 H, m); ^{13}C NMR ($CDCl_3$) δ 25.1 (C-5), 30.65 (CH_3),

41.0 (C-4), 53.8, 54.4, and 62.2 (C-2,6,7), 55.0 (C-3), 208.4 (C=O). The oxalate salt was crystallized from acetone, mp 100–102 °C. Anal. ($C_8H_{13}NO·C_2H_2O_4·0.3H_2O$) C, H, N.

4-Acetyl-1-azabicyclo[2.2.1]heptane (4f). Compound **4f** was prepared from **4d** as for **3f** to afford an oil **4f** in 68% yield: bp 100–110 °C at 0.5 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.40–1.52 (2 H, m), 1.92–2.05 (2 H, m), 2.4 (3 H, s, Me), 2.58–2.72 (4 H, m), 2.98–3.10 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 28.3 (CH_3), 34.5 (C-3,5), 55.5 (C-2,6), 62.5 (C-4), 63.4 (C-7), 210.1 (C=O). The oxalate salt was crystallized from acetone, mp 90–92 °C. Anal. ($C_8H_{13}NO·C_2H_2O_4$) C, H, N.

5-Acetyl-1-azabicyclo[3.2.1]octane (5f). Compound **5f** was prepared from **5d** as for **3f**, using dry Et_2O instead of THF, to afford an oil **5f** in 88% yield: bp 150 °C oven temperature at 0.4 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.45–1.55 (1 H, m), 1.65–1.90 (4 H, m), 2.00–2.10 (1 H, m), 2.15 (3 H, s), 2.65–3.00 (5 H, m), 3.05–3.20 (1 H, m); IR (film) ν (C=O) 1695 cm^{-1}. The hydrochloride salt was crystallized from MeOH/Et_2O, mp 190–191 °C. Anal. ($C_9H_{15}NO·HCl$) C, H, N.

***endo*-3-[[(Triphenylphosphoranylidene)methyl]carbonyl]-1-azabicyclo[2.2.1]heptane (3g).** ***exo*-3-[[(Triphenylphosphoranylidene)methyl]carbonyl]-1-azabicyclo[2.2.1]heptane (2g).** Compound **3f** (2.8 g, 0.02 mol) in Et_2O (50 mL) was treated with excess HCl gas at room temperature to complete precipitation and then evaporated to dryness. The residue was dissolved in MeOH (50 mL) and treated with Cl_2 in MeOH (1.5 g in 50 mL, 0.021 mol) at 0 °C. The solution was allowed to warm to room temperature over 4 h whereupon the solution was colorless and then evaporated to dryness, and the residue was treated with Ph_3P (10 g, 0.038 mol) in dry MeCN (50 mL) under N_2 and heated at reflux for 16 h. The solution was then evaporated to dryness and partitioned between saturated aqueous K_2CO_3 and $CHCl_3$, and the organic extracts were dried and evaporated to dryness to afford a gum which was purified by column chromatography on basic alumina eluting with EtOAc/MeOH (14:1) to afford a mixture of **3f** and **2f** (1.15 g) and eluting with EtOAc/MeOH (5:1) to afford **3g** which was crystallized from Et_2O (1.9 g, 23%): mp 228–230 °C; ^{1}H NMR ($CDCl_3$) δ 1.10–1.20 (1 H, m), 1.5–1.64 (1 H, m), 2.20–2.31 (2 H, m), 2.50–2.65 (1 H, m), 2.65–2.86 (4 H, m), 3.03–3.14 (1 H, m), 3.67 (1 H, d, J = 26 Hz, CH=P), 7.36–7.70 (15 H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 30.6 (C-5), 42.1 (C-4), 50.15 (CH=P, d, J = 108 Hz), 52.4 (C-3, d, J = 13 Hz), 54.0, 58.9, 60.0 (C-2,6,7), 127.3 (d, J = 90 Hz), 128 (d, J = 12 Hz), 131 (d, J = 3 Hz), 133.0 (d, J = 0.4 Hz), 194 (d, J = 2 Hz). Anal. ($C_{26}H_{26}NOP·H_2O$) C, H, N. Elution with EtOAc/MeOH (4:1) afforded **2g** which was crystallized from Et_2O (0.9 g, 11%): mp 215–217 °C; ^{1}H NMR ($CDCl_3$) δ 1.30–1.45 (1 H, m), 1.6–1.72 (1 H, m), 2.35–2.43 (1 H, m), 2.50–3.0 (7 H, m), 3.73 (1 H, d, J = 26 Hz, CH=P), 7.40–7.70 (15 H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 25.1 (C-5), 42.9 (C-4), 50.6 (CH=P, d, J = 108 Hz), 51.8 (C-3, d, J = 14 Hz), 54.3, 56.2 (d, J = 2.6 Hz), 62.0 (C-2,6,7), 127.4 (d, J = 90 Hz), 128.8 (d, J = 12.5 Hz), 131.9 (d, J = 2.6 Hz), 133.0 (d, J = 10.4 Hz), 192.2 (d, J = 2 Hz, C=O). Anal. ($C_{26}H_{26}NOP$) C, H, N.

4-[[(Triphenylphosphoranylidene)methyl]carbonyl]-1-azabicyclo[2.2.1]heptane (4g). Compound **4g** was prepared from **4f** as for **3g** in 59% yield: mp 203–205 °C; ^{1}H NMR ($CDCl_3$) δ 1.4–1.55 (2 H, m), 1.9–2.1 (2 H, m), 2.53–2.7 (4 H, m), 2.9–3.1 (2 H, m), 3.7 (1 H, d, J = 26 Hz), 7.3–7.7 (15 H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 35.3 (C-3,5), 50.5 (CH=P, d, J = 108 Hz), 55.5 (C-2,6), 58.7 (C-4, d, J = 13 Hz), 63.4 (C-7), 127.2 (d, J = 90 Hz), 128.8 (d, J = 12 Hz), 132.0 (d, J = 3 Hz), 133.0 (d, J = 10 Hz), 192.8 (d, J = 2 Hz, C=O). Anal. ($C_{26}H_{26}NOP·1.2H_2O$) C, H, N.

5-[[(Triphenylphosphoranylidene)methyl]carbonyl]-1-azabicyclo[3.2.1]octane (5g). Compound **5g** was prepared from **5f** as for **3g** in 30% yield: mp 206–208 °C; ^{1}H NMR ($CDCl_3$) δ 1.4–1.52 (1 H, m), 1.7–2.0 (4 H), 2.08–2.22 (1 H, td, J = 11 Hz, 5 Hz), 2.74–2.94 (4 H, m), 2.97–3.14 (2 H, m), 3.7 (1 H, d, J = 26.5 Hz), 7.4–7.7 (15 H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 20.8 (C-3), 35.5 and 35.8 (C-4,6), 49.6 (CH=P, d, J = 109 Hz), 52.9, 55.32, 64.5 (C-2,6,7), 53.3 (C-5, d, J = 13 Hz), 127.9 (d, J = 12 Hz), 132.3 (d, J = 3 Hz), 133.4 (d, J = 10 Hz), 196.8 (d, J = 2 Hz, C=O). Anal. ($C_{27}H_{28}NOP$) C, H, N.

***exo*-3-(2*H*-1,2,3-Triazol-4-yl)-1-azabicyclo[2.2.1]heptane (2h).** Compound **2g** (0.9 g, 0.0026 mol) in MeCN (50 mL) was treated with *m*-nitrobenzoyl azide[14] (1.0 g, 0.0052 mol) and heated under reflux for 1 h. The solution was evaporated to dryness, and the residue was dissolved in MeOH (50 mL) and heated under reflux for 24 h. The solution was evaporated to dryness and purified by column chromatography on basic alumina eluting with $CHCl_3$/MeOH (4:1) to afford **2h** (130 mg, 20%): mp 155–160 °C; ^{1}H NMR (CD_3OD) δ 1.40–1.50 (1 H, m), 1.70–1.85 (1 H, m), 2.45 (1 H, d, J = 8 Hz), 2.60–3.15 (7 H, m), 7.65 (1 H, s); ^{13}C NMR (CD_3OD) δ 30.7 (C-5), 39.9 and 44.6 (C-3,4), 49.9, 54.2, 58.6 (C-2,6,7), 128.3 (ArCH), 149.7 (ArC). Anal. ($C_8H_{12}N_4·0.15H_2O$) C, H, N.

***endo*-3-(2*H*-1,2,3-Triazol-4-yl)-1-azabicyclo[2.2.1]heptane (3h).** Compound **3g** (0.4 g, 0.001 mol) in MeCN (30 mL) was treated with *m*-nitrobenzoyl azide[21] (0.39 g, 0.002 mol) under N_2 and heated at reflux for 1 h. The solution was evaporated to dryness and purified by column chromatography on basic alumina eluting with $CHCl_3$/MeOH (6:1) to afford **3h** (0.11 g, 67%) which was crystallized from MeOH/Et_2O: mp 145–147 °C; ^{1}H NMR ($CDCl_3$) δ 1.18–2.4 (1 H, m), and 2.4–2.58 (1 H, m), 2.6–2.75 (2 H, m), 2.75–3.05 (4 H, m), 3.30–3.52 (2 H, m), 7.48 (1 H, s), 8.73 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 24.0 (C-5), 37.8 and 42.4 (C-3,4), 54.0, 58.3 and 61.1 (C-2,6,7), 131.1 (C-5′), and 146.8 (C-4′). Anal. ($C_8H_{12}N_4·0.1H_2O$) C, H, N.

4-(2*H*-1,2,3-Triazol-4-yl)-1-azabicyclo[2.2.1]heptane (4h). Compound **4h** was prepared from **4g** as for **2h**, using MeOH saturated with NH_3 gas for 3 days at room temperature instead of heating under reflux in MeOH, to afford **4h** in 36% yield: mp 164–166 °C; ^{1}H NMR (DMSO) δ 1.45–1.60 (2 H, m), 1.8–1.95 (2 H, m), 2.49–2.65 (4 H, m), 2.83–2.97 (2 H, m), 7.7 (1 H, s); ^{13}C NMR (DMSO) δ 36.4 (C-3,5), 45.7 (C-4), 54.7 (C-2,6), 64.5 (C-7), 128.6 (C-5′), 145.6 (C-4′). Anal. ($C_8H_{12}N_4·0.2H_2O$) C, H, N.

5-(2*H*-1,2,3-Triazol-4-yl)-1-azabicyclo[3.2.1]octane (5h). Compound **5h** was prepared from **5g** as for **3h** in 54% yield: mp 70–75 °C; ^{1}H NMR (CD_3OD) δ 1.70–1.90 (1 H, m), 2.0–2.25 (3 H, m), 2.28–2.41 (2 H, m), 3.02–3.42 (6 H, m), 7.8 (1 H, s); ^{13}C NMR (CD_3OD) δ 20.2 (C-4), 37.2 (C-3,6), 42.2 (C-5), 52.5, 54.8 65.03 (C-2,7,8), 127.4 (C-5′), 150.7 (C-4′). Anal. ($C_9H_{14}N_4·H_2O$) C, H, N.

***exo*-3-(2-Methyl-1,2,3-triazol-4-yl)-1-azabicyclo[2.2.1]heptane (2e).** Compound **2h** (300 mg, 0.0018 mol) in EtOH (10 mL) was treated with a solution of diazomethane in Et_2O (0.01 mol in 10 mL) at 0 °C. The solution was allowed to warm to room temperature over 4 h and evaporated to dryness and chromatographed on alumina eluting with EtOAc/MeOH (3:1). The major fraction **2e** was crystallized from acetone/Et_2O as an oxalate salt in 24% yield: mp 122–125 °C; ^{1}H NMR (CD_3OD) δ 1.85–2.00 (1 H, m), 2.10–2.30 (1 H, m), 3.00 (1 H, d, J = 3 Hz), 3.15–3.75 (7 H, m), 4.13 (3 H, s, Me), 7.6 (1 H, s); ^{13}C NMR (CD_3OD) δ 28.2, 38.3 (CH_3), 43.8, 49.3, 53.5, 58.5, 133.4, 149.5, 166.8 (oxalate). Anal. ($C_9H_{14}N_4·C_2H_2O_4·0.2H_2O$) C, H, N.

***endo*-3-(2-Methyl-1,2,3-triazol-4-yl)-1-azabicyclo[2.2.1]heptane (3e).** Compound **3e** was prepared from **3h** as for **2e**, and the major fraction was crystallized from acetone/Et_2O as an oxalate salt (61 mg, 13%): mp 63–65 °C; ^{1}H NMR [free base] ($CDCl_3$) δ 1.13–1.25 and 1.25–1.43 each (1 H, m), 2.40–2.85 (6 H, m), 3.10–3.30 (2 H, m), 4.08 (3 H, s), 7.28 (1 H, s); ^{13}C NMR [oxalate] (CD_3OD) δ 23.0, 36.9, 41.9, 42.4, 54.0, 57.0, 61.2, 134.3, 146.6, 165.1. Anal. ($C_9H_{14}N_4·1.08C_2H_2O_4$) C, H, N.

***exo*-4-(2-Methyl-1,2,3-triazol-4-yl)-1-azabicyclo[2.2.1]heptane (4e).** Compound **4e** was prepared from **4h** as for **2e** in 35% yield, which was crystallized from MeOH/Et_2O as an oxalate salt: mp 130–135 °C; ^{1}H NMR (CD_3OD) δ 2.13–2.27 (2 H, m), 2.35–2.50 (2 H, m), 3.38–3.55 (4 H, m), 3.60–3.75 (2 H, m), 4.17 (3 H, s, Me), 7.70 (1 H, s), ^{13}C NMR (CD_3OD) δ 34.0, 41.9 (CH_3), 46.2, 54.4, 62.8, 133.2, 146.2, 166.8 (oxalate). Anal. ($C_9H_{14}N_4·C_2H_2O_4$) C, H, N.

5-(2-Methyl-1,2,3-triazol-4-yl)-1-azabicyclo[3.2.1]octane (5e). Compound **5e** was prepared from **5h** as for **2e** in 22% yield. Data is identical to sample described previously.

***exo*- and *endo*-(1-Azabicyclo[2.2.1]heptan-3-yl)hydrazine Dihydrochloride (2i, 3i).** Compound **8** (4.2 g, 0.038 mol) was dissolved in petroleum ether (250 mL) and Et_2O (10 mL). ^{t}Butyl carbazate (10 g, 0.0758 mol) was added, and the solution was heated at reflux for 24 h, allowed to cool overnight, and then evaporated to dryness. The residue was dissolved in EtOH (300 mL), excess anhydrous oxalic acid (4 g) and 10% Pd-C (0.5 g) were added, and the mixture was hydrogenated at atmospheric

pressure and 45 °C for 6 h. The solution was filtered through Celite, evaporated to dryness, and partitioned between saturated aqueous K_2CO_3 and EtOAc. The organic extracts were dried and evaporated to dryness, and the residue was purified by column chromatography on basic alumina eluting with EtOAc/MeOH (36:1). This was dissolved in MeOH/HCl (250 mL of a 1 M solution) and heated at reflux for 20 min. The mixture was evaporated to dryness and recrystallized from MeOH/Et_2O to afford **2i, 3i** (4.34 g, 60%): mp 245–246 °C; ^1H NMR (DMSO) δ 1.46 and 1.79 together (1 H, m), 2.01 (1 H, complex m), 2.75–3.85 (8 H, complex bm); ^{13}C NMR (DMSO) δ 19.8 (CH_2), 23.6 (CH_2), 50.9 and 51.7 (CH_2), 55.4 and 55.6 (CH_2), 56.1 and 56.4 (CH), 57.9 and 58.9 (CH). Anal. ($C_8H_{13}N_3 \cdot 2HCl$) C, H, N.

5-Bromo-1-azabicyclo[3.2.1]octane (16). Ethyl 1-azabicyclo[3.2.1]octane-5-carboxylate[1] (19.0 g, 0.104 mol) in 8 N HCl (200 mL) was heated under reflux for 3 h. The solution was evaporated to dryness, dissolved in $SOCl_2$ (150 mL), and heated under reflux for 30 min. The solution was evaporated to dryness and azeotroped with toluene. This solid was added in portions to a mixture of the sodium salt of 1-hydroxypyridine-2(1*H*)-thione (17.35 g, 0.116 mol), Et_3N (29 mL, 0.208 mol), and DMAP (0.5 g, 0.004 mol) in dry MeCN (300 mL) at −20 °C. The mixture was allowed to warm slowly to room temperature and then heated under reflux for 2 h and evaporated to dryness. Bromotrichloromethane (250 mL) was added to the residue, and the resulting solution was heated under reflux for 3 h.[16] After cooling, the mixture was partitioned between saturated aqueous K_2CO_3 and $CHCl_3$. The combined organic extracts were dried, evaporated to dryness, and purified by column chromatography on silica eluting with $CHCl_3$/MeOH (12:1) to afford an oil which was purified by vacuum distillation to afford **16** (9.18 g, 47%): bp 140 °C at 1.5 mmHg; ^1H NMR ($CDCl_3$) δ 1.57 (1 H, m), 1.88 (1 H, m), 2.16–2.37 (4 H, m), 2.71–2.92 (3 H, m), 3.07 (2 H, s), 3.18 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 23.83, 40.73, 42.99, 52.01, 53.86, 62.45, 68.43, which was crystallized from MeOH/Et_2O as an oxalate salt, mp 134–135 °C. Anal. ($C_7H_{12}NBr \cdot C_2H_2O_4$) C, H, N.

***exo*-3-(1,2,4-Triazol-1-yl)-1-azabicyclo[2.2.1]heptane (2j).** Compounds **2i** and **3i** (500 mg, 2.5 mmol) and Gold's reagent [[3-(dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride] (409 mg, 2.5 mmol) were dissolved in dry $CHCl_3$ (40 mL) under N_2, and dry Et_3N (0.70 mL) was added. The solution was heated under reflux for 2.5 h and cooled, and saturated aqueous K_2CO_3 was added. The organic layer was separated, the aqueous layer further extracted with $CHCl_3$, and the combined organic extracts dried, evaporated to dryness, and purified by column chromatography on basic alumina eluting with EtOAc/MeOH (50:1) to yield **2j** (0.21 g, 51%) which was crystallized from MeOH/Et_2O as a dihydrochloride salt: mp 215–219 °C; ^1H NMR (DMSO) δ 1.86 (1 H, m), 2.16 (1 H, m), 3.20–4.03 (7 H, complex m), 5.12 (1 H, m), 8.42 (1 H, bs, triazole-H), 9.21 (1 H, bs, triazole-H); ^{13}C NMR (DMSO) δ 24.3 (CH_2), 41.8 (CH), 50.9 (CH_2), 56.7 (CH_2), 57.3 (CH_2), 58.6 (CH), 150.0 (both triazole CH). Anal. ($C_8H_{12}N_4 \cdot 1.5C_2H_2O_4$) C, H, N.

5-(1,2,4-Triazol-1-yl)-1-azabicyclo[3.2.1]octane (5j). Compound **16** (1 g, 5.3 mmol) in anhydrous hydrazine (10 mL) was heated at reflux for 30 min. The mixture was then cooled and evaporated to dryness, the residue taken up in MeOH, and an aqueous solution of NaOH (2.63 mL of a 2 M solution, 5.3 mmol) was added. The solution was evaporated to dryness and this procedure repeated twice more to remove the last traces of water to afford a gum **5i**, compound **5j** was then prepared from **5i** as for **2j**, omitting Et_3N, to give **5j** in 53% yield, which was crystallized from MeOH/acetone as a dihydrochloride salt: mp 198–200 °C; ^1H NMR (DMSO) δ 1.9–2.3 (4 H, m), 2.52 (2 H, m), 3.30 (2 H, m), 3.53 (1 H, m), 3.60–3.84 (3 H, m), 5.0 (1 H, br), 8.30 (1 H, s), 9.08 (1 H, s), 11.90 (1 H, br); ^{13}C NMR (DMSO) δ 16.89, 32.01, 34.24, 48.95, 50.96, 58.28, 64.05, 142.50, 150.07. Anal. ($C_9H_{14}N_4 \cdot 2HCl$) C, H, N.

***exo*-3-(3-Methyl-1,2,4-triazol-1-yl)-1-azabicyclo[2.2.1]heptane (2k).** Compounds **2i** and **3i** (0.5 g, 2.5 mmol) were dissolved in dry MeOH (30 mL), and methyl acetimidate hydrochloride (0.274 g, 2.5 mmol) was added, followed by dry Et_3N (1.05 mL, 7.5 mmol). The solution was stirred for 3 h at 25 °C under N_2 and evaporated to dryness at a temperature not exceeding 30 °C, and anhydrous pyridine (2 mL) and triethyl orthoformate (20 mL) were added. The suspension was stirred overnight at room temperature and then heated at reflux for 1.5 h under N_2. The mixture was cooled and evaporated to dryness, and the residue was partitioned between saturated aqueous K_2CO_3 and EtOAc. The organic extracts were dried, evaporated to dryness, and purified by column chromatography on basic alumina eluting with EtOAc/MeOH (14:1) to afford **2k** which was crystallized from MeOH/Et_2O as a dihydrochloride salt (30 mg, 5%): mp 236–240 °C; ^1H NMR (DMSO) δ 1.75 (1 H, m), 2.08 (1 H, m), 2.31 (3 H, s, Me), 3.13 (1 H, d), 3.28 (3 H, complex m), 3.63 (2 H, m), 3.82 (1 H, m), 4.92 (1 H, m), 8.90 (1 H, s, triazole-CH); ^{13}C NMR (DMSO) δ 13.1 (CH_3), 24.3 (CH_2), 41.7 (CH), 51.0 (CH_2), 56.8 (CH_2), 57.3 (CH_2), 58.4 (CH), 143.9 (CH), 158.7 (quat C). Anal. ($C_9H_{14}N_4 \cdot 2HCl \cdot 0.5H_2O$) C, H, N.

5-(3-Methyl-1,2,4-triazol-1-yl)-1-azabicyclo[3.2.1]octane (5k). Compound **5k** was prepared from **5i** as for **2k** in 5% yield, which was crystallized from MeOH/acetone as a hygroscopic dihydrochloride salt: mp 165–167 °C; ^1H NMR (DMSO) δ 1.91–2.24 (4 H, m), 2.21 (3 H, s), 2.47 (2 H, m), 3.28 (2 H, m), 3.48 (1 H, m), 3.57–3.80 (3 H, m), 8.90 (1 H, br s), 11.65 (1 H, br s). Anal. ($C_{10}H_{16}N_4 \cdot 2HCl \cdot 0.25H_2O$) C, H, N.

Ethyl 1-Benzyl-4-[*N*,*N*′-bis[(*tert*-butyloxy)carbonyl]hydrazino]piperidine-4-carboxylate (18). Ethyl 1-benzylpiperidine-4-carboxylate (17) was prepared by reaction of ethyl isonipecotate with 1 equiv of benzyl bromide and 1 mol equiv of K_2CO_3 in acetone with stirring at room temperature. A solution of diisopropylamine (8.8 mL, 0.063 mol) in Et_2O (400 mL) at −70 °C under N_2 was treated with 1.6 M ^{n}butyllithium in hexane (37.5 mL, 0.060 mol) and stirred for 10 min. A solution of ethyl 1-benzylpiperidine-4-carboxylate (17) (13.6 g, 0.055 mol) in Et_2O (70 mL) was added over 5 min and the resulting mixture then stirred at −70 °C for 40 min, before adding a solution of di-*tert*-butyl azodicarboxylate (13.5 g, 0.058 mol) in Et_2O (80 mL). The reaction mixture was allowed to warm to room temperature over 30 min and then stirred for a further 2 h before adding saturated aqueous K_2CO_3. The organic layer was separated, dried, and evaporated to dryness under reduced pressure to yield an orange oil, which was purified by column chromatography using silica and eluting with petroleum ether/Et_2O (4:1) and then Et_2O to afford **18** (14.2 g, 54%) as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.24 (3 H, t, J = 7 Hz), 1.38–1.62 (18 H, m), 1.85–1.97 (1 H, m), 2.02–2.15 (1 H, m), 2.34–2.55 (4 H, m), 2.61–2.75 (2 H, m), 3.50 (2 H, s), 4.07–4.25 (2 H, m), 6.02 and 6.30 (together 1 H, each br s), 7.20–7.35 (5 H, m). The oxalate salt crystallized from MeOH/Et_2O, mp 108–110 °C. Anal. ($C_{25}H_{39}N_3O_6 \cdot 1.5C_2H_2O_4$) C, H, N.

Ethyl 1-Benzyl-4-(1,2,4-triazol-1-yl)piperidine-4-carboxylate (20). A solution of **18** (14.2 g, 0.030 mol) in MeOH (50 mL) was treated with 10% HCl/MeOH (100 mL) and heated under reflux for 2 h. The solution was evaporated to dryness under reduced pressure, and the residue was treated with dry toluene (80 mL) and again evaporated to dryness under reduced pressure. The residue was triturated with ether, and the solid was filtered off and placed immediately in a vacuum desiccator to give **19** (9.48 g, 90%) as a very hygroscopic orange solid: ^1H NMR (CD_3OD) δ 1.31 (3 H, t, J = 7 Hz), 2.05–2.20 (2 H, m), 2.38–2.58 (2 H, m), 3.25–3.60 (4 H, m), 4.29 (2 H, q, J = 7 Hz), 4.35–4.45 (2 H, m), 7.43–7.66 (5 H, m). A stirred suspension of **19** (2.0 g, 0.0057 mol) in $CHCl_3$ (200 mL) was treated with Gold's reagent [[3-(dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride] (930 mg, 0.0057 mol) and Et_3N (1.6 mL, 0.0114 mol) and the mixture heated at reflux under N_2 for 2.5 h. The solution was treated with saturated aqueous K_2CO_3 and the organic phase separated, dried, and evaporated to dryness under reduced pressure to yield an orange oil. This was purified by column chromatography using silica eluting with EtOAc to afford **20** (770 mg, 43%) as an orange oil: ^1H NMR ($CDCl_3$) δ 1.20 (3 H, t, J = 7 Hz), 2.20–2.75 (8 H, m), 3.46 (2 H, s), 4.17 (2 H, q, J = 7 Hz), 7.22–7.38 (5 H, m), 7.99 (1 H, s), 8.26 (1 H, s). The oxalate salt was crystallized from EtOH, mp >250 °C. Anal. ($C_{17}H_{22}N_4O_2 \cdot C_2H_2O_4$) C, H, N.

4-(1,2,4-Triazol-1-yl)-1-azabicyclo[2.2.1]heptane (4j). A solution of **20** (460 mg, 0.00147 mol) in Et_2O (15 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (67 mg, 0.00175 mol) in Et_2O (25 mL) and dry THF (8 mL) at 0 °C under N_2. The reaction mixture was allowed to warm to 15 °C over 20 min and then treated with water (60 μL), 10% aqueous NaOH (180 μL)

and water (60 μL). The suspension was filtered, and the organic solution was dried and evaporated to dryness under reduced pressure to yield a yellow oil. This was purified by column chromatography using silica eluting with EtOAc/MeOH (9:1) to afford the alcohol (320 mg, 80%): ^{1}H NMR ($CDCl_3$) δ 1.97–2.28 (4 H, m), 2.33–2.50 (2 H, m), 2.60–2.75 (2 H, m), 3.44 (2 H, s), 3.70 (2 H, s), 4.45 (1 H, br s, OH), 7.22–7.40 (5 H, m), 7.77 (1 H, s), 8.10 (1 H, s). A stirred solution of the above alcohol (320 mg, 0.0018 mol) in dry pyridine (5 mL) at 0 °C was treated with 4-toluenesulphonyl chloride (225 mg, 0.00118 mol) and the resulting red solution kept at 5 °C for 20 h, followed by room temperature for 3 days. The solution was evaporated to dryness under reduced pressure, and the residue was treated with saturated aqueous K_2CO_3 and extracted with $CHCl_3$. The organic extracts were dried and evaporated to dryness under reduced pressure to yield an orange oil, which was treated with toluene (30 mL) and heated under reflux for 2 h. The organic solution was decanted off, and the orange gum remaining was dissolved in EtOH (40 mL) together with glacial acetic acid (1 mL) and hydrogenated over 10% Pd–C (200 mg) at atmospheric pressure and 40 °C for 1 h. The suspension was filtered through Kieselguhr, and the filtrate was evaporated to dryness under reduced pressure. The residue was partitioned between saturated aqueous K_2CO_3 and $CHCl_3$, and the organic extracts were separated, dried, and evaporated to dryness under reduced pressure to yield a yellow oil, which was filtered through a plug of basic alumina eluting with EtOAc to give a colorless oil **4j** (30 mg, 16%) which crystallized on standing. The oxalate salt was crystallized from MeOH/Et_2O (42 mg, 11%): mp 142–144 °C; ^{1}H NMR (DMSO) δ 2.20–2.50 (4 H, m, 3-CH_2, 5-CH_2), 3.33–3.46 (2 H, m, 2-CH_2, 6-CH_2), 3.48–3.65 (4 H, m, 2-CH_2, 6-CH_2, 7-CH_2), 8.11 (1 H, s, Ar-H), 8.77 (1 H, s, Ar-H); ^{13}C NMR (DMSO) δ 32.33 (C-3,5), 52.67 (C-2,6), 59.43 (C-7), 66.39 (C-4), 143.61 (C-5′), 151.77 (C-3′), 164.05 (oxalate). Anal. ($C_9H_{12}N_4 \cdot C_2H_2O_4$) C, H, N.

Ethyl 1-Benzyl-4-(3-methyl-1,2,4-triazol-1-yl)piperidine-4-carboxylate (21). A solution of **19** (3.0 g, 0.0086 mol) in MeOH (100 mL) under N_2 was treated with methyl acetimidate hydrochloride (940 mg, 0.0086 mol) and Et_3N (3.7 mL, 0.026 mol) and stirred at room temperature for 3 h. The solution was evaporated to dryness under reduced pressure, the residue treated with triethyl orthoformate (50 mL) and dry pyridine (5 mL), and the heterogeneous mixture stirred at room temperature for 18 h, followed by heating under reflux for 1.5 h. The mixture was evaporated to dryness under reduced pressure, and the residue was treated with saturated aqueous K_2CO_3 and extracted with EtOAc. The organic extracts were dried and evaporated to dryness under reduced pressure to yield a dark red oil, which was purified by column chromatography using silica gel eluting with EtOAc/Et_2O (1:1) to afford **21** (430 mg, 15%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.18 (3 H, m, J = 7 Hz), 2.25–2.70 (8 H, m), 2.40 (3 H, s), 3.45 (2 H, s), 4.15 (2 H, q, J = 7 Hz), 7.20–7.40 (5 H, m), 8.12 (1 H, s). **21** was crystallized from EtOH as an oxalate salt, mp 189–190 °C. Anal. ($C_{18}H_{24}N_4O_2 \cdot C_2H_2O_4$) C, H, N.

4-(3-Methyl-1,2,4-triazol-1-yl)-1-azabicyclo[2.2.1]heptane (4k). A solution of **21** (0.43 g, 1.3 mmol) in Et_2O (5 mL) was added to a stirred suspension of $LiAlH_4$ (59 mg, 1.6 mmol) in Et_2O (25 mL) and THF (10 mL) at 0 °C under N_2. The mixture was stirred for 20 min and then treated with water (60 μL), 10% aqueous NaOH (180 μL), and water (60 μL). The mixture was filtered, and the filtrate was dried and evaporated to dryness under reduced pressure to yield the alcohol as a yellow oil (0.37 g, 100%): ^{1}H NMR ($CDCl_3$) δ 1.96–2.12 (2 H, m), 2.15–2.43 (4 H, m), 2.31 (3 H, m), 2.58–2.70 (2 H, m), 3.47 (2 H, s), 3.70 (2 H, s), 4.17 (1 H, br s), 7.20–7.40 (5 H, m), 7.97 (1 H, s). A solution of the alcohol (0.37 g, 1.3 mmol) in pyridine (5 mL) at 0 °C under N_2 was treated with 4-toluenesulphonyl chloride (0.26 g, 1.4 mmol) and then allowed to warm to room temperature and stand for 4 days. The solution was concentrated under reduced pressure, and the residue was treated with saturated aqueous K_2CO_3 and extracted with $CHCl_3$ (3 × 100 mL). The organic extracts were dried and evaporated to dryness under reduced pressure, and the residue was dissolved in MeOH (40 mL) and heated under reflux for 26 h. The solution was evaporated to dryness under reduced pressure, and the residual gum was washed with Et_2O, dissolved in EtOH (50 mL), and hydrogenated over 10% Pd–C (0.3 g) at atmospheric pressure and 40 °C. The catalyst was filtered off, the filtrate evaporated to dryness under reduced pressure, and the residue basified with saturated aqueous K_2CO_3 and extracted with $CHCl_3$. The organic extracts were dried and evaporated to dryness under reduced pressure, and the residue was purified by column chromatography using silica eluting with $CHCl_3$/MeOH (17:3) to afford **4k** as a colorless oil (60 mg, 26%). Oxalate salt: mp 135–136 °C (MeOH/Et_2O); ^{1}H NMR (DMSO) δ 2.18–2.46 (4 H, m, 3-CH_2, 5-CH_2), 2.27 (3 H, s, CH_3), 3.33–3.46 (2 H, m, 2-CH,6-CH), 3.47–3.66 (4 H, m, 2-CH, 6-CH, 7-CH_2), 8.58 (1 H, s, Ar-H); ^{13}C NMR (DMSO) δ 13.63 (CH_3), 32.09 (3-C and 5-C), 52.49 (2-C and 6-C), 59.23 (7-C), 66.03 (4-C), 143.87 (5′-C), 160.26 (3′-C), 164.37 (COOH). Anal. ($C_9H_{14}N_4 \cdot C_2H_2O_4$) C, H, N.

3-[(Methanesulfonyl)oxy]-1-azabicyclo[2.2.2]octane (11).[2] Quinuclidin-3-ol (10.0 g, 0.0787 mol) was dissolved in dry CH_2Cl_2 (200 mL) under N_2 and cooled to 0 °C. Methanesulfonyl chloride (7.3 mL, 10.8 g, 0.094 mol) and dry pyridine (7.64 mL, 7.46 g, 0.094 mol) were added, and the mixture was stirred at 0 °C for 20 min. The solution was then allowed to warm to room temperature and stirred under N_2 for 1 h, followed by addition of saturated aqueous K_2CO_3 (150 mL) and extraction with EtOAc (3 × 200 mL). The organic solution was dried and evaporated to dryness to yield a pale yellow oil which was exposed to high vacuum to remove traces of pyridine to afford the mesylate **11** (15.8 g, 98%): ^{1}H NMR ($CDCl_3$) δ 1.67 (4 H, m), 2.18 (1 H, pentet), 2.85 (5 H, bm), 3.03 (3 H, s, SO_2Me), 3.38 (1 H, q), 4.82 (1 H, m, *CH*OMs).

3-(3-Amino-1,2,4-triazol-1-yl)-1-azabicyclo[2.2.2]octane (1m). Compound **11**[2] (5.0 g, 0.024 mol) was dissolved in dry DMF (60 mL) and treated with the sodium salt of 3-amino-1,2,4-triazole prepared from the triazole as described previously[2] (7.0 g, 0.066 mol). The mixture was heated at reflux for 1 h, allowed to cool, and evaporated to dryness. The residue was partitioned between saturated aqueous K_2CO_3 and $CHCl_3$. The combined organic extracts were dried, evaporated to dryness, and purified by column chromatography on basic alumina eluting with $CHCl_3$/MeOH (30:1) to afford **1m**, which was crystallized from EtOAc/petroleum ether to afford **1m** (150 mg, 3.2%): mp 144–146 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (1 H, m), 1.78 (1 H, m), 2.05 (2 H, m), 2.18 (1 H, m), 2.89 (3 H, m), 3.05 (1 H, m), 4.08 (2 H, m, NH_2), 4.20 (1 H, m, CH-azole), 7.73 (1 H, s, azole-H); ^{13}C NMR ($CDCl_3$) δ 20.2 (CH_2), 26.8 (CH_2), 27.5 (CH), 46.9 (CH_2), 47.4 (CH_2), 52.4 (CH_2), 56.8 (CH), 141.9 (azole-CH), 163.1 (C-3′). Anal. ($C_9H_{15}N_5 \cdot 2HCl \cdot 0.5H_2O$) C, H, N.

***exo*-3-(3-Amino-1,2,4-triazol-1-yl)-1-azabicyclo[2.2.1]heptane (2m).** Compound **2m** was prepared from **9**, as for **1m** from quinuclidinol, in 10% yield, which was crystallized from acetone: mp 154–155 °C; ^{1}H NMR ($CDCl_3$) δ 1.21 (1 H, m), 1.74 (1 H, m), 2.47 (2 H, m), 2.87 (2 H, complex m), 3.08 (3 H, complex m), 3.92 (1 H, m), 4.30 (2 H, bs NH_2), 7.72 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 28.3 (C-5), 43.1 (C-4), 53.6, 58.2, 61.8 (C-2,6,7), 62.1 (C-3), 140.7 (C-5′), 163.4 (C-3′). Anal. ($C_8H_{13}N_5$) C, H, N.

5-(3-Amino-1,2,4-triazol-1-yl)-1-azabicyclo[3.2.1]octane (5m). Compound **5m** was prepared from **16**, as for **1m** from **11**, in 14% yield, which crystallized from MeOH/Et_2O as the free base: mp 172–174 °C; ^{1}H NMR ($CDCl_3$) δ 1.72 (1 H, m), 1.90 (1 H, m), 2.09 (2 H, m), 2.22 (2 H, m), 2.74–3.05 (4 H, m), 3.27–3.36 (2 H, m), 4.20 (2 H, br s), 7.68 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 20.40, 35.82, 37.04, 51.25, 54.19, 63.50, 64.53, 139.69, 163.19. Anal. ($C_9H_{15}N_5 \cdot 2HCl \cdot 0.5MeOH$) C, H, N.

***exo*-3-(Tetrazol-2-yl)-1-azabicyclo[2.2.1]heptane (2n).** Compound **3l** (0.70 g, 3.66 mmol) prepared from **9**, as for **1l** from quinuclidinol, and the sodium salt of 1*H*-tetrazole[2] (1.0 g, 11 mmol) were dissolved in dry DMF (50 mL) and heated under reflux for 2 h. The solution was evaporated to dryness and partitioned between saturated aqueous K_2CO_3 and EtOAc, and the combined organic extracts were dried and evaporated to dryness. The residue was purified by column chromatography on basic alumina eluting with EtOAc/MeOH (36:1) to afford **2n** (70 mg, 12%) which was crystallized from MeOH/Et_2O as a hydrochloride salt: mp 241–245 °C; ^{1}H NMR (DMSO) δ 1.92 (1 H, m), 2.12 (1 H, m), 3.32 (4 H, complex m), 3.50 (1 H, d), 3.84 (1 H, dm), 4.00 (1 H, dm), 5.51 (1 H, m), 9.11 (1 H, s); ^{13}C NMR (DMSO) δ 23.9 (CH_2), 41.6 (CH), 51.2 (CH_2), 56.8 (CH_2), 57.5 (CH_2), 62.1 (CH), 153.4 (CH). Anal. ($C_7H_{11}N_5 \cdot HCl$) C, H, N.

5-(Tetrazol-2-yl)-1-azabicyclo[3.2.1]octane (5n). Following the procedure described previously to prepare **2n** from **3l**, **5n** was prepared from **16** by heating at reflux for 5 h to afford **5n**, which

was crystallized from water/MeOH/acetone as an oxalate salt in 57% yield: mp 205–207 °C; ^{1}H NMR (DMSO) δ 1.96 (1 H, m), 2.18–2.33 (3 H, m), 2.60 (2 H, m), 3.24 (2 H, m), 3.44 (1 H, m), 3.57–3.94 (3 H, m), 9.08 (1 H, s); ^{13}C NMR (DMSO) δ 17.32, 32.37, 34.83, 49.18, 51.27, 58.75, 67.71, 153.30. Anal. ($C_8H_{13}N_5 \cdot C_2H_2O_4$) C, H, N.

***exo*-3-(5-Methyltetrazol-2-yl)-1-azabicyclo[2.2.1]heptane (2o).** Compound **2o** was prepared in 14% yield from **3l** as for **2n**, but using the sodium salt of 5-methyltetrazole[2] and was crystallized from MeOH/Et_2O as a hydrochloride salt: mp 238–239 °C; ^{1}H NMR (DMSO) δ 1.93 (1 H, m), 2.14 (1 H, m), 2.50 (3 H, s, Me), 3.38 (5 H, complex m), 3.81 (1 H, dt), 4.00 (1 H, m), 5.43 (1 H, m); ^{13}C NMR (DMSO) δ 10.5 (CH_3), 23.9 (CH_2), 41.6 (CH), 51.1 (CH_2), 56.8 (CH_2), 57.4 (CH_2), 61.9 (CH), 162.5 (quat C). Anal. ($C_9H_{13}N_5 \cdot HCl \cdot 0.25H_2O$) C, H, N.

5-(5-Methyltetrazol-2-yl)-1-azabicyclo[3.2.1]octane (5o). Compound **5o** was prepared from **1**6 as for **2o** in 47% yield, which was crystallized from MeOH/acetone as an oxalate: mp 145–147 °C; ^{1}H NMR (DMSO) δ 1.97 (1 H, m), 2.10–2.28 (3 H, m), 2.48 (3 H, s), 2.48–2.68 (2 H, m), 3.26 (2 H, m), 3.44 (1 H, m), 3.66 (1 H, m), 3.73 and 3.85 (2 H, q, J = 11 Hz); ^{13}C NMR (DMSO) δ 10.46, 17.25, 32.29, 34.67, 49.10, 51.21, 58.65, 67.40, 162.39. Anal. ($C_9H_{15}N_5 \cdot C_2H_2O_4$) C, H, N.

3-(5-Aminotetrazol-2-yl)-1-azabicyclo[2.2.2]octane (1p). Compound **1p** was prepared in 7% yield from **1**l as for **2n** using the sodium salt of 5-aminotetrazole[2] prepared from the aminotetrazole as described in ref 2, instead of the sodium salt of 1*H*-tetrazole and was crystallized from Et_2O: mp 132–134 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (1 H, m), 1.68 (3 H, complex m), 2.35 (1 H, m), 2.87 (1 H, m), 3.11 (1 H, m), 3.39 (1 H, dm), 3.71 (1 H, dt), 4.38 (2 H, bs), 4.70 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 20.4 (CH_2), 26.0 (CH_2), 27.6 (CH), 47.2 (CH_2), 47.5 (CH_2), 52.1 (CH_2), 61.3 (CH), 166.1 (C-5′). Anal. ($C_9H_{14}N_6 \cdot C_2H_2O_4$) C, H, N.

***exo*-3-(5-Aminotetrazol-2-yl)-1-azabicyclo[2.2.1]heptane (2p).** Compound **2p** was prepared from **3l** as for **1p** in 11% yield, which was crystallized from Et_2O: mp 132–134 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (1 H, m), 1.77 (1 H, m), 2.50 (2 H, m), 2.88 (1 H, tm), 3.06 (3 H, complex m), 3.32 (1 H, dm), 4.36 (2 H, bs), 4.44 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 27.9 (CH_2), 43.3 (CH), 53.7 (CH_2), 58.3 (CH_2), 61.6 (CH_2), 65.8 (CH), 165.9 (C-5′). Anal. ($C_7H_{12}N_6 \cdot C_2H_2O_4$) C, H, N.

5-(5-Aminotetrazol-2-yl)-1-azabicyclo[3.2.1]octane (5p). Compound **5p** was prepared from **1**6 as for **1p** in 24% yield, which was crystallized from MeOH/Et_2O: mp 173–175 °C; ^{1}H NMR (CD_3OD) δ 1.77 (1 H, m), 1.94–2.26 (1 H, m), 2.22 (2 H, m), 2.41 (1 H, t, J = 9 Hz), 2.86 (2 H, m), 3.06 (1 H, m), 3.18–3.36 (3 H, m), 4.90 (2 H, br); ^{13}C NMR (CD_3OD) δ 21.33, 36.66, 37.88, 52.03, 55.04, 63.78, 70.28, 168.80; UV λ_{max} 247 nm (ε 3570, EtOH). Anal. ($C_8H_{14}N_6 \cdot 0.5H_2O$) C, H, N.

3-(5-Chlorotetrazol-2-yl)-1-azabicyclo[2.2.2]octane (1q). ^{t}BuLi (7.0 mL of a 1.7 M solution in pentane, 10.4 mmol) was mixed with dry hexane (25 mL) under N_2 at −65 °C and treated dropwise with **1n** (1.0 g, 5.2 mmol) in dry THF (25 mL) maintaining an internal temperature below −50 °C. The resulting yellow suspension was treated dropwise with a solution of Cl_2 (0.74 g, 10.4 mmol) in dry hexane (20 mL) over 5 min. The reaction mixture was then quenched with AcOH (2 equiv) and partitioned between saturated aqueous K_2CO_3 and $CHCl_3$, and the organic extracts were dried and evaporated to dryness to an orange oil. Purification by column chromatography on silica eluting with EtOAc afforded **1q** which was crystallized from MeOH/Et_2O as an oxalate salt (0.441 g, 37%): mp 127–129 °C dec; ^{1}H NMR (CD_3OD) δ 1.80–2.04 (2 H, m), 2.18–2.28 (2 H, m), 2.70–2.78 (1 H, m), 3.39–3.61 (4 H, m), 3.95–4.28 (2 H, m), 5.52–5.62 (1 H, m); ^{13}C NMR (CD_3OD) δ 17.32, 21.43 (C-5 and C-7), 25.44 (C-4), 45.28 (C-6), 45.62 (C-8), 49.78 (C-2), 59.16 (C-3), 154.34 (C-5′), 163.87 (oxalate). Anal. ($C_8H_{12}N_5Cl \cdot C_2H_2O_4$) C, H, N.

***exo*-3-(5-Chlorotetrazol-2-yl)-1-azabicyclo[2.2.1]heptane (2q).** Compound **2q** was prepared in 65% yield from **2n** as for **1q**, using a solution of Cl_2 in CCl_4 instead of a solution of Cl_2 in hexane, and was crystallized from MeOH/Et_2O as an oxalate salt: mp 125–128 °C; ^{1}H NMR (DMSO) δ 1.73 (1 H, m), 2.00 (1 H, m), 3.05 (2 H, m), 3.21 (1 H, m), 3.31 (2 H, t), 3.71 (2 H, complex m), 5.28 (1 H, m); ^{13}C NMR (DMSO) δ 24.7 (CH_2), 41.6 (CH), 51.6 (CH_2), 57.0 (CH_2), 58.3 (CH_2), 64.3 (CH), 154.3 (C-5′), 163.7 (oxalate). Anal. ($C_7H_{10}N_5Cl \cdot C_2H_2O_4$) C, H, N.

5-(5-Chlorotetrazol-2-yl)-1-azabicyclo[3.2.1]octane (5q). Compound **5q** was prepared from **5n** as for **2q** in 50% yield, mp 72–74 °C, which was crystallized from acetone/MeOH as an oxalate salt: mp 189 °C dec; ^{1}H NMR (DMSO) δ 1.87–2.34 (4 H, m), 2.60 (2 H, m), 3.23 (2 H, m), 3.53 (1 H, m), 3.52–3.74 (2 H, m), 3.81 (1 H, m); ^{13}C NMR (DMSO) δ 17.40, 32.20, 34.48, 49.20, 51.31, 58.74, 69.10, 154.30. Anal. ($C_9H_{12}N_5Cl \cdot C_2H_2O_4$) C, H, N.

3-(5-Bromotetrazol-2-yl)-1-azabicyclo[2.2.2]octane (1r). Compound **1r** was prepared from **1n** as for **2q**, but using a solution of bromine (2 equiv) in dry pentane to afford **1r**, which was crystallized from acetone/Et_2O as an oxalate salt in 6% yield: mp 165 °C dec; ^{1}H NMR (DMSO) δ 1.58–1.78 (2 H, m), 1.90–2.03 (2 H, m), 2.52–2.61 (1 H, m), 3.12–3.25 (4 H, m), 3.78–3.84 (2 H, d, J = 5.5 Hz), 5.39–5.50 (1 H, m); ^{13}C NMR (DMSO) δ 18.4 and 22.4 (C-5,8), 27.4 (C-4), 47.3, 47.6 and 50.8 (C-2,6,7), 60.3 (C-3), 144.1 (C-5′), 166.7 (oxalate). Anal. ($C_8H_{12}N_5Br \cdot C_2H_2O_4$) C, H, N.

3-(5-Bromotetrazol-2-yl)-1-azabicyclo[2.2.1]heptane (2r). Compound **2r** was prepared from **2n** as for **1r** in 67% yield, which was crystallized from MeOH/Et_2O as an oxalate salt: mp 144–146 °C; ^{1}H NMR (DMSO) δ 1.83 (1 H, m), 2.00 (1 H, m), 3.04 (2 H, d), 3.23 (3 H, complex m), 3.67 (2 H, m), 5.30 (1 H, m); ^{13}C NMR (DMSO) δ 24.7 (CH_2), 41.9 (CH), 51.7 (CH_2), 57.1 (CH_2), 58.2 (CH_2), 64.1 (CH), 142.3 (C-5′), 163.6 (oxalate). Anal. ($C_7H_{10}N_5Br \cdot C_2H_2O_4$) C, H, N.

5-(5-Bromotetrazol-2-yl)-1-azabicyclo[3.2.1]octane (5r). Compound **5r** was prepared from **5n** as for **1r** in 56% yield: mp 108–110 °C; ^{1}H NMR ($CDCl_3$) δ 1.72–2.05 (2 H, m), 2.28 (2 H, m), 2.46 (2 H, m), 2.80–3.08 (3 H, m), 3.22–3.41 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 20.74, 36.28, 37.10, 51.53, 54.30, 63.92, 70.81, 142.68, which was crystallized from MeOH/Et_2O as an oxalate salt: mp 189–191 °C. Anal. ($C_8H_{12}N_5Br \cdot C_2H_2O_4$) C, H, N.

3-(5-Iodotetrazol-2-yl)-1-azabicyclo[2.2.2]octane (1s). Compound **1s** was prepared in 37% yield from **1n** as for **1r**, but using I_2 (2 equiv) in dry THF: mp 160–165 °C dec; ^{1}H NMR (CD_3OD) δ 1.63–1.85 (2 H, m), 2.05–2.12 (2 H, m), 2.58–2.62 (1 H, m), 3.20–3.39 (4 H, m), 3.78–3.86 (1 H, m), 3.95–4.02 (1 H, m), 5.39–5.45 (1 H, m); ^{13}C NMR (CD_3OD) δ 19.2 (CH_2), 23.8 (CH_2), 27.9 (CH_2), 47.5 (CH_2), 47.9 (CH_2), 51.5 (CH_2), 61.0 (CH), 114.4 (C-5′). Anal. ($C_8H_{12}N_5I \cdot C_2H_2O_4$) C, H, N.

3-(5-Iodotetrazol-2-yl)-1-azabicyclo[2.2.1]heptane (2s). Compound **2s** was prepared from **2n** as for **1s** in 42% yield, which was crystallized from MeOH/Et_2O as an oxalate salt: mp 158–161 °C; ^{1}H NMR (DMSO) δ 1.83 (1 H, m), 2.08 (1 H), 3.13 (2 H, d), 3.33 (3 H, complex m), 3.78 (2 H), 5.38 (1 H, m); ^{13}C NMR (DMSO) δ 24.8 (CH_2), 41.9 (CH), 51.7 (CH_2), 57.1 (CH_2), 58.6 (CH_2), 63.6 (CH), 115.5 (C-5′), 163.7 (oxalate). Anal. ($C_7H_{10}N_5I \cdot C_2H_2O_4$) C, H, N.

3-(5-Cyanotetrazol-2-yl)-1-azabicyclo[2.2.2]octane (1t). ^{t}BuLi (4.54 mL of a 1.7 M solution in pentane, 6.7 mmol) was mixed with dry hexane (10 mL) under N_2 at −65 °C and treated dropwise with **1n** (1.0 g, 5.6 mmol) in dry THF (20 mL) maintaining an internal temperature below −50 °C. The resulting yellow suspension was treated dropwise with *N*-methylformanilide (0.9 g, 6.7 mmol) in dry THF (10 mL), again maintaining an internal temperature below −50 °C, and stirring at this temperature was continued for 30 min. The mixture was then poured into dilute HCl (25 mL) and stirred for 10 min. The reaction mixture was basified with saturated aqueous K_2CO_3 and extracted with $CHCl_3$. The combined organic extracts were dried and evaporated to dryness, and the resulting crude aldehyde was dissolved in MeOH (10 mL) and treated with hydroxylamine hydrochloride (0.43 g, 6.14 mmol) at room temperature. The mixture was stirred for 5 h and evaporated to dryness, the residue treated with saturated aqueous K_2CO_3, and the aldoxime extracted with $CHCl_3$. The combined organic extracts were dried and evaporated to dryness, and the crude aldoxime was dissolved in Ac_2O (20 mL) and heated at 80 °C for 1 h. The solution was evaporated to dryness, and the resulting viscous oil was treated with saturated aqueous K_2CO_3 and extracted with $CHCl_3$. The organic extracts were dried, evaporated to dryness, and purified by column chromatography on neutral alumina eluting with EtOAc/MeOH (40:1) to afford a yellow oil **1t**, which was crystallized from acetone/Et_2O as an oxalate salt (0.088 g, 5.4%): mp 175 °C dec; ^{1}H NMR (CD_3OD) δ 1.66–1.93 and 2.08–2.20 each (2 H, m), 2.64–2.72 (1 H, m), 3.22–3.45 (4 H, m), 3.85–4.09 (2 H,

m), 5.55–5.64 (1 H, m); ^{13}C NMR (CD_3OD) δ 18.86, 23.35 (C-5 and C-7), 27.74 (C-4), 47.25 (C-6), 47.63 (C-8), 51.35 (C-2), 61.76 (C-3), 110.19 (C≡N), 143.56 (C-5′), 167.74 (oxalate). Anal. ($C_9H_{12}N_6 \cdot 0.5C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

3-[5-(Diphenylhydroxymethyl)tetrazol-2-yl]-1-azabicyclo[2.2.2]octane (1u). A solution of **1n** (200 mg, 1.11 mmol) in dry THF (20 mL) was added dropwise to *tert*-butyllithium (1.2 mL of a 1.7 M solution in toluene, 2.08 mol) in dry pentane (4 mL) at −60 °C under N_2. The solution was stirred at this temperature for 1 h, then treated with benzophenone (0.38 g, 2.08 mmol) in dry THF (4 mL), and allowed to warm to room temperature over 1.5 h. The reaction was then partitioned between saturated aqueous K_2CO_3 and $CHCl_3$. The organic phase was separated, evaporated to dryness, and purified by chromatography on basic alumina eluting with EtOAc/MeOH (100:1 to 20:1) to afford **1u** (110 mg, 27%), which crystallized from Et_2O: mp 185–187 °C; ^{1}H NMR ($CDCl_3$) δ 1.35–1.60 (2 H, m), 1.70–1.85 (2 H, m), 2.35–2.45 (1 H, m), 2.75–2.97 (3 H, m), 2.97–3.15 (1 H, m), 3.32–3.45 (1 H, m), 3.68–3.82 (1 H, m), 4.88–5.02 (1 H, m), 7.23–7.46 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 19.7, 25.2, 27.6, 46.5, 51.8, 61.2, 127.1, 127.8, 128.1, 129.0, 144.5. Anal. ($C_{21}H_{23}N_5O \cdot 0.25H_2O$) C, H, N.

***exo*-3-(3-Chloro-1,2,4-triazol-1-yl)-1-azabicyclo[2.2.1]heptane (2w).** Compound **2m** (150 mg, 0.84 mmol) was dissolved in concentrated HCl (30 mL) at 0 °C and treated with $NaNO_2$ (117 mg, 1.70 mmol) in water (3 mL). After stirring for 5 min at 0 °C, the suspension was added dropwise to a cold suspension of Cu(I)Cl (168 mg, 1.70 mmol) in water (10 mL), and the mixture was stirred for 5 min at 0 °C. The resulting blue solution was heated to 80 °C, until N_2 ceased to evolve. The mixture was cooled, treated with saturated aqueous K_2CO_3 until basic, and extracted with $CHCl_3$. The organic extracts were dried and evaporated to dryness to give an orange oil, which was purified by column chromatography on basic alumina eluting with EtOAc/MeOH (36:1) to afford **2w** (73 mg, 44%). Anal. ($C_8H_{11}N_4Cl$) C, H, N. It was crystallized from MeOH/Et_2O as a hydrochloride salt: mp 107–108 °C; ^{1}H NMR (DMSO) δ 1.66–1.80 (1 H, m), 2.00–2.16 (1 H, m), 3.13–3.90 (7 H, m), 4.87–5.00 (1 H, m), 8.78 (1 H, s); ^{13}C NMR (DMSO) δ 24.3 (C-5), 41.5 (C-4), 51.0, 56.7 and 57.4 (C-2,6,7), 59.0 (C-3), 146.2 (C-5′), 151.0 (C-3′).

***exo*-3-(3-Bromo-1,2,4-triazol-1-yl)-1-azabicyclo[2.2.1]heptane (2v).** Compound **2v** was prepared from **2m** as for **2w**, but using 49% HBr and Cu(I)Br (29% yield of **2o**), which crystallizes on standing (60 mg, 29%): mp 105–107 °C; ^{1}H NMR ($CDCl_3$) δ 1.20–1.33 (1 H, m), 1.70–1.85 (1 H, m), 2.42–2.58 (2 H, m), 2.82–2.98 (2 H, m), 2.98–3.22 (3 H, m), 4.05–4.13 (1 H, m), 8.00 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 28.2 (C-5), 43.4 (C-4), 58.3, 62.0 and 63.2 (C-2,6,7), 59.0 (C-3), 139.8 (C-5′), 143.3 (C-3′). Anal. ($C_8H_{11}N_4Br$) C, H, N.

***exo*-3-(3-Azido-1,2,4-triazol-1-yl)-1-azabicyclo[2.2.1]heptane (2x).** Compound **2x** was prepared from **2m** as for **2w**, but using 1 N H_2SO_4 and NaN_3. After addition to NaN_3 solution, the reaction was allowed to warm to room temperature, after which solid K_2CO_3 was added and the basic solution extracted with $CHCl_3$. Further workup as for **2w** yielded **2x** (70 mg), which was crystallized from acetone as oxalate salt (49 mg, 23%): mp 148–150 °C; ^{1}H NMR (CD_3OD) δ 1.80–2.00 (1 H, m), 2.13–2.33 (1 H, m), 3.15 (1 H, d), 3.25–3.40 (3 H, m), 3.40–3.60 (1 H, m), 3.75–3.90 (2 H, m), 3.90–4.02 (1 H, d, J = 8 Hz), 8.43 (1 H, s); ^{13}C NMR (CD_3OD) δ 25.9 (C-5), 43.9 (C-4), 53.4, 58.9 and 59.5 (C-2,6,7), 60.4 (C-3), 146.5 (C-3′), 159.9 (C-5′). Anal. ($C_8H_{11}N_7 \cdot C_2H_2O_4$) C, H, N.

***exo*-3-(3-Nitro-1,2,4-triazol-1-yl)-1-azabicyclo[2.2.1]heptane (2y).** Compound **2m** (500 mg, 2.79 mmol) was dissolved in 2 N H_2SO_4 (10 mL) at 0 °C and added to aqueous 2 N $NaNO_2$ (5 mL, 10 mmol) at 0 °C. The mixture was then warmed to 45 °C for 30 min, basified with saturated aqueous K_2CO_3, and extracted with $CHCl_3$. The organic extracts were dried, evaporated to dryness, and purified by elution with Et_2O through a plug of alumina to yield **2y** as an oil, which was crystallized from acetone as an oxalate salt (0.43 g, 51%): mp 151–153 °C; ^{1}H NMR (CD_3OD) δ 1.90–2.05 (1 H, m), 2.20–2.40 (1 H, m), 3.27–3.63 (4 H, m), 3.90–4.00 (3 H, m), 5.13–5.24 (1 H, m), 8.80 (1 H, s); ^{13}C NMR [Me oxalate] (CD_3OD) δ 25.8 (C-5), 43.9 (C-4), 52.5 (CH_3), 53.3, 58.8, 59.7 (C-2,6,7), 61.5 (C-3), 147.9 (C-5′), 163.4, 164.8 (Me oxalate), 166.3 (C-3′). Anal. ($C_9H_{11}N_5O_2 \cdot C_3H_4O_4$) C, H, N.

Biology. Radioligand Binding. Cerebral cortex from Hooded Lister rats (Olac, UK) was homogenized in 2.5 vols of ice-cold 50 mM tris buffer pH 7.7 (at 25 °C). After centrifugation at 25 000*g* at 4 °C for 15 min, the pellet was resuspended in 2.5 vols of buffer and the wash repeated three times more. The final resuspension was in 2.5 volumes, and the homogenates were stored in 1-mL aliquots at −20 °C. Incubations (total volume 2 mL) were prepared using the above buffer with the addition of 2 mM magnesium chloride in the [^{3}H]oxotremorine-M ([^{3}H]OXO-M) experiments. For [^{3}H]quinuclidinyl benzilate ([^{3}H]QNB), 1 mL of stored membranes was diluted to 30 mL and 0.1 mL mixed with test compound and 0.27 nM (ca. 25 000 cpm) [^{3}H]QNB (Amersham International). For [^{3}H]OXO-M, 1 mL of membranes was diluted to 6 mL and 0.1 mL mixed with test compound and 2 nM (ca. 250 000 cpm) [^{3}H]OXO-M (New England Nuclear). Nonspecific binding of [^{3}H]QNB was defined using 1 μM atropine sulphate (2 μM atropine) and of [^{3}H]OXO-M using 10 μM oxotremorine. Nonspecific binding values typically were 5% and 25% of total binding, respectively. Incubations were carried out at 37 °C for 30 min and the samples filtered using Whatman GF/B filters. (In the [^{3}H]OXO-M experiments the filters were presoaked for 30 min in 0.05% polyethylenamine in water.) Filters were washed with 3 × 4 mL of ice-cold buffer. Radioactivity was assessed using a Packard BPLD scintillation counter and 3 mL Pico-Fluor 30 (Packard) as scintillant.

Molecular Modeling. Structures were built using standard bond lengths and angles in SYBYL developed and distributed by Tripos Associates Inc., St. Louis, MO. Geometry optimizations were carried out using the semiempircal AM1 method[30] in the AMPAC program.[31] Ab initio calculations were carried out using the extended 4-31G basis set[32] in GAMESS (Generalised Atomic and Molecular Electronic Structure System, Revision A, M.F. Guest).[33] Two-dimensional potential maps were displayed on an Iris Silicon Graphics work station (Model 4D 70G) using software developed by Dr. F.E. Blaney in collaboration with Polygen Corp.

Acknowledgment. We thank Mr. Duncan M. Smith for NMR analysis, Dr. Christopher B. Naylor for electrostatic potential calculations, and Miss Emma Collings for technical assistance.

(30) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. AM1: A New General Purpose Quantum Mechanical Molecular Model. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.
(31) Stewart, J. J. P. *QCPE Bulletin* **1986**, *6*, 24a.
(32) Ditchfield, R.; Hehre, W. J.; Pople, J. A. Self-Consistent Molecular Orbital Methods. IX. An Extended Gaussian type Basis for Molecular Orbital Studies of Organic Molecules. *J. Chem. Phys.* **1971**, *54*, 724–728.
(33) Guest, M. F.; Kendrick, J. *GAMESS User Manual*, ccpi/86/1, Daresbury Laboratory, 1986.