Design of [*R*-(*Z*)]-(+)-α-(Methoxyimino)-1-azabicyclo[2.2.2]octane-3-acetonitrile (SB 202026), a Functionally Selective Azabicyclic Muscarinic M1 Agonist Incorporating the *N*-Methoxy Imidoyl Nitrile Group as a Novel Ester Bioisostere

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Loss of cholinergic function is believed to be implicated in the cognitive decline associated with senile dementia of the Alzheimer type (SDAT). The disease is characterized by progressive loss of muscarinic receptors located on nerve terminals while postsynaptic muscarinic M1 receptors appear to remain largely intact. Muscarinic agonists acting directly on postsynaptic receptors offer the prospect of countering the cholinergic deficit in SDAT. This study describes a novel series of azabicyclic muscarinic agonists, which incorporate an oxime ether or modified oxime ether group as an ester bioisostere. Modification of the oxime ether function by the introduction of electron withdrawing groups led to the finding that the (*Z*)-*N*-methoxy imidoyl nitrile group serves as a stable methyl ester bioisostere. This culminated in the discovery of the quinuclidinyl *N*-methoxy imidoyl nitrile **R-(+)-(*Z*)-5g** which is a functionally selective muscarinic M1 partial agonist currently in phase III clinical trials for the treatment of SDAT. The selective profile of **R-(+)-(*Z*)-5g** can be rationalized in terms of the relative affinity of the compound at muscarinic receptor subtypes, the degree of agonist efficacy, and brain penetrancy.

Senile dementia of the Alzheimer type (SDAT) is characterized by atrophy of cholinergic neurons which project from the basal forebrain to the cerebral cortex and hippocampus. Muscarinic receptors, primarily of the M1 subtype, which are located postsynaptically appear to survive largely intact,[1] whereas the presynaptically located M2 receptors are lost as these neurones degenerate in the disease.[2] These observations provide the basis for the hypothesis that memory-related problems in SDAT should be amenable to treatment using muscarinic agonists acting directly at postsynaptic receptors.[3] Unfortunately, muscarinic agonists such as arecoline (**1**)[4] and RS-86 (2-ethyl-8-methyl-2,8-diazaspiro-[4.5]decane-1,3-dione)[5] have produced only marginal cognitive benefit in clinical studies, and dose-limiting peripheral side effects have proved to be a major liability. This has spurred intensive interest in the discovery of a new generation of centrally selective muscarinic agonists.[6]

There are a number of considerations which are critical to the design of compounds with suitable muscarinic profiles for the treatment of cognitive disorders. The multiplicity and widespread distribution of muscarinic receptors in both the central and peripheral nervous systems have important implications for the discovery of centrally selective compounds. Five different muscarinic receptor subtypes m1−m5 have been cloned and identified.[7] Distribution studies indicate that the different muscarinic receptor subtypes are localized in discrete brain areas associated with particular functions. In rat brain the m1 receptor is most abundant in the cerebral cortex and hippocampus, regions which are intimately associated with memory and learning, whereas m2 predominates in brain stem, cerebellum, and thalamus.[8] The m2 receptor is also widely distributed in peripheral tissues, and it is the predominant subtype in heart and ileum. Studies on cloned receptors have shown that m1−m4 correspond to the pharmacologically defined M1−M4 receptors, respectively.[9] In SDAT postsynaptic receptors which are spared are of the M1 type. Consequently, a compound with intrinsic selectivity for m1 over m2 would offer the prospect of achieving cognitive benefit while minimising peripheral side effects. Intensive efforts in this direction have, unfortunately, met with only limited success. Compounds with reduced intrinsic selectivity for m2 receptors have been described,[10] but the goal of a truly m1 selective muscarinic agonist remains elusive. Functional selectivity, as opposed to intrinsic receptor subtype selectivity, offers a significant alternative route toward the goal of reducing peripheral or central side effects, while maintaining cognitive action. Agonists with reduced efficacy can display tissue selectivity by exploiting regional differences in receptor reserve.[11] It is therefore possible to achieve a high degree of functional selectivity, even in the absence of significant differences in affinity with respect to receptor subtypes, and this represents a powerful strategy. Finally, it is important to give careful consideration to physicochemical properties such as lipophilicity and amine basicity in order to optimize brain penetration.

In a previous report we described a novel group of azabicyclic oxadiazoles[12] which were designed using arecoline (**1**) and methyl quinuclidine-3-carboxylate (**2**) as starting points. This work showed that potent metabolically stable muscarinic agonists such as **3** and

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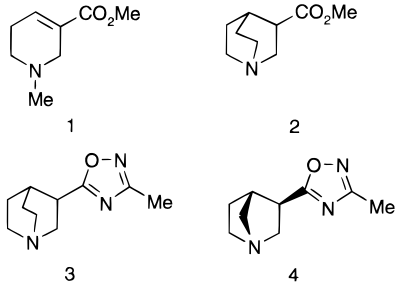
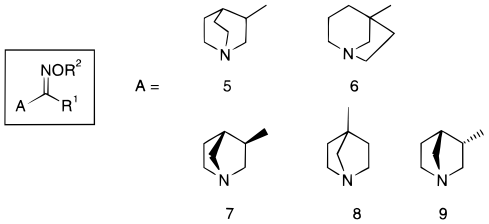


4 could be constructed by replacing the ester group with a 1,2,4-oxadiazole ring. An important feature of this study was the finding that quite subtle changes in the steric properties of the azabicyclic ring resulted in profound effects on agonist efficacy. For example, the efficacy of **3** is significantly lower than that of the more compact 1-azabicyclo[2.2.1]heptane analogue **4**. Examination of electrostatic potential maps revealed broad similarities between the methyl ester and the 3-methyl-1,2,4-oxadiazole ring. In each case two specific regions of negative potential corresponding to possible hydrogen-bonded interactions with the receptor were observed. Subsequent studies demonstrated that other heteroaromatic ring systems, e.g. 1-methyl-1,2,4-triazole,[13,14] 5-methyl-1,2,3,4-tetrazole,[13,14] and 3-methyl-1,2,4-triazine,[15] could also function as ester bioisosteres in the context of interactions at muscarinic receptors. As part of a search for alternative nonaromatic ester bioisosteres, we examined a series of azabicyclic analogues incorporating an oxime ether or modified oxime ether group (Chart 1).[16,17] A range of R^1 and R^2 substituents was investigated in order to explore the scope for increasing lipophilic character and modifying agonist efficacy. It also occurred to us that it might be possible to manipulate the physicochemical properties of compounds in this series, and maintain affinity, by replacing R^1 with small groups such as halogen or nitrile. We anticipated that the electron-withdrawing property of such groups would assist brain penetration by reducing the pK_a of the azabicyclic ring. The introduction of lipophilic halogens was also expected to have a positive effect on log *P* values. Azabicyclic rings included in this study were those which in previous studies were found to be tolerated on steric grounds.

Chart 1

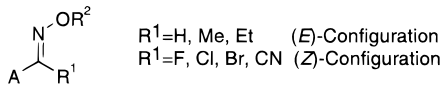


a	R^1 = H	R^2 = Me	f	R^1 = Br	R^2 = Me	k	R^1 = H	R^2 = Propargyl
b	R^1 = Me	R^2 = Me	g	R^1 = CN	R^2 = Me	l	R^1 = H	R^2 = Allyl
c	R^1 = Et	R^2 = Me	h	R^1 = H	R^2 = Et	m	R^1 = H	R^2 = But-2-ynyl
d	R^1 = F	R^2 = Me	i	R^1 = H	R^2 = n-Pr			
e	R^1 = Cl	R^2 = Me	j	R^1 = H	R^2 = n-Bu			

Chemistry

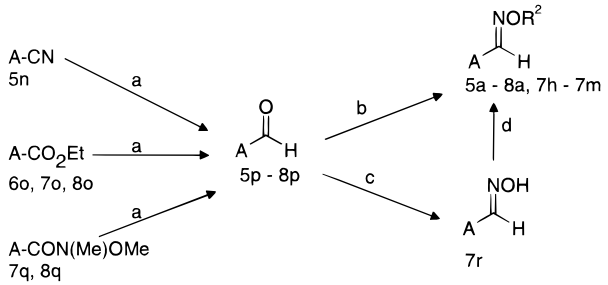
The stereochemistry of all oxime ethers and modified oxime ethers in this study is described using *E*/*Z* notation. In effect this means that the relative orientation of the groups R^1 and R^2 is the same in (*E*)-aldoxime ethers, (*E*)-ketoxime ethers, and (*Z*)-imidoyl halides and nitriles (Chart 2).

Chart 2



Azabicyclic aldehydes required for the preparation of the corresponding aldoxime ethers were accessed using several different procedures (Scheme 1). Aldehyde **5p** was obtained by reduction of 3-cyano-1-azabicyclo[2.2.2]-octane **5n** with diisobutylaluminum hydride (DIBAL-H). Azabicyclic aldehydes **6p** and **7p** were prepared by controlled reduction of the corresponding esters **6o** and **7o** with DIBAL-H. More satisfactorily, the esters **7o** and **8o** were first converted into the *N*-methyl-*N*-methoxycarboxamides **7q** and **8q** which were then reduced to the aldehydes **7p** and **8p** with DIBAL-H according to the method of Weinreb.[18] The azabicyclic aldoxime ethers were generally obtained by treatment of the corresponding aldehydes with the appropriate *O*-alkylhydroxylamine. However, in the case of the *O*-propyl and *O*-butyl aldoxime ethers **7i** and **7j**, the aldehyde precursor **7p** was first converted into the oxime derivative **7r** with hydroxylamine and then O-alkylated under basic conditions with the appropiate alkyl mesylate. Aldoxime ethers **5a**, **7a**, and **7h**−**m** were obtained as mixtures of *E* and *Z* isomers (Table 1). In contrast, **6a** and **8a**, in which the aldoxime ether group is attached to the more hindered bridgehead position of the azabicyclic ring system, were obtained in pure *E* form. Stereochemical assignments were made on the basis of ^{1}H NMR. In the case of the *E* isomers the vinylic proton resonates in the range δ 7.3−7.9 ppm compared to δ 6.6−7.1 ppm in the case of the *Z* isomers. Where mixtures were obtained the difference in chemical shift was in the range 0.52−0.74 ppm.

Scheme 1[a]

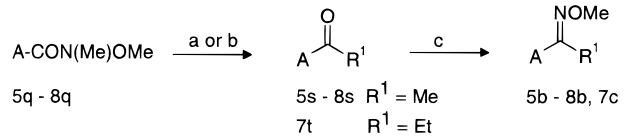


[a] Reagents (a) DIBAL-H/toluene; (b) R^2ONH_2·HCl/MeOH; (c) NH_2OH·HCl; (d) R^2OSO_2Me/KOBu^t/THF.

Methyl ketones **5s**−**8s** were prepared by treating the *N*-methyl-*N*-methoxycarboxamides **5q**−**8q** with methyllithium in tetrahydrofuran (Scheme 2). Similarly, ethyl ketone **7t** was obtained from **7q** upon treatment with ethylmagnesium bromide. Treatment of ketones **5s**−**8s** and **7t** with methoxylamine afforded the corresponding ketoxime ethers. Oxime ether derivatives **5b**−**7b** and **7c** were obtained as *E* isomers, whereas **8b** was isolated as a 4:1 mixture of *E* and *Z* isomers. Assignment of *E* stereochemistry was confirmed by NOE experiments.

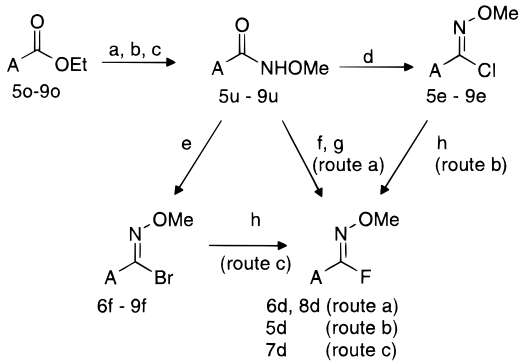
N-Methoxy imidoyl fluoride, chloride, bromide, and nitrile analogues were all synthesized *via* the *N*-meth-

Scheme 2[a]



[a] Reagents (a) MeLi/THF; (b) EtMgBr/THF; (c) $MeONH_2$·HCl/MeOH.

Scheme 3[a]

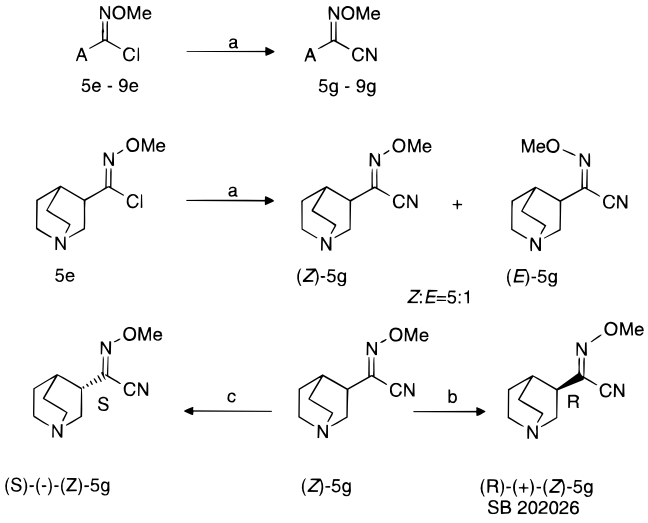


[a] Reagents (a) aqueous HCl/reflux; (b) $SOCl_2/CH_2Cl_2$; (c) $MeONH_2$·HCl/pyridine; (d) $P(Ph)_3/CCl_4$/MeCN; (e) $P(Ph)_3/CBr_4$/MeCN; (f) HF−pyridine; (g) DAST/MeCN; (h) CsF/CaF_2/DMF/145 °C.

oxycarboxamides **5u**−**9u** which were accessed from the corresponding esters **5o**−**9o** (Scheme 3). Treatment of **5u**−**9u** with triphenylphosphine and carbon tetrachloride in refluxing acetonitrile[19] afforded the *N*-methoxy imidoyl chlorides **5e**−**9e**. The corresponding bromo analogues **6f**−**9f** were prepared under similar conditions using triphenylphosphine and carbon tetrabromide. The *N*-methoxy imidoyl fluorides **6d** and **8d** were obtained by treatment of the hydrogen fluoride salts of the *N*-methoxyamides **6u** and **8u** with diethylaminosulfur trifluoride (DAST) in refluxing acetonitrile. This novel use of the DAST reagent proved to be applicable only to those analogues where the functional group is attached to a bridgehead carbon, and consequently alternative procedures were developed for the synthesis of **5d** and **7d**. These compounds were obtained from the *N*-methoxy imidoyl chloride **5e** and bromide **7f**, respectively, by halogen exchange using caesium fluoride supported on calcium fluoride in dimethylformamide as a fluoride source.[20] In all of the above reactions the products were isolated as single geometrical isomers, but stereochemistry could not be assigned unambiguously using either ^1H or ^{13}C NMR. By analogy with the imidoyl nitriles **5g**−**9g** (see the following section), the imidoyl halides were tentatively assigned the *Z* configuration.

N-Methoxy imidoyl nitriles **5g**−**9g** were obtained by treatment of the corresponding *N*-methoxy imidoyl chlorides **5e**−**9e** with sodium cyanide in dimethyl sulfoxide[21] (Scheme 4). The reaction of **5e** with sodium cyanide gave a 5:1 mixture of *Z* and *E* imidoyl nitriles **(*Z*)-5g** and **(*E*)-5g** which could be separated by column chromatography (combined yield = 60%). Stereochemistry was assigned by ^1H NMR. Irradiation of the OMe protons at δ 4.1 ppm in the ^1H NMR spectrum of the slower running isomer **(*Z*)-5g** showed no NOE effects to any other protons in the molecule, whereas irradiation of the corresponding signal at δ 4.05 ppm in the spectrum of the faster running isomer **(*E*)-5g** gave a

Scheme 4[a]



[a] Reagents (a) NaCN/DMSO/100 °C; (b) (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate; (c) (*S*)-(+)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate.

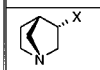
small positive NOE to the 4-H proton at δ 2.04 ppm. The chemical shift of the C═N carbon is diagnostic of stereochemistry. In the case of **(*Z*)-5g** this carbon appears at δ 134.3, whereas the corresponding signal in **(*E*)-5g** is shifted to δ 142.4. The *Z* isomer **(*Z*)-5g** was resolved into the corresponding (+) and (−) enantiomers **(+)-(*Z*)-5g** and **(−)-(*Z*)-5g** by the sequential use of (*R*)-(−)- and (*S*)-(+)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate.[22] A single-crystal X-ray determination on the hydrochloride salt of **(+)-(*Z*)-5g**[23] confirmed the configurational assignments and allowed the absolute stereochemistry to be assigned as *R*. The *N*-methoxy imidoyl nitriles **6g**−**9g** were obtained as single geometric isomers from the reaction between the corresponding *N*-methoxy imidoyl chlorides **6e**−**9e** and sodium cyanide. In the ^{13}C NMR spectra of **6g**−**9g**, the chemical shift of the C═N carbon falls in the range δ 130.1−133.6 which is indicative of *Z* stereochemistry.

The individual geometric isomers **(*Z*)-5g** and **(*E*)-5g** were found to be chemically stable in 1 M DCl in D_2O with no sign of isomerization over several days at room temperature. However, in 5.5 M DCl in D_2O both **(*Z*)-5g** and **(*E*)-5g** slowly isomerized to a 5:1 equilibrium mixture of *Z* and *E* isomers (half-life ∼15 h by NMR experiments). In contrast, aldoxime ethers are much more prone to isomerization. For example, the aldoxime ether **7k** (9:1 ratio *E*/*Z*) isomerized rapidly to give a 2:1 mixture of *E* and *Z* isomers upon exposure to 2 M DCl. The relative stability of **(*Z*)-5g** and **(*E*)-5g** in aqueous acid, compared to simple aldoxime and ketoxime ethers,[24] is presumably due to the effect of the electron withdrawing cyano group on the basicity of the imino nitrogen.

In Vitro Affinities for Muscarinic Receptors in Rat Brain

The affinity of compounds for muscarinic receptors in rat cerebral cortex was assessed as previously described[12] using an *in vitro* radioligand binding assay. The ability of compounds to displace [^3H]oxotremorine (OXO-M) binding was used to provide a measure of affinity for the high-affinity agonist state of the receptor.

Table 1. *In Vitro* Affinities for Muscarinic Receptors in Rat Cerebral Cortex[a]

Structure X= NOR^2 / R^1	Compound	R^1	R^2	Ratio[b] *E:Z*	IC_{50}, nM OXO-M	IC_{50}, nM QNB	Ratio IC_{50} QNB/ IC_{50}OXO-M
	**5a**	H	Me	3:2	95 (65-110)	5800 (3400-10000)	61
	5b	Me	Me	*E*	69 (66-83)	2000 (1400-2900)	29
	5d	F	Me	*Z*	34 (23-58)	2200 (2100-2250)	65
	5e	Cl	Me	*Z*	69 (51-93)	1100 (900-1450)	16
	(*Z*)-5g	CN	Me	*Z*	33 (26-36)	470 (440-490)	14
	(+)-(*Z*)-5g	CN	Me	*Z*	14 (10-21)	310 (200-340)	22
	(-)-(*Z*)-5g	CN	Me	*Z*	140 (57-270)	1130 (420-1800)	8
	(*E*)-5g	CN	Me	*E*	240 (230-250)	1300 (950-1750)	5
	**6a**	H	Me	*E*	60 (44-170)	5200 (4800-6300)	87
	6b	Me	Me	*E*	46 (44-48)	3400 (2600-4400)	74
	6d	F	Me	*Z*	43 (27-85)	2400 (1900-3000)	56
	6e	Cl	Me	*Z*	72 (45-120)	3000 (2300-3800)	42
	6f	Br	Me	*Z*	190 (185-190)	2300 (1950-2800)	12
	6g	CN	Me	*Z*	11 (7.4-17.5)	220 (200-250)	20
	**7a**	H	Me	7:1	15 (10-30)	3100 (2000-4800)	210
	7b	Me	Me	*E*	99 (83-128)	7500 (6200-9000)	76
	7c	Et	Me	*E*	210 (155-265)	5200 (3400-8000)	25
	7d	F	Me	*Z*	8.5 (7-11)	3100 (3000-3200)	370
	7e	Cl	Me	*Z*	64 (48-85)	3000 (2650-3300)	47
	7f	Br	Me	*Z*	59 (22-120)	3000 (2350-11000)	51
	7g	CN	Me	*Z*	23 (22-25)	2300 (2100-2600)	100
	7h	H	Et	13:1	160 (160, 160)	3700 (2500-5600)	23
	7i	H	n-Pr	7:1	280 (230-335)	2900 (2700-3000)	10
	7j	H	n-Bu	16:1	250 (205-310)	3600 (3600, 3600)	14
	7k	H	Propargyl	9:1	25 (12-62)	1950 (1400-2700)	78
	7l	H	Allyl	8:1	250 (215-280)	9700 (8500-11000)	39
	7m	H	But-2-ynyl	5:2	115 (110-120)	2900 (1900-4400)	25
	**8a**	H	Me	*E*	120 (90-155)	38000 (36000-40000)	320
	8b	Me	Me	4:1	55 (50-65)	14000 (12500-16500)	260
	8d	F	Me	*Z*	44 (40-48)	15500*	350
	8e	Cl	Me	*Z*	51 (38-67.5)	8500 (8000-9000)	170
	8f	Br	Me	*Z*	160 (150-170)	8100 (6500-10000)	51
	8g	CN	Me	*Z*	19 (18-21)	1950 (1900-2000)	100
	**9e**	Cl	Me	Z	100 (57-150)	8880 (7000-11250)	90
	9f	Br	Me	Z	170 (86-370)	2300 (1500-3600)	14
	9g	CN	Me	Z	21 (6.5-38)	3175 (1800-3600)	150
	**2**	-	-	-	520 (440-600)	25000 (16000-36000)	49
Arecoline	**1**	-	-	-	115 (75-200)	19000 (10000-110000)	165

[a] All values with the exception of the entry marked with an asterisk are the geometric means of results obtained in two to six separate experiments. Ranges are given in parentheses. [b] For consistency *E*/*Z* nomenclature is used for all compounds.

The ratio of the IC_{50} values for displacement of [^{3}H]-quinuclidinyl benzilate (QNB) and OXO-M (QNB/OXO-M) was used to predict efficacy. Ratios greater than 100 are associated with full agonists; antagonists give ratios close to unity and intermediate values indicate partial agonism. Affinities derived from radioligand binding assays are shown in Table 1. All the compounds in this study, with the exception of the 4-substituted 1-azabicyclo[2.2.1]heptane derivatives, have a chiral center. Unless otherwise stated, the biological data refer to the racemic mixture. In those cases where oxime ether derivatives were isolated as a mixture of geometric isomers, the isomer ratio has been indicated.

In a preliminary study the ester group of methyl quinuclidine-3-carboxylate **2** was replaced by an aldoxime methyl ether group. This afforded **5a** which showed improved affinity for muscarinic receptors (Table 1). Extension of this work to other azabicyclic ring systems produced a range of oxime ether analogues **6a**−**8a** with moderately high affinity. The 3-substituted 1-azabicyclo[2.2.1]heptane **7a** shows the highest affinity in this series. The high affinity of the 1-azabicyclo[2.2.1]-heptane ring system in this context parallels earlier work which highlighted the exceptional affinity of the corresponding 3-methyl-1,2,4-oxadiazole **4**.[12] The predicted efficacy ratios of compounds in this series suggest that whereas **5a** and **6a** have partial agonist character, **7a** and **8a** are full agonists. The high QNB/OXO-M ratios generally observed with compounds incorporating the 1-azabicyclo[2.2.1]heptane ring indicate that the smaller size of this azabicyclic ring is a major factor contributing to higher efficacy.

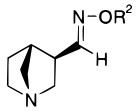
Variation of the ether alkyl group was investigated using the high affinity full agonist **7a** as a starting point (Table 1). Increasing the ether chain length from methyl to ethyl as in **7h** resulted in a marked decreasein both the affinity and predicted efficacy ratio. The corresponding *n*-propyl and *n*-butyl ethers **7i** and **7j** are also predicted to be relatively weak partial agonists. On the other hand, the propargyl ether **7k** displayed an affinity comparable to that of the methyl ether **7a** and a ratio indicating partial agonist character. The affinity of the allyl ether **7l** was 10-fold lower than that of **7k**. Interestingly, the butynyl analogue **7m** retained reasonable affinity and a ratio predictive of partial agonism. The marked drop in affinity of the saturated homologated ethers **7h**−**j** relative to **7a** indicates that in this series the methyl ether group is optimal. This finding accords with earlier work pointing to the existence of a small lipophilic pocket in the receptor capable of accommodating the methyl group of acetylcholine.[13] Unsaturated alkyl ether groups, and in particular alkynyl groups, are better accommodated than the corresponding saturated alkyl chains. The higher affinity and efficacy ratio of the propargyl ether **7k** relative to the propyl analogue **7i** are striking. This observation can probably be accounted for by the lower steric demand of the propargyl relative to the propyl group, although the possibility of a more specific interaction involving the acetylenic triple bond and the

Table 2. *In Vitro* Affinities for Human Cloned Muscarinic Receptors[a]

R^1	compound	QNB IC_{50}, nM hm1	hm2	hm3	hm4	hm1:hm2 selectivity ratio	efficacy ratio IC_{50}(QNB)/ IC_{50}(OXO-M)
CN	**(+)-(*Z*)-5g**	170 (120, 230)	180 (125, 250)	60 (48, 75)	90 (58, 140)	1.1	22
	6g	99 (54, 180)	31 (30, 32)	28 (26, 30)	49 (34, 70)	0.31	20
	7g	1180 (925, 1500)	610 (340, 1100)	380 (310, 460)	800 (530, 1200)	0.52	100
	8g	1650 (1600, 1700)	240 (160, 370)	300 (300, 300)	495 (340, 720)	0.15	100
	9g	1500 (1100−1950)	700 (500−975)	1200 (1150−1200)	975 (950−1000)	0.47	150
H	**7a**	10000 (7500, 14000)	220 (130, 380)	2200 (1200, 3900)	1100 (730, 1600)	0.02	210
	McN-A343	13000 (12000−15000)	18000 (13000−23500)	5400 (4700−6200)	8000 (7400−8700)	1.3	37
	arecoline	65000 (56000−75000)	1800 (1350−2300)	11000 (9500−13000)	13500 (13000−14000)	0.028	165
	carbachol	150000 (125000−180000)	1400 (1300−1600)	9100 (9000−9200)	7200 (4500−11500)	0.0093	810

[a] In all cases results are quoted as the mean of at least two independent assays. Individual values are shown in parentheses.

Table 3. Central Selectivity of Oxime Ethers[a]



compound	R^2	RSA (ED_{Arec}) (mg/kg iv)	BP (ED_{50}) (mg/kg iv)	HR (ED_{50}) (mg/kg iv)	BP (ED_{50})/ RSA (ED_{Arec})	HR (ED_{50})/ RSA (ED_{Arec})	IC_{50}(QNB)/ IC_{50}(OXO-M)
7a	Me	0.0021 (0.0010−0.0045)	0.0031 (0.0016−0.0063)	0.0031 (0.0022−0.0043)	1.5	1.5	210
7h	Et	0.23 (0.12−0.43)	>1.8	>1.8	>7.8	>7.8	23
7k	propargyl	0.016 (0.009−0.028)	0.17 (0.13−0.21)	0.059 (0.035−0.097)	10.6	3.7	78
arecoline		0.32	0.022 (0.012−0.041)	0.024 (0.018 −0.032)	0.07	0.075	165

[a] $ED_{(Arec)}$ reflects the dose required to produce a change in the mean power spectrum of the EEG equivalent to that of a standard dose (0.32 mg/kg iv) of arecoline. BP(ED_{50}) and HR(ED_{50}) are the doses producing transient 50% falls in mean blood pressure and heart rate respectively. Values in parentheses indicate 95% confidence limits.

receptor cannot be ruled out. There is an interesting parallel between this result and the increased muscarinic potency reported for arecaidine propargyl ester relative to the propyl ester in the isolated rat ileum preparation.[25]

Moderately high affinity was retained by the methyl ketoxime *O*-methyl ethers **5b**−**8b**. Variation of the azabicyclic ring exerts only a small influence over affinity in this series. The effect of increasing the steric bulk of the R^1 substituent was further examined in the 1-azabicyclo[2.2.1]heptane series. The affinity of the ethyl ketoxime ether **7c** was found to be lower than that of the methyl analogue **7b**. The observed order of affinity for R^1 in this series is H ≫ Me > Et. This progressive drop in both affinity and predicted efficacy as the size of the R^1 group is increased points to a low tolerance of steric bulk at this position.

In view of the limited scope for introducing alkyl R^1 groups, the possibility of employing alternative sterically less demanding groups was explored. Initial work focused on the introduction of halogens. The *N*-methoxy imidoyl halides generally displayed high affinities with IC_{50} values in the range 9−190 nM. The most potent member of this series is the imidoyl fluoride **7d** which has an IC_{50} value of 9 nM and an efficacy ratio of 344. This profile is similar to that of the corresponding aldoxime ether **7a**. The same pattern is observed in the case of the imidoyl fluorides **5d**, **6d**, and **8d**, which have affinities and efficacy ratios comparable to those of the corresponding aldoxime ethers **5a**, **6a**, and **8a**. Affinities of the *N*-methoxy imidoyl chlorides **5e**−**8e** are generally lower than those of the corresponding imidoyl fluorides **5d**−**8d**. In broad terms, replacement of H and Me by the halogens F and Cl, respectively, which have similar steric properties,[26] results in muscarinic agonists with similar affinities and efficacy ratios. The larger bromine atom can also be tolerated although efficacy ratios of the imidoyl bromides **6f**−**9f** are generally lower than those of the corresponding *N*-methoxy imidoyl fluorides and chlorides. A consistent trend within each azabicyclic series is the reduction in the efficacy ratio with increasing size of the halogen. This is in line with previous observations linking an increase in steric bulk to a reduction in efficacy ratio.

The *N*-methoxy imidoyl nitriles **5g**−**9g** displayed very high affinities with IC_{50} values in the range 11−33 nM. Efficacy ratios ranged from 14 to 150 with the bulkier azabicyclic octanes **5g** and **6g** showing lower ratios than the azabicyclic heptanes **7g**, **8g**, and **9g**. In the case of **(*Z*)-5g** affinity for muscarinic receptors resides pre-

Table 4. Central Selectivity of *N*-Methoxy Imidoyl Halides and Nitriles[a]

Structure X= NOMe, R^1	Compound	R^1	RSA (ED_{Arec}) (mg/kg iv)	BP (ED_{50}) (mg/kg iv)	HR (ED_{50}) (mg/kg iv)	BP (ED_{50})/ RSA(ED_{Arec})	HR (ED_{50})/ RSA(ED_{Arec})	IC_{50} QNB/ IC_{50} OXO-M
	**5b**	Me	0.31 (0.21-0.46)	>0.32	>0.32	>1	>1	29
	(*Z*)-5g	CN	0.052 (0.035 - 0.077)	>0.56	>0.56	>10.9	>10.9	14
	(+)-(*Z*)- 5g	CN	0.017 (0.012-0.024)	>0.32	>0.32	>18.8	>18.8	22
	(-)-(*Z*)- 5g	CN	>1.0	>1.0	>1.0	-	-	8
	**6b**	Me	0.068 (0.041-0.110)	0.068 (0.057-0.082)	0.042 (0.033-0.11)	1.0	0.6	74
	6d	F	0.012 (0.007-0.020)	0.03 (0.013-0.069)	0.024 (0.015-0.039)	2.5	2.0	56
	6e	Cl	0.032 (0.025-0.039)	0.32 (0.18-0.56)	0.24 (0.17-0.35)	10.0	8.3	42
	6g	CN	0.005 (0.001-0.023)	0.02 (0.018-0.021)	0.01 (0.009-0.011)	4.0	2.0	20
	**7g**	CN	0.0032 (0.0018-0.0056)	0.015 (0.009-0.023)	0.009 (0.007-0.012)	4.7	2.8	100
	**8g**	CN	0.0056 (0.003-0.008)	0.01 (0.007-0.014)	0.0044 (0.004-0.0049)	1.8	0.79	100
	**9g**	CN	0.005 (0.003-0.008)	0.024 (0.017-0.032)	0.021 (0.017-0.027)	4.8	4.2	150
Arecoline	**1**	-	0.32	0.022 (0.012-0.041)	0.024 (0.018-0.032)	0.07	0.075	165

[a] ED_{Arec} reflects the dose required to produce a change in the mean power spectrum of the EEG equivalent to that of a standard dose (0.32 mg/kg iv) of arecoline. $BP(ED_{50})$ and $HR(ED_{50})$ are the doses producing transient 50% falls in mean blood pressure and heart rate respectively. Values in parentheses indicate 95% confidence limits.

dominantly in the **R-(+)-(*Z*)-5g** enantiomer, which was found to have an affinity 10 times greater than that of the **S-(−)-(*Z*)-5g** enantiomer. The high affinities in this series indicate that the cyano group is well tolerated. On steric grounds this is consistent with previous observations, since the size of the cyano group is roughly comparable to that of a methyl group.[26]

Only limited conclusions about the preferred oxime ether geometry can be inferred from the data in Table 1. The aldoxime ethers were isolated and tested as mixtures in which the *E* isomer predominated. Interconversion of the *E* and *Z* isomers of aldoxime ethers was facile, and precluded affinity measurements on individual geometric isomers. Ketoxime ethers were isolated and tested as pure *E* isomers with the exception of **8b**. Similarly, the *N*-methoxy imidoyl halides were isolated as single isomers which were tentatively assigned *Z* stereochemistry. In the case of the methoxy imidoyl nitriles **(*E*)-5g** and **(*Z*)-5g**, where the individual isomers are stable isolable entities, the situation is clearer. Affinity for muscarinic receptors resides predominantly in the *Z* isomer **(*Z*)-5g** which has an 18-fold higher affinity than that of **(*E*)-5g**.

From the foregoing arguments it is clear that steric factors play a major role in determining both affinity and predicted efficacy. However, electronic factors also need to be addressed. Insight into the electronic properties of oxime ethers and modified oxime ethers was derived from a comparison of electrostatic potential maps. In order to simplify the calculations, model compounds in which the azabicyclic ring is replaced by a methyl group were used, and the study was limited to *O*-methyl ethers. (The Experimental Section contains details.) Broad similarities between the methyl carboxylic acid ester and the aldoxime and ketoxime *O*-methyl ether groups emerge from an examination of their respective electrostatic potential maps (Figure 1). In the case of the ester group there are two regions of negative potential, one associated with the ether oxygen and the second in the vicinity of the carbonyl oxygen. The aldoxime and ketoxime groups each give rise to two areas of negative potential which are likely to be important in receptor binding. Moreover, there is sufficient overlap between the locations of the potential minima in the oxime ethers and the ester to suggest that the methyl ester and oxime *O*-methyl ether groups probably interact with muscarinic receptors in a similar manner (Figure 2). Electrostatic potential maps of the *N*-methoxy imidoyl fluoride and chloride are broadly similar to those of the aldoxime and ketoxime ethers. In the case of the *N*-methoxy imidoyl nitrile there is a third potential minimum associated with the CN group. This interesting observation raises the possibility that the nitrile may engage in an additional binding interaction.

Affinities for Human Cloned Muscarinic Receptors

Specificity for muscarinic receptor subtypes was investigated using human cloned muscarinic receptors hm1−hm4 expressed in chinese hamster ovary (CHO) cells. When [^{3}H]oxotremorine was employed as the radioligand, no significant binding could be detected in the hm1 transfected cell line. This observation accords with reports that the agonist [^{3}H]-*cis*-methyldioxolane does not produce measurable affinity in CHO cells transfected with the hm1 receptor[27] and probably reflects a low abundance of high-affinity binding sites in these cells. Consequently, affinities for hm1−hm4 were assessed by measuring the displacement of the antagonist [^{3}H]quinuclidinyl benzilate (QNB). Results for the *N*-methoxy imidoyl nitriles **5g**−**9g** are shown in Table 2. The quinuclidine analogue **(+)-(*Z*)-5g** dis-

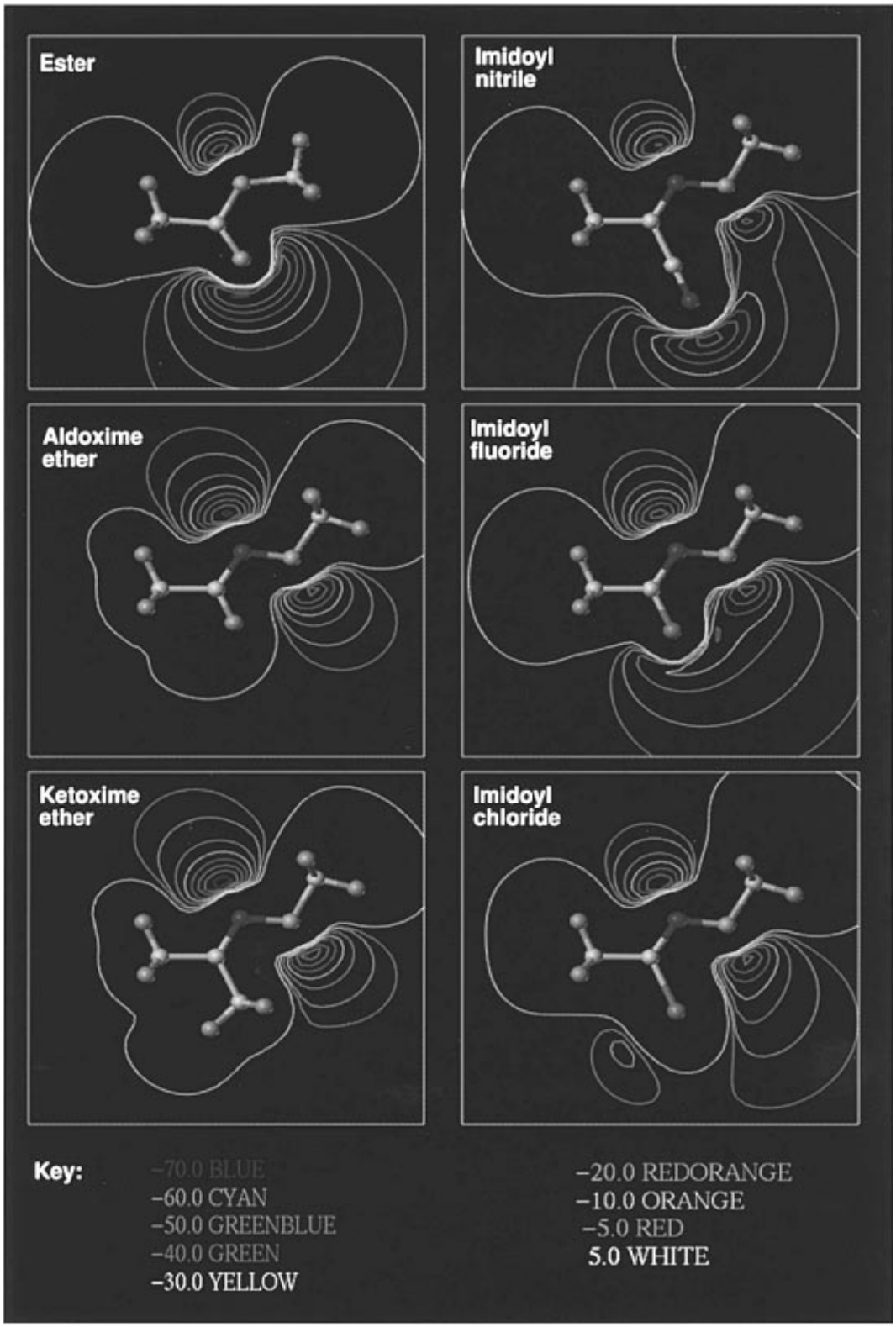


Figure 1. Molecular electrostatic potential maps of model compounds.

played similar affinities for hm1 and hm2 receptors with marginally higher affinities for hm3 and hm4. The related compounds **6g**−**9g** showed a small preference (2−7-fold) for hm2 over hm1. In contrast, the aldoxime ether **7a** which has already been highlighted as a high-affinity full agonist, showed a 46-fold preference for hm2 over hm1. Comparative data for standard muscarinic agonists was also generated. McN-A343 [[4-[[(*m*-chlorophenyl)carbamoyl]oxy]-2-butynyl]trimethylammonium chloride] is a relatively weak partial agonist which showed similar affinities at hm1 and hm2 receptors. On the other hand, arecoline and carbachol which are high-efficacy agonists displayed marked selectivites (36-fold and 111-fold, respectively) for hm2 over hm1 receptors. In broad terms there appears to be an inverse correlation between the QNB/OXO-M efficacy ratio and the hm1 vs hm2 selectivity ratio. Partial agonists such as **(+)-(*Z*)-5g** and McN-A343 have similar affinities for hm1 and hm2 receptors whereas high-efficacy agonists such as **7a**, arecoline, and carbachol are selective for

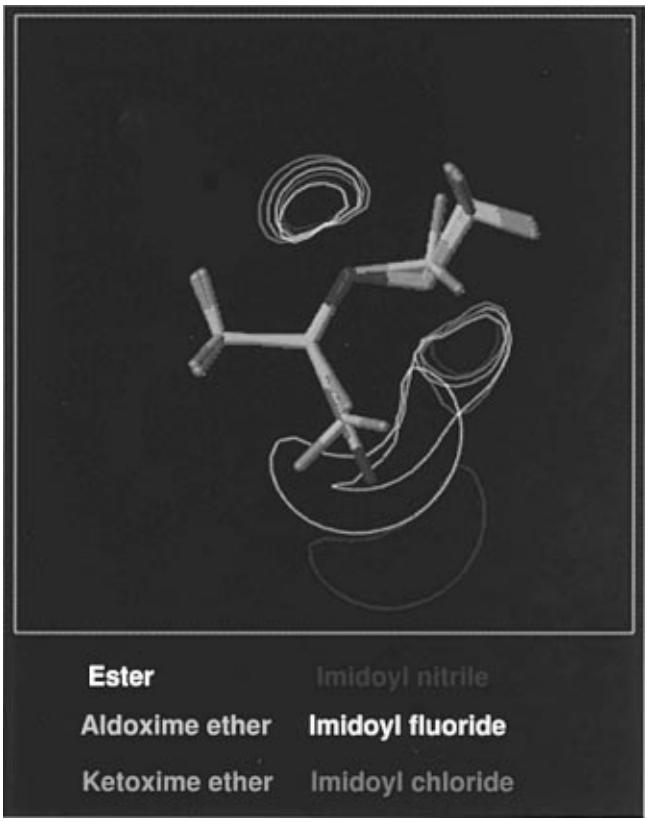


Figure 2. Comparison of electrostatic potential minima contoured at −30 kcal/mol.

hm2. This trend accords with previous studies using a structurally diverse range of full and partial agonists which demonstrated a reasonably good correlation between the QNB/OXO-M efficacy ratio and the loss of high selectivity for hm2.[28] There are, however, some inconsistencies between the selectivity and efficacy ratio in the series **5g**−**9g** which suggest that other factors must also be involved.

Functional Effects on Muscarinic Receptors In Vivo

Functional assessment of central muscarinic agonist activity was based on *in vivo* electrophysiological measurements. Muscarinic agonists produce well-characterized changes in the electrical activity of the brain.[29,30] It has been shown that in the anesthetized rat both arecoline and oxotremorine induce hippocampal rhythmical slow wave activity (RSA or theta wave activity) as assessed by changes in the power spectrum at 3−7 Hz. These effects are mediated by central muscarinic receptors since they can be reversibly blocked by scopolamine but not *N*-methylscopolamine. In the present study RSA induced by test compounds was measured using electrodes placed in the CA1 region of the hippocampus in urethane anesthetized rats. Peripheral effects were blocked with atropine methyl nitrate. Changes in the mean power spectrum were quantified and expressed as the dose of test compound able to elicit a change in power equivalent to that of a standard dose of arecoline (0.32 mg/kg iv, ED_{arec}). Hypotensive effects were assessed in anesthetized rats, and selectivity for central muscarinic receptors was determined by comparing the dose required to induce RSA (ED_{arec}) against the doses producing a transient 50% fall in blood pressure (BP ED_{50}) and a 50% reduction in heart rate (HR ED_{50}).

The 1-azabicyclo[2.2.1]heptanes **7a**, **7h**, and **7k**, which have efficacy ratios spanning the range from full to partial agonism, were selected for evaluation in the EEG model. This subset of structurally related compounds provided an opportunity to probe for a possible link between CNS selectivity and reduced efficacy. Results are shown in Table 3. All three compounds produced RSA. The methyl ether **7a**, which displayed the highest affinity and efficacy ratio, was also the most potent in the rat EEG model, but it produced cardiovascular effects at comparable doses. On the other hand, the ethyl and propargyl ethers **7h** and **7k**, which have QNB/OXO-M ratios predictive of partial agonist character, were able to elicit RSA at doses well below those producing hypotensive effects. In particular, the propargyl ether **7k** (BRL 49277) stands out as as a potent partial agonist with good central selectivity.

Effects of *N*-methoxy imidoyl halides and nitriles on the EEG and cardiovascular system are shown in Table 4. Selected data on aldoximes and ketoximes are included for comparison. A key feature of this series is that both full and partial agonists potently induce RSA. The most impressive profiles were observed with the *N*-methoxy imidoyl nitriles which display high RSA potencies combined with reduced cardiovascular effects. The quinuclidinyl imidoyl nitrile **(*Z*)-5g**, which has a QNB/OXO-M ratio predictive of low efficacy partial agonist character, displayed BP/RSA and HR/RSA selectivity ratios >10. In the case of the more active enantiomer **(+)-(*Z*)-5g** the BP/RSA and HR/RSA selectivity ratios were both >18. In contrast, **(−)-(*Z*)-5g**, which has a QNB/OXO-M ratio pointing toward antagonist character, failed to produce RSA even at 60 times the (ED_{arec}) dose of the (+) enantiomer. It is also worth noting that the imidoyl nitriles **7g** and **9g**, which have QNB/OXO-M ratios predictive of full agonist character, still show moderate central selectivity. A more detailed comparison of the imidoyl fluoride, imidoyl chloride, and imidoyl nitrile groups emerged from studies on the isomeric 1-azabicyclo[2.2.2]-oct-5-yl series. The methyl ketoxime ether **6b** elicited RSA and cardiovascular effects at the same dose, whereas the imidoyl nitrile **6g** displayed moderate selectivity. The imidoyl chloride **6e** showed a 10-fold separation between doses eliciting RSA and hypotension and an 8-fold separation with respect to bradycardia.

Physicochemical properties of selected *N*-methoxy imidoyl halides and nitriles are shown in Table 5 together with comparative data for the corresponding methyl ketoximes. The basicities of the imidoyl fluoride, chloride and nitrile analogues **6d**, **6e**, and **6f**, respectively, are significantly lower than that of the corresponding methyl ketoxime ether **6b**. Measured log *P* values follow the expected trend with the imidoyl chloride **6e** being more lipophilic than the corresponding fluoride **6d**. The log *P* value of the imidoyl nitrile **6g** is only slightly lower than that of the ketoxime ether **6b**, and the same trend is observed for **5g** relative to **5b**. The reduced basicity of the imidoyl nitriles relative to the corresponding methyl ketoxime ethers is reflected in higher log *D* values which are predictive of improved brain penetration, and this probably contributes to the high degree of central selectivity observed with this group of compounds. In the case of the imidoyl chloride

Table 5. Physicochemical Properties of *N*-Methoxy Imidoyl Halides and Nitriles

Structure	Compound	R^1	IC_{50} QNB/ IC_{50} OXO-M	BP (ED_{50})/ RSA(ED_{Arec})	pKa	LogP^a	LogD^b
	**5b**	Me	29	>1.0	10.27	1.88	-1.09
	(Z)-5g	CN	14	>10.9	8.96	1.56	-0.11
	**6b**	Me	74	1.0	10.07	1.65	-1.13
	6d	F	56	2.5	9.06	1.01	-0.76
	6e	Cl	42	10.0	9.24	2.12	+0.18
	6g	CN	20	4.0	8.96	1.49	-0.18

[a] log *P* values measured for octanol/buffer (pH = 12). [b] log *D* values calculated for pH = 7.3 The distribution coefficient (*D*) is defined as the ratio of the concentration of compound in the lipid phase to the concentration of all species in the aqueous phase at a given pH.

Table 6. ***In Vivo*** **Profile of (+)-(*Z*)-5g**

compound	RSA (ED_{Arec})	tremor ED_{50} mg/kg (sc)	tremor/ RSA	IC_{50}(QNB)/ IC_{50}(OXO-M)
(+)-(*Z*)-5g	0.017	>10	>500	22
SB 202026	(0.012−0.024)			
RS86	0.35	3.8	8.6	42
	(0.21−0.60)	(1.4−10.0)		
oxotremorine	0.023	0.07	3.0	190
	(0.016−0.033)	(0.03−0.19)		

6e the chloro substituent has the combined effect of reducing basicity and increasing log *P*, and this could explain the impressive central selectivity observed with this compound.

Tremorigenic effects were assessed in mice (Table 6). The separation between the dose required to induce RSA (ED_{arec}) and the dose producing tremor gives a measure of the propensity of a compound to induce extrapyramidal effects. The quinuclidinyl imidoyl nitrile **(+)-(*Z*)-5g** showed >500-fold separation between the doses required to induce tremor and RSA. This represents a marked improvement relative to muscarinic agonists such as oxotremorine and RS-86.

Discussion

The objective of this study was the discovery of centrally selective muscarinic agonists. Hippocampal RSA was used as a measure of central activation since it is likely to be predictive of cognitive enhancement. Peripherally mediated cardiovascular effects are potentially limiting side effects resulting from indiscriminate muscarinic receptor activation. Consequently, the separation between RSA and cardiovascular effects represents a critical measure of selectivity, and this criterion was used as the basis for assessing compounds. The quinuclidinyl imidoyl nitrile **(+)-(*Z*)-5g** was found to be a highly selective muscarinic agonist and its selective profile *in vivo*, which is reflected in high BP/RSA and HR/RSA ratios, can be rationalized in terms of relative affinities at muscarinic receptor subtypes, the degree of agonist efficacy, and brain penetrancy.

Hippocampal RSA is mediated by M1 receptors,[31] whereas peripherally mediated vasorelaxant effects of muscarinic agonists involve activation of both M2 and M3 receptors.[32] Muscarinic M3 receptors mediate release of nitric oxide which produces vasodilation, while muscarinic agonists acting presynaptically at M2 receptors reduce vascular tone *via* an inhibitory effect on noradrenaline release. Stimulation of M2 receptors in the heart produces bradycardia.[33] The potent full agonist **7a**, which shows apparent selectivity for hm2 over hm1, produced marked reductions in blood pressure. In contrast, the partial agonists **(+)-(*Z*)-5g** and **6g**−**9g** which contain the imidoyl nitrile funtion show reduced cardiovascular effects. The quinuclidinyl imidoyl nitrile **(+)-(*Z*)-5g** which has BP/RSA and HR/RSA ratios >18 stands out as the compound with optimal central selectivity, and it is significant that **(+)-(*Z*)-5g** shows similar affinities at hm1 and hm2 receptors. This lack of intrinsic bias toward hm2 receptors probably contributes to the high degree of central selectivity.

An additional factor which needs to be taken into account is the possibility that functional selectivity may be a consequence of regional differences in receptor reserve, which in turn could be due to differences either in receptor density or in the efficiency of the coupling between occupancy and end response. Tissues which have a high receptor reserve will produce a maximal response with both high- and low-efficacy agonists. On the other hand, tissues with a low receptor reserve will only produce maximal responses with high-efficacy agonists.[11] This means that partial agonists can achieve functional selectivity by exploiting regional differences in receptor reserve.[34−36] In this study full agonists tended to produce cardiovascular effects at doses similar to those responsible for producing RSA, whereas several partial agonists showed good separation between these effects. This is apparent from the enhanced selectivity of the propargyl ether **7k** relative to the methyl ether **7a**. This trend is also evident in the case of the imidoyl nitriles **5g**−**9g**. The quinuclidine **(+)-(*Z*)-5g** which has one of the lowest efficacy ratios in this group displays the highest BP/RSA and HR/RSA selectivity ratios. The reduced propensity of partial agonists in this study to elicit cardiovascular effects points to a low receptor reserve in tissues mediating hypotension and bradycardia. This is consistent with studies indicating a low receptor reserve for relaxant effects in rat aorta mediated by M3 receptors[37] as well as bradycardia mediated by M2 receptors.[38]

In SDAT the reduction in acetylcholine release which accompanies nerve terminal degeneration might be expected to lead to supersensitivity of the surviving postsynaptic receptors. Supporting evidence is provided by studies pointing to modest increases in the density of hippocampal M1 sites in the brains of patients with SDAT.[1] Such upregulation of M1 receptors would favor functional discrimination by an M1 partial agonist.

Differences in brain penetration are also likely to contribute to the profiles observed *in vivo*. It was anticipated that the introduction of electron withdrawing groups such as halogen or nitrile would lower the pK_a of the azabicyclic ring nitrogen[39] and lead to improved brain penetrancy. The diminished basicity of imidoyl halides and nitriles relative to the corresponding methyl ketoxime ethers was confirmed experimentally. This reduction in basicity translates into higher log *D* values which are predictive of improved brain penetration.[40] In the case of **(+)-(*Z*)-5g**, improved brain penetrancy undoubtedly contributes to the high degree of central selectivity observed with this compound.

Reduced tremorigenic effects were also observed with **(+)-(*Z*)-5g**. This is particularly apparent when **(+)-(*Z*)-**

5g is compared with higher efficacy muscarinic agents such as oxotremorine. Tremor is mediated centrally *via* M2 receptors, and it is associated with a low receptor reserve.[41] This profile suggests that **(+)-(*Z*)-5g** should have a low propensity to induce extrapyramidal effects in the clinic.

Conclusion

This study establishes the imidoyl nitrile function as a valuable new ester bioisostere. The quinuclidinyl imidoyl nitrile **R-(+)-(*Z*)-5g** was found to be a functionally selective M1 partial agonist. It induces hippocampal RSA, which is believed to be predictive of cognitive enhancement, and subsequent studies have demonstrated that **R-(+)-(*Z*)-5g** is effective in animal models of learning and memory.[42] Compared with high efficacy agonists such as arecoline, **R-(+)-(*Z*)-5g** shows a markedly reduced propensity toward peripherally mediated cardiovascular effects. This profile can be rationalized in terms of differential affinities at muscarinic receptor subtypes, agonist efficacy, and brain penetration. This functional selectivity provides an opportunity to test the cholinergic hypothesis of SDAT without the limiting side effects associated with full agonists. Phase III clinical trials with **R-(+)-(*Z*)-5g** (SB 202026) are currently in progress.

Experimental Section

Chemistry. Melting 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, JEOL GX-270, or a Varian EM-360A spectrometer using Me_4Si as internal standard. IR spectra were recorded on a Perkin-Elmer 197 spectrometer. All evaporations of solvents were carried out under reduced pressure, and organic solutions were dried over Na_2SO_4. For column chromatography, the silica gel used was Merck Kieselgel 60, and the alumna, Camag Brockmann type II alkaline or BDH Brockmann type I, neutral. Petroleum ether refers to the fraction with bp 60−80 °C.

General Procedure for the Preparation of Aldoxime and Ketoxime Ethers. Aldoxime and ketoxime ethers were prepared by treating a solution in methanol of the appropriate aldehyde or ketone with an *O*-alkylhydroxylamine hydrochloride (1 equiv) and stirring the mixture at room temperature overnight. The reaction was concentrated, and the residue was partitioned between saturated aqueous potassium carbonate and chloroform. The aqueous layer was washed with chloroform, and the combined organic layers were dried and concentrated to give the required aldoxime and ketoxime ethers which were further purified as described below.

***O*-But-2-ynylhydroxylamine.** A solution of 2-butyn-1-ol (4.26 g, 0.061 mol), *N*-hydroxyphthalimide (9.92 g, 0.061 mol), and triphenylphosphine (15.94 g, 0.061 mol) in THF (300 mL) was treated dropwise with diethyl azodicarboxylate (10.53 mL, 0.067 mol).[43] The reaction mixture was stirred at room temperature overnight and then evaporated to dryness. The solid residue was triturated with benzene (300 mL) and the insoluble material was removed by filtration. The filtrate was evaporated to dryness, and the residue was recrystallized from ethanol to give *N*-(but-2-ynyloxy)phthalimide: mp 138−140 °C. A portion of this material (3 g, 0.014 mol) in ethanol (30 mL) was treated with hydrazine hydrate (0.68 mL, 0.014 mol) at reflux for 2 h. The reaction mixture was cooled to 0 °C and filtered to give a solution of *O*-but-2-ynylhydroxylamine, which was used immediately.

1-Azabicyclo[2.2.2]octane-3-carboxaldehyde *O*-Methyloxime (5a). 3-Cyano-1-azabicyclo[2.2.2]octane **(5n)**[12] (2.1 g, 0.0154 mol) in dry toluene (50 mL) was treated dropwise with diisobutylaluminum hydride (13.3 mL of a 1.5 M solution in toluene) at −65 °C. The solution was maintained at this temperature for 0.5 h and then warmed slowly to room temperature over 2 h. Aqueous 10% sodium hydroxide solution (50 mL) was then added, and the mixture was extracted with chloroform (3 × 60 mL). The combined organic extracts were dried and concentrated to give impure 1-azabicyclo[2.2.2]-oct-3-yl carboxaldehyde **(5p)** (2.3 g) containing approximately 50% starting material. This crude mixture was treated with methoxylamine hydrochloride to give an oil which was chromatographed using 10% methanol/chloroform as eluant to give **5a** as a pale yellow oil (0.55 g). The hydrochloride salt crystallized from methanol/acetone as a 3:2 mixture of *E* and *Z* isomers (0.54 g, 46%): mp 162−164 °C; ^{1}H NMR (DMSO-d_6) δ 1.64−1.96 (4H, m), 2.14 (1H, m), 2.86−3.51 (7H, m), 3.78 and 3.82 (3H, s), 7.06 (*Z* isomer) and 7.58 (*E* isomer) (1H, d, J = 6 Hz). Anal. ($C_9H_{16}N_2O$·HCl) C, H, N.

***(E)*-1-Azabicyclo[3.2.1]octane-5-carboxaldehyde *O*-Methyloxime (6a).** A solution of ethyl 1-azabicyclo[3.2.1]octane-5-carboxylate **(6o)**[12] (6.0 g, 0.033 mol) in dry toluene (150 mL) at −65 °C under nitrogen was treated dropwise over 15 min with 1.5 M diisobutylaluminum hydride in toluene (30 mL, 0.045 mol) and the reaction stirred at −65 °C for 1.25 h. The solution was poured into 10% sodium hydroxide solution (100 mL), stirred for 5 min, and then extracted with ethyl acetate (1 × 150 mL) followed by chloroform (1 × 100 mL). The two extracts were dried and concentrated separately. The ethyl acetate extract gave a gelatinous white solid semisolid which was shaken with ether (200 mL) and then filtered through a pad of kieselguhr. The filtrate was concentrated to leave a pale yellow oil which was combined with the product from the chloroform extract to give 1-azabicyclo[3.2.1]octane-5-carboxaldehyde **(6p)** as a yellow oil (5.0 g). This aldehyde (3.61 g, 0.023 mol) was treated with methoxylamine hydrochloride, and the crude product was chromatographed on silica gel using 10% methanol/chloroform as eluent to yield the (*E*)-oxime (2.8 g) as a single isomer which was converted into the hydrochloride salt (2.69 g, 57%). Hydrochloride salt: mp 190−191 °C (MeOH/acetone); ^{1}H NMR (DMSO-d_6) δ 1.62−2.17 (6H, m), 3.10−3.48 (6H, m), 3.75 (3H, s), 7.54 (1H, s); ^{13}C NMR (DMSO-d_6) δ 16.49, 30.59, 31.06, 44.09, 49.55, 51.26, 58.59, 61.15, 151.49. Anal. ($C_9H_{16}N_2O$·HCl) C, H, N.

***exo*-1-Azabicyclo[2.2.1]heptane-3-carboxaldehyde *O*-Methyloxime (7a).** A stirred solution of *exo*-ethyl 1-azabicyclo-[2.2.1]heptane-3-carboxylate **(7o)**[12] (1.7 g, 0.010 mol) in dry toluene (50 mL) at −65 °C under nitrogen was treated with 1.5 M diisobutylaluminum hydride in toluene (9.2 mL, 0.014 mol) and stirred at −65 °C for 4 h. The solution was treated with glacial acetic acid (3 mL) and allowed to warm up to room temperature, then basified with 10% sodium hydroxide solution, saturated with potassium carbonate, and extracted with chloroform (3 × 60 mL). The combined extracts were dried and concentrated *in vacuo* to give a colorless oil (1.0 g), containing the aldehyde **(7p)**. This aldehyde was treated with methoxylamine hydrochloride, and the crude product was chromatographed on silica gel using 10% methanol in chloroform as eluant to give **7a** as an oil. The oxalate salt crystallized from methanol/acetone giving a 7:1 mixture of *E* and *Z* isomers (0.53 g, 20%): mp 133−135 °C; ^{1}H NMR (DMSO-d_6) δ 1.68 (1H, m), 1.99 (1H, m), 2.74−2.90 (2H, m), 3.00−3.42 (6H, m), 3.76 (*E* isomer) and 3.82 (*Z* isomer) (3H, s), 6.95 (*Z* isomer) and 7.54 (*E* isomer) (1H, d, J = 6 Hz). Anal. ($C_8H_{14}N_2O$·$C_2H_2O_4$) C, H, N.

***exo*-1-Azabicyclo[2.2.1]heptane-3-carboxaldehyde *O*-ethyloxime (7h)** was prepared as a yellow oil from aldehyde **(7p)** and *O*-ethylhydroxylamine hydrochloride. The oxalate salt crystallized from methanol/acetone as a 13:1 mixture of *E* and *Z* isomers (31% yield): mp 102−104 °C; ^{1}H NMR (DMSO-d_6) δ 1.18 (3H, t, J = 7 Hz), 1.69 (1H, m), 1.99 (1H, m), 2.75−2.88 (2H, m), 3.02−3.40 (6H, m), 4.02 (2H, q, J = 7 Hz), 6.94 (*Z* isomer) and 7.53 (*E* isomer) (1H, d, J = 6 Hz). Anal. ($C_9H_{16}N_2O$·$C_2H_2O_4$) C, H, N.

***exo*-1-Azabicyclo[2.2.1]heptane-3-carboxaldehyde *O*-propargyloxime (7k)** was prepared as a yellow oil from aldehyde **(7p)** and *O*-propargylhydroxylamine hydrochloride. The oxalate salt crystallized as a 9:1 mixture of *E* and *Z* isomers (39% yield): mp 118−121 °C; ^{1}H NMR (DMSO-d_6) δ 1.68 (1H, m), 1.99 (1H, m), 2.75−2.90 (2H, m), 3.00−3.55 (7H, m), 4.63 (*E* isomer) and 4.73 (*Z* isomer) (2H, d, J = 1.5 Hz),

7.06 (*Z* isomer) and 7.62 (*E* isomer) (1H, d, $J = 6$ Hz). Anal. ($C_{10}H_{14}N_2O \cdot 1.1C_2H_2O_4$) C, H, N.

***exo*-1-Azabicyclo[2.2.1]heptane-3-carboxaldehyde *O*-allyloxime (7l)** was prepared as a colorless oil (28% yield) from aldehyde **(7p)** and *O*-allylhydroxylamine[43] hydrochloride. The hydrochloride salt crystallized from acetone/ether as an 8:1 mixture of *E* and *Z* isomers: mp 80−84 °C; ^{1}H NMR (DMSO-d_6) δ 1.15−1.30 (1H, m), 1.5−1.7 (1H, m), 2.18−2.95 (8H, m), 4.46−4.61 (2H, m), 5.15−5.35 (2H, m), 5.88−6.07 (1H, m), 6.58 (*Z* isomer) and 7.32 (*E* isomer) (1H, d, $J = 6$ Hz). Anal. ($C_{10}H_{16}N_2O \cdot HCl \cdot 0.25H_2O$) C, H, N.

***exo*-1-Azabicyclo[2.2.1]heptane-3-carboxaldehyde *O*-but-2-ynyloxime (7m)** was prepared as an oil (25% yield) from **7p** and a solution of *O*-but-2-ynylhydroxylamine by the general method described above. The oxalate salt crystallized from actone/ether as a 5:2 mixture of *E* and *Z* isomers: mp 105−8 °C; ^{1}H NMR (DMSO-d_6) δ 1.56−1.72 (1H, m), 1.83 (3H, s), 1.85−2.03 (1H, m), 2.72−2.88 (2H, m), 2.96−3.50 (6H, m), 4.57 (*E* isomer) and 4.64 (*Z* isomer) (1H, m), 7.00 (*Z* isomer) and 7.56 (*E* isomer) (1H, d, $J = 6$ Hz). Anal. ($C_{11}H_{16}N_2O \cdot C_2H_2O_4$) C, H, N.

***exo*-1-Azabicyclo[2.2.1]heptane-3-carboxaldehyde *O*-Propyloxime (7i).** A solution of *exo*-1-azabicyclo[2.2.1]heptane-3-carboxaldehyde **(7p)** (0.89 g, 0.0071 mol) was treated with hydroxylamine hydrochloride (1.0 g, 0.014 mol) in methanol (30 mL) at room temperature overnight. The reaction mixture was evaporated to dryness, and the residue was partitioned between saturated potassium carbonate and chloroform (5 × 50 mL). The combined organic extracts were dried and evaporated to give *exo*-1-azabicyclo[2.2.1]heptane-3-carboxaldehyde oxime **(7r)** (0.56 g). A portion of this crude oxime **(7r)** (0.19 g, 1.4 mmol) in THF (20 mL) was treated with potassium *tert*-butoxide (0.16 g, 1.4 mmol) at 0 °C. The reaction mixture was maintained at this temperature for 1 h, and then *n*-propyl methanesulfonate (0.18 g, 1.4 mmol) in THF (2 mL) was added dropwise at 0 °C. The mixture was stirred at room temperature for 18 h and then evaporated *in vacuo* and the residue partitioned between saturated aqueous potassium carbonate and chloroform (3 × 50 mL). The combined organic extracts were dried and evaporated to an oil which was chromatographed on silica gel using 0−5% methanol/chloroform as eluant. The resulting oil crystallized as the oxalate salt from methanol/ether as a 7:1 mixture of *E* and *Z* isomers (0.052 g, 21%): mp 108−111 °C; ^{1}H NMR (DMSO-d_6) δ 0.98 (3H, t, $J =$ 8 Hz), 1.58−1.81 (3H, m), 1.98−2.14 (1H, m), 2.80−2.95 (2H, m), 3.05−3.48 (6H, m), 4.00 (2H, t, $J = 8$ Hz), 7.00 (*Z* isomer) and 7.60 (*E* isomer) (1H, d, $J = 7$ Hz); ^{13}C NMR (DMSO-d_6) δ 10.21, 21.75, 26.92, 39.50, 40.12, 51.48, 54.46, 56.31, 74.57, 149.87. Anal. ($C_{10}H_{18}N_2O \cdot C_2H_2O_4$) C, H, N.

***exo*-1-Azabicyclo[2.2.1]heptane-3-carboxaldehyde *O*-Butyloxime (7j).** The oxime **(7r)** (0.33 g, 0.0024 mol) was treated with potassium *tert*-butoxide and *n*-butyl methanesulfonate as described for **7i** to give **7j** as an oil. The oxalate salt crystallized as a 16:1 mixture of *E* and *Z* isomers (0.124 g, 20%): mp 106−108 °C; ^{1}H NMR (DMSO-d_6) δ 0.95 (3H, t, J = 8 Hz), 1.30−1.50 (2H, m), 1.58−1.81 (3H, m), 1.98−2.13 (1H, m), 2.80−2.96 (2H, m), 3.07−3.45 (6H, m), 4.05 (2H, t, $J = 8$ Hz), 7.00 (*Z* isomer) and 7.60 (*E* isomer) (2H, d, $J = 7$ Hz); ^{13}C NMR (DMSO-d_6) δ 13.73, 18.58, 26.91, 30.55, 39.56, 40.11, 51.44, 54.40, 56.28, 72.78, 149.84. Anal. ($C_{11}H_{20}N_2O \cdot C_2H_2O_4$) C, H, N.

(*E*)-1-Azabicyclo[2.2.1]heptane-4-carboxaldehyde *O*-Methyloxime (8a). *N*-Methoxy-*N*-methyl-1-azabicyclo[2.2.1]-heptane-4-carboxamide **(8q)**[13] (0.38 g, 0.0021 mol) in dry THF (20 mL) was treated dropwise with diisobutylaluminum hydride (3.0 mL of a 1.5 M solution in toluene, 0.0045 mol) at −78 °C. The reaction mixture was warmed to room temperature over 2 h and then cooled to −60 °C and poured into 2 M HCl (30 mL) at −20 °C with vigorous stirring. The mixture was warmed to room temperature, potassium carbonate was added until the aqueous layer was saturated, and the mixture was extracted with chloroform (3 × 75 mL). The combined organic extracts were dried and evaporated *in vacuo* to give the crude aldehyde **(8p)** (0.18 g, 70%), which was treated with methoxylamine hydrochloride to afford **9a**. The hydrochloride salt crystallized as a single isomer from methanol/acetone (0.11 g, 39%): mp 189−193 °C; ^{1}H NMR (DMSO-d_6) δ 1.82−2.03 (2H, m), 2.19−2.33 (2H, m), 3.33 (2H, s), 3.35−3.62 (4H, m), 3.91 (3H, s), 7.86 (1H, s), 11.35−11.50 (1H, br s); ^{13}C NMR (DMSO-d_6) δ 30.36, 47.74, 51.94, 59.68, 61.25, 148.07. Anal. ($C_8H_{14}N_2O \cdot HCl$) C, H, N.

(*E*)-3-Acetyl-1-azabicyclo[2.2.2]octane *O*-Methyloxime (5b). 3-Acetyl-1-azabicyclo[2.2.2]octane **(5s)**[13] was reacted with methoxylamine hydrochloride in methanol followed by evaporation to give the hydrochloride salt of **(5b)** which was crystallized from methanol/acetone as a single isomer (62%): mp 182−184 °C; ^{1}H NMR (DMSO-d_6) δ 1.65 (2H, m), 1.80 (3H, s), 1.90 (2H, m), 2.26 (1H, m), 2.87 (1H, t, $J = 8$ Hz), 3.00−3.38 (5H, m), 3.54 (1H, dd, $J = 6$ Hz, 12 Hz); ^{13}C NMR (DMSO-d_6) δ 13.98, 18.18, 22.28, 22.96, 40.42, 45.13, 45.23, 46.02, 61.27, 154.94. Anal. ($C_{10}H_{18}N_2O \cdot HCl$) C, H, N.

(*E*)-5-Acetyl-1-azabicyclo[3.2.1]octane *O*-Methyloxime (6b). 5-Acetyl-1-azabicyclo[3.2.1]octane **(6s)**[14] was treated with methoxylamine hydrochloride in methanol overnight, followed by evaporation, and crystallization from acetone/ether to afford the hydrochloride salt as a white crystalline solid: mp 172−173 °C; ^{1}H NMR (DMSO-d_6) δ 1.50−1.64 (1H, m), 1.74−2.15 (5H, m), 1.80 (3H, m), 3.15−3.50 (6H, m), 3.77 (3H, s); ^{13}C NMR (DMSO-d_6) δ 11.37, 16.73, 29.92, 32.04, 47.85, 49.26, 51.12, 58.11, 58.28, 61.08, 157.88. Anal. ($C_{10}H_{18}N_2O \cdot HCl \cdot 0.2H_2O$) C, H, N.

(*E*)-*exo*-3-Acetyl-1-azabicyclo[2.2.1]heptane *O*-Methyloxime (7b). *exo*-3-Acetyl-1-azabicyclo[2.2.1]heptane **(7s)** was prepared in 65% yield by treating **(7q)** with methyllithium according to the general procedure described for the preparation of **7c**. Reaction of the methyl ketone **(7s)** with methoxylamine hydrochloride gave **7b** as a yellow oil (94%), which was crystallized as the oxalate salt from ether/acetone as a single isomer: mp 103−105 °C; ^{1}H NMR (DMSO-d_6) δ 1.70 (1H, m), 1.84 (3H, s), 2.02 (1H, m), 2.76 (1H, m), 2.92−3.35 (6H, m), 3.58 (1H, m), 3.77 (3H, s); ^{13}C NMR (DMSO-d_6) δ 14.62, 27.02, 38.58, 45.27, 51.37, 53.11, 55.90, 61.24, 155.08. Anal. ($C_9H_{16}N_2O \cdot C_2H_2O_4 \cdot 0.1H_2O$) C, H, N.

(*E*)-*exo*-3-(1-Oxopropyl)-1-azabicyclo[2.2.1]heptane *O*-Methyloxime (7c). *exo*-Ethyl 1-azabicyclo[2.2.1]-heptane-3-carboxylate **(7o)**[12] was converted to *exo*-*N*-methyl-*N*-methoxy-1-azabicyclo[2.2.1]heptane-3-carboxamide **(7q)** *via* the the acid chloride as previously described.[14] The carboxamide **7q** (0.5 g, 0.0027 mol) in THF (25 mL) was treated dropwise with ethylmagnesium bromide (1.36 mL of a 3 M solution in ether, 0.0041 mol) at 0 °C. The mixture was stirred at 0 °C for 2 h and then poured into ice-cold 2.5 M hydrochloric acid (30 mL). The mixture was made basic, then saturated with potassium carbonate, and extracted with chloroform (4 × 50 mL). The combined extracts were dried and evaporated to give the ethyl ketone **(7t)** as an oil (0.23 g, 54%). The crude ketone (0.2 g, 0.0013 mol) was treated with methoxylamine hydrochloride to give **7c** (0.22 g, 92%), which was crystallized as the hydrochloride salt from methanol/acetone: mp 119−121 °C; ^{1}H NMR (DMSO-d_6) δ 1.01 (3H, t, $J = 7$ Hz), 1.70 (1H, m), 2.02 (1H, m), 2.12−2.45 (2H, m), 2.83−3.62 (8H, m), 3.78 (3H, s); ^{13}C NMR (DMSO-d_6) δ 10.32, 21.98, 27.21, 39.21, 43.33, 51.45, 53.55, 56.09, 61.67, 159.69. Anal. ($C_{10}H_{18}N_2O \cdot HCl \cdot 0.3H_2O$) C, H, N.

4-Acetyl-1-azabicyclo[2.2.1]heptane *O*-Methyloxime (8b). 4-Acetyl-1-azabicyclo[2.2.1]heptane **(8s)**[14] was treated with methoxylamine hydrochloride. The oxalate salt crystallized from methanol/ether as a 4:1 mixture of *E* and *Z* isomers (59%): mp 124−126 °C; ^{1}H NMR (DMSO-d_6) δ 1.95 (3H, s), 1.95−2.02 (1H, m), 2.05−2.18 (2H, m), 3.22 (*Z*) and 3.29 (*E*) (2H, s), 3.29−3.40 (2H, m), 3.45−3.58 (2H, m), 3.79 (*Z*) and 3.87 (*E*) (3H, s); ^{13}C NMR (DMSO-d_6) δ 12.10, 30.13 (*Z*) and 30.82 (*E*), 51.77, 52.12, 59.37 (*E*) and 59.70 (*Z*), 61.15 (*Z*) and 61.40 (*E*), 154.88, 164.79. Anal. ($C_9H_{16}N_2O \cdot C_2O_4H_2$) C, H, N.

***N*-Methoxy-1-azabicyclo[2.2.2]octane-3-carboximidoyl Chloride (5e).** A solution of ethyl 1-azabicyclo[2.2.2]-octane-3-carboxylate **(5o)**[12] (178.4 g, 0.975 mol) in 8 M hydrochloric acid (1 L) was heated under reflux for 5 h with slow distillation of ethanol to drive the reaction to completion. The mixture was then concentrated *in vacuo* to a solid which was dried by the addition and evaporation of toluene. To the resulting white solid (186 g) were added dichloromethane (1

L) and thionyl chloride (200 mL, 2.74 mol), and the mixture was heated under reflux for 4 h when the copious evolution of sulfur dioxide and hydrogen chloride had ceased. The reaction mixture was then concentrated *in vacuo* to give the acid chloride as a gum, which was freed from excess thionyl chloride by coevaporation with toluene. A solution of this residue in a mixture of dry acetonitrile (400 mL) and chloroform (600 mL) was added slowly over 1 h to a mixture of methoxylamine hydrochloride (91.3 g, 1.093 mol) and pyridine (394 mL, 4.871 mol) in acetonitrile at −10 °C. After complete addition the mixture was warmed to room temperature and stirred for 2 h and then poured into saturated aqueous potassium carbonate solution (1 L). The aqueous phase was separated and extracted with chloroform (3 × 700 mL). The combined organic extracts were dried and evaporated to a gum, which was triturated with diethyl ether to afford *N*-methoxy-1-azabicyclo-[2.2.2]octane-3-carboxamide **(5u)** (164.5 g, 92%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.41 (1H, m), 1.63 (2H, m), 1.95 (2H, m), 2.70−3.12 (6H, m), 3.35 (1H, m), 3.76 (3H, s), 6.6 (1H, br). Triphenylphosphine (137 g, 0.522 mol) was carefully added in a single portion to the carboxamide **5u** (87.1 g, 0.473 mol) and carbon tetrachloride (140 mL) in acetonitrile (700 mL) at reflux. After 20 min at reflux the reaction mixture was cooled and then evaporated and partitioned between chloroform (500 mL) and 2.5 M aqueous HCl (500 mL). The aqueous phase was separated and further extracted with chloroform (200 mL), then basified with solid potassium carbonate, and extracted with chloroform (2 × 500 mL). The combined organic extracts were dried and evaporated to give an oil which was chromatographed on silica using 5−10% methanol/chloroform as eluant to give the imidoyl chloride **5e** as a crystallizing oil (54.64 g, 57%): ^{1}H NMR ($CDCl_3$) δ 1.42 (1H, m), 1.68 (3H, m), 2.23 (1H, m), 2.63−2.96 (5H, m), 3.05 (1H, dt, J = 10 Hz, 1 Hz), 3.35 (1H, dd, J = 10 Hz, 5 Hz), 3.98 (3H, s); ^{13}C NMR ($CDCl_3$) δ 21.62, 25.03, 27.33, 44.69, 47.41, 47.49, 50.62, 63.10, 140.82; IR (film) 1660, 1040 cm^{-1}. A portion of this material was converted to the oxalate salt which was recrystallized from methanol/acetone as a white crystalline solid: mp 143−146 °C; ^{1}H NMR (DMSO-d_6) δ 1.73 (2H, m), 1.92 (2H, m), 2.39 (1H, m), 3.08−3.30 (5H, m), 3.46 (2H, m), 3.94 (3H, s); ^{13}C NMR (DMSO-d_6) δ 18.26, 22.58, 23.27, 40.79, 45.14, 45.22, 47.19, 62.77, 137.95. Anal. ($C_9H_{15}N_2OCl\cdot C_2H_2O_4$) C, H, N.

***N*-Methoxy-1-azabicyclo[3.2.1]octane-5-carboximidoyl Chloride (6e).** Ethyl 1-azabicyclo[3.2.1]octane-5-carboxylate **(6o)**[12] (7.33 g, 0.040 mol) was converted to the acid chloride as in the preparation of **5e**. This crude material was dissolved in dry acetonitrile (200 mL), and methoxylamine hydrochloride (3.51 g, 0.042 mol) was added. After the mixture was cooled to −20 °C, triethylamine (27.9 mL, 0.200 mol) was added dropwise over 0.5 h, and the reaction mixture was allowed to warm to room temperature overnight. The solvent and excess triethylamine were removed *in vacuo*, and the residue was partitioned between saturated aqueous potassium carbonate solution (100 mL) and chloroform (5 × 100 mL). The combined organic extracts were dried and evaporated to a gum, which was chromatographed on neutral alumina using 3−15% methanol/chloroform as eluant to afford *N*-methoxy-1-azabicyclo-[3.2.1]octane-5-carboxamide **(6u)** (2.86 g, 39%) as a low-melting solid: ^{1}H NMR ($CDCl_3$) δ 1.55 (1H, m), 1.67−2.00 (4H, m), 2.12 (1H, m), 2.73−3.01 (5H, m), 3.12 (1H, m), 3.76 (3H, s), 5.60 (1H, broad). The carboxamide **6u** (1.54 g, 0.0084 mol) was treated with triphenylphosphine (2.20 g, 0.0084 mol) and carbon tetrachloride (2 mL) in acetonitrile (50 mL) as in the preparation of **5e** to give the imidoyl chloride **6e** as a crystallizing oil (0.84 g, 50%). A portion of this material was converted to the oxalate salt and recrystallized from methanol/acetone as colorless flakes: mp 130−132 °C; ^{1}H NMR (DMSO-d_6) δ 1.72−2.29 (6H, m), 3.16−3.56 (6H, m), 3.90 (3H, s); ^{13}C NMR (DMSO-d_6) δ 16.68, 31.09, 32.44, 49.20, 49.34, 51.32, 58.58, 62.63, 139.74. Anal. ($C_9H_{15}N_2OCl\cdot C_2H_2O_4$) C, H, N.

***exo*-*N*-Methoxy-1-azabicyclo[2.2.1]heptane-3-carboximidoyl Chloride (7e).** *exo*-Ethyl 1-azabicyclo[2.2.1]heptane-3-carboxylate **(7o)**[12] (1 g, 0.0059 mol) was converted to the acid chloride hydrochloride salt and treated with methoxylamine hydrochloride (0.54 g, 0.0065 mol) and triethylamine as in the preparation of **5u** to give *exo*-*N*-methoxy-1-azabicyclo[2.2.1]-heptane-3-carboxamide **(7u)** (0.40 g, 40%) as a low-melting solid: ^{1}H NMR ($CDCl_3$) δ 1.18 (1H, m), 1.63 (1H, m), 2.40−2.58 (2H, m), 2.63−2.98 (5H, m), 3.06 (1H, m), 3.73 (3H, s). The carboxamide **7u** (0.4 g, 0.0024 mol) was treated with triphenylphosphine (0.62 g, 0.0024 mol) and carbon tetrachloride (1 mL) in acetonitrile (30 mL) as in the preparation of **5e** to give the imidoyl chloride **7e** as a colorless oil (0.15 g, 34%). A portion of this material was treated with oxalic acid and recrystallized from acetone/methanol to yield the oxalate salt as a white crystalline solid: mp 118−120 °C; ^{1}H NMR (DMSO-d_6) δ 1.68 (1H, m), 1.98 (1H, m), 3.02−3.53 (8H, m), 3.91 (3H, s); ^{13}C NMR (DMSO-d_6) δ 26.73, 38.58, 39.81, 46.91, 51.43, 54.78, 56.54, 62.69, 137.73. Anal. ($C_8H_{13}N_2OCl\cdot C_2H_2O_4$) C, H, N.

1-Azabicyclo[2.2.1]heptane-4-*N*-methoxycarboximidoyl Chloride (8e). Ethyl 1-azabicyclo[2.2.1]heptane-4-carboxylate hydrobromide salt **(8o)**[14] (16.85 g, 0.067 mol) was converted to the acid chloride hydrochloride salt and treated with methoxylamine hydrochloride (6.19 g, 0.074 mol) and triethylamine as in the preparation of **5u** to give *N*-methoxy-1-azabicyclo[2.2.1]heptane-4-carboxamide **(8u)** as a pale brown crystalline solid (4.60 g, 40%): mp 129−134 °C; ^{1}H NMR ($CDCl_3$) δ 1.48 (2H, m), 1.97 (2H, m), 2.66 (4H, m), 3.05 (2H, m), 3.80 (3H, s).

The carboxamide **8u** (2 g, 0.0118 mol) was treated with triphenylphosphine (3.09 g, 0.0118 mol) and carbon tetrachloride (4 mL) in acetonitrile (100 mL) as in the preparation of **5e** to give the imidoyl chloride **8e** as a low-melting solid (1.70 g, 77%). A portion of this material was converted to the oxalate salt and recrystallized from methanol/acetone as a white crystalline solid: mp 128−130 °C; ^{1}H NMR (DMSO-d_6) δ 1.96 (2H, m), 2.20 (2H, m), 3.22−3.34 (4H, m), 3.45 (2H, m), 3.92 (3H, s); ^{13}C NMR (DMSO-d_6) δ 31.59 (2C), 52.24 (2C), 52.73, 59.92, 62.72, 136.54. Anal. ($C_8H_{13}N_2OCl\cdot C_2H_2O_4$) C, H, N.

***endo*-*N*-Methoxy-1-azabicyclo[2.2.1]heptane-3-carboximidoyl Chloride (9e).** *endo*-Ethyl 1-azabicyclo[2.2.1]heptane-3-carboxylate **(9o)**[14] (3 g, 0.018 mol) was converted to the acid chloride hydrochloride salt and treated with methoxylamine hydrochloride (1.42 g, 0.017 mol) and triethylamine as in the preparation of **5u** to give *endo*-*N*-methoxy-1-azabicyclo[2.2.1]-heptane-3-carboxamide **(9u)** (2.00 g, 66%) as a low-melting solid: ^{1}H NMR ($CDCl_3$) δ 1.40−1.65 (2H, m), 2.49−3.05 (9H, m), 3.77 (3H, s). Similarly when a 7:2 mixture of *exo*- and *endo*-ethyl 1-azabicyclo[2.2.1]-heptane-3-carboxylate isomers **7o** and **9o** (4.06 g, 0.024 mol) was employed in the above reaction a 7:2 mixture (3.15 g, 78%) of the *exo*- and *endo*-*N*-methoxycarboxamides **7u** and **9u** was obtained. The *endo*-carboxamide **9u** (1.42 g, 0.0083 mol) was treated with triphenylphosphine (2.19 g, 0.0083 mol) and carbon tetrachloride (2 mL) in acetonitrile (50 mL) as in the preparation of **5e** to give the imidoyl chloride **9e** as a colorless oil (0.6 g, 38%). A portion of this material was converted to the oxalate salt and recrystallized from ethanol/diethyl ether as a white crystalline solid: mp 123−125 °C; ^{1}H NMR (DMSO-d_6) δ 1.55−1.68 (1H, m), 1.95−2.05 (1H, m), 3.10−3.70 (8H, m), 4.01 (3H, s); ^{13}C NMR (DMSO-d_6) δ 22.13, 39.27, 45.61, 51.91, 52.59, 58.47, 62.78, 136.78. Anal. ($C_8H_{13}N_2OCl\cdot C_2H_2O_4$) C, H, N.

***N*-Methoxy-1-azabicyclo[3.2.1]octane-5-carboximidoyl Bromide (6f).** Triphenylphosphine (0.86 g, 0.0033 mol) was added to a mixture of *N*-methoxy-1-azabicyclo[3.2.1]-octane-5-carboxamide **(6u)** (0.6 g, 0.0033 mol) and carbon tetrabromide (1.09 g, 0.0033 mol) in acetonitrile (30 mL) at reflux. The reaction mixture was refluxed for 4 h, then poured into saturated potassium carbonate (30 mL), and extracted with chloroform (5 × 50 mL). The combined extracts were dried and evaporated to give an oil which was chromatographed on silica using 12% methanol/chloroform as eluant to afford the imidoyl bromide **6f** as an oil. The oxalate salt was recrystallized from acetone/ether as a white crystalline solid (0.15 g, 14%): mp 145−147 °C; ^{1}H NMR (DMSO-d_6) δ 1.72−2.26 (6H, m), 3.15−3.55 (6H, m), 3.93 (3H, s); ^{13}C NMR (DMSO-d_6) δ 16.74, 31.82, 33.14, 49.10, 50.39, 51.33, 58.94, 62.55, 133.70. Anal. ($C_9H_{15}N_2OBr\cdot C_2H_2O_4$) C, H, N.

***exo*- and *endo*-*N*-Methoxy-1-azabicyclo[2.2.1]heptane-3-carboximidoyl Bromide (7f and 9f).** A 7:2 mixture of *exo*-

and *endo*-*N*-methoxy-1-azabicyclo[2.2.1]heptane-3-carboxamide **(7u** and **9u)** (1.5 g, 0.0088 mol) was converted to the hydrobromide salt by addition of 1 equiv of HBr in acetone. The mixture was evaporated to dryness and the residue dissolved in refluxing acetonitrile (50 mL). Carbon tetrabromide (2.9 g, 0.0088 mol) was added followed by triphenylphosphine (2.3 g, 0.0088 mol). The mixture was heated under reflux for 30 min. A further amount of carbon tetrabromide (1.0 g, 0.003 mol) was added to drive the reaction to completion followed by a further 30 min at reflux. The mixture was allowed to cool and partitioned between 2 N hydrochloric acid (2 × 100 mL) and chloroform (100 mL). The combined acid extracts were then saturated by careful addition of potassium carbonate and extracted into chloroform (3 × 100 mL) which was dried, filtered, and evaporated to dryness. The residue was chromatographed on silica gel, eluting with 0−5% methanol/chloroform. This gave the *exo* compound **7f** as the less polar fraction (0.37 g, 18%). Treatment with oxalic acid followed by trituration with diethyl ether gave the oxalate salt as a white crystalline solid: mp 98−102 °C; ^{1}H NMR (DMSO-d_6) δ 1.72−1.83 (1H, m), 2.01−2.15 (1H, m), 3.12−3.62 (8H, m), 4.02 (3H, s); ^{13}C NMR (DMSO-d_6) δ 26.94, 40.39, 49.45, 51.70, 55.56, 56.70, 62.92, 131.27. Anal. ($C_8H_{13}N_2OBr{\cdot}C_2H_2O_4$) C, H, N. The more polar fraction gave the *endo* isomer **9f** (0.07 g, 4%), which was converted to the oxalate salt and crystallized from ethanol/diethyl ether as a white crystalline solid (0.068 g): mp 144−148 °C; ^{1}H NMR (DMSO-d_6) δ 1.55−1.70 (1H, m), 1.91−2.07 (1H, m), 3.09−3.73 (8H, m), 4.04 (3H, s); ^{13}C NMR (DMSO-d_6) δ 22.03, 40.12, 47.64, 51.91, 52.96, 58.20, 62.68, 129.87. Anal. ($C_8H_{13}N_2OBr{\cdot}C_2H_2O_4$) C, H, N.

***N*-Methoxy-1-azabicyclo[2.2.1]heptane-4-carboximidoyl Bromide (8f).** *N*-Methoxy-1-azabicyclo[2.2.1]heptane-4-carboxamide **(8u)** (0.7 g, 0.0041 mol) was converted to the hydrobromide salt by addition of 1 equiv of HBr in acetone followed by removal of the solvent *in vacuo*. The residue was treated with triphenylphosphine (1.08 g, 0.0041 mol) and carbon tetrabromide (1.37 g, 0.0041 mol) in acetonitrile (50 mL) at reflux for 1 h. The reaction mixture was poured into saturated potassium carbonate (30 mL) and extracted with chloroform (5 × 50 mL). The combined organic extracts were dried and evaporated to an oil which was chromatographed on silica using 2−3% methanol/chloroform as eluant to afford the imidoyl bromide **8f** as an oil (0.49 g, 51%). A portion of this material was converted to the oxalate salt and recrystallized from acetone/ether to as colorless flakes: mp 133−134 °C; ^{1}H NMR (DMSO-d_6) δ 1.96 (2H, m), 2.18 (2H, m), 3.22−3.36 (4H, m), 3.46 (2H, m), 3.94 (3H, s); ^{13}C NMR (DMSO-d_6) δ 32.14 (2C), 52.17 (2C), 54.07, 60.35, 62.61, 129.66. Anal. ($C_8H_{13}N_2OBr{\cdot}C_2H_2O_4$) C, H, N.

***N*-Methoxy-1-azabicyclo[2.2.2]octane-3-carboximidoyl fluoride (5d).** A mixture of *N*-methoxy-1-azabicyclo-[2.2.2]octane-3-carboximidoyl chloride **(5e)** (0.1 g, 0.0005 mol) and caesium fluoride supported on calcium fluoride (5 g, prepared by slowly evaporating to dryness a slurry of calcium fluoride in a solution of caesium fluoride in methanol for 1 h at 80 °C under reduced pressure in a mole ratio of 5:1)[20] in DMF (15 mL) were heated at 145 °C for 5 days. The reaction mixture was filtered, concentrated *in vacuo*, and partitioned between saturated potassium carbonate (50 mL) and chloroform (4 × 50 mL). The combined organic extracts were dried and evaporated to give an oil which was chromatographed on silica gel using 10% methanol/chloroform as eluant to yield the imidoyl fluoride **5d** as an oil. Conversion to the oxalate salt afforded a white crystalline solid (0.042 g, 31%): mp 102−108 °C; ^{1}H NMR (DMSO-d_6) δ 1.70−1.97 (5H, m), 3.10−3.37 (6H, m), 3.46 (1H, m), 3.79 (3H, s); ^{13}C NMR (DMSO-d_6) δ 18.57, 21.99, 22.28, 33.62 (d, $^2J_{CF}$ = 28 Hz), 45.08, 45.34, 46.09, 62.60, 151.40 (d, $^1J_{CF}$ = 329 Hz); MS calculated mass for $C_9H_{15}N_2OF$ 186.1168, observed mass 186.1162.

***N*-Methoxy-1-azabicyclo[3.2.1]octane-5-carboximidoyl Fluoride (6d).** Pyridine (3 mL, 0.037 mol) was added to a solution of *N*-methoxy-1-azabicyclo[3.2.1]octane-5-carboxamide **(6u)** (5.4 g, 0.029 mol) in acetone (100 mL). The solution was then made just acidic by the addition of hydrogen fluoride−pyridine (Aldrich) and evaporated *in vacuo*. The resultant gum was coevaporated with toluene, dried under vacuum, and then taken up in refluxing dry acetonitrile (300 mL). (Diethylamido)sulfur trifluoride (DAST) (4.26 mL, 0.032 mol) in acetonitrile (20 mL) was added in a single portion, and the reaction mixture was immediately cooled and poured into saturated potassium carbonate (150 mL). The mixture was extracted with chloroform (3 × 200 mL), and the combined extracts were dried and evaporated to an oil. Chromatography on silica using 4% methanol/chloroform as eluant afforded the imidoyl fluoride **6d** as a yellow oil (1.62 g, 31%). Addition of oxalic acid and recrystallization from methanol/acetone gave the oxalate salt as a white crystalline solid: mp 104−107 °C; ^{1}H NMR (DMSO-d_6) δ 1.70−2.30 (6H, m), 3.10−3.55 (6H, m), 3.76 (3H, s); ^{13}C NMR (DMSO-d_6) δ 16.31, 29.78, 30.52, 43.82 (d, $^2J_{CF}$ = 27 Hz), 49.55, 51.33, 57.63, 62.50, 152.36 (d, $^1J_{CF}$ = 333 Hz). Anal. ($C_9H_{15}N_2OF{\cdot}C_2H_2O_4$) C, H, N.

***exo*-1-Azabicyclo[2.2.1]heptane-3-*N*-methoxycarboximidoyl Fluoride (7d).** *exo*-1-Azabicyclo[2.2.1]heptane-3-*N*-methoxycarboximidoyl bromide **(7f)** (0.14 g, 0.0006 mol) in dry dimethylformamide (10 mL) was heated at 140 °C for 20 h with cesium fluoride supported on calcium fluoride (6.0 g).[20] The mixture was allowed to cool and then filtered washing the filter cake with dimethylformamide (10 mL). The filtrate was evaporated to dryness, and the residue chromatographed on silica eluting with 0−5% methanol/chloroform. This gave the fluoro compound **7d** as an oil (0.025 g, 24%). This material was converted to the oxalate and crystallized from ethanol/diethyl ether as a white crystalline solid: mp 115−117 °C; ^{1}H NMR (DMSO-d_6) δ 1.59−1.83 (1H, m), 1.88−2.03 (1H, m), 2.95−3.41 (8H, m), 3.77 (3H, s); MS calculated mass for $C_8H_{12}N_2OF$ 172.1012, observed mass 172.1012.

***N*-Methoxy-1-azabicyclo[2.2.1]heptane-4-carboximidoyl Fluoride (8d).** *N*-Methoxy-1-azabicyclo[2.2.1]heptane-4-carboxamide **(8u)** (1.6 g, 0.0094 mol) was converted to the hydrofluoride salt with hydrogen fluoride pyridine and treated with (diethylamido)sulfur trifluoride (DAST) (1.25 mL, 0.0095 mol) in acetonitrile (150 mL) as in the preparation of **6d** to yield the imidoyl fluoride **8d** as an oil (0.40 g, 25%). Addition of oxalic acid and recrystallization from methanol/acetone gave the oxalate salt as a white crystalline solid: mp 114−116 °C; ^{1}H NMR (DMSO-d_6) δ 1.89 (2H, m), 2.17 (2H, m), 3.16−3.29 (4H, m), 3.42 (2H, m), 3.77 (3H, s); ^{13}C NMR (DMSO-d_6) δ 29.86 (2C), 46.78 (d, $^2J_{CF}$ = 29 Hz), 52.08 (2C), 59.22, 62.66, 150.60 (d, $^1J_{CF}$ = 330 Hz). Anal. ($C_8H_{13}N_2OF{\cdot}C_2H_2O_4$) C, H, N.

***(E)*- and *(Z)*-α-(Methoxyimino)-1-azabicyclo[2.2.2]-octane-3-acetonitrile [(*E*)-5g and (*Z*)-5g].** *N*-Methoxy-1-azabicyclo[2.2.2]octane-3-carboximidoyl chloride **(5e)** (96.25 g, 0.475 mol) in dry DMSO (1.2 L) was treated with sodium cyanide (46.58 g, 0.951 mol) at 95 °C for 7 h. The solvent was evaporated *in vacuo* and the residue partitioned between 5% aqueous potassium carbonate (500 mL) and ether (3 × 500 mL). The combined organic extracts were dried and evaporated to an oil which contained the *Z* and *E* isomers in a ratio of 5:1 by NMR in a combined yield of about 60%. This crude product was repeatedly chromatographed on silica using 10% methanol/ether to afford in order of elution (*E*)-**5g** and (*Z*)-**5g** (25 g, 27%) as crystallizing oils.

(*E*)-5g: ^{1}H NMR ($CDCl_3$) δ 1.50 (1H, m), 1.58−1.68 (2H, m), 1.89 (1H, m), 2.04 (1H,m), 2.77−3.30 (7H, m), 4.06 (3H, s); ^{13}C NMR ($CDCl_3$) δ 22.0, 24.4, 27.2, 35.0, 46.9, 47.2, 51.2, 64.1, 114.3, 142.4. Anal. (oxalate salt: $C_{10}H_{15}N_3O{\cdot}C_2H_2O_4$) C, H, N.

(*Z*)-5g: ^{1}H NMR ($CDCl_3$) δ 1.46 (1H, m), 1.56−1.77 (3H, m), 2.14 (1H, m), 2.62−3.00 (5H, m), 3.06 (1H, dt, J = 10 Hz), 3.27 (1H, dd, J = 10 Hz, 5 Hz), 4.01 (3H, s); ^{13}C NMR ($CDCl_3$) δ 21.2, 25.2, 27.1, 39.6, 47.0, 47.2, 49.3, 63.7, 110.4, 134.3.

A portion of this material was converted to the hydrochloride salt which was recrystallized from acetone/ether as a white crystalline solid: mp 176−182 °C; ^{1}H NMR (DMSO-d_6) δ 1.63−2.02 (4H, m), 2.32 (1H, m), 3.01−3.67 (7H, m), 4.07 (3H, s); ^{13}C NMR (DMSO-d_6) δ 18.1, 22.7, 23.3, 35.9, 44.9, 45.2, 46.2, 64.0, 109.9, 131.7. Anal. ($C_{10}H_{15}N_3O{\cdot}HCl$) C, H, N.

[*S*-(*Z*)]-(−)-α-(Methoxyimino)-1-azabicyclo[2.2.2]octane-3-acetonitrile [(−)-(*Z*)-5g] and [*R*-(*Z*)]-(+)-α-(methoxyimino)-1-azabicyclo[2.2.2]octane-3-acetonitrile [(+)(*Z*)-

5g]. (−)-(*Z*)-5g. A solution of (*Z*)-(±)-α-(methoxyimino)-1-azabicyclo[2.2.2]octane-3-acetonitrile (**Z**)**-5g** (0.3 g, 1.55 mmol) in methanol (10 mL) was treated with (*S*)-(+)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (0.38 g, 1.09 mmol), and the resulting solution was concentrated *in vacuo* to leave a colorless oil. This material was dissolved in hot acetone (15 mL), diluted with ether (5 mL), and left to stand at room temperature for 24 h. The resulting white crystalline solid was filtered off (372 mg) and recrystallized three times from methanol/acetone. This material (260 mg) was treated with saturated potassium carbonate (50 mL) and extracted with chloroform (3 × 50 mL). The combined extracts were dried and concentrated *in vacuo* to give **(−)-(*Z*)-5g** as a colorless oil (90 mg, 60%), which was converted to its oxalate salt and recrystallized from methanol/acetone as a white solid: mp 151−153 °C; $[\alpha]^{20}_D = -13.4°$ (*c* 0.932, EtOH). Optical purity of the enantiomer was confirmed as >95% by chiral HPLC [2 × (chiral-AGP, 100 × 4.0 mm) coupled in series to make a total column length of 200 mm using 0.02 M of phosphate (pH 7.0) as eluant]. Anal. ($C_{10}H_{15}N_3O \cdot C_2H_2O_4$) C, H, N.

(+)-(*Z*)-5g. The mother liquors from the above recrystallizations were combined and concentrated *in vacuo*, and the residue was partitioned between saturated potassium carbonate (50 mL) and chloroform (3 × 50 mL). The combined extracts were dried and concentrated *in vacuo* to leave a colorless oil (188 mg), which was dissolved in methanol (10 mL) and treated with (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (0.27 g, 0.78 mmol). The resulting solution was concentrated *in vacuo* to give a colorless oil which was taken up into hot acetone (15 mL), treated with ether (5 mL), and left to stand at room temperature for 24 h. The resulting white solid was filtered off (416 mg) and recrystallized twice from methanol/acetone. This material (297 mg) was then treated with saturated potassium carbonate (50 mL) and extracted with chloroform (3 × 50 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **(+)-(*Z*)-5g** as a colorless oil (94 mg, 63%), which was converted to the oxalate salt and recrystallized from methanol/acetone as a white crystaline solid: mp 154−156 °C; $[\alpha]^{20}_D = +14.4°$ (*c* 0.424, EtOH). Anal. ($C_{10}H_{15}N_3O \cdot C_2H_2O_4$) C, H, N.

The hydrochloride of **(+)-(*Z*)-5g**, mp 218−219 °C, exhibited $[\alpha]^{20}_D = +25.3°$ (*c* 1.00, EtOH) and ^{1}H NMR (400 MHz, D_2O) δ 1.96 (2H, m, 8-CH_2), 2.13 (2H, m, 5-CH_2), 2.55 (1H, m, 4-CH), 3.25−3.45 (5H, m, 3-CH, 6-CH_2 and 7-CH_2), 3.56 (1H, m, 2-CH_{ax}), 3.80 (1H, m, 2-CH_{eq}), 4.13 (3H, s, OMe). Optical purity was determined by HPLC on a Chiracel OB column (>98% ee) and chemical purity by HPLC on a Rainin Microsorb column (99.2%).

(*Z*)-α-(Methoxyimino)-1-azabicyclo[3.2.1]octane-5-acetonitrile (6g). *N*-Methoxy-1-azabicyclo[3.2.1]octane-5-carboximidoyl chloride **(6e)** (0.65 g, 0.0032 mol) in dry DMSO (10 mL) was treated with sodium cyanide (0.23 g, 0.0047 mol) at 100 °C for 5 h. The solvent was evaporated *in vacuo* and the residue partitioned between saturated aqueous potassium carbonate solution (50 mL) and chloroform (5 × 75 mL). The combined organic extracts were dried and evaporated to an oil, which was chromatographed on silica using 7% methanol/chloroform as eluant to afford the nitrile **6g** as an oil (0.41 g, 66%). A portion of this material was converted to the hydrochloride salt and recrystallized from acetone/ether as a white crystalline solid: mp 196−198 °C; ^{1}H NMR (DMSO-d_6) δ 1.76−2.33 (6H, m), 3.18−3.28 (2H, m), 3.33−3.56 (4H, m), 4.05 (3H, s); ^{13}C NMR (DMSO-d_6) δ 16.51, 30.37, 31.92, 45.70, 49.31, 50.94, 57.84, 64.06, 109.01, 133.57. Anal. ($C_{10}H_{15}N_3O \cdot$HCl) C, H, N.

(*Z*)-*exo*-α-(Methoxyimino)-1-azabicyclo[2.2.1]heptane-3-acetonitrile (7g). *exo-N*-Methoxy-1-azabicyclo[2.2.1]heptane-3-carboximidoyl chloride **(7e)** (0.14 g, 0.0007 mol) was treated with sodium cyanide (0.06 g, 0.0012 mol) as in the preparation of **6g** to give the nitrile **7g** as a pale yellow oil (0.09 g, 68%). A portion of this material was converted to the hydrochloride salt and recrystallized from methanol/acetone as a white crystalline solid: mp 213−215 °C; ^{1}H NMR (DMSO-d_6) δ 1.76 (1H, m), 2.04 (1H, m), 3.03−3.38 (5H, m), 3.52 (2H, m), 4.04 (3H, s); ^{13}C NMR (DMSO-d_6) δ 26.72, 39.67, 42.05, 51.50, 53.97, 56.55, 64.25, 110.44, 131.86. Anal. ($C_9H_{13}N_3O \cdot$HCl) C, H, N.

(*Z*)-α-(Methoxyimino)-1-azabicyclo[2.2.1]heptane-4-acetonitrile (8g). *N*-Methoxy-1-azabicyclo[2.2.1]heptane-4-carboximidoyl chloride **(8e)** (0.4 g, 0.0021 mol) was treated with sodium cyanide (0.16 g, 0.0033 mol) as in the preparation of **6g** to give the imidoyl cyanide **8g** as a crystallizing oil. Conversion to the hydrochloride salt afforded a white crystalline solid (0.20 g, 44%): mp 186−187 °C; ^{1}H NMR (DMSO-d_6) δ 1.99 (2H, m), 2.24 (2H, m), 3.32−3.44 (4H, m), 3.53 (2H, m), 4.09 (3H, s); ^{13}C NMR (DMSO-d_6) δ 30.66 (2C), 48.94, 51.89 (2C), 59.33, 64.16, 109.00, 130.10; MS calculated mass for $C_9H_{13}N_3O$ 179.1059, observed mass 179.1057.

(*Z*)-*endo*-α-(Methoxyimino)-1-azabicyclo[2.2.1]heptane-3-acetonitrile (9g). *endo-N*-Methoxy-1-azabicyclo[2.2.1]-heptane-3-carboximidoyl chloride **(9e)** (0.5 g, 0.0027 mol) was treated with sodium cyanide (0.2 g, 0.004 mol) as in the preparation of **6g** to give the nitrile **9g** as a pale yellow oil (0.035 g, 8%). A portion of this material was converted to the oxalate salt and recrystallized from ethanol/diethyl ether as a white crystalline solid: mp 125−130 °C; ^{1}H NMR (DMSO-d_6) δ 1.59−1.72 (1H, m), 1.97−2.11 (1H, m), 3.11−3.73 (8H, m), 4.17 (3H, s); ^{13}C NMR (DMSO-d_6) δ 22.05, 39.06, 40.88, 52.03, 52.18, 58.93, 64.05, 110.10, 130.36; MS calculated mass for $C_9H_{13}N_3O$ 179.1058, observed mass 179.1062.

Radioligand Binding. [^{3}H]OXO-M and [^{3}H]QNB binding assays in rat cerebral cortex were carried out as previously described.[12] Chinese hamster ovary (CHO) cells transfected with hm1−hm4 were obtained from NIMH. Membranes were prepared in 50 mM Tris buffer (pH 7.4 at 37 °C) and stored frozen until required. [^{3}H]QNB radioligand binding experiments employed 0.1 nM [^{3}H]QNB. Nonspecific binding was defined by 10 mM atropinesulfate. Incubation was to equilibrium at 37 °C and was terminated by rapid vacuum filtration.

Cardiovascular Effects in the Anesthetized Rat. Male rats (Hooded Lister, Olac UK, 300−380 g) were used. Experiments were conducted under general anesthesia, and each animal was subjected to a single test compound. General anesthesia was induced by urethane (25% w/v, 0.6 mL/kg ip). Body temperature was maintained at 37 °C using a thermostatically controlled heated blanket. The femoral vein and carotid artery were cannulated for drug administration and to monitor blood pressure (BP), respectively. BP was recorded via a Druck pressure transducer connected to a polygraph (Lectromed Multitrace 4). Heart rate (HR) was derived electronically using a ratemeter triggered by the BP signal (BRL Instrument Services, Harlow). Tracheae were cannulated in order to assist respiration. Increasing doses of test compound were administered iv at 45 min intervals. BP and HR were recorded continuously throughout the experiment. Transient changes in both BP and HR were recorded after iv administration, with the peak effect occurring within 1 min of iv administration. Peak effects were expressed as a percentage of predose values. The effects on BP and HR were expressed as the dose of test drug causing a transient 50% fall in mean BP or HR.

Induction of Hippocampal Rhythmical Slow Wave Activity (RSA). Male rats (Hooded Lister, Olac UK, 300−380 g) were used. Experiments were conducted under general anesthesia, and each animal was subjected to a single test compound. General anesthesia was induced by urethane (25% w/v, 0.6 mL/kg ip). Body temperature was maintained at 37 °C by a thermostatically controlled heated blanket. The femoral vein was cannulated for drug administration in all animals. Animals were placed in a Kopf stereotaxic frame and the dorsal skull was exposed. A small burr hole was drilled in the skull, and a bipolar electrode (Clark Electromedical, model NE-100) was positioned in the CA1 region of the right hippocampus using predetermined coordinates calculated from a stereotaxic atlas.[44] These were (mm, relative to the interaural line): AP +4.6; L −2.3; V +6.6. All rats were pretreated with atropine methyl nitrate (0.1 mg/kg iv), a muscarinic antagonist that does not cross the blood−brain barrier, in order to prevent peripherally mediated muscarinic effects.

Hippocampal EEG was monitored continuously using an oscilloscope. The signal was amplified and filtered using Neurolog System modules (NL100AK headstage, NL103 AC

preamplifier, NL106 ACDC amplifier, NL125 filters; Digitimer Ltd, UK). The sampling rate was 128 Hz. Fifteen 2-s control samples were recorded after iv injection of the vehicle (physiological saline). Raw data were collected, digitized, and analyzed using a CED1401 Laboratory Interface and a commercial software package (EEG Analysis System, Cambridge Electronic Design Ltd, Cambridge, UK). Mean power spectra were produced that divided the EEG signal into 0.5 Hz bandwidths. Arecoline (0.32 mg/kg iv) was used as a standard. Drug effects were analyzed quantitatively as changes in mean power (uV) in the θ bandwidth of the frequency spectrum (3−7 Hz). CNS selectivity was calculated as the ratio ED_{50}(BP)/ED_{arec}(RSA).

Tremor in Mice. Male mice (CD1, Charles River, 25−35 g) were used and test compounds were administered by the sc route. Induction of tremor was assessed subjectively using a scoring system: 0 = absent, 1 = mild, 2 = moderate, 3 = severe. The ED_{50} was calculated as the dose causing a mean score of 1.5 for the group.

Molecular Modeling. All molecular modeling work was performed with SYBYL (version V6.22)[45] running on a Silicon Graphics Indigo2 Extreme workstation under the IRIX5.3 operating system. Structures were built up from standard fragments and groups using standard bond lengths and geometries, and each structure was energy minimized with the standard Sybyl force field. Electrostatic potential map calculations were submitted directly from Sybyl to Gaussian94 (Revision B.3)[46] running on a DEC Alpha Server 2100/4 under OSF1 V3.2, utilizing an in-house interface written in SPL (Sybyl Programming Language). All calculations were performed with the standard internal 3-21G* basis set, and the resultant electrostatic potential maps were read back into Sybyl for display.

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