Articles

Synthesis and Biological Activity of 1,2,4-Oxadiazole Derivatives: Highly Potent and Efficacious Agonists for Cortical Muscarinic Receptors

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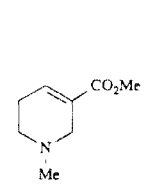
The synthesis and biochemical evaluation of novel 1,2,4-oxadiazole-based muscarinic agonists which can readily penetrate into the CNS is reported. Efficacy and binding of these compounds are markedly influenced by the structure and physicochemical properties of the cationic head group. In a series of azabicyclic ligands efficacy and affinity are influenced by the size of the surface area presented to the receptor, at the active site, and the degree of conformational flexibility. The *exo*-1-azanorbornane **16a** represents the optimum arrangement, and this compound is one of the most efficacious and potent muscarinic agonists known. In a series of isoquinuclidine based muscarinic agonists efficacy and affinity are influenced by the geometry between the cationic head group and hydrogen bond acceptor pharmacophore and steric bulk in the vicinity of the base. The anti configuration represented by **22a** is optimal for muscarinic activity. Ligands with pK_a below 6.5 show poor binding to the muscarinic receptor as exemplified by the diazabicyclic derivative **42**.

There has been a surge of pharmaceutical interest recently[1,2] in agents capable of stimulating central cholinergic transmission following reports[3,4,5,6] which consistently indicate major deficits in cerebral cholinergic transmission in patients with senile dementia of the Alzheimers type (SDAT). Clinical and animal behavior studies have suggested that this loss in cholinergic function may be one of the causes of disturbances in learning and memory in SDAT patients.[7] Several approaches to improving cholinergic transmission and hence cognitive function have been followed and include the use of acetylcholinesterase (AChE) inhibitors, e.g. tacrine,[8] 9-amino-1,2,3,4-tetrahydroacridinol (HP-029),[9] and physostigmine,[10] and directly acting agonists[11] at post-synaptic muscarinic receptors in the cortex, e.g. arecoline (**1**), RS-86 (**2**), and pilocarpine (**3**). Of these, clinical studies with AChE



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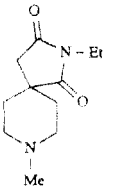

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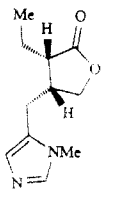

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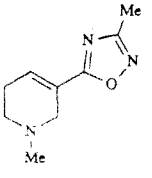

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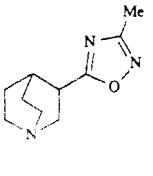

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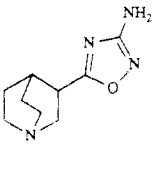

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inhibitors[8,9,10] which potentiate the effects of the high efficacy endogenous neurotransmitter acetylcholine have shown the most success although their role in therapy has still to be firmly established. We suggested recently[12] that one of the reasons for the limited clinical improvement using directly acting agonists **1**, **2**, and **3** could be attributed to their low efficacy at cortical muscarinic receptors, compared with acetylcholine.

Previous reports from these laboratories have described the synthesis and biochemical evaluation of a series of quinuclidine-based ligands for the muscarinic cholinergic receptor.[12] It was found from a series of 5-membered ester bioisosteres studied that the 1,2,4-oxadiazole ring was optimal for affinity and efficacy at central muscarinic receptors. This was interpreted in terms of the hydrogen-bonding capability of the pharmacophore and the conclusion that high efficacy requires two H-bond acceptor sites in an exact location of the heterocycle. Increasing the hydrogen-bonding capability of the 1,2,4-oxadiazole in going from **5** to **6** improved the efficacy of the ligand by increasing binding to the agonist state[13] of the receptor. However, the gain in efficacy obtained by replacing methyl by amino in this series was offset by a reduction in CNS penetration, as indicated by ex vivo binding experiments,[14] on going to the relatively hydrophilic amino substituent.

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(1) Perry, E. K. *Br. Med. Bull.* **1986**, *42*, 63.
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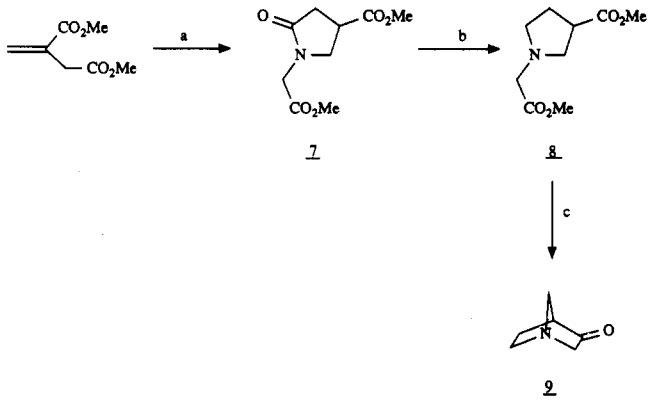
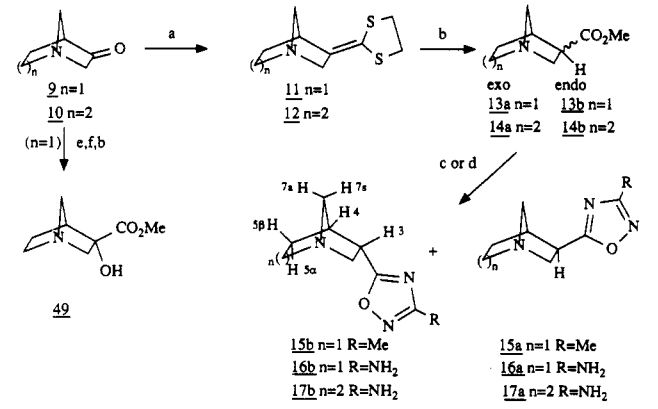
Scheme I[a]



[a] Reagents: (a) NaOMe, MeOH, $NH_2CH_2CO_2Me$·HCl, reflux, 16 h; (b) BH_3·THF, THF, reflux, 1 h then K_2CO_3 solution reflux, 1 h; (c) Bu^{t}OK, PhMe, 140 °C, then reflux concentrated HCl, 16 h.

Scheme II[a]



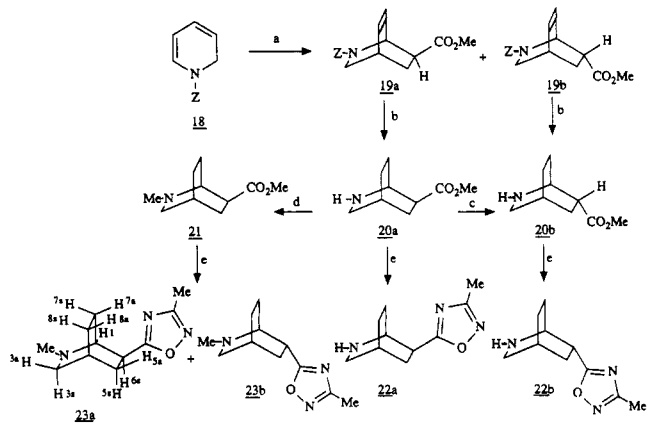
[a] Reagents: (a) Bu^{n}Li, 2-(trimethylsilyl)-1,3-dithiane, −35 °C to 20 °C; (b) MeOH, HCl (gas), 55 °C, 4 h; (c) Na, EtOH, powdered molecular sieve, $(NH_2C(=NOH)NH_2)_2$·H_2SO_4·H_2O, reflux; (d) NaH, THF, MeC(=NOH)NH_2, reflux; (e) NaCN, H_2O, 0 °C; (f) concentrated HCl, 25 °C, 16 h.

In order to study in detail the role of cholinergic mechanisms in memory and cognition, muscarinic ligands were sought which would have equal or greater affinity and efficacy to the quinuclidine amino oxadiazole **6** and the tetrahydropyridine-based ligand **4**, with an improved ability to equilibrate into the CNS. This paper describes the design, synthesis and cortical muscarinic receptor activity of a range of mono- and diazacyclic and mono- and diazabicyclic based 1,2,4-oxadiazole ligands (Schemes II–VI) leading to the discovery of cerebrally active agonists with affinity and efficacy comparable with or greater than that of classical quaternary ammonium based ligands. In addition, the effect of changes in steric bulk, conformational flexibility, geometry, and pK_a of the base, on binding and efficacy at cortical muscarinic receptors, was studied.

Synthetic Chemistry

A novel route to the construction of the 1-azanorbornane ring system was developed[15] which would allow for stereoselective synthesis of both diastereoisomers of the methyl oxadiazoles **15a** and **15b** and the aminooxadiazoles **16a** and **16b** (Schemes I and II). Dieckmann cyclization of the diester **8** with K^{t}OBu in refluxing toluene followed by hydrolysis and decarboxylation gave 1-azabicyclo-[2.2.1]heptan-3-one[16] (**9**) in 60% yield (Scheme I). The

Scheme III[a]



[a] Reagents: (a) CH_2=$CHCO_2Me$, MeCN, reflux; (b) H_2, Pd/C, MeOH; (c) NaOMe, MeOH; (d) aqueous CH_2O, HCO_2H; (e) NaH, THF, MeC(=NOH)NH_2, reflux.

cyanohydrin procedure of Grob[17] to convert quinuclidinone to methyl quinuclidine-3-carboxylate could not be used here because of the extreme resistance of hydroxy ester **49** to elimination, presumably due to the strained nature of the azabicycle. Instead, treatment of **9** with 2-(trimethylsilyl)-2-lithio-1,3-dithiane[18] gave the crystalline ketene dithioacetal **11**; methanolysis of which gave a thermodynamic 9:1 mixture of esters **13a** and **13b**, respectively (Scheme II). Oxadiazole formation with acetamide oxime and sodium hydride in refluxing THF gave a 9:1 mixture of *exo*-[19] and *endo*-oxadiazoles **15a** and **15b**, respectively, which were readily separated by chromatography. Similarly, a 9:1 mixture of aminooxadiazoles **16a** and **16b** was obtained by using hydroxy guanidine sulfate and sodium ethoxide in ethanol at reflux. The stereochemical assignments for **13a,b**, **15a,b**, and **16a,b** were made based on detailed analysis of the ^{1}H/COSY NMR spectra,[20] by making use of four bond couplings between transantiperiplanar protons. For the endo isomers four ^{1}H couplings to H3 are observed namely, $^3J_{2\alpha,3}$ = 4.2 Hz, $^3J_{2\beta,3}$ = 11.3 Hz, $^3J_{3,4}$ = 4.1 Hz, and $^4J_{3,5\beta}$ = 1.9 Hz, consistent with H3 being exo. For the exo isomers three ^{1}H couplings to H3 are observed namely, $^3J_{2\alpha,3}$ = 8.6 Hz, $^3J_{2\beta,3}$ = 5.5 Hz, and $^4J_{3,7a}$ = 1 Hz, consistent with H3 being endo, $^3J_{3,4}$ not being observed due to an unfavorable dihedral bond angle. The endo diastereoisomer could be obtained as the major isomer (ratio 3:1) by kinetic proton capture at the least hindered face of the azacycle, of the anion generated from the exo diastereoisomers with LDA at −78 °C. Under thermodynamic conditions (NaOMe/MeOH) the endo isomers **13b**, **15b**, and **16b** epimerized to the thermodynamically more stable exo isomers **13a**, **15a**, and **16a**, respectively. By use of essentially the same chemistry, the isotropane oxadiazoles **17a** and **17b** (Scheme II) were prepared from 1-azabicyclo[3.2.1]octan-6-one[21] (**10**). The stereochemistry of the major isomer, **17a**, was assigned exo from analysis of the ^{1}H NMR spectra of **17a** and **17b**. Analogous to **15a** and **15b**, $^4J_{3,7a}$ is observed for **17a** but not **17b**.

(15) Saunders, J.; MacLeod, A. M.; Merchant, K.; Showell, G. A.; Snow, R. J.; Street, L. J., Baker, R. *J. Chem. Soc., Chem. Commun.* **1988**, 1618.

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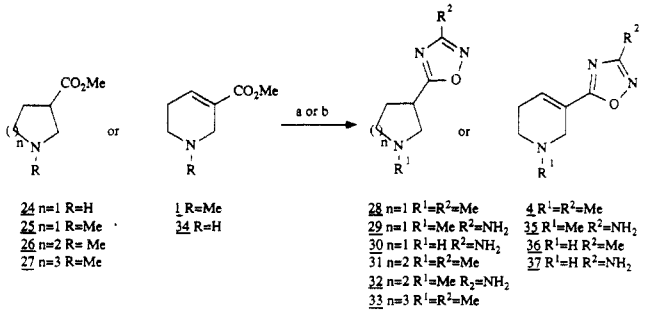
(18) Jones, P. F.; Lappert, M. F. *J. Chem. Soc., Chem. Commun.* **1972**, 526.

(19) Exo is defined here as that in which the substituent is on the same face as the smallest carbon bridge.

(20) Analysis of the COSY 45/^{1}H NMR data for methyloxadiazoles **15a** and **15b** is given in the supplementary material.

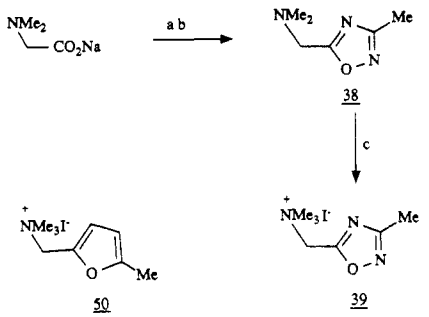
(21) Sternbach, L. H.; Kaiser, S. *J. Am. Chem. Soc.* **1952**, *74*, 2215.

Scheme IV[a]



[a] Reagents: (a) NaH, THF, $MeC(=NOH)NH_2$, reflux; (b) Na, EtOH, powdered molecular sieve, $(NH_2C(=NOH)NH_2)_2 \cdot H_2SO_4 \cdot H_2O$, reflux.

Scheme V[a]

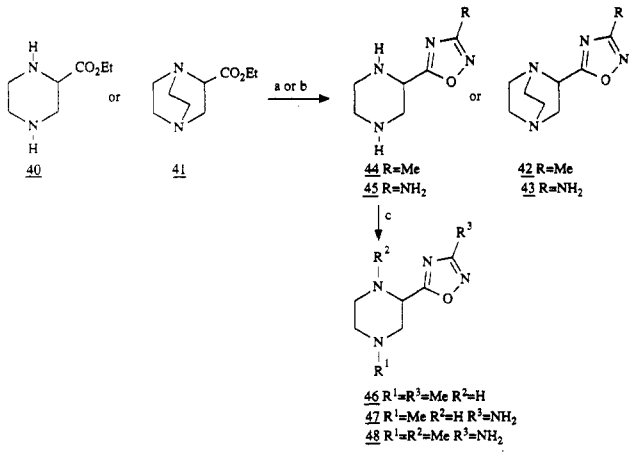


[a] Reagents: (a) $ClCO_2Et$, CH_2Cl_2; (b) $MeC(=NOH)NH_2$, dioxane, reflux; (c) MeI, Et_2O.

The isoquinuclidine ring system was constructed by Diels–Alder reaction of dihydropyridine **18** with methyl acrylate[22] (Scheme III). Separation of the resultant 4:1 mixture of **19a** and **19b**, respectively, followed by hydrogenation gave the required isoquinuclidine esters **20a** and **20b**. Further quantities of the minor product **20b** could be obtained by epimerization of **20a** by using sodium methoxide in refluxing methanol. Reaction of **20a** with aqueous formaldehyde and formic acid gave the N-methylated isoquinuclidine **21**. Oxadiazole formation under normal conditions gave **22a**, **22b**, **23a**, and **23b**. As for **13a,b**, **15a,b**, and **16a,b**, the relative stereochemistries of **22a,b**, and **23a,b** were determined using 2D NMR (COSY) to provide complete proton assignment. In addition, crosspeaks were observed corresponding to coupling over four bonds between transantiperiplanar protons. For **22a** and **23a** these ^4J were found for $H3_{anti}/H5_{anti}$, $H3_{syn}/H8_{anti}$, $H5_{syn}/H8_{syn}$, and $H6_{syn}/H7_{syn}$ thus placing the oxadiazole moiety anti (Scheme III). This was supported by the observation that $^3J_{H6,H5syn}$ (11.0 Hz) was greater than $^3J_{H6,H5anti}$ (6.9 Hz) indicating that H6 was cis to $H5_{syn}$. Similarly, for **22b** and **23b** $H5_{syn}$ and $H5_{anti}$ were assigned by ^4J, and H6 shown to be anti from the magnitudes of $^3J_{H6,H5anti}$ (11.9 Hz) and $^3J_{H6,H5syn}$ (6.1 Hz), consistent with the oxadiazole moiety being syn.

Modifications to the azacycle of the tetrahydropyridine[23] based ligand **4** are shown in Scheme IV. The azacyclic esters **24–27** were prepared according to literature procedures.[24,25,26] The (N,N-dimethylamino)methyl oxadiazole

Scheme VI[a]



[a] Reagents: (a) NaH, THF, $MeC(=NOH)NH_2$, reflux; (b) Na, EtOH, powdered molecular sieve, $(NH_2C(=NOH)NH_2)_2 \cdot H_2SO_4 \cdot H_2O$, reflux; (c) MeI, Et_2O.

38 was prepared from N,N-dimethyl glycine sodium salt and acetamide oxime (Scheme V). Quaternization with methyl iodide gave **39** which is structurally similar to the known muscarinic agonist 5-methyl furmethide **50**. The two carbon chain analogue of **38**, which would be more analogous to the azacyclic and azabicyclic ligands, could not be prepared because of its tendency to eliminate dimethylamine to give the unsaturated derivative. The diazacyclic ester **40** and diazabicyclic ester **41** were prepared as described in the literature[27] and converted to oxadiazoles **42–48** (Scheme VI).

Results and Discussion

We have previously described[13,28] a binding assay to measure affinity and also predict the cortical efficacy of compounds from the antagonist–agonist binding ratio in rat cortical membranes. By use of [^{3}H]oxotremorine-M (OXO-M) to label the high affinity state of the cerebral cortex muscarinic receptors and [^{3}H]-*N*-methylscopolamine (NMS) to label predominantly the low affinity state, it is possible to get an approximate measure of affinity for either state of the receptor. The log of the NMS/OXO-M ratio, thus obtained, has been shown to be predictive of the ability of the ligand to stimulate cortical PI hydrolysis.[13] Antagonists, e.g. atropine, show equal affinity in both binding assays and have ratios close to 1, weak partial agonists have ratios between 10–200, partial agonists, e.g. arecoline (**1**), have intermediate ratios of 200–800 and full agonists, e.g. carbachol, have ratios greater than 800. All of the compounds synthesized in this study have been assessed in the NMS/OXO-M binding assay and the results are presented in Tables I–V.

Reductions in the bulk size and pK_a of the quinuclidine ring were studied since these were anticipated to improve binding to the high affinity agonist binding state of the receptor[13] and to aid CNS availability, respectively. The most simple conceptual change was to remove a carbon atom from one of the bridges in quinuclidine (Scheme II) since this would result in slightly lower bulk and pK_a[16] while maintaining a similar geometry in the pharmacophore. A comparison of the binding data and NMS/OXO-M ratios for the 1-azabicyclic oxadiazoles in Table

(22) Wiley, R. A.; Faraj, A. J.; Jantz, A. *J. Med. Chem.* **1972**, *15*, 374.
(23) A more detailed description of tetrahydropyridine oxadiazoles is the subject of a forthcoming publication.
(24) Terao, Y.; Kotaki, H.; Imai, N.; Achiwa, K. *Chem. Pharm. Bull.* **1985**, *33*, 2762.
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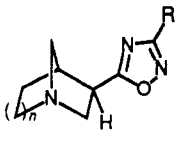
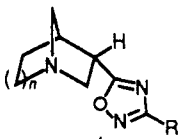
Table I. In Vitro Binding Data for Azabicyclic Oxadiazoles Compared to Standard Muscarinic Ligands

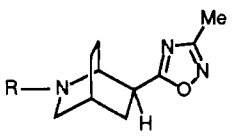

exo

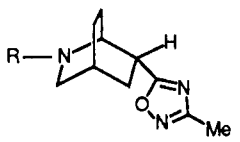

endo

compd	R	n	stereo-chemistry	binding data: K_{app}, μM[a] [^{3}H]NMS[b]	[^{3}H]OXO-M[c]	ratio[d]
arecoline (1)	-	-	-	6.2	0.011	560
RS-86 (2)	-	-	-	5.0	0.040	130
pilocarpine (3)	-	-	-	4.0	0.040	100
atropine	-	-	-	0.0010	0.00048	2.1
carbachol	-	-	-	22	0.0049	4500
15a	Me	1	exo	0.10	0.00009	1110
15b	Me	1	endo	3.6	0.0021	1700
16a	NH_2	1	exo	0.031	<0.000043	>1000
16b	NH_2	1	endo	1.6	0.0015	1060
17a	NH_2	2	exo	0.77[e]	0.00067[e]	1100
17b	NH_2	2	endo	1.8[e]	0.0030[e]	600
5	Me	-	-	0.44	0.00096	460
6	NH_2	-	-	0.60	0.00047	1270

[a] Displacement of tritiated radioligand from rat cortical homogenates. Results are expressed as the geometric mean of the affinity constant (K_{app}) corrected for ligand occupancy by using the Cheng and Prusoff equation.[13] Unless otherwise stated each value is the geometric mean of three determinations performed on separate occasions. Each curve is typically four concentrations performed in triplicate. Variability in the determinations is ±10–15%. [b] Displacement of [^{3}H]-*N*-methylscopolamine. [c] Displacement of [^{3}H]oxotremorine-M. [d] The ratio of NMS/OXO-M,$K_{app,s}$. [e] Value derived from a single determination.

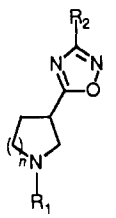
Table II. In Vitro Binding Data for Isoquinuclidine-Based Ligands (Footnotes as in Table I)


anti


syn

compd	R	stereo-chemistry	binding data: K_{app}, μM[a] [^{3}H]NMS[b]	[^{3}H]OXO-M[c]	ratio[d]
22a	H	anti	1.1	0.0032	340
22b	H	syn	5.2	0.025	210
23a	Me	anti	8.9	0.3	30
23b	Me	syn	29.0	0.95	31

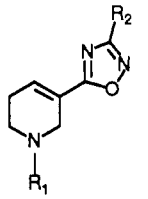
Table III. In Vitro Binding Data for Azacyclic Oxadiazoles (Footnotes as in Table I)



compd	R_1	R_2	n	binding data: K_{app}, μM[a] [^{3}H]NMS[b]	[^{3}H]OXO-M[c]	ratio[d]
28	Me	Me	1	27	0.024	1100
29	Me	NH_2	1	17	0.010	1700
30	H	NH_2	1	21	0.040	530
31	Me	Me	2	54	0.43	130
32	Me	NH_2	2	53	0.24	220
33	Me	Me	3	18	0.73	25

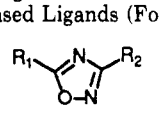
I reveals an enhancement in both affinity and predicted cortical efficacy on going from the quinuclidine methyloxadiazole **5** to the *exo*-1-azanorbornane **15a**. The endo diastereoisomer **15b** has somewhat reduced affinity for both the high and low affinity states of the receptor but has efficacy predicted to be higher than for **15a**. As pre-

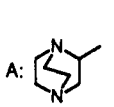
Table IV. In Vitro Binding Data for Tetrahydropyridine-Based Muscarinic Ligands (Footnotes as in Table I)

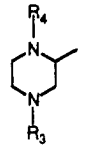


compd	R_1	R_2	binding data: K_{app}, μM[a] [^{3}H]NMS[b]	[^{3}H]OXO-M[c]	ratio[d]
4	Me	Me	2.1	0.0054	390
35	Me	NH_2	2.8	0.0026	1100
36	H	Me	2.4	0.0016	1500
37	H	NH_2	3.3	0.0017	1900

Table V. In Vitro Binding Data for Aminomethyl-, Piperazinyl-, and Diazabicyclooctyl-Based Ligands (Footnotes as in Table I)




A:


B: $R_3 = R_4 = H$
C: $R_3 = Me$, $R_4 = H$
D: $R_3 = R_4 = Me$

compd	R_1	R_2	binding data: K_{app}, μM[a] [^{3}H]-NMS[b]	[^{3}H]-OXO-M[c]	ratio[d]	pK_a
38	Me_2NCH_2	Me	>50	3.3	>15	5.6
39	$Me_3^+NCH_2$	Me	3.6	0.0014	2600	-
42	A	Me	36	0.44	82	6.0
43	A	NH_2	>50	0.13	>380	6.3
44	B	Me	>50	0.64	>78	7.1
45	B	NH_2	>50	0.45[e]	>100	7.1
46	C	Me	>50	7.6	>6.6	6.2
47	C	NH_2	>50	9.1	>5.5	6.2
48	D	NH_2	>50	>14	-	6.0

viously reported,[12] increasing the hydrogen-bonding capability of the oxadiazole ring, by replacing methyl with amino, increases binding to the agonist high affinity state of the receptor usually resulting in an enhancement in efficacy. Thus the *exo*-aminooxadiazole **16a** shows higher affinity for the receptor than **15a**. The figure of 0.04 nM for the high affinity state binding of **16a** is probably an underestimate of the compound's true affinity for the OXO-M labeled state because of significant ligand depletion in the binding assay. When the determination was repeated at lower membrane dilutions, the binding constant was reduced and this gave a ratio in excess of 1000. The 30–60-fold difference in binding between the exo isomers **15a** and **16a** and endo isomers **15b** and **16b** may be attributed to the difference in size of the binding surface presented to the active site of the receptor, in the location of the oxadiazole. The 5-membered ring of the exo face is smaller and less hindered, and consequently, sterically less demanding on the receptor, than the bulkier endo surface. Increasing the conformational flexibility and bulk of the azabicyclic ring on going to the isotropane **17a** results in a loss of affinity compared to **16a** although activity compares favorably with the quinuclidine **6**. Again the exo diastereoisomer is the most active in this series presumably due to less steric demand of the smaller ring face, in the active site of the receptor.

The methyloxadiazole **15a** produced a dose-dependent stimulation of PI turnover in rat cerebral cortex with a maximal response equal to 90% of that seen with 1 mM carbachol. This compares with 16% for the quinuclidine **5**. The aminooxadiazole **16a** stimulated cortical PI turnover with a maximum response of 170% of that seen with carbachol and is equivalent to that seen with acetylcholine (EC_{50} = 30 μM), though **16a** is 100-fold more potent (EC_{50} = 0.25 μM). The responses produced by these compounds were inhibited by the muscarinic antagonist atropine (1 μM). Thus amino oxadiazole **16a** is among the most potent and efficacious muscarinic agonists known, having affinity and efficacy greater than that of classical quaternary-ammonium-based ligands. It is to be appreciated that the potent muscarinic agonists **15a** and **16a** are racemic and that a single enantiomer may have even greater potency and efficacy. The ability of methyl oxadiazole **15a** to penetrate the CNS was measured by using an ex vivo binding assay.[14] In this assay **15a** was 40000-fold more potent[29] than arecoline (**1**) and showed >10-fold higher penetration into the CNS, over the quinuclidine amino oxadiazole **6**. The improved CNS availability of the azanorbornane oxadiazoles over the quinuclidines can be explained by reference to the log *P*s of the ligands at pH 7.4. For **5**, **6**, and **15a**, these are respectively −0.88, −1.16, and −0.59. The pK_a of **15a** is 7.95 and is less protonated at physiological pH than the quinuclidines **5** and **6**, with pK_as of 8.6 and 8.7, respectively, resulting in a higher log *P* and greater equilibration into the CNS. More detailed in vitro and in vivo evaluation of **15a** and **16a**, including a discussion of their potency and efficacy on ganglion (M_1), heart (M_2), and ileal (M_3) tissues, will be reported elsewhere.[29]

The change in muscarinic activity with change in geometry of the oxadiazole relative to the basic pharmacophore, is illustrated by the results for the isoquinuclidines given in Table II. The anti isomers of the isoquinuclidines are more active at the muscarinic receptor than the syn isomers, which have been shown to have affinity for the nicotinic site.[30] Recent observations[31] on the conformation of acetylcholine when bound to the high affinity state of the nicotinic receptor in *Torpedo californica* suggest that the ligand attains a "bent" (i.e. gauche) conformation where the acetyl methyl group is close (3.3 Å) to the choline methyl groups. The enforced geometry constraints of the isoquinuclidine ring match very closely this conformation when the oxadiazole substituent is syn (A, Figure 1). In contrast, acetylcholine has an extended conformation in solution and, it is proposed, at the muscarinic receptor, and this is represented by the anti arrangement of the isoquinuclidine (B, Figure 1). Increasing the steric bulk at the active site of the receptor by N-methylation, to give isoquinuclidines **23a** and **23b**, results in a significant loss in both binding and predicted efficacy.

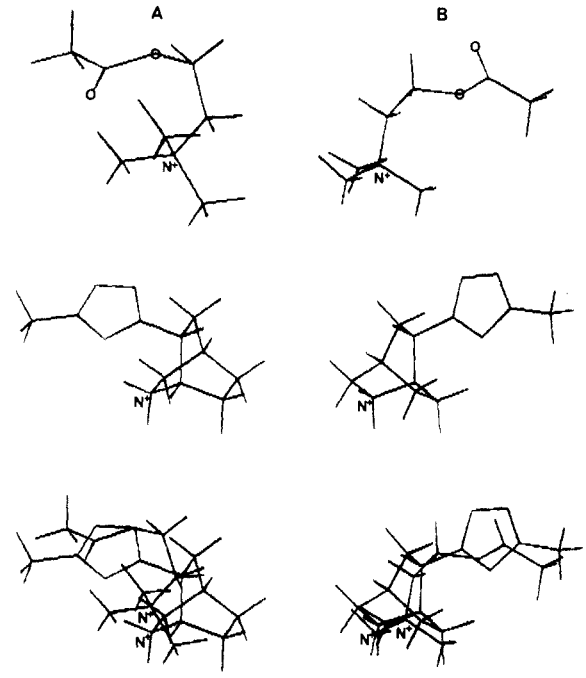


Figure 1. The putative nicotinic (A) versus muscarinic (B) pharmacophore. In A the gauche form of acetylcholine is compared with the syn diastereoisomer of the isoquinuclidine **22b**. For B, the comparison is between the extended acetylcholine conformation and the *anti*-isoquinuclidine **22a**.

The binding results for the azacyclic series are presented in Tables III and IV. A structure–activity analysis here reveals that increasing the ring size and thus the conformational flexibility in the saturated series (Table III), on going from pyrrolidine **28** to azepine **33**, reduces the predicted cortical efficacy of the ligand. All compounds in this series have reduced affinity compared with the azabicycles. Both affinity and efficacy are significantly enhanced in the tetrahydropyridine[23] series, providing a semirigid template which has good affinity for the muscarinic receptor (Table IV). Thus the tetrahydropyridine **4** has 100-fold higher affinity over the piperidine **31**. As demonstrated in the isoquinuclidine series, demethylation of the azacyclic N results in an improvement in efficacy. In most of the series studied increasing the hydrogen bonding capabilities of the oxadiazole[12] by replacing methyl with amino results in an increase in efficacy.

Finally, the effect of pK_a based on affinity of the ligand for the muscarinic receptor is illustrated by the binding

(29) Freedman, S. B.; Harley, E. A.; Patel, S.; Newberry, N. R.; Gilbert, M. J.; McKnight, A. T.; Tang, J. K.; Maguire, J. J.; Mudunkotuwa, N. T.; Baker, R.; Street, L. J; MacLeod, A. M.; Saunders, J.; Iversen, L. L. *Br. J. Pharmacol.* **1990**, in press.

(30) Freedman, S. B.; Harley, E. A.; Patel, S. Unpublished results.

(31) Behling, R. W.; Yamane, T.; Navon, G.; Jelinski, L. W. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 6721.

results presented in Table V. The tertiary amine **38** (Scheme V) with a pK_a of 5.6 is not significantly protonated at physiological pH and consequently does not bind to the receptor. As in the case of acetylcholine and 5-methylfurmethide (**50**), quaternization of **38** to give **39** results in activation of the ligand. Thus **39** has affinity and efficacy comparable to acetylcholine and has greater affinity and efficacy than the known muscarinic agonist **50** (NMS = 4.2 μM; NMS/OXO-M = 1400). The reduction in affinity on going from the azabicycle **5** to the diazabicycle **42** can also be partially explained in terms of pK_a (Table V). Introduction of nitrogen into the 4-position of quinuclidine **5** to give the diazabicycle **42** results in a reduction in pK_a from 8.6 to 6.0. As a consequence, the percentage of ligand protonated at physiological pH is reduced from 90% for **5** to 4% for **42** and, since it is the protonated form of the base which binds to the receptor, results in a loss in binding. A combination of conformational flexibility and low pK_a for the diazacycles **44–48** results in a complete loss of muscarinic activity.

It can be concluded from the results that the 1-azanorbornane ring system represents the optimum basic pharmacophore for high efficacy and affinity at the cortical muscarinic receptor and has produced some of the most potent and efficacious, CNS active muscarinic agonists known. Studies on compounds such as **15a** could help to elucidate the functional importance of cholinergic mechanisms in the brain and the results of studies of these compounds on animal models of dementia will be presented in due course.

Experimental Section

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

1-Azabicyclo[2.2.1]heptan-3-one (9). Sodium methoxide (205 g, 3.79 mol) was added to ice-bath-cooled methanol (900 mL). Glycine methyl ester hydrochloride (476 mg, 3.79 mol) was added portionwise, followed by dimethyl itaconate (500 g, 3.16 mol) and the reaction stirred at reflux for 16 h. The reaction mixture was cooled to 0 °C, the precipitate filtered, and the solvent evaporated under vacuum. The residue was taken up into 5 N HCl (550 mL) and extracted (6×) with CH_2Cl_2. The dried extracts were evaporated, and the residue was distilled (145–155 °C, 0.5 mmHg) to give 1-(carbomethoxymethyl)-3-carbomethoxypyrrolidin-5-one (360 g, 53%) as a clear ligand: ^1H NMR ($CDCl_3$) δ 2.5–3.6 (5 H, m, 2-CH_2, 3-CH, and 4-CH_2), 3.75 (6 H, s, 2 of CO_2CH_3), 4.0–4.1 (2 H, br s, $CH_2CO_2CH_3$).

A solution of **7** (86 g, 0.4 mol) in anhydrous THF (500 mL) was added over a 0.5-h period to ice-bath-cooled BH_3·THF complex (800 mL of a 1 M solution in THF, 0.8 mol). The solution was refluxed for 1 h and stirred for 16 h at 25 °C. A saturated solution of K_2CO_3 (55.2 g, 0.4 mol) was added, and after 0.75 h at reflux temperature the solid was removed by filtration and the solvent evaporated. The residue was taken up into 5 N HCl (200 mL) and washed with CH_2Cl_2 (400 mL). The aqueous was basified to pH 10 with K_2CO_3 and extracted (5×) with CH_2Cl_2. Flash chromatography of the residue isolated from the organic layer on silica gel, in ethyl acetate gave 1-(carbomethoxymethyl)-3-carbomethoxypyrrolidine (**8**) (43 g, 27%): ^1H NMR ($CDCl_3$) δ 2.0–3.2 (6 H, m, 2-CH_2, 4-CH_2, and 5-CH_2), 3.35 (2 H, s, $CH_2CO_2CH_3$), 3.45–3.55 (1 H, m, 3-CH), 3.70 (3 H, s, CH_3), 3.75 (3 H, s, CH_3).

A solution of **8** (14 g, 69.8 mmol) in anhydrous toluene (150 mL) was added over a 0.75-h period to a rapidly stirred solution of K^{t}OBu (23.5 g, 0.21 mol) in toluene (600 mL) at 140 °C. The reaction was heated under reflux for 4 h and cooled to 10 °C and concentrated HCl (200 mL) added. The organic phase was separated and extracted (3×) with hydrochloric acid. The combined aqueous was heated at 110 °C for 8 h, evaporated to half volume, basified with K_2CO_3 and extracted (5×) with CH_2Cl_2. The residue remaining after removal of solvent was taken up into ether (300 mL), filtered through a cotton wool plug, and evaporated to give the title compound (5 g, 65%): mp 25–27 °C; ^1H NMR ($CDCl_3$) δ 1.6–2.3 (2 H, m, 5-CH_2), 2.3–3.5 (7 H, m, 2-CH_2, 4-CH, 6-CH_2, and 7-CH_2). Anal. (C_6H_9NO) C, H, N.

***exo*- and *endo*-3-Carbomethoxy-1-azabicyclo[2.2.1]heptane Hydrogen Oxalates (13a and 13b).** A solution of *n*-butyllithium in hexane (1.6 M, 33 mL, 54.0 mmol) was added to a stirred solution of 2-(trimethylsilyl)-1,3-dithiane (10.5 g, 54.5 mmol) in dry THF (200 mL), at −35 °C, under N_2. After 1.5 h, a solution of **9** (5 g, 45.0 mmol) in THF (30 mL) was added at −45 °C. The solution was warmed to 22 °C, stirred for 1 h, and then quenched with H_2O (50 mL). The residue obtained after extraction (4×) with CH_2Cl_2 was chromatographed on alumina in CH_2Cl_2 to give 3-(1,3-dithian-2-ylidene)-1-azabicyclo[2.2.1]heptane (**11**) (9.6 g, 100%): mp 74–77 °C; R_f 0.15 in CH_2Cl_2 on alumina; MS *m/z* 213 (M^+), ^1H NMR ($CDCl_3$) δ 1.36–1.44 and 1.76–1.84 (1 H and 2 H, each m, 5-CH_2 and CH of dithiane), 2.08–2.20 (2 H, m, 6-CH and CH of dithiane), 2.43 (1 H, dd, J = 3 and 9 Hz, 7-CH), 2.42–2.52 (1 H, m, 6-CH), 2.60 (1 H, d, J = 9 Hz, 7-CH), 2.70–2.96 (5 H, m, 4-CH and 2 × CH_2S), 3.02 (1 H, dd, J = 3 and 18 Hz, 2-CH), 3.41 (1 H, dd, J = 3 and 18 Hz, 2-CH). Anal. ($C_{10}H_{15}NS_2$) C, H, N.

A solution of **11** (6 g, 28.2 mmol) in methanolic hydrogen chloride (300 mL) was stirred at 55 °C for 4 h. The solvent was removed under vacuum, the residue taken up into water (35 mL), basified with K_2CO_3, and extracted (5×) with CH_2Cl_2. The material isolated from the extracts was purified by chromatography on alumina in CH_2Cl_2. The less polar component was identified as the title exo ester (3.5 g, 80%) and was isolated as a pale yellow oil. The hydrogen oxalate salt: mp 123–126 °C (iPA/Et_2O); R_f 0.5 in CH_2Cl_2/MeOH (97.3) on alumina; MS *m/z* 155 (M^+) free base; ^1H NMR (D_2O) δ 1.84 (1 H, dddd, J = 2.6, 5.6, 8.2, and 12.6 Hz, 5-CH), 2.16 (1 H, dddd, J = 4.9, 4.9, 12.6, and 12.6 Hz, 5-CH), 3.07 (1 H, dd, J = 5.9 and 8.3 Hz, 3-CH), 3.17 (1 H, br d, J = 3.0 Hz, 7-CH), 3.22 (1 H, dddd, J = 2.0, 4.9, 8.2, and 12.1 Hz, 6-CH), 3.25 (1 H, br d, J = 4.9 Hz, 4-CH), 3.27 (1 H, br d, J = 2.0 Hz, 7-CH), 3.43 (1 H, ddd, J = 3.0, 8.3, and 12.2 Hz, 2-CH), 3.49 (1 H, dddd, J = 3.0, 5.6, 12.1, and 12.6 Hz, 6-CH), 3.71 (1 H, ddd, J = 3.0, 5.9, and 12.2 Hz, 2-CH), 3.75 (3 H, s, CH_3). Anal. ($C_8H_{13}NO_2 \cdot C_2H_2O_4$) C, H, N.

The minor more polar component was identified as the title endo ester **13b** (0.3 g, 7%). The hydrogen oxalate salt: mp 125–127 °C (iPA); R_f 0.6 in CH_2Cl_2/MeOH (97:3) on alumina; MS *m/z* 155 (M^+) free base; ^1H NMR (D_2O) δ 1.69–1.78 (1 H, m, 5-CH), 2.04–2.14 (1 H, m, 5-CH), 3.24–3.38 and 3.43–3.61 (8 H, m, 2-CH_2, 3-CH, 4-CH, 6-CH_2, and 7-CH_2), 3.78 (3 H, s, CH_3). Anal. ($C_8H_{13}NO_2 \cdot C_2H_2O_4$) C, H, N.

***exo*- and *endo*-3-(3-Methyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane Hydrochlorides (15a and 15b).** Acetamide oxime (4 g, 54.0 mmol) suspended in THF (150 mL) under N_2 was heated at 60 °C with NaH (1.4 g of a 80% dispersion in oil, 59.6 mmol) for 1 h in the presence of 4A molecular sieves (4 g). **13a** (3.5 g, 22.6 mmol) in THF (15 mL) was added and the reaction heated under reflux for 1.5 h. After cooling, the reaction was filtered and the solvent removed under reduced pressure. Water was added to the residue which was extracted (4×) with CH_2Cl_2. The extracts were evaporated and the residue chromatographed on alumina in CH_2Cl_2 to give the free base of the *exo*-oxadiazole **15a** (2 g, 50%) as the less polar of two components. The hydrochloride salt was prepared and recrystallized from iPA/ether: mp 214–216 °C; R_f 0.4 in CH_2Cl_2/MeOH (97:3) on alumina; MS, *m/z* 179 (M^+) free base; ^1H NMR ($CDCl_3$) δ 1.98 (1 H, dddd, J = 2.1, 5.2, 8.1, and 12.3 Hz, 5-CH), 2.32 (1 H, dddd, J = 5.0, 5.0,

12.3, and 12.3 Hz, 5-CH), 2.39 (3 H, s, CH_3), 3.25 (1 H, br d, J = 5.0 Hz, 4-CH), 3.26 (1 H, br d, J = 9.9 Hz, 7-CH), 3.41 (1 H, dddd, J = 1.8, 5.0, 8.1, and 12.0 Hz, 6-CH), 3.50 (1 H, br d, J = 9.9 Hz, 7-CH), 3.53 (1 H, dd, J = 5.5 and 8.6 Hz, 3-CH), 3.67 (1 H, dddd, J = 2.0, 5.2, 12.0, and 12.3 Hz, 6-CH), 3.77 (1 H, ddd, J = 2.9, 8.6, and 12.4 Hz, 2-CH), 3.95 (1 H, ddd, J = 2.0, 5.5, and 12.4 Hz, 2-CH). Anal. ($C_9H_{13}N_3O$·HCl) C, H, N.

The more polar component was identified as the free base of the title *endo*-oxadiazole **15b** (0.3 g, 7.5%). The hydrochloride salt was prepared and recrystallized from iPA/ether: mp 192–195 °C; R_f 0.3 in CH_2Cl_2/MeOH (97:3) on alumina; MS m/z 179 (M^+) free base; ^1H NMR ($CDCl_3$) δ 1.64 (1 H, dddd, J = 2.3, 4.5, 8.6, and 13.5 Hz, 5-CH), 2.08 (1 H, ddddd, J = 1.9, 4.1, 5.5, 12.1, and 13.5 Hz, 5-CH), 2.41 (3 H, s, CH_3), 3.24 (1 H, dddd, J = 1.9, 5.5, 8.6, and 12.0 Hz, 6-CH), 3.38 (1 H, dd, J = 4.1 and 4.1 Hz, 4-CH), 3.42 (1 H, dd, J = 2.4 and 9.3 Hz, 7-CH), 3.64 (1 H, ddd, J = 2.4, 4.2, and 11.3 Hz, 2-CH), 3.69 (1 H, dddd, J = 2.7, 5.0, 12.0, and 12.1 Hz, 6-CH), 3.79 (1 H, br d, J = 9.3 Hz, 7-CH), 4.13 (1 H, dddd, J = 1.9, 4.2, 4.1, and 11.3 Hz, 3-CH), 4.20 (1 H, ddd, J = 2.7, 11.3, and 11.3 Hz, 2-CH). Anal. ($C_9H_{13}N_3O$·HCl·0.25H_2O) C, H, N.

***exo*- and *endo*-3-(3-Amino-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane Hydrochlorides (16a and 16b).** Sodium metal (0.8 g, 33 mmol) was added to a suspension of molecular sieve (type 4A, 2 g) in absolute EtOH (25 mL) stirred under N_2. After 0.25 h at room temperature, hydroxyguanidine hemisulfate hemihydrate (2.5 g, 9.3 mmol) was added and stirring continued a further 0.5 h. **13a** (0.8 g, 4.7 mmol) in EtOH (3 mL) was added to the mixture which was then heated under reflux for 3.5 h. After removal of the molecular sieve by filtration, the filtrate was evaporated and the resulting gum partitioned between CH_2Cl_2 and water. The material isolated from the organic layer was chromatographed on silica gel in CH_2Cl_2/MeOH (2:1) to give the free base of the title *exo*-aminooxadiazole (0.27 g, 29%) as the less polar of two compounds. The hydrochloride salt was prepared: mp 230–232 °C (MeOH/ether); MS m/z 180 (M^+) free base; ^1H NMR (D_2O) δ 1.94–2.08 (1 H, m, 5-CH), 2.22–2.31 (1 H, m, 5-CH), 3.30–3.85 (8 H, m, 2-CH, 3-CH, 4-CH, 6-CH_2 and 7-CH_2), 4.8–4.9 (2 H, br s NH_2). Anal. ($C_8H_{12}N_4O$·HCl) C, H, N.

The more polar component was identified as the title *endo*-aminooxadiazole **16b** (0.06 g, 6.5%). The hydrochloride salt was prepared: mp 214–216 °C (MeOH/ether); MS m/z 180 (M^+) free base; ^1H NMR (D_2O) δ 1.65–1.74 (1 H, m, 5-CH), 2.08–2.15 (1 H, m, 5-CH), 3.36–3.57 (5 H, m, 2-CH, 4-CH, 6-CH_2 and 7-CH), 3.66–3.71 (1 H, m, 7-CH), 3.86–4.01 (1 H, m, 3-CH), 4.02–4.07 (1 H, m, 2-CH). Anal. ($C_8H_{12}N_4O$·HCl) C, H, N.

***exo*-6-Carbomethoxy-1-azabicyclo[3.2.1]octane Hydrochloride (14a).** This was prepared from 1-azabicyclo[3.2.1]octan-6-one,[21] with use of the procedure described for the preparation of **13a** from 1-azabicyclo[2.2.1]heptan-3-one, in 34% yield. Hydrochloride salt: mp 151–154 °C (iPA); MS m/z 169 (M^+) free base; ^1H NMR (D_2O) δ 1.30–1.41 (1 H, m, 4-CH), 1.54–1.72 (3 H, m, 3-CH_2 and 4-CH), 2.41–2.48 (1 H, m, 5-CH), 2.78–2.87 (5 H, m, 2-CH_2, 6-CH and 8-CH_2), 3.05–3.20 (2 H, m, 7-CH_2), 3.68 (3 H, s, CH_3). Anal. ($C_9H_{15}NO_2$·HCl·0.13H_2O) C, H, N.

***exo*- and *endo*-6-(3-Amino-1,2,4-oxadiazol-5-yl)-1-azabicyclo[3.2.1]octanes (17a and 17b).** Prepared from **14a** as for **16a** and **16b**. Chromatography on alumina in CH_2Cl_2/MeOH (19:1) gave a white solid. Recrystallization of this material from iPA/hexane gave the title *exo*-aminooxadiazole **17a** (35%): mp 156–158 °C; MS m/z 194 (M^+); ^1H NMR ($CDCl_3$) δ 1.40–1.96 (4 H, m, 3-CH_2 and 4-CH_2), 2.55 (1 H, br s, 5-CH), 2.70–3.00 (4 H, m, 2-CH_2 and 8-CH_2), 3.10–3.40 (3 H, m, 6-CH and 7-CH_2), 4.40 (2 H, br s, NH_2). Anal. ($C_9H_{14}N_4O$·0.5H_2O) C, H, N.

The mother liquors from the preceding recrystallization were concentrated, and the solid obtained was recrystallized from iPA to give the *endo*-aminooxadiazole **17b** (10%): mp 190–195 °C; MS m/z 194 (M^+); ^1H NMR ($CDCl_3$) δ 1.20–1.80 (4 H, m, 3-CH_2 and 4-CH_2), 2.60 (1 H, br s, 5-CH), 2.80–3.00 (5 H, m, 2-CH_2, 6-CH, and 8-CH_2), 3.43 (2 H, br s, 7-CH_2), 4.34 (2 H, br s, NH_2). Anal. ($C_9H_{14}N_4O$·0.5H_2O) C, H, N.

***anti*-6-Carbomethoxy-2-azabicyclo[2.2.2]octane Hydrogen Oxalate (20a).** Sodium borohydride (5.7 g, 0.15 mmol) was added portionwise to a solution of anhydrous pyridine (12.1 mL, 0.15 mmol) in methanol (100 mL) at −65 °C. The reaction was cooled to −70 °C and benzyl chloroformate (24.8 mL, 0.15 mmol) added dropwise and the reaction stirred for 1 h. The mixture was warmed slowly to 22 °C, the solvent evaporated, and the residue taken up into water (40 mL) and extracted (2×) with ether. The extracts were washed with 0.1 N HCl and water (3×), the residue remaining after evaporation was dissolved in MeCN (90 mL), and methyl acrylate (13.3 g, 0.15 mmol) and hydroquinone (1.0 g) were added. The reaction was heated at reflux for 6.5 days and the product chromatographed on alumina in CH_2Cl_2 to give the endo Diels–Alder adduct **19a** (4.82 g, 10%) as the less polar of two components: R_f 0.8 in CH_2Cl_2 on alumina; MS m/z 301 (M^+); ^1H NMR ($CDCl_3$) δ 1.80–1.90 (2 H, m, 5-CH_2), 2.81–3.38 (4 H, m, 3-CH_2, 4-CH, and 6-CH), 3.65 (3 H, s, CH_3), 5.05–5.20 (3 H, m, 1-CH and benzyl-CH_2), 6.25–6.35 and 6.35–6.48 (each 1 H, each m, 7-CH and 8-CH), 7.30–7.42 (5 H, m, C_6H_5).

The more polar component was identified as the exo Diels–Alder adduct **19b** (1.7 g, 4%): R_f 0.62 in CH_2Cl_2 on alumina; MS m/z 301 (M^+); ^1H NMR ($CDCl_3$) δ 1.50–1.60 and 2.05–2.15 (each 1 H, each m, 5-CH_2), 2.52–2.58 and 2.75–2.80 (each 1 H, each m, 4-CH and 6-CH), 3.00–3.12 and 3.36–3.48 (each 1 H, each m, 3-CH_2), 3.65 (3 H, s, CH_3), 4.93–5.10 (3 H, m, 1-CH and benzyl-CH_2), 6.41–6.50 (2 H, m, 7-CH and 8-CH), 7.25–7.38 (5 H, m, C_6H_5).

Hydrogenation of **19a** (3.56 g, 11.8 mmol) in MeOH (35 mL) over 10% Pd/C (0.35 g) at atmospheric pressure gave the title *anti*-6-carbomethoxy ester **20a** (2 g, 100%) as a clear oil. The hydrogen oxalate salt was prepared: mp 109–110 °C (CH_2Cl_2); R_f 0.54 in CH_2Cl_2/MeOH (10:1) on alumina; MS m/z 169 (M^+) free base; ^1H NMR (D_2O) δ 1.71–2.10 (7 H, m, 4-CH, 5-CH_2, 7-CH_2, and 8-CH_2), 3.15–3.28 (3 H, m, 3-CH_2 and 6-CH), 3.75 (3 H, s, CH_3), 3.81 (1 H, br s, 1-CH). Anal. ($C_9H_{15}NO_2$·1.3$C_2H_2O_4$) C, H, N.

***syn*-6-Carbomethoxy-2-azabicyclo[2.2.2]octane Hydrochloride (20b).** Hydrogenation of **19b** as described for **19a** gave the title *syn*-6-carbomethoxy ester **20b** (100%). The hydrochloride salt: mp 157–158 °C (iPA/ether); R_f 0.59 in CH_2Cl_2/MeOH (10:1) on alumina; MS m/z 169 (M^+) free base; ^1H NMR (D_2O) δ 1.60–1.85 and 1.99–3.06 (each 4 H, each m, 4-CH, 5-CH_2, 6-CH, 7-CH_2, and 8-CH_2), 3.24 (2 H, br s, 3-CH_2), 3.78 (3 H, s, CH_3), 3.75–3.90 (1 H, m, 1-CH). Anal. ($C_9H_{15}NO_2$·HCl) C, H, N.

Isoquinuclidine Oxadiazoles 22a, 22b, 23a, and 23b. The following isoquinuclidine methyloxadiazoles were prepared with use of the procedure described for **15a** and **15b**.

22a: 39%; hydrochloride salt; mp 215–216 °C (iPA/ether); R_f 0.51 in CH_2Cl_2/MeOH (10:1) on alumina; MS m/z 193 (M^+) free base; ^1H NMR (D_2O) δ 1.80–2.05 (4 H, m, 7-CH_2 and 8-CH_2), 2.10–2.30 (2 H, m, 5-CH_2), 2.25–2.40 (1 H, m, 4-CH), 2.40 (3 H, s, CH_3), 3.34 (2 H, s, 3-CH_2), 3.82–3.92 and 3.80–3.95 (each 1 H, each m, 1-CH and 6-CH). Anal. ($C_{10}H_{15}N_3O$·HCl) C, H, N.

22b: 20%; hydrochloride salt; mp 183–185 °C (iPA/ether); R_f 0.78 in CH_2Cl_2/MeOH (10:1) on alumina; MS m/z 193 (M^+) free base; ^1H NMR (D_2O) δ 1.70–2.10 and 2.10–2.40 (2 H and 4 H, each m, 5-CH_2, 7-CH_2, and 8-CH_2), 2.45 (3 H, s, CH_3), 2.32–2.50 (1 H, m, 4-CH), 3.29 (2 H, br s, 3-CH_2), 3.60–3.79 and 3.93–4.10 (each 1 H, each m, 1-CH and 6-CH). Anal. ($C_{10}H_{15}N_3O$·HCl) C, H, N.

23a: 15%; hydrochloride salt; mp 170–172 °C (iPA/ether); R_f 0.59 in EtOAc on alumina; MS m/z 207 (M^+) free base; ^1H NMR (D_2O) δ 1.68–1.92 and 2.08–2.26 (each 3 H, each m, 5-CH_2, 7-CH_2, and 8-CH_2), 2.29–2.41 (1 H, m, 4-CH), 2.41 (3 H, s, CH_3), 3.02 (3 H, s, CH_3), 3.38 (2 H, br s, 3-CH_2), 3.80–3.84 and 3.96–4.02 (each 1 H, each m, 1-CH and 6-CH). Anal. ($C_{11}H_{17}N_3O$·HCl) C, H, N.

23b: 18%; hydrochloride salt; mp 154–156 °C (iPA/ether); ^1H NMR (D_2O) δ 1.73–2.08 (4 H, m, 7-CH_2 and 8-CH_2), 2.20–2.38 (2 H, m, 5-CH_2), 2.42 (3 H, s, CH_3), 2.42–2.44 (1 H, m, 4-CH), 2.93 (3 H, s, CH_3), 3.06 and 3.59 (each 1 H, each br s, 3-CH_2), 3.77–3.82 and 3.94–3.96 (each 1 H, each m, 1-CH and 6-CH). Anal. ($C_{11}H_{17}N_3O$·HCl) C, H, N.

Pyrrolidinyl-, Piperidinyl-, Tetrahydropyridinyl-, and Hexahydroazepinyloxadiazoles (4, 28–33 and 35–37). The azacyclic esters **1**, **24–27**, and **34** were prepared by literature procedures.[24,25,26] The following oxadiazoles were prepared by using either acetamide oxime or hydroxyguanidine hemisulfate hemihydrate by using procedures previously described. **4**: 65%; mp 214–216 °C. Anal. ($C_9H_{13}N_3O$·HCl) C, H, N. **28**: 40%; mp 133–135 °C. Anal. ($C_8H_{13}N_3O$·HCl·0.25H_2O) C, H, N. **29**: 45%; mp 62–65 °C. Anal. ($C_7H_{12}N_4O$) C, H, N. **30**: 20%; mp 168–172 °C. Anal. ($C_6H_{10}N_4O$·HCl·0.4H_2O) C, H, N. **31**: 60%; mp 245–246 °C. Anal. ($C_9H_{15}N_3O$·HCl) C, H, N. **32**: 55%; mp 72–73 °C.

Anal. ($C_8H_{14}N_4O \cdot 0.4H_2O$) C, H, N. **33**: 30%; mp 144–146 °C. Anal. ($C_9H_{13}N_3O \cdot HCl$) C, H, N. **35**: 17%; mp 118–119 °C. Anal. ($C_8H_{12}N_4O \cdot 0.05H_2O$) C, H, N. **36**: 66%; mp 205–206 °C. Anal. ($C_8H_{11}N_3O \cdot HCl$) C, H, N. **37**: 16%; mp 216–218 °C. Anal. ($C_7H_{10}N_4O \cdot HCl$) C, H, N.

5-[(*N*,*N*-Dimethylamino)methyl]-3-methyl-1,2,4-oxadiazole Hydrochloride (38). *N*,*N*-Dimethylglycine sodium salt (1.14 g, 9.1 mmol) suspended in CH_2Cl_2 (30 mL) was treated with ethyl chloroformate (1.0 mL, 10.4 mmol) for 0.5 h. Acetamide oxime (1.0 g, 13.5 mmol) was added and the mixture stirred for 2 h then diluted with CH_2Cl_2 and washed with aqueous K_2CO_3. The organic layer was dried and concentrated in vacuo and the residue heated under reflux in dioxane for 2 h. The solution was concentrated and the residue treated with ethereal HCl to give the title compound as a white solid (0.56 g, 35%): mp 150–151 °C; MS m/z 142 (FAB)$^+$, $(M + H)^+$ free base; ^{1}H NMR ($CDCl_3$) δ 2.48 (3 H, s, CH_3), 3.01 (6 H, s, $N(CH_3)_2$), 4.57 (2 H, s, CH_2). Anal. ($C_6H_{11}N_3O \cdot HCl$) C, H, N.

5-[(*N*,*N*-Dimethylamino)methyl]-3-methyl-1,2,4-oxadiazole Methiodide (39). **38** (0.14 g, 1.0 mmol) in Et_2O (10 mL) was treated with MeI (0.25 mL) for 16 h. The precipitate was filtered and washed with Et_2O to give **39** (0.14 g, 49%): mp 180 °C; MS m/z 156 (FAB)$^+$, (M^+); ^{1}H NMR (D_2O) δ 2.50 (3 H, s, CH_3), 3.35 (9 H, s, $N(CH_3)_3$), 5.01 (2 H, s, CH_2). Anal. ($C_7H_{14}IN_3O \cdot 0.5H_2O$) C, H, N.

Piperazinyl- and 1,4-Diazabicyclooctyloxadiazoles 42–48. 2-Carbethoxypiperazine **40** was prepared according to literature procedure.[27] Reaction of **40** with 1,2-dibromobutane and NEt_3 gave 2-carbethoxy-1,4-diazabicyclo[2.2.2]octane (**41**) (27%).

The following piperazinyl and 1,4-diazabicyclo[2.2.2]octane oxadiazoles were prepared using the standard procedures. **42**: 40%; hydrogen oxalate; mp 156–158 °C; R_f 0.9 in CH_2Cl_2/MeOH (95:5); MS m/z 195 $(M + H)^+$ free base; ^{1}H NMR (D_2O) δ 2.43 (3 H, s, CH_3), 3.00–3.22 and 3.32–3.50 (2 H and 6 H, each m, 5-CH_2, 6-CH_2, 7-CH_2 and 8-CH_2), 3.77 (1 H, ddd, J = 1.8, 7.7, and 13.0 Hz, 3-CH), 3.84–3.92 (1 H, m, 3-CH), 4.92 (1 H, t, J = 8.2 Hz, 2-CH). Anal. ($C_9H_{14}N_4O \cdot C_2H_2O_4$) C, H, N. **43**: 25%; mp 238–240 °C. Anal. (M^+ = 195.1115, $C_8H_{13}N_3O$ requires M^+ = 195.1120). **44**: 50%; mp 74–75 °C; R_f 0.4 in CH_2Cl_2/MeOH (95:5) on alumina; MS m/z 168 (M^+); ^{1}H NMR (D_2O) δ 1.95 (2 H, brs, NH_2), 2.41 (3 H, s, CH_3), 2.81–3.11 (5 H, m, 3-CH, 5-CH_2, and 6-CH_2), 3.32–3.35 (1 H, m, 3-CH), 4.12–4.16 (1 H, m, 2-CH_2). Anal. ($C_7H_{12}N_4O$) C, H, N. **45**: 10%; mp 115–117 °C. Anal. ($C_6H_{11}N_5O$) C, H, N. **46**: 30%; mp 180–181 °C. Anal. ($C_8H_{14}N_4O \cdot 1.55C_2H_2O_4$) C, H, N. **47**: 30%; mp 102–104 °C. Anal. ($C_7H_{13}N_5O$) C, H, N. **48**: 10%; mp 172–174 °C. Anal. ($C_8H_{15}N_5O \cdot 0.2H_2O$) C, H, N.

Acknowledgment. The authors would like to thank Dr. Roger Snow for helpful discussions.

Supplementary Material Available: Tables of detailed analysis of the ^{1}H NMR spectra of methyloxadiazoles **15a** and **15b** and microanalytical data for novel compounds (3 pages). Ordering information is given on any current masthead page.

Substituted 1,3-Dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-ones as Potential Antiinflammatory Agents

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A series of analogues based on the 1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one ring system have been synthesized and shown to possess oral antiinflammatory activity in both the reverse passive Arthus reaction (RPAR) pleural cavity assay in rats and in the adjuvant-induced arthritic rat model (AAR). Several members of this series additionally exhibit an inhibitory effect on the in vivo production of prostaglandin- and leukotriene-derived products or arachidonic acid metabolism although these compounds exhibit no significant inhibitory activity against the cyclooxygenase and 5-lipoxygenase enzymes in vitro. Structure–activity relationships in this series are discussed.

The *acidic* nonsteroidal antiinflammatory drugs (NSAID's) are well-known for thier antiinflammatory, analgesic, and antipyretic properties. The antiinflammatory activity of these classical agents has been attributed to inhibition of the production of inflammatory prostaglandin products arising from metabolism of arachidonic acid via the cyclooxygenase (CO) dependent pathway.[1] Despite the significant antiinflammatory potency exhibited by the NSAID's in clinical use today, these drugs tend to have limited efficacy in altering the course of diseases, such as rheumatoid arthritis, and are used only as palliative treatments.

Rheumatoid arthritis is a complex disease involving an interactive relationship between antibody (humoral) mediated and cellular-mediated mechanisms of inflammatory reactions. In addition, these inflammatory reactions can involve the synergistic interplay between a number of chemically distinct and diverse inflammatory mediators. For example, in addition to the cyclooxygenase-dependent pathway of arachidonic acid metabolism leading to the prostaglandins, arachidonic acid can also be metabolized by the 5-lipoxygenase (5-LO) dependent pathway to the proinflammatory leukotrienes, including leukotriene B_4 (LTB_4), a potent chemoattractant for neutrophils.[2] The leukotrienes possess the ability to increase capillary permeability[3] and thereby cause edema, as well as the capability to stimulate neutrophil degranulation.[4] Neutrophil degranulation in turn releases lysosomal enzymes and reactive oxygen species, such as superoxide radical anion, singlet oxygen, hydroxyl radical, and hydrogen peroxide. Consequently, an ideal antiinflammatory agent may have to exhibit some degree of nonspecificity, in the sense of being able to block more than one target enzyme, receptor, or inflammatory process, in order to elicit a disease-modifying antiinflammatory effect.

As both cyclooxygenase- and 5-lipoxygenase-dependent pathways of arachidonic acid metabolism lead to formation of putative mediators of inflammation, agents that inhibit both of these metabolic pathways, *dual inhibitors*, may offer some advantage in the treatment of inflammatory diseases over the *classical* nonsteroidal antiinflammatory drugs, which affect only the cyclooxygenase-dependent pathway of arachidonic acid metabolism. Since gastroin-

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