Tetrahydropyridyloxadiazoles: Semirigid Muscarinic Ligands

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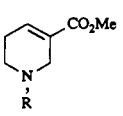
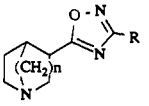
Recent studies have described novel azabicycle-based muscarinic agonists which readily penetrate into the central nervous system and are capable of displaying high efficacy at cortical sites. The current paper describes the synthesis and biochemical assessment of semirigid muscarinic ligands which were used to map the requirements of the cortical muscarinic receptor and to study the degree of conformational flexibility required to cause receptor activation. Analogues **6** and **9** provide high-efficacy muscarinic agonists at cortical sites; however, C-alkylation on the tetrahydropyridine ring resulted in more rigid analogues and showed lower predicted efficacy. Molecular mechanics calculations indicated a preference for the *E* rotameric form. This conformation was also observed in the X-ray crystal structure of ethenyloxadiazole **12**. The new compounds were tested in a biochemical assay designed to measure receptor affinity and to predict cortical efficacy.

The cholinergic hypothesis of Alzheimer's disease[1] (AD) has led to the belief that enhancement of the muscarinic cholinergic transmission, within the cerebral cortex, would be beneficial for the treatment of memory and cognitive disorders associated with the disease. A mechanism by which this may be achieved is the use of ligands which directly stimulate postsynaptic receptors usually activated by endogenous acetylcholine in normal subjects. The natural product arecoline (**1**) has been evaluated in the



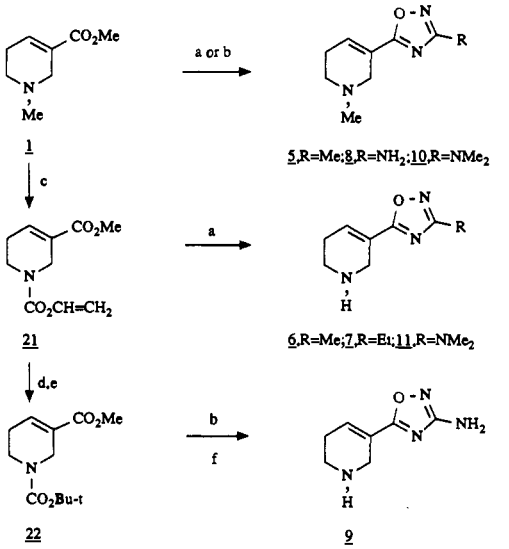
1, R=Me
2, R=H



3a, n=2, R=Me
3b, n=2, R=NH_2
3c, n=1, R=Me
3d, n=1, R=NH_2

clinic[2] but only a marginal cognitive improvement in Alzheimer's patients was observed. This may be due to the compound's short duration of action (a function of the metabolically and hydrolytically labile methyl ester moiety[3]) or its low efficacy[4] compared to those of the endogenous transmitter (acetylcholine) in the cortex.[5] In order to study the cholinergic hypothesis in the treatment of AD, we sought to develop nonquaternary muscarinic agonists related to arecoline but displaying higher cortical efficacy while readily penetrating the central nervous system. Recent work from this laboratory[6,7] has described the synthesis and biochemical evaluation of oxadiazole-based muscarinic agonists containing nonquaternary azabicyclic ring systems (**3**). These agonists display high affinity and efficacy at cortical muscarinic receptors. It has been concluded[7] that predicted efficacy, assessed by a two-stage binding assay,[8] correlated with the magnitude of the negative electrostatic potential near the oxadiazole ring nitrogen atoms. It was also observed that a combination of hydrophilicity and electron-donating properties of the oxadiazole substituent is required for optimal binding to the agonist (high-affinity) binding site. This paper describes the synthesis, conformational, and biochemical profiles of a series of semirigid tetrahydropyridyloxadiazoles used as ligands to map the muscarinic receptor. The effects on affinity and efficacy of analogues bearing alkyl substituents on the tetrahydropyridine ring and of analogues containing oxadiazole ring substituents which possess hydrogen bond donating or accepting capabilities are discussed.

Scheme I[a]



[a] Reagents: (a) NaH, THF, RC(=NOH)NH_2, 4A molecular sieves; (b) Na, EtOH, $H_2NC(=NOH)NH_2$, 4A molecular sieves; (c) $ClCO_2CH=CH_2$, $ClCH_2CH_2Cl$; (d) HCl (g), MeOH; (e) $(BOC)_2O$, NEt_3, CH_2Cl_2; (f) 2 M HCl.

We required a hydrolytically and metabolically stable bioisostere of the carboxylic ester functionality in arecoline **1**. Methyloxadiazole **5**[6] was chosen since it had been demonstrated[7,9] that this approach in both azabicyclic

† Chemistry Department.
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(1) Perry, E. K. *Br. Med. Bull.* **1986**, *42*, 63.
(2) Christie, J.; Shering, A.; Ferguson, J. *Br. J. Psychiatry* **1981**, *138*, 46.
(3) Nieschulz, O.; Schmersahl, P. *Arzneim. Forsch.* **1968**, *18*, 222.
(4) Kenakin, T. P. *Pharmacol. Rev.* **1984**, *36*, 615.
(5) Saunders, J.; Showell, G. A.; Snow, R. J.; Baker, R.; Harley, E. A.; Freedman, S. B. *J. Med. Chem.* **1988**, *31*, 486.
(6) 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.
(7) (a) Saunders, J.; Cassidy, M.; Freedman, S. B.; Harley, E. A.; Iversen, L. L.; Kneen, C. O.; MacLeod, A. M.; Merchant, K.; Snow, R. J.; Baker, R. *J. Med. Chem.* **1990**, *33*, 1128. (b) Street, L. J.; Baker, R.; Book, T.; Kneen, C. O.; MacLeod, A. M.; Merchant, K.; Showell, G. A.; Saunders, J.; Herbert, R. H.; Freedman, S. B.; Harley, E. A. *J. Med. Chem.* **1990**, *33*, 2690.
(8) Freedman, S. B.; Harley, E. A.; Iversen, L. L. *Br. J. Pharmacol.* **1988**, *93*, 437.
(9) Watjen, F.; Baker, R.; Engelstoff, M.; Herbert, R.; MacLeod, A.; Knight, A.; Merchant, K.; Moseley, J.; Saunders, J.; Swain, C. J.; Wong, E.; Springer, J. P. *J. Med. Chem.* **1989**, *32*, 2282.

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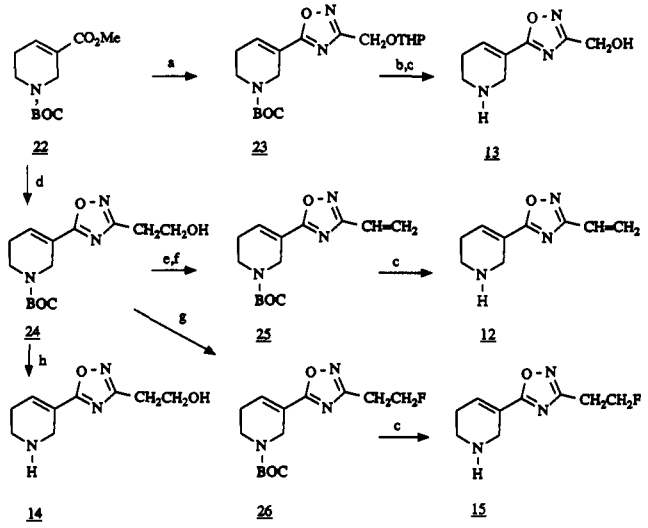
Scheme II[a]



[a] Reagents: (a) NaH, THF, $THPOCH_2C(NOH)NH_2$, 4A molecular sieves; (b) PPTS, EtOH; (c) TFA, CH_2Cl_2; (d) Na, EtOH, $HOCH_2CH_2C(NOH)NH_2$, 4A molecular sieves; (e) $MeSO_2Cl$, NEt_3, CH_2Cl_2; (f) DBU, toluene; (g) DAST, CH_2Cl_2; (h) 2 M HCl.

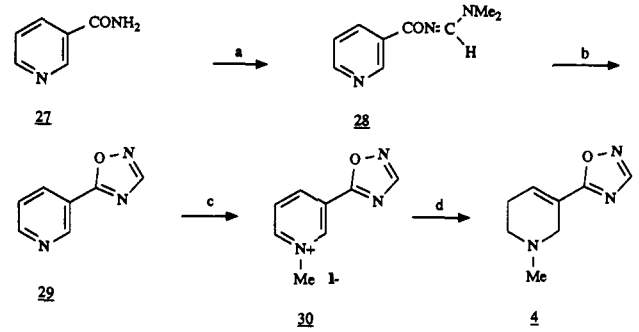
muscarinic agonists and benzodiazepine analogues had proved successful. The 1,2,4-oxadiazole group is stable[10] in aqueous medium within the full pH range at ambient temperature and would not be a substrate for the esterases that may metabolize arecoline **1**. Molecular orbital calculations[7a] revealed that the charge distribution of the protonated form of quinuclidine rather than piperidine more closely resembled that of the quaternary functionality in acetylcholine. However tetrahydropyridine analogues **4–20** provide semirigid ligands which may be used as templates in order to map closely the requirements of the muscarinic receptor for effective binding. Analogues synthesized were chosen to (a) give varying degrees of rigidity to the ligand and (b) probe the environment in the receptor at the pocket normally occupied by the acetyl methyl group of the endogenous ligand.

Chemistry

Oxadiazoles **5**, **8**, and **10** were prepared in one step from arecoline **1** by the reaction of the appropriate amide oxime or hydroxyguanidine in refluxing THF or ethanol (Scheme I). The NH analogues **6**, **7**, **9**, and **11** were synthesized from methyl 1-[(ethenyloxy)carbonyl]-1,2,5,6-tetrahydropyridine-3-carboxylate (**21**)[11] or methyl 1-[(*tert*-butyloxy)carbonyl]-1,2,5,6-tetrahydropyridine-3-carboxylate (**22**). The VOC protecting group is removed with use of the oxadiazole-forming conditions on **21** when NaH was employed as base in THF. However in the case when it was necessary to use ethanol as solvent (formation of **9**) exchange of the VOC group occurred, leading to a stable ethoxycarbonyl derivative. It was therefore necessary to switch to the BOC group (derivative **22**), which could be removed easily under mild acidic conditions after preparation of aminooxadiazole **9** (Scheme I). For the functionalized 3-substituted oxadiazole derivatives **12–15** (Scheme II) ester **22** proved to be a valuable intermediate.

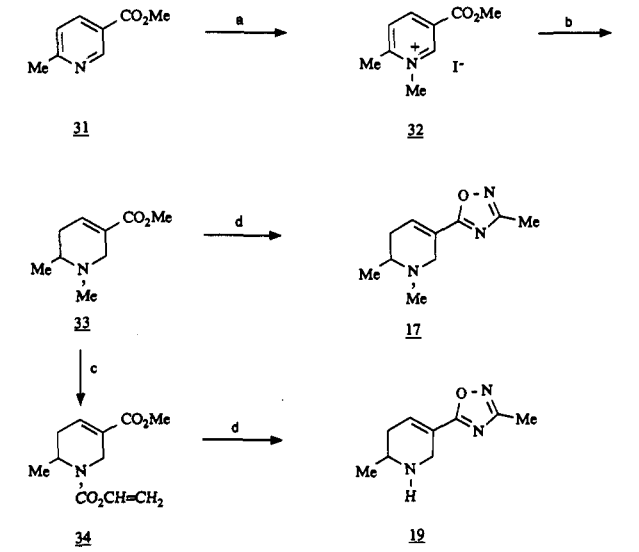
In order to obtain **13** in good yield it was necessary to react **22** with the tetrahydropyranyl-protected amide oxime. Clean deprotection of **23** required a two-stage process,

Scheme III[a]



[a] Reagents: (a) $Me_2NCH(OMe)_2$, CH_2Cl_2; (b) HOSA; (c) MeI, acetone; (d) $NaBH_4$, EtOH, H_2O.

Scheme IV[a]



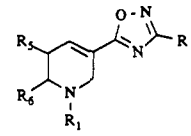
[a] Reagents: (a) MeI, acetone; (b) $NaBH_4$, EtOH, H_2O; (c) $ClCO_2CH{=}CH_2$, $ClCH_2CH_2Cl$; (d) NaH, THF, $MeC(NOH)NH_2$, 4A molecular sieves.

first removal of the THP group using pyridinium *p*-toluenesulfonate followed by BOC removal under standard TFA conditions. Synthesis of 2-hydroxyethyl derivative **14** proceeded smoothly without requiring protection of 3-hydroxypropionamide oxime to give BOC product **24**, subsequently deprotected under aqueous acidic conditions. On considering the synthesis of **12** we were concerned with the stability of the 3-ethenyl substituent. In order to keep potential side reactions to a minimum, we incorporated the ethenyl group at a later stage by modification of the 2-hydroxyethyl substituent under standard mild elimination conditions via the mesylate. The 2-fluoroethyl analogue **15** was obtained from **24** with (diethylamido)sulfur trifluoride[12] in dichloromethane at low temperature. During replacement of an OH group with fluorine, elimination or carbonium ion rearrangements may occur. Both of these side reactions are less likely to occur when using DAST and no byproducts arising via these mechanisms were observed in this case.

In general the relative inertness of 1,2,4-oxadiazoles is lost when there is a hydrogen at C_3 or C_5. With a hydrogen at C_3 stability is improved by introduction of an aryl substituent at C_5.[13] The C_3 unsubstituted analogue **4**

(10) Clapp, L. B. *Adv. Heterocycl. Chem.* **1976**, 65.
(11) Olofson, R. A.; Schnur, R. C.; Bunes, L.; Pepe, J. P. *Tetrahedron Lett.* **1977**, 1567.
(12) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.
(13) Lenaers, R.; Moussebois, C.; Eloy, F. *Helv. Chim. Acta* **1962**, *45*, 441.

Table I. In Vitro Binding Data for Tetrahydropyridyloxadiazoles Compared with Standard Muscarinic Ligands



no.	R_1	R_5	R_6	R	K_{app},[b] μM NMS binding[a]	K_{app},[b] μM Oxo-M binding[c]	ratio[d]
carbachol					24	0.0058	4100
atropine					0.001	0.00048	2.1
arecoline (1)					6.2	0.011	560
norarecoline (2)					23	0.012	1900
4	Me	H	H	H	8.9[e]	0.0077[e]	1200
5	Me	H	H	Me	2.1	0.0054	390
6	H	H	H	Me	2.3	0.0031	740
7	H	H	H	Et	4.3[e]	0.0074[e]	580
8	Me	H	H	NH_2	2.7	0.0026	1000
9	H	H	H	NH_2	3.4	0.0017	2000
10	Me	H	H	NMe_2	2.5	0.12	21
11	H	H	H	NMe_2	3.5	0.082	43
12	H	H	H	$CH{=}CH_2$	2.5	0.035	73
13	H	H	H	CH_2OH	34	0.11	300
14	H	H	H	CH_2CH_2OH	13	0.23	57
15	H	H	H	CH_2CH_2F	5.7	0.021	270
16	Me	Me	H	Me	15	0.87	17
17	Me	H	Me	Me	2.4	0.061	40
18	H	Me	H	Me	2.7	0.037	73
19	H	H	Me	Me	16	0.12	130
20	H	Et	H	Me	25	0.97	26

[a] Displacement of [^{3}H]-*N*-methylscopolamine in rat cortex. [b] The apparent affinity constant corrected for radioligand occupancy and expressed in micromolar concentrations. The value is the geometric mean of at least three independent experiments performed on separate occasions, the standard error in the geometric mean was not greater than ±12%. [c] Displacement of [^{3}H]oxotremorine-M in rat cortex. [d] The ratio of NMS/Oxo-M K_{app}'s. [e] Value derived from a single determination.

(Scheme III) was available by a route originally devised to produce related thiadiazoles,[14] and upon isolation **4** was found to be a stable entity suitable for biological evaluation. Reaction of nicotinamide (**27**) with dimethylformamide dimethyl acetal followed by cyclization of **28** with hydroxylamine-*O*-sulfonic acid provided the stable pyridyloxadiazole **29**. The target compound **4** was obtained from **29** under standard conditions via the reduction of quaternary salt **30**. The quaternary pyridyl route was also chosen for the 6-methyl derivatives **17** and **19** (Scheme IV), originating from commercially available methyl 6-methylnicotinate (**31**). Clean demethylation was achieved at the ester stage to yield the VOC-protected tetrahydropyridine **34**, which afforded the NH analogue **19** directly with the oxadiazole-forming conditions as described above. The 5-methyl series **16** and **18** was obtained by building the tetrahydropyridine ring using a Dieckmann cyclization (Scheme V). Methyl methacrylate (**35**) provided the starting point by reaction with benzylamine followed by a second Michael addition with methyl acrylate. In order to overcome stability problems[15] associated with **36**, we protected the nitrogen as its BOC derivative **37**. Dieckmann cyclization proceeded smoothly to keto ester **38**, which existed as both enol and keto forms by NMR and IR. The key unsaturated ester intermediate **39** was obtained by borohydride reduction of the ketone followed by subsequent mesylation and elimination. Formation of the oxadiazole by standard conditions then removal of the BOC protecting group gave **18**, which upon alkylation with bromomethane yielded **16**. Similar chemistry provided 5-ethyl analogue **20**.

Results and Discussion

Although molecular orbital calculations have revealed that the charge distribution of a protonated quinuclidine more closely resembled that of a quaternary ammonium moiety than did a protonated piperidine ring, the series of muscarinic ligands recently described[7] are relatively flexible analogues.

Free rotation can occur around the quinuclidine–oxadiazole bond, giving rise to great difficulties in elucidating the active conformation of the molecules and shape of the receptor binding pocket. In order to map more specifically structural requirements of the muscarinic receptor for agonists, we synthesized this series of semirigid ligands.

Fully rigid ligands may not have the required flexibility to evoke the conformational change of the receptor protein necessary for a full agonist response, since conformational changes of both the agonist and receptor may be required.[5,16] In order to introduce some ligand flexibility, the tetrahydropyridyloxadiazoles provided an ideal template (Table I). We were interested in ascertaining "goodness of fit" to the receptor and therefore compared observed binding energies ($\Delta G_{OBS} = -1.44 \log K_{app}$ at physiological temperature) with calculated average binding energies[17] (Table II). The average binding energies for 10 common functional groups were obtained with empirical binding constants and the structural information of 200 biologically active compounds.[17] Average binding energies for the tetrahydropyridyloxadiazoles were calculated by using the equation $\Delta G = T\Delta S_{rt} + n_{dof}E_{dof} + \sum n_x E_x$ (where $T\Delta S_{rt}$ is the overall rotational and translational loss of entropy of the receptor bound molecule, n_{dof} is the number

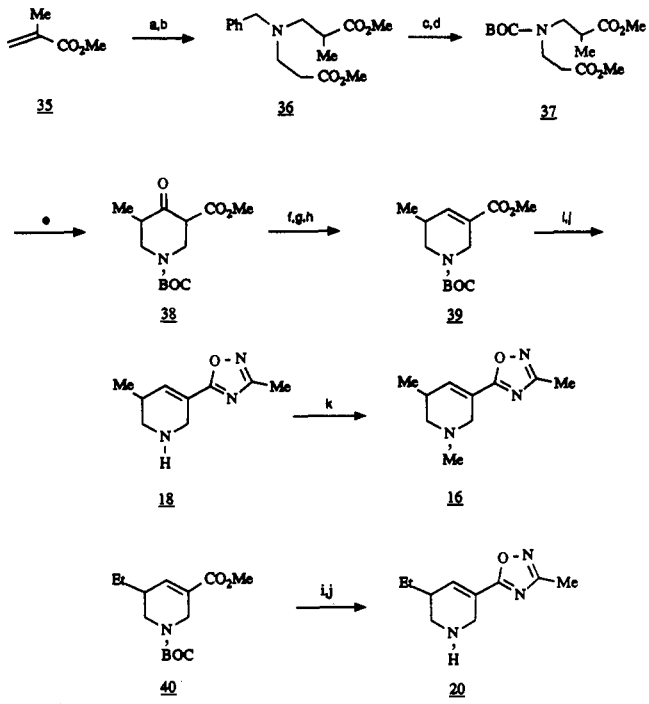
(14) MacLeod, A. M.; Baker, R.; Freedman, S. B.; Harley, E. A.; Merchant, K. J.; Roe, M.; Saunders, J. *J. Med. Chem.* **1990**, *33*, 2052.

(15) Harper, N. J.; Beckett, A. H.; Balon, A. D. J. *J. Chem. Soc.* **1960**, 2704.

(16) Burgen, A. S. V. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1981**, *40*, 2723.

(17) Andrews, P. R.; Craik, D. J.; Martin, J. L. *J. Med. Chem.* **1984**, *27*, 1648.

Scheme V[a]



[a] **Reagents:** (a) $PhCH_2NH_2$, MeOH; (b) $CH_2{=}CHCO_2Me$; (c) H_2, 20% $Pd(OH)_2$ on C, MeOH, 5 M HCl; (d) $(BOC)_2O$, NEt_3, CH_2Cl_2; (e) KOtBu, toluene; (f) $NaBH_4$, MeOH; (g) $MeSO_2Cl$, NEt_3, CH_2Cl_2; (h) DBU, CH_2Cl_2; (i) NaH, THF, $MeC(NOH)NH_2$; 4A molecular sieves; (j) TFA, CH_2Cl_2; (k) NaH, MeBr, THF.

Table II. Binding Energies and pK_a Values for Tetrahydropyridyloxadiazoles

no.	ΔG_{NMS}[a]	$\Delta G_{Oxo\text{-}M}$[b]	ΔG_{av}[c]	pK_a[d]
4	7.1	11.4	7.0	*e*
5	7.9	11.9	7.8	7.16
6	7.9	11.9	7.0	8.24
7	7.5	11.4	7.1	*e*
8	7.8	12.0	8.2	*e*
9	7.6	12.3	7.4	8.25
10	7.8	9.7	9.1	7.24
11	7.6	9.9	8.3	8.58
12	7.8	10.4	7.6	8.23
13	6.3	9.7	6.7	*e*
14	6.8	9.3	6.8	*e*
15	7.3	10.8	7.0	8.29
16	6.8	8.5	8.6	7.34
17	7.9	10.1	8.6	7.35
18	7.8	10.4	7.8	8.17
19	6.7	9.7	7.8	8.20
20	6.4	8.4	7.9	*e*

[a] Calculated from NMS binding data using the relationship $\Delta G = -1.4 \log K_{app}$. [b] Calculated from Oxo-M binding data. [c] Calculated from the equation $\Delta G = T\Delta S_{rt} + n_{dof}E_{dof} + \sum n_x E_x$ where $T\Delta S_{rt}$ is the overall rotational and translational loss of entropy of the receptor bound molecule, n_{dof} is the number of internal (conformational) degrees of freedom in the molecule, E_{dof} is the correspondng energy associated with the entropy change on the loss of each n, and E_x is the intrinsic binding energy associated with each of the n_x functional groups, x. [d] Measured pK_a values, mean values of two or more independent measurements. [e] Not measured.

of internal (conformational) degrees of freedom in the molecule, E_{dof} is the energy associated with the entropy change on loss of each n, and E_x is the intrinsic binding energy associated with each of the n_x functional groups, x). Oxadiazole **5** showed improved affinity over arecoline (**1**) but marginally lower cortical predicted efficacy (as shown by the NMS/Oxo-M ratio[8]). Des-*N*-methyl analogue **6** displayed identical NMS affinity but higher efficacy as a result of improved affinity to the high-affinity state (Oxo-M binding) and appeared well matched to the receptor ($\Delta G_{Oxo\text{-}M} \gg \Delta G_{NMS} > \Delta G_{AV}$). As observed with the quinuclidine series[7] small electron-donating substituents enhance the hydrogen bond acceptor properties of the oxadiazole ring, giving rise to **9** being the compound retaining the highest efficacy. In general the NH analogues had greater predicted efficacy than the corresponding *N*-methyl analogues (**6** vs **5**, **9** vs **8**, **19** vs **17**, **18** vs **16**). Unsubstituted oxadiazole **4**[14] surprised us by retaining similar predicted efficacy to that of **6**. However a slight reduction in binding to both affinity states of the receptor was observed, suggesting **4** was not as efficient in utilizing all its functional groups in binding (ΔG_{NMS} (**6**) > ΔG_{NMS} (**4**) $\approx \Delta G_{AV}$). Vinyloxadiazole **12** was chosen to introduce further rigidity to the system and as expected this analogue had lower efficacy (NMS/Oxo-M = 73) than the saturated alkyl analogues **6** and **7**.

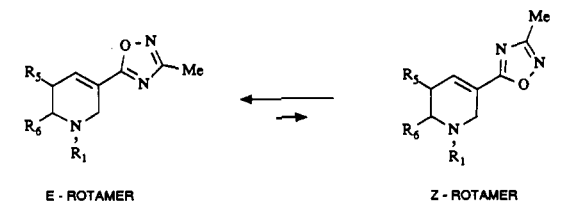


Figure 1. Rotameric forms of tetrahydropyridyloxadiazoles.

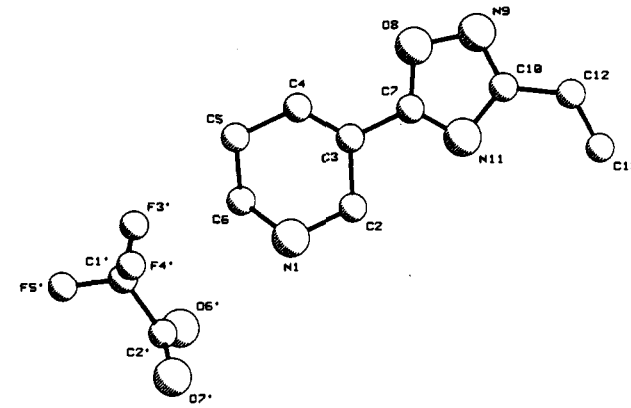


Figure 2. Computer-generated drawing of **12** derived from X-ray coordinates.

In order to probe further into the pocket of the receptor normally occupied by the acetyl methyl group of acetylcholine, we synthesized various analogues to study the H bond donating/acceptor characteristics of this site. The presence of hydroxyl groups (**13**, **14**) as hydrogen-bond donors reduced affinity for both states of the receptor by approximately 10-fold, whereas fluoroethyl analogue **15** (designed as an H-bond acceptor) retained a more acceptable level of affinity and predicted efficacy (**15** vs **7**). It is reasonable to assume from this data that a hydrogen bond donating group in this area of the receptor is not acceptable unless concomitant secondary lipophilic binding is achieved (e.g., quinuclidinyl benzilate).

Two rotamers (*E* and *Z*, Figure 1) are possible for these semirigid compounds. Molecular mechanics calculations[18] on the protonated forms for all analogues revealed a preference for the *E* rotamer by ~2.3 kcal/mol. The X-ray crystal structure for **12** as the trifluoroacetate salt (Figure

(18) OPTIMOL, a molecular mechanics based procedure (T. Halgren, MSD Rahway, unpublished) within the Merck Molecular Modelling System. OPTIMOL is based on MM2 (Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. See supplementary material for further details).

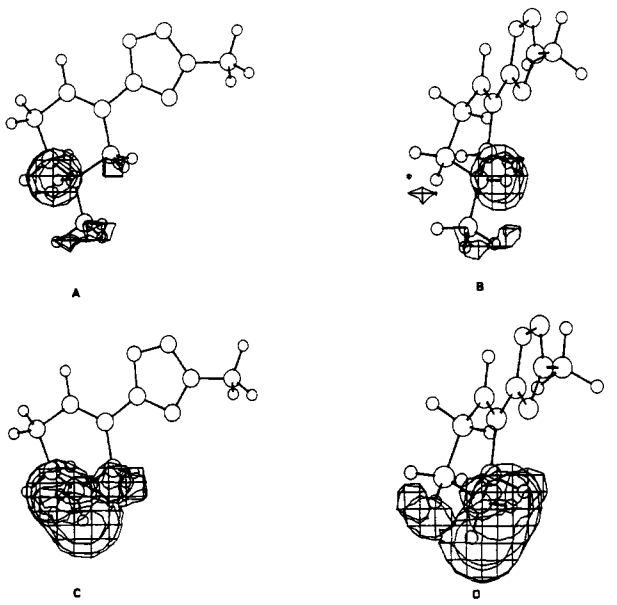


Figure 3. (A) Positive electrostatic potential (>165 kcal·mol^{-1}) around the protonated nitrogen of compound **5**, (B) rotated by 90°, (C) positive electrostatic potential around the protonated nitrogen of compound **6**, (D) rotated by 90°.

2) was determined and showed the preference for the *E* rotamer in the crystal lattice. The crystal structure revealed that atoms C_3, C_7, O_8, N_9, C_{10}, N_{11}, C_{12}, and C_{13} are coplanar as are atoms C_2, C_3, C_4, C_5 and C_7, with an angle of 10.9° between these two planes. We submitted the trifluoroacetate salt for the X-ray determination as we required information on the carboxylic acid–NH^+ interaction, since it is likely that the protonated nitrogen would interact with an aspartate residue within the muscarinic receptor.[7] The crystal structure of **12** showed that one of the oxygen atoms of the carboxylic acid group forms a hydrogen bond at N_1 with –O···H–N = 2.81 Å and θ = 160.5°. Acetylcholine itself cannot hydrogen bond but would form an electrostatic interaction with the aspartate. Quantum mechanical calculations[19] on **5**, **6**, and **16–19** revealed differences between the secondary and tertiary amines. Figure 3 shows the area of positive electrostatic potential around the protonated ring nitrogen for **5** and **6**. The secondary amines (**6**, **18**, **19**) have this charge delocalized over a wide area including the hydrogens of the protonated nitrogen, C_2, and C_6. In contrast the tertiary amines (**5**, **16**, **17**) have more distinct areas of positive charge around the *N*-methyl group, N_1, C_2, and C_6. Methylation on C_5 or C_6 of the tetrahydropyridine ring had no substantial effect on this charge distribution. The use of ab initio molecular orbital methods to study the possible binding modes of muscarinic ligands have previously dealt with tertiary amines within a caged ring system or a quaternary species.[7a,20]

The nitrogen of the tetrahydropyridine ring can flip from one conformer to another, therefore alkylation on the C_5 or C_6 positions results in decreased mobility of the ring (supported by molecular mechanics calculations[18,21]). The biochemical results for these analogues reveal a reduction in predicted cortical efficacy compared to that of **6** and in three cases (**16**, **19**, **20**) reduced NMS affinity. Comparison of measured binding energies with calculated average binding energies (Table II) indicate that the C-alkylated analogues are not fully utilizing available functional groups in productive interactions with the receptor ($\Delta G_{OBS} < \Delta G_{AV}$). It was observed that the occurrence of C-alkylation had no effect on the pK_a of the core structure (Table II). The secondary amines have a pK_a of approximately 1 unit higher than the tertiary amines. Since all of these analogues will be sufficiently protonated at physiological pH, this difference in pK_a does not appear to be an important factor in the affinity and efficacy relationship within the series.

In conclusion, ligands **6** and **9** represent high-efficacy muscarinic agonists at cortical sites and in addition were also capable of stimulating phosphatidylinositol (PI) hydrolysis in vitro.[22] These analogues are well matched to the receptor with respect to the calculated average binding energies for the series. An increase in rigidity to the system resulted in decreased cortical efficacy, providing weak partial agonists. This series of compounds will provide useful tools for future biochemical and pharmacological evaluation of muscarinic receptor subtypes.

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 or at 250 MHz on a Bruker AC250 instrument, mass spectra with a VG 70-250 mass spectrometer, and infrared spectra on a Perkin-Elmer 782 IR spectrometer. GC was performed on a 12-m SE30 capillary column with a Perkin-Elmer gas chromatograph (8320). Organic solvents were purified when necessary by the methods described by Perrin et al. (Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *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 anhydrous sodium sulfate and evaporated on a Büchi rotary evaporator at reduced pressure. Thin-layer chromatography was carried out using silica (Merck Art 5719) or alumina plates (Merck Art 5550). Column chromatography was carried out using silica (Merck Art 7734) or alumina (Merck Art 1077, activity Brockman Grade III). Melting points were determined on a Buchi 512 capillary apparatus and are uncorrected. pK_a's were determined with a radiometer autotitration system (PHM84 Research pH meter, ABU80 autoburette, and Hewlett-Packard 85B). log *P*'s were determined at pH 10.6 using 1-octanol and aqueous buffer by the shake flask method.

3-[3-(Dimethylamino)-1,2,4-oxadiazol-5-yl]-1-methyl-1,2,5,6-tetrahydropyridine Hydrochloride (10). *N,N*-Dimethylhydroxyguanidine hydrochloride (3.63 g, 26 mmol) was suspended in dry THF (100 mL) under N_2 and stirred at 50 °C with NaH (2.27 g of a 55% dispersion in oil, 52 mmol) for 1 h in the presence of 4A molecular sieves (20 g). **1** (2.00 g, 13 mmol) in dry THF (30 mL) was added and the reaction heated under reflux for 2 h. After cooling, H_2O (50 mL) and CH_2Cl_2 (130 mL) were added, the mixture was filtered, and the organic layer was separated. The aqueous was reextracted with CH_2Cl_2 (100 mL), and the combined organics were dried then evaporated to give an oil which was purified by column chromatography on silica using CH_2Cl_2/MeOH (25:1). **10** free base was isolated as a pale yellow oil (1.50 g, 55%). The hydrochloride salt had mp 202–203 °C (*i*PA/MeOH); R_f 0.50 in CH_2Cl_2/MeOH (9:1) on silica plates; MS (CI^+) *m/z* 209 $(M + H)^+$ of free base; ^1H NMR (D_2O) δ 2.78–2.86 (2 H, m, 5-CH_2), 3.00 (6 H, s, $N(CH_3)_2$), 3.07 (3 H, s, NCH_3), 3.40–3.64 (2 H, m, 6-CH_2), 4.08–4.36 (2 H, m, 2-CH_2), 7.22–7.26 (1 H, m, 4-CH). Anal. ($C_{10}H_{16}N_4O$·HCl) C, H, N.

With the procedure above, but using acetamide oxime, the following was prepared.

5: 65%; mp 214–216 °C dec (iPA/Et_2O). Anal. ($C_9H_{13}N_3O$·HCl) C, H, N.

(19) Gaussian 80 program (QCPE 446) by Chandra Singh, U. and Kollman, P. Molecules displayed and electrostatic potentials calculated with CHEMX, developed and distributed by Chemical Design Ltd., Oxford, U.K.

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3-(3-Amino-1,2,4-oxadiazol-5-yl)-1-methyl-1,2,5,6-tetrahydropyridine (8). Sodium (2.20 g, 95 mmol) was added to a stirred suspension of hydroxyguanidine hemisulfate hemihydrate (6.65 g, 50 mmol) and 4A molecular sieves (10 g) in absolute EtOH (50 mL) under N_2. 1·HBr (2.30 g, 10 mmol) was added and after 0.5 h at 20 °C the reaction was heated to reflux for a further 0.5 h. The mixture was cooled then neutralized with AcOH (5.7 g), filtered, and evaporated. The residue was dissolved in H_2O saturated with K_2CO_3. Exhaustive extraction with CH_2Cl_2 followed by evaporation of the combined organic extracts gave the crude product which was purified by column chromatography on alumina using EtOAc then EtOAc/MeOH (99:1). Evaporation of the single-component fractions afforded **8** (310 mg, 17%): mp 118–119 °C; MS m/z 180 (M^+); ^1H NMR ($CDCl_3$) δ 2.45 (5 H, br s, 5-CH_2 and NCH_3), 2.58 (2 H, dd, J = 5.7 Hz, 6-CH_2), 3.30–3.32 (2 H, m, 2-CH_2), 4.39 (2 H, br s, NH_2), 6.99–7.01 (1 H, m, 4-CH). Anal. ($C_8H_{12}N_4O \cdot 0.05H_2O$) C, H, N.

1-Methyl-3-(1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine Hydrochloride (4). **27** (10.0 g, 82 mmol) and dimethylformamide dimethyl acetal (20 mL) were stirred in CH_2Cl_2 (200 mL) overnight. Evaporation of the solvent gave a white solid which was dissolved in MeOH (150 mL). Hydroxylamine-*O*-sulfonic acid (14 g, 124 mmol) and pyridine (12.5 mL, 156 mmol) were added, then the mixture was left to stir at room temperature overnight. The mixture was evaporated and the crude product treated with aqueous K_2CO_3 solution. The mixture was extracted with CH_2Cl_2 (3 times), and the combined organics were dried then evaporated. Two recrystallizations from Et_2O/*n*-hexane yielded **29** as a colorless solid (1.55 g, 13%). **29** was stirred in acetone (12 mL) with MeI (1 mL) for 2 days, diluted with Et_2O, then filtered to obtain **30** as a yellow solid (2.15 g). **30** (2.05 g) was treated with $NaBH_4$ (500 mg, 13.2 mmol) in EtOH (20 mL) and H_2O (20 mL) with ice-bath cooling for 3 h. The mixture was extracted with Et_2O (three times), and the combined organics were evaporated to dryness. After treatment of the crude product with charcoal in CH_2Cl_2 followed by chromatography on alumina, the free base was treated with ethereal HCl to give **4** as a colorless solid of mp 146–147 °C dec; R_f 0.50 in Et_2O/*n*-hexane (3:2) on alumina plates; MS (CI^+) m/z 166 ($M + H)^+$ of free base; ^1H NMR (D_2O) δ 2.80–2.88 (2 H, m, 5-CH_2), 3.08 (3 H, s, NCH_3), 3.44–3.60 (2 H, m, 6-CH_2), 4.18–4.32 (2 H, m, 2-CH_2), 7.36–7.40 (1 H, m, 4-CH), 8.72 (1 H, s, oxadiazole-H). Anal. ($C_8H_{11}N_3O \cdot HCl$) C, H, N.

3-(3-Methyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine Hydrochloride (6). Acetamide oxime (6.95 g, 94 mmol) was dissolved in dry THF (250 mL) under N_2 and stirred at 50 °C with NaH (4.30 g, 98 mmol, of a 55% dispersion in oil) for 1 h in the presence of 4A molecular sieves (80 g). **21**[11] (10.0 g, 47 mmol) in dry THF (50 mL) was added and the reaction heated under reflux for 2 h. After cooling, H_2O (200 mL) and CH_2Cl_2 (300 mL) were added, the mixture was filtered, and the organic layer was separated. The aqueous layer was reextracted with CH_2Cl_2 (300 mL), and the combined organics were dried then evaporated to give an oil (7.90 g) which was purified by column chromatography on alumina using CH_2Cl_2/MeOH (70:1). **6** free base was isolated as a pale yellow oil (5.20 g, 66%). The hydrochloride salt had mp 205–206 °C (*i*PA/Et_2O); R_f 0.65 in CH_2Cl_2/MeOH (9:1) on alumina plates; MS (CI^+) m/z 166 (M + H)$^+$ of free base; ^1H NMR (D_2O) δ 2.42 (3 H, s, CH_3), 2.72–2.78 (2 H, m, 5-CH_2), 3.47 (2 H, dd, J = 6 Hz, 6-CH_2), 4.15 (2 H, dd, J = 2 Hz, 2-CH_2), 7.30–7.34 (1 H, m, 4-CH). Anal. ($C_8H_{11}N_3O \cdot HCl$) C, H, N.

With the procedure above, but using propionamide oxime and *N,N*-dimethylhydroxyguanidine, respectively, the following were prepared.

7: 44%; mp 115–116 °C (*i*PA/Et_2O). Anal. ($C_9H_{13}N_3O \cdot HCl$) C, H, N.

11: 68%; mp 200–201 °C (*i*PA). Anal. ($C_9H_{14}N_4O \cdot HCl$) C, H, N.

Methyl 1-[(*tert*-Butyloxy)carbonyl]-1,2,5,6-tetrahydropyridine-3-carboxylate (22). **21**[11] (69.70 g, 0.33 mol) was dissolved in saturated methanolic hydrogen chloride (600 mL) and after 16 h was evaporated to dryness. The resulting solid was dried in vacuo over P_2O_5 then suspended in CH_2Cl_2 (1 L). NEt_3 (92 mL, 0.66 mol) was added followed by di-*tert*-butyl dicarbonate (96.0 g, 0.44 mol) over 15 min. After stirring for 6 h at room temperature the mixture was filtered and washed with 0.5 M HCl (2 × 500 mL), H_2O (2 × 500 mL), and finally saturated $NaHCO_3$ solution (1 × 500 mL). The organic layer was dried then evaporated to give an orange oil which was distilled under vacuum. **22** was obtained as a pale yellow oil (65.2 g, 82%): bp 134–136 °C (1.5 mmHg); R_f 0.75 in EtOAc on silica plates; MS m/z 240 $(M - H)^+$; ^1H NMR ($CDCl_3$) δ 1.48 (9 H, s, C_4H_9), 2.26–2.36 (2 H, m, 5-CH_2), 3.48 (2 H, dd, J = 6 Hz, 6-CH_2), 3.76 (3 H, s, OCH_3), 4.08–4.14 (2 H, m, 2-CH_2), 7.02–7.10 (1 H, m, 4-CH). Anal. ($C_{12}H_{19}NO_4$) C, H, N.

1-[(*tert*-Butyloxy)carbonyl]-3-(3-amino-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine (41). Sodium (9.70 g, 0.42 mol) was added in portions to a stirred suspension of hydroxyguanidine hemisulfate hemihydrate (55.90 g, 0.42 mol) and 4A molecular sieves (50 g) in absolute EtOH (250 mL) under N_2. **22** (10.0 g, 0.041 mol) in absolute EtOH (50 mL) was added and the mixture heated to reflux for 4 h. After cooling, the mixture was filtered and then evaporated to dryness. The residue was partitioned between H_2O (200 mL) and CH_2Cl_2 (200 mL). The organic layer was separated and the aqueous layer reextracted with CH_2Cl_2 (2 × 200 mL). The combined organics were dried then evaporated, and the crude product was purified by column chromatography on silica using EtOAc/petroleum ether (1:2). **41** was isolated as a hygroscopic colorless solid (1.72 g, 16%): mp 126–127 °C; R_f 0.38 in EtOAc/petroleum ether (1:1) on silica plates; MS m/z 266 (M^+); ^1H NMR ($CDCl_3$) δ 1.49 (9 H, s, C_4H_9), 2.36–2.44 (2 H, m, 5-CH_2), 3.56 (2 H, dd, J = 6 Hz, 6-CH_2), 4.25–4.30 (2 H, m, 2-CH_2), 4.40 (2 H, br resonance, NH_2), 7.02–7.12 (1 H, m, 4-CH). Anal. ($C_{12}H_{18}N_4O_3 \cdot 0.25H_2O$) C, H, N: calcd, 20.69; found, 20.10.

3-(3-Amino-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine Hydrochloride (9). A suspension of **41** (0.65 g, 2.4 mmol) was stirred in 2 M HCl (50 mL) for 16 h. The resulting solution was washed with CH_2Cl_2 (50 mL); the aqueous layer was separated and evaporated to yield a colorless solid which was recrystallized twice from *i*PA/MeOH (3:1) to afford pure **9** (0.34 g, 70%): mp 216–218 °C; R_f 0.50 in CH_2Cl_2/MeOH (5:1) on alumina plates; MS (CI^+) m/z 167 $(M + H)^+$ of free base; ^1H NMR (D_2O) δ 2.68–2.76 (2 H, m, 5-CH_2), 3.45 (2 H, dd, J = 6 Hz, 6-CH_2), 4.06–4.14 (2 H, m, 2-CH_2), 7.22–7.26 (1 H, m, 4-CH). Anal. ($C_7H_{10}N_4O \cdot HCl$) C, H, N: calcd, 27.65; found, 26.89.

3-Hydroxypropionamide Oxime (42). Hydroxylamine hydrochloride (43.8 g, 0.63 mol) in MeOH (200 mL) was added to a stirred solution of sodium (13.8 g, 0.60 mol) in MeOH (400 mL) under nitrogen. After 10 min 3-hydroxypropionitrile (58.1 mL, 0.57 mol) was added and the mixture stirred for 3 days. The mixture was filtered and evaporated to approximately 200 mL. Addition of *i*PA and cooling promoted precipitation and the solid obtained was recrystallized from a minimum volume of MeOH to give **42** as a colorless solid (13.1 g, 22%): mp 68 °C; ^1H NMR (DMSO-d_6) δ 2.12 (2 H, t, J = 7 Hz, CH_2), 3.52–3.57 (2 H, m, CH_2O), 4.53 (1 H, m, OH), 5.31 (2 H, s, NH_2), 8.70 (1 H, s, OH); IR ν_{max} (Nujol) 3450, 3350 (NH, OH), 1670 cm^{-1} (C=N). Anal. ($C_3H_8N_2O_2$) C, H, N: calcd, 26.91; found, 26.25.

1-[(*tert*-Butyloxy)carbonyl]-3-[3-(2-hydroxyethyl)-1,2,4-oxadiazol-5-yl]-1,2,5,6-tetrahydropyridine (24). **24** was obtained as a colorless oil (8.00 g, 45%) from **42** (15.90 g, 0.15 mol), **22** (14.48 g, 0.06 mol), and sodium (3.45 g, 0.15 mol) as described for the synthesis of **41**. R_f 0.58 in EtOAc on silica plates; MS m/z 296 $(M + H)^+$; HRMS $(M + H)^+$ 296.1607, $C_{14}H_{22}N_3O_4$ requires 296.1610; ^1H NMR ($CDCl_3$) δ 1.49 (9 H, s, C_4H_9), 2.38–2.44 (2 H, m, 5-CH_2), 2.50–2.62 (1 H, m, OH), 3.00 (2 H, t, J = 6 Hz, CH_2CH_2OH), 3.58 (2 H, dd, J = 6 Hz, 6-CH_2), 4.01 (2 H, br t, J = 6 Hz, CH_2OH), 4.32–4.36 (2 H, m, 2-CH_2), 7.14–7.20 (1 H, m, 4-CH); IR ν_{max} (film) 3600–3200 (OH), 1700 (C=O), 1660 cm^{-1} (C=N). Anal. ($C_{14}H_{21}N_3O_4$) C, H, N.

1-[(*tert*-Butyloxy)carbonyl]-3-[3-[2-[(methylsulfonyl)oxy]ethyl]-1,2,4-oxadiazol-5-yl]-1,2,5,6-tetrahydropyridine (43). NEt_3 (3.33 mL, 24 mmol) was added to a stirred, cooled (4 °C) solution of **24** (6.76 g, 23 mmol) in dry CH_2Cl_2 (50 mL). Methanesulfonyl chloride (1.8 mL, 23 mmol) was added dropwise and the mixture stirred at room temperature for 4 h. H_2O (50 mL) was added and the organic layer separated and washed with H_2O (50 mL), then dried and evaporated to dryness. The crude product was purified by column chromatography on silica using CH_2Cl_2/MeOH (200:1) to afford pure **43** as a pale yellow oil (8.00 g, 93%): R_f 0.60 in EtOAc on silica plates; MS (CI^+) m/z 318 (McLafferty rearrangement ion); ^1H NMR ($CDCl_3$) δ 1.50 (9 H,

s, C_4H_9), 2.38–2.44 (2 H, m, 5-CH_2), 3.04 (3 H, s, SO_2CH_3), 3.21 (2 H, t, J = 7 Hz, CH_2CH_2O), 3.58 (2 H, dd, J = 6 Hz, 6-CH_2), 4.30–4.36 (2 H, m, 2-CH_2), 4.62 (2 H, t, J = 7 Hz, CH_2O), 7.14–7.21 (1 H, m, 4-CH). Anal. ($C_{15}H_{23}N_3O_6S$) C, H, N.

1-[(*tert*-Butyloxy)carbonyl]-3-(3-ethenyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine (25). DBU (3.1 mL, 21 mmol) was added to a solution of **43** (7.70 g, 21 mmol) in toluene (30 mL) and heated at 65 °C for 4.5 h. After cooling, H_2O (30 mL) was added and the organic layer separated, dried, then evaporated. The yellow solid obtained was purified through a short silica column using CH_2Cl_2/MeOH (200:1) to give **25** as a colorless solid (4.44 g, 76%): mp 81–82 °C; R_f 0.58 in EtOAc/petroleum ether (1:1) on silica plates; MS m/z 221 (McLafferty rearrangement ion); ^{1}H NMR ($CDCl_3$) δ 1.50 (9 H, s, C_4H_9), 2.38–2.46 (2 H, m, 5-CH_2), 3.58 (2 H, dd, J = 6 Hz, 6-CH_2), 4.34–4.40 (2 H, m, 2-CH_2), 5.77 (1 H, dd, J = 1.2, 11 Hz, CH=CH_2), 6.41 (1 H, dd, J = 1.2, 17 Hz, CH=CH_2), 6.72 (1 H, dd, J = 11, 17 Hz, CH=CH_2), 7.14–7.22 (1 H, m, 4-CH). Anal. ($C_{14}H_{19}N_3O_3$) C, H, N.

3-(3-Ethenyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine Trifluoroacetate (12). Trifluoroacetic acid (22 mL, 280 mmol) was added to a cooled (4 °C) solution of **25** (4.00 g, 14 mmol) in CH_2Cl_2 (20 mL). After 2 h at room temperature the reaction mixture was evaporated and the solid obtained was recrystallized from *i*PA to afford **12** as a colorless solid (2.95 g, 72%): mp 92–94 °C; R_f 0.38 in CH_2Cl_2/MeOH (9:1) on silica plates; MS m/z 117 (M^+) of free base; ^{1}H NMR (D_2O) δ 2.73–2.80 (2 H, m, 5-CH_2), 3.48 (2 H, dd, J = 6 Hz, 6-CH_2), 4.19 (2 H, dd, J = 2.3, 4.3 Hz, 2-CH_2), 5.93 (1 H, d, J = 12 Hz, CH=CH_2), 6.39 (1 H, d, J = 18 Hz, CH=CH_2), 6.78 (1 H, dd, J = 12, 18 Hz, CH=CH_2), 7.35–7.39 (1 H, m, 4-CH). Anal. ($C_9H_{11}N_3O$·CF_3CO_2H) C, H, N.

***O*-Tetrahydropyranylglycolic Acid Nitrile (44).** Glycolic acid nitrile (50 mL of a 70% aqueous solution, 0.66 mol) was azeotroped with toluene (100 mL). After the theoretical amount of H_2O had been removed, the solution cooled to 0 °C. *p*-Toluenesulfonic acid monohydrate (10 mg) was added followed by dihydropyran (60 mL, 0.66 mol) dropwise, then the mixture stirred at room temperature for 18 h. Saturated $NaHCO_3$ solution (100 mL) was added and the organic layer separated, washed with H_2O (100 mL), dried, then evaporated to give an orange oil which was distilled under vacuum. **44** was obtained as a colorless oil (63.5 g, 68%), bp 97–98 °C (5 mmHg). Anal. ($C_7H_{11}NO_2$) C, H, N.

2-(Tetrahydropyranyloxy)acetamide Oxime (45). Hydroxylamine hydrochloride (32.1 g, 0.46 mol) was added to a stirred solution of sodium (11.3 g, 0.49 mol) in MeOH (1 L) with stirring under nitrogen. After 15 minutes **44** (72 g, 0.51 mol) was added and the mixture stirred for 3 days. The reaction mixture was filtered, evaporated, then redissolved in warm, dry MeOH (300 mL), filtered, and evaporated to give **45** as a pale yellow, viscous oil (83.2 g, 94%): R_f 0.40 in CH_2Cl_2/MeOH (9:1) on silica plates; MS m/z 175 $(M + H)^+$; HRMS, $(M + H)^+$ 175.1089, $C_7H_{15}N_2O_3$ requires 175.1083; ^{1}H NMR (DMSO-d_6) δ 1.34–1.78 (6 H, m, $CH_2CH_2CH_2$), 3.39–3.49 (1 H, m, CH_2O), 3.68–3.78 (1 H, m, CH_2O), 3.80 (1 H, d, J = 12 Hz, CH_2C=N), 3.94 (1 H, d, J = 12 Hz, CH_2C=N), 4.56–4.60 (1 H, m, OC*H*O), 5.00–5.70 (3 H, br resonance, NO*H*, NH_2); IR ν_{max} (film) 3600–2500 (OH, NH, NH_2), 1670 cm^{-1} (C=N).

1-[(*tert*-Butyloxy)carbonyl]-3-[3-[(tetrahydropyranyloxy)methyl]-1,2,4-oxadiazol-5-yl]-1,2,5,6-tetrahydropyridine (23). **23** (1.92 g, 42%) was obtained from **45** (4.35 g, 25 mmol) and **22** (3.0 g, 12.5 mmol) using NaH (1.2 g of a 55% dispersion in oil, 27.5 mmol) in THF (100 mL) as described for 10: R_f 0.90 in CH_2Cl_2/MeOH (12:1) on silica plates; MS m/z 364 $(M - H)^+$; HRMS $(M - H)^+$ 364.1890, $C_{18}H_{27}N_3O_5$ requires 364.1872; ^{1}H NMR ($CDCl_3$) δ 1.49 (9 H, s, C_4H_9), 1.55–1.92 (6 H, m, $CH_2CH_2CH_2$), 2.38–2.45 (2 H, m, 5-CH_2), 3.48–3.60 (3 H, m, 6-CH_2, CH_2O), 3.82–3.96 (1 H, m, CH_2O), 4.31–4.38 (2 H, m, 2-CH_2), 4.58–4.70 (2 H, m, oxadiazole-CH_2O), 4.73–4.86 (1 H, m, OCHO), 7.16–7.22 (1 H, m, 4-CH).

3-[3-(Hydroxymethyl)-1,2,4-oxadiazol-5-yl]-1,2,5,6-tetrahydropyridine Hydrogen Oxalate (13). Pyridinium *p*-toluenesulfonate (0.014 g, 0.05 mmol) was added to a stirred solution of **23** (0.20 g, 0.5 mmol) in EtOH (5 mL). After 3 h at 55 °C the solvent was removed in vacuo and the residue dissolved in CH_2Cl_2, washed with H_2O, then dried and evaporated to afford 1-[(*tert*-butyloxy)carbonyl]-3-[3-(hydroxymethyl)-1,2,4-oxadiazol-5-yl]-1,2,5,6-tetrahydropyridine as a pale yellow gum (0.14 g). This gum (0.123 g, 0.44 mmol) was dissolved in CH_2Cl_2 (25 mL) and trifluoroacetic acid (0.5 g, 4.4 mmol) was added. After 16 h H_2O was added and the aqueous layer separated, basified with 2 M K_2CO_3 solution, then extracted with CH_2Cl_2. The combined organics were dried and evaporated to give **13** free base as an oil (78 mg, 99%). The hydrogen oxalate salt had mp 184–188 °C dec (*i*PA/MeOH); MS m/z 180 $(M - H)^+$ of free base; HRMS $(M - H)^+$ 180.0715, $C_8H_{10}N_3O_2$ requires 180.0773; ^{1}H NMR (D_2O) δ 2.70–2.80 (2 H, m, 5-CH_2), 3.46 (2 H, dd, J = 6 Hz, 6-CH_2), 4.12–4.22 (2 H, m, 2-CH_2), 4.75–4.88 (2 H, m, CH_2O), 7.32–7.39 (1 H, m, 4-CH). Anal. ($C_8H_{11}N_3O_2$·$C_2H_2O_4$) C, H, N: calcd, 15.49; found, 14.57.

3-[3-(2-Hydroxyethyl)-1,2,4-oxadiazol-5-yl]-1,2,5,6-tetrahydropyridine Hydrogen Oxalate (14). **24** (0.6 g, 2 mmol) was deprotected with 2 M HCl (20 mL). The hydrochloride salt obtained was not crystalline and the product was converted to its hydrogen oxalate salt: mp 96–98 °C (*i*PA/Et_2O); MS (CI^+) m/z 196 $(M + H)^+$ of free base. Anal. ($C_9H_{13}N_3O_2$·$1.2C_2H_2O_4$) C, H, N.

1-[(*tert*-Butyloxy)carbonyl]-3-[3-(2-fluoroethyl)-1,2,4-oxadiazol-5-yl]-1,2,5,6-tetrahydropyridine (26). DAST (2.2 mL, 17 mmol) was added dropwise to a stirred, cooled (−78 °C) solution of **24** (1.00 g, 3.4 mmol) in dry CH_2Cl_2 (25 mL) under N_2. After 3 h at −78 °C the reaction was warmed to room temperature. The mixture was then quenched with a solution of K_2CO_3 (5.0 g, 36 mmol) in H_2O (25 mL) at −78 °C and again allowed to warm to room temperature. The organic layer was separated, and the aqueous layer reextracted with CH_2Cl_2 (25 mL). The combined organics were washed with H_2O (25 mL), dried, then evaporated. The product obtained was purified by column chromatography on silica using CH_2Cl_2/MeOH (200:1) to give **26** as a yellow oil (0.64 g, 63%) which solidified on standing: mp 63 °C; R_f 0.80 in EtOAc on silica plates; MS m/z 297 (M^+); HRMS (M^+) 297.1473, $C_{14}H_{20}FN_3O_3$ requires 297.1489. Anal. ($C_{14}H_{20}FN_3O_3$) C, H, N: calcd, 14.13; found, 13.63.

3-[3-(2-Fluoroethyl)-1,2,4-oxadiazol-5-yl]-1,2,5,6-tetrahydropyridine Hydrochloride (15). **15** free base (0.34 g, 82%) was obtained from **26** (0.625 g, 2.1 mmol) and TFA (3.2 mL, 42 mmol) in CH_2Cl_2 (5 mL). The hydrochloride salt had mp 128–129 °C (*i*PA/MeOH); R_f 0.36 in CH_2Cl_2/MeOH (9:1) on silica plates; MS (CI^+) m/z 198 $(M + H)^+$ of free base. Anal. ($C_9H_{12}FN_3O$·HCl) C, H, N.

Methyl 6-Methylnicotinate Methiodide (32). MeI (12.4 mL, 0.198 mol) and **31** (10.0 g, 0.066 mol) were heated under reflux in acetone (35 mL) for 6 h. On cooling, **32** precipitated as a pale yellow solid (18.00 g, 93%), mp 140–142 °C. Anal. ($C_9H_{12}INO_2$) C, H, N.

Methyl 1,6-Dimethyl-1,2,5,6-tetrahydropyridine-3-carboxylate Hydrogen Oxalate (33). $NaBH_4$ (2.30 g, 61 mmol) was added in portions to a stirred, cooled (0 °C) solution of **32** (17.80 g, 61 mmol) in EtOH (100 mL) and H_2O (50 mL). After 2 h at room temperature the mixture was evaporated to dryness, the residue was dissolved in H_2O (40 mL) then extracted with CH_2Cl_2 (3 × 40 mL). The combined organics were dried and evaporated, and the crude product was purified by column chromatography on silica using CH_2Cl_2/MeOH (30:1) to afford **33** free base as a pale yellow oil (7.05 g, 69%). The hydrogen oxalate salt had mp 100–102 °C (*i*PA); R_f 0.40 in CH_2Cl_2/MeOH (9:1) on silica plates; MS m/z 169 (M^+) of free base. Anal. ($C_9H_{15}NO_2$·$C_2H_2O_4$·$0.25H_2O$) C, H, N.

Methyl 1-[(Ethenyloxy)carbonyl]-6-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate (34). **34** was obtained (5.20 g, 82%) from **33** free base (4.80 g, 28 mmol) and vinyl chloroformate (2.7 mL, 30 mmol) as described for **21**.[11] R_f 0.48 in EtOAc on silica plates; MS m/z 225 (M^+); HRMS (M^+) 225.1004, $C_{11}H_{15}NO_4$ requires 225.1001; ^{1}H NMR ($CDCl_3$) δ 1.15 (3 H, d, J = 7 Hz, CH_3), 2.12 (1 H, dm, J = 19 Hz, 5-CH_2), 2.62 (1 H, dm, J = 19 Hz, 5-CH_2), 3.71–3.90 (1 H, m, 6-CH), 3.79 (3 H, s, CO_2CH_3), 4.48 (1 H, dd, J = 2 and 6 Hz, CH=CH_2), 4.58–4.68 (2 H, m, 2-CH_2), 4.83 (1 H, br d, J = 14 Hz, CH=CH_2), 7.00–7.05 (1 H, m, 4-CH), 7.25 (1 H, dd, J = 6 and 14 Hz, CH=CH_2).

6-Methyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine Hydrochloride (19). **19** free base (1.0 g, 70%)

was obtained from **34** (1.80 g, 8 mmol) and acetamide oxime (0.89 g, 12 mmol) using NaH (0.524 g of a 55% dispersion in oil) in dry THF (80 mL) as described for **6**. The hydrochloride salt had mp 180–181 °C (*i*PA/MeOH); R_f 0.24 in CH_2Cl_2/MeOH (9:1) on silica plates; MS *m/z* 179 (M^+) of free base; ^1H NMR (D_2O) δ 1.46 (3 H, d, *J* = 7 Hz, CH_3), 2.42 (3 H, s, oxadiazole-CH_3), 2.52 (1 H, dm, *J* = 20 Hz, 5-CH_2), 2.84 (1 H, dm, *J* = 20 Hz, 5-CH_2), 3.61–3.68 (1 H, m, 6-CH), 4.15 (1 H, dm, *J* = 16 Hz, 2-CH_2), 4.22 (1 H, dm, *J* = 16 Hz, 2-CH_2), 7.26–7.30 (1 H, m, 4-CH). Anal. ($C_9H_{13}N_3O$·HCl) C, H, N.

With the procedure above, but using acetamide oxime and **33**, the following was prepared.

17: 60%; mp 109–110 °C (*i*PA/Et_2O). Anal. ($C_{10}H_{15}N_3O$·$C_2H_2O_4$·0.25H_2O) C, H, N.

Methyl 2-[[*N*-[2-(Methoxycarbonyl)ethyl]amino]methyl]propionate Hydrochloride (46). **36** (300 g, 1.02 mol) was hydrogenated at 50 psi over 20% $Pd(OH)_2$ on C (3 g) in MeOH (100 mL) and 5 M aqueous HCl (210 mL) for 6 h. The reaction mixture was filtered and the aqueous layer separated. The organic layer was extracted with H_2O (200 mL), then the combined aqueous extracts were evaporated to dryness, and the residue was dried over P_2O_5 to give **46** as a colorless gum (235 g, 79%): R_f 0.80 in CH_2Cl_2/MeOH (9:1) on alumina plates. Anal. ($C_9H_{17}NO_4$·HCl·H_2O) C, H, N.

Methyl 2-[[*N*-[(*tert*-Butyloxy)carbonyl]-*N*-[2-(methoxycarbonyl)ethyl]amino]methyl]propionate (37). NEt_3 (272 mL, 1.96 mol) was added dropwise to a stirred suspension of **46** (234 g, 0.98 mol) in dry CH_2Cl_2 (1.5 L). After 15 min di-*tert*-butyl dicarbonate (285 g, 1.30 mol) was added dropwise over 40 min. After 18 h at room temperature the mixture was filtered, washed with 0.5 M HCl (2 × 500 mL), H_2O (2 × 500 mL), and saturated $NaHCO_3$ solution (500 mL), dried, and evaporated, then the product distilled in vacuo. **37** was obtained as a colorless oil (151.5 g, 51%): bp 155–158 °C (2 mmHg); R_f 0.65 in EtOAc on silica plates; MS *m/z* 304 $(M + H)^+$. Anal. ($C_{14}H_{25}NO_6$) C, H, N.

Methyl 1-[(*tert*-Butyloxy)carbonyl]-5-methyl-4-oxopiperidine-3-carboxylate (38). A solution of **37** (30.0 g, 99 mmol) in toluene (30 mL) was added dropwise to a stirred solution of K*t*OBu (11.1 g, 99 mmol) in toluene (100 mL) at 80 °C under N_2. After a further 1 h at 80 °C the mixture was cooled in an ice bath for 1 h. The solid was filtered off, washed with EtOAc (100 mL), then dissolved in H_2O (100 mL). CH_2Cl_2 (100 mL) was added and the aqueous layer was acidified to pH ~4 with concentrated HCl. The organic layer was separated and the aqueous layer reextracted with CH_2Cl_2 (100 mL). The combined organics were washed with H_2O (100 mL), dried, then evaporated. The oil obtained was purified through a short silica column using CH_2Cl_2 to afford **38** as a colorless oil (17.8 g, 66%): bp 120–122 °C (0.2 mmHg); R_f 0.70 in EtOAc/petroleum ether (1:1) on silica plates; IR ν_{max} (film) 3300–2700 (OH, enol), 1750, 1700, and 1665 cm^{-1} (CH=O). Anal. ($C_{13}H_{21}NO_5$) H, N, C: calcd, 57.55; found, 56.96.

Methyl 1-[(*tert*-Butyloxy)carbonyl]-5-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate (39). $NaBH_4$ (0.98 g, 26 mmol) was added portionwise to a stirred, cooled (0 °C) solution of **38** (14.0 g, 52 mmol) in MeOH (30 mL). After 30 min at 0 °C the mixture was poured into H_2O (30 mL), then CH_2Cl_2 (40 mL) was added. Aqueous HCl (2 M) was added dropwise to pH ~4. The organic layer was separated and the aqueous layer reextracted with CH_2Cl_2 (2 × 40 mL). The combined organics were washed with H_2O (40 mL), dried, then evaporated to give the alcohol as a colorless oil (14.05 g, 99%): MS *m/z* 274 $(M + H)^+$; IR ν_{max} (film) 3600–3400 (OH), 1740, 1680, and 1660 cm^{-1} (C=O). Methanesulfonyl chloride (3.9 mL, 50 mmol) was added dropwise to a stirred, cooled (0 °C) solution of the foregoing alcohol (13.80 g, 50 mmol) and NEt_3 (6.9 mL, 50 mmol) in dry CH_2Cl_2 (50 mL). After 2 h, H_2O (50 mL) was added and the organic layer was separated, washed with H_2O (50 mL), dried, and evaporated to give the mesylate as a yellow gum (15.5 g, 88%): MS *m/z* 352 $(M + H)^+$. DBU (6.6 mL, 44 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a stirred solution of the mesylate (15.4 g, 44 mmol) in CH_2Cl_2 (80 mL). After 2 h at room temperature H_2O (50 mL) was added. The organic layer was separated and the aqueous layer reextracted with CH_2Cl_2 (50 mL). The combined organics were washed with 0.5 M HCl (50 mL) and H_2O (50 mL), then dried and evaporated. The crude product was purified by column chromatography on silica using CH_2Cl_2/MeOH (100:1) to afford **39** as a pale yellow oil (5.72 g, 51%): bp 115–116 °C (0.2 mmHg); R_f 0.65 in EtOAc on silica plates; MS *m/z* 256 $(M + H)^+$; HRMS $(M + H)^+$ 256.1527, $C_{13}H_{21}NO_4$ requires 256.1549; ^1H NMR (DMSO-d_6) δ 0.99 (3 H, d, *J* = 7 Hz, CH_3), 1.41 (9 H, s, C_4H_9), 2.38–2.56 (1 H, m, 5-CH), 2.80–3.10 (1 H, m, 6-CH_2), 3.57–3.63 (1 H, m, 6-CH_2), 3.69 (3 H, s, CO_2CH_3), 3.93 (1 H, dm, *J* = 18 Hz, 2-CH_2), 4.00–4.08 (1 H, m, 2-CH_2), 6.84–6.87 (1 H, m, 4-CH); IR ν_{max} (film) 1710 and 1695 cm^{-1} (C=O). Anal. ($C_{13}H_{21}NO_4$·H_2O) C, H, N.

With an analogous procedure, the following was prepared.

40: colorless oil; MS *m/z* 269 (M^+). Anal. ($C_{14}H_{23}NO_4$) C, H, N.

1-[(*tert*-Butyloxy)carbonyl]-5-methyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine (47). Acetamide oxime (1.11 g, 15 mmol) was stirred in dry THF (40 mL) under N_2 at 50 °C with NaH (0.65 g, of a 55% dispersion in oil, 15 mmol) for 1 h in the presence of 4A molecular sieves (12 g). **39** (1.60 g, 6.3 mmol) in dry THF (20 mL) was added. After 1 h at reflux the mixture was cooled, H_2O (60 mL) and CH_2Cl_2 (60 mL) were added, then the mixture was filtered. The organic layer was separated and the aqueous layer reextracted with CH_2Cl_2 (60 mL). The combined organics were dried and evaporated, then the residue was purified by column chromatography on silica using EtOAc/petroleum ether (1:4) to give **47** as a colorless oil (0.90 g, 51%): R_f 0.60 in EtOAc/petroleum ether (1:1) on silica plates; MS *m/z* 279 (M^+); HRMS (M^+) 279.1581, $C_{14}H_{21}N_3O_3$ requires 279.1583. Anal. ($C_{14}H_{21}N_3O_3$) C, H, N.

5-Methyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine Hydrochloride (18). **47** (0.80 g, 2.9 mmol) was stirred with TFA (1.33 mL, 17 mmol) in CH_2Cl_2 (10 mL) for 16 h. The free base was liberated and obtained as a pale yellow oil (0.435 g, 83%). The hydrochloride salt had mp 135–137 °C (*i*PA/Et_2O); R_f 0.40 in CH_2Cl_2/MeOH (9:1) on silica plates; MS *m/z* 179 (M^+) of free base; ^1H NMR (D_2O) δ 1.24 (3 H, d, *J* = 7 Hz, CH_3), 2.41 (3 H, s, oxadiazole-CH_3), 2.95–3.05 (2 H, m, 5-CH and 6-CH), 3.60–3.67 (1 H, m, 6-CH), 4.10 (1 H, dm, *J* = 16 Hz, 2-CH), 4.15 (1 H, dm, *J* = 16 Hz, 2-CH), 7.21 (1 H, d, *J* = 2 Hz, 4-CH). Anal. ($C_9H_{13}N_3O$·HCl·0.25H_2O) C, H, N.

With the procedure above, but using the product obtained from acetamide oxime and **40**, the following was prepared.

20: mp 146–147 °C (*i*PA). Anal. ($C_{10}H_{15}N_3O$·1.3$C_2H_2O_4$·0.2H_2O) C, H, N: calcd, 13.39; found, 13.85.

1,5-Dimethyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine Hydrogen Oxalate (16). NaH (87 mg, 55% dispersion in oil, 2 mmol) was added to a stirred solution of **18** (335 mg, 1.9 mmol) in dry THF (10 mL) under N_2. Bromomethane (1 mL, 2 mmol of a 2 M Et_2O solution) was added and the mixture stirred for 6 h. H_2O (20 mL) and CH_2Cl_2 (20 mL) were added. The organic layer was separated and the aqueous layer reextracted with CH_2Cl_2 (2 × 20 mL). The combined organics were washed with H_2O (20 mL), then dried and evaporated. The oil obtained was purified by column chromatography on silica using CH_2Cl_2/MeOH (gradient) to afford **16** free base as a pale yellow oil (115 mg, 32%). The hydrogen oxalate salt had mp 115–120 °C (*i*PA/MeOH); R_f 0.60 in CH_2Cl_2/MeOH (9:1) on silica plates; MS *m/z* 193 (M^+) of free base. Anal. ($C_{10}H_{15}N_3O$·1.25$C_2H_2O_4$·0.25H_2O) C, H, N.

Biochemical Methods. Binding Studies. Membranes were prepared from 250–300 g Male Sprague-Dawley rats as described previously[8] and resuspended in 20 mM HEPES Kreb's buffer (pH 7.4) for [^{3}H]-*N*-methylscopolamine binding and 20 mM HEPES buffer (pH 7.4) for [^{3}H]oxotremorine-M-binding (1 mL of total assay volume). Assays were incubated at 30 °C for 60 and 40 min, respectively, and were terminated by filtration through Whatman GF/B and 0.05% polyethyleneimine-presoaked GF/C filters by using a Brandel cell harvester. Drug displacement curves were assessed by using 0.1 nM [^{3}H]-*N*-methylscopolamine and 3.0 nM [^{3}H]oxotremorine-M.

X-Ray Crystal Analysis of 12. Suitable crystals of **12** ($C_{11}H_{12}F_3N_3O_3$) were formed from *i*PA with a space group symmetry of triclinic *P*1 and cell constants of *a* = 6.247 (1) Å, *b* = 7.709 (1) Å, *c* = 14.349 (1) Å, α = 101.41 (1)°, β = 93.01 (1)°, and γ = 98.78 (1)° for *Z* = 1 and a calculated density of 1.450 g/cm^3. Of the 2528 reflections measured with a CAD4 diffractometer 1824 were observed ($I > 3\sigma(I)$). The structure was solved by random-solution direct methods (SHELXS), and tables of data for

the positional and thermal parameters and bond angles and distances are available as supplementary material. Figure 2 is a computer-generated drawing of **12** from the final X-ray coordinates.

Acknowledgment. We thank J. Springer and K. Hoogsteen (MSD Rahway) for the X-ray crystal structure of **12**, R. Herbert and R. Williams for NMR, mass spectrum, and pK_a data, R. Barnaby for log P data, and S. Burton for typing this manuscript.

Registry No. 1, 63-75-2; 1·HBr, 300-08-3; 4·HCl, 128164-84-1; **5**, 114724-55-9; 6·HCl, 129594-87-2; 7·HCl, 131041-73-1; **8**, 114724-86-6; 9·HCl, 129594-88-3; **10**, 131041-74-2; 11·HCl, 131041-75-3; 12·CF_3CO_2H, 131041-77-5; 13·Oxalate, 131041-79-7; 14·oxalate, 131041-81-1; **15**, 131041-82-2; 15·HCl, 131041-83-3; 16·oxalate, 124218-45-7; 17·oxalate, 131041-85-5; **18**, 124218-27-5; 18·HCl, 124218-41-3; **19**, 131041-86-6; 19·HCl, 131041-87-7; **20**·oxalate, 131041-89-9; **21**, 57933-84-3; **22**, 125097-83-8; **23**, 131041-90-2; **24**, 131041-91-3; **25**, 131041-92-4; **26**, 131041-93-5; **27**, 98-92-0; **29**, 128164-72-7; **31**, 5470-70-2; **32**, 63065-25-8; **33**, 26563-33-7; 33·oxalate, 131041-94-6; **34**, 131041-95-7; **36**, 40871-16-7; **37**, 124218-55-9; **38**, 124218-56-0; **39**, 124232-59-3; **40**, 131041-96-8; **41**, 131041-97-9; **42**, 53370-50-6; **43**, 131041-98-0; **44**, 17521-49-2; **45**, 131041-99-1; **46**, 131042-00-7; **47**, 131042-01-8; *N,N*-dimethylhydroxyguanidine hydrochloride, 32098-89-8; acetamide oxime, 22059-22-9; hydroxyguanidine hemisulfate, 6345-29-5; dimethylformamide dimethylacetal, 4637-24-5; hydroxylamine *O*-sulfonic acid, 2950-43-8; propionamide oxime, 29335-36-2; di-*tert*-butyl carbonate, 34619-03-9; hydroxylamine hydrochloride, 5470-11-1; 3-hydroxypropionitrile, 109-78-4; palladium hydroxide, 63310-18-9; bromomethane, 74-83-9; vinyl chloroformate, 5130-24-5; glycolic acid nitrile, 107-16-4; [^{3}H]-*N*-methylscopolamine, 83945-36-2; methyl 1-[(*tert*-butoxy)carbonyl]-4-hydroxy-5-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate, 124218-57-1; methyl 1-[(*tert*-butoxy)carbonyl]-5-methyl-4-(methylsulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylate, 124218-58-2; [^{3}H]oxotremorine-M, 131042-02-9.

Supplementary Material Available: Tables of the atomic positional and thermal parameters, bond distances, and bond angles for **12**, microanalyses for all novel compounds, and molecular modeling details (11 pages). Ordering information is given on any current masthead page.

Identification and Exploitation of the σ-Opiate Pharmacophore

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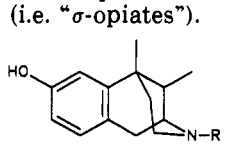
Certain benzomorphan "σ-opiates" such as *N*-allylnormetazocine (NANM) bind at σ receptors with modest affinity and with little selectivity (i.e., they also bind at phencyclidine or PCP sites). In order to identify the primary pharmacophore of the benzomorphans, we prepared several amine-substituted derivatives of 1-phenyl-2-aminopropane. Several simple alkyl-substituted analogues were shown to bind at σ sites with affinities comparable to that of NANM itself; among these was the *N*-benzyl derivative **9** (K_i = 117 nM). Lengthening the spacer between the terminal amine and the phenyl group from one to five methylene units resulted in a significant increase in affinity (e.g. **15**, K_i = 6.3 nM). In addition, unlike the benzomorphans, these phenalkylamines do not bind at PCP sites. The results of the present study reveal that (a) the 1-phenyl-2-aminopropane nucleus of the benzomorphans is sufficient for binding at σ sites provided that the terminal amine is not a primary amine and that (b) introduction of (phenylalkyl)amine substituents affords compounds that represent a new class of high-affinity σ-selective agents.

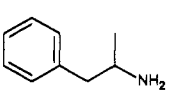
Certain benzomorphan opiates, in particular cyclazocine (**1**), pentazocine (**2**), and *N*-allylnormetazocine (SKF-10047; NANM) (**3**), are capable of producing psychotomimetic effects in animals and in humans.[1-3] An examination of the optical isomers of these benzomorphan derivatives reveals that their classical opiate agonist or antagonist actioins are primarily attributable to their (−)-isomers (e.g. ref 4), and binding profiles suggest that (−)-NANM, for example, may be acting at μ and κ opiate receptors.[5,6] (+)-NANM, on the other hand, displays a low affinity for these receptors.[5-7] Furthermore, most of the behavioral effects of (+)-NANM, unlike those of (−)-NANM, can not be antagonized by classical opiate antagonists such as naloxone.[8-12] Martin et al.[3] postulated the existence of "σ-opiate" receptors to account for the actions of these agents (i.e. "σ-opiates").



1 R = $-CH_2-C_3H_5$

2 R = $-CH_2CH=C(CH_3)_2$

3 R = $-CH_2CH=CH_2$



4

Because the σ-opiates can produce behavioral effects similar to those of phencyclidine (PCP),[11-17] and because they bind at PCP sites,[18,19] it was initially thought that the

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