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Z-(±)-1-AZABICYCLO[2.2.1]HEPTAN-3-ONE, O-(3-ARYL-2-PROPYNYL) OXIMES AS POTENTIAL m1-SUBTYPE SELECTIVE MUSCARINIC AGONISTS.

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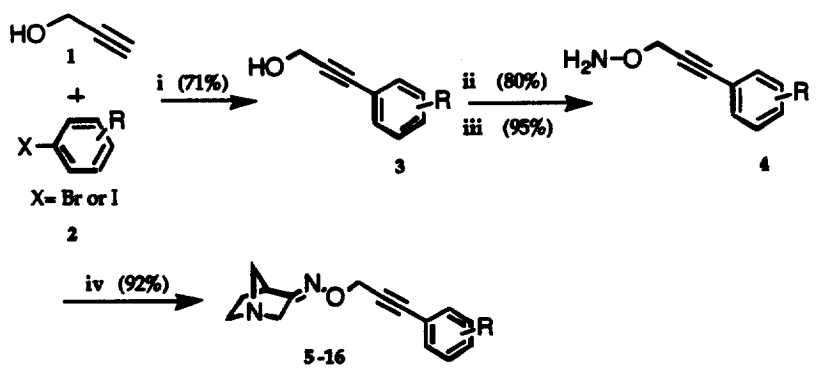
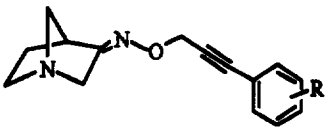
Abstract. The synthesis and SAR of a series of Z-(±)-1-azabicyclo[2.2.1]heptan-3-one, O-(3-aryl-2-propynyl) oximes are described. The biochemistry and pharmacology of PD 142505 (**5b**), an oxime with pronounced functional m1 selectivity, are highlighted.

Five muscarinic receptor subtypes (m1-m5) with unique protein structures have been described (1). Because of the unique distribution of m1 receptors in the peripheral and central nervous system, m1 agonists have the potential to enhance cognitive function in conditions such as Alzheimer's disease that are associated with a cholinergic deficit, without inducing unwanted cholinomimetic side-effects. Muscarinic agonists are usually small molecules with very little tolerance for steric bulk (2). Consequently, within a series, the number of active analogs is severely limited. We have previously described the preparation of some bulky 1-azabicyclo[2.2.1]heptan-3-one oximes and demonstrated their effectiveness as muscarinic agonists (2). This paper describes the preparation and evaluation of a series of such oximes as pharmaceutically useful, m1-subtype selective muscarinic agonists.



Scheme 1. *Reagents and conditions*; **i**, $(Ph_3P)_4Pd$, CuI, Et_2NH, THF, RT; **ii**, N-hydroxyphthalimide, Ph_3P/THF; **iii**, H_2NNHCH_3/CH_2Cl_2, RT; **iv**, 1-azabicyclo[2.2.1]heptan-3-one, MeOH, RT.

Table 1. Muscarinic Binding Profile of of Z-(±)-1-Azabicyclo[2.2.1]heptan-3-one, O-(3-aryl-2-propynyl) oximes.



No	R	IC_{50} nM[a] (% inhib.)[b] CMD	QNB	QNB/CMD	m2 (IC_{50})[c] / m1 (IC_{50})[d]
5a	p-OCH_3	110	13101	119	8.0
5b	m-OCH_3	28	6927	250	6.8
5c	o-OCH_3	219	17658	81	4.2
6a	p-F	30	6092	204	5.0
6b	m-F	37	4925	132	5.0
6c	o-F	28	4443	159	5.2
7a	p-Cl	53	6300	119	6.2
7b	m-Cl	19	3882	202	6.2
7c	o-Cl	12	1305	107	3.6
8	*H*	46	5012	109	4.8
9	m-NO_2	28	6399	226	3.1
10a	p-CH_3	89	11089	125	2.7
10b	m-CH_3	28	5195	186	-
10c	o-CH_3	(82%)	(56%)	-	-
11	m-CF_3	32	4237	134	1.7
12	3,4-di-CH_3O	140	42449	303	-
13	3,4-(OCH_2O)	23	2547	110	
14	3,4-(OCH_2CH_2O)	(39%)	(0%)	-	-
15	3,5-di-Cl	(53%)	(18%)	-	-
16	3,5-di-(CF_3)$_2$	(55%)	(18%)	-	-
	Carbachol	6.7	33000	4925	0.05

[a]For IC_{50} determination, each drug was investigated in triplicate at 5-6 concentrations. [b]Values represent % inhibition of QNB and CMD binding at drug concentrations of 1μM and 100 nM respectively. [c]IC_{50} value determined from inhibition of [^{3}H]-QNB to membranes from CHO-Hm2 cells. [d]IC_{50} value determined from inhibition of [^{3}H]-QNB to membranes from CHO-Hm1 cells.

Table 2. Second Messenger Activation in CHO-Hm1- CHO-Hm5 Cells

	PI[a] % Carbachol			cAMP[b] % Inhibition	
Compound	Hm1	Hm3	Hm5	Hm2	Hm4
8	40	8	1	0	0
5b (PD 142505)	51	6	11	0	0
Carbachol	100	100	100	58	60

[a]Stimulation of inositol phospate (PI) accumulation in transfected CHO cells. Values are maximal response obtained from each drug, tested up to 100 μM, normalized to the effects of carbachol. Assays run in triplicate. [b]Reversal of forskoline-stimulated adenylate cyclase in transfected CHO cells. Values are the maximal reversal obtained for each drug, tested up to concentrations of 1 mM.

We propose that compounds which are longer and larger than their non-selective counterparts may bring the agonist into proximity with parts of the receptor unique to a particular subtype. PD 142505 (**5b**), a member of the Z-(±)-1-azabicyclo[2.2.1]heptan-3-one, O-(3-aryl-2-propynyl) oximes, appears to fulfill this requirement. The synthesis and SAR of a series of Z-(±)-1-azabicyclo[2.2.1]heptan-3-one, O-(3-aryl-2-propynyl) oximes in general and the biochemistry and pharmacology of PD 142505 (**5b**), in particular is outlined.

The target oximes were prepared as shown in Scheme 1. Palladium (0)-assisted cross-coupling reaction between propargyl alcohol (**1**) and an aryl bromide or aryl iodide gave the corresponding alcohols, **3**. The alcohols reacted with N-hydroxyphthalimide via the Mitsunobu reaction to give the corresponding O-substituted phthalimides. Hydrolysis of the phthalimides at room temperature with N-methylhydrazine afforded hydroxylamines **4**. Appropriately substituted hydroxylamines reacted with 1-azabicyclo[2.2.1]heptan-3-one (**3**), to give a 60:40 mixture of Z/E oximes. An equilibrium mixture of 85:15 Z/E oximes was obtained when a methanolic-HCl solution of the 60:40 mixture was kept at room temperature for one hour. The Z oximes **5-16** (Table 1) were separated from the corresponding E oximes by medium pressure chromatography on silica eluted with CH_2Cl_2:MeOH (99.5:0.5). The E oximes are devoid of muscarinic activity.

Muscarinic receptor binding assays (Table 1) were conducted using [^{3}H]-quinuclidinyl benzilate (QNB) to label antagonist sites and [^{3}H]-cis-methyldioxolane (CMD) to label agonist sites in membrane preparations from rat neocortex (4, 5). The ratio of QNB/CMD binding affinities has been shown to predict agonist efficacy at muscarinic receptors (6). Selectivity for m1 over m2 muscarinic subtypes was determined by estimating the affinity of compounds for m1 and m2 receptor subtypes labelled by [^{3}H]-QNB in CHO cells selectively expressing human m1 and m2 receptors (7). The ability of PD 142505 (**5b**) and parent oxime (**8**) to stimulate inositol phosphate accumulation (8) or inhibit forskolin-stimulated accumulation of cAMP in CHO cells selectively expressing human m1 or m2 receptors (7) respectively, was determined (Table 2). Effects of PD 142505 on cellular metabolic activity in live CHO cells expressing human m1- and m2 receptors (Figs 1 and 2)

Fig. 1. Effects of PD 142505 and Carbachol on Cellular Metabolic Activity in CHO-Hm1 Cells

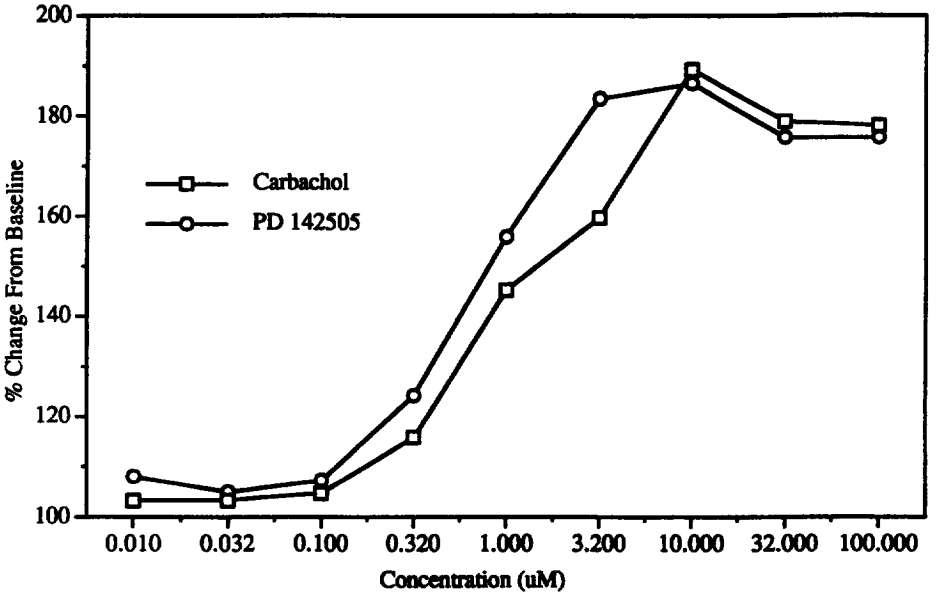


Fig. 2. Effects of PD 142505 and Carbachol on Cellular Metabolic Activity in CHO-Hm2 Cells

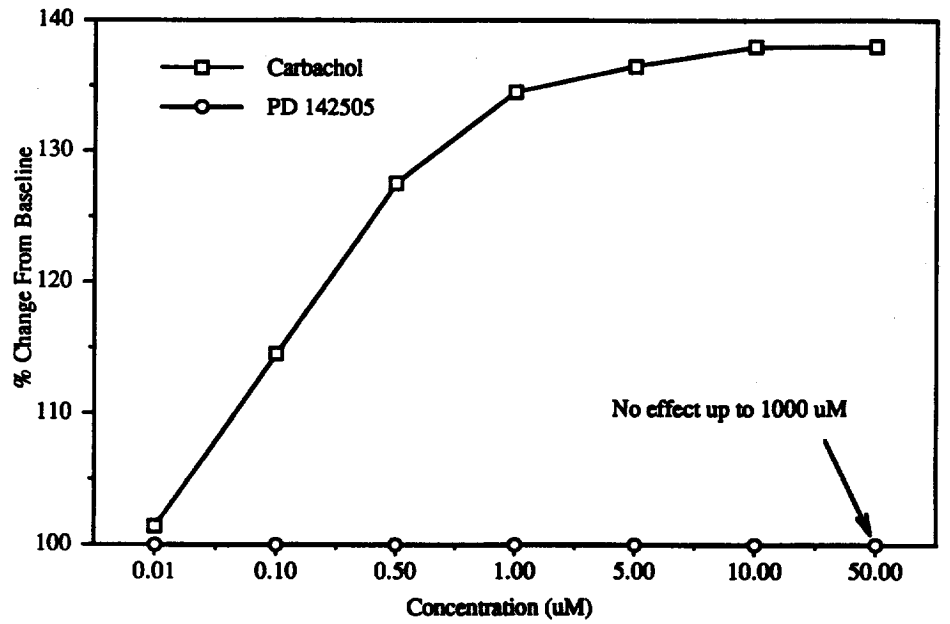
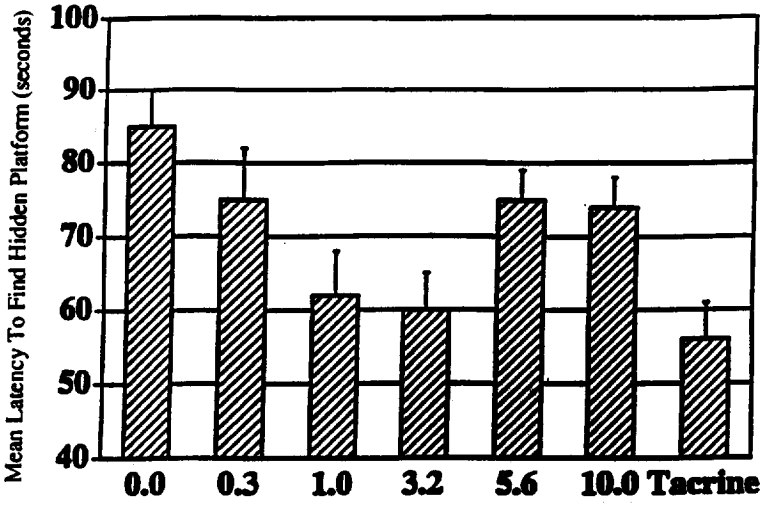


Fig. 3. Effects of PD 142505 in the Mouse Water Maze Performance



was measured with a Cytosensor™ Microphysiometer (9). Metabolically active cells excrete protons to their environment. The Cytosensor™ Microphysiometer measures the rate of proton excretion. GI motility and related cholinomimetic side effects (lachrymation, diarrhea, salivation) were assessed in rats (data not shown). The effects of PD 142505 on the ability of hippocampally deficient C57BL/10 mice to locate a hidden platform in a modified water -maze (10) was used to measure improvement in spatial memory (Fig 3).

Several oximes (**7c**, **7b**, **5b**, **6c**, **9**, **10b**, with CMD IC_{50} values of 12 nM, 19 nM, 28 nM, 28 nM, 28 nM, and 28 nM respectively) are potent muscarinic agonists (Table 1). Electronic factors do not seem to influence potency. Both electron withdrawing, F, Cl, and NO_2 (**6c**, **7c** and **9** respectively) and electron donating groups, OMe and CH_3 (**5b** and **10b** respectively) lead to potent analogs. The effect of regioisomeric substitution on the phenyl ring is unpredictable. For example: The m-OMe oxime (**5b**) is 8-fold more potent than the o-OMe analog (**5c**). On the other hand, the m-Cl analog **7b** is equipotent to the o-Cl analog (**7c**). A similar argument may be made regarding selectivity for m1 muscarinic syptypes as measured by m2/m1 ratio. The most m1-selective analogs, **5a** and **5b** (PD 142505) have OMe for substituent. At the second messenger level, PD 142505 is selective for m1 over m2, m3, and m4 muscarinic receptor subtypes (Table II). PD 142505 has no detectable effect on the cellular metabolism of CHO-Hm2 cells but increases the metabolic rate of CHO-Hm1 cells by 40% over baseline (Fig 1 and Fig. 2). Preliminary data indicate a good separation between behaviorally efficacious doses and doses at which side effects (GI, salivation, lachrymation and diarrhea, data not shown) occur. No

overt signs of peripheral cholinomimetic stimulation at oral doses up to 178 mg/kg were evident. On the other hand, PD 142505 improved the ability of C57/B10J mice to locate a hidden platform in a modified water-maze at oral doses of 1.0 and 3.2 mg/kg (Fig. 3).

PD 142505 is a selective, centrally active m1 muscarinic agonist with a decreased liability for inducing unwanted peripheral cholinergic effects. Additional information on the enantiomers of PD 142505 will be published elsewhere.

References

1. Hulme, E.C.; Birdsall, N.J.M.; Buckley, N.J. *Ann. Rev. Pharmacol. Toxicol.* **1990**, 30, 633.
2. Tecle, H.; Lauffer, D. J.; Mirzadegan, T.; Moos, W. H.; Moreland, D. W.; Pavia, M. R.; Schwarz, R. D.; Davis, R. E. *Life Sci.* **1993**, 52, 505.
3. Saunders, J.; MacLeod, A. M.; Merchant, J. K.; Showel, G. A.; Snow, R. J.; Street, L. J.; Baker, R. *J. Chem. Soc., Chem. Comm.* 1988, 1618.
4. Vickroy, T.W.; Roeske, W.R.; Yamamura, H.I.; *J. Pharmacol. Exp. Ther.* **1984**, 229, 747.
5. Watson, M.; Yamamura, H.T.; Roeske, W.R. *J. Pharmacol. Exp. Ther.* **1986**, 237, 411.
6. Tecle, H.; Bergmeier, S.; Moos,W.; Hershenson, F.; Coughenour, L.; Davis, R.; Schwarz,R.; Moreland, D.; Dudley, D. *Abstracts of papers,* 197th National Meeting of the American Chemical Society, Dallas, Tex; American Chemical Society; Washington, DC, **1989**; Abstract MEDI-47.
7. Schwarz, R.D.; Boyd, D.K.; Spencer, C.J.; Woodard, G. *Abstract of papers*, 21st Annual Meeting of the Society for Neuroscience, New Orleans, LA; Society for Neuroscience; Washington, D.C. **1991**; Abstract 233.5
8. Schwarz, R. D.; Coughenour, L. L.; Davis, R. E.; Moos, W.; Spencer, C. J. *Abstracts of papers,* 17th Annual Meeting of the Society for Neuroscience, New Orleans, LA Society for Neuroscience; Washington, D.C. **1987**; Abstract 135.14
9. McConnell, H.M.; Owicki, J. C.; Parce, J.W.; Miller, D. L.; Baxter, G. T.; Wanda, H. G.; Pitchford, S. *Science* **1992**, 257, 1906.
10. Symons, J. P.; Davis, R. E.; Marriot, J. G. *Life Sci.* **1988**, 42, 375 .

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