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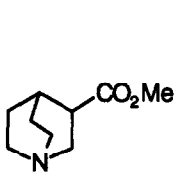
DESIGN AND SYNTHESIS OF NOVEL MUSCARINIC AGONISTS CONTAINING THE 1,2,4-TRIAZINE RING AS AN ESTER BIOISOSTERE

Barry S. Orlek*, Frederick Cassidy, Michael S. G. Clark, Richard E. Faulkner, Emma J. Collings, Julie Hawkins and Graham J. Riley.

SmithKline Beecham Pharmaceuticals,
Coldharbour Road, The Pinnacles, Harlow, Essex, CM19 5AD UK.

Abstract: Replacement of the ester group in methyl quinuclidine-3-carboxylate **1** with a 1,2,4-triazine ring afforded the high affinity muscarinic partial agonist **6a**. Analogues **7a**, **7b** and **7d** which incorporate the 1-azabicyclo[2.2.1]heptane ring also display high affinity for muscarinic receptors.

The recent upsurge of interest in cholinomimetics, stimulated by the potential of such agents as cognition enhancers, has resulted in the discovery of new and structurally diverse muscarinic agonists.[1] Using the weak muscarinic agonist methyl quinuclidine-3-carboxylate **1** as a starting point, we have shown that replacement of the ester group with a 1,2,4-oxadiazole ring results in a marked increase in affinity.[2] An additional facet of this earlier work was the finding that in addition to quinuclidine other bridged azabicyclic ring systems could be tolerated at muscarinic receptors, and this culminated in the discovery of the very potent agonist **2**. Subsequent studies which focused on triazoles and tetrazoles as ester replacements, led to novel muscarinic agonists such as **3**.[3,4]



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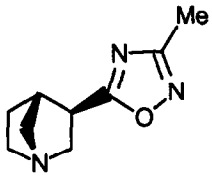

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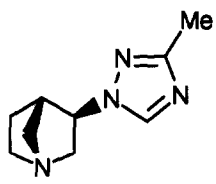
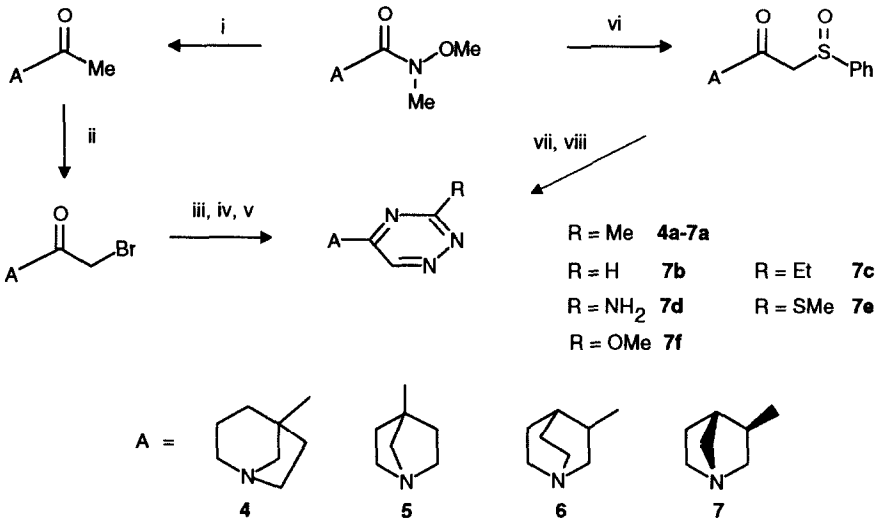


3

In view of the success of this approach it was of interest to determine whether six membered heteroaromatic rings could also function as ester bioisosteres.[5] Comparison of electrostatic potential maps of the 1,2,4-triazine and 1,2,4-oxadiazole rings revealed similarities in terms of the location of the potential minima. In this letter we describe the synthesis and biological profiles of a novel series of muscarinic agonists which incorporate the 1,2,4-triazine ring in conjunction with azabicyclic ring systems derived from earlier studies.

Two synthetic approaches to the the target 1,2,4-triazines were developed (Scheme 1). Both sequences rely on N-methoxy-N-methylcarboxamide precursors which are readily accessible from the corresponding azabicyclic esters.[3,4] The route to the 3-methyl-1,2,4-triazines **4a** and **5a** required conversion of the N-methoxy-N-methylcarboxamides into the corresponding methyl ketones with methyl lithium.[4] Bromination of the ketones, protected as hydrobromide salts, with bromine in methanol[6] afforded the α-bromomethyl ketones which were oxidised with dimethyl sulfoxide using a modified Kornblum procedure. The resulting crude α-keto aldehydes were immediately treated with acetamidrazone to give moderate yields (33-44%) of the 1,2,4-triazines **4a** and **5a**. However for **6a** and **7a**, where the heteroaromatic ring is not attached to the bridgehead carbon, yields were low. A more general route proceeds via the α-keto sulfoxides derived from the corresponding N-methoxy-N-methylcarboxamides. Pummerer rearrangement of the sulfoxides using a combination of trifluoroacetic acid anhydride and trifluoroacetic acid, followed by treatment with the appropriate amidrazone, afforded good yields of **6a** and **7a-c**.[7,8] The 3-amino and 3-methylthio analogues **7d** and **7e** were obtained using aminoguanidine and S-methylisothiosemicarbazide, respectively, in the final step. Treatment of the 3-methylthio analogue **7e** with sodium methoxide afforded the methoxy analogue **7f.**

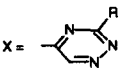


Scheme 1. *Reagents and conditions:* **i**, MeLi; **ii**, a) HBr b) Br_2, MeOH ; **iii**, DMSO, 18 h ; **iv**, Concentration *in vacuo* then 120°C, N_2, 5 min ; **v**, Aqueous $NaHCO_3$, R-C(=NH_2)$NHNH_2$·HCl; **vi**, PhS(=O)Me, n-BuLi, THF ; **vii**, CF_3CO_2H, $(CF_3CO)_2O$, CH_2Cl_2 ; **viii**, Aqueous $NaHCO_3$ then R-C(=NH_2)$NHNH_2$·HCl.

Affinity for muscarinic receptors was assessed by measuring the ability of compounds to inhibit [^{3}H] oxotremorine-M (OXO-M) binding. The ratio of the IC_{50} values for inhibition of [^{3}H] quinuclidinyl benzilate (QNB) and OXO-M was used to predict efficacy.[2]

As indicated in Table 1 the 3-methyl-1,2,4-triazines **6a** and **7a** display affinities in the OXO-M assay which are comparable to that of the potent 1,2,4-oxadiazole **2**. In contrast, affinities of the bridgehead substituted isomers **4a** and **5a** are approximately ten fold lower. The desmethyl analogue **7b** has similar affinity to **7a**. This finding stands in contrast to earlier studies with five membered ring bioisosteres.[3,4] For example, the 3-methyl-1,2,4-triazole **3** displays higher affinity relative to the analogue unsubstituted at the 3-position and this was interpreted in terms of a binding pocket at the receptor capable of accommodating the methyl group. The observation that **7a** and **7b** bind with comparable affinities suggests that there are differences in the steric accommodation of the larger heteroaromatic ring. Increasing the size of the 3-substituent to ethyl as in **7c** resulted in a ten fold drop in affinity. The higher efficacy ratio of **7b** relative to the 3-methyl and 3-ethyl analogues **7a** and **7c** is consistent with earlier studies linking size and efficacy.[2] The 3-amino analogue **7d** is an exceptionally high affinity agonist with a ratio predictive of full agonist character, and this profile is similar to that reported for muscarinic agonists containing the 3-amino-1,2,4-oxadiazole group.[9] The bulkier heteroatom containing groups in **7e** and **7f** produced compounds with reduced affinities and efficacy ratios.

Table 1. Affinities of 1,2,4-Triazines for Muscarinic Receptors in Rat Cerebral Cortex[a]

X = 	Cmpd	R	IC_{50}, nM		IC_{50} QNB/ IC_{50}OXO-M
			OXO-M	QNB	
	**4a**	Me	33 (29.5-35)	1800 (1800)	55
	**5a**	Me	70 (54-87)	4100 (3800-4400)	59
	**6a**	Me	4 (3.3-4.9)	225 (175-290)	56
	**7a**	Me	3.9 (3.1-4.8)	410 (255-650)	105
	7b	H	3.8 (2.15-6.6)	1400 (975-2100)	370
	7c	Et	46 (45-65)	410 (240-600)	9
	7d	NH_2	2.1 (1.1-3.0)	990 (320-1800)	460
	7e	SMe	290 (240-360)	1300 (1050-1600)	4.5
	7f	OMe	140 (130-160)	2400 (2050-2900)	17
	2		2.8 (1.6-3.9)	1000 (930-1100)	360

[a] The ability of compounds to inhibit [^{3}H] oxotremorine-M (OXO-M) binding provides a measure of affinity for the high affinity agonist state of the receptor. The ratio of the IC_{50} values for inhibition of [^{3}H] quinuclidinyl benzilate (QNB) and OXO-M (QNB/OXO-M) can be 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] All values are the geometric means of results obtained in two to four separate experiments. Ranges are given in parenthesis.

In conclusion, the 1,2,4-triazines described here constitute a new series of muscarinic agonists which rank with the most potent agonists reported to date. This study establishes the 1,2,4-triazine ring as a valuable ester bioisostere in the context of muscarinic receptor ligands.

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