Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 4, pp. 557-562, 1994

0960-894X/94 $6.00+0.00

0960-894X(94)E0008-3

1,2,5,6-TETRAHYDROPYRIDINE OXIME ETHERS INCORPORATING ELECTRON WITHDRAWING GROUPS ARE POTENT AND SELECTIVE MUSCARINIC AGONISTS

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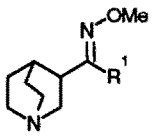
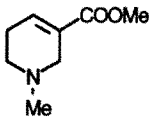
Abstract: The combination of N-methoxy imidoyl halide and nitrile moieties with the 1,2,5,6-tetrahydropyridine ring system afforded a novel series of potent muscarinic agonists. Members of this class, exemplified by the imidoyl nitriles **2c** and **3c**, show favourable central selectivity. The incorporation of fluoroacetyl oxime ethers gave compounds with weak affinity for muscarinic receptors.

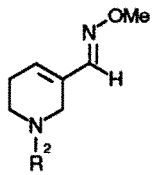
The past few years have seen an explosion of interest in cholinomimetics as potential cognition enhancers for the treatment of senile dementia of the Alzheimer type (SDAT).[1] However, the potential utility of many of these agents is compromised by unwanted peripheral effects and consequently much recent effort has been directed towards the search for more selective agents. In a previous report[2] we described the design and synthesis of a series of azabicyclic muscarinic agonists incorporating an oxime ether functionality. Modulation of the oxime ether group by introduction of electron-withdrawing groups, to give N-methoxy imidoyl halides and nitriles, produced a series of potent agonists some of which, for example **1c** (BRL55473), showed favourable central selectivity which was rationalized in terms of partial agonist character and increased brain penetration due to a reduction in the pKa of the azabicyclic ring.[3]



1a R^1 = Cl
1b R^1 = F
1c R^1 = CN (BRL55473)



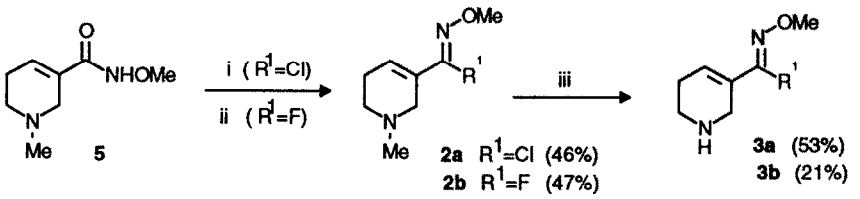
Arecoline



2h R^2 = Me (RU35926)
3h R^2 = H (RU35963)

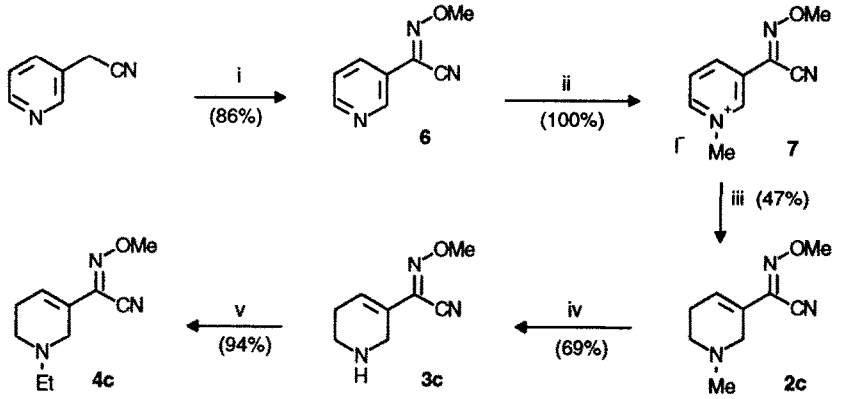
We hypothesised that replacing the azabicyclic ring by a less basic aza-monocyclic ring might generate a novel series of muscarinic agonists with further enhanced lipophilic character and this paper reports the combination of N-methoxy imidoyl halide and nitrile functionality with the 1,2,5,6-tetrahydropyridine ring system of the naturally occurring muscarinic agonist arecoline. In addition, the use of fluoromethyl groups as electron withdrawing substituents has been investigated. Recently the bioisosteric replacement of the methyl carboxylate of arecoline with aldoxime[4] or ketoxime[5] ethers has been described and the aldoxime **3h** (RU35963) reported as a candidate for clinical studies in SDAT patients.

The N-methoxy imidoyl chloride **2a** and fluoride **2b** were prepared by treatment of the N-methoxyamide **5**, itself available from the corresponding ester, with triphenylphosphine and carbon tetrachloride or diethylaminosulphur trifluoride (DAST) respectively (Scheme 1).[3] This extends the scope of our recently discovered[3] application of the DAST reagent. Demethylation using α–chloroethyl chloroformate gave the N-unsubstituted analogues **3a** and **3b**.[6]



Scheme 1 *Reagents and conditions;* **i**, PPh_3/CCl_4, acetonitrile, reflux 0.5h; **ii**, a) HF-pyridine b) DAST, acetonitrile, reflux 2 min; **iii**, a) α-chloroethyl chloroformate, CH_2Cl_2, rt 4h b) MeOH, reflux 1h

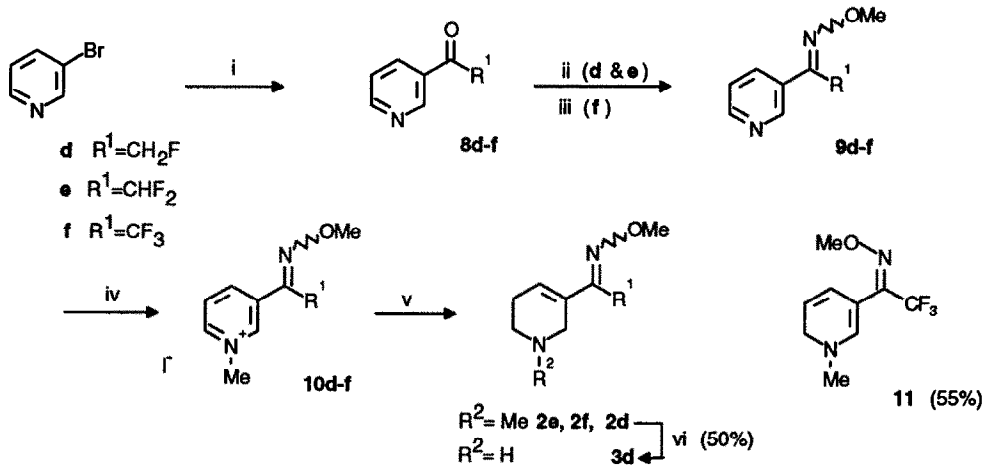
The N-methoxy imidoyl nitriles **2c-4c** were prepared according to Scheme 2. The key intermediate **6** was obtained by a one-pot nitrosation and alkylation of 3-pyridylacetonitrile, using potassium *t*-butoxide and *t*-butylnitrite, followed by methyl iodide. Quaternisation with methyl iodide in refluxing methanol, followed by sodium borohydride reduction of the pyridinium ring of the salt **7**,[7] afforded the 1-methyl-1,2,5,6-tetrahydropyridine-3-N-methoxy imidoyl nitrile **2c** in moderate yield. Demethylation gave **3c** which was N-alkylated with ethyl iodide to give **4c**.



Scheme 2 *Reagents and conditions;* **i**, a) ^{t}BuOK, THF, -20°C 1h b) ^{t}BuONO, rt 2h
c) MeI, rt overnight; **ii**, MeI, methanol, reflux 60h; **iii**, $NaBH_4$, methanol/water, 0°C to rt 2h;
iv, a) α-chloroethyl chloroformate, CH_2Cl_2, rt 4h b) MeOH, reflux 1h; **v**, EtI, acetone/K_2CO_3, rt 4h

Fluoroacetyl oxime ethers **2d-f** and **3d** were obtained by the route shown in Scheme 3. Lithiation of 3-bromopyridine followed by addition of the appropriate N-methyl-N-methoxyfluoroacetamide, prepared by standard methods from the corresponding fluoroacetic acid or anhydride and N,O-dimethylhydroxylamine

hydrochloride, gave the 3-fluoroacetylpyridines **8**.[8] The trifluoroacetylpyridine **8f** hydrated readily and did not react with methoxylamine hydrochloride under conventional conditions. However, the use of toluene as solvent under Dean-Stark conditions gave **9f** in good yield. Interestingly, whereas the imidoyl halides and nitriles **2a-c** were isolated as the *Z*-isomers, **9f** was obtained exclusively as the *E*-isomer. These conditions were also employed to prepare the difluoroacetyl oxime ether **9e** which was isolated as a 3:1 mixture of *E* and *Z*-isomers.[9] The monofluoro analogue **9d** was prepared as a 1:4 mixture of *E* and *Z*-isomers by treating **8d** with methoxylamine hydrochloride in refluxing methanol. Quaternisation of the fluoroacetyl oxime ethers **9** with methyl iodide followed by reduction of the salt **10** with sodium borohydride gave moderate yields of the target 1-methyl-1,2,5,6-tetrahydropyridines **2d-f**. In the case of the trifluoroacetyl oxime ether **10f** the reduction gave the 1,6-dihydropyridine **11** as the major product in 55% yield. Irradiation[10] of the trifluoroacetyl oxime ether **2f** at 254 nm in benzene for three days converted the 14:1 mixture of *E* and *Z*-isomers to a 3:1 mixture. This was converted to the oxalate salt and the *E*-isomer was crystallised leaving mother liquors which when concentrated gave a 1:1 mixture of isomers **2g**. The ratio of geometric isomers and yields of the fluoroacetyl oxime ethers as isolated from the reaction mixtures are shown in Table 1.



Scheme 3 *Reagents and conditions;* **i**, a) ^{n}BuLi, diethyl ether, -78°C 0.25h b) $CR^{1}CONMeOMe$, -78°C to rt 1h; **ii**, $NH_2OMe.HCl$, toluene, reflux (Dean-Stark) 2h; **iii**, $NH_2OMe.HCl$, methanol, reflux 1h; **iv**, MeI, acetonitrile, reflux 2h; **v**, $NaBH_4$, methanol/water, 0°C to rt 1h; **vi**, a) α-chloroethyl chloroformate, CH_2Cl_2, rt 4h b) MeOH, reflux 1h;

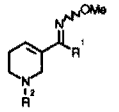
Table 1. Ratio of Geometric Isomers (*E*:*Z*) and Total Yields of Fluoroacetyl Oxime Ethers

CMPD	R^1	9	10	2	3
d	CH_2F	1:4 (58%)*	1:4 (94%)	1:6 (50%)[a]	0:1 (50%)
e	CHF_2	3:1 (77%)*	5:2 (92%)	1:1 (37%)	
f	CF_3	1:0 (80%)*	1:0 (100%)	14:1 (23%)[b]	

[a,b]Recrystallised as pure *Z*- and *E*-isomer respectively for biological assays. *Yields from 3-bromopyridine

The ability of compounds to inhibit the binding of [^{3}H] oxotremorine-M (OXO-M), which is a muscarinic agonist, provided a measure of affinity for the high affinity agonist state of the receptor. The ratio of the IC_{50} values for inhibition of the muscarinic antagonist [^{3}H] quinuclidinyl benzilate (QNB) and OXO-M was used to predict efficacy. Efficacy ratios greater than 100 are associated with full agonists; antagonists give ratios close to unity and intermediate values indicate partial agonists.[11] The results are shown in Table 2 together with those for **3h** (RU35963), **2h** (RU35926), and the quinuclidine analogues **1a-c** for comparison.

Table 2. In Vitro Affinities of 1,2,5,6-Tetrahydropyridine Oxime Ethers for Muscarinic Receptors in Rat Cerebral Cortex[a]



CMPD	R^1	R^2	*E* : *Z*	IC_{50}, nM		Efficacy ratio IC_{50} QNB/ IC_{50}OXO-M
				OXO-M	QNB	
1a	Cl	#	*Z*	69 (51-93)	1100 (900-1500)	16
1b	F	#	*Z*	34 (23-58)	2200 (2100-2300)	65
1c BRL55473	CN	#	*Z*	33 (26-36)	470 (440-490)	14
3a	Cl	H	*Z*	150 (120-180)	5600 (4700-6700)	37
3b	F	H	*Z*	41*	2900*	70
3c	CN	H	*Z*	28 (23-35)	1500 (1200-1800)	54
3d	CH_2F	H	*Z*	420*	17000*	40
3h RU35963	H	H	*Syn*	71 (46-110)	20000 (18000-23000)	280
2a	Cl	Me	*Z*	260 (240-290)	2800*	11
2b	F	Me	*Z*	39 (28-58)	4000 (1500-7200)	100
2c	CN	Me	*Z*	150 (120-220)	4500 (4300-9500)	30
2d	CH_2F	Me	*Z*	450 (330-620)	8300 (8000-8500)	18
2e	CHF_2	Me	1 : 1	1100 (990-1300)	15000 (15000-15000)	14
2f	CF_3	Me	*E*	11000*	-	-
2g	CF_3	Me	1 : 1	2800 (2300-3500)	13000 (11000-17000)	5
2h RU35926	H	Me	*Syn*	110 (65-260)	14000 (9700-23000)	130
4c	CN	Et	*Z*	1000 (840-1200)	9400 (9100-9600)	9

[a] Entries marked with an asterisk are single results, all other values are geometric means of results obtained in two to five separate experiments. Ranges are given in parenthesis. # Denotes quinuclidine ring system.

A striking feature is that whereas the aldoximes **2h** and **3h** have QNB/OXO-M ratios predictive of full agonism, compounds of the new class display a range of affinities for muscarinic receptors with efficacy ratios predictive of partial agonism. The secondary amines **3a-c** have comparable affinities to the corresponding quinuclidinyl analogues[3] **1a-c** and moderately increased efficacy ratios. The imidoyl fluorides **2b** and **3b** and the imidoyl nitrile **3c** are the most potent compound of the series. N-Methylation of the imidoyl fluoride (**3b** to **2b**) has little effect on affinity or efficacy ratio, whereas in the case of the imidoyl nitriles, introduction of N-methyl (**3c** to **2c**) causes a significant decrease in both affinity and predicted efficacy. The N-ethyl analogue **4c** shows a dramatic decrease in potency indicating severe steric constraints. As we previously reported in the azabicyclic series,[3] replacing fluoro by chloro causes a drop in affinity and efficacy ratio (**2b** vs

2a and **3b** vs **3a**). The fluoromethyl oximes **2d-g** and **3d** display only weak affinity. In the case of the trifluoromethyl oxime, the pure *E*-isomer **2f** is inactive, suggesting that the weak activity observed with the 1:1 mixture of geometric isomers **2g** is associated with the *Z*-isomer.

The induction of atropine sensitive rhythmical slow wave activity (RSA) in the CA1 region of the hippocampus of urethane anaesthetised rats was used as a model of cholinergic activation in a region of the brain critical in cognitive function.[12] The central selectivity of the compounds was assessed by comparing the dose required to cause a 50% fall in mean blood pressure to that required to induce a standard increase in rhythmical slow wave activity (RSA).[2] This transient decrease in blood pressure is peripherally mediated since it can be blocked by atropine methyl nitrate. Results for selected compounds together with those of **3h** (RU35963), **2h** (RU35926) and **1c** (BRL55473) for comparison are shown in Table 3. The N-methoxy imidoyl nitriles **2c** and **3c** have lower efficacy ratios than the corresponding aldoximes **2h** and **3h** but induced RSA at similar doses with significantly improved central selectivities. This is in line with our previous studies[2,3] which demonstrated improved selectivity with partial agonists. A possible explanation is that a lower receptor reserve mediates the observed effect on blood pressure in comparison to the effect on RSA.[13]

Table 3. Central Selectivity of 1,2,5,6-Tetrahydropyridine Oxime Ethers[a]

Cmpd	IC_{50}QNB/ IC50OXO-M	RSA (ED_{Arec}) (mg/kg iv)	BP (ED_{50}) (mg/kg iv)	BP (ED_{50})/ RSA(ED_{Arec})	pKa	LogP[b]	LogD[c]
1c **BRL55473**	14	0.052 (0.035-0.077)	>0.56 (35%)	>10.8	8.96	1.56	-0.11
3h (R^2=H) **RU35963**	280	0.019 (0.012-0.033)	0.067 (0.04-0.11)	3.5	9.18	1.01	-0.79
2h (R^2=Me) **RU35926**	130	0.15 (0.08-0.26)	0.15 (0.06-0.37)	1	8.21	1.45	+0.57
3c (R^2=H)	54	0.032 (0.012-0.089)	>0.32 (44%)	>10	8.60	1.41	+0.14
2c (R^2=Me)	30	0.16 (0.07-0.36)	>1 (24%)	>6.3	7.65	1.76	+1.30
2b (R^2=Me)	100	0.054 (0.026-0.11)	0.04 (0.023-0.072)	0.74	7.39	1.48	+1.16

[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 either 95% confidence limits or the greatest fall in blood pressure observed upto the maximum dose shown. [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].[14]

Measurement of physicochemical properties indicated that the imidoyl nitriles **2c** and **3c** have lower pKa, and hence higher logD values, than the corresponding aldoximes **2h** and **3h**, presumably due to the electron withdrawing effect of the nitrile group. This should assist brain penetration and probably contributes to the

greater selectivities observed for **2c** and **3c** relative to **2h** and **3h**. As predicted the logD values of the 1,2,5,6-terahydropyridine oximes were higher than the corresponding azabicyclic analogues[3] (eg **1c**) due to lower pKa values. This may account for the observation that the selectivities shown by **2c** and **3c** were comparable to that of **1c** (BRL55473) despite higher efficacies. The imidoyl fluoride **2b** has similar logD to **2c** but is non-selective presumably due to its full agonist profile.

In view of their higher efficacy ratios and lower logD values, the findings that the secondary amines **3c** and **3h** showed similar or maginally increased central selectivities compared to the corresponding N-methyl analogues **2c** and **2h** was somewhat surprising. It is clear that in addition to the efficacy and physicochemical properties of agonists, other factors such as intrinsic subtype selectivity, transport and metabolic properties[4] are also involved.

Acknowledgement. We wish to thank L. A. Senior, E. Meenan and M. J. Graham in the Analytical Sciences Department for carrying out the logP and pKa measurements.

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(*Received in USA* 23 *November* 1993; *accepted* 17 *December* 1993)