Comparison of Azabicyclic Esters and Oxadiazoles as Ligands for the Muscarinic Receptor

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The link between the cognitive deficit associated with Alzheimer type dementia and the loss of cholinergic function in the disease provides a basis for examining muscarinic agonists as potential therapeutic agents. This paper describes the design and synthesis of novel azabicyclic methyl esters as ligands for the muscarinic receptor. Replacement of the methyl ester by a 3-methyl-1,2,4-oxadiazole ring produces potent metabolically more stable muscarinic agonists capable of penetrating the central nervous system. These compounds generally show improved affinity relative to the corresponding methyl esters. 3-Methyl-1,2,4-oxadiazole **7b** has an affinity 4 times that of acetylcholine. Receptor affinity is discussed in relation to the size and geometry of the azabicyclic ring and the electronic properties of the heteroaromatic ring.

The deterioration in cognitive function which is a feature of Alzheimer's disease is believed to be linked to the loss of cholinergic activity in the cortex and hippocampus.[1] There is a major deficit in cholinergic transmission which is due to the degeneration of cholinergic neurones. Postsynaptic receptors, which are of the muscarinic type, appear to survive largely intact.[2] This has provided the basis for the hypothesis that memory-related problems in Alzheimer's disease could be amenable to treatment using muscarinic agonists acting directly at postsynaptic receptors.[3] Clinical evaluation[4] of the classical muscarinic agonist arecoline (1) (Chart I) in patients suffering from Alzheimer's disease produced small improvements in perception, but viewed as a whole, the effect of the drug on cognition was not significant. The potential of arecoline for treating senile dementia is compromised by its poor metabolic stability and peripheral side effects. Disappointing results have also been reported for the muscarinic agonists oxotremorine[5] and RS 86 (2-ethyl-8-methyl-2,8-diazaspiro[4.5]decane-1,3-dione),[6] and in both cases peripheral side effects were a significant problem. These findings highlight the urgent need for agonists with greater central selectivity and acceptable duration of action. With this goal in mind studies were initiated in order to find suitable compounds for treating the disease.

A useful starting point for the design of novel agents was provided by a consideration of the muscarinic activity of arecoline (1) and dihydroarecoline (2) (Chart I). An early study[7] showed that the affinity of arecoline for muscarinic receptors in guinea pig ileum is 250 times that of the racemic dihydro analogue (2). It was argued that this could be attributed to the difference in the orientation of the ester group, depending on whether the site of attachment is saturated or unsaturated. However, it occurred to us that conformational preferences may also play an important role. In order to clarify this point the low-energy chair conformers of arecoline (1) and dihydroarecoline (2) were investigated. Energies of conformers $\mathbf{1}_{eq}$ and $\mathbf{2}_{eq}$, each of which contains an equatorial *N*-methyl group, were compared with those of the corresponding conformers $\mathbf{1}_{ax}$ and $\mathbf{2}_{ax}$, in which the methyl substituent is axial. Calculations using an ab initio method were carried out on the protonated forms since these predominate at physiological pH (see Experimental Section for details). As expected, conformers $\mathbf{1}_{eq}$ and $\mathbf{2}_{eq}$ are of lower energy than $\mathbf{1}_{ax}$ and $\mathbf{2}_{ax}$ (Chart I). There is, however, a significant difference in the energy gap separating the respective axial and equatorial *N*-methyl conformers. In the case of arecoline (1) the calculated energy difference between $\mathbf{1}_{eq}$ and $\mathbf{1}_{ax}$ is 1.87 kcal/mol.[8] In contrast, for dihydroarecoline (2), the energy difference between $\mathbf{2}_{eq}$ and $\mathbf{2}_{ax}$ is greater, 3.30 kcal/mol. Boltzmann population distributions calculated from these energies at 37 °C indicate that the proportion of $\mathbf{1}_{ax}$ in arecoline is ca. 10 times that of $\mathbf{2}_{ax}$ in dihydroarecoline. These results suggest that the muscarinic affinity of arecoline (1) and dihydroarecoline (2) may be associated with the minor conformers $\mathbf{1}_{ax}$ and $\mathbf{2}_{ax}$, respectively, because the population differences would partially account for the reported differences in biological activity.

With these arguments in mind, it was interesting to find that quinuclidine ester **3a**, which can be considered as an analogue of $\mathbf{2}_{ax}$ in which the *N*-methyl group is tied back in a rigid structure, is reported[9] to have an affinity 40 times that of **2**. The possibility of using other azabicyclic structures in order to fulfill the requirement for an axially orientated nitrogen substituent led us to consider esters of general structure (**I**). The target azabicycles are substituted by a methoxycarbonyl group β to nitrogen. It was of interest to investigate attachment of the ester at both bridgehead and nonbridgehead positions. Ring size was a factor to be examined, as well as the conformation of the ring bearing the methoxycarbonyl group. In view of the evidence pointing to $\mathbf{2}_{ax}$ as the active conformer of dihydroarecoline we were particularly interested in preparing azabicyclic esters containing bridged six-membered ring chair conformers. A series of azabicyclic esters (**4a–9a**) was selected in order to assess the importance of these factors.

A further question to be addressed was the susceptibility of the methyl ester group to metabolic cleavage. In order to overcome this drawback we investigated the possibility

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Chart I

1_{eq} 95.44% 1_{ax} 4.56%

2_{eq} 99.54% 2_{ax} 0.46%

a X = CO_2Me
b X = 3-methyl-1,2,4-oxadiazol-5-yl
c X = 5-methyl-1,2,4-oxadiazol-3-yl
d X = 5-methyl-1,3,4-oxadiazol-2-yl
e X = =O
f X = CN
g X = $CONH_2$

Scheme I[a]

[a] Reagents: (a) H_2/10% Rh–C/AcOH/EtOH; (b) $PhCH_2Br$/K_2CO_3/EtOH; (c) HBr/EtOH; (d) aqueous K_2CO_3; (e) 10% Pd–C/AcOH/EtOH; (f) 8 M HCl; (g) HCl/MeOH; (h) LDA/TMEDA/THF then ethylene oxide; (i) HBr/EtOH; (j) aqueous K_2CO_3; (k) 6 M HCl; (l) HCl/MeOH; (m) $BrCH_2CH_2Cl$/K_2CO_3/acetone; (n) LDA/TMEDA/Et_2O; (o) 8 M HCl; (p) HCl/MeOH.

of using a stable heteroaromatic ring as an ester replacement. This report describes the synthesis and biological activity of a series of muscarinic agents incorporating 1,2,4-oxadiazole and 1,3,4-oxadiazole rings as ester replacements.[10] On completion of this study we learned that other workers[11] had also prepared muscarinic agonists incorporating oxadiazoles, although they confined their reports to analogues containing quinuclidine and 1-azabicyclo[2.2.1]heptane. In the present study a wider range of azabicyclic ring systems has been examined. The azabicyclic ring system can be viewed as a rigid framework which controls the orientation of the heteroaromatic ring relative to the direction of the N–H bond of the protonated nitrogen. We hoped that by investigating a range of azabicyclic rings it would be possible to gain further insight into the optimal spatial relationship required for binding at the muscarinic receptor. A further aspect of this work was the opportunity it afforded for examining the effectiveness of the oxadiazole ring as an ester replacement in a variety of structural contexts.

Chemistry

Azabicyclic esters **3a**–**6a** were obtained by treatment of the corresponding ketones **3e**–**6e** with tosylmethyl isocyanide to give nitriles **3f**–**6f**, followed by acid hydrolysis and esterification. The reaction of ketones **4e** and **5e** with tosylmethyl isocyanide afforded exclusively the *exo*-nitriles **4f** and **5f**.[12] A mixture of isomers, from which *exo*-nitrile **6f** could be isolated, was obtained from **6e**. Ketone precursors **4e**,[13] **5e**,[14] and **6e**[15] were obtained by using conventional procedures.

exo-Methyl 1-azabicyclo[2.2.1]heptane-3-carboxylate (**7a**) was synthesized by using the route outlined in Scheme I. Lactone **10** was obtained by preferential reduction of 3,4-pyridinedicarboxylic acid anhydride at the more electrophilic 4-position of the pyridine ring. The use of sodium borohydride in *N,N*-dimethylformamide[16] proved superior to an earlier reported method[17] using lithium aluminum hydride. Hydrogenation over Rh–C followed by benzylation afforded **11**. Cleavage of lactone **11** in HBr–ethanol[18] and cyclization with aqueous potassium carbonate pro-

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

a: X = $-CO_2Me$

b: X = 3-methyl-1,2,4-oxadiazol-5-yl; c: X = 5-methyl-1,2,4-oxadiazol-3-yl; d: X = 5-methyl-1,3,4-oxadiazol-2-yl

compound[b]		IC_{50}, nM		IC_{50} QNB/IC_{50} OXO-M
		OXO-M	QNB	
	3a	520 (440–600)	25000 (16000–36000)	49
	3b	14 (6–29)	1800 (1700–2000)	130
	3c	1100 (650–1900)	12000 (8000–17000)	10
	3d	980 (950–1000)	19000 (15000–25000)	20
	4a	130 (100–150)	4800 (3900–5800)	37
	4b	260 (250–280)	1730 (1300–2300)	7
	5a	77 (75–80)	12000 (11000–14000)	160
	5b	28 (25–31)	2400 (1800–3000)	84
	6a	1400 (1000–1900)	62000 (60000–65000)	46
	6b	44 (41–48)	2400 (2300–2600)	55
	7a	230 (190–280)	51000 (44000–60000)	220
	7b	2.8 (1.6–3.9)	1000 (930–1100)	360
	7c	92 (73–120)	27000 (15000–45000)	290
	7d	120 (78–200)	29000 (23000–38000)	240
	8a	48 (36–85)	31000 (29000–33000)	650
	8b	130 (93–190)	23000 (14000–38000)	170
	8d	180 (93–280)	70000 (48000–100000)	380
	9a	19 (14–27)	6400 (6200–6700)	340
	9b	15 (12–18)	3500 (1700–3100)	230
	9c	260 (200–340)	4200 (2800–6300)	16
	9d	42 (34–52)	9400 (8000–11000)	220
acetylcholine[c]		12 (7–20)	24000 (12000–50000)	2000

[a] All values are the geometric means of results obtained in two to four separate experiments. Ranges are given in parentheses. [b] All compounds were tested as oxalate salts with the exception of **5a** and **6a**, which were tested as hydrochloride salts. [c] Assays carried out in the presence of eserine.

duced quaternary salt **12**. Subsequent hydrogenolysis and transesterification completed the synthesis of methyl ester **7a**.

The isomeric bridgehead-substituted ester **8a** was prepared in similar fashion by rearrangement of spiro lactone **14** derived from the reaction of the enolate of methyl 1-benzyl-3-pyrrolidinecarboxylate (**13**) with ethylene oxide.[19] The corresponding ester **9a** in the 1-azabicyclo[3.2.1]octane series could be obtained from ethyl *N*-benzylnipecotate (**15a**) by using the same method, but in this case the rearrangement proceeded in low yield. A more convenient procedure involved alkylation of ethyl nipecotate (**15b**) with 1-bromo-2-chloroethane followed by cyclization in the presence of lithium diisopropylamide and subsequent transesterification. Yields were good, provided that an excess of the alkylating agent was used to suppress formation of the bis adduct.

3-Methyl-1,2,4-oxadiazoles **3b**, **5b**, and **6b** were prepared by using the procedure described by Lin et al.[20] (Scheme II, method A). The required carboxamides **3g**, **5g**, and **6g** were obtained by selective alkaline hydrolysis of the corresponding nitriles. In the case of **6g** milder conditions (H_2O_2, NaOH) were used in order to avoid epimerization, and this necessitated protection of the tertiary amine by quaternization with benzyl bromide. Subsequent reaction of carboxamides **3g**, **5g**, and **6g** with *N*,*N*-dimethylacetamide dimethyl acetal and cyclization of the intermediate acylamidines with hydroxylamine afforded **3b**, **5b**, and **6b** in good yield. 3-Methyl-1,2,4-oxadiazoles **4b** and **7b**–**9b** were prepared conventionally via amidoxime ester intermediates[21] (Scheme II, method B). Isomeric 5-methyl-1,2,4-oxadiazoles were obtained in similar fashion from amidoxime precursors (Scheme II, method C). Synthesis of 5-methyl-1,3,4-oxadiazoles **3d**, **7d**, and **8d** was achieved by treatment of esters **3a**, **7a**, and **8a** with hydrazine followed by cyclization with triethyl orthoacetate[22] (Scheme II, method D).

Affinities for Central Muscarinic Receptors

The ability of the compounds under study to displace radiolabeled ligands from rat cerebral cortex was used as measure of their affinity for central muscarinic receptors. [^{3}H]Oxotremorine-M (OXO-M), which is an agonist, labels a state of the muscarinic receptor which has a high affinity for both muscarinic agonists and antagonists.[23] Conversely, [^{3}H]quinuclidinyl benzilate (QNB), which is an antagonist, labels more than one state of the receptor with high affinity. One of these states labeled by QNB has a low affinity for agonists, and this state is predominant in this assay. Antagonists bind with high affinity in both assays so that the ratio of the IC_{50} values for inhibition of OXO-M and QNB approaches unity. Agonists bind with high affinity in the OXO-M assay (high affinity agonist binding state) and with low affinity to a state labeled by QNB. The differential affinity of agonists for the two states results in higher ratios for agonists. In our experience,[24] ratios of the IC_{50} values of greater than 100 are usually indicative of agonist character. Ratios which fall

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Scheme II[a]

Method A

3g,5g,6g → (a) → (b) → 3b,5b,6b

Method B

4a,7a-9a → (c,d,e) → (f) → 4b,7b-9b

Method C

3f 7f, 9f → (g) → (h) → 3c,7c,9c

Method D

3a,7a,8a → (i) → (j) → 3d,7d,8d

[a] Reagents: (a) $MeC(OMe)_2NMe_2$; (b) $NH_2OH/AcOH$/dioxane; (c) 8 M HCl; (d) $SOCl_2$; (e) $MeC(NH_2)$=NOH; (f) xylene/reflux; (g) $NH_2OH/MeOH$; (h) Ac_2O; (i) $NH_2NH_2 \cdot H_2O$; (j) $MeC(OEt)_3$.

between 1 and 100 suggest partial agonism.

Centrally mediated muscarinic agonist responses can be demonstrated in vivo by measuring the induction of hypothermia in mice.[25] This approach has been used to compare the in vivo stability of esters and oxadiazoles.

Results

Affinities derived from radioligand binding assays are shown in Table I. All the compounds in this study, with the exception of the 4-substituted 1-azabicyclo[2.2.1]heptane derivatives, have a chiral center. The biological data reported for these compounds refer to the racemic mixture. Quinuclidine ester **3a** displaced [^{3}H]OXO-M binding with an IC_{50} value of 520 nM. Azabicyclic esters **4a** and **5a** showed affinities which are ca. 4- and 6-fold greater than that of **3a**. A common feature of **4a** and **5a** is that the ester is attached to a six-membered azacycle which is constrained in a chair conformation. Azabicyclic ester **9a**, which is isomeric with **5a** and bears the methyl ester at the bridgehead position, shows the highest affinity in this series with an IC_{50} of 19 nM. This is comparable to that of the natural transmitter acetylcholine and represents a 27-fold enhancement of affinity relative to quinuclidine ester **3a**.

Azabicyclic ester **6a**, in which the ester group is attached to a bridged five-membered azacycle, displayed modest affinity. In the case of **7a** and **8a**, which contain the more compact 1-azabicyclo[2.2.1]heptane ring, affinities of 230 and 48 nM, respectively, were observed. It is of interest that substitution at the bridgehead, as in **8a** and **9a**, produced compounds with higher affinities than those of the corresponding isomeric analogues **7a** and **5a**.

Quinuclidine ester **3a** has a QNB/OXO-M ratio of 49, which is predictive of partial agonism. Ratios for the remaining esters range from 37 to 650. The size of the azabicyclic ring appears to be an important factor affecting efficacy. Thus 1-azabicyclo[3.3.1]nonane **4a** has the lowest ratio in the group, whereas esters **7a** and **8a**, which incorporate the smaller 1-azabicyclo[2.2.1]heptane ring, give ratios which suggest full agonist character.

Replacement of the ester group by the 3-methyl-1,2,4-oxadiazole ring resulted in a series of potent muscarinic agonists **3b–9b** which displayed IC_{50} values against OXO-M in the range 2.8–260 nM. The order of affinities observed for this group is strikingly different to that of the corresponding ester analogues, and in several instances significant enhancements in affinity relative to the esters are apparent (Table I). Quinuclidine derivative **3b** produced an IC_{50} value against OXO-M of 14 nM. This represents a 37-fold improvement in affinity over the corresponding ester **3a**. In view of the high affinities associated with azabicycles in which the ester is attached to a six-membered ring constrained in a chair conformation, it was of interest to evaluate the corresponding oxadiazoles **4b**, **5b**, and **9b**. The affinity of **4b**, which incorporates the 1-azabicyclo[3.3.1]nonane ring system, is $^1/_2$ that of the corresponding ester **4a**, and the QNB/OXO-M ratio suggests antagonist character. Oxadiazoles **5b** and **9b** incorporating the smaller 1-azabicyclo[3.2.1]octane ring system showed profiles similar to that of quinuclidine **3b**. From these results it is apparent that when the ester is replaced by the larger 3-methyl-1,2,4-oxadiazole ring the size of the azabicyclic ring system becomes a more critical factor. On the other hand, conformational differences between constrained boat and chair forms, which appear to play a major role in determining the affinity of esters, seem to be less important in the case of the 3-methyl-1,2,4-oxadiazoles. This suggests that there are key differences between the methyl ester and the 3-methyl-1,2,4-oxadiazole in terms of their binding orientation at the receptor.

3-Methyl-1,2,4-oxadiazole **7b** containing the compact 1-azabicyclo[2.2.1]heptane ring system displayed the highest affinity, ca. 80 times that of the corresponding ester **7a**. It is worth noting that **7b** has an affinity 4 times that of the natural transmitter acetylcholine, and is one of the most potent cholinomimetic agents tested to date. The high affinity of **7b** has also been reported by other workers[11] using a similar radioligand binding assay. The QNB/OXO-M ratio of **7b** is the highest in the group of 3-methyl-1,2,4-oxadiazoles. This observation points once again to a link between the steric demands of the azabicyclic ring and the degree of agonist character. That other factors are also important in indicated by the lower affinity and efficacy ratio of the isomeric bridgehead-substituted analogue **8b** which may reflect the importance of the relative orientations of the heteroaromatic ring and the protonated azabicyclic nitrogen atom.

The 5-methyl-1,2,4-oxadiazole ring was less effective as a replacement for the methoxycarbonyl group. Analogues incorporating this isomer were consistently less potent than the corresponding 3-methyl-1,2,4-oxadiazoles. For example, in the series of quinuclidine analogues an 80-fold drop in affinity was observed for 5-methyl-1,2,4-oxadiazole **3c** relative to 3-methyl isomer **3b**, and similar trends emerged with **7c** and **9c** relative to **7b** and **9b**, respectively.

The pattern of affinities produced by compounds containing the 5-methyl-1,3,4-oxadiazole ring highlighted some

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interesting differences between azabicyclic ring systems. Whereas the affinities of **3d** and **7d** are poor compared with the corresponding 3-methyl-1,2,4-oxadiazoles **3b** and **7b**, **9d** displays an affinity only 3-fold lower than that of 3-methyl-1,2,4-oxadiazole **9b**. This clearly emphasizes the importance of achieving the optimal match between azabicyclic and heterocyclic components of the structure. It is also worth noting that the affinities and predicted efficacies of quinuclidines **3b–d** are consistent with the data recorded for these compounds by other workers[11] who used a similar binding assay.

A prime objective of the study was the discovery of centrally active muscarinic agonists with acceptable duration of action. To assess these factors in vivo we examined the induction of hypothermia which has been shown to be a centrally mediated effect of muscarinic agonists (Table II). In this test the high affinity of 3-methyl-1,2,4-oxadiazole **7b** translates into very potent in vivo activity by both subcutaneous and oral routes. By contrast, the corresponding ester **7a** is much weaker in vivo even after taking into account its lower affinity. A similar picture emerges from a comparison of **9a** and **9b**. Although their muscarinic affinities are almost identical, in vivo potencies are separated by a factor of greater than 10. These potency differences, particularly after oral dosing, indicate a significant improvement in the metabolic stability of the 3-methyl-1,2,4-oxadiazole ring relative to the methyl ester group.

Discussion

The primary binding interaction of the bridged azabicycles under study probably involves a hydrogen bond between the protonated tertiary amine and the carboxylate of an aspartate residue[26] located at the active site of the receptor. The directionality of this type of interaction is governed by the nitrogen–hydrogen vector.[27] In the case of methyl esters **3a–9a** a key factor which is likely to determine affinity is the ability of the ester group to achieve an optimal orientation relative to the protonated nitrogen atom. Examination of molecular models of **3a–5a** and **9a** shows that when the ester group is attached to a bridged piperidine ring, the orientation of the ester group relative to the N–H bond direction is different, depending on whether the piperidine ring adopts a chair or a boat form. The higher affinities of **4a**, **5a**, and **9a** compared with **3a** suggest that the chair form is better accommodated than the boat, and this can probably be attributed to a more favorable orientation of the key receptor binding groups in this case. However, other factors such as the different location of the steric bulk of the azabicyclic ring systems may also be of importance and could account for the enhanced affinity of **9a** over **5a**.

Arguments presented earlier suggested that the poor affinity of dihydroarecoline is partly due to a preponderance of the "inactive" conformer $\mathbf{2}_{eq}$. Following this line of reasoning, we anticipated that azabicyclic rings containing the imbedded part structure corresponding to the minor "active" chair conformer $\mathbf{2}_{ax}$, with the methyl group axially orientated, would show good affinity. The results observed for the methyl esters **4a**, **5a**, and **9a** confirm this expectation.

The effectiveness of the three isomeric oxadiazoles as ester mimics was studied in conjunction with a range of azabicyclic rings, and this has provided useful insights into

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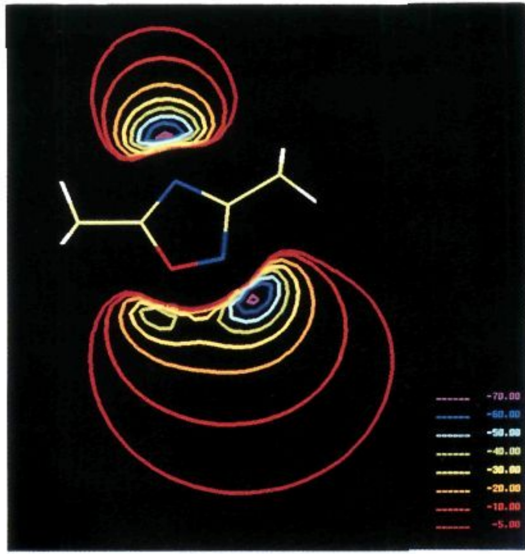
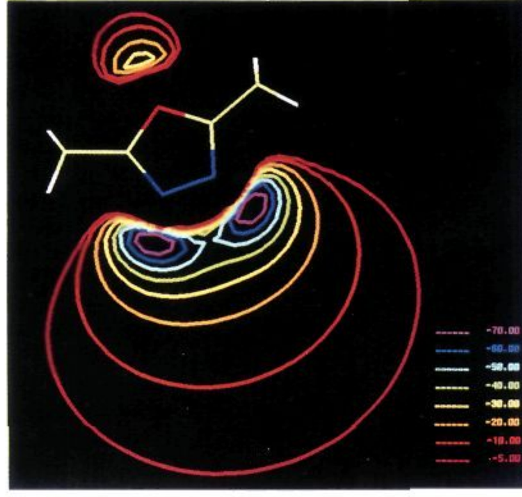
methyl acetate



3,5-dimethyl-1,2,4-oxadiazole



2,5-dimethyl-1,3,4-oxadiazole

Figure 1. Molecular electrostatic potential maps of methyl acetate and the dimethyl 1,2,4- and 1,3,4-oxadiazoles.

Table II. Comparison of in Vivo Potencies of Azabicyclic Methyl Esters and the Corresponding 3-Methyl-1,2,4-Oxadiazoles

compd		X	OXO-M IC_{50}, nM	IC_{50} QNB/ IC_{50} OXO-M	hypothermia[a]	
					ED_3 mg/kg sc	ED_3 mg/kg po
	7a	$-CO_2Me$	230	220	0.41 (0.12–1.35)	>10[b]
	7b	3-methyl-1,2,4-oxadiazol-5-yl	2.8	360	0.0005 (0.00015–0.0018)	0.0011 (0.00016–0.0079)
	9a	$-CO_2Me$	19	340	0.078 (0.014–0.427)	>0.3[b]
	9b	3-methyl-1,2,4-oxadiazol-5-yl	15	230	0.0029 (0.00013–0.069)	0.018 (0.0036–0.094)

[a] ED_3 values reflect the dose causing a fall of 3 °C in mean rectal temperature in groups of five mice. Values in parentheses indicate the 95% confidence intervals. [b] No activity observed at this dose.

Table III. Location of Electrostatic Potential Minima in the Oxadiazoles and the Methyl Ester

oxadiazole/ester	D_1, Å	P_1, kcal/mol	D_2, Å	P_2, kcal/mol
3-methyl-1,2,4-oxadiazole	3.04	−73.4	4.66	−72.9
5-methyl-1,2,4-oxadiazole	2.95	−73.4	3.25	−72.9
2-methyl-1,3,4-oxadiazole	2.84	−36.8	4.77[a]	−81.7
$-CO_2Me$	2.42	−53.1	3.62[b]	−65.7

[a] There is a second potential minimum of −81.2 kcal/mol in the region of the N–N bond at a distance D_2 = 2.98 Å. [b] The carbonyl produces a second potential minimum of −69.2 kcal/mol at a distance D_2 = 2.97 Å.

similarities and differences between esters and oxadiazoles. In terms of affinity at the agonist site, the 3-methyl-1,2,4-oxadiazole proved to be the most useful ester replacement. A key feature highlighted by the present study is the different order of affinities of the esters **3a–9a** compared with the corresponding 3-methyl-1,2,4-oxadiazoles **3b–9b**. For example, the most potent 3-methyl-1,2,4-oxadiazole analogue, **7b**, is derived from ester **7a**, which displays modest receptor affinity. Clearly the affinities of the 3-methyl-1,2,4-oxadiazoles cannot be readily predicted from those of the corresponding esters. Isomeric 5-methyl-1,2,4-oxadiazole **7c** shows significantly lower affinity than the 3-methyl analogue, and this is a consistent trend observed with all azabicyclic rings. The picture which emerges in the case of the 1,3,4-oxadiazoles is more complex. Whereas **3d** and **7d** display poor affinity, attachment of the 1,3,4-oxadiazole ring to the 1-azabicyclo[3.2.1]octane ring, as in **9d**, produces a compound with affinity comparable to that of 3-methyl-1,2,4-oxadiazole **9b**.

Electrostatic potential maps provide a useful technique for comparing the electronic properties of the various heteroaromatic rings. Ab initio calculations were carried out on model compounds in which the azabicyclic ring is replaced by a methyl group (Figure 1) (see Experimental Section for details). Cursory examination reveals broad similarities between the methyl ester and the 1,2,4- and 1,3,4-oxadiazoles. 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 carbonyl produces two electrostatic potential minima, corresponding to the directions of the oxygen lone pairs. Each oxadiazole ring has two regions of negative potential which are likely to be important in receptor binding. There are, however, key differences in the magnitude and location of the potential minima. In the 1,2,4-oxadiazole the regions of negative potential are not symmetrically oriented relative to the heteroaromatic ring, whereas the 1,3,4-oxadiazole gives rise to a symmetrical map. The location and magnitude of the potential minima in the methyl ester and the oxadiazoles are illustrated in Table III. The potential minima P_1 and P_2 are located at distances D_1 and D_2, which are measured from the methyl carbon which represents the point of attachment on the azabicyclic ring. In the 3-methyl-1,2,4-oxadiazole the minima P_1 = −73.4 kcal/mol and P_2 = −72.9 kcal/mol are located at distances D_1 = 3.04 Å and D_2 = 4.66 Å. The reversed substitution in the 5-methyl isomer maintains a similar value for D_1, but shortens D_2 to 3.25 Å. As discussed previously, compounds incorporating the 3-methyl-1,2,4-oxadiazole ring consistently show higher affinities than their 5-methyl counterparts. The location of the potential minimum P_2 appears to be a key factor responsible for this difference. In the 2-methyl-1,3,4-oxadiazole, D_1 = 2.84 Å is similar to the corresponding distance in the 3-methyl-1,2,4-oxadiazole. There are two potential minima of similar energy in the vicinity of the N–N bond. The distance to the further of these minima (D_2 = 4.77 Å) matches the corresponding value in the 3-methyl-1,2,4-oxadiazole. The magnitude of the potential P_1 is, however, significantly lower in the 1,3,4-oxadiazole and this could account for the reduced affinity generally observed for compounds containing this heteroaromatic ring. In the methyl ester D_1 = 2.42 Å and D_2 = 3.62 Å, where D_2 is taken as the distance to the further of the two minima associated with the carbonyl oxygen. These distances are shorter than those observed in the 3-methyl-1,2,4-oxadiazole. It has been shown that compounds incorporating the 1,2,4-oxadiazole ring generally show better affinity than the corresponding esters, and the difference in the location of the potential minima is probably a contributing factor. Other factors, such as the geometry of the azabicyclic ring system, are also important, and the high affinity of the methyl ester **9a** emphasizes this point.

The high QNB/OXO-M ratios generally observed with compounds incorporating the 1-azabicyclo[2.2.1]heptane ring suggest that the size of the azabicyclic ring is major factor determining efficacy. For example 1-azabicyclo[2.2.1]heptanes **7b–d** have high QNB/OXO-M ratios despite differences in the electronic properties of the heteroaromatic rings. The increased steric demand of the 3-methyl-1,2,4-oxadiazole ring relative to the methyl ester

becomes critical with the 1-azabicyclo[3.3.1]nonane system. Whereas ester **4a** has moderate affinity at the OXO-M site and a QNB/OXO-M ratio indicative of partial agonism, the corresponding 3-methyl-1,2,4-oxadiazole **4b** shows reduced affinity and an antagonistic ratio. By contrast oxadiazole **5b** in the 1-azabicyclo[3.2.1]octane series displays higher affinity than the corresponding ester **5a**. Although it is well-established that the introduction of very bulky groups can produce muscarinic antagonists, this work demonstrates that quite marked changes in efficacy can be effected by relatively subtle structural changes. This observation provides insight into the critical size which can be accommodated at the agonist binding site. Recent labeling and site mutagenesis studies[28] suggest that aspartate residues buried within the transmembrane region of the receptor might be involved in agonist binding. Since such a binding site is likely to be less accessible to bulkier ligands, this could explain the observed loss of agonist character which accompanies an increase in the size of the azabicyclic ring.

Conclusion

Using arecoline (**1**) and quinuclidine ester **3a** as starting points, we have designed a novel series of azabicyclic oxadiazoles. Compounds incorporating the 3-methyl-1,2,4-oxadiazole ring are particularly potent muscarinic agonists which penetrate the brain and show improved metabolic stability relative to the corresponding esters. This work confirms the value of the oxadiazole ring as an ester replacement in the context of muscarinic agonists and provides a broader understanding of the range of azabicyclic ring systems which can be accommodated at the muscarinic receptor.

Experimental Section

Chemistry. Melting points and boiling points are uncorrected. The elemental analyses were within 0.4% of the theoretical values. NMR spectra were recorded on a Bruker AM-400, Bruker AC-250, 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 alumina, Camag Brockmann type II alkaline or BDH Brockmann type I, neutral. Petroleum ether refers to the fraction with bp 60–80 °C.

3-Cyano-1-azabicyclo[2.2.2]octane (3f).[29] A mixture of 3-quinuclidinone (12.5 g, 0.10 mol), tosylmethyl isocyanide (25.4 g, 0.13 mol), and dry ethanol (10 mL, 0.17 mol) in dry 1,2-dimethoxyethane (350 mL) was cooled in ice and treated portionwise with potassium *tert*-butoxide (28.0 g, 0.25 mol) while the temperature was maintained at 5–10 °C. After addition was complete the ice bath was removed and stirring was continued for a further 0.5 h. The reaction was then heated at 40 °C for 2.5 h. After cooling, the precipitate was filtered off and the filtrate was evaporated to dryness. Purification of the residue on neutral alumina using EtOAc/MeOH (50:1) as eluant afforded **3f** as a syrup (10.0 g, 74%): IR (film) 2240 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4–1.78 (3 H, m) and 1.85–2.1 (1 H, m) (5-CH_2 and 8-CH_2), 2.15 (1 H, m, 4-CH), 2.60–3.35 (7 H, m, 2-CH_2, 6-CH_2, 7-CH_2, and 3-CH).

***exo*-3-Cyano-1-azabicyclo[3.3.1]nonane (4f)** was prepared from 1-azabicyclo[3.3.1]nonan-3-one[13] (**4e**) by using the procedure described for **3f**. Purification by chromatography on neutral alumina eluting with $CHCl_3$/MeOH (10:1) afforded **4f** as an orange oil (65% yield): IR (film) 2225 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25–2.50 (7 H, m, 4-CH_2, 6-CH_2, 7-CH_2, and 5-CH), 2.80–3.60 (7 H, m, 2-CH_2, 8-CH_2, 9-CH_2, and 3-CH).

***exo*-3-Cyano-1-azabicyclo[3.2.1]octane (5f)** was obtained as an oil (66% yield) from 1-azabicyclo[3.2.1]octan-3-one (**5e**)[14] by using the procedure described for **3f**: IR (film) 2225 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (1 H, m, 6-CH), 1.84 (1 H, m, 6-CH), 1.92–2.01 (2 H, m, 4-CH_2), 2.31 (1 H, m, 5-CH), 2.59 (1 H, m, 8-CH), 2.79–2.88 (3 H, m, 7-CH_2 and 3-CH), 2.93 (1 H, m, 8-CH), 3.01 (1 H, t, J = 13.5 Hz, 2-CH_{ax}), 3.13 (1 H, dd, J = 13.5 and 5.9 Hz, 2-CH_{eq}). Assignments derived from COSY spectrum.

***exo*-6-Cyano-1-azabicyclo[3.2.1]octane (6f)** was prepared from 1-azabicyclo[3.2.1]octan-6-one (**6e**)[15] by using the procedure described for **3f**. The crude product consisting of a mixture of exo and endo isomers was chromatographed on neutral alumina using a graded eluant of 3–15% MeOH in EtOAc. The faster running component which corresponded to **6f** was obtained as a colorless oil (40% yield) after Kugelrohr distillation (bp ca. 120 °C at 0.1 mmHg): IR (film) 2225 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38–1.80 (4 H, m, 3-CH_2 and 4-CH_2), 2.62 (1 H, m, 5-CH), 2.80–3.0 (5 H, m, 2-CH_2, 8-CH_2, and 6-CH), 3.16 (1 H, dd, J = 14, 5 Hz, 7-CH), 3.36 (1 H, ddd, J = 14, 8, 2 Hz, 7-CH); ^{13}C NMR ($CDCl_3$) δ 19.0, 29.8, 32.4, 41.5, 54.4, 57.5, 60.0, 122.7. Stereochemistry was confirmed by COSY coupling experiments.

Methyl 1-Azabicyclo[2.2.2]octane-3-carboxylate (3a). A solution of **3f** (3.4 g, 0.025 mol) in concentrated HCl (50 mL) was heated on a steam bath for 3 h. The reaction mixture was evaporated to dryness and the residue was dissolved in methanolic HCl and refluxed for 12 h. After evaporation of solvents the residue was treated with a saturated solution of K_2CO_3 and extracted into $CHCl_3$. The dried extracts afforded **3a** (3.8 g, 90%): IR (film) 1725 (s) cm^{-1}. Oxalate salt: mp 117–119 °C (MeOH/Et_2O); ^1H NMR (DMSO-d_6) δ 1.55–1.98 (4 H, m, 5-CH_2 and 8-CH_2), 2.32 (1 H, m, 4-CH), 3.02–3.50 (7 H, m, 2-CH_2, 6-CH_2, 7-CH_2, and 3-CH), 3.70 (3 H, s, CH_3).

***exo*-Methyl 1-Azabicyclo[3.3.1]nonane-3-carboxylate (4a)** was prepared from **4f** by using the procedure described for **3a** as a colorless oil (70% yield). Oxalate salt: mp 101–104 °C (MeOH/Et_2O); ^1H NMR (DMSO-d_6) δ 1.62–1.95 (4 H, m) and 1.97–2.25 (3 H, m) (4-CH_2, 6-CH_2, 7-CH_2, and 5-CH), 3.07–3.20 (2 H, m), 3.20–3.42 (3 H, m) and 3.43–3.60 (2 H, m) (2-CH_2, 8-CH_2, 9-CH_2, and 3-CH), 3.65 (3 H, s, CH_3). Anal. ($C_{12}H_{19}NO_6$) C, H, N. Stereochemistry confirmed by COSY NMR.

***exo*-Methyl 1-Azabicyclo[3.2.1]octane-3-carboxylate (5a)** was prepared from **5f** by using the procedure described for **3a**. Hydrochloride salt: mp 184.5–185 °C (MeOH/Et_2O); ^1H NMR (DMSO-d_6) δ 1.70–2.00 (3 H, m), 2.00–2.20 (1 H, m), 2.65 (1 H, m), 3.00–3.50 (7 H, m), 3.65 (3 H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ 26.48, 31.01, 32.64, 33.08, 49.77, 51.91, 51.94, 56.88, 171.90. Anal. ($C_9H_{16}ClNO_2 \cdot 0.1H_2O$) C, H, N.

***exo*-Methyl 1-Azabicyclo[3.2.1]octane-6-carboxylate (6a)** was prepared from **6f** by using the procedure described for **3a**: ^1H NMR ($CDCl_3$) δ 1.35–1.50 (1 H, m), 1.60–1.75 (3 H, m), 2.45–2.53 (1 H, m), 2.75–2.90 (5 H, m), 3.10–3.20 (2 H, m), 3.70 (3 H, s, CH_3); hydrochloride salt mp 60–70 °C. Anal. ($C_9H_{16}ClNO_2 \cdot 0.1H_2O$) C, H, N.

Furo[3,4-*c*]pyridin-3(1*H*)-one (10). A solution of pyridine-3,4-dicarboxylic acid anhydride (137 g, 0.92 mol) in toluene (1 L) at −20 °C under N_2 was treated with a solution of $NaBH_4$ (40 g, 1.05 mol) in dry DMF (1 L), then warmed to 35 °C over 1.5 h. The mixture was treated with acetone (160 mL), followed by 5 M HCl (1 L), and evaporated to dryness. The residue was treated with 5 M HCl (600 mL) and heated under reflux for 0.5 h, then concentrated to dryness. The residue was basified with concentrated K_2CO_3 solution and extracted with $CHCl_3$, and the dried extracts evaporated to dryness to leave a yellow solid, which was recrystallized from toluene to give **10** as a beige solid (50 g, 40%): mp 150–153 °C; ^1H NMR ($CDCl_3$) δ 5.25 (2 H, s, CH_2), 7.45 (1 H, d, J = 5.5 Hz, 7-CH), 8.80 (1 H, d, J = 5.5 Hz, 6-CH), 9.08 (1 H, s, 4-CH).

***cis*-5-Benzyl-3a,4,5,6,7,7a-hexahydrofuro[3,4-*c*]pyridin-3(1*H*)-one (11).** A solution of **10** (73 g, 0.54 mol) in EtOH (1.5 L) together with AcOH (50 mL) was hydrogenated over 10% Rh/C (5 g) at 1000 psi and 90 °C for 24 h. The catalyst was removed by filtration and the filtrate concentrated to about 1 L in volume, then treated with anhydrous K_2CO_3 (250 g, 1.8 mol) and benzyl bromide (92 g, 0.54 mol). The mixture was stirred at room temperature for 0.75 h, then concentrated to leave a white

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slurry, which was treated with H_2O (800 mL) and extracted with $CHCl_3$. The dried extracts were concentrated, and the residue was chromatographed on silica gel eluting with Et_2O to give 11 as a pale yellow oil (49.3 g, 40%): ^1H NMR ($CDCl_3$) δ 1.52–1.65 (1 H, m, 7-CH_{ax}), 1.77–1.86 (1 H, m, 7-CH_{eq}), 1.95 (1 H, dt, J = 2.5, 13.5 Hz, 4-CH_{ax}), 2.42–2.52 (1 H, m, 7a-CH_{ax}), 2.59–2.65 (1 H, m, 3a-CH_{eq}), 2.67–2.74 (1 H, m, 6-CH_{eq}), 3.21–3.28 (1 H, m, 4-CH_{eq}), 3.48 and 3.59 (each 1 H, d, J = 13.5 Hz, CH_2Ph), 4.00 (1 H, d, J = 9 Hz, 1-CH), 4.22 (1 H, dd, J = 5, 9 Hz, 1-CH), 7.20–7.34 (5 H, m, Ph).

***exo*-Methyl 1-Azabicyclo[2.2.1]heptane-3-carboxylate (7a).** A solution of lactone 11 (2.80 g, 0.012 mol) in EtOH (150 mL) was saturated with HBr gas, and the mixture stirred at room temperature for 9 days. After evaporation to dryness the residue was basified with saturated K_2CO_3 solution and extracted with $CHCl_3$. The dried extracts were concentrated to give 12 as a yellow gum (4.0 g) which was dissolved in EtOH (150 mL) containing AcOH (2 mL), and hydrogenated over 10% Pd–C (500 mg) at atmospheric pressure and 40 °C until uptake of hydrogen ceased. The catalyst was filtered off and the filtrate concentrated to leave a beige semisolid, which was treated with 8 M HCl (70 mL) and heated under reflux for 2 h. The solution was concentrated and the residue was treated with methanolic HCl (100 mL) and heated under reflux for 0.5 h. After evaporation to dryness the residue was basified with saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The dried extracts were concentrated and distilled in a Kugelrohr apparatus (bp ca. 110–120 °C at 0.4 mmHg) to give **7a** (1.3 g, 70%). Oxalate salt: mp 134–136 °C (MeOH/Et_2O); ^1H NMR (DMSO-d_6) δ 1.65–1.76 (1 H, m, 5-CH), 1.90–2.05 (1 H, m, 5-CH), 2.85–2.95 (1 H, m, 4-CH), 2.95–3.15 (4 H, m, 6-CH_2 and 7-CH_2), 3.22–3.50 (3 H, m, 2-CH_2 and 3-CH), 3.68 (3 H, s, CH_3). Anal. ($C_{10}H_{15}NO_6$) C, H, N.

7-Benzyl-7-aza-2-oxaspiro[4.4]nonan-1-one (14). A solution of diisopropylamine (6.6 mL, 0.047 mol) in dry Et_2O (100 mL) at −65 °C under N_2 was treated with 1.6 M *n*-butyllithium in hexane (26.2 mL, 0.042 mol) and the solution stirred for 0.25 h, before treating with *N,N,N*[1],*N*[1]-tetramethylethylenediamine (12.3 mL). After stirring for a further 10 min, the solution was treated dropwise over 10 min with a solution of methyl 1-benzyl-3-pyrrolidinecarboxylate[30] (7.50 g, 0.034 mol) in dry Et_2O (20 mL) and stirring continued at −65 °C for 0.25 h. Ethylene oxide (3.1 g, 0.070 mol) was then bubbled into the solution over 20 min and the mixture was allowed to warm to room temperature over 2 h followed by 40 min at reflux. The reaction mixture was treated with saturated $NaHCO_3$ solution (50 mL) and extracted with Et_2O. The combined extracts were dried and concentrated to leave an orange oil. The unreacting starting material was removed by heating under reflux in 8 M HCl (50 mL) for 2 h, followed by basifying to saturation with $NaHCO_3$ and extraction with Et_2O. The organic extract was dried and concentrated to leave an orange oil, which was distilled in a Kugelrohr apparatus (bp ca. 190–210 °C at 0.5 mmHg) followed by column chromatography on silica gel eluting with Et_2O to give 14 as a pale yellow oil (2.50 g, 36%): ^1H NMR ($CDCl_3$) δ 1.77–1.92 (1 H, m, 9-CH), 2.15–2.40 (3 H, m, 4-CH_2, 9-CH), 2.48–2.78 (3 H, m) and 2.85–2.98 (1 H, m, 6-CH_2, 8-CH_2), 3.61 and 3.71 (each 1 H, d, J = 13 Hz, CH_2Ph), 4.10–4.30 (2 H, m, 3-CH_2), 7.15–7.35 (5 H, m, Ph). HCl salt mp 155.5–157 °C (acetone/Et_2O). Anal. ($C_{14}H_{18}ClNO_2$) C, H, N.

Methyl 1-Azabicyclo[2.2.1]heptane-4-carboxylate (8a). A solution of 7-Benzyl-7-aza-2-oxaspiro[4.4]nonan-1-one (14; 2.5 g, 0.012 mol) in EtOH (150 mL) was saturated with HBr gas, and the mixture allowed to stand at room temperature for 3.5 days. The solution was concentrated and the residue basified with saturated K_2CO_3 solution, stirred for 10 min, and then extracted with $CHCl_3$. The combined extracts were dried and concentrated to give a beige solid, which was dissolved in EtOH (150 mL) and hydrogenated over 10% Pd–C (0.5 g) at atmospheric pressure and 40 °C until the uptake of hydrogen ceased. The mixture was filtered and the filtrate concentrated to leave a white solid, which was dissolved in 6 M HCl (70 mL) and heated under reflux for 10 h. The solution was concentrated and the residue was dissolved in methanolic HCl (80 mL) and heated under reflux for 2 h. The solution was concentrated and the residue basified with saturated K_2CO_3 solution and extracted with $CHCl_3$. The dried extract was concentrated and the residue chromatographed on silica gel eluting with $CHCl_3$/MeOH (20:1) to give **8a** as a yellow oil (900 mg, 50%): IR (film) 1730 (s) cm^{-1}. Oxalate salt: mp 130–132 °C (MeOH/Et_2O); ^1H NMR (MeOH-d_4) δ 2.00–2.15 (2 H, m, 3-CH and 5-CH), 2.30–2.45 (2 H, m, 3-CH and 5-CH), 3.30–3.47 (2 H, m, 2-CH and 6-CH), 3.43 (2 H, s, 7-CH_2), 3.51–3.65 (2 H, m, 2-CH and 6-CH), 3.77 (3 H, s, CH_3). Anal. ($C_{10}H_{15}NO_6$) C, H, N.

Ethyl 1-(2-Chloroethyl)-3-piperidinecarboxylate (16). A solution of ethyl nipecotate (100 g, 0.64 mol) in acetone (800 mL) was treated with 1-bromo-2-chloroethane (106.5 mL, 1.28 mol) and anhydrous K_2CO_3 (138 g, 1.00 mol) and the mixture stirred at room temperature for 24 h. The mixture was concentrated and the residue treated with H_2O (300 mL) and extracted with Et_2O. The extracts were dried and concentrated and the residue chromatographed on silica gel eluting with Et_2O/petroleum ether (1:1) to give 16 as a pale yellow oil (78.2 g, 56%): ^1H NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 7 Hz, CH_3CH_2), 1.40–3.10 (11 H, m), 3.58 (2 H, t, J = 7 Hz, CH_2Cl), 4.15 (2 H, q, J = 7 Hz, CH_2CH_3).

Methyl 1-Azabicyclo[3.2.1]octane-5-carboxylate (9a). A solution of diisopropylamine (33.6 mL, 0.24 mol) in dry Et_2O (1.5 L) at −65 °C under N_2 was treated with 1.5 M *n*-butyllithium in hexane (150 mL, 0.225 mol) and the solution stirred for 0.25 h, before adding *N,N,N*[1],*N*[1]-tetramethylethylenediamine (68 mL, 0.45 mol). After stirring for a further 0.25 h, the solution was treated with a solution of 16 (44.7 g, 0.204 mol) in dry Et_2O (100 mL) and the mixture allowed to warm up to room temperature over 2 h. The reaction mixture was treated with K_2CO_3 solution (300 mL) and the Et_2O layer separated, dried, and concentrated to leave an orange oil (39.6 g). A portion of this material (3.40 g) was dissolved in 8 M HCl (150 mL) and heated under reflux for 11 h. The solution was concentrated and the residue dissolved in methanolic HCl (140 mL) and heated under reflux for 1.5 h. The solution was concentrated, then basified with concentrated K_2CO_3 solution and extracted with $CHCl_3$. The dried extracts were concentrated, and the residue was chromatographed on silica gel eluting with $CHCl_3$/MeOH (10:1) to give **9a** as a pale yellow oil (2.50 g, 84%): IR (film) 1730 (s) cm^{-1}. Oxalate salt: mp 114–116 °C (MeOH/Et_2O); ^1H NMR (MeOH-d_4) δ 1.90–2.25 (5 H, m), 2.32–2.47 (1 H, m), 3.20–3.38 (3 H, m), 3.40–3.53 (1 H, m), 3.57–3.80 (2 H, m), 3.73 (3 H, s). Anal. ($C_{11}H_{17}NO_6$) C, H, N.

1-Azabicyclo[2.2.2]octane-3-carboxamide (3g). A solution of **3f** (4.1 g, 0.03 mol) in EtOH (250 mL) was treated with KOH (7.9 g, 0.12 mol) and the mixture was refluxed under N_2 for 30 h. After evaporation of the solvent, the residue was diluted with Et_2O (50 mL), saturated with K_2CO_3, and extracted into EtOAc. The combined organic extracts were washed with brine, dried, and concentrated to give **3g** (3.3 g, 72%). Oxalate salt: mp 162–163 °C (MeOH/Et_2O); ^1H NMR (DMSO-d_6) δ 1.60–1.74 and 1.76–1.92 (each 2 H, m, 5-CH_2 and 8-CH_2), 2.27 (1 H, m, 4-CH), 2.78–2.90 (1 H, m) and 3.00–3.60 (6 H, m) (2-CH_2, 6-CH_2, 7-CH_2, and 3-CH). Anal. ($C_{10}H_{16}N_2O_5$) C, H, N.

***exo*-1-Azabicyclo[3.2.1]octane-6-carboxamide (6g).** A solution of **6f** (2.0 g, 0.015 mol) in Et_2O (50 mL) was treated with benzyl bromide and stirred overnight. Filtration afforded the quaternary salt (4.5 g, 99%): mp 250–253 °C; ^1H NMR δ 1.7–2.0 (4 H, m, 3-CH_2 and 4-CH_2), 3.1 (1 H, m, 5-CH), 3.3–3.7 (4 H, m, 2-CH_2 and 8-CH_2), 3.8–4.0 (2 H, m, 6-CH and 7-CH), 4.1–4.2 (1 H, m, 7-CH), 4.7 (2 H, AB q, J = 14 Hz, CH_2Ph), 7.6 (5 H, m, aromatic). A solution in MeOH (250 mL) was treated with hydrogen peroxide (100 vol, 10 mL) and 10% aqueous NaOH (5 mL) at room temperature. After 1 h the reaction was adjusted to pH 4 with AcOH and evaporated to dryness. The residue was taken up in MeOH (250 mL) and hydrogenated over 10% Pd–C (0.5 g) until the uptake of hydrogen ceased. After filtration, the solution was concentrated. The residue was treated with saturated aqueous K_2CO_3 and extracted exhaustively with $CHCl_3$. Concentration of the dried organic extracts afforded **6g** (1.3 g, 58%): mp 145–150 °C (Et_2O); ^1H NMR ($CDCl_3$) δ 1.3–1.8 (4 H, m, 3-CH_2 and 4-CH_2), 2.4 (1 H, m, 5-CH), 2.6–3.0 (5 H, m, 2-CH_2, 8-CH_2, and 6-CH), 3.15 (2 H, d, J = 6 Hz, 7-CH_2), 6.0 (2 H, m, NH_2).

3-(3-Methyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.2]octane (3b). A solution of **3g** (0.85 g, 5.5 mmol) in *N,N*-dimethylacetamide dimethyl acetal (5 mL) was heated at 120 °C for 1.5 h under N_2. After evaporation of excess reagent the residue was treated

(30) Terao, Y.; Kotaki, H.; Imai, N.; Achiwa, K. *Chem. Pharm. Bull.* 1985, *33* (7), 2762.

with a solution of hydroxylamine hydrochloride (0.53 g, 7.5 mmol) in 1 M NaOH (7.5 mL) and then diluted with dioxane (7.5 mL) followed by AcOH (10 mL). After stirring at room temperature for 0.5 h, the mixture was heated at 90 °C for 1 h. The reaction was concentrated, diluted with H_2O (20 mL), and saturated with K_2CO_3. After extraction with $CHCl_3$ the dried organic layers were concentrated. Removal of polar impurities by extraction of the product into Et_2O and filtration afforded **3b** (0.85 g, 72%). Oxalate salt: mp 112–115 °C (acetone/MeOH); ^1H NMR (DMSO-d_6) δ 1.55–1.85 (2 H, m) and 1.85–2.10 (2 H, m) (5-CH_2 and 8-CH_2), 2.37 (3 H, s, CH_3), 2.43 (1 H, m, 4-CH), 3.15–3.83 (7 H, m, 2-CH_2, 6-CH_2, 7-CH_2, and 3-CH); ^{13}C NMR (MeOH-d_4 + DMSO-d_6) 12.08, 20.04, 23.90, 25.63, 33.52, 46.90, 47.22, 49.92, 166.40, 168.34, 180.10. Anal. ($C_{12}H_{17}N_3O_5$) C, H, N.

***exo*-3-(3-Methyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[3.2.1]octane (5b)** was prepared from **5a** by using the procedure described for **3b**. Oxalate salt: mp 152–154 °C (acetone/MeOH); ^1H NMR (DMSO-d_6) δ 1.84–2.04 (2 H, m), and 2.06–2.20 (2 H, m) (4-CH_2 and 6-CH_2), 2.44 (3 H, s, CH_3), 2.71 (1 H, m, 5-CH), 3.10–3.15 (1 H, m) and 3.40–3.65 (5 H, m) and 3.86 (1 H, m) (2-CH_2, 7-CH_2, 8-CH_2, and 3-CH); ^{13}C NMR (DMSO-d_6) δ 11.02, 26.69, 27.17, 32.18, 32.63, 48.88, 52.71, 57.26, 164.54, 166.68, 178.26. Anal. ($C_{12}H_{17}N_3O_5$) C, H, N.

***exo*-6-(3-Methyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[3.2.1]octane (6b)** was prepared from **6g** by using the procedure described for **3b**. Purification of the crude product on alumina using a graded eluant of 3–10% MeOH in EtOAc afforded **6b** as a colorless oil (44% yield). Oxalate salt: mp 137–138 °C (MeOH/Et_2O); ^1H NMR (DMSO-d_6) δ 1.70–2.10 (4 H, m, 3-CH_2 and 4-CH_2), 2.32 (3 H, s, CH_3), 2.82 (1 H, m, 5-CH), 3.20–3.35 (4 H, m, 2-CH_2 and 8-CH_2), 3.60–3.70 (1 H, m, 6-CH), 3.80–3.95 (2 H, m, 7-CH_2); ^{13}C NMR (DMSO-d_6) δ 11.1, 16.5, 27.3, 37.7, 39.7, 51.8, 53.6, 56.7, 164.9, 166.8, 179.8. Anal. ($C_{12}H_{17}N_3O_5$) C, H, N.

***exo*-3-(3-Methyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane (7b).** A solution of **7a** (0.95 g, 6.2 mmol) in 8 M HCl (70 mL) was heated under reflux for 2.5 h. After evaporation to dryness the residue was treated with $SOCl_2$ (20 mL) and heated under reflux for 4.5 h. The solution was concentrated and the residue dissolved in absolute $CHCl_3$ (130 mL), treated with acetamide oxime (0.55 g, 7.4 mmol), and heated under reflux for 4 h. The reaction mixture was basified with saturated K_2CO_3 solution and extracted with $CHCl_3$. The dried extracts were concentrated, and the residue was heated under reflux in xylene (100 mL) for 1.5 h, using a Dean–Stark head to trap water formed. The reaction mixture was concentrated and the residue was chromatographed on silica gel eluting with $CHCl_3$/MeOH (50:1) to give **7b** as a colorless oil (0.16 g, 14%). Oxalate salt: mp 116–120 °C (EtOH/Et_2O); ^1H NMR (DMSO-d_6) δ 1.75–1.87 (1 H, m, 5-CH), 1.95–2.10 (1 H, m, 5-CH), 2.35 (3 H, s, CH_3), 3.10–3.40 (5 H, m, 4-CH, 6-CH_2, and 7-CH_2), 3.53–3.70 (3 H, m, 2-CH_2 and 3-CH). Anal. ($C_{11}H_{15}N_3O_5 \cdot 0.5H_2O$) C, H, N.

3-(3-Methyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[3.3.1]nonane (4b) was prepared from **4a** by using the procedure described for **7b**. Purification of the crude product by chromatography on neutral alumina eluting with EtOAc/MeOH (50:1) afforded **4b** (20% yield). Oxalate salt: mp 145–146.5 °C (MeOH/Et_2O); ^1H NMR (DMSO-d_6) δ 1.65–2.40 (7 H, m, 4-CH_2, 6-CH_2, 7-CH_2, and 5-CH), 2.32 (3 H, s, CH_3), 3.15–3.60 (5 H, m, 2-CH, 8-CH_2, and 9-CH_2), 3.65–3.80 (1 H, m, 2-CH), 4.07–4.25 (1 H, m, 3-CH); ^{13}C NMR (MeOH-d_4) δ 11.33, 20.38, 26.13, 26.98, 30.86, 32.43, 52.61, 52.99, 53.49, 166.57, 168.51, 180.04. Anal. ($C_{13}H_{19}N_3O_5$) C, H, N.

4-(3-Methyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane (8b) was prepared from **8a** by using the procedure described for **7b**. Purification of the crude product by chromatography on silica gel eluting with $CHCl_3$/MeOH (20:1) afforded **8b** as a pale yellow oil (28% yield). Oxalate salt: mp 172–174 °C (EtOH/Et_2O); ^1H NMR (DMSO-d_6) δ 2.05–2.18 (2 H, m, 3-CH and 5-CH), 2.27–2.43 (2 H, m, 3-CH and 5-CH), 2.37 (3 H, s, CH_3), 3.20–3.35 (2 H, m, 2-CH and 6-CH), 3.37–3.55 (2 H, m, 2-CH and 6-CH), 3.43 (2 H, s, 7-CH_2). Anal. ($C_{11}H_{15}N_3O_5$) C, H, N.

5-(3-Methyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[3.2.1]octane (9b) was prepared from **9a** by using the procedure described for **7b**. Purification of the crude product by chromatography on silica gel eluting with $CHCl_3$/MeOH (20:1) afforded **9b** as a pale yellow oil (56% yield). Oxalate salt: mp 124–127 °C (EtOH/Et_2O); ^1H NMR (MeOH-d_4) δ 2.00–2.35 (4 H, m) and 2.40–2.65 (2 H, m) (3-CH_2, 4-CH_2, and 6-CH_2), 2.36 (3 H, s, CH_3), 3.35–3.48 and 3.54–3.68 and 3.70–3.85 (each 2 H, m) (2-CH_2, 7-CH_2, and 8-CH_2). Anal. ($C_{12}H_{17}N_3O_5$) C, H, N.

***exo*-3-Cyano-1-azabicyclo[2.2.1]heptane (7f).** A solution of **7a** (3.2 g, 0.021 mol) in 8 M HCl (80 mL) was heated under reflux for 2 h, then concentrated to dryness. The residue was treated with $SOCl_2$ (25 mL) and stirred at room temperature for 1.5 h. The solution was concentrated and the residue dissolved in CH_2Cl_2 (100 mL), cooled to 0 °C, and treated with excess of NH_3 in CH_2Cl_2. The mixture was filtered and the filtrate concentrated. The residue was treated with $SOCl_2$ (30 mL) and heated under reflux for 1 h, then concentrated, and the residue was basified with K_2CO_3 solution and extracted with $CHCl_3$. The dried extracts were concentrated, and the residue was chromatographed on silica gel eluting with $CHCl_3$/MeOH (20:1) to afford **7f** as a yellow oil (1.3 g, 52%): IR (film) 2240 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07–1.22 (1 H, m, 5-CH), 1.60–1.75 (1 H, m, 5-CH), 2.18–2.28 (1 H, m), 2.38–2.57 (2 H, m), 2.64–2.74 (1 H, m), 2.75–3.10 (4 H, m).

5-Cyano-1-azabicyclo[3.2.1]octane (9f). A solution of **9a** (3.1 g, 0.018 mol) in 8 M HCl (40 mL) was heated under reflux for 18 h, then concentrated to dryness. The residue was treated with $SOCl_2$ (25 mL), heated under reflux for 6 h, then concentrated to leave a gum. This was dissolved in CH_2Cl_2 (100 mL), cooled to 0 °C, and treated with excess NH_3 in CH_2Cl_2. After 1 h at room temperature, the mixture was treated with concentrated K_2CO_3 solution and extracted with $CHCl_3$. The dried extracts were concentrated, and the residue was suspended in toluene (100 mL), treated with phosphorus pentoxide (3.9 g), and heated under reflux for 7 h. The mixture was basified with K_2CO_3 solution and extracted with Et_2O. The dried extracts were concentrated to afford **9f** as a yellow oil (1.6 g, 65%): IR (CCl_4) 2240 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40–1.53 (1 H, m), 1.60–1.80 (1 H, m), 1.85–2.22 (4 H, m), 2.70–3.18 (6 H, m).

3-(5-Methyl-1,2,4-oxadiazol-3-yl)-1-azabicyclo[2.2.2]octane (3c). A solution of NaOMe generated from Na (0.34 g, 14.7 mmol) in MeOH (40 mL) was treated with hydroxylamine hydrochloride (1.0 g, 14.7 mmol). To this was added a solution of **3f** (1.0 g, 7.35 mmol) in methanol (10 mL) and the mixture was refluxed for 18 h. After evaporation of solvent the residue was extracted with $CHCl_3$. Concentration of the organic solution followed by crystallization of the residue from MeOH/Et_2O afforded the amidoxime (0.57 g, 46%), mp 188.5–190 °C. A solution of the amidoxime (0.37 g, 2.2 mmol) in Ac_2O (5 mL) was heated at 120 °C for 2 h. Excess reagent was evaporated and the residue was treated with H_2O and saturated with K_2CO_3. After extraction into EtOAc the dried organic layers were concentrated. Removal of polar impurities by extraction of product into Et_2O afforded **3c** as a colorless gum (0.29 g, 70%). Oxalate salt: mp 142–143 °C (MeOH/Et_2O); IR (KBr) 1580 (m) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.66–1.82 and 1.85–2.15 (each 2 H, m, 5-CH_2 and 8-CH_2), 2.34 (1 H, m, 4-CH), 2.60 (3 H, s, CH_3), 3.16–3.38 (4 H, m, 6-CH_2 and 7-CH_2), 3.40–3.70 (3 H, m, 2-CH_2 and 3-CH); ^{13}C NMR (DMSO-d_6) δ 11.99, 18.51, 22.82, 23.98, 31.30, 45.13, 45.44, 47.90, 164.70, 170.12, 177.50. Anal. ($C_{12}H_{17}N_3O_5$) C, H, N.

***exo*-3-(5-Methyl-1,2,4-oxadiazol-3-yl)-1-azabicyclo[2.2.1]heptane (7c).** A solution of NaOMe generated from Na (0.57 g, 0.025 mol) in MeOH (70 mL) was treated with hydroxylamine hydrochloride (2.1 g, 0.030 mol), stirred at room temperature for 1.5 h, then filtered. To the filtrate was added **7f** (1.3 g, 0.011 mol), the mixture heated under reflux for 5 h, then concentrated, and the residue dissolved in Ac_2O (20 mL). This solution was heated at 90 °C for 40 min, then concentrated, and the residue was basified with K_2CO_3 solution and extracted with $CHCl_3$. The dried extracts were concentrated, and the residue was chromatographed on silica gel eluting with $CHCl_3$/MeOH (10:1) followed by basic alumina in EtOAc to afford **7c** as a colorless oil (220 mg, 11%). Oxalate salt: mp 107–110 °C (MeOH/Et_2O); ^1H NMR (DMSO-d_6) δ 1.75–1.88 (1 H, m, 5-CH), 1.95–2.10 (1 H, m, 5-CH), 2.58 (3 H, s, CH_3), 3.00–3.70 (8 H, m, 2-CH_2, 3-CH, 4-CH, 6-CH_2, and 7-CH_2). Anal. ($C_{11}H_{15}N_3O_5 \cdot 0.25H_2O$) C, H, N.

5-(5-Methyl-1,2,4-oxadiazol-3-yl)-1-azabicyclo[3.2.1]octane (9c) was prepared from **9f** by using the procedure described for **3c**. Purification of the crude product by chromatography on basic alumina eluting with Et_2O/EtOAc (10:1) afforded **9c** as a colorless

oil (18% yield). Oxalate salt: mp 126–127 °C ($MeOH/Et_2O$); ^1H NMR ($DMSO$-d_6) δ 1.80–2.40 (6 H, m, 3-CH_2, 4-CH_2, and 6-CH_2), 2.58 (3 H, s, CH_3), 3.15–3.65 (6 H, m, 2-CH_2, 7-CH_2, and 8-CH_2). Anal. ($C_{12}H_{17}N_3O_5$) C, H, N.

3-(5-Methyl-1,3,4-oxadiazol-2-yl)-1-azabicyclo[2.2.2]octane (3d). A mixture of **3a** (0.36 g, 2.1 mmol) and hydrazine hydrate (0.35 mL, 7.0 mmol) was heated at 120 °C for 2 h. The reaction was diluted with H_2O (10 mL), saturated with K_2CO_3, and extracted into $CHCl_3$. Concentration of the dried organic extracts afforded an oil (0.36 g) which was treated with triethyl orthoacetate (3 mL) and heated at 120 °C for 2 h. Excess triethyl orthoacetate was evaporated and the residue was heated for a further 2 h at 140 °C. The reaction was diluted with H_2O (10 mL), saturated with K_2CO_3, and extracted into Et_2O. Evaporation of the dried extracts afforded **3d** as an oil (0.29 g, 72%). Oxalate salt: mp 147–148 °C (acetone/MeOH); IR (KBr) 1590, 1560 cm^{-1}; ^1H NMR ($DMSO$-d_6) δ 1.60–1.80 and 1.80–2.08 (each 2 H, m, 5-CH_2 and 8-CH_2), 2.38 (1 H, m, 4-CH), 2.48 (3 H, s, CH_3), 3.15–3.32 (4 H, m, 6-CH_2 and 7-CH_2), 3.52–3.73 (3 H, m, 2-CH_2 and 3-CH); ^{13}C NMR ($DMSO$-d_6) 10.5, 18.6, 22.5, 23.6, 30.8, 45.1, 45.3, 47.6, 164.3, 164.5, 166.0. Anal. ($C_{12}H_{17}N_3O_5$) C, H, N.

***exo*-3-(5-Methyl-1,3,4-oxadiazol-2-yl)-1-azabicyclo[2.2.1]heptane (7d)** was prepared from **7a** by using the procedure described for **3d**. Purification of the crude product by chromatography on silica gel eluting with $CHCl_3/MeOH$ (20:1), followed by Kugelrohr distillation (bp ca. 180 °C at 0.7 mmHg) afforded **7d** as a yellow oil, which solidified on standing (47% yield). Oxalate salt: mp 119–122 °C ($MeOH/Et_2O$); ^1H NMR ($DMSO$-d_6) δ 1.76–1.90 (1 H, m, 5-CH), 1.97–2.14 (1 H, m, 5-CH), 2.48 (3 H, s, CH_3), 3.10–3.55 (5 H, m, 4-CH, 6-CH_2, and 7-CH_2), 3.50–3.70 (3 H, m, 2-CH_2, 3-CH). Anal. ($C_9H_{13}N_3O \cdot 1.25(COOH)_2$) C, H, N.

4-(5-Methyl-1,3,4-oxadiazol-2-yl)-1-azabicyclo[2.2.1]heptane (8d) was prepared from **8a** by using the procedure described for **3d**. Purification of the crude product by Kugelrohr distillation (bp ca. 180–185 °C at 0.1 mmHg) afforded **8d** as a pale yellow oil (53% yield). Oxalate salt: mp 136–138 °C ($MeOH/Et_2O$); ^1H NMR ($DMSO$-d_6) δ 2.00–2.15 (2 H, m, 3-CH and 5-CH), 2.30–2.45 (2 H, m, 3-CH and 5-CH), 2.47 (3 H, s, CH_3), 3.20–3.40 (2 H, m, 2-CH and 6-CH), 3.34 (2 H, s, 7-CH_2), 3.45–3.60 (2 H, m, 2-CH and 6-CH). Anal. ($C_{11}H_{15}N_3O_5$) C, H, N.

5-(5-Methyl-1,3,4-oxadiazol-2-yl)-1-azabicyclo[3.2.1]octane (9d) was prepared from **9a** by using the procedure for **3d**. Purification of the crude product by chromatography on basic alumina eluting with EtOAc/MeOH (20:1) afforded **8d** as a yellow oil (20% yield). Oxalate salt: mp 153–155 °C ($MeOH/Et_2O$); ^1H NMR ($DMSO$-d_6) δ 1.80–2.18 (4 H, m) and 2.23–2.45 (2 H, m) (3-CH_2, 4-CH_2, and 6-CH_2), 2.48 (3 H, s, CH_3), 3.20–3.30 (2 H, m) and 3.38–3.66 (4 H, m) (2-CH_2, 7-CH_2, and 8-CH_2). Anal. ($C_{12}H_{17}N_3O_5$) C, H, N.

Radioligand Binding. Cerebral cortex from Hooded Lister rats (Olac, UK) was homogenized in 2.5 vol of ice-cold 50 mM Tris buffer, pH 7.7 (at 25 °C). After centrifugation at 25000*g* at 4 °C for 15 min the pellet was resuspended in 2.5 vol of buffer and the wash repeated three times more. The final resuspension was in 2.5 vol and the homogenates were stored in 1-mL aliquots at −20 °C. Incubations (total volume 2 mL) were prepared by using the above buffer with the addition of 2 mM magnesium chloride in the [^3H]oxotremorine-M ([^3H]OXO-M) experiments. For [^3H]quinuclidinyl benzilate ([^3H]QNB), 1 mL of stored membranes was diluted to 30 mL, and 0.1 mL was mixed with test compound and 0.27 nM (ca. 25000 cpm) [^3H]QNB (Amersham International). For [^3H]OXO-M, 1 mL of membranes was diluted to 6 mL, and 0.1 mL was mixed with test compound and 2 nM (ca. 250000 cpm) [^3H]OXO-M (New England Nuclear). Nonspecific binding of [^3H]QNB was defined with 1 μM atropine sulfate (2 μM atropine) and of [^3H]OXO-M with 10 μM oxotremorine. Nonspecific binding values typically were 5% and 25% of total binding, respectively. Incubations were carried out at 37 °C for 30 min and the samples filtered with Whatman GF/B filters. (In the [^3H]OXO-M experiments the filters were presoaked for 30 min in 0.05% polyethylenimine in water.) Filters were washed with 3 × 4 mL ice-cold buffer. Radioactivity was assessed with a Packard BPLD scintillation counter (3 mL of Pico-Fluor 30 (Packard) as scintillant).

Pharmacology. Hypothermia was measured in male mice CDI strain (Charles River) of body weight 25–32 g. Mice were weighed and allocated singly into individual compartments of cages. After acclimatization (5–30 min) their rectal temperatures were read with a calibrated electric thermocouple thermometer with the probe inserted to a depth of 2.5 cm. The measurement was repeated twice more at 20–30-min intervals to achieve stable baselines. The test compound was then administered and rectal temperatures were recorded at 15-min intervals. ED_3 values were calculated graphically as the dose that caused a fall of 3 °C in mean rectal temperature of groups of five mice.

Molecular Modeling. Structures were built with standard bond lengths and angles in CHEM-X, developed and distributed by Chemical design Ltd., Oxford, England. Geometry optimizations were carried out with the semiempirical AM1 method[31] in the AMPAC program.[32] Ab initio calculations were carried out with the extended 4-31G basis set[33] in GAMESS (Generalized Atomic and Molecular Electronic Structure System, Revision A, M. F. Guest).[34] Two-dimensional potential maps were displayed on an Iris Silicon Graphics work station (Model 4D 70G) using software developed by Dr. F. E. Blaney in collaboration with Polygen Corp.

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Registry No. 3a, 38206-86-9; **3a**·oxalate, 134967-27-4; **3b**, 114724-64-0; **3b**·oxalate, 134967-28-5; **3c**, 114724-62-8; **3c**·oxalate, 134967-29-6; **3d**, 114724-71-9; **3d**·oxalate, 134967-30-9; **3f**, 51627-76-0; **3g**, 75426-71-0; **3g**·oxalate, 135004-12-5; **4a**, 134967-31-0; **4a**·oxalate, 134967-32-1; **4b**, 134967-33-2; **4b**·oxalate, 134967-34-3; 4e, 29170-80-7; 4f, 134967-51-4; **5a**, 134967-49-0; **5a**·HCl, 134967-35-4; **5b**, 134967-36-5; **5b**·oxalate, 134967-37-6; **5e**, 17604-28-3; **5f**, 134967-52-5; **6a**, 134967-50-3; **6a**·HCl, 129594-83-8; **6b**, 134967-38-7; **6b**·oxalate, 134967-39-8; **6e**, 45675-76-1; **6f**, 134967-53-6; **6g**, 134967-55-8; **7a**, 121564-88-3; **7a**·oxalate, 129594-82-7; **7b**, 121564-89-4; **7b**·oxalate, 134967-40-1; **7c**, 134967-41-2; **7c**·oxalate, 134967-42-3; **7d**, 134967-43-4; **7d**·oxalate, 134967-44-5; **7f**, 134967-56-9; **8a**, 119102-22-6; **8a**·oxalate, 119102-51-1; **8b**, 119102-27-1; **8b**·oxalate, 119102-56-6; **8d**·oxalate, 119102-67-9; **9a**, 119102-44-2; **9a**·oxalate, 119102-45-3; **9b**, 119102-26-0; **9b**·oxalate, 134967-45-6; **9c**, 119102-32-8; **9c**·oxalate, 134967-47-8; **9d**, 119102-29-3; **9d**·oxalate, 134967-48-9; **9f**, 134967-57-0; **10**, 5657-52-3; 11, 133745-54-7; **12**, 133745-58-1; 14, 119102-90-8; **16**, 134967-54-7; 3-quinuclidinone, 3731-38-2; pyridine-3,4-dicarboxylic acid anhydride, 4664-08-8; methyl 1-benzyl-3-pyrrolidinecarboxylate, 17012-21-4; ethylene oxide, 75-21-8; ethyl nipecotate, 5006-62-2; 1-bromo-2-chloroethane, 107-04-0; acetamide oxime, 22059-22-9; 1-azabicyclo[2.2.2]octane-3-carboxamide amidoxime, 123837-16-1.

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