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BRIDGED 1,2,5,6-TETRAHYDROPYRIDINE ESTERS AND OXIME ETHERS RELATED TO ARECOLINE ARE NOVEL AND POTENT MUSCARINIC AGONISTS

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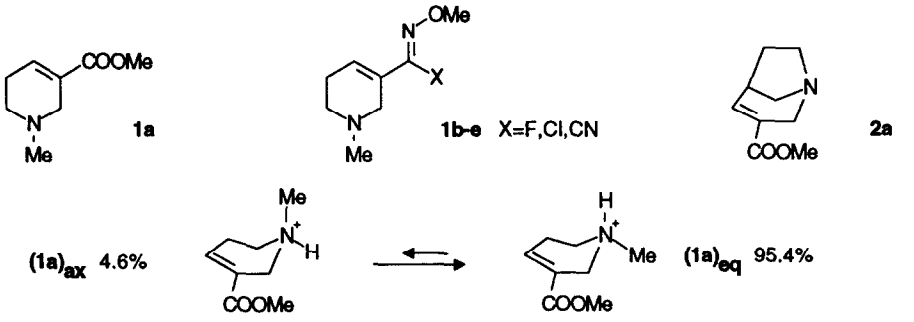
Abstract: Constraining the 1,2,5,6-tetrahydropyridine ring of arecoline **1a** and the related muscarinic agonists **1b-e** by replacing the N-methyl group by an ethano bridge between the nitrogen and the C5-position afforded compounds **2a-e.** These compounds have enhanced affinities for muscarinic receptors which supports our proposed binding conformation $(\mathbf{1a})_{ax}$ of arecoline.

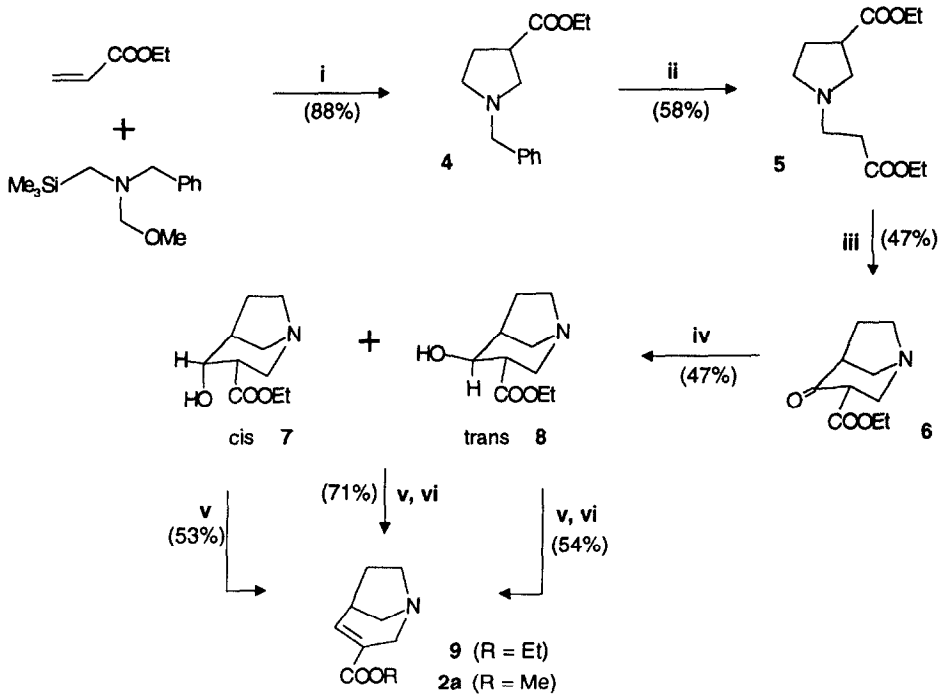
There has been considerable recent interest in the potential of cholinomimetics as cognition enhancers for the treatment of senile dementia of the Alzheimer type (SDAT).[1] Clinical evaluation of the classical muscarinic agonist arecoline **1a** produced small improvements in patients suffering from SDAT. However, the potential benefits of the drug are compromised by its poor metabolic stability and peripheral side effects.[2] This has led to the development of muscarinic agonists related to arecoline in which the ester group has been replaced by a metabolically stable bioisostere such as a heteroaromatic ring[3] or an oxime ether group.[4] We recently reported that the combination of N-methoxy imidoyl halide or nitrile moieties with the 1,2,5,6-tetrahydropyridine ring system afforded potent muscarinic agonists **1b-e.**[5] In addition to metabolic stability, some of these compounds showed favourable functional selectivity which we related to their partial agonist nature.



In an earlier report[6] we hypothesised that the muscarinic affinity of arecoline is associated with the conformer in which the N-methyl group adopts an axial orientation $(\mathbf{1a})_{ax}$. Although the calculated energy of the axial conformer $(\mathbf{1a})_{ax}$ is higher than that of the equatorial conformer $(\mathbf{1a})_{eq}$, the difference is only 1.87 kcal/mol and the Boltzmann population distribution at 37°C indicates a significant contribution from $(\mathbf{1a})_{ax}$.

This reasoning led us to prepare azabicyclic esters in which a six-membered piperidine ring is constrained in either a boat or a chair conformation by a bridging group which effectively fulfills the requirement for an axially orientated nitrogen substituent. We then went on to develop a wide range of ester bioisosteres some of which gave compounds of extremely high affinities for muscarinic receptors with a range of efficacies.[6,7]

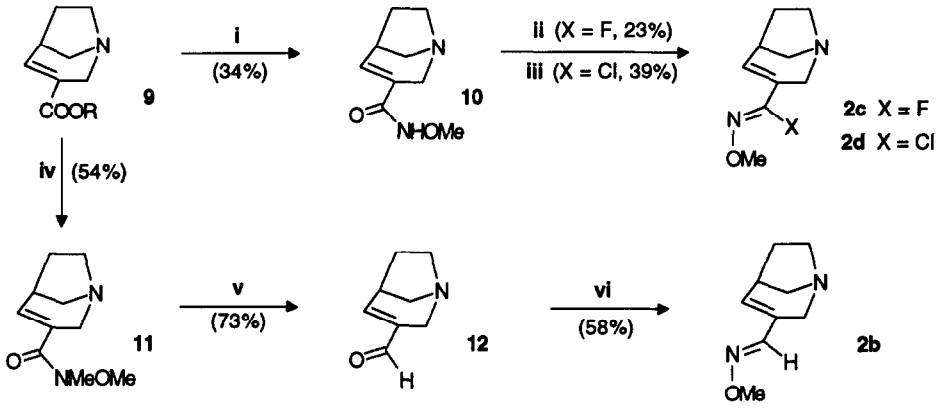
The success of this approach has encouraged us to test our hypothesis further and this paper reports the preparation of the ester **2a** in which the 1,2,5,6-tetrahydropyridine ring has been constrained in a half-chair conformation by an ethano bridge between the nitrogen and the 5-position.[8] As with the azabicyclic compounds, the nitrogen substituent is tied back in the proposed "axial" binding conformation. In addition bioisosteric replacements of the ester group by aldoxime ether, N-methoxy imidoyl halide and N-methoxy imidoyl nitrile moieties have been investigated in this novel ring system.[9]



Scheme 1 *Reagents and conditions;* **i**, TFA, CH_2Cl_2, -5°C - reflux, 2h; **ii**, a) HCO_2NH_4 / 10% Pd/C, EtOH, 70°C, 2h, b) ethyl acrylate, EtOH, reflux, 1h; **iii**, a) ^tBuOK, toluene, reflux, 3h, b) acetic acid, -15°C; **iv**, $NaBH_4$, EtOH, 0°C to rt, 1h; **v**, MsCl, pyridine, 0°C to rt, 3h; **vi**, NaOAc, DMF, 100°C, 2h

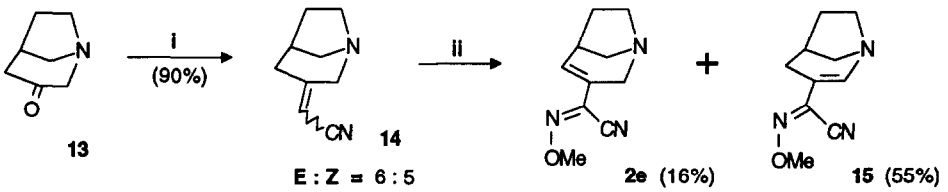
The target ester **2a** was prepared by the route shown in Scheme 1. Treatment of N-benzyl-N-(methoxy)methyl-N-[(trimethylsilyl)methyl]amine with trifluoroacetic acid in dichloromethane generated the azomethine ylide which underwent smooth 1,3-dipolar cycloaddition with ethyl acrylate to afford the pyrrolidinyl ester **4** in good yield.[10] Debenzylation, followed by Michael addition of the resulting secondary amine to ethyl acrylate, yielded the diester **5**, which underwent Dieckmann cyclization[11] to the β-keto ester **6**

on treatment with potassium *t*-butoxide followed by quenching with acetic acid. Reduction of **6** with sodium borohydride yielded an easily separable 4:3 mixture of *cis* **7** and *trans* **8** alcohols. The *cis* isomer **7** readily underwent dehydration on treatment with methanesulphonyl chloride in pyridine to afford the unsaturated ester **9**. In the case of the *trans* isomer **8** it was necessary to heat the intermediate mesylate with sodium acetate in DMF in order to achieve the conversion to **9**. We later discovered that mixtures of the isomers could be conveniently processed to **9** under the conditions developed for the *trans* isomer **8**. The ethyl ester **9** was converted to the required methyl ester **2a** by transesterification using methanolic HCl.



Scheme 2 *Reagents and conditions;* **i**, a) 85% KOH, EtOH, reflux, 9h, b) $SOCl_2$, reflux, 0.5h, c) $NH_2OMe.HCl$/pyridine, CH_3CN, -30°C, overnight; **ii**, DAST, CH_3CN, reflux, 2 min; **iii**, PPh_3/CCl_4, CH_3CN, reflux, 0.5h; **iv**, a) 5M HCl, reflux, 7h, b) $SOCl_2$, reflux, 10 min, c) MeONHMe.HCl/pyridine, $CHCl_3$, 0°C - rt, overnight; **v**, DIBAL, THF, -70°C - 0°C, 1h; **vi**, $NH_2OMe.HCl$, MeOH, rt, 17h

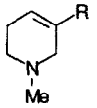
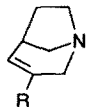
The unsaturated ester **9** was also used as the starting point for the synthesis of the N-methoxy imidoyl chloride **2d**, fluoride **2c** and the aldoxime **2b** (Scheme 2). The ester **9** was converted to the methoxyamides **10** and **11** by standard methodology *via* the acid chlorides. Treatment of the methoxyamide **10** in refluxing acetonitrile with triphenylphosphine and carbon tetrachloride or diethylaminosulphur trifluoride (DAST), respectively, afforded the N-methoxy imidoyl chloride **2d** and fluoride **2c** as single stereoisomers.[12] The N-methyl-N-methoxyamide **11** was converted using the Weinreb approach[13] to the aldehyde **12** which afforded the *syn*-aldoxime **2b** on treatment with methoxylamine hydrochloride.



Scheme 3 *Reagents and conditions;* **i**, $(EtO)_2POCH_2CN$/^{t}BuOK, THF, -20°C - rt, 1h; **ii**, a) ^{t}BuOK, THF, -60°C, 0.5h, b) ^{t}BuONO, -60°C - rt, 2h, c) MeOTs, rt, overnight

The N-methoxy imidoyl nitrile **2e** was prepared by a one-pot nitrosation and alkylation procedure[5] on the acrylonitrile **14**, itself obtained by Wittig reaction of diethyl cyanomethylphosphonate with the known[11] ketone **13**. Unfortunately, the isomeric compound **15** was obtained as the major product (Scheme 3).

Table. Affinities of Oxime Ethers for Muscarinic Receptors in Rat Cerebral Cortex[#]

1 =  **2** = 

R	Cmpd	IC_{50}, nM		Efficacy ratio IC_{50} QNB/ IC_{50}OXO-M
		OXO-M	QNB	
COOMe (a)	**1a** (arecoline)	120 (75-170)	25000 (10000-110000)	210
	2a	27 (21-36)	3800 (3400-4200)	140
 (b)	**1b**	110 (65-260)	14000 (9700-23000)	130
	2b	64 (62-70)	960 (730-1300)	15
 (c)	**1c**	39 (28-58)	4000 (1500-7200)	100
	2c	26 (15-56)	630 (320-1100)	24
 (d)	**1d**	260 (240-290)	2800*	11
	2d	69 (48-100)	770 (530-1100)	11
 (e)	**1e**	150 (120-220)	4500 (4300-9500)	30
	2e	20 (18-21)	350 (330-360)	17

[#]The entry marked with an asterisk is a single result, all other values are geometric means of results obtained in two or more separate experiments. Ranges are given in parenthesis.

The affinity and efficacy of the compounds were assessed by a two stage binding assay designed to measure both parameters. The ability of the compounds to inhibit the binding of the muscarinic agonist [^{3}H] oxotremorine-M (OXO-M) provided a measure of affinity for the high affinity agonist state of the receptor. The ratio of the IC_{50} values for inhibition of binding of [^{3}H] quinuclidinyl benzilate (QNB), a muscarinic antagonist, and 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.[6] The results are shown in the Table together with those of the N-methyl-1,2,5,6-tetrahydropyridine analogues **1a-e**[5] for comparison.

The azabicyclic ester **2a** shows an affinity for muscarinic receptors about four times that of arecoline **1a** with an efficacy ratio approximately 2/3 that of **1a**, but still predictive of full agonism. Similarly the azabicyclic oximes **2b-e** display higher affinity than the monocyclic analogues **1b-e**, although the enhancements in affinity are modest. The efficacy ratios are also generally lowered (with the exception of **1d** vs **2d**) and are predictive of partial agonists. This decrease in efficacy is probably related to the increased steric demands of the azabicyclic ring and is consistent with our earlier findings that marked changes in efficacy can be effected by relatively subtle structural changes.[6]

The increased affinities of **2a-2e** over **1a-1e** provides additional support for the hypothesis that the N-methyl group of arecoline is axial in the binding conformation. Recent efforts by others to mimic alternative binding conformations of arecoline have been less successful.[14,15] The enantiomers of 6-carbomethoxy-2-methyl-2-azabicyclo[2.2.1]heptane were prepared as rigid analogues of the X-ray conformations of arecoline and found to be only weak partial agonists.[14] Interestingly, their lack of muscarinic activity was attributed to an unfavourable equatorial orientation of the N-methyl group. A related study reported that bridging the C-2 and C-5 positions of the potent muscarinic agonist 3-(3-amino-1,2,4-oxadiazol-5-yl)-1-methyl-1,2,5,6-tetrahydropyridine by an ethano bridge also led to loss of affinity for muscarinic receptors.[15]

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References and Notes

1. Pavia, M. R., Davis, R. E., Schwarz, R. D., *Annu. Rep. Med. Chem.*, **1990**, 25, 21.

2. Christie, J. E., Shering, A., Ferguson, J., Glen, A. I., *Br. J. Psychiatry*, **1981**, 138, 46.

3. Saunders, J., Cassidy, M., Freedman, S. B., Harley, E. A.,Iversen, L. L., Kneen, C., MacLeod, A. M., Merchant, K. J., Snow, R. J., Baker, R., *J. Med. Chem.*, **1990**, 33, 1128.

4. (a) Toja, E., Bonetti, C., Butti, A., Hunt, P., Fortin, M., Barzaghi, F., Formento, ML., Maggioni, A., Nencioni, A., Galliani, G., *Eur. J. Med. Chem.*, **1991**, 26, 853. (b) Bergmeier, S. C., Downs, D. A., Moos, W. H., Moreland, D. W., Tecle, H., *U. S. Pat. Applic.* Dec. 1, **1987**, 4 710 508, Warner-Lambert Company.

5. Bromidge, S. M., Brown, F., Cassidy, F., Clark, M. S. G., Collings, E. J., Dabbs, S., Faulkner, R. E., Loudon, J. M., Orlek, B. S., Riley, G. J., *BioMed. Chem. Lett.*, **1994**, 4, 557.

6. 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.

7. a) 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. b) Jenkins, S. M., Wadsworth, H. J., Bromidge, S. M., Orlek, B. S., Wyman, P. A., Riley, G. J., Hawkins, J., *J. Med. Chem.*, **1992**, 35, 2392. c) Bromidge, S. M., Brown, F., Cassidy, F., Clark, M. S. G., Dabbs, S., Hadley, M. S., Loudon, J. M., Orlek, B. S., Riley, G. J., *BioMed. Chem. Lett.*, **1992**, 2, 787. d) Bromidge, S. M., Brown, F., Cassidy, F., Clark, M. S. G., Dabbs, S., Hawkins, J., Loudon, J. M., Orlek, B. S., Riley, G. J., *ibid*, **1992**, 2, 791.

8. Orlek, B. S., Bromidge, S. M., Faulkner, R. E., WO 92/03435.

9. We thank a referee for pointing out that subsequent to our work an alternative synthesis of the ester **2a** from 1-azabicyclo[3.2.1]octan-3-one in an overall yield of 10% has been reported : Dick, M. R., Chang, C., Dripps, J. E., Wollowitz, S., WO 93/14636.

10. The procedure used was that developed by Terao *et al.* for the synthesis of methyl N-benzyl-3-pyrrolidinylcarboxylate : Terao, Y., Kotaki, H., Imai, N., Achiwa, K., *Chem. Pharm. Bull.*, **1985**, 33, 2762.

11. Dieckmann cyclisation of ethyl N-(2-ethoxycarbonylethyl)-3-pyrrolidinylcarboxylate **5** to give 1-azabicyclo[3.2.1]octan-4-one has been reported, however, the intermediate β-keto ester **6** was not isolated : Thill, P. T., Aaron, H. S., *J. Org. Chem.*, **1968**, 33, 4376.

12. Stereochemistry was tentatively assigned as *Z* on the basis of NMR studies and precedent with the 1,2,5,6-tetrahydropyridine analogues **1c** and **1d** : see reference 5.

13. Nahm, S., Weinreb, S. M., *Tetrahedron Lett.*, **1981**, 22, 3815.

14. Pombo-Villar, E., Supavilai, P.,Weber, H. P., Boddeke, H. W. G. M., *BioMed. Chem. Lett.*, **1992**, 2, 501.

15. Triggle, D. J., Kwon, Y. W., Abraham, P., Rahman, M. A., Carroll, F. I., *Pharmaceutical Research*, **1992**, 9, 1474.

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