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A NOVEL AND SELECTIVE CLASS OF AZABICYCLIC MUSCARINIC AGONISTS INCORPORATING AN N-METHOXY IMIDOYL HALIDE OR NITRILE FUNCTIONALITY

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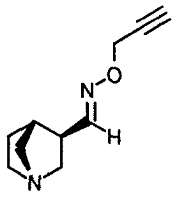
Abstract: Structural modulation of the oxime ether group of a series of azabicyclic oxime ethers by the incorporation of electron-withdrawing groups has led to a novel class of N-methoxy imidoyl halides and nitriles which are potent muscarinic agonists. Members of this class, exemplified by **2e** and **3c**, show favourable central selectivity which can be rationalised in terms of partial agonist character, improved physicochemical properties, and receptor sub-type selectivity.

In the preceding paper[1] we described the design and synthesis of a series of azabicyclic oxime ethers, for example **1**, **2a** and **3a**, which bind with high affinity to muscarinic receptors. The propargyl ether **1** was identified as a high affinity partial agonist with good separation between central and peripheral actions, and this selectivity was related to the partial agonist nature of the compound.



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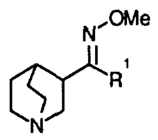
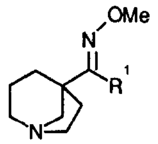
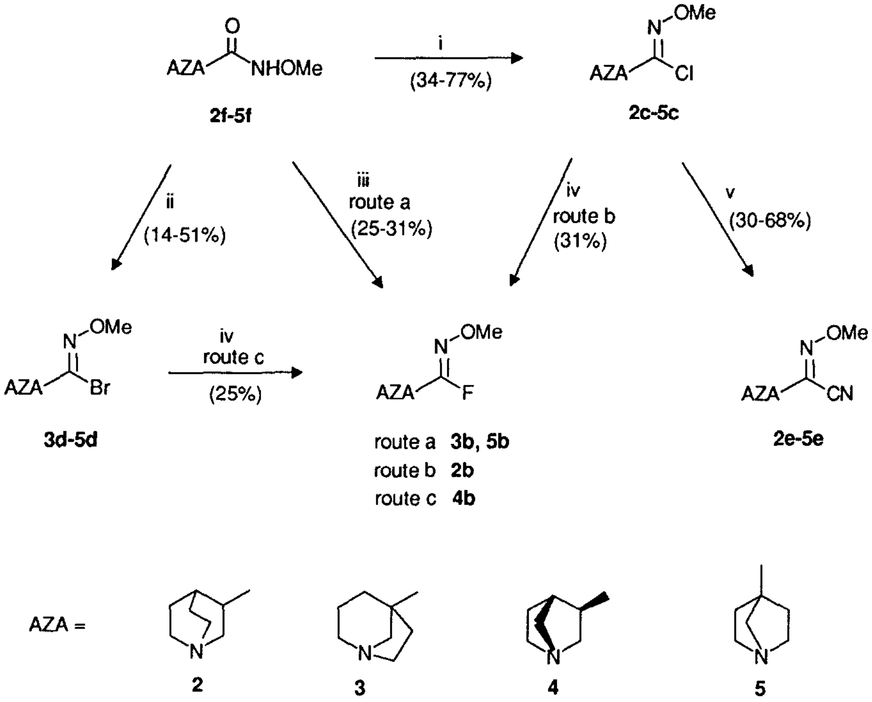


2a $R^1 = Me$



3a $R^1 = Me$

An additional property which affects central selectivity is the ability of the compounds to penetrate into the CNS. Consequently, our attention was directed towards strategies for optimising their physicochemical properties in order to increase CNS penetration. Our previous studies revealed that the scope for further enhancement of lipophilic character of the oxime ethers by homologation was extremely limited by the steric constraints on agonist binding. However, it occurred to us that it might be possible to manipulate the physicochemical properties of the compounds, whilst maintaining affinity, by replacement of R^1 with small groups such as halogen or nitrile. We anticipated that the electron-withdrawing property of such groups would assist brain penetration by reducing the pKa of the azabicyclic ring.[2] The introduction of lipophilic halogens would also have a positive effect on logP values. Furthermore, comparison of the electrostatic potential maps of the proposed structures with those generated from aldoxime and methyl ketoxime ethers revealed broad similarities in terms of the location of the two areas of negative potential which are believed to be important in receptor binding.[3]



Scheme 1 *Reagents and conditions:* **i**, PPh_3 / CCl_4, acetonitrile, reflux 5 min; **ii**, a) HBr b) PPh_3 / CBr_4, acetonitrile, reflux 1 h; **iii**, a) HF-pyridne b) DAST, acetonitrile, reflux 2 min; **iv**, CsF / CaF_2, DMF, 145°C, 5 days; v, NaCN, DMSO, 100°C, 5 h

With these arguments in mind, the synthesis of a range of N-methoxy imidoyl fluoride, chloride, bromide and nitrile analogues was undertaken (Scheme 1). The N-methoxy imidoyl chlorides **2c-5c** were prepared by treatment of the N-methoxyamide precursors **2f-5f**, themselves prepared by standard methodology from the corresponding known esters,[3] with triphenylphosphine and carbon tetrachloride in refluxing acetonitrile.[4] The corresponding bromo analogues **3d-5d** were prepared in a similar manner with triphenylphosphine and carbon tetrabromide. The N-methoxy imidoyl fluorides **3b** and **5b** were obtained by treatment of the hydrogen fluoride salts of the N-methoxyamides **3f** and **5f** with diethylaminosulphur trifluoride (DAST) in refluxing acetonitrile.[5] This reaction represents a novel use of the DAST reagent. Unfortunately, this method was only applicable to those analogues where the functional group is attached to a bridgehead carbon and consequently an alternative procedure was developed for the synthesis of **2b** and **4b**. These compounds were obtained from the N-methoxy imidoyl chloride **2c** and bromide **4d**, respectively, by halogen exchange using CsF supported on CaF_2 in DMF.[6] Treatment of the N-methoxy imidoyl chlorides **2c**-**5c** with NaCN in DMSO[7] afforded the N-methoxy imidoyl nitriles **2e**-**5e**. All the compounds prepared were isolated as single geometrical isomers which were tentatively assigned the *Z* configuration.[8]

Table 1. In Vitro Affinities of N-Methoxy Imidoyl Halides and Nitriles for Muscarinic Receptors in Rat Cerebal Cortex[a]

Compound	R^1	IC_{50}, nM		IC_{50} QNB/ IC_{50}OXO-M[b]
		OXO-M	QNB	
2b	F	34 (23-58)	2200 (2100-2250)	65
2c	Cl	69 (51-93)	1100 (900-1450)	16
2e	CN	33 (26-36)	470 (440-490)	14
3b	F	43 (27-85)	2400 (1900-3000)	56
3c	Cl	72 (45-120)	3000 (2300-3800)	42
3d	Br	190 (185-190)	2300 (1950-2800)	12
3e	CN	11 (7.4-17.5)	220 (200-250)	20
4b	F	9 (7-11)	3100 (3000-3200)	344
4c	Cl	64 (48-85)	3000 (2650-3300)	47
4d	Br	59 (22-120)	3000 (2350-3800)	51
4e	CN	23 (22-25)	2300 (2100-2600)	100
5b	F	44 (40-48)	15500*	352
5c	Cl	51 (38-67.5)	8500 (8000-9000)	167
5d	Br	160 (150-170)	8100 (6500-10000)	51
5e	CN	19 (18-21)	1950 (1900-2000)	103

[a] With the exception of the entry marked with an asterisk, all values are the geometric means of results obtained in two to four separate experiments. [b] Ratios greater than 100 are associated with full agonists, antagonists give ratios close to unity and intermediate values indicate partial agonists.[3]

The affinity and efficacy of the compounds for muscarinic receptors was determined as previously described[1] and the results are shown in Table 1. A striking feature is that compounds of this class display high affinity for muscarinic receptors, with a range of profiles from full agonists, such as **4b** and **5b**, to partial agonists, such as **2e** and **3e**. Although the nature of the azabicyclic ring has little influence on affinity, the ratio predicting efficacy is sensitive to the steric demands of the ring moiety. High ratios, predictive of full agonist character, are associated with analogues incorporating the compact 1-azabicyclo[2.2.1]heptane ring, whereas larger rings tend to produce compounds with partial agonist character. Steric influence is probably also implicated in the observed trend of decreasing affinities and efficacies of the N-methoxy imidoyl halides as the size of halogen substituent is increased from fluorine through to bromine for a particular azabicyclic ring system (eg **3b**-**3d**). However, electronic effects may also be important.

The central selectivity of the compounds was assessed by comparing the dose required to cause a transient 50% fall in mean blood pressure to that required to induce rhythmical slow wave activity (RSA) equivalent to that of a standard dose of arecoline (BP-ED_{50}/RSA-ED_{Arec}).[1] Both full and partial agonists were able to elicit RSA. In agreement with our earlier work,[1] partial agonists generally induced RSA with a greater degree of selectivity with respect to peripheral cardiovascular effects and, consequently, our attention was focused on these compounds. Results for selected partial agonists are shown in Table 2 together with those for the corresponding ketoximes **2a** and **3a** for comparison. The N-methoxy imidoyl chloride **3c**, and to a lesser degree the N-methoxy imidoyl fluoride **3b**, showed improved selectivity when compared with the corresponding ketoxime **3a**. Improved selectivity profiles were also observed for the N-methoxy imidoyl nitriles **2e** and **3e** relative to the corresponding ketoximes **2a** and **3a**, respectively.

Table 2. Central Selectivity of N-Methoxy Imidoyl Halides and Nitriles[a]

Compd	RSA (ED_{Arec}) (mg/kg iv)	BP (ED_{50}) (mg/kg iv)	BP (ED_{50})/ RSA(ED_{Arec})	pKa	LogP[b]	LogD[c]
2a	0.31 (0.21-0.46)	>0.1	>0.35	10.27	1.88	-1.09
3a	0.068 (0.041-0.110)	0.068 (0.046-0.10)	1.0	10.07	1.65	-1.13
3b	0.012 (0.007-0.020)	0.03 (0.013-0.069)	2.5	9.06	1.01	-0.76
3c	0.029 (0.016-0.053)	0.32 (0.18-0.56)	11.0	9.24	2.12	+0.18
3e	0.005 (0.001-0.023)	0.02 (0.018-0.021)	4.0	8.96	1.49	-0.18
2e	0.052 (0.035-0.077)	>0.56	>10.8	8.96	1.56	-0.11

[a] ED_{Arec} reflects the dose required to produce a change in the mean power spectrum of the EEG equivalent to that of a standard dose (0.32 mg/kg) of arecoline, BP (ED_{50}) is the dose producing a 50% fall in mean blood pressure. Values in parenthesis indicate 95% confidence limits. [b] LogP values measured for octanol/water. [c] LogD values calculated for pH=7.3 [The distribution coefficient (D) is defined as the ratio of the concentration of compound in the lipid phase to the concentration of all species in the aqueous phase at a given pH].[9]

Measurement of physicochemical properties confirmed that, as predicted, pKa values of the N-methoxy imidoyl halides **3b** and **3c** and nitriles **2e** and **3e** are significantly lower than those observed for the corresponding methyl ketoximes **2a** and **3a** (Table 2). This is reflected in higher logD values and would predict greater brain penetration and central selectivity.[9] In the case of the N-methoxy imidoyl chloride **3c**, the chloro substituent has the combined effect of reducing pKa and increasing logP, resulting in a logD value predictive of good central penetration. In contrast, the fluoro analogue **3b**, which is significantly less lipophilic, displays only marginal selectivity.

A further factor which is likely to influence the functional selectivity of this class of compounds is receptor sub-type selectivity. The pharmacologically defined M_1 sub-type is considered to be the predominant post-synaptic receptor in neuronal tissue associated with cognitive function, whereas peripheral cardiovascular events are mainly mediated via M_2 and M_3 receptors. A muscarinic agonist in which the relative activity at M_1 receptors is increased should, therefore, offer advantages in terms of cognitive versus cardiovascular effects.[10] At least five different muscarinic receptors (m1 to m5) have been cloned and identified. Studies on human cloned receptors have shown that hm1-hm3 receptors correlate with the pharmacologically defined M_1-M_3 receptors respectively.[11] We have found that full muscarinic agonists in general, which show a strong bias towards peripheral hypertensive activity, are highly selective for hm2 over hm1 receptors.[12] In contrast, some of the partial agonists described here, such as **3c** and **3e,** have been assessed in human cloned receptors and show similar affinities at hm1 and hm2 receptors.[13] This absence of intrinsic bias towards hm2 receptors is likely to contribute to the observed selectivity profiles.

In conclusion, we have described a novel series of muscarinic agonists and partial agonists, some of which show remarkable central selectivity which can be rationalised in terms of the partial agonist character of the compounds, physicochemical properties and intrinsic receptor sub-type preferences.

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5. A representative procedure is as follows; pyridine (3ml) was added to a solution of 1-azabicyclo[3.2.1]oct-5-yl-N-methoxycarboxamide **3f** (5.4g) in acetone (100ml). The solution was treated with a slight excess of hydrogen fluoride-pyridine (Aldrich) and evaporated *in vacuo*. The resultant gum was co-evaporated with toluene , dried under vacuum and taken-up in dry acetonitrile (300ml). The solution was heated to reflux and diethylaminosulphur trifluoride (DAST) (4.3ml) in acetonitrile (20ml) was added in a single portion. The reaction mixture was immediately cooled and poured into saturated aqueous potassium carbonate (150ml). The mixture was extracted with chloroform (3 x 100ml) and the combined extracts were dried (Na_2SO_4) and evaporated to an oil. Chromatography on silica gel using 4% methanol in chloroform as eluant afforded the N-methoxy imidoyl fluoride **3b** as a yellow oil (1.62g, 31%) which was characterised as the oxalate salt (m. p. 104-107°C).
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