Bioorganic & Medicinal Chemistry Letters, Vol.2, No.8, pp. 787-790, 1992
Printed in Great Britain

0960-894X/92 $5.00 + .00

DESIGN AND SYNTHESIS OF AZABICYCLIC MUSCARINIC AGONISTS INCORPORATING AN OXIME ETHER FUNCTIONALITY

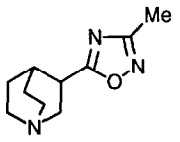
Steven M. Bromidge*, Frank Brown, Frederick Cassidy, Michael S. G. Clark, Steven Dabbs, Michael S. Hadley, Julia M. Loudon, Barry S. Orlek* and Graham J. Riley.

SmithKline Beecham Pharmaceuticals Medicinal Research Centre
Coldharbour Road, The Pinnacles, Harlow, Essex, CM19 5AD UK

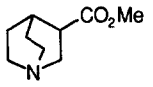
(*Received* 24 *March* 1992; *accepted* 24 *June* 1992)

Abstract: Replacement of the ester group of methyl quinuclidine-3-carboxylate **2** with an oxime ether afforded a series of potent muscarinic agonists with efficacies ranging from full to partial agonism. From an investigation of the relationship between central selectivity and efficacy, the propargyl ether **5g** emerged as a high affinity partial agonist with a good separation between central and peripheral actions.

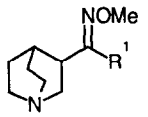
Despite extensive interest in cholinomimetics as potential cognition enhancers for the treatment of senile dementia of the Alzheimer type (SDAT), clinical results with "classical" muscarinic agonists have been disappointing. The utility of such compounds is compromised by unwanted peripheral effects, and these problems have encouraged the search for more CNS selective agents.[1] In a previous report[2] we described the design and synthesis of a series of azabicyclic oxadiazoles which bind with high affinity to muscarinic receptors. The prototype of that series, 3-(3-methyl-1,2,4-oxadiazol-5-yl)quinuclidine **1**, was obtained by bioisosteric replacement of the ester group of the known muscarinic agonist methyl quinuclidine-3-carboxylate **2** with a 1,2,4-oxadiazole ring.



1



2



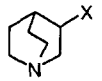
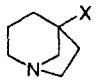
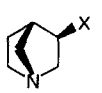
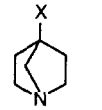
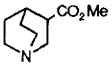
3 R^1 = H, Me

Our subsequent studies identified a range of related azabicyclic analogues which could be accommodated at muscarinic receptors. The high affinity and efficacy of these compounds was related to the electrostatic potential around the heteroaromatic ring and we concluded that two specific regions of negative potential are important for binding.[2] In our search for alternative non-heteroaromatic bioisosteres, modelling studies indicated that the electrostatic potential about the oxime ether moiety, as in **3**, showed broad similarities to those of the ester **2** and the 1,2,4-oxadiazole **1**. We now describe the use of the oxime ether function as an ester replacement which in combination with the azabicyclic systems identified in our earlier work has led to a

novel series of muscarinic partial agonists with distinct advantages in terms of their CNS selectivity. Although some groups have argued that a full agonist is necessary for cognitive enhancement,[3] the propensity of such compounds to cause side effects is well known. Partial agonists may produce selective actions by exploiting regional differences in receptor reserve[4] and we have set out to explore the potential of such compounds to selectively elicit effects predictive of cognitive enhancement.[5]

Initially, a range of simple aldoxime and ketoxime ethers related to the lead ester **2** was prepared (Table 1). The compounds were obtained by reaction of the appropriate O-alkyl hydroxylamine (NH_2OR^2) with the corresponding azabicyclic aldehydes or ketones which were accessed from the known carboxylic acid esters[2] using the Weinreb approach.[6] Aldoxime ethers **3a**, **5a**, and **5d-g** were obtained and tested as mixtures of *syn* and *anti* isomers, whereas **4a** and **6a**, were isolated in pure *syn* form. Ketoxime ethers were obtained as pure *syn* isomers.[7]

Table 1. In Vitro Affinities of Aldoxime and Ketoxime Ethers for Muscarinic Receptors in Rat Cerebral Cortex[a]

Structure X= 	Cmpd	R^1	R^2	*Syn: Anti*	IC_{50}, nM		IC_{50} QNB/ IC_{50}OXO-M
					OXO-M	QNB	
	**3a**	H	Me	3:2	95 (65-110)	5800 (3400-10000)	61
	3b	Me	Me	*Syn*	69 (66-83)	2000 (1400-2900)	29
	**4a**	H	Me	*Syn*	60 (44-170)	5200 (4800-6300)	87
	4b	Me	Me	*Syn*	46 (44-48)	3400 (2600-4400)	74
	**5a**	H	Me	7:1	15 (10-30)	3100 (2000-4800)	207
	5b	Me	Me	*Syn*	99 (83-128)	7500 (6200-9000)	76
	5c	Et	Me	*Syn*	208 (155-265)	5200 (3400-8000)	25
	5d	H	Et	13:1	160 (160, 160)	3700 (2500-5600)	23
	5e	H	n-Pr	7:1	278 (230-335)	2900 (2700-3000)	10
	5f	H	n-Bu	16:1	252 (205-310)	3600 (3600, 3600)	14
	5g	H	Propargyl	9:1	25 (12-62)	1950 (1400-2700)	78
	**6a**	H	Me	*Syn*	118 (90-155)	38000 (36000-40000)	321
	6b	Me	Me	*Syn*	55 (50-65)	14000 (12500-16500)	255
	**2**				520 (440-600)	25000 (16000-36000)	48

[a] All values are the geometric means of results obtained in two to six separate experiments. Ranges are given in parenthesis.

The ability of compounds to displace [^{3}H] oxotremorine-M (OXO-M) binding provided a measure of affinity for the high affinity agonist state of the receptor. The ratio of the IC_{50} values for displacement of [^{3}H] quinuclidinyl benzilate (QNB) and OXO-M (QNB/OXO-M) was used to predict efficacy. Ratios greater than 100 are associated with full agonists; antagonists give ratios close to unity and intermediate values indicate partial agonists.[2] The effects of varying the azabicyclic ring, the oxime ether substituent R^2 and the substituent R^1 are shown in Table 1. Attachment of the aldoxime (R^1=H) and methyl ketoxime (R^1=Me) groups to the quinuclidine ring as in **3a** and **3b** resulted in affinities in the OXO-M assay which were at least 5-fold greater than that of the lead ester **2**. The QNB/OXO-M ratios of **3a** and **3b** suggest that the partial agonist character of the ester **2** is retained in these analogues. Variation of the azabicyclic ring produced a series of analogues **4a-6a** and **4b-6b** with moderate to high affinity. The more compact azabicyclo[2.2.1]heptane systems such as **5a** and **6a** showed moderately enhanced efficacies and **5a**, which has the highest affinity in the group and a ratio indicative of full agonist character, was used as the starting point for studying modifications of the substituent R^1, and the oxime ether alkyl group R^2. The scope for increasing the size of the R^1 substituent is extremely limited as illustrated by the drop in affinity and efficacy of the ethyl analogue **5c** relative to **5a**. A similar effect was observed on variation of the ether group R^2 as evidenced by the considerable decrease in both affinity and predicted efficacy observed as the size of the group is increased from methyl to butyl (see compounds **5a,d-f**). Interestingly, the propargyl ether **5g**[8] emerged as a high affinity partial agonist with an intermediate efficacy compared with the methyl and ethyl ethers **5a** and **5d**.

Table 2. Central Selectivity of Oxime Ethers[a]

COMPOUND	RSA (ED_{Arec}) (mg/kg iv)	BP (ED_{50}) (mg/kg iv)	BP (ED_{50})/ RSA (ED_{Arec})
5a	0.0021 (0.0010-0.0045)	0.0031 (0.0016-0.0063)	1.5
5d	0.23 (0.12-0.43)	>1.8	>7.8
5g	0.016 (0.009-0.028)	0.17 (0.13-0.21)	10.6

[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 iv) of arecoline. BP is the dose producing a 50% fall in mean blood pressure. Values in parenthesis indicate 95% confidence limits.

The availability of the sub-set of structurally related compounds **5a-5g** with efficacy ratios spanning the range from full to partial agonists provided an opportunity to probe for a possible link between CNS selectivity and efficacy. The induction of rhythmical slow wave activity (RSA) is a well characterised action of centrally penetrating muscarinic agonists.[9] We have used the induction of atropine sensitive RSA in the CA1 region of

the hippocampus of urethane anaesthetised rats as a model of cholinergic activation in a region of the brain critical in cognitive function. Effects of muscarinic agonists in this model are expressed as the dose of test drug able to elicit a change in the power spectrum equivalent to that of a standard dose (0.32 mg/kg iv) of arecoline (ED_{Arec}). Hypotension was also assessed in this model and recorded as the dose causing a transient 50% fall in mean blood pressure. This effect is peripherally mediated since it can be blocked by atropine methyl nitrate and therefore the ratio BP-ED_{50}/RSA-ED_{Arec} is a measure of central versus peripheral selectivity. Both partial and full agonists were able to elicit RSA (Table 2). Significantly, the partial agonists **5d** and **5g** produced RSA at doses well below those which gave rise to hypotension, whereas no such separation of effects was observed with the full agonist **5a**. These results demonstrate that central selectivity can be achieved with partial agonists. A possible explanation is a lower receptor reserve for the observed effect on blood pressure compared with the effect on the EEG. An additional factor likely to contribute to the observed selectivity is the increase in lipophilic character resulting from homologation of the oxime ether group R^1 which should facilitate CNS penetration. However, as shown above, the scope for further enhancement of lipophilic character is severely limited by the steric constraints on agonist binding.

In conclusion, we have shown that the oxime ether group serves as a versatile replacement for the ester function providing access to a series of muscarinic agonists with a range of efficacies. The propargyl ether **5g** stands out as a high affinity partial agonist with good central selectivity.

References and Notes

1. Pavia, M. R., Davis, R. E., Schwarz, R. D., *Annu. Rep. Med. Chem.*, **1990**, 25, 21.
2. Orlek, B. S., Blaney, F. E., Brown, F., Clark, M. S. G., Hadley, M. S., Hatcher, J., Riley, G. J., Rosenberg, H. E., Wadsworth, H. J., Wyman, P., *J. Med. Chem.*, **1991**, 34, 2726.
3. MacLeod, A. M., Baker, R., Freedman, S. B., Patel, S., Merchant, K. J., Roe M., Saunders, J., *J. Med. Chem.*, **1990**, 33, 2052.
4. Ringdahl, B., Roch M., Jenden, D. J., *J. Pharmacol. Exp. Ther.*, **1987**, 242(2), 464.
5. Loudon, J. M., Anderson, C. W., Brown, F., Clark, M. S. G., **1991**, Muscarinic agonists for counteracting the acetylcoline deficit. Functional selectivity for muscarinic effects on hippocampal EEG and the cardiovascular system in the anaesthetised rat. In: Neurodegeneration, Hunter, J., Clark, M., Eds., Academic Press, London, p 240 (in press).
6. Wadsworth, H. J., Jenkins, S. M., Orlek, B. S., Cassidy, F., Clark, M. S. G., Brown, F., Riley, G. J., Graves, D., Hawkins, J., Naylor, C. B., *J. Med. Chem.*, **1992**, 35, 1280.
7. Stereochemical assignments were based on ^1H NMR. The aldehydic protons in the *anti* oxime ethers resonate at higher field than those of the *syn* by 0.5-0.7ppm. (Lustig, E., *J. Phy. Chem.*, **1961**, 65, 491). Where mixtures were obtained ready isomerization precluded separation. Ketoxime ethers were confirmed as *syn* by nOe experiments.
8. The use of the propargyl group in a series of arecoline analogues has previously been described: Mosser, U., Lambrecht, G., Wagner, M., Wess, J., Mutschler, E., *Br. J. Pharmacol.*, **1989**, 96, 319.
9. Bevan, P., *Br. J. Pharmacol.*, **1984**, 82, 431.