Design and Synthesis of m1-Selective Muscarinic Agonists: (*R*)-(−)-(*Z*)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-(3-(3′-Methoxyphenyl)-2-propynyl)-oxime Maleate (CI-1017), a Functionally m1-Selective Muscarinic Agonist

Haile Tecle,* Stephen D. Barrett, David J. Lauffer, Corinne Augelli-Szafran, Mark R. Brann,†
Michael J. Callahan, Bradley. W. Caprathe, Robert E. Davis, Patricia D. Doyle, David Eubanks,†
William Lipiniski, Tara Mirzadegan, Walter H. Moos, D. W. Moreland, Carrie B. Nelson, Michael R. Pavia,
Charlotte Raby, Roy D. Schwarz, Carolyn J. Spencer, Anthony J. Thomas, and Juan C. Jaen

Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan 48106-1047, and Receptor Technologies, Inc., Winooski, Vermont 05404

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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 **24Z** (PD 142505) and its enantiomers are highlighted. **24Z** is functionally an m1-selective muscarinic agonist. Efficacy and m1 selectivity reside in the *R* enantiomer, **(*R*)-24Z** (CI-1017).

Introduction

Alzheimer's disease (AD) is generally characterized by symptoms of forgetfulness, confusion, memory loss, attentional deficits, and, in some cases, affective disturbances. Many of these symptoms, especially impaired memory, are associated with decreased acetylcholine synthesis and the impairment of cholinergic neurons.[1−3] The cholinergic hypothesis suggests that drugs that mimic the action of acetylcholine at muscarinic receptors are effective in correcting this neurotransmitter deficit and may provide palliative treatment for AD. In 1981, arecoline, a muscarinic agonist, was shown to ameliorate some of the symptoms of cognitive disorders in patients clinically diagnosed as having presenile primary degenerative dementia.[4] Since then, a host of classical muscarinic agonists (arecoline, oxotremorine, pilocarpine, RS-86) and their analogues have been studied extensively as potential antidementia agents.[5−14] Five muscarinic receptor subtypes (m1−m5)[15,16] have been identified and cloned. Because of the unique distribution of m1 receptors primarily in the central nervous system, selective m1 agonists have the potential to enhance cognitive function without inducing unwanted parasympathetic side effects. Classical muscarinic agonists are not subtype selective. The dose-limiting clinical side effects (primarily peripheral side effects) associated with these agonists at or below therapeutic doses are attributed to their lack of selectivity. Classical muscarinic agonists are small molecules with very little tolerance for steric bulk.[21] Addition of even a single carbon atom to these agonists usually leads to antagonists or partial agonists.[21] Thus, systematic optimization of potency and subtype selectivity through synthesis of analogues of known agonists has been severely limited. Muscarinic antagonists can show as much as 20-fold selectivity (e.g., pirenzepine) for the m1 receptor.[22−24] In contrast, true m1 selectivity has been hard to achieve with muscarinic agonists.

An approach to the design and synthesis of muscarinic subtype selective agonists is required. This paper emphasizes and describes the preparation of large, elongated, muscarinic agonists as pharmaceutically useful m1-subtype-selective muscarinic agonists. The five muscarinic receptor subtypes (m1−m5) belong to the G-protein-coupled family of receptors.[25−27] Receptors of this family are characterized by seven transmembrane helices that define a transmembrane cavity. Key amino acid residues within the cavity appear to play a major role in positioning, orienting and binding agonists to the receptors. The receptor subtypes are sufficiently different to permit good antagonist selectivity. However, the differences in amino acid sequence and internal topography are very limited,[28] strongly constraining the selectivity of classical muscarinic agonists. Traditionally, muscarinic agonists have been considerably less bulky than antagonists. The design of subtype selective agonists, therefore, dictates that the agonists be longer and larger than their nonselective counterparts to ensure increased contact between the agonist and the internal surface of the binding cavity. Such a contact may bring the agonist into proximity with parts of the receptor unique to a particular subtype. Such unique ligand−receptor interaction may lead to greater subtype selectivity.

Recently, several extremely potent and efficacious, although not subtype selective, muscarinic agonists based on the 1-azabicyclo[2.2.1]heptane ring system have been described in the literature.[29−40] For this reason, the 1-azabicyclo[2.2.1]heptane nucleus was chosen as a starting point and 1-azabicyclo[2.2.1]heptan-3-one oxime muscarinic agonists with extended and bulky appendages were prepared (Tables 1 and 2).

Chemistry

The target oximes were prepared as shown in Scheme 1. Appropriately substituted propargyllic alcohols were obtained commercially or synthesized as shown in the scheme. Cuprous chloride mediated coupling of ap-

† Receptor Technologies, Inc.

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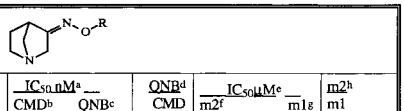
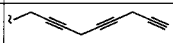
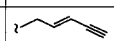
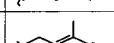
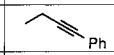
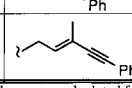
Table 1. Muscarinic Receptor Binding Profile of 1-Azabicyo[2.2.1]heptan-3-one *O*-Alkyl- -Alkenyl-, and -Alkynyloximes



NO	R	IC_{50} nM[a] CMD[b]	IC_{50} nM[a] QNB[c]	QNB[d] CMD	IC_{50} μM[e] m2[f]	IC_{50} μM[e] m1[g]	m2[h] m1
12[i]		18.1	24200	1337	16.8	26.9	0.62
13Z		3.50	4350	1242	6.03	4.89	0.811
14Z[i]		22.0	8834	402	8.07	8.83	1.09
15Z		8.04	958	119	2.18	2.03	1.07
16Z		52.0	4770	91.7	10.8	4.05	2.67
17Z[i]		34.7	13800	398	0.519	0.216	2.40
18Z		7.08	1270	179	0.519	0.216	2.40
19Z		4.29	2060	480	6.01	2.59	2.35
20Z		1.02	806	790	1.90	1.58	1.20
21Z		46.4	5010	108	25.8	5.42	4.78
22Z		12.4	1580	127	7.93	1.09	7.28

[a] IC_{50} values were calculated from inhibition of radioligand binding at 5-6 concentrations of compound, determined in triplicate. [b] CMD:[^{3}H]-cis-methyldioxolane. [c] QNB: [^{3}H]-quinuclidinyl benzilate. [d] ratio of QNB to CMD binding. [e] IC_{50} values were calculated from inhibition of QNB binding at 5-6 concentrations of compound, determined in triplicate. [f] CHO cells expressing human m2 receptors. [g] CHO cells expressing human m1 receptors. [h] Ratio of inhibition of QNB binding to m1 vs m2 receptors {IC_{50}(m2)/IC_{50}(m1)}. [i] Mixture of Z and E.

propriately substituted propargyl bromides with propargyl alcohols gave 2,5-hexadiynyl (**3**, R_1 = H) and 2,5,8-nonatrienyl (**3**, R_1 = propargyl) alcohols.[41] Palladium(0)-assisted cross-coupling reaction between alcohols **1** or **6** and an aryl bromide or aryl iodide **4** gave the corresponding arylated alcohols **5** and **7**, respectively.[41] The alcohols were reacted with *N*-hydroxyphthalimide via the Mitsunobu reaction to give the corresponding O-substituted phthalimides **9**. Cleavage of the phthalimides at room temperature with *N*-methylhydrazine afforded hydroxylamines **10**. The hydroxylamines were condensed with 1-azabicyclo[2.2.1]heptan-3-one[29] to give a mixture of *Z* (**12Z**−**35Z**) and *E* (**12E**−**35E**) oximes. The *Z* oximes were separated from the corresponding *E* oximes by medium-pressure chromatography on silica gel eluting with CH_2Cl_2:MeOH (99.5:0.5). In the case of *O*-(3-aryl-2-propynyl)oximes, a 60:40 mixture of *Z*/*E* oximes is obtained. An 85:15 equilibrium mixture of *Z* and *E* oximes results when a methanolic-HCl solution of the 60:40 mixture is kept at room temperature for 1 h. Generally the *E* oximes are devoid of muscarinic activity (e.g., **21E**, **22E**, **23E**, **26E**, **27E**). Some (**16E**, **18E**, **19E**, **24E**, and **31E**) are weak muscarinic agonists. Very few *E* oximes (**15E**, **34E**, and **35E**) were found to have muscarinic agonist properties approaching that of the *Z* oximes. The pharmacology of the *E* oximes will be discussed elsewhere. Enantiomerically pure *Z* oximes were made from enantiomerically pure **(*R*)-11** and **(*S*)-11** ketones prepared in accordance with literature procedures.[38,42,43]

Results and Discussion

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.[44,45] The ratio of QNB/CMD binding affinities has been shown to predict agonist efficacy at muscarinic receptors.[46] It has been our experience that full agonists have a ratio greater than 100. It does not, however, follow that all agonists with QNB/CMD ratio greater than 100 are full agonists. To this end, functional assays were carried out to validate results obtained from binding studies. In a first approximation, selectivity for m1 over m2 muscarinic subtypes was estimated by determining the affinity of compounds for m1 and m2 receptors labeled by [^{3}H]QNB in CHO cells selectively expressing human m1 and m2 receptors (Table 1).[47]

Starting with the potent full agonist *O*-methyloxime **12Z**/**E** (discovered in our laboratories[21]), we gradually increased the size of the O-substituent (Table 1). Increasing the size of the alkyl group to ethyl, *n*-propyl, isopropyl, and *tert*-butyl led to a rapid decline in efficacy (small QNB/CMD ratio) and potency (CMD binding).[21] When the methyl substituent was replaced by a propargyl group, compound **13Z**, an oxime with efficacy comparable to that of **12Z**/**E** was obtained. The bioequivalence of the methyl and propargyl was first observed in the arecadine ester series. The methyl ester (arecoline) and propargyl ester are equipotent.[48] Extending the side chain length in an iterative manner by adding a second and a third propargyl moieties gave compounds **14Z** and **15Z**, respectively. These analogues, despite their considerable length, are potent (CMD binding 22 nM, 8 nM) and efficacious (QNB/CMD ratios of 402 and 119) muscarinic agonists. Replacement of the propargyl moiety with an allyl group resulted in a weaker agonist, **16Z**. However, very potent and/or efficacious analogues (**17Z**−**20Z**) were prepared when one or both of the vinyl hydrogens of **16Z** were replaced with a methyl or an acetylene group. Oximes **13Z**−**20Z** are longer and larger than previously described muscarinic agonists. They are potent (CMD binding 1−35 nM) and efficacious (QNB/CMD ratios 119−1242) muscarinic agonists. These compounds, however, still lack m1 selectivity (m2/m1 ratios ranging from 0.8 to 2.7). Enhanced, though modest, m1 binding selectivity was achieved when the acetylenic hydrogen of **13Z** or **19Z** was replaced with a phenyl ring to give analogues **21Z** (m2/m1 = 4.8) and **22Z** (m2/m1 = 7.3). Selectivity for the m1 receptor was further substantiated by measuring the ability of **21Z** to stimulate phosphoinositide accumulation or inhibit forskolin-stimulated accumulation of cAMP in CHO cells selectively expressing human m1, m3, m5 receptors or m2 or m4 receptors, respectively (Table 2).[47] Oxime **21Z** is clearly m1 selective with little or no efficacy at m2−m5 muscarinic receptor subtypes (Table 2). This finding prompted us to synthesize aryl analogues of **21Z** and to study the effect of substituents on the phenyl ring on m1 selectivity, potency, and efficacy (Table 3). The chemistry, SAR, and pharmacology of compounds of type **22**, the 1-azabicyclo[2.2.1]heptan-3-one, *O*-(3-methyl-5-aryl-2-penten-4-ynyl)oximes will be discussed elsewhere.

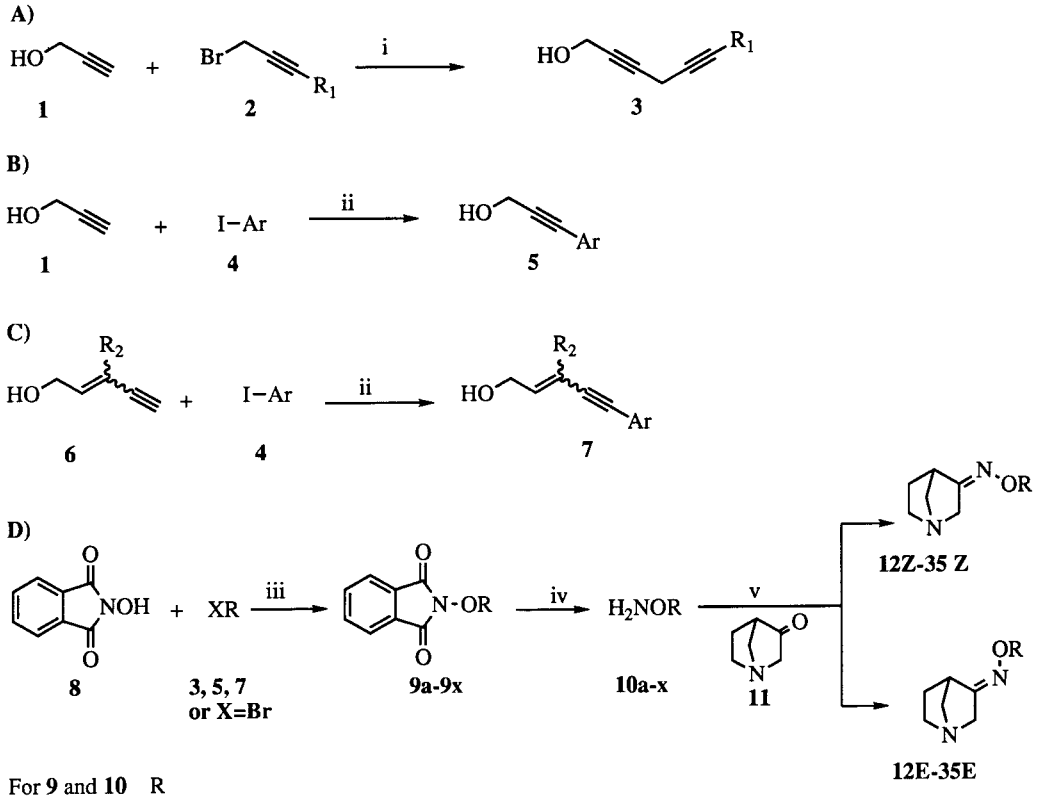
Several oximes such as **31Z**, **26Z**, **24Z**, and **32Z** (CMD IC_{50} = 12, 19, 28, and 28 nM, respectively), are potent muscarinic agonists. Electronic characteristics of the phenyl ring do not seem to significantly influence potency. Both electron-withdrawing, F, Cl, and NO_2 (**27Z**, **31Z**, and **32Z**, respectively), and electron-donat-

Table 2. Functional Selectivity for the Hm1 Muscarinic Receptor Subtype (PI Turnover Stimulation and Inhibition of Adenylate Cyclase) by **21Z**

	PI turnovers[a] (% stimulation)			aden cycl[b] (% inhibition)	
compound	m1	m3	m5	m2	m4
21Z	40% ± 4	8% ± 3	1% ± 1	NA[c]	NA
[Carbachol	100% ± 3.0	100% ± 5.5	100% ± 5.0	61% ± 3.0	60% ± 2.0

[a] Stimulation of inositol phosphate (PI) accumulation in transfected CHO cells. Values are the maximal response obtained from drug, tested at 100 μM, normalized to the effects of carbachol. Assays run in triplicate. [b] EC_{50} values for reversal of forskolin-stimulated accumulation of adenylate cyclase (aden cycl) in transfected CHO cells. Values represent the maximal inhibition obtained for drug, tested up to concentrations of 1 mM. [c] Not active up to 1 mM.

Scheme 1. Synthesis of 1-Azabicyclo[2.2.] 3-One Oximes[a]



For **9** and **10** R

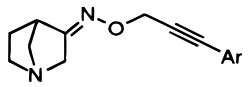
a	CH_3	i	Z-$CH_2CH{=}C(CH_3)C{\equiv}CH$	q	$CH_2C{\equiv}C$(4-F-Ph)
b	$CH_2C{\equiv}CH$	j	$CH_2C{\equiv}CPh$	r	$CH_2C{\equiv}C$(3-F-Ph)
c	$CH_2C{\equiv}CCH_2C{\equiv}CH$	k	E-$CH_2CH{=}C(CH_3)C{\equiv}CPh$	s	$CH_2C{\equiv}C$(2-MeO-Ph)
d	$CH_2C{\equiv}CCH_2C{\equiv}CCH_2C{\equiv}CH$	l	$CH_2C{\equiv}C$(4-MeO-Ph)	t	$CH_2C{\equiv}C$(2-Cl-Ph)
e	$CH_2C{=}CH_2$	m	$CH_2C{\equiv}C$(3-MeO-Ph)	u	$CH_2C{\equiv}C$(3-NO_2-Ph)
f	$CH_2CH{=}CHC{\equiv}CH$	n	$CH_2C{\equiv}C$(4-Cl-Ph)	v	$CH_2C{\equiv}C$(4-CH_3-Ph)
g	$CH_2CH{=}C(CH_3)_2$	o	$CH_2C{\equiv}C$(3-Cl-Ph)	w	$CH_2C{\equiv}C$(2-thienyl)
h	E-$CH_2CH{=}C(CH_3)C{\equiv}CH$	p	$CH_2C{\equiv}C$(2-F-Ph)	x	$CH_2C{\equiv}C$(3-thienyl)

[a] Reagents: (i) CuCl, EtMgBr, THF, Δ; (ii) $PdP(Ph_3)_4$, CuI, THF; (iii) DEAD, Ph_3P, THF, room temperature (for X = OH) or K_2CO_3, DMSO, room temperature (for X = Br); (iv) H_2NNHCH_3, THF, CH_2Cl_2, room temperature; (v) MeOH, room temperature.

ing, OCH_3 (**24Z**), groups lead to potent analogues. However, the electron-donating group, OCH_3, is most effective when it is placed in the meta position. By contrast the electron-withdrawing groups, F and Cl, are most effective when placed in the ortho position. Clearly, replacing the acetylenic hydrogen of **13Z** with aryl groups (**21Z**, **23Z**−**35Z**) leads to loss of potency (CMD) and efficacy (QNB/CMD ratio) relative to **13Z**. Yet, these analogues with CMD IC_{50} values and QNB/CMD ratios ranging from 12 to 218 nM and 81 to 250 nM, respectively, were excellent candidates for further subtype selectivity evaluation.

The muscarinic receptor subtype selectivity of these compounds was initially evaluated from their binding to membranes from CHO cells selectively expressing human m1 or m2 receptors. In the radiolabeled binding assay the *p*-OCH_3 analogue (**23Z**) was found to be the most Hm1-selective (m2/m1 = 8.0) agonist and the *p*-CH_3 analogue (**33Z**) the least selective (m2/m1 = 2.7) agonist. As theorized, the overall size of the muscarinic agonists seem to play a significant role in determining selectivity and efficacy. As a group, the arylated analogues (**21Z**, **23Z**−**35Z**) are more m1-selective than the nonarylated analogues (**12Z**/**E**-**20Z**). Selectivity is

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



		IC_{50}, nM[a]			IC_{50}, μM[e]			PI turnover (%CCh)[f]		
no.	Ar	CMD[b]	QNB[c]	QNB/CMD[d]	m2[f]	m1[g]	m2/m1[h]	m1	m3	m5
23Z	4-OCH_3Ph	110	13100	119	84.4	10.6	7.96	89	2	3
24Z	3-OCH_3Ph	27.7	6920	250	52.0	7.68	6.77	82	6	11
25Z	4-ClPh	53.1	6300	119	24.7	4.01	6.16	48	0	0
26Z	3-ClPh	19.1	3880	203	20.6	3.34	6.17	41	4	3
27Z	2-FPh	27.8	4440	160	20.8	4.03	5.16	45	2	6
28Z	4-FPh	29.8	6090	204	27.2	5.46	4.98	57	10	13
29Z	3-FPh	37.2	4920	132	47.9	9.85	4.86	54	12	9
21Z	Ph	46.4	5010	108	25.8	5.42	4.78	40	8	1
30Z	2-OCH_3Ph	218	17600	80.7	69.3	16.6	4.17	NT[g]	NT	NT
31Z	2-ClPh	12.2	1300	107	4.01	1.12	3.58	32	6	4
32Z	3-NO_2Ph	28.2	6390	227	46.6	15.1	3.09	NT	NT	NT
33Z	4-CH_3Ph	88.9	11000	124	38.6	14.1	2.74	NT	NT	NT
34Z	2-thienyl	13.5	2330	173	8.90	1.62	5.49	86	NT	NT
35Z	3-thienyl	16.5	2690	163	15.2	4.84	3.14	54	19	13
13Z	H	3.50	4500	1242	6.03	4.89	0.811	95	47	42
	carbachol	6.7	33000	4925	4.09	119	0.03	100	100	100

[a] IC_{50} values were calculated from inhibition of radioligand binding at five or six concentrations of compound, determined in triplicate. [b] CMD:[^{3}H]-*cis*-methyldioxolane. [c] QNB:[^{3}H]quinuclidinyl benzilate. [d] Ratio of QNB to CMD binding. [e] Ratio of inhibition of QNB binding to m1 vs m2 receptors {IC_{50}(m2)/IC_{50}(m1)]. [f] Values represent stimulation of PI hydrolysis, normalized to the maximal effect of carbacol, at the screening concentration of 100 μM. [g] NT: not tested.

Table 4. Stimulation of PI Turnover (Hm1, Hm3, Hm5) and Inhibition of Forskolin-Stimulated Accumulation of Adenylate Cyclase (Hm2 and Hm4) in CHO Cells

	ED_{50}, μM (% stimulation)				
	PI turnover[a]			aden cycl inhibition[b]	
compound	m1	m3	m5	m2	m4
24Z	2.5 ± 2.3	–	–		
	(82.3 ± 0.5%)	(5.9 ± 1.1%)	(11.0 ± 2.0%)	NA[c]	NA
(*R*)-24Z	1.0 ± 0.3	–	–		1.6
	(85.2 ± 5.0%)	(10.4 ± 1.2%)	(12.3 ± 5.8%)	NA	(64%)
(*S*)-24Z	3.7 ± 1.3	–	–		
	(81.7 ± 2.6%)	(5.2 ± 0.5%)	(1.9 ± 0.4%)	NT[d]	NT
carbachol	4.7 ± 1.2	2.5 ± 0.4	2.7 ± 0.5	4.4 ± 0.3	6.3 ± 0.6
	(100 ± 3.0%)	(100 ± 5.5%)	(100 ± 5.0%)	(61 ± 3.0%)	(60 ± 2.0%)

[a] Stimulation of inositol phosphate (PI) accumulation in transfected CHO cells. Value in parentheses is the maximal response obtained from each drug, tested at 100 μM, normalized to the effects of carbachol. Assays run in triplicate. ED_{50} values are the concentrations of drug required to produce a half-maximal effect for each compound. [b] EC_{50} values for reversal of forskolin-stimulated accumulation of adenylate cyclase (aden cycl) in transfected CHO cells. Values in parentheses represent the maximal inhibition obtained for each drug, tested up to concentrations of 1 mM. [c] Not active up to 1 mM. [d] Not tested.

achieved with some loss of efficacy. The most m1-selective analogues, **23Z** and **24Z**, favor a para or meta substituent (**23Z** vs **30Z**; **24Z** vs **30Z**; **25Z** vs **31Z**). Because of the size of the F substituent, there is little steric difference among the ortho, meta, and para analogues. This may explain the identical selectivity for the ortho, para, and meta analogues **27Z**−**29Z**.

Binding selectivity may or may not be biologically relevant unless accompanied by functional selectivity. To this end, the effects of the oximes **23Z**−**35Z** on phosphatidylinositol (PI) turnover mediated by m1, m3, and m5 receptors were studied (Table 3).[47] Although the rank order for m1 selectivity from the subtype binding and second messenger assays do not correlate well, the second messenger assay indicates the *p*-OCH_3 analogue (**23Z**) to be once again the most m1-selective agonist. The *p*-OCH_3 (**23Z**), *m*-OCH_3 (**24Z**), *p*-Cl (**25Z**), and *o*-F (**27Z**) analogues have negligible efficacy at the m3 and m5 receptors. On the other hand, *p*-F (**28Z**) and *m*-F (**29Z**), analogues, although predominantly m1 selective, exhibited appreciable efficacy at the m3 and m5 receptor subtypes. With the exception of **23Z** and **24Z**, the compounds are partial agonists at the second messenger level. On the basis of the binding and second messenger m1 selectivity data (Table 3) compounds **23Z** and **24Z** (PD 142505) were selected for additional pharmacologic evaluation. Compound **23Z** was found inactive in vivo (mouse water maze) and was not pursued further. On the other hand, compound **24Z** (PD 142505) was active in vivo (mouse water maze) and was selected for additional pharmacologic evaluation. Compounds **23Z**−**35Z** are chiral and as such exist in two enantiomeric forms. The enantiomers of **24Z**, **(*R*)-24Z**, and **(*S*)-24Z** were prepared. The effects of these enantiomers and the reference agent carbachol on second messenger signaling by cloned human m1−m5 receptors were evaluated. Effects on stimulation of PI hydrolysis (Hm1-, Hm3-, and Hm5-CHO cells) and inhibition of forskolin-stimulated adenylate cyclase (Hm2 and Hm4) are shown in Table 4. Both **(*R*)-24Z** and **(*S*)-24Z** display very pronounced functional selectivity for m1 receptors. In the case of **(*R*)-24Z**, pronounced activation of m4 receptor is also observed. Compound **(*S*)-24Z** activates m1 receptors selectively over m3 and m5

Table 5. Cellular Metabolic Activation in Hm1−Hm5 CHO Cells

	cellular metabolism:[a] EC_{50}, μM				
compound	m1	m3	m5	m2	m4
24Z	0.6 ± 0.02	3.9 ± 0.6	NT[b]	NA[c]	14.2 ± 1.2
(*R*)-24z	0.3 ± 0.01	1.5 ± 0.2	NT	NA	6.0 ± 0.8
(*S*)-24Z	3.7 ± 0.1	11.3 ± 2.0	NT	NA	31.0 ± 3.4
carbachol	1.0 ± 0.1	0.5 ± 0.1	NT	0.3 ± 0.2	1.0 ± 0.1

[a] Cellular metabolism measured by the rate of excretion of acidic metabolites in transfected CHO cells. [b] NT = not tested. [c] NA = not active.

receptors. It is about 4 times less potent at m1 receptors than **(*R*)-24Z**. It is of great interest to note that whereas the **(*R*)-24Z** is active at the m4 receptor, the racemate, **24Z**, is completely devoid of activity at this receptor. Is it possible that the **(*S*)-24Z** isomer is an m4 antagonist? Unfortunately the necessary data to confirm or negate the speculation is not available at this time.

Next, the effect of these oximes on cellular metabolic activity in live CHO cells expressing human m1−m5 receptors (Table 5) was measured with a Cytosensor microphysiometer.[49] Metabolically active cells excrete protons to their environment. The Cytosensor microphysiometer measures the rate of proton excretion. The results show moderate m2 selectivity for carbachol. By contrast enantiomers **(*R*)-24Z** and **(*S*)-24Z** have no detectable effect on cellular metabolism in Hm2-CHO cells even at the very high concentration of 1 mM, but significantly increase the metabolic rate of Hm1-CHO cells. Both *R* and *S* enantiomers activate the m3 and m4 receptors. The *R* enantiomer activates the m3 and m4 receptors at doses 5 and 20 times, respectively, higher than those required to activate the m1 receptor. Similarly the *S* enantiomer is 3 and 3 times, respectively, less potent at the m3 and m4 receptors than at m1 receptors. The *R* enantiomer is 12 times more potent than the *S* enantiomer at the m1 receptor. It is also of interest to note again that **(*R*)-24Z** is considerably more potent at the m4 receptor than either **(*S*)-24Z** or **24Z**.

Receptor selection and amplification technology (R-SAT, Receptor Technologies Inc.)[50,51] provided further evidence of functional potency and selectivity of **(*R*)-24Z** (Table 6) for the m1 receptor. In this assay human m1−m5 muscarinic receptors are transiently expressed along with the marker gene, β-galactosidase in NIH 3T3 cells. Proliferative signals allow ligands to amplify cells that express compatible receptors and the marker, thus allowing the assay of receptor activation using colorimetric assays. Proliferative signals for the m2 and m4 receptor require co-expression with a chimeric G-protein that allows these receptors to activate phospholipase C. In this assay, as in the previously described two functional assays, the **(*R*)-24Z** enantiomer is significantly more selective for the m1 receptor relative to m3 (20-fold), m5 (20-fold), and m2 (30-fold) receptors. In this paradigm, **(*R*)-24Z** displays similar selectivity for m1 and m4 receptors (ED_{50} values: 42 and 51 nM, respectively). By contrast, **(*S*)-24Z** displays greatly reduced (30−109-fold) potency (ED_{50}) and efficacy (%CCh) across all of the receptor subtypes relative to **(*R*)-24Z**. The standard errors for **24Z** and **(*S*)-24Z** are high in this assay. However, this does not alter the conclusion, particularly when all the functional and binding data are taken together, that **(*R*)-24Z** is selective for m1 and m4 receptors.

In all three (second messenger, cell metabolism, and cell amplification) functional assays, **(*R*)-24Z** (CI-1017)[52] consistently emerged as a full (Table 4) or partial (Table 6) muscarinic agonist with greatly enhanced m1 selectivity over m2 receptors. Its selectivity for m1 over m3 and m4 receptors is not as pronounced and is assay dependent. The overall order of receptor subtype selectivity may be summarized as: m1 ≥ m4 > m3 ≈ m5 >> m2.

As expected, the selectivity of **(*R*)-24Z** for m1 receptors resulted in very few peripheral and central side effects in vivo (Figure 1). Very minor peripheral side effects (salivation, lacrimation, urination, gastrointestinal[53] effects, etc.) were detected at oral doses as high as 178 mg/kg in rats. On the other hand, **(*R*)-24Z** significantly improved spatial memory of hippocampally deficient C57BL/10 mice[54] (Figure 2) and nbM-lesioned rats[55,56] (Figure 3) at oral doses ranging from 0.3 to 3.2 mg/kg and 0.03 to 0.10 mg/kg, respectively.

Typically, several of the classical muscarinic agonists (RS-86, arecoline, or carbachol) display pronounced parasympathetic side effects (salivation, lacrimation, urination, gastrointestinal effects, etc.) at doses lower than those required for central effects. This may be due to lack of muscarinic receptor subtype selectivity of these agents. This lack of central selectivity has severely limited the clinical utility of many of these older agents.

Conclusion

In radioligand binding and functional assays using CHO and NIH-3T3 cells transfected with human muscarinic receptor subtypes, **(*R*)-24Z** (CI-1017) was identified as a novel m1-selective muscarinic agonist. In vitro, **(*R*)-24Z** displays very large selectivity for m1 vs m2 receptors. Its selectivity for m1 versus m3 and m4 receptors appears to be less pronounced and assay dependent. In vivo, **(*R*)-24Z** improves spatial memory in cholinergically impaired rats and mice. Mild peripheral side effects are observed only at doses 100-fold greater than the efficacious dose. Unlike currently available muscarinic agonists, **(*R*)-24Z** appears to be free of severe dose-limiting side effects and thus holds promise for alleviating cognitive disorders associated with cholinergic deficits.

Experimental Section

Chemistry. General. The following alcohols, halides, phthalimides and hydroxylamines are commercially available: *trans*-2-penten-4-yn-1-ol (**6**, R_2 = H), *cis*-3-methyl-2-penten-4-yn-1-ol) (**6**, R_2 = CH_3), *trans*-3-methyl-2-penten-4-yn-1-ol (**6**, R_2 = CH_3), 3-phenyl-2-propyn-1-ol (**5**, Ar = Ph), 4-bromo-2-methyl-2-butene, *O*-methylhydroxylamine (**10a**, R = CH_3), *O*-allylhydroxylamine (**10e**, R = $CH_2CH{=}CH_2$). Solvents and reagents were used without further purification unless otherwise noted. Melting points were determined using Thomas Hoover capillary melting point apparatus and were not corrected. ^1H and ^{13}C NMR spectra were recorded on a 250 MHz Bruker Aspect-3000 spectrometer with chemical shifts reported in δ (parts per million) relative to tetramethylsilane used as internal standard. Infrared spectra were recorded on a Bio-Rad FTS-45 or a Mattson Cygnus 100 infrared spectrometer. Thin layer chromatography (TLC) was

Table 6. R-SAT Results in Hm1−Hm5 CHO Cells

	amplification[a] ED_{50}, nM (%CCh)				
compound	m1	m3	m5	m2	m4
24Z	42 ± 31 (30%)	3857 ± 1840 (93%)	5990 ± 4635 (103%)	1322 ± 529 (81%)	93 ± 66 (68%)
(*R*)-24Z	42 ± 26 (41%)	865 ± 180 (87%)	868 ± 272 (104%)	1283 ± 550 (92%)	51 ± 18 (72%)
(*S*)-24Z	1605 ± 790 (51%)	4568 ± 2518 (57%)	2590 ± 2409 (60%)	1535 ± 1718 (33%)	1078 ± 633 (65%)
carbachol	6500 ± 600 (100%)	100 ± 40 (100%)	1400 ± 700 (100%)	270 ± 70 (100%)	100 ± 50 (100%)

[a] Muscarinic receptor mediated selection and amplification of transfected NIH-3T3 cells is measured. Values in parentheses represent the maximal response obtained for each drug, normalized to the effects of carbachol. ED_{50} values are the concentration of drug required to produce a half-maximal effect.

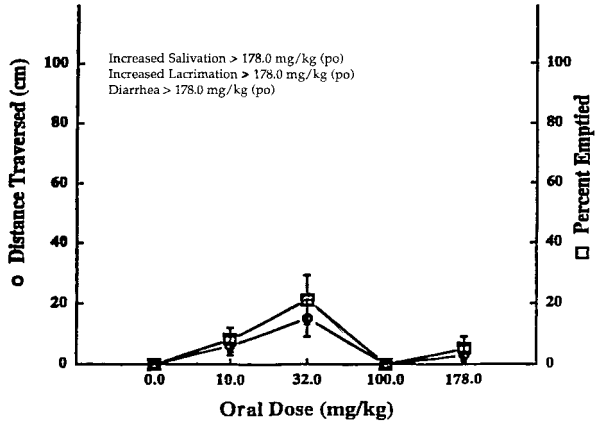


Figure 1. The effects of **(*R*)-24Z** on GI-motility.

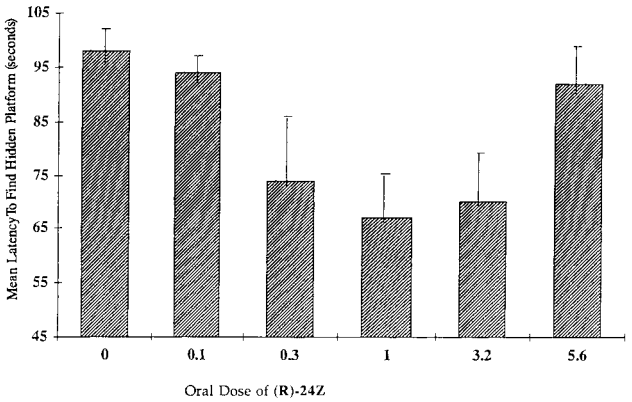


Figure 2. The effect of **(*R*)-24Z** on mouse water maze performance in hippocampally deficient C57BL/10 mice.

performed on silica gel 60 F_{254} plates from E. Merck, and components were visualized by ultraviolet light (254 nm) and/or iodine vapor. E. Merck silica gel (230−400 mesh) was used for all column chromatography unless otherwise specified. Solvent systems used in chromatography and TLC are reported in v/v ratio. Elemental analyses were performed in-house; analyses for all the elements indicated are within 0.4% of the corresponding calculated values unless otherwise specified.

Typical Procedures. Preparations of **12Z/E, 16Z, 14Z, 15Z, 22Z**, and **23Z** are typical examples of the procedures used to prepare the oximes. The oximes were prepared as a *Z*/*E* mixture. The fast moving *Z* isomers were separated (with the exception of **12**) by column chromatography.

(*Z*/*E*)-(±)-1-Azabicyclo[2.2.1]heptan-3-one, O-Methyloxime Hydrochloride (12Z/12E). (+)1-Azabicyclo[2.2.1]-heptan-3-one (**11**)[29] (1.9 g, 17.1 mmol) was dissolved in 10 mL of methanol Methoxyamine hydrochloride (1.40 g, 17.1 mmol) was added, and the mixture was stirred at room temperature for 18 h. The reaction was concentrated in vacuo to afford a white solid. Recrystallization of the residue from ethanol−diisopropyl ether afforded 2.27 g (75%) of the title product as a mixture of *Z* and *E* isomers: mp 210−211 °C; ^{1}H NMR ($CDCl_3$) δ 4.29−4.21 (m, 1H), 4.00−3.80 (m, 5H), 3.61−3.38 (m, 4H), 2.48 (m, 1H), 2.00 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 153.56, 153.03, 62.36, 59.62, 59.04, 56.54, 55.71, 51.72, 51.53, 40.04, 37.24, 26.05, 25.02; IR (KBr) 3437, 2850, 2706, 2560, 2446, 1465, 1450, 1048, 880 cm^{-1}; MS (CI) M + 1 = 141. Anal. ($C_7H_{12}N_2O$·HCl) C, H, N.

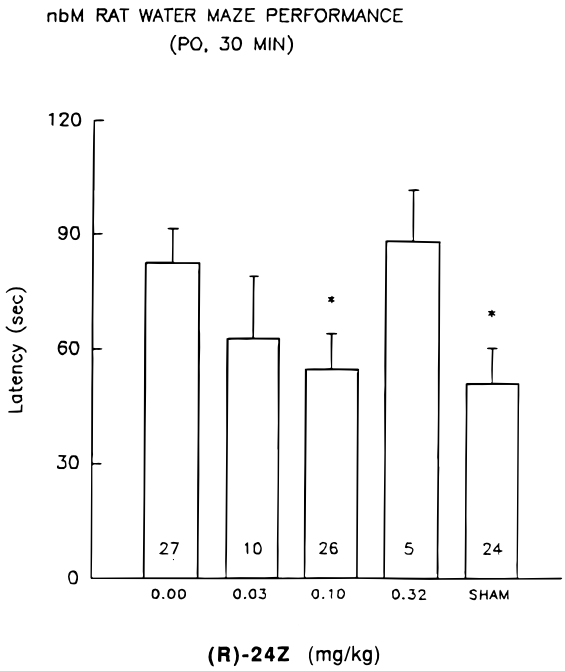


Figure 3. The effects of **(*R*)-24Z** on mouse water maze performance in nbM-lesioned rats. **(*R*)-24Z** significantly improves on day 4/trial 4 of testing equivalent to the performance of sham lesioned rats (*N*: number noted on bars). *$P < 0.05$.

(*Z*/*E*)-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-2-Propenyloxime Oxalate (16Z/16E). 1-Azabicyclo[2.2.1]heptan-3-one (2.0 g, 18 mmol) and *O*-allylhydroxylamine hydrochloride hydrate (1.97 g, 18 mmol) were dissolved in 25 mL of methanol and stirred at room temperature for 18 h. The reaction was evaporated in vacuo to give a viscous oil. The crude oil was dissolved in 50 mL of water, made basic with a saturated solution of potassium carbonate, and extracted with ether (3 × 100 mL). The combined extracts were dried over anhydrous sodium sulfate and evaporated to give a mixture of **16Z** and **16E** as a clear, yellow liquid. The *Z* (fast-moving isomer) and *E* isomers were separated on silica gel, eluting with dichloromethane−methanol (10:1), and converted to the corresponding oxalate or hydrochloride salts.

(*Z*)-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-2-propenyloxime oxalate (16Z): yield 80%; mp 130−132 °C; ^{1}H NMR (250 MHz; DMSO) δ 12.10 (broad s, 2H), 6.02−5.87 (m, 1H), 5.32−5.17 (m, 2H), 4.52 (d, 2H, J = 5.5 Hz), 4.07−3.85 (m, 2H), 3.42−3.17 (m, 5H), 2.21 (m, 1H), 1.70 (m, 1H); ^{13}C NMR

(DMSO) δ 164.58, 158.02, 134.23, 117.66, 74.29, 58.74, 55.04, 50.71, 25.79; IR (KBr) 3433, 2920, 2869, 1636, 1401, 1278, 1206, 1033, 720 cm^{-1}; MS (CI) M + 1 = 167. Anal. ($C_9H_{14}N_2O \cdot C_2H_2O_4$) C, H, N.

(*Z*)-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-(2,5-Hexadiynyl)oxime Oxalate (14Z) (Contains ~15% *E* Isomer). 1. 3 (R_1 = H). (±)-Acetaldehyde ethyl propargyl acetal (34 mL, 0.25 mol) was added to a heated (45 °C) solution of ethylmagnesium bromide (3.0 M solution in diethyl ether; 90 mL, 0.27 mol) in dry THF (300 mL). After the mixture was stirred for 30 min, copper(I) chloride (1.25 g) was added and the temperature raised to and kept at 50 °C for 30 min. Propargyl bromide (32 mL, 0.28 mol) was added and the temperature raised to 60 °C and kept 60 °C for 1.5 h. The reaction was cooled to room temperature and then poured into 250 mL of aqueous solution of 5 g of KCN containing 38 g of NH_4Cl. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 200 mL). The combined organic layers were washed with saturated NH_4Cl solution, dried (Na_2SO_4), and evaporated in vacuo to give a brown oil. The oil was dissolved in 100 mL of methanol containing 1 mL of concentrated HCl and refluxed for 45 min, and the solvent was removed in vacuo to give a brown liquid. The liquid was dissolved in saturated NH_4Cl (100 mL) and extracted with diethyl ether (6 × 150 mL). The combined extracts were dried (Na_2SO_4), and the solvent was removed in vacuo to give the crude product as a brown liquid. The product was purified by vacuum distillation (bp 60 °C/0.2 mmHg) to give 16.2 g (75%) of 2,5-hexadiyn-1-ol, **3** (R_1 = H): ^1H NMR δ ($CDCl_3$) 4.2 (m, 2H), 3.1−3.3 (m, 2H), 2.8−3.1 (broad, 1H), 2.1−2.2 (m, 1H).

2. 9c (R = $CH_2C{\equiv}CCH_2C{\equiv}CH$). Diethyl azodicarboxylate (24 mL, 117 mmol) was added dropwise to a solution of *N*-hydroxyphthalimide (17.33 g, 106 mmol), triphenylphosphine (27.9 g, 106 mmol), and **3** (R_1 = H) (10 g, 106 mmol) in 400 mL of tetrahydrofuran and stirred for 72 h at room temperature. The solvent was removed in vacuo and the resulting yellow solid purified by column chromatography. Elution with dichloromethane gave a light yellow solid product. This was recrystallized from ethanol to give 15.3 g (60%) of **9c** (R = $CH_2C{\equiv}CCH_2C{\equiv}CH$), mp 134−135 °C. Anal. ($C_{14}H_9NO_3$) C, H, N.

3. 10c (R = $CH_2C{\equiv}CCH_2C{\equiv}CH$) Hydrochloride. Methylhydrazine (2 mL, 37.6 mmol) was added dropwise to a well-stirred solution of **9c** (R = $CH_2C{\equiv}CCH_2C{\equiv}CH$) (9 g, 37.6 mmol) in 75 mL of dichloromethane at room temperature. After a short period of stirring, a heavy white precipitate separated out. The reaction mixture was stirred for an additional 3 h. The white precipitate was separated by filtration and discarded. The filtrate was diluted with diethyl ether to a total volume of 400 mL. Anhydrous hydrogen chloride gas was bubbled into the ether solution to give 3.96 g (100%) of **10c** (R = $CH_2C{\equiv}CCH_2C{\equiv}CH$) as a white precipitate: mp 143−1435 °C; ^1H NMR ($CDCl_3$) δ 11.2−10.4 (broad, 3H), 4.46 (s, 2H), 2.94−2.93 (m, 2H), 1.90−1.88 (m, 1H); ^{13}C NMR (CDCl3) δ 84.48, 72.74, 69.82, 62.44, 39.66, 9.66; IR (KBr) 3500, 2900, 1500, 1000, 650 cm^{-1}; MS (CI) M = 109 (100), 95.1 (52). Anal. ($C_6H_7NO \cdot HCl$) C, H, N.

4. 14Z: yield 81%; mp 144−146 °C; ^1H NMR (DMSO) δ 11.42 (broad s, 1.9H), 4.66 (s, 2H), 4.03−3.71 (m, 2.5H), 3.44−3.02 (m, 7.5H), 2.21 (m, 1H), 1.70 (m, 1H); ^{13}C NMR (DMSO) δ 164.38, 159.34, 81, 78.5, 77, 71.77, 61.43, 58.80, 55.14, 50.76, 25.84, 8.78; IR (KBr) 3428, 1617, 1403, 1278, 1210, 1002, 721 cm^{-1}; MS (CI) M + 1 = 203. Anal. ($C_{12}H_{14}N_2O \cdot 1.2C_2H_2O_4$) C, H, N.

(*Z*)-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-(2,5,8-Nonatriynyl) oxime Oxalate (15Z). 1. 3 (R_1 = $CH_2C{\equiv}CH$). A solution of 2,5-hexadiyn-1-ol (16 g, 0.17 mol) and pyridine (2 mL) in diethyl ether (100 mL) was cooled to −35 °C. Phosphorus tribromide (5.7 mL, 0.06 mol) was added dropwise over 30 min while an internal temperature of −30 °C was maintained. The temperature was raised to and kept at −25 °C for 2 h. The reaction mixture was then allowed to warm to room temperature, heated at reflux for 30 min, cooled back to room temperature, and stirred at room temperature for 16 h. The reaction mixture was washed with saturated NaCl solution, dried (Na_2SO_4), and concentrated to give 26.2 g (98%) of 1-bromo-2,5-hexadiyne. The crude bromide was reacted with (±)-acetaldehyde ethyl propargyl acetal to give **3** (R_1 = $CH_2C{\equiv}CH$) in 93% yield as an oil in a manner analogous to the preparation of **3** (R_1 = CH_3).

2. 9d (R = $CH_2C{\equiv}CCH_2C{\equiv}CCH_2C{\equiv}CH$): Crystallized from ethanol−DMF; 55% yield; mp 133−137 °C dec; ^1H NMR ($CDCl_3$) δ 7.89−7.76 (m, 4H), 5.00−4.86 (s, 2H), 3.32−3.10 (m, 4H), 2.07−2.05 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 134.58, 128.85, 123.67, 84.34, 77.91, 74.29, 73.42, 68.93, 65.53, 10.05, 9.52; IR (KBr) 3272, 1740 cm^{-1}; MS (CI) M + 1 = 278 (42), 165 (35), 164 (100), 148 (97), 147 (85), 130 (76), 115 (34), 104 (50), 103 (36). Anal. ($C_{17}H_{11}NO_3$) C, H, N.

3. 10d (R = $CH_2C{\equiv}CCH_2C{\equiv}CCH_2C{\equiv}CH$) hydrochloride: yield 100%; mp 123−124 °C.

4. 15Z: yield 39%; mp 113−117 °C; ^1H NMR (DMSO) δ 9.98 (broad s, 1.8H), 4.66 (s, 2H), 4.02−3.82 (m, 2H), 3.91 (s, 1H), 3.44−2.95 (m, 9H), 2.20 (m, 1H), 1.70 (m, 1H); ^{13}C NMR (DMSO) δ 164.24, 159.42, 81.15, 78.63, 76.50, 74.60, 71.57, 61.44, 58.83, 55.19, 50.80, 25.87, 8.86, 8.56; IR (KBr) 1653, 1216, 1029, 1001, 709 cm^{-1}; MS (CI) M + 1 = 241. Anal. ($C_{15}H_{16}N_2O \cdot 1.1C_2H_2O_4$) C, H, N.

(*Z*)-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-((*E*)-3-Methyl-5-phenyl-2-penten-4-ynyl)oxime Oxalate (22Z). 1. 7 (R_2 = CH_3, Ar = Ph). To a stirred solution of *trans*-3-methyl-2-penten-4-yn-1-ol (10.57 g, 0.11 mol), diethylamine (80 mL), copper(I) iodide (0.7 g), and tetrakis(triphenylphosphine)-palladium(0) (1.0 g) in tetrahydrofuran (30 mL) under nitrogen was added dropwise iodobenzene (11.2 mL, 0.1 mol). After 24 h of stirring at room temperature, the reaction mixture was concentrated in vacuo to give a brown semisolid residue. The residue was dissolved in water (200 mL) and the aqueous solution extracted with diethyl ether (4 × 200 mL). The combined ether extracts were dried (Na_2SO_4) and evaporated in vacuo to give a clear brown liquid product. The product was purified by column chromatography. Elution with hexane−ethyl acetate (2:1) afforded 12.5 g (66%) of **7** (R_2 = CH_3, Ar = Ph): ^1H NMR ($CDCl_3$) δ 7.45−7.40 (m, 2H), 7.35−7.20 (m, 3H), 6.12−6.06 (t, 1H, J = 5.5 Hz), 4.28−4.25 (d, 2H, J = 5.5 Hz); ^{13}C NMR ($CDCl_3$) δ 135.59, 131.56, 128.31, 128.16, 123.23, 120.85, 91.51, 87.68, 60.48, 59.19, 17.62; IR (KBr) 3317, 1488, 1001, 755, 690 cm^{-1}; MS (CI + 1% NH_3 in CH_4) M + 2 = 174 (3), M + 1 = 173 (21), M = 172 (13), 155 (100).

2. 9k (R = $CH_2CH{=}C(CH_3)C{\equiv}CPh$): yield 56%; mp 96−98 °C; ^1H NMR ($CDCl_3$) δ 7.88−7.81 (m, 2H), 7.78−7.73 (m, 2H), 7.45−7.39 (m, 2H), 7.33−7.26 (m, 3H), 6.24−6.17 (t, 1H, J = 6.6 Hz), 4.85 (d, 2H, J = 6.6 Hz), 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.70, 134.54, 131.66, 128.90, 128.40, 128.31, 128.20, 126.59, 123.59, 122.92, 90.89, 89.43, 73.37, 17.98; MS (CI + 1% NH_3 in CH_4) M + 1 = 318 (31), 156 (38), 155 (100); IR (KBr), 1791, 1737, 1728, 1386, 970, 943, 876 cm^{-1}. Anal. ($C_{20}H_{15}NO_3$) H, N; C: calcd, 75.10; found, 75.56.

3. 10k (R = $CH_2CH{=}C(CH_3)C{\equiv}CPh$): yield 96%; mp 192−194 °C; ^1H NMR($CDCl_3$) δ 11.2 (b, 3H). 7.49−7.39 (m, 5H), 6.05−6.00 (t, 1H, J = 7.0 Hz), 4.75−4.72 (d, 2H, J = 7.0 Hz), 1.97 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 131.34, 128.90, 128.76, 128.64, 125.35, 121.97, 95.83, 91.04, 88.90, 69.41, 17.88; MS (CI) M + 1 = 188 (10), 171 (9), 156 (15), 155 (58), 85 (100); IR (KBr) 2960, 2856, 2832, 2816, 2676, 2656, 915 cm^{-1}. Anal. ($C_{12}H_{13}NO \cdot HCl$) H; C: calcd, 64.43; found, 63.37; N: calcd, 6.26; found, 5.57.

4. 22Z: yield 59%; mp 133−134 °C; ^1H NMR (DMSO) δ 11.60 (broad s, 1H), 7.47−7.37 (m, 5H), 6.04 (t, 1H, J = 6.1 Hz), 4.67 (d, 2H, J = 6.7 Hz), 4.04−3.82 (m, 2H), 3.42−3.15 (m, 5H), 2.20 (m, 1H), 1.90 (s, 3H), 1.72 (m, 1H); ^{13}C NMR (DMSO) δ 164.35, 158.71, 133.39, 131.26, 128.72, 128.66, 122.27, 120.96, 91.54, 87.64, 69.51, 58.82, 55.16, 50.82, 25.85, 17.64; IR (KBr) 3454, 2916, 1719, 1631, 1402, 1279, 1208, 1029, 720 cm^{-1}; MS (CI) M + 1 = 281. Anal. ($C_{18}H_{20}N_2O \cdot C_2H_2O_4$) C, H, N.

(*Z*)-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-2-Propynyloxime Hydrochloride (13Z). 1. Hydrazinolysis of commercially available phthalimide **9b** (R = $CH_2CH{\equiv}CH_3$) with

N-methylhydrazine and subsequent treatment with HCl gas gave **10b** (R = $CH_2C{\equiv}CH_3$) hydrochloride: yield 63%; mp 95−110−150 °C; ^{1}H NMR (DMSO) δ 11.30 (broad s, 3H), 4.80 (dd, 2H, J = 2.4 Hz, 1.0 Hz), 3.90−3.89 (d, 1H, J = 1.0 Hz); ^{13}C NMR (DMSO) δ 81.20, 76.41, 60.67; IR (KBr) 3255.70, 2925.16, 2675.91, 2122.30, 1568.89, 1537.78, 1025.12, 861.17 cm^{-1}. Used with out further purification.

2. 13Z: yield 23%; mp 199−200 °C; ^{1}H NMR (DMSO) δ 12.05 (broad s, 1H), 4.65 (d, 2H, J = 2.4 Hz), 4.18−4.02 (m, 2H), 3.56−3.32 (m, 7H), 2.27 (m, 1H), 1.71 (m, 1H); ^{13}C NMR (DMSO) δ 157.45, 79.88, 77.91, 61.39, 58.53, 54.64, 50.51, 25.36; IR (KBr) 3248, 2866, 2759, 2535, 1358, 1032, 917 cm^{-1}; MS (CI) M + 1 = 165. Anal. ($C_9H_{12}N_2O{\cdot}HCl$) C, H, N.

(*Z*/*E*)-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-((*E*)-2-penten-4-ynyl)oxime Oxalate (17Z/E). 1. 9f (R = CH_2-CH=CHC≡CH): yield 60%; mp 128−130 °C; ^{1}H NMR ($CDCl_3$) δ 788−7.74 (m 4H), 6.49−6.37 (m 1H), 5.84−5.76 (m, 1H), 4.76−4.68 (m 2H), 2.99−2.98 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 163.44, 136.82, 134.47, 128.60, 123.49, 115.54, 80.46, 79.70; IR (KBr) 3261, 3249, 1786, 1737, 1718, 1378, 1358, 1329, 1131, 983, 711702, 665 cm^{-1}; MS (EI) M = 227 (0.1), 163 (44), 130 (21), 104 (43), 76 (35), 65 (100). Anal. ($C_{13}H_9NO_3$) H, N; C: calcd, 68.72; found, 67.99.

2. 10f (R = $CH_2CH{=}CHC{\equiv}CH$) hydrochloride: yield 70%; mp 133−135 °C; ^{1}H NMR (DMSO) δ 11.6 (broad s, 3H), 6.29−6.22 (dt, 1H, J = 16 Hz, J = 6.26 Hz), 5.95−5.90 (dd, 1H, J = 16 Hz, J = 1.4 Hz), 4.63−4.61 (d, 2H), J = 6.26 Hz), 4.14−4.13 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 136.76, 134.52, 122.96, 114.64, 83.03, 81.18, 73.27, 71.63; IR (KBr) 3290, 2926, 2884, 2662, 1721, 1544, 1518, 1009, 955 cm^{-1}. Anal. ($C_5H_7NO{\cdot}HCl$) H, N; C: calcd, 44.96; found, 44.29.

3. 17Z/E: yield 78%; mp 130−134 °C; ^{1}H NMR (DMSO) δ 9.84 (broad s, 1.7H), 6.34−6.21 (m, 1H), 5.82−5.74 (m, 1H), 4.58 (m, 2H), 4.08−3.71 (m, 3.5H), 3.42−3.08 (m, 4.5H), 2.25−2.09 (m, 17 1H), 1.71−1.55 (m, 1H); ^{13}C NMR (DMSO) δ 164.42, 158.62, 158.31, 140.95, 140.76, 111.17, 111.06, 81.63, 72.84, 58.76, 58.29, 55.80, 55.08, 50.75, 50.60, 37.82, 25.76, 24.89; IR (KBr) 3430, 2921, 1635, 1402, 1278, 1211, 721 cm^{-1}; MS (CI) M + 1 = 191. Anal. ($C_{11}H_{14}N_2O{\cdot}C_2H_2O_4$) C, H, N.

(*Z*)-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-(3-Methyl-2-butenyl)oxime Oxalate (18Z). 1. 9g (R = $CH_2CH{=}C(CH_3)_2$). Potassium carbonate (7.55 g, 54.6 mmol) was added to a solution of *N*-hydroxyphthalimide (13.93 g, 85.4 mmol) in 150 mL of DMSO to give a wine-red colored solution. 4-Bromo-2-methyl-2-butene (20 g, 134 mmol) was added dropwise, and the reaction was stirred for 16 h at room temperature. The reaction was poured into 600 mL of ice water, giving a white crystalline solid precipitate. The solid was separated by filteration, washed with ice water, air-dried, and recrystallized from ethanol to give 15.7 g (85%) of **9g** (R = $CH_2CH{=}C(CH_3)_2$): mp 98−100 °C; ^{1}H NMR ($CDCl_3$) δ 7.85−7.78 (m 2H), 7.77−7.73 (m, 2H), 5.57−5.51 (t, 1H, J = 7.7 Hz), 4.74−4.71 (d, 2H, J = 7.7 Hz), 1.77−1.74 (d, 6H); ^{13}C NMR ($CDCl_3$) δ 163.82, 143.64, 134.39, 128.94, 123.42, 117.08, 74.04, 25.93, 18.11; IR (KBr) 1783, 172, 1720, 1393, 1186, 1127, 966, 700 cm^{-1}; MS (CI) M + 1 = 232 (11), M = 231 (0.2), 196 (40), 165 (13), 164 (95), 163 (100), 148 (23). Anal. C, H, N.

2. 10g (R = $CH_2CH{=}C(CH_3)_2$) hydrochloride: yield 100%; mp 138−142 °C; ^{1}H NMR (DMSO) δ 11.1 (s 3H), 5.34−5.27 (t, 1H, J = 7.3 Hz), 4.55−4.52 (d, 2H, J = 7.3 Hz), 1.75−1.71 (d, 6H); ^{13}C NMR (DMSO) δ 142.55, 116.46, 69.97, 25.47, 18.10; IR (KBr) 3010, 2997, 2990, 2952, 2673, 1507 cm^{-1}; MS (CI + 1% NH3 in CH4) M + 2 = 103 (8), M + 1 = 102 (53), M = 101 (0.9), 88 (4), 87 (24), 86 (58), 85 (98). Anal. C,H,N.

3. 18Z: yield 73%; mp 130−131 °C; ^{1}H NMR (DMSO) δ 7.77 (broad s, 3.5H), 5.34 (t, 1H, J = 7.0 Hz), 4.50 (d, 2H, J = 7.0 Hz), 4.01−3.80 (m, 2H), 3.40−3.15 (m, 5H), 2.20 (m, 1H), 1.71 (s, 3H), 1.70 (m, 1H), 1.65 (s, 3H); ^{13}C NMR (DMSO) δ 164.49, 157.43, 137.08, 120.11, 70.12, 58.72, 55.05, 50.72, 25.81, 25.47, 17.92; IR (KBr) 3437, 3122, 2925, 1624, 1404, 1199, 1013, 721 cm^{-1}; MS (CI) M + 1 = 195. Anal. ($C_{11}H_{18}N_2O{\cdot}C_2H_2O_4$) C, H, N.

(*Z*)-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-((*E*)-3-Methyl-2-penten-4-ynyl)oxime Oxalate (19Z). 1. 9h (R = (*E*)-$CH_2CH{=}C(CH_3)C{\equiv}CH$): yield 73%; mp 123−125 °C; ^{1}H NMR ($CDCl_3$) δ 7.83 (s, 4H), 6.09−6.04 (t, 1H, J = 7.3 Hz), 4.78−4.75 (d, 2H, J = 7.3 Hz), 3.91 (s, 1H), 1.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.16, 134.73, 130.05, 128.36, 124.60, 123.20, 85.19, 80.06, 72.06, 72.60, 17.40; IR (KBr) 3239, 1729, 1726, 1722, 1716 cm^{-1}; MS (CI) M + 1 = 242 (80), 192 (35), 164 (98), 79 (100). Anal. C, H, N.

2. 10h (R = (*E*)-$CH_2CH{=}C(CH_3)C{\equiv}CH$) hydrochloride: yield 97%; mp 138−141; ^{1}H NMR (DMSO) δ 11.1 (broad, 3H), 5.96−5.92 (t, 1H, J = 7.2 Hz), 4.67−4.66 (d, 2H, J = 7.2 Hz), 4.07 (s, 1H), 1.85 (s, 3H), ^{13}C NMR (DMSO) δ 129.25, 124.79, 85.22, 80.53, 69.26, 17.73; IR (KBr) 3290, 2993, 2925, 2668, 1599, 1510, 997, 915 cm^{-1}; MS (DEI) M + 1 = 79 (100), 77 (93), 66 (58), 65 (30), 53 (47), 51 (44), 50 (22). Anal. ($C_6H_9NO{\cdot}HCl$) C, H, N.

3. 19Z: yield 43%; mp 125−128 °C; ^{1}H NMR (DMSO) δ 12.19 (broad s, 2H), 5.95 (t, 1H, J = 6.6 Hz), 4.61 (d, 2H, J = 6.7 Hz), 4.02−3.80 (m, 2H), 3.91 (s, 1H), 3.41−3.14 (m, 5H), 2.19 (m, 1H), 1.79 (s, 3H), 1.70 (m, 1H); ^{13}C NMR (DMSO) δ 164.36, 158.72, 133.85, 120.45, 85.70, 79.00, 69.35, 58.80, 55.13, 50.80, 25.84, 17.47; IR (KBr) 3308, 2969, 1638, 1214, 1202, 1002, 705 cm^{-1}; MS (CI) M + 1 = 205. Anal. ($C_{12}H_{16}N_2O{\cdot}C_2H_2O_4$) C, H, N.

(*Z*)-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-(*Z*)-3-Methyl-2-penten-4-ynyl)oxime Oxalate (20Z). 1. 9i (R = (*Z*)-$CH_2CH{=}C(CH_3)C{\equiv}CH$): yield 58%; mp 102−103 °C; ^{1}H NMR ($CDCl_3$) δ 7.86−7.82 (m, 4H), 6.12−6.07 (t, 1H, J = 7.3 Hz), 4.93−4.90 (d, 2H, J = 7.3 Hz), 3.11 (s, 1H), 1.89 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.72, 134.45, 130.80, 128.90, 125.54, 123.42, 83.00, 80.86, 75.56, 23.16; IR (KBr) 3241,1731, 1718, 1713, 981, 701 cm^{-1}; MS (CI) M + 1 = 242 (80), 164 (100), 95 (45), 79 (50). Anal. ($C_{14}H_{11}NO_3$) C, H, N.

2. 10i (R = (*Z*)-$CH_2CH{=}C(CH_3)C{\equiv}CH$) hydrochloride: yield 85%; mp 91−94 °C (turns to glass, it melts completely at 135 °C); ^{1}H NMR (DMSO) 11.2 (broad s, 3H), 5.97−5.94 (t, 1H, J = 6 Hz), 4.71−4.69 (d, 2H, J = 6 Hz), 4.46 (s, 1H), 1.88 (s, 3H); ^{13}C NMR (DMSO) δ 129.78, 123.92, 86.94, 81.55, 71.94, 22.74; IR (KBr) 3277, 2983, 2952, 2920, 2894, 2672, 1509, 1016 cm^{-1}; MS (DEI) M + 1 = 93 (24), 86 (39), 85 (81), 79 (100), 78 (92), 66 (68), 53 (49). Anal. ($C_6H_9NO{\cdot}HCl$) C, H, N.

3. 20Z: yield 37%; mp 127−129 °C; ^{1}H NMR (DMSO) δ 12.20 (broad s, 1H), 6.00−5.94 (t, 1H, J = 6.6 Hz), 4.67−4.65 (d, 2H, J = 6.6 Hz), 4.29 (s, 1H), 3.91−3.80 (m, 2H), 3.41−3.14 (m, 5H), 2.23−2.14 (m, 1H), 1.85 (s, 3H), 1.78−1.70 (m, 1H); ^{13}C NMR (DMSO) δ 164.37, 158.51, 133.83, 120.63, 85.82, 81.73, 71.72, 58.80, 55.15, 50.79, 25.84, 22.65; IR (KBr) 3251, 2962, 1636, 1402, 1278, 1207, 1013, 704 cm^{-1}; MS (CI) M + 1 = 205. Anal. ($C_{12}H_{16}N_2O{\cdot}C_2H_2O_4$) C, H, N.

(*Z*)-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-(3-phenyl-2-propynyl)oxime oxalate (21Z). 1. 9j (R = $CH_2C{\equiv}CPh$): yield 77%; mp 112−113 °C; ^{1}H NMR ($CDCl_3$) δ 7.88−7.82 (m, 2H), 7.79−7.74 (m, 2H), 7.42−7.40 (m, 2H), 7.39−7.25 (m, 3H), 5.10 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 163.48, 134.62, 131.79, 128.95, 128.86, 128.32, 123.67, 121.79, 89.70, 81.67, 77.58, 77.08, 76.57, 65.96; IR (KBr) 1724, 1734, 1390, 875, 695 cm^{-1}; MS (EI) M + 1 = 278 (31), 223 (31), 130 (51), 115 (100), 104 (32). Anal. ($C_{17}H_{11}NO_3$) C, H, N.

2. 10j (R = $CH_2C{\equiv}CPh$): yield 75%; mp 130−133 °C; ^{1}H NMR (DMSO) δ 11.30 (broad s, 3H), 7.56−7.54 (m, 2H), 7.46−7.40 (m, 3H), 5.03 (s, 2H); ^{13}C NMR ($CDCl_3$) 131.70, 129.44, 128.75, 121.09, 88.74, 82.10; IR (KBr) 3052, 2925, 2874, 2656, 1519, 1490, 1034, 909, 753, 690 cm^{-1}; MS (EI) M + 1 = 147 (12), 146 (24), 116 (65), 115 (100), 104 (51), 89 (60). Anal. ($C_9H_9NO{\cdot}HCl$) C, H, N.

3. 21Z: yield 52%; mp 162−164 °C; ^{1}H NMR (DMSO) δ 7.47−7.41 (m, 5H), 4.91 (s, 2H), 4.03−3.83 (m, 2H), 3.45−3.12 (m, 5H), 2.19 (m, 1H), 1.70 (m, 1H); ^{13}C NMR (DMSO) δ 164.09, 160.05, 131.52, 129.00, 128.76, 121.70, 85.76, 61.78, 58.93, 55.35, 50.91, 25.99; IR (KBr) 3266, 2950, 1645, 1206, 1034, 705 cm^{-1}; MS (EI) M + 1 = 241. Anal. ($C_{15}H_{16}N_2O_1{\cdot}C_2H_2O_4$) C, H, N.

(Z)-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-(3-(4′-Methoxyphenyl)-2-propynyl)oxime Oxalate (23Z). 1. 5 (Ar = 4-MeOPh). A solution of 4-iodoanisole (23.4 g, 0.1 mol) in

tetrahydrofuran (40 mL) was added dropwise over 30 min to a solution of diethylamine (80 mL), propargyl alcohol (6.4 mL, 0.11 mol), copper(I) iodide (0.7 g), and tetrakis(triphenylphosphine)palladium(0) (1.2 g) in tetrahydrofuran (25 mL) under nitrogen. The reaction was stirred for 16 h at room temperature and concentrated in vacuo to give a dark brown residue. The residue was dissolved in water (200 mL) and the aqueous solution extracted with diethyl ether (4 × 50 mL). The combined extracts were dried (Na_2SO_4), and the solvent was evaporated to give a dark brown solid product. The product was purified by column chromatography. Elution with hexane−ethyl acetate (9:1) gave 15.38 g (91%) of **5** (Ar = 4-MeOPh): ^{1}H NMR ($CDCl_3$) δ 7.40−7.10 (d, 2H), 6.85−6.60 (d, 2H), 4.40−4.25 (d, 2H), 3.65 (s, 3H), 2.05−1.85 (t, 1H).

2. 91 (R = CH$_2$C≡C(4-MeOPh)). Diethyl azodicarboxylate (21 mL, 104 mmol) was added dropwise to a solution of **5** (Ar = 4-MeOPh) (15.38 g, 94.8 mmol), *N*-hydroxyphthalimide (15.47 g, 94.8 mmol), and triphenylphosphine (24.9 g, 94.8 mmol) in tetrahydrofuran (500 mL) at room temperature under nitrogen. The reaction was stirred for 24 h, and the volatiles removed in vacuo to give a crude solid product. The product was purified by column chromatography. Elution with chloroform gave, after recrystallization from ethanol, 20.13 g (68%) of **91** [R = CH$_2$C≡C(4-MeOPh)]: mp 145−147 °C; ^{1}H NMR ($CDCl_3$) δ 7.87−7.83 (m, 2H), 7.78−7.72 (m, 2H), 7.34−7.26 (d, 2H), 6.81−6.78 (d, 2H), 5.08 (s, 2H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.50, 160.09, 134.57, 133.38, 128.87, 123.64, 113.81, 89.80, 80.30, 66.11, 55.29, 18.14; IR (KBr) 2220, 1742, 1510 cm^{-1}; MS (CI) M + 1 = 308 (25), 164 (37), 160 (45), 148 (48), 146 (54), 145 (100), 133 (80). Anal. ($C_{18}H_{13}NO_4$) C, H, N.

3. 101 [R = CH$_2$C≡C(4-MeOPh)] Hydrochloride. Methylhydrazine (2 mL, 37.6 mmol) was added dropwise to a solution of phthalimide **91 (R = CH$_2$C≡C(4-MeOPh))** (11.55 g, 37.6 mmol) in 40 mL of dichloromethane at 0 °C. The reaction was warmed to room temperature and stirred for 3 h. The resulting precipitate was separated by filtration and discarded. The filtrate was diluted with diethyl ether to a total volume of 500 mL. Anhydrous hydrogen chloride gas was bubbled into the diluted solution to give 8.02 g (100%) of **101** [R = CH$_2$C≡C(4-MeOPh)] hydrochloride as a white precipitate: mp 140−142 °C; ^{1}H NMR (DMSO) δ 11.3 (broad s, 3H), 7.85−7.45 (d, 2H), 7.00−6.96 (d, 2H), 5.03 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (DMSO) δ 159.98, 133.41, 114.36, 112.92, 89.00, 80.57, 62.39, 55.31; IR (KBr) 3022, 3014, 3008, 2995, 2984, 2978, 2970, 2961, 2947, 2925, 2909, 2900, 2659, 2656, 2635, 1608, 1510, 1293, 1251, 1026 cm^{-1}; MS (CI + 1% NH_3 in CH_4) M + 2 = 179 (13), M + 1 = 178 (90), M 177 (25), M − 1 = 176(29), 146 (44), 145 (100), 133 (89). Anal. ($C_{10}H_{11}NO_2$·HCl) H, N; C: calcd, 56.21; found, 55.65.

4. 23Z: yield 31%; mp 158−159 °C; ^{1}H NMR (DMSO) δ 12.15 (broad s, 1.5H), 7.40 (d, 2H, *J* = 8.7 Hz), 6.95 (d, 2H, *J* = 8.7 Hz), 4.88 (s, 2H), 4.05−3.85 (m, 2H), 3.78 (s, 3H), 3.45−3.14 (m, 5H), 2.20 (m, 1H), 1.70 (m, 1H); ^{13}C NMR (DMSO) δ 164.29, 159.63, 159.57, 133.17, 114.34, 113.58, 85.94, 84.20, 61.92, 58.85, 55.25, 50.81, 25.92; IR (KBr) 2958, 1636, 1607, 1511, 1250, 1032, 837 cm^{-1}; MS (CI) M + 1 = 271. Anal. ($C_{16}H_{18}N_2O_2$·$C_2H_2O_4$) C, H, N.

(*Z*)-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-(3-(3′-Methoxyphenyl)-2-propynyl)oxime Oxalate (24Z). 1. 5 (Ar = 3-MeOPh): oil; yield 80%; ^{1}H NMR ($CDCl_3$) 7.20−6.70 (m, 4H), 4.40 (s, 2H), 3.70 (s, 3H), 2.80−2.60 (broad, 1H).

2. 9m [R = CH$_2$C≡C[3-MeOPh)]: brown solid; yield 72%; mp 134−137 °C; ^{1}H NMR ($CDCl_3$) δ 7.88−7.73 (m, 4H), 7.19−7.16 (t, 1H), 7.00−6.92 (m, 3H), 5.10 (s, 2H0, 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.46, 159.22, 134.60, 129.40, 128.84, 124.26, 123.67, 122.73, 115.86, 115.60, 100.29, 89.61, 81.44, 65.93, 55.27; IR (KBr) 2962, 2263, 1734, 1728, 1723, 1584, 1468, 1384, 1290, 1187, 1130, 1039, 876, 700 cm^{-1}; MS (CI) M + 2 = 309 (19), M + 1 = 308 (90), 161 (37), 160 (65), 145 (100), 133 (65). Anal. ($C_{18}H_{13}NO_4$) C, H, N.

3. 10m [R = CH$_2$C≡C(3-MeOPh)]: hygroscopic solid; yield 99%; used without further purification.

4. 24Z: yield 53%; mp 126−127 °C; ^{1}H NMR (DMSO) δ 12.05 (broad s, l.lH), 7.34−7.27 (m, 1H), 7.05−6.98 (m, 3H), 4.91 (s, 2H), 4.05−3.85 (m, 2H), 3.76 (s, 3H), 3.46−3.14 (m, 5H), 2.20 (m, 1H), 1.71 (m, 1H); ^{13}C NMR (DMSO) δ 164.23, 159.84, 159.12, 129.92, 123.90, 122.75, 116.31, 115.41, 85.76, 85.58, 61.78, 58.88, 55.26, 50.84, 25.93; IR (KBr) 2939, 1719, 1605, 1290, 1204, 1043, 721 cm^{-1}; MS (CI) M + 1 = 271. Anal. ($C_{16}H_{18}N_2O_2$·$C_2H_2O_4$) C, H, N.

(*Z*)-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-(3-(4′-Chlorophenyl)-2-propynyl)oxime Oxalate (25Z). 1. 5 (Ar = 4-ClPh): dark brown solid: yield 84%; ^{1}H NMR ($CDCl_3$) δ 7.20 (s, 4H), 4.38 (s, 2H), 1.88 (broad, 1H).

2. 9n [R = CH$_2$C≡C(4-ClPh)]: light yellow solid; yield 76%; mp 154−155 °C; ^{1}H NMR ($CDCl_3$) δ 7.90−7.83 (m, 2H), 7.80−7.73 (m, 2H), 7.35−7.24 (m, 4H), 5.08 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 163.46, 135.07, 134.66, 133.00, 128.79, 128.70, 123.70, 120.24, 88.55, 82.71, 65.87; IR (KBr) 1743, 1737, 1488, 1379, 1187, 975, 829 cm^{-1}; MS (CI + 1% NH_3 in CH_4) M + 2 = 315 (9), M + 1 = 314 (23), M = 312 (100), 167 (17), 166 (28), 165 (42), 164 (77), 149 (89), 148 (76). Anal. ($C_{17}H_{10}ClNO_3$) C, H, N.

3. 10n [R = CH$_2$C≡C(4-ClPh)] hydrochloride: yield 100%; mp 177−179 °C; ^{1}H NMR (DMSO) δ 11.3 (broad, 2H), 7.85−7.49 (m, 4H), 5.07 (s, 2H); ^{13}C NMR (DMSO) δ 142.33, 134.19, 133.45, 128.91, 122.92, 119.98, 96.33, 87.62, 83.18, 62.19; IR (KBr) 3058, 2919, 2874, 2653, 1515, 1490, 1482, 1391, 1095, 1034, 830 cm^{-1}; MS (CI) M + 2 = 184 (7), M + 1 = 183 (4), M = 182 (17), 151 (37), 149 (96), 137 (46), 85 (100). Anal. (C_9H_8ClNO·HCl) C, H, N.

4. 25Z: yield 81%; mp 163−164 °C; ^{1}H NMR (DMSO) δ 11.95 (broad s, 1.5H), 7.51−7.44 (m, 4H), 4.91 (s, 2H), 4.07−3.86 (m, 2H), 3.45 (d, 1H, *J* = 3.7 Hz), 3.40−3.14 (m, 4H), 2.21 (m, 1H), 1.71 (m, 1H); ^{13}C NMR (DMSO) δ 164.35, 159.81, 133.74, 133.29, 128.91, 120.56, 86.93, 84.65, 61.73, 58.83, 55.20, 50.78, 25.89; IR (KBr) 3393, 2860, 1719, 1702, 1624, 1489, 1405, 1214, 1034, 1005, 838, 721 cm^{-1}; MS (CI) M + 1 = 275. Anal. ($C_{15}H_{15}ClN_2O$·$C_2H_2O_4$) C, H, N.

(*Z*)-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-(3-(3′-Chlorophenyl)-2-propynyl)oxime Oxalate (26Z). 1. 5 (Ar = 3-ClPh): brown liquid; yield 89%; ^{1}H NMR ($CDCl_3$) δ 7.42−7.00 (m, 4H), 4.40 (s, 2H), 2.80 (s, 1H).

2. 9o [R = CH$_2$C≡C(3-ClPh)]: yellow solid; yield 52%; mp 119−120 °C; ^{1}H NMR ($CDCl_3$) δ 7.89−7.84 (m, 2H), 7.81−7.78 (m, 2H), 7.36−7.19 (m, 4H), 5.09 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 163.45, 134.68, 134.15, 131.56, 129.92, 129.27, 128.79, 123.72, 123.42, 101.29, 88.15, 82.91, 65.77; IR (KBr) 1731, 1694, 1687, 1610, 1401, 1140, 716 cm^{-1}; MS (CI = 1% NH_3 in CH_4) M + 2 = 315 (8), M + 1 = 314 (34), M = 312 (96), 257 (34), 167 (24), 166 (46), 165 (71), 164 (90), 149 (100), 148 (87), 130 (48). Anal. ($C_{17}H_{10}ClNO_3$) C, H, N.

3. 10o [R = CH$_2$C≡C(3-ClPh)] hydrochloride: yield 99%; mp 146−148 °C; ^{1}H NMR (DMSO) δ 11.3 (broad, 2H), 7.67 (s, 1H), 7.55−7.43 (m, 3H), 5.07 (s, 2H); ^{13}C NMR (DMSO) δ 133.23, 131.14, 130.62, 130.32, 129.53, 123.08, 96.34, 87.26, 83.47, 62.14; IR (KBr) 3024, 2922, 2863, 2655, 1517, 1392, 1035, 906 cm^{-1}; MS (CI) M + 2 = 184 (7), M + 1 = 183 (4), M = 182 (27), 151 (67), 149 (100), 137 (71), 85 (77). Anal. (C_9H_8ClNO·HCl) C, H, N.

4. 26Z: yield 64%; mp 140−142 °C; ^{1}H NMR (DMSO) δ 12.52 (broad s, 1.5H), 7.53−7.42 (m, 4H), 4.92 (s, 2H), 4.06−3.85 (m, 2H), 3.45 (d, 1H, *J* = 4.1 Hz), 3.40−3.14 (m, 4H), 2.21 (m, 1H), 1.71 (m, 1H); ^{13}C NMR (DMSO) δ 164.27, 160.02, 133.29, 130.91, 130.64, 130.30, 129.17, 123.65, 87.23, 84.28, 61.66, 58.86, 55.25, 50.82, 25.93; IR (KBr) 3448, 2929, 1734, 1653, 1636, 1362, 1204, 1032, 1004, 707, 682 cm^{-1}; MS (CI) M + 1 = 275. Anal. ($C_{15}H_{15}ClN_2O$·$C_2H_2O_4$) C, H, N.

(*Z*)-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-(3-(2′-Fluorophenyl)-2-propynyl)oxime Oxalate (27Z). 1. 5 (Ar = 2-FPh): golden yellow liquid; yield 68%; ^{1}H NMR ($CDCl_3$) δ 7.55−6.80 (m, 4H), 4.50 (s, 2H), 3.18−2.90 (broad, 1H).

2. 9p [R = CH$_2$C≡C(2-FPh)]: yellow solid; yield 79%; mp 122−125 °C; ^{1}H NMR ($CDCl_3$) δ 7.88−7.74 (m, 4H), 7.44−7.27 (m, 2H), 7.10−6.98 (m, 2H), 5.13 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 164.82, 163.42, 160.80, 134,59, 133.73, 130.82, 130.70, 128.84, 124.01, 123.96, 123.66, 122.15, 115.68, 115.34, 110.50, 110.27,

86.69, 83.16, 65.79; IR (KBr) 3504, 3498, 3085, 1790, 1738, 1727, 1704, 1612, 1469, 1449, 1387, 1260, 1219, 1188, 1124, 1004, 694 cm^{-1}; MS (CI) M + 2 = 297 (33), M + 1 296. (100), 164 (18), 163 (83), 148 (83), 133 (87). Anal. ($C_{17}H_{10}FNO_3$) H, N; C: calcd, 69.15; found, 69.63.

3. 10p [R = $CH_2C{\equiv}C$(2-FPh)] hydrochloride: white solid; yield 100%; mp 132−133 °C; ^{1}H NMR (DMSO) O 11.4 (brOad, 2H), 7.8−7.61 (m, 1H), 7.58−7.48 (m, 1H), 7.39−7.25 (m, 1H), 5.11 (s, 2H); ^{13}C NMR (DMSO) δ 164.11, 160.13, 133.97, 131.91, 131.78, 127.03, 124.88, 124.82, 115.94, 115.62, 109.51, 109.26, 87.13, 87.08, 82.08, 62.14; IR (KBr) 2950, 2923, 2915, 1492 cm^{-1}; MS (CI + 1% NH_3 in CH_4) M + 1 = 166 (7), 133 (43), 85 (100). Anal. ($C_9H_8FNO{\cdot}HCl$) H, N; C: calcd, 53.61; found, 52.20.

4. 27Z: yield 64%; mp 141−142 °C; ^{1}H NMR (DMSO) δ 12.25 (broad 5, 1.6H), 7.58−7.20 (m, 4H), 4.96 (s, 2H), 4.10−3.85 (m, 2H), 3.47−3.15 (m, 5H), 2.21 (m, 1H), 1.71 (m, 1H); ^{13}C NMR (DMSO) δ 164.29, 164.07, 160.00, 133.67, 131.31 (d, J_{C-F} = 8.2 Hz), 124.82 (d, J_{C-F} = 3.6 Hz), 115.75 (d, J_{C-F}= 20.7 Hz), 109.98 (d, J_{C-F}= 15.1 Hz), 90.98 (d, J = 2.9 Hz), 79.13, 61.73, 58.85, 55.24, 50.81, 25.92; IR (KBr) 2858, 1636, 1492, 1214, 1006, 721 cm^{-1}; MS (CI) M + 1 = 259. Ana1. ($C_{15}H_{15}FN_2O{\cdot}C_2H_2O_4$) C, H, N.

(*Z*)-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-(3-(4′-Fluorophenyl)-2-propynyl)oxime Oxalate (28Z). 1. 5 (Ar = 4-FPh): dark brown liquid; yieid 90%; ^{1}H NMR ($CDCl_3$) δ 7.48−7.18 (m, 2H), 7.10−6.70 (m, 2H), 4.50 (broad, 2H), 2.75−2.48 (broad, 1H).

2. 9q [R = $CH_2C{\equiv}C$(4-FPh)]: yellow solid; yield 73%; mp 124−125 °C; ^{1}H NMR ($CDCl_3$) δ 7.88−7.75 (m, 4H), 7.41−7.27 (m, 2H), 7.02−6.95 (m, 2H), 5.08 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 164.85, 163.47, 160.86, 134.63, 133.86, 133.72, 128.81, 123.67, 117.88, 115.83, 115.48, 113.48, 88.61, 85.89, 81.44; MS (CI) M + 2 = 297 (16), M + 1 = 296 (79), 164 (30), 163 (100), 148 (92), 133 (93), 121 (42). Anal. ($C_{17}H_{10}FNO_3$) C, H, N.

3. 10q [R = $CH_2C{=}C$(4-FPh)] obtained as a white solid: yield 100%; mp 160−161 °C; ^{1}H NMR (DMSO) δ 11.4 (broad, 2H), 7.67−7.61 (m, 2H), 7.56−7.25 (m, 2H), 5.06 (s, 2H); ^{13}C NMR (DMSO) δ 164.34, 160.39, 134.24, 134.10, 117.57, 11619, 115.84, 87.81, 81.81, 62.20; IR (KBr) 3019, 3013, 3000, 2983, 2870, 2655, 1511, 1241, 838 cm^{-1}; MS (CI + 1% NH_3 in CH_4) M + 1 = 166 (7), 133 (30), 85 (100). Anal. ($C_9H_8FNO{\cdot}HCl$) H, N; C: calcd, 53.61; found, 4.56.

4. 28Z: yield 60%; mp 144−145 °C; ^{1}H NMR (DMSO) δ 11.32 (broad s, 1.5H), 7.60−7.45 (m, 2H), 7.30−7.20 (m, 2H), 4.91 (s, 2H), 4.10−3.87 (m, 2H), 3.47−3.16 (m, 5H), 2.22 (m, 1H), 1.72 (m, 1H); ^{13}C NMR (DMSO) δ 164.40, 164.09, 160.15, 159.66, 133.94 (d, J_{C-F} = 8.6 Hz), 118.13 (d, J_{C-F} = 3.1 Hz), 115.99 (d, J_{C-F} = 22.3 Hz), 85.51, 84.79, 61.75, 58.82, 55.18, 50.77, 25.87; IR (KBr) 2939, 1726, 1636, 1601, 1507, 1358, 1223, 1032, 1003, 840, 712 cm^{-1}; MS (CI) M + 1 = 259. Anal. ($C_{15}H_{15}FN_2O{\cdot}C_2H_2O_4$) C, H, N.

(*Z*)-(±) -1-Azabicyclo[2.2.1]heptan-3-one, *O*-(3-(3′-Fluorophenyl)-2-propynyl)oxime Oxalate (29Z). 1. 5 (Ar = 3-F-Ph): dark brown liquid; yield 97%.

2. 9r [R = $CH_2C{\equiv}C$(3-FPh)]: yellow solid; yield 71%; mp 124−125 °C; ^{1}H NMR ($CDCl_3$) δ 7.89−7.84 (m, 2H), 7.81−7.75 (m, 2H), 7.31−7.24 (m, 2H), 7.22−7.04 (m, 2H), 5.09 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 164.18, 163.46, 160.86, 134.68, 130.04, 129.90, 128.80, 127.68, 127.63, 123.71, 123.47, 118.74, 118.38, 116.52, 116.19, 88.34, 82.65, 65.78; IR (KBr) 1735, 1611, 1582, 1386, 1188, 1174, 1152, 1019, 977, 878, 783, 699 cm^{-1}; MS (CI) M + 2 = 297 (16), M + 1 = 296 (19), 164 (17), 163 (89), 148 (50), 133 (100). Anal. ($C_{17}H_{10}FNO_3$).

3. 10r [R = $CH_2C{\equiv}C$(3-FPh)] hydrochloride: yield 100%; mp 147−151 °C; ^{1}H NMR (DMSO) δ 11.3 (broad, 2H), 7.53−7.24 (m, 4H), 5.06 (s, 2H); ^{13}C NMR (DMSO) δ 163.66, 159.77, 130.78, 130.83, 128.04, 128.03, 123.11, 122.95, 118.51, 118.14, 116.93, 116.60, 87.47, 87.42, 83.11, 62.12; IR (KBr) 3019, 2990, 2896, 2849, 2664, 1582, 1488, 1176, cm^{-1}; MS (CI + 1% NH_3 in CH_4) M = 165 (35), 134 (100), 122 (60). Anal. ($C_9H_8FNO{\cdot}HCl$) C, H, N.

4. 29Z: yield 37%; mp 123−125 °C; ^{1}H NMR (DMSO) δ 8.25 (broad s, 2H), 7.50−7.25 (m, 4H), 4.92 (s, 2H), 4.10−3.86 (m, 2H), 3.46−3.15 (m, 5H), 2.21 (m, 1H), 1.71 (m, 1H); ^{13}C NMR (DMSO) δ 164.24, 164.07, 159.89, 130.91 (d, J_{C-F} = 8.7 Hz), 127.96 (d, J_{C-F} = 3.0 Hz), 123.62 (d, J_{C-F} = 9.6 Hz), 118.12 (d, J_{C-F} = 22.9 Hz), 116.37 (d, J_{C-F} = 20.9 Hz), 95.92, 86.86, 84.54, 61.67, 58.86, 55.24, 50.83, 25.90; IR (KBr) 3407, 2928, 1610, 1581, 1404, 1280, 1172, 1152, 1033, 721 cm^{-1}; MS (CI) M + 1 = 259. Anal. ($C_{15}H_{15}FN_2O{\cdot}C_2H_2O_4$) C, H, N.

(*Z*)-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-(3-(2′-Methoxyphenyl)-2-propynyl)oxime Oxalate (30Z). 1. 5 (Ar = 2-MeOPh): brown solid; yield 65%; mp 65−69 °C; ^{1}H NMR δ 7.40−7.10 (m, 2H), 6.90−6.60 (m, 2H), 4.50 (d, 2H), 3.80 (s, 3H), 2.8 (broad, 1H).

2. 9s [R = $CH_2C{\equiv}C$(2-MeOPh)]: brown solid; yield 78%; mp 147−148 °C; ^{1}H NMR ($CDCl_3$) δ 7.87−7.73 (m, 4H), 7.38−7.28 (m, 2H), 6.90−6.79 (m, 2H), 5.16 (s, 2H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.42, 160.16, 134.48, 133.83, 130.40, 128.94, 123.57, 120.57, 120.42, 117.97, 117.50, 117.01, 116.87, 110.96, 110.53, 86.29, 85.49, 66.11, 55.60; IR (KBr) 2220, 1741, 1606, 1510, 1380, 1298, 1186, 1030, 970, 699 cm^{-1}; MS (CI) M + 2 = 309, M + 1 = 308. Anal. ($C_{18}H_{13}NO_4$) C, H, N.

3. 10s [R = $CH_2C{\equiv}C$(2-MeOPh)]: white solid; yield 100%; mp 113−114 °C; ^{1}H NMR (DMSO) δ 11.3 (broad, 2H), 7.85−7.39 (m, 2H), 7.11−7.07 (d, 1H), 6.97−6.94 (t, 2H), 5.06 (s, 1H), 3.83 (s, 3H); ^{13}C NMR (DMSO) δ 160.00, 133.67, 131.12, 120.44, 111.35, 109.90, 85.57, 85.37, 62.43, 55.58; MS (CI + 1% NH_3 in CH_4) M + 2 = 179 (32), M + 1 = 178 (100), M = 177 (65), 176, 146 (73), 145 (94), 133 (64), 105 (78); IR (KBr) 2908, 2900, 2896, 2834, 2653, 2646, 1266, 747. Anal. ($C_{10}H_{11}NO_2{\cdot}HCl$) H, N; C: calcd, 56.21; found, 55.69.

4. 30Z: yield 34%; mp 155−157 °C; ^{1}H NMR (DMSO) δ 11.60 (broad s, 1.2H), 7.41−7.35 (m, 2H), 7.06 (d, 1H, J = 8.9 Hz), 6.94 (t, 1H, J = 7.1 Hz), 4.91 (s, 2H), 4.06−3.86 (m, 2H), 3.81 (s, 3H), 3.45−3.15 (m, 5H), 2.21 (m, 1H), 1.71 (m, 1H); ^{13}C NMR (DMSO) δ 164.31, 159.86, 159.62, 133.41, 130.58, 120.44, 111.33, 110.60, 96.12, 89.13, 82.62, 62.05, 58.85, 55.53, 55.26, 50.81, 25.91; IR (KBr) 2937, 1762, 1639, 1493, 1264, 1028, 721 cm^{-1}; MS (CI) M + 1 = 271. Anal. ($C_{16}H_{18}N_2O_2{\cdot}C_2H_2O_4$) C, H, N.

(*Z*)-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-(3-(2′-Chlorophenyl)-2-propynyl)oxime Oxalate (31Z). 1. 5 (Ar = 2-ClPh): brown liquid; yield 66%; ^{1}H NMR ($CDCl_3$) δ 7.58−6.92 (m, 4H), 4.55 (s, 2H), 3.12 (s, 1H).

2. 9t [R = $CH_2C{\equiv}C$(2-ClPh)]: mp 104−105 °C; ^{1}H NMR ($CDCl_3$) δ 7.89−7.83 (m, 2H), 7.79−7.74 (m, 2H), 7.47−7.44 (m, 1H), 7.33−7.16 (m, 3H), 5.17 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.42, 135.90, 134.59, 133.70, 129.99, 129.21, 128.88, 126.49, 123.65, 121.77, 86.65, 86.34, 65.73; IR (KBr) 1784, 1736, 1730, 1727, 1718, 1380, 1355, 1186, 1124, 1016, 980, 972, 877, 767, 762, 707 cm^{-1}; MS (CI) M + 2 = 314 (38), M + 1 = 315 (15), M = 312 (100), 167 (12), 166 (34), 165 (33), 164 (78), 151 (79), 149 (94), 148 (66). Anal. ($C_{17}H_{10}ClNO_3$) C, H, N.

3. 10t [R = $CH_2C{\equiv}C$(2-ClPh)] hydrochloride: yield 41%; mp 161−163 °C; ^{1}H NMR (DMSO) δ 11.2 (broad s, 2H), 7.74−7.71 (m, 1H), 7.69−7.58 (m, 1H), 7.62−7.38 (m, 2H), 5.11 (s, 2H); ^{13}C NMR (DMSO) δ 134.74, 134.07, 131.08, 129.39, 120.82, 96.26, 87.05, 85.15, 62.15; IR (KBr) 3058, 3021, 2989, 2977, 2968, 2877, 2653, 1507, 1477, 1021, 857 cm^{-1}; MS (CI + 1% NH_3 in CH_4) M + 2 = 184 (9), M + 1 = 183 (5), M = 182 (29), 180 (19), 151 (66), 149 (10), 137 (60), 85 (81). Anal. ($C_9H_8ClNO{\cdot}HCl$) C, H, N.

4. 31Z: yield 51%; mp 143−145 °C; ^{1}H NMR (DMSO) δ 11.46 (broad s, 1.1H), 7.61−7.33 (m, 4H), 4.97 (s, 2H), 4.06−3.86 (m, 2H), 3.45 (d, 1H, J = 4.1 Hz), 3.40−3.14 (m, 4H), 2.21 (m, 1H), 1.71 (m, 1H); ^{13}C NMR (DMSO) δ 164.24, 160.10, 134.69, 133.68, 130.60, 129.40, 127.40, 121.41, 90.96, 82.42, 61.72, 58.88, 55.28, 50.84, 25.95; IR (KBr) 2843, 2707, 2566, 2534, 1718, 1702, 1636, 1474, 1404, 1228, 995, 762, 722 cm^{-1}; MS (CI) M + 1 = 275. Anal. ($C_{15}H_{15}ClN_2O{\cdot}C_2H_2O_4$) C, H, N.

(*Z*)-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-(3-(3′-Nitrophenyl) -2-propynyl)oxime Oxalate (32Z). 1. 5 (R_2 = 3-NO_2Ph): yield 78%.

2. 9u [R = $CH_2C{\equiv}C$(3-NO_2Ph)]: yield 82%; mp 162−163 °C; ^{1}H NMR ($CDCl_3$) δ 8.22−8.17 (m, 2H), 7.91−7.86 (m, 2H), 7.82−7.72 (m, 3H), 7.54−7.27 (t, 1H, J = 8.0 Hz), 5.11 (s, 2H);

^{13}C NMR ($CDCl_3$) δ 137.43, 134.79, 129.45, 126.58, 123.79, 123.70, 86.00, 84.00, 65.64; IR (KBr) 1784, 1735, 1731, 1532, 1352, 1187, 698 cm^{-1}; MS (CI + 1% NH3 in CH4) M + 2 = 324 (17), M + 1 = 323 (100), M = 322 (0.7), 177 (8), 176 (30), 160 (69), 148 (42). Anal. ($C_{17}H_{10}N_2O_5$) C, H, N.

3. 10u [R = $CH_2C{\equiv}C$(3-NO_2Ph)] hydrochloride: yield 85%; mp 139−140.5 °C; ^{1}H NMR (DMSO) δ 11.2 (broad s, 3H), 8.40−8.39 (t, 1H, J = 1.8 Hz), 8.30−8.28 (dd, 1H, J = 8Hz, J = 1.8 Hz), 8.03−7.91 (d, 1H, J = 8.0 Hz), 7.76−7.72 (t, 1H, J = 8 Hz), 5.10 (s, 2H); ^{13}C NMR (DMSO) δ 147.79, 137.79, 130.48, 126.23, 124.14, 122.68, 86.61, 84.45, 62.13; IR (KBr) 3060, 2922, 2870, 2662, 1723, 1533, 794 cm^{-1}; MS (CI + 1% NH3 in CH4) M + 1 = 193 (96), M = 192 (16), 191 (43), 160 (100), 148 (95), 119 (87). Anal. ($C_9H_8N_2O_3$·HCl) C, H, N.

4. 32Z: yield 35%; mp 157−160 °C; ^{1}H NMR (DMSO) δ 8.25 (d, 1H, J = 7.9 Hz), 8.20 (s, 1H), 7.90 (d, 1H, J = 7.7 Hz), 7.70 (t, 1H, J = 8.0 Hz), 7.23 (broad s, 2.9 H), 4.95 (s, 2H), 4.07−3.85 (m, 2H), 3.45 (d, 1H, J = 4.0 Hz), 3.41−3.13 (m, 4H), 2.20 (m, 1H), 1.71 (m, 1H); ^{13}C NMR (DMSO) δ 164.15, 160.18, 147.84, 137.75, 130.49, 125.91, 123.76, 123.18, 88.24, 83.53, 61.59, 58.90, 55.29, 50.87, 25.93; IR (KBr) 3450, 2960, 1719, 1636, 1531, 1352, 721 cm^{-1}; MS (CI) M + 1 = 286. Anal. ($C_{15}H_{15}N_3O_3$·$C_2H_2O_4$) C, H, N.

***(Z)*-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-(3-(4′-Methylphenyl)-2-propynyl)oxime Oxalate (33Z). 1. 5 (R_2 = 4-MePh):** dark brown oil; yield 58%.

2. 9V [R = $CH_2C{\equiv}C$(4-CH_3Ph)]: yield 66%; mp 122−124 °C; ^{1}H NMR ($CDCl_3$) δ 7.89−7.82 (m, 2H), 7.79−7.74 (m, 2H), 7.30−7.27 (m, 2H), 7.10−7.08 (m, 2H), 5.09 (s, 2H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.00, 134.58, 131.69, 129.07, 123.65, 119.90, 80.94, 66.04, 21.53; IR (KBr) 1749, 1743, 1510, 1384, 1186, 968, 699 cm^{-1}; MS (CI) M = 293 (10), 292 (152), 148 (71), 145 (70), 129 (1003. Anal. ($C_{18}H_{13}NO_3$) C, H, N.

3. 10v [R = $CH_2C{\equiv}C$(4-CH_3Ph)] hydrochloride: mp 152−154 °C; ^{1}H NMR (DMSO) δ 11.2 (broad, 2H), 7.45−7.42 (d, 2H, J = 8.0 Hz), 7.29−7.22 (d. 2H, J = 8.0 Hz), 7.62−7.38 (m, 2H), 5.04 (s, 2H), 2.62 (s, 3H); ^{13}C NMR (DMSO) δ 139.30, 134.07, 131.62, 131.20, 129.34, 118.05, 88.97, 81.37, 62.31, 21.05; IR (KBr) 2920, 2650, 1511, 821 cm^{-1}; MS (CI + 1% NH_3 in CH_4) M + 2 = 163 (7), M + 1 = 162 (47), M = 161 (10), 130 (55), 129 (100). Anal. ($C_{10}H_{11}NO$·HCl) H, N; C: calcd, 60.76; found, 60.04.

4. 33Z: yield 81%; mp 157−158 °C; ^{1}H NMR (DMSO) δ 8.45 (broad s, 2H), 7.34 (d, 2H, J = 8.0 Hz), 7.20 (d, 2H, J = 8.1 Hz), 4.89 (s, 2H), 4.06−3.85 (m, 2H), 3.45−3.14 (m, 5H), 2.31 (s, 3H), 2.20 (m, 1H), 1.70 (m, 1H); ^{13}C NMR (DMSO) δ 164.27, 159.66, 138.76, 131.45, 129.34, 118.69, 85.99, 85.03, 61.86, 58.86, 55.25, 50.82, 25.92, 21.00; IR (KBr) 2950, 1635, 1510, 1221, 1004, 712 cm^{-1}; MS (CI) M + 1 = 255. Anal. ($C_{16}H_{18}N_2O$·$C_2H_2O_4$) C, H, N.

***(Z)*-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-(3-(2-Thienyl)-2-propynyl)oxime Oxalate (34Z). 1. 5 (Ar = 2-thienyl):** brown oil: yield 76%; ^{1}H NMR ($CDCl_3$) δ 7.27−7.21 (m, 2H), 6.98−6.96 (m, 1H), 4.51 (s, 2H), 1.94 (braod s, 1H); ^{13}C NMR ($CDCl_3$) 132.43, 127.47, 127.00, 122.43, 91.15, 79.08, 51.7. Anal. (C_7H_6OS) C, H.

2. 9w [R = $CH_2C{\equiv}C$(2-thienyl)]: yield 71%; mp 123−124 °C; ^{1}H NMR ($CDCl_3$) δ 7.89−7.83 (m, 2H), 7.80−7.73 (m, 2H), 7.29−7.27 (m, 1H), 7.26−7.21 (m, 1H), 6.97−6.93 (m, 1H), 5.10 (s, 2H); ^{13}C NMR ($CDCl_3$) 163.42, 152.63, 134.63, 133.35, 128.82, 128.27, 127.02, 123.70, 121.52, 101.50, 85.58, 83.14, 65.96, 34.07; IR (Br) 3093, 1732, 1721, 1715, 1360, 1128, 927, 935, 874, 724, 715 cm^{-1}; MS (CI + 1% NH3 in CH4) M + 2 = 285 (10), M + 1 = 284 (54), M = 283 (9), 149 (22), 148 (85), 121 (100), 109 (68). Anal. ($C_{15}H_9NO_3S$) C, H, N.

3. 10w [R = $CH_2C{\equiv}C$(2-thienyl)] hydrochloride: white solid: yield 100%; mp 134−136 °C; ^{1}H NMR (DMSO) δ 11.4 (broad, 2H), 7.73−7.71 (m, 1H), 7.69−7.43 (m, 1H), 7.15−7.11 (m, 1H), 5.09 (s, 2H); ^{13}C NMR (DMSO) δ 134.07, 133.62, 129.91, 127.72, 120.43, 96.42, 86.03, 82.26, 62.29. IR (Br) 3016, 2940, 2918, 2878, 2847, 2686, 1569, 1006, 894, 714 cm^{-1}; MS (CI + 1% NH_3 in CH_4) M + 2 = 155 (24), M + 1 = 154 (80), M = 153 (10), 150 (23), 123 (26), 122 (44), 121 (93), 87 (42), 86 (66), 85 (86). Anal. (C_7H_7NOS·HCl) C, H, N.

4. 34Z: yield 68%; mp 135−136 °C; ^{1}H NMR (DMSO) δ 11.60 (broad s, 1H), 7.65 (dd, 1H, J = 4.9, 0.9 Hz), 7.37 (dd, 1H, J = 3.6, 0.9 Hz), 7.09 (m, 1H), 4.93 (s, 2H), 4.05−3.84 (m, 2H), 3.44 (d, 1H, J = 4.1 Hz), 3.33−3.13 (m, 4H), 2.20 (m, 1H), 1.70 (m, 1H); ^{13}C NMR (DMSO) δ 164.26, 159.98, 133.25, 129.14, 127.71, 121.18, 89.88, 79.20, 61.85, 58.89, 55.28, 50.85, 25.96; IR (Br) 3448, 1636, 1193, 999, 721 cm^{-1}; MS (CI) M + 1 = 247. Anal. ($C_{13}H_{14}N_2OS$·$C_2H_2O_4$) C, H, N.

(*Z*)-(±)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-(3-(3-Thienyl)-2-propynyl)oxime Oxalate (35Z). 1. 3-(3-Thienyl)-2-propyn-1-ol.

2. 9X [R = $CH_2C{\equiv}C$(3-thienyl)]: yield 61%; mp 110−112 °C; ^{1}H NMR ($CDCl_3$) δ 7.89−7.79 (m, 2H), 7.78−7.74 (m, 2H), 7.46−7.27 (m, 1H), 7.25−7.22 (m, 1H), 7.08−7.05 (m, 1H), 5.08 (s, 2H); ^{13}C NMR ($CDCl_3$) 163.42, 134.61, 130.13, 129.78, 128.83, 125.46, 123.67, 83.14, 81.35, 65.96; IR (Br) 1733, 1725, 1382, 1187, 1183, 784 cm^{-1}; MS (CI + 1% NH_3 in CH_4) M + 2 = 285 (18), M + 1 = 284 (100), M = 283 (0.8), 149 (11), 148 (50), 121 (85), 109 (30). Anal. ($C_{15}H_9NO_3S$) C, H, N.

3. 10x [R = $CH_2C{\equiv}C$(3-thienyl)] hydrochloride: yield 96%; mp 133−136 °C; ^{1}H NMR (DMSO) δ 11.4 (broad, 2H), 7.96−7.94 (m, 1H), 7.67−7.64 (m, 1H), 7.26−7.24 (m, 1H), 5.08 (s, 2H); ^{13}C NMR (DMSO) δ 131.46, 129.67, 127.09, 119.98, 96.42, 84.46, 81.47, 62.30; IR (KBr) 2871, 1545, 1025, 794 cm^{-1}; MS (CI + 1% NH_3 in CH_4) M + 1 = 154 (35), M = 153 (10), 152 (18), 122 (30), 121 (100), 109 (45). Anal. (C_7H_7NOS·HCl) H, N; C: calcd, 44.33; found, 43.20.

4. 35Z: yield 35%; mp 146−148 °C; ^{1}H NMR (DMSO) δ 7.82 (dd, 1H, J = 3.0, 1.0 Hz), 7.60 (m, 1H), 7.17 (dd, 1H, J = 5.0, 1.0 Hz), 4.88 (s, 2H), 4.06−3.85 (m, 2H), 3.44 (d, 1H, J = 4.1 Hz), 3.39−3.15 (m, 4H), 2.21 (m, 1H), 1.72 (m, 1H); ^{13}C NMR (DMSO) δ 164.20, 159.59, 130.45, 129.61, 126.84, 120.60, 85.06, 81.38, 61.86, 58.87, 55.25, 50.84, 25.91; IR (KBr) 1628, 1211, 1029, 721 cm^{-1}; MS (CI) M + 1 = 247. Anal. ($C_{13}H_{14}N_2OS$·$C_2H_2O_4$) C, H, N.

***(R)*-(−)-(*Z*)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-(3-(3′-methuxyphenyl)-2-propynyl)oxime maleate [(*R*)-(−)-24Z]:** mp 116.5−118.5 °C; 99.72% pure by HPLC (column: Zorbax SB-CN; 250 × 4.6 mm, 5 μm; mobile phase: 180 parts acetonitrile, 820 parts of 0.03 M aqueous KH_2PO_4 plus 6 mL of TEA per liter adjusted to pH 3.0 with H_3PO_4, flow rate 1.0 mL/min; UV detection at 250 nM) t_R 15.7 min; 99% ee (ee estimated by chiral HPLC, column: Diacel Chiralpak AD, 250 × 46 mm,10 μm; mobile phase: hexane/ethanol/diethylamine {90:10:0.1}; flow rate 1.0 mL/min, UV detection at 250 nm) t_R 21 min; rotation $[\alpha]_D$ = −10.7 (methanol; c = 0.512); ^{1}H NMR (400 MHz; DMSO) δ 7.31 (t, 1H, J = 7.7 Hz), 7.04−7.00 (m, 2H), 6.99 (s, 1H), 6.06 (s, 2H), 4.93 (s, 2H), 4.19−4.03 (m, 2H), 3.77 (s, 3H), 3.52 (d, 1H, J = 4.1 Hz), 3.45−3.29 (m, 4H), 2.24 (m, 1H), 1.75 (m, 1H); ^{13}C NMR (100 MHz; DMSO) 167.67, 159.60, 158.62, 136.19, 130.41, 124.37, 123.18, 116.82, 115.87, 86.33, 85.92, 62.40, 59.48, 55.79, 55.69, 51.58, 26.02; IR (KBr) 1697 (C═O stretch) cm^{-1}; MS (CI) M + 1 = 271. Anal. ($C_{16}H_{18}N_2O_2$·$C_4H_4O_4$) C, H, N.

***(S)*-(±)-(*Z*)-1-Azabicyclo[2.2.1]heptan-3-one, *O*-(3-(3′-methoxyphenyl)-2-propynyl)oxime maleate [(*S*)-(+)-24Z]:** mp 115−116 °C; ee 99.6% (determined as described for the *R* isomer) 16 min; rotation $[\alpha]_D$ = +11.9 (methanol; c = 0.629); ^{1}H NMR (400 MHz; DMSO) δ 7.31 (t, 1H, J = 7.5 Hz), 7.04−7.00 (m, 2H), 6.98 (s, 1H), 6.05 (s, 2H), 4.92 (s, 2H), 4.19−4.03 (m, 2H), 3.76 (s, 3H), 3.52 (d, 1H, = 4.3 Hz), 3.42−3.29 (m, 4H), 2.24 (m, 1H), 1.75 (m, 1H); ^{13}C NMR (100 MHz; DMSO) δ 167.64, 159.60, 158.59, 136.12, 130.42, 124.37, 123.17, 116.83, 115.87, 86.33, 85.92, 62.41, 59.48, 55.79, 55.69, 51.58, 26.01; IR (KBr) 1697 (C═O stretch) cm^{-1}; MS (CI) M + 1 = 271. Anal. ($C_{16}H_{18}N_2O_2$·$C_4H_4O_4$) C, H, N.

Pharmacological Methods. Radioligand Binding Assays. Muscarinic receptor binding assays were conducted using [^{3}H]quinuclidinyl benzilate (QNB) to label antagonist sites and [^{3}H]-*cis*-methyldioxolane (CMD) to label agonist sites in the rat neocortex.[44,45] The ratio of QNB/CMD has been shown to predict intrinsic efficacy at muscarinic receptors.[46] Selectivity for m1 over m2 muscarinic subtypes was determined by comparing affinity for m1 and m2 receptor subtypes

labeled with [^{3}H]QNB in CHO cells selectively expressing human m1 and m2 receptors.[47]

Second Messenger Activation Assays. The ability of selected agonists to stimulate phosphoinositide accumulation (for m1, m3, and m5 receptors) or to inhibit forskolin-stimulated accumulation of cAMP (for m2 and m4 receptors) was determined in CHO cells transfected with the corresponding human receptors.[47]

Cellular Metabolic Activity. The effects of selected compounds on the cellular metabolic activity (rate of excretion of acidic metabolites) of CHO cells transfected with human muscarinic receptor subtypes were determined utilizing a Cytosensor microphysiometer.[49]

Muscarinic Receptor Mediated Cell Amplification. The ability of cloned muscarinic receptors to mediate responses related to proliferation of living mammalian cells was evaluated. In this assay, ligand/receptor interactions allow the selection and amplification of NIH-3T3 cells that also express β-galactosidase (receptor selection and amplification technology, R-SAT, Receptor Technologies Inc.)[50,51]

In Vivo Assays. Rat Stomach Emptying and Intestinal Propulsion. Fasted male rats were treated by gavage with 20 Amberlite resin-based pellets and were killed 20 min later. Their stomachs and small intestines were removed, and the distribution of pellets between the lumen of the stomach and the intestines, as well as the longest distance travelled by the pellets in the intestine were measured.[53]

Mouse Water Maze. The effects of selected compounds on the performance of C57/B10J mice on a spatial working memory task in a square water-maze was assessed 30 min following the administration of a solution of drug by oral gavage. Four trials were conducted, separated by 30-s inter-trial intervals. Latency to find a platform hidden below the surface of the opaque water served as the dependent measure.[54]

nbM-Lesioned Rats.[55] Male, Long-Evans rats were lesioned with ibotenic acid (3 mg/μL) at four sites within the nucleus basalis of Meynert (nbM); two sites in each hemisphere. Following at least 3 weeks of recovery, animals were tested in a Morris water maze task. **(*R*)-24Z** was administered orally 30 min prior to testing with each rat given one daily trial for 7 days, and a different corner chosen as the starting point for each trial. The latency to find the hidden platform was measured for each animal to a maximum of 120 s. Swim latency data were analyzed using *t*-tests for grouped data (*$p < 0.05$ and **$p < 0.001$). The number of animals per group is indicated by the number on each bar.

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