Articles

Bioisosteres of Arecoline: 1,2,3,6-Tetrahydro-5-pyridyl-Substituted and 3-Piperidyl-Substituted Derivatives of Tetrazoles and 1,2,3-Triazoles. Synthesis and Muscarinic Activity

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A series of arecoline bioisosteres, where the ester group is replaced by a 1,2,3-triazol-4-yl or a tetrazol-5-yl group, was synthesized and evaluated *in vitro* for affinity and efficacy at muscarinic receptors and *in vivo* for cholinergic side effects. The corresponding piperidine derivatives were also studied. In the 1,2,3,6-tetrahydropyridyl-1,2,3-triazole series, only derivatives with 2-substituents in the 1,2,3-triazole ring exert muscarinic agonist activity. The same trend is seen in the corresponding tetrazole series, where only 2-substituted derivatives display muscarinic agonist activity. The methyl derivatives in both series are full agonists, whereas the derivatives with longer side chains are partial agonists. Introduction of methyl substituents in the 1,2,3,6-tetrahydropyridine ring generally lowers affinity considerably except for the 3-substituted derivatives, where some activity is retained. In both the 1,2,3-triazole and tetrazole series, derivatives without substituents at the basic nitrogen in the 1,2,3,6-tetrahydropyridine ring are unselective full agonists, whereas the methyl-substituted derivatives generally are more M_1 selective compared to M_2. Larger substituents than methyl abolish activity. The 4-(3-piperidyl)-1,2,3-triazole and 5-(3-piperidyl)-2H-tetrazole derivatives are generally less active than the corresponding 1,2,3,6-tetrahydropyridine derivatives, and only the 2-allyl- and 2-propargyl-1,2,3-triazole derivatives display activities comparable to the most active compounds in the 1,2,3,6-tetrahydropyridine series. The propargyl derivative is an unselective full agonist, and resolution did not reveal any stereoselectivity. The allyl derivative is a partial agonist with some selectivity for the M_1 receptor, and testing of the enantiomers showed that the (+)-enantiomer is an unselective partial agonist, whereas the (−)-enantiomer is a partial agonist with preference for the M_1 receptor. Generally, the structure−activity relationships of the 1,2,3-triazole and tetrazole series are very similar, and two compounds, 2-ethyl-4-(1-methyl-1,2,3,6-tetrahydro-5-pyridyl)-1,2,3-triazole and 2-ethyl-5-(1-methyl-1,2,3,6-tetrahydro-5-pyridyl)-2H-tetrazole, are M_1 agonists/M_2 antagonists. Muscarinic compounds with this profile are of particular interest as drugs for the treatment of Alzheimer's disease.

Introduction

The cholinergic hypothesis of geriatric memory loss, which attributes the cognitive decline in Alzheimer patients to degeneration of cortical cholinergic neurons, was formulated in the late 1970s[1,2] and has since then been of widespread scientific and clinical interest (for reviews, see refs 3 and 4). Although this hypothesis in recent years has been subject to some controversy,[5,6] it is remarkable that so far the only compound that has been approved as a drug for the treatment of Alzheimer's disease (AD), Tacrine, is a result of research based on the cholinergic hypothesis.

The concept of counterbalancing deficiencies of acetylcholine (ACh) with directly acting muscarinic agonists has been focus of much attention. Early clinical trials with muscarinic agonists like RS-86,[7,8] pilocarpine,[7] and arecoline[7] (1) demonstrated either lack of clinical efficacy and/or induction of intolerable side effects. With the current knowledge of muscarinic receptors in mind, these rather disappointing clinical

results are most likely explained by lack of selectivity of the compounds. Realizing the shortcomings of the available muscarinic agonists, an intensive quest for better compounds started in the mid-1980s, and this quest has today resulted in a multitude of muscarinic compounds (for a recent review, see ref 9).

In Alzheimer's disease multiple neurochemical changes occur,[10] both in white and gray matter. Although several of these changes probably are of importance to the ethiology and progress of the disease, it is well-documented that the decline of cognitive functions in AD patients correlates well with the observed loss of cholinergic activity in cortex and hippocampus.[11,12] Muscarinic agonists may thus improve this defective cholinergic function.

As of today, five subtypes of muscarinic receptors, m1−m5 have been cloned[13−15] and four subtypes, M_1−M_4 have been characterized pharmacologically.[14,16,17] In human tissue M_1−M_3 have been characterized by binding assays.[18] Tentative conclusions of the molecular identities (m1−m5) of the pharmacologically defined receptors M_1−M_4 have been drawn, and in certain
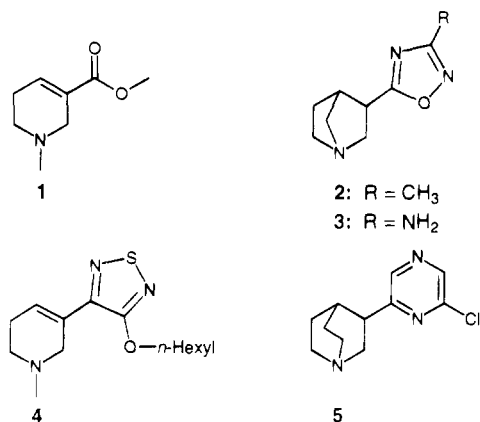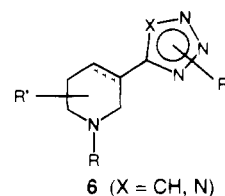
Figure 1.

Figure 2.

situations the correspondence between molecular and pharmacological classifications is good, but in other cases significant differences are revealed.[19]

It is proposed that the postsynaptically located M_1 receptors preferentially are involved in memory processes.[20-22] Selective stimulation of M_1 receptors should, therefore, be beneficial in the treatment of AD. This hypothesis is further supported by the fact that M_1 receptor densities are relatively unaffected in AD patients,[23] while ACh levels are diminished, thus resulting in understimulation of these receptors in AD patients. Hippocampal presynaptic muscarinic autoreceptors are of the M_2 and/or M_4 types[24] and blockade of these receptors leads to increased release of ACh. Blockade of M_2/M_4 autoreceptors might thus be beneficial in AD. M_2 receptors are widely distributed in peripheral tissues and especially abundant in heart, lung, and ileum,[19,25] whereas M_3 receptors are especially abundant in lung.[19] Stimulation of these peripheral receptors constitutes a major side effect liability for nonselective muscarinic agonists as already demonstrated in the above-mentioned clinical trials. It is also important to notice that cholinergic side effects are induced not only by peripheral stimulation of M_2 and M_3 receptors, but also by central stimulation of these receptors.[26,27] Besides receptor selectivity, another issue of importance in this context is the efficacy. Unwanted side effects might be eliminated by manipulating the efficacy in order to obtain functionally selective compounds.[28] All in all, it may be concluded that M_1 agonism optionally combined with M_2 antagonism constitute the most promising compound profile for potential antidementia drugs acting on muscarinic receptors.

The naturally occurring muscarinic agonist arecoline[29] (1, Figure 1) has been subject to considerable interest as a therapeutic drug in AD, but low efficacy, lack of subtype selectivity, and poor metabolic stability are major drawbacks. Numerous structural modifications of arecoline have been performed in order to improve the pharmacological and pharmacokinetic properties toward a clinically more useful profile (for a recent review, see ref 9). These modifications generally include replacement of the tetrahydropyridine ring with other monocyclic or bicyclic aza ring systems, replacement of the biologically unstable ester group with ester bioisosteres (for a recent general discussion of the principle of bioisosterism, see ref 30), and introduction of substituents in the tetrahydropyridine ring.

One of the most persued strategies for improving the pharmacological profile of arecoline has been replace-

ment of the metabolically unstable ester group with bioisosteric five-membered heterocyclic rings. Among the first achievements were the oxadiazoles L-670,548 (2) and L-670,207 (3), which are some of the most potent and efficacious nonselective muscarinic agonists known.[31-35] The 1,2,5-thiadiazole derivative xanomeline (4) represents another type of bioisostere, which recently has been reported to be in clinical testing.[36] The compound is reported to be functionally moderately selective for M_1 receptors vs M_2 receptors.[37-39] A somewhat different type of ester bioisostere is represented by compound 5, and it is the result of a SAR study of various pyrazine, pyridazine, and pyrimidine derivatives.[4] The chloropyrazine derivative 5 has high affinity to M_1 and M_3 receptors, and in functional assays it shows potent agonistic activity at M_1 and M_3 receptors, whereas it is an antagonist at M_2 receptors.[40]

The applicability of alkylated 1,2,3-triazole and tetrazole rings, respectively, as bioisosteres for the ester group in arecoline, shown in Figure 2, was previously reported by us,[41] and the concept has been applied to bicyclic amines by Jenkins and Wadsworth et al.[42,43] In this work we present a series of 1,2,3-triazoles and tetrazoles of general structure 6, including both 1,2,3,6-tetrahydropyridine and piperidine derivatives, and we mainly focus on the effects of various alkyl substituents on the biological activity. This work also includes a study of a series of enantiomers of 3-piperidyl-1,2,3-triazole derivatives.

Chemistry

Two general strategies were applied in the syntheses of 1,2,3,6-tetrahydropyridine derivatives. One strategy consisted of preparation of a cyano- or acetylene-substituted tetrahydropyridine ring followed by ring closure to the tetrazole ring or the 1,2,3-triazole ring, respectively. The other strategy consisted of preparation of a substituted 3-pyridyltetrazole or 3-pyridyl-1,2,3-triazole, followed by transformation of the pyridine ring to the 1,2,3,6-tetrahydropyridine ring. Piperidine derivatives were obtained by catalytic hydrogenation of pyridine or tetrahydropyridine derivatives.

1,3-Dipolar cycloaddition of trimethylsilyl azide to acetylenes (Scheme 1) is a convenient way to prepare 1,2,3-triazoles in good yields.[44] Since use of autoclaves in this reaction is inconvenient for the preparation of larger amounts of 16, we modified the method and found that reflux in neat trimethylsilyl azide for 72 h followed by treatment with water affords 16 in 74% yield. The corresponding cycloaddition of sodium azide to nitriles to give tetrazoles (17) is well-known.[45] In our hands 17 was obtained in good yield by refluxing the reagents in 1-butanol in the presence of glacial acetic acid.[46]

Alkylation of the 1,2,3-triazole ring of 16 with alkyl halides resulted in a mixture of all three possible isomers, which could be separated by flash chromatography. Quaternization of the pyridine nitrogen could

Scheme 1[a]
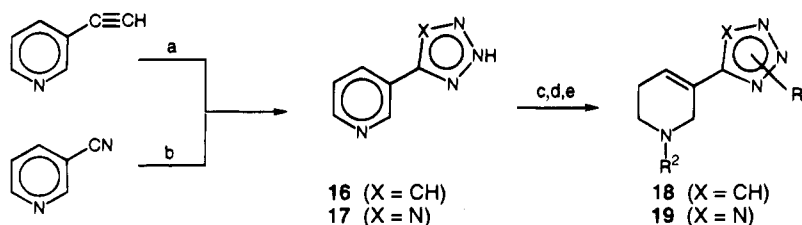
[a] Reagents and conditions: (a) neat Me$_3$SiN$_3$, reflux; (b) NaN$_3$, AcOH, BuOH, reflux; (c) R^{1}Br, acetone, K$_2$CO$_3$; (d) R^{2}Br or R^{2}I, acetone, reflux; (e) NaBH$_4$, EtOH, reflux.

Scheme 2[a]
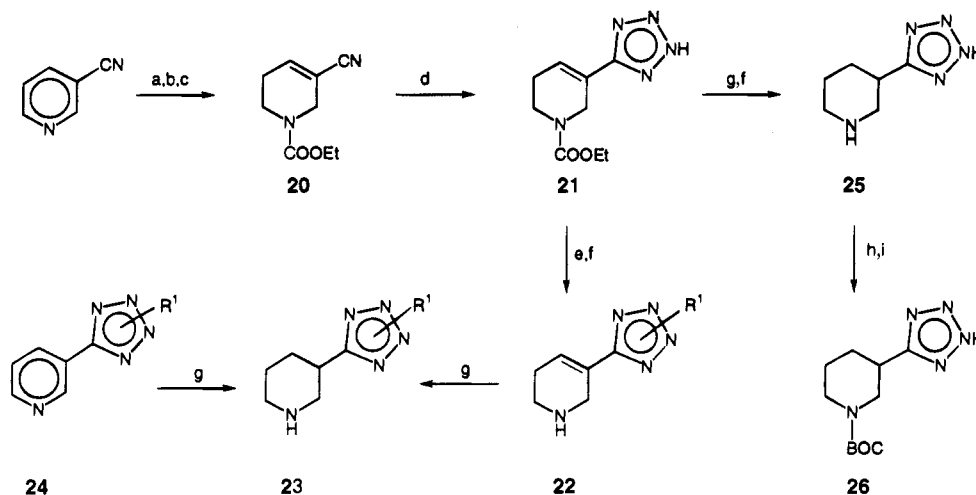
[a] Reagents and conditions: (a) MeI, acetone, reflux; (b) NaBH$_4$, MeOH, reflux; (c) ClCOOEt; (d) NaN$_3$, AlCl$_3$, THF, reflux; (e) R^{1}Br or R^{1}I, acetone, K$_2$CO$_3$; (f) HBr/AcOH; (g) H$_2$, PtO$_2$, EtOH; (h) di-*tert*-butyl dicarbonate, K$_2$CO$_3$, THF/water; (i) K$_2$CO$_3$, MeOH.

largely be avoided by using alkyl bromides instead of alkyl iodides. The positions of the substituents in the three isomers were assigned using NOE difference experiments, as described by Wadsworth *et al.*[42] The main product was the 2-isomer, which was formed in ca. 60% yield, whereas the 1-isomer was formed in ca. 30% yield. The yield of the 3-isomer was less than 5%. Alkylation of the tetrazole ring of **17** mainly resulted in the 2-isomer with only small amounts of the 1-isomer formed. The isomers could be separated by flash chromatography, and structural assignment was performed by NMR studies, as described by Wadsworth *et al.*[42] Quaternization of **16** and **17** with alkyl bromide or iodide followed by reduction with sodium borohydride gave the corresponding *N*-alkylated 1,2,3,6-tetrahydropyridines **18** and **19** in good to excellent yields.[47] The tetrazoles **9b–e**, **12b–i**, and **13f** were prepared by this method as were the 1,2,3-triazoles **8a–b**, **11a–d**, and **13b–c** (compounds with code numbers 7–15 are target compounds listed in Table 1).

The method depicted in Scheme 1 results in *N*-alkylated derivatives, and if R^2 is methyl or benzyl, the corresponding secondary amines can be obtained by treatment with ethyl chloroformate followed by hydrolysis of the resulting carbamate ester with HBr/glacial acetic acid.[48] Compounds **10a–d** were prepared by this method. This dealkylation procedure requires rather stable substituents in the five-membered heterocycle, and an alternative approach to the secondary amines is shown in Scheme 2. Quaternization of 3-cyanopyridine with MeI, followed by reduction with sodium borohydride and subsequent treatment with ethyl chloroformate, afforded **20** in moderate yield. Cyclization with sodium azide in the presence of aluminium chloride

resulted in the protected 1,2,3,6-tetrahydropyridyltetrazole **21**, which could be alkylated and deprotected, either by alkaline or acidic hydrolysis, to give **22**. Compounds **7a** and **9a** were prepared by this method. Of course, the secondary amine **22** can be alkylated to give tertiary amines, and compounds **8c**, **12a**, and **13e** were obtained by Eschweiler–Clarke methylation of **22**.

Catalytic hydrogenation of **22** gave the 3-piperidyltetrazoles **23**. Compound (±)-**14b** was prepared by this method, as was the corresponding 1,2,3-triazole derivative (±)-**15a**; (±)-**14a** was obtained by Eschweiler–Clarke methylation of (±)-**14b**. A more direct route to **23** consists of catalytic hydrogenation of **24**. This method was used for the preparation of (±)-**14c**. Another method was applied for the preparation of (±)-**14d**, since the propargyl group cannot stand either hydrogenation or the conditions required to remove the ethyl carbamate protection group. Catalytic hydrogenation of the tetrahydropyridine ring of **21** followed by deprotection of the amino group gave **25**, which was treated with di-*tert*-butyl dicarbonate to give **26**. During the reaction some BOC protection of the tetrazole ring occurs. Since both unsubstituted tetrazoles and 1,2,3-triazoles chemically can be compared to more or less acidic phenols, we assumed that treatment with methanolic potassium carbonate, which is reported to selectively deprotect *O*-alkoxycarbonyl groups in phenols without affecting *N*-alkoxycarbonyl groups,[49] selectively would deprotect the tetrazole ring. Indeed, complete and selective deprotection occurred. Alkylation with propargyl bromide followed by treatment with HCl/ether gave (±)-**14d**.

Preparation of 3-piperidinyl-1,2,3-triazoles is shown in Scheme 3. Catalytic hydrogenation of **16** followed

Scheme 3^a
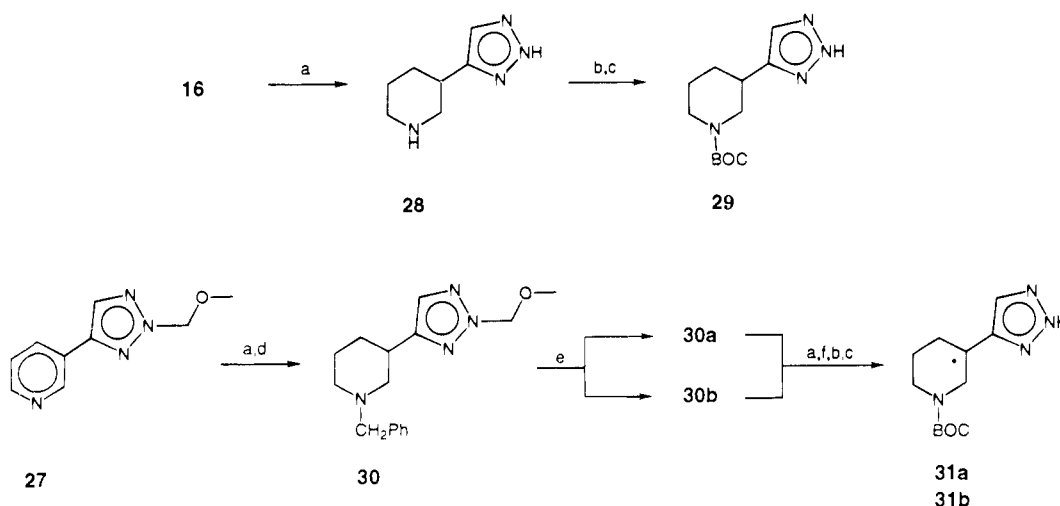
^{a} Reagents and conditions: (a) H$_2$, PtO$_2$, EtOH; (b) di-*tert*-butyl dicarbonate, K$_2$CO$_3$, THF/water; (c) K$_2$CO$_3$, MeOH; (d) PhCH$_2$Br, K$_2$CO$_3$, DMF; (e) classical resolution; (f) 2 M HCl.

Scheme 4^a
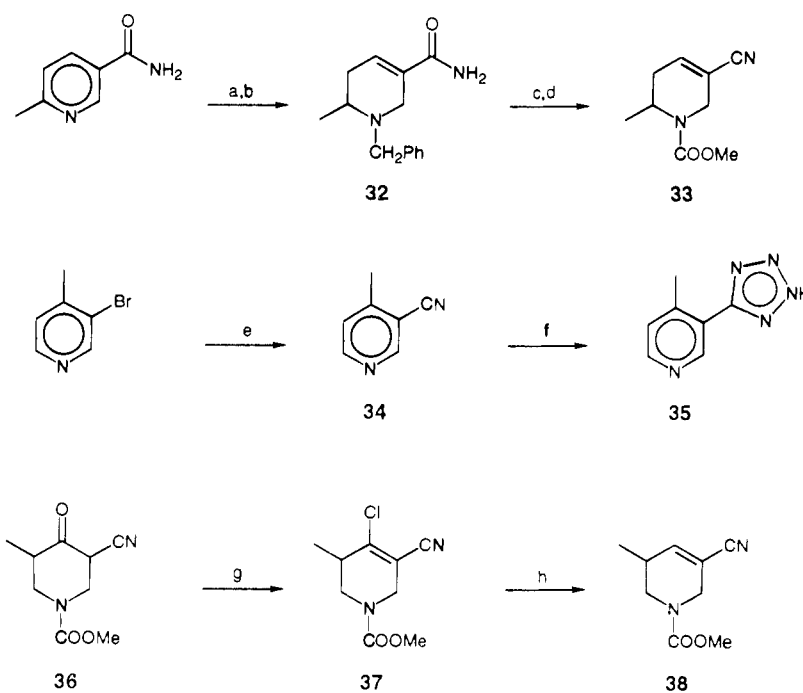
^{a} Reagents and conditions: (a) PhCH$_2$Br, acetone, reflux; (b) NaBH$_4$, MeOH; (c) Cl$_3$CCOCl, Et$_3$N; (d) ClCOOMe; (e) CuCN, DMF; (f) NaN$_3$, DMF; (g) CCl$_4$, Ph$_3$P; (h) Bu$_3$SnH.

by removal of the protecting group by treatment with dilute hydrochloric acid gave **28**, which was BOC-protected, according to the procedure described above, to afford **29**. Alkylation and deprotection gave (±)-**15b** and (±)-**15c**. Attempts to resolve (±)-**15b** and (±)-**15c** directly by fractional crystallizations of diastereomeric salts were unsuccessful. Instead, the resolution was performed by fractional crystallizations of the diastereomeric salts of the *N*-benzyl derivative **30** (obtained from **27**) and (+)- and (−)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (BNPA),[50] respectively. The enantiomeric purities of the enantiomers of **30**, **30a** and **30b**, were determined by NMR spectroscopy using the chiral shift reagent (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol[51] and were estimated to be better than 98%. Catalytic debenzylation and acidic hydrolysis of the methoxymethyl group followed by the previously described

reaction sequence gave **31a** and **31b**, which were alkylated and deprotected to give (+)- and (−)-**15b** and (+)- and (−)-**15c**.

The syntheses of tetrazole derivatives with substituents in the tetrahydropyridine ring are outlined in Scheme 4. Quaternization and reduction of 2-methylnicotinamide gave **32**, which was dehydrated to the corresponding cyano derivative with trichloroacetyl chloride/triethylamine.[52] Treatment with methyl chloroformate afforded **33**, which was converted to **7b** by the method shown in Scheme 2. Copper cyanide treatment of 3-bromo-4-methylpyridine gave 3-cyano-4-methylpyridine (**34**). Cyclization with sodium azide afforded the tetrazole **35**, which was converted to the 4-methyl derivative **7e** by the method shown in Scheme 1. Finally, the β-keto derivative **36** was treated with tetrachloromethane in the presence of triphenylphos-

Scheme 5[a]

39   a,b →   40   c,d,e →   41

43   ← i   42   ↑ f,g,h
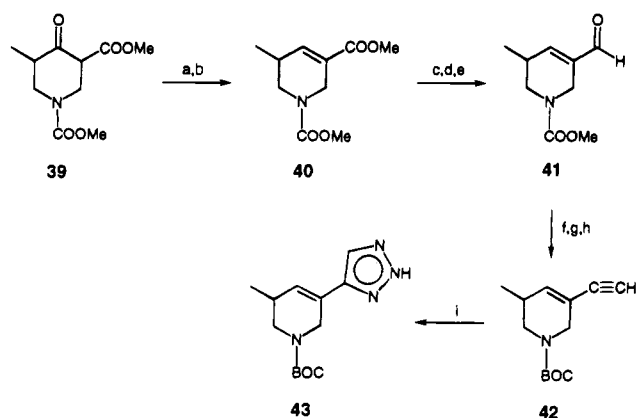
[a] Reactions and conditions: (a) H_2, PtO_2; (b) Ac_2O, AcONa; (c) 2 M NaOH, reflux; (d) $SOCl_2$; (e) Li(t-BuO)$_3$AlH, THF, -78 °C; (f) CBr_4, Ph_3P; (g) BuLi, THF; (h) di-*tert*-butyl dicarbonate, K_2CO_3, THF/water; (i) Me_3SiN_3.

phine to give **37**, which was dechlorinated to afford **38**. The 3-methyl derivative **7c** was obtained from **38** by the method shown in Scheme 2.

The 3-methylated 1,2,3-triazole derivative **7d** was prepared as shown in Scheme 5. The β-keto ester **39** was catalytically hydrogenated to the corresponding hydroxy derivative followed by elimination of water to give **40** in good yield. The ester group was converted to the corresponding acid chloride group, which was reduced with Li(t-Bu)$_3$AlH to give **41**. Treatment with tetrabromomethane in the presence of triphenylphosphine in a Wittig type reaction resulted in the *gem*-dibromovinyl derivative.[53] Elimination in order to give the acetylene derivative was accomplished by treatment with butyllithium.[53] This treatment also removed the methoxycarbonyl protection group, and it was necessary to reprotect in order to obtain **42**. Treatment with trimethylsilyl azide afforded the 1,2,3-triazole **43**, which was alkylated and deprotected in order to give **7d**.

Finally, it shall be mentioned that the vinyl derivatives **13a** and **13d** were prepared in excellent yields by alkylation with 1-bromo-2-chloroethane in order to give the corresponding 2-chloroethyl derivatives followed by elimination of HCl by treatment with potassium *tert*-butoxide in toluene.

Results and Discussion

The pharmacological test models are described in detail in the Experimental Section. The K_i values for inhibition of binding of tritiated muscarinic ligands by the compounds studied in this work are shown in Table 1 together with the corresponding Ago and M_2/M_1 ratios (*vide infra*). Functional *in vitro* effects of selected compounds are shown in Table 2. *In vivo* testings for induction of cholinergic side effects of selected compounds are shown in Table 3.

The efficacy of muscarinic agonists is generally measured by three biological methods: by comparing ratios of binding data, by testing the compounds in functional pharmacological models using isolated organs, which differ in receptor reserve for the various muscarinic receptor subtypes, and by measuring effects on second messenger systems.

Estimation of efficacy of agonists at muscarinic receptors using the ratio between a nonselective antagonist and a nonselective agonist was introduced several years

ago[54,55] and has since then proved valuable in numerous studies. We define this so-called Ago ratio as $QNB_{brain}/$Oxo-M. Oxo-M is the binding affinity in a binding assay using the nonselective muscarinic agonist [^{3}H]oxotremorine-M as radioligand. Oxo-M labels primarily the high affinity state of the receptors. QNB_{brain} is the binding affinity in a binding assay using [^{3}H]quinuclidinyl benzilate (QNB) binding in rat brain homogenates. QNB is a nonselective muscarinic antagonist. In our hands, ratios of >100 indicate full agonism, ratios between 10 and 100 indicate partial agonism, whereas ratios <10 indicate antagonism.
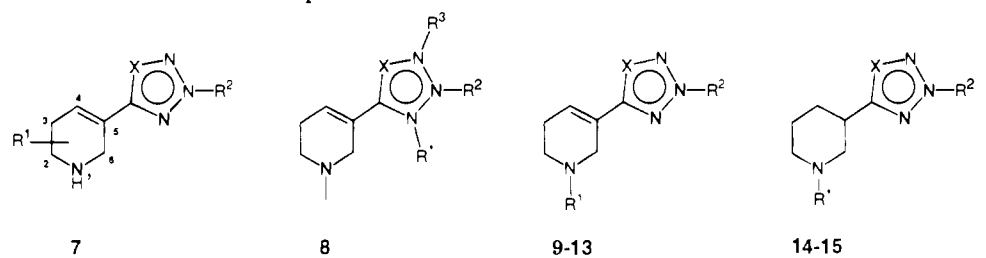
Such ratios are, of course, purely empirical, and in our work testings in functional assays were performed to substantiate the functional selectivity of the compounds indicated by the Ago ratio. The functional assays applied are contraction of guinea pig ileum (measures mainly M_2 and M_3 receptor activity[19]), depolarization of the rat superior cervical ganglion (measures M_1 receptor activity[56]), and depression of atrial contractility in guinea pig left atrium (measures M_2 receptor activity[19]). Only testings of selected compounds are presented here.

A similar ratio has also been defined for estimation of the M_2/M_1 selectivity of muscarinic compounds.[55,57] We define the M_2/M_1 ratio as QNB_{stem}/PZ. QNB_{stem} binding takes advantage of the very high proportion of M_2 receptors in brain stem tissue.[19] PZ is the binding affinity in a binding assay using the selective M_1 antagonist [^{3}H]pirenzepine as radioligand. The M_2/M_1 ratio thereby estimates the preference of the compounds for either M_1 or M_2 receptors.

As mentioned above for the Ago ratio, it must be emphasized that the M_2/M_1 ratio is purely empiric and, as pointed out by Freedman *et al.*,[57] radio receptor assays have severe limitations when examining the specificity of compounds due to tissue-dependent variations in receptor populations and the existence of high- and low-affinity states of the receptors. By characterizing the compounds pharmacologically in transfected cell lines expressing m1−m5 receptors, both with respect to affinity and to effects on second messengers, these problems are circumvented and this type of testing is rapidly becoming generally available.[58−60] However, as a qualitative tool in structure−activity analyses the Ago and M_2/M_1 ratios have proven valuable as demonstrated in the present work and in works by others.

Introduction of a methyl substituent in the tetrahydropyridine ring of **7a** generally reduces the affinity as demonstrated by **7b**, **7c**, and **7e**. This finding is in accordance with similar studies on arecoline itself[61] and on 1,2,4-oxadiazoles.[62,63] The only position where activity is retained to some extent is the 3-position, and it is interesting to note the increased affinity in [^{3}H]PZ binding of **7c**, when compared to **7a**. This indicates increased M_1 affinity and selectivity. This trend is even more obvious when going to the propargyl-substituted 1,2,3-triazole derivative **7d**.

The position of the substituent in the 1,2,3-triazole or tetrazole ring is highly important for affinity for muscarinic receptors. In the 1,2,3-triazole series, 1- and 3-alkyl substituents, as in **8a** and **8b**, result in compounds with very low affinity, whereas the 2-alkyl derivatives, exemplified by **11b**, exert high affinity for

Table 1. *In Vitro* Affinities for Muscarinic Receptors[a]

compd	X	R[1]	R[2]	R[3]	Oxo-M[b]	PZ[c]	QNB_brain[d]	QNB_stem[e]	Ago[f]	M2/M1[g]
7a	N	H	Me		4.5	1350	NT	NT		
7b	N	2-Me	Me		180	900	NT	NT		
7c	N	3-Me	Me		69	180	NT	NT		
7d	CH	3-Me	proparg.		31	30	NT	NT		
7e	N	4-Me	Me		570	960	NT	NT		
8a	CH			Et	990	770	NT	NT		
8b	CH	Et			318	1700	NT	NT		
8c	N	Me			5400	24000	NT	NT		
9a	N	H	Et		23	960	1600	280	70	0.3
9b	N	Et	Et		78	140	NT	NT		
9c	N	Pr	Et		450	900	NT	NT		
9d	N	i-Pr	Et		300	270	NT	NT		
9e	N	Bu	Et		340	1400	NT	NT		
10a	CH	H	Me		0.34	500	570	90	1700	0.2
10b	CH	H	Et		3.7	120	290	170	78	1.4
10c	CH	H	Pr		6.1	77	270	210	44	2.7
10d	CH	H	Bu		4.9	100	250	130	51	1.3
11a	CH	Me	Me		0.78	35	280	160	360	4.5
11b	CH	Me	Et		1.7	24	110	61	65	2.5
11c	CH	Me	Pr		2.6	15	47	38	18	2.5
11d	CH	Me	Bu		2.5	13	48	37	19	2.8
12a	N	Me	Me		6.1	250	790	230	130	0.9
12b	N	Me	Et		9.2	36	430	340	47	9.4
12c	N	Me	Pr		2.8	57	100	180	36	3.2
12d	N	Me	i-Pr		85	84	530	270	6.2	3.2
12e	N	Me	Bu		5.0	37	81	220	16	5.9
12f	N	Me	pentyl		16	26	130	110	8.1	4.2
12g	N	Me	hexyl		52	32	100	220	1.9	6.9
12h	N	Me	heptyl		120	37	140	160	1.2	4.3
12i	N	Me	octyl		71	27	38	75	0.5	2.8
13a	CH	Me	vinyl		33	40	NT	NT		
13b	CH	Me	allyl		4.7	6.3	43	32	9.1	5.1
13c	CH	Me	proparg.		1.6	7.7	41	22	26	2.9
13d	N	Me	vinyl		92	120	230	90	2.5	0.8
13e	N	Me	allyl		13	21	140	46	11	2.2
13f	N	Me	proparg.		4.5	44	230	100	51	2.3
(±)-14a	N	Me	Me		1200	4800	NT	NT		
(±)-14b	N	H	Me		33	2300	NT	NT		
(±)-14c	N	H	Et		230	1100	NT	NT		
(±)-14d	N	H	proparg.		31	260	NT	NT		
(±)-15a	CH	H	Et		11	260	530	280	48	1.1
(±)-15b	CH	H	allyl		25	100	910	300	36	3.0
(+)-15b	CH	H	allyl		45	210	190	330	4.2	1.6
(−)-15b	CH	H	allyl		37	170	530	310	14	1.8
(±)-15c	CH	H	proparg.		2.5	84	320	130	130	1.5
(+)-15c	CH	H	proparg.		5.2	170	230	30	44	0.2
(−)-15c	CH	H	proparg.		7.8	140	270	30	35	0.2
arecoline					1.3	640	1100	140	850	0.2
RS-86					14	400	690	400	49	1.0
McN-A-343					18	600	500	460	28	0.8

[a] K_i values in nM. [b] [^{3}H]Oxotremorine-M binding on rat brain homogenate. [c] [^{3}H]Pirenzepine binding on rat brain homogenate. [d] [^{3}H]Quinuclidinyl benzilate binding on rat brain homogenate. [e] [^{3}H]Quinuclidinyl benzilate binding on rat brain stem homogenate. For details see ref 77. [f] Ago = $K_i(\text{QNB}_{brain})/K_i(\text{Oxo-M})$. [g] M2/M1 = $K_i(\text{QNB}_{stem})/K_i(\text{PZ})$. NT = not tested.

muscarinic receptors. In the tetrazole series a similar difference is seen when comparing 1- and 2-substituted tetrazoles. The 2-methyl derivative **12a** has high affinity, and the 1-methyl derivative **8c** is inactive. These results are similar to the results obtained by Wadsworth *et al.*[42] in the corresponding 3-quinuclidinyl series where only the 2-substituted 1,2,3-triazol-4-yl derivative is active.

The only allowed substituent at the basic nitrogen in the 1,2,3,6-tetrahydropyridine ring is methyl. The

Table 2. Functional *in Vitro* Effects at Rat Superior Cervical Ganglion, Guinea Pig Left Atrium, and Guinea Pig Ileum[a]

compd	ganglion EC$_{50}$ (SD factor)	RM ± SD	atrium EC$_{50}$ (SD factor)	RM ± SD	ileum EC$_{50}$ (SD factor)	RM ± SD
9a	≥3300(1.5)[b]	≥0.62 ± 0.13	1900(1.4)	0.84 ± 0.04	6400(1.3)	1.00 ± 0.10
10b	≥650(1.9)	≥0.79 ± 0.14	270(1.3)	0.81 ± 0.10	770(1.5)	0.98 ± 0.04
11a	≥430(1.5)	≥0.81 ± 0.09	NT	NT	130(1.2)	0.92 ± 0.10
11b	>1200(1.8)	≥0.45 ± 0.19	>51000	ND	940(1.9)	0.47 ± 0.07
12b	≥2000(1.4)	≥0.41 ± 0.24	>51000	ND	3200(1.7)	0.38 ± 0.13
(±)-15b	≥2800(1.4)	≥0.48 ± 0.04	1100(1.2)	0.48 ± 0.14	4400(1.7)	0.55 ± 0.12
(+)-15b	≥3400(1.2)	≥0.43 ± 0.10	680(4.2)	0.42 ± 0.18	4300(1.4)	0.68 ± 0.01
(−)-15b	≥2500(2.3)	≥0.39 ± 0.14	≥840(3.8)	0.20 ± 0.19	NT	NT
arecoline	≥530(1.7)	≥0.74 ± 0.18	110(1.5)	0.99 ± 0.03	190(1.5)	1.03 ± 0.03
RS-86	≥1100(1.4)	≥1.14 ± 0.05	400(1.6)	0.99 ± 0.02	430(1.3)	0.99 ± 0.05
McN-A-343	≥3900(1.5)	≥1.39 ± 0.16	NT	NT	6500(1.6)	0.99 ± 0.01
carbachol	≥220(2.1)	0.88 ± 0.18	83(1.4)	1.0	140(1.4)	1.0

[a] EC$_{50}$ values in nM (log mean with standard deviation factor) and RM values, i.e., relative maximum effects (mean with standard deviation). Values are means of three to seven separate experiments. For explanation of RM, see the Experimental Section. [b] For explanation of the "≥" signs, see the Experimental Section. ND = not determined. NT = not tested.

Table 3. Hypothermia, Tremor, and Salivation[a]

compd	hypothermia	tremor	salivation
9a	78(24−250)	>150	41(26−65)
10b	19(7.0−51)	60(33−110)	12(7.1−20)
11a	5.3(1.9−15)	>110	3.6(2.0−6.5)
11b	b	180(150−220)	400(330−480)
11d	60(23−160)	72(51−100)	>160
12b	>120	>120	>120
(±)-15b	>350	>350	320(230−450)
(+)-15b	>260	>260	>260
(−)-15b	>130	>130	>130
(±)-15c	10(4.5−22)	54(34−86)	8.1(4.3−15)
(+)-15c	23(2.7−190)	32(17−61)	7.0(3.9−13)
(−)-15c	11(2.0−59)	41(21−42)	20(8.3−48)
arecoline	90(36−230)	>170	120(92−160)
RS-86	8.6(4.3−17)	38(19−76)	2.5(1.3−4.8)
McN-A-343	>63	>63	>63

[a] ED$_{50}$ values in μmol/kg and 95% confidence intervals in parentheses. For further details see the Experimental Section. [b] Very flat dose−response curve with about 50% of maximum response at 350 μmol/kg.

N-methyltetrazole derivative **12b** has higher affinity than the unsubstituted analogue **9a**, but more bulky groups significantly reduce affinity as shown by **9b,c**. A dramatic change in both efficacy and selectivity, however, is seen when going from the secondary amine **9a** to the *N*-methyl derivative **12b**. The Ago ratio indicates a more partial agonistic profile of **12b** when compared to **9a**, and the M$_2$/M$_1$ ratios of the two compounds indicate a shift from M$_2$ selectivity to M$_1$ selectivity. This difference in profile is substantiated in functional tests (Table 2). Both **9a** and **12b** are agonists of comparable potency in the ganglion test, but **9a** is a potent agonist in the atrium test contrary to **12b**, which has no agonistic effect at all (**12b** actually exerts antagonistic properties in the atrium test). Thus **9a** is a mixed M$_1$/M$_2$ agonist, whereas **12b** is an M$_1$ agonist/ M$_2$ antagonist. In the ileum test **12b** exerts a more partial effect than **9a**, also indicating that **12b** has a much lower functional effect on M$_2$ and possibly on M$_3$ receptors than **9a**. *In vivo* (Table 3) this difference between **9a** and **12b** is obvious. Hypothermia and salivation, which are believed to be cholinergic side effects mediated by peripheral M$_2$ receptors,[26] were induced rather potently by **9a**, while **12b** did not induce any such side effects at up to 120 μmol/kg.

In the 1,2,3-triazole series a similar trend is seen when comparing **10b** and **11b**, although their binding profiles are more similar than the binding profiles of **9a** and **12b**. The secondary amine **10b** is a potent

unselective agonist both *in vitro* and *in vivo*, whereas the corresponding *N*-methyl derivative **11b** is a partial M$_1$ agonist without M$_2$ agonism. Only at high doses does **11b** induce cholinergic side effects. The size of the alkyl side chain of the 1,2,3-triazole and tetrazole rings is important for both affinity and in particular for efficacy and selectivity. The secondary amine **10a** is an extremely potent and unselective agonist, and although *N*-methylation (**11a**) does change the profile as mentioned above, **11a** is still a very potent and unselective agonist both in functional *in vitro* tests and in *in vivo* tests. The change in profile when going from a methyl substituent, as in **11a**, to an ethyl substituent, as in **11b**, is remarkable. A fall in efficacy is seen by increasing the chain length in both the **10a−d** and **11a−d** series, although less dramatically than the change from methyl to ethyl. However, although **11d**, according to the ratios, is a partial agonist with preference for M$_1$, it still induces cholinergic side effects *in vivo*. The same trend is seen in the tetrazole series. Increasing the chain length as in the series **12a−i** gradually lowers the efficacy of the compounds and finally results in compounds with antagonistic profiles. It is interesting to note that even compounds with rather long chains maintain affinity. The isopropyl derivative **12d** is atypical and has low affinity in Oxo-M binding. Bulky groups attached directly to the ring can probably not be accommodated by the receptor, while flexible chains up to six carbons long are allowed. The M$_2$/M$_1$ ratio does not show a similarly clear trend through this series. When comparing 1,2,3-triazoles and tetrazoles, it seems that the structure−activity relationships of the two series are parallel, but the tetrazoles are generally less potent than the corresponding 1,2,3-triazoles, both *in vitro* and *in vivo*.

In several types of muscarinic agonists, unsaturated side chains have attracted some attention.[64−68] In both the 1,2,3-triazole and the tetrazole series we have found that the vinyl-substituted derivatives **13a** and **13d** have rather low affinity. This result is in some contrast to the profile reported for the corresponding 3-vinyl-1,2,4-oxadiazole[63] which exerts affinity comparable to arecoline. The allyl and propargyl derivatives in both series, **13b,c** and **13e,f**, exert high affinity. The tetrazoles **13e,f** have some preference for M$_1$, as indicated by the M$_2$/M$_1$ ratios. Although the 1,2,3-triazole **13b** has a rather high M$_2$/M$_1$ ratio, the low Ago ratio indicates antagonistic properties.

Nipecotic acid esters, the saturated analogues of arecoline and related esters, have been described as muscarinic agonists.[68] However, only a few bioisosteres of nipecotic acid have been described. Among these are 3-amino- and 3-methyl-5-(3-piperidyl)-1,2,4-oxadiazole, which are weak compounds compared to the very potent parent tetrahydropyridines.[32] Furthermore, the enantiomers of these nipecotic acid bioisosteres have not been described, and since the stereoselectivity of several types of muscarinic agonists is well-documented,[69-73] we found it interesting to investigate this aspect.

The piperidine derivatives in the tetrazole series are generally weak. The affinity of (±)-**14a** is 200-fold less than the unsaturated analogue **12a** in Oxo-M binding. The corresponding demethylated derivative, (±)-**14b**, has only 7-fold lower affinity compared to **7a**, but by going to the ethyl derivative, (±)-**14c**, a significant loss in affinity is observed. Only the propargyl derivative (±)-**14d** has an interesting profile, due to the increased affinity in PZ binding, compared to (±)-**14a–c**. However, since 1,2,3-triazoles generally are more potent than tetrazoles, we decided to focus on the former in the piperidine series.

Although the ethyl derivative (±)-**15a** has affinity comparable to **10b**, the M_2/M_1 ratio indicates very moderate selectivity. The same is true with the propargyl derivative (±)-**15c**, which according to the ratios is a rather high efficacy agonist with moderate selectivity. *In vivo*, (±)-**15c** very potently induced cholinergic side effects (Table 3). However, testing of (+)-**15c** and (−)-**15c** did not reveal any significant differences in pharmacological profiles. Binding data indicate similar affinity of racemate and enantiomers (the deviation in the binding assays is approximately a factor 2), and both enantiomers are partial agonists, which potently induce cholinergic side effects *in vivo*. The allyl derivative (±)-**15b**, however, has a different profile. Although (±)-**15b** has lower affinity than, for example, (±)-**15c**, the M_2/M_1 ratio is higher indicating a better selectivity. Furthermore, (±)-**15b** only induces side effects *in vivo* in very high doses. Functional assays show that (±)-**15b** is a partial agonist at M_1, M_2, and M_3 receptors. The Ago ratio of the enantiomers (+)-**15b** and (−)-**15b** indicates that (+)-**15b** is an antagonist and (−)-**15b** is a partial agonist and as with the racemate, none of the enantiomers induced any side effects *in vivo*. Functional assays revealed that both compounds are partial agonists at the M_1 receptor, but while (+)-**15b** according to the atrium test is a rather potent M_2 agonist, (−)-**15b** exerts a very low efficacy in the atrium test. Thus (−)-**15b** is a rather selective M_1 partial agonist.

Conclusion

The results from this study clearly state that both the 1,2,3-triazole ring and the tetrazole ring can be used as ester bioisosteres in arecoline-related compounds. By varying the substituents in both the tetrahydropyridine ring and in the 1,2,3-triazole or tetrazole ring, a series of compounds covering a wide range of affinity, efficacy, and selectivity is obtained. In the 3-piperidyl-1,2,3-triazole series, stereoselectivity does not appear to be as pronounced as in other types of muscarinic agonists. In our opinion a partial M_1 agonist without any M_2 agonism, optionally combined with moderate M_2 antagonism, will be beneficial in the treatment of Alzhei-

mer's disease. Several of the compounds presented in this study exert such promising profiles.

Experimental Section

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 80 MHz on a Bruker WP 80 DS spectrometer or at 250 MHz on a Bruker AC 250 spectrometer; where nothing is stated the spectrum is recorded at 250 MHz. Deuterated chloroform (99.8% D), benzene (99.5% D), or dimethyl sulfoxide (99.9% D) were used as solvents. TMS was used as internal reference standard. Chemical shifts are expressed in ppm values. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, six = sextet, h = heptet, dd = double doublet, dt = double triplet, tt = triplet of triplets, m = multiplet. NMR signals corresponding to acidic protons are omitted. Content of water in crystalline compounds was determined by Karl Fischer titration. Microanalyses were performed by Lundbeck Analytical Department, and results obtained were within ±0.4% of the theoretical values except where otherwise stated. It shall be mentioned that the relatively high nitrogen content of the target compounds in several cases caused instrument problems, and higher deviations from the theoretical values than ±0.4% were therefore allowed. Standard workup procedure refers to extraction with an organic solvent from a proper aqueous solution, drying of the organic extracts over anhydrous magnesium sulfate, filtration, and removal of solvent *in vacuo*. In all chromatographic purifications silica gel of type Kiselgel 60, 230–400 mesh ASTM was used.

General Method for the Preparation of 1,2,3-Triazoles According to Scheme 1. 1-Ethyl-4-(1-methyl-1,2,3,6-tetrahydro-5-pyridyl)-1,2,3-triazole Hydrochloride (8a). 3-Pyridylacetylene[74] (25 g, 0.24 mol) and trimethylsilyl azide (52 g, 0.45 mol) were refluxed under a nitrogen atmosphere for 72 h. After cooling, ether (500 mL) and water (9 mL) were added followed by stirring for 2 h at room temperature. Filtration and drying *in vacuo* gave 4-(3-pyridyl)-1,2,3-triazole (**16**, 26 g, 74%) as a solid. Mp: 187–92 °C. ^{1}H NMR (DMSO-d_6): δ 7.50 (dd, 1H), 8.25 (dt, 1H), 8.50 (s, 1H), 8.60 (dd, 1H), 9.10 (d, 1H).

A mixture of **16** (6.8 g, 47 mmol), ethyl bromide (4 mL, 50 mmol), and potassium carbonate (14 g, 100 mmol) in acetone (100 mL) was kept at reflux temperature for 16 h. Filtration and removal of solvent *in vacuo* gave a red oil, which was applied to flash chromatography (eluent: MeOH/triethylamine/ether, 5:5:90). Three fractions were collected as colorless oils in the following order: 2-ethyl-4-(3-pyridyl)-1,2,3-triazole (5.0 g, 60%, ^{1}H NMR (CDCl₃) δ 1.60 (t, 3H), 4.50 (q, 2H), 7.35 (dd, 1H), 7.90 (s, 1H), 8.10 (dt, 1H), 8.60 (dd, 1H), 9.05 (d, 1H)), 3-ethyl-4-(3-pyridyl)-1,2,3-triazole (0.2 g, 2.4%, ^{1}H NMR (CDCl₃) δ 1.50 (t, 3H), 4.45 (q, 2H), 7.50 (dd, 1H), 7.70–7.85 (m, 2H), 8.65–8.80 (m, 2H)), and 1-ethyl-4-(3-pyridyl)-1,2,3-triazole (2.1 g, 26%, ^{1}H NMR (CDCl₃) δ 1.60 (t, 3H), 4.50 (q, 2H), 7.35 (dd, 1H), 7.90 (s, 1H), 8.20 (dt, 1H), 8.55 (dd, 1H), 9.00 (d, 1H)).

A solution of 1-ethyl-4-(3-pyridyl)-1,2,3-triazole (2.0 g, 12 mmol) and methyl iodide (1.3 mL, 20 mmol) in acetone (25 mL) was refluxed for 18 h. Cooling and filtration gave the methylpyridinium iodide (3.1 g, 10 mmol, 87%), which was suspended in ethanol (40 mL) and treated portionwise with sodium borohydride (1.2 g, 30 mmol) at 0 °C. After reflux for ¹/₂ h the solvent was removed *in vacuo* and brine (50 mL) was added followed by standard workup with ether. The free base of **8a** (1.1 g, 47%) was obtained as a yellow oil. The hydrochloride, **8a**, was obtained by crystallization of 0.4 g of free base from acetone by addition of an etheral solution of dry HCl (0.4 g, 84%). Mp: 196–99 °C. ^{1}H NMR (DMSO-d_6): δ 1.45 (t, 3H), 2.35–2.50 (m, 1H), 2.60–2.80 (m, 1H), 2.85 (s, 3H), 3.10–3.25 (m, 1H), 3.40–3.55 (m, 1H), 3.80–4.00 (m, 1H), 4.10–4.25 (m, 1H), 4.40 (q, 2H), 6.40–6.50 (m, 1H), 8.40 (s, 1H). Anal. ($C_{10}H_{16}N_4 \cdot HCl \cdot 0.44H_2O$) C, H, N.

In a similar manner and in similar yields the following 1,2,3-triazoles were prepared.

3-Ethyl-4-(1-methyl-1,2,3,6-tetrahydro-5-pyridyl)-1,2,3-triazole Hydrochloride (8b). Mp: 172–76 °C (acetone). ¹H NMR (DMSO-d_6): δ 1.40 (t, 3H), 2.45–2.60 (m, 1H), 2.65–2.80 (m, 1H), 2.85 (s, 3H), 3.10–3.25 (m, 1H), 3.40–3.55 (m, 1H), 3.75–3.90 (m, 1H), 3.95–4.10 (m, 1H), 4.40 (q, 2H), 6.20–6.30 (m, 1H), 7.75 (s, 1H). Anal. ($C_{10}H_{16}N_4 \cdot 2HCl \cdot 0.5H_2O$) C, H, N.

2-Methyl-4-(1-methyl-1,2,3,6-tetrahydro-5-pyridyl)-1,2,3-triazole Fumarate (11a). Mp: 144–45 °C (acetone). ¹H NMR (DMSO-d_6, 80 MHz): δ 2.25–2.50 (m, 2H), 2.50 (s, 3H), 2.80 (t, 2H), 3.45–3.65 (m, 2H), 4.10 (s, 3H), 6.30–6.55 (m, 1H), 6.50 (s, 2H), 7.95 (s, 1H). Anal. ($C_9H_{14}N_4 \cdot 1.5C_4H_4O_4$) H, N; C: calcd, 51.12; found, 50.54.

2-Ethyl-4-(1-methyl-1,2,3,6-tetrahydro-5-pyridyl)-1,2,3-triazole Hydrochloride (11b). Mp: 185–87 °C (acetone). ¹H NMR (DMSO-d_6): δ 1.40 (t, 3H), 2.50–2.70 (m, 2H), 2.85 (s, 3H), 3.20–3.50 (m, 2H), 3.90–4.15 (m, 2H), 4.40 (q, 2H), 6.50–6.60 (m, 1H), 8.05 (s, 1H). Anal. ($C_{10}H_{16}N_4 \cdot HCl$) C, H, N.

4-(1-Methyl-1,2,3,6-tetrahydro-5-pyridyl)-2-propyl-1,2,3-triazole Hydrochloride (11c). Mp: 146–48 °C (acetone/ether). ¹H NMR (DMSO-d_6): δ 0.85 (t, 3H), 1.90 (sx, 2H), 2.50–2.70 (m, 2H), 2.85 (s, 3H), 3.20–3.45 (m, 2H), 3.90–4.10 (m, 2H), 4.35 (t, 2H), 6.50–6.60 (m, 1H), 8.00 (s, 1H). Anal. ($C_{11}H_{18}N_4 \cdot HCl$) C, H; N: calcd, 23.08; found, 22.62.

2-Butyl-4-(1-methyl-1,2,3,6-tetrahydro-5-pyridyl)-1,2,3-triazole Hydrochloride (11d). Mp: 166–68 °C (acetone). ¹H NMR (DMSO-d_6): δ 0.90 (t, 3H), 1.25 (sx, 2H), 1.85 (qui, 2H), 2.50–2.70 (m, 2H), 2.85 (s, 3H), 3.15–3.40 (m, 2H), 3.90–4.10 (m, 2H), 4.40 (t, 2H), 6.55 (h, 1H), 8.00 (s, 1H). Anal. ($C_{12}H_{20}N_4 \cdot HCl$) C, H, N.

2-Allyl-4-(1-methyl-1,2,3,6-tetrahydro-5-pyridyl)-1,2,3-triazole Hydrochloride (13b). Mp: 155–57 °C (acetone). ¹H NMR (DMSO-d_6): δ 2.50–2.70 (m, 2H), 2.90 (s, 3H), 3.10–3.40 (m, 2H), 3.90–4.10 (m, 2H), 5.05 (d, 2H), 5.20 (d, 1H), 5.20 (d, 1H), 5.90–6.10 (m, 1H), 6.55 (h, 1H), 8.05 (s, 1H). Anal. ($C_{11}H_{16}N_4 \cdot HCl$) C, H; N: calcd, 23.27; found, 22.80.

4-(1-Methyl-1,2,3,6-tetrahydro-5-pyridyl)-2-propargyl-1,2,3-triazole Hydrochloride (13c). Mp: 171–74 °C (acetone). ¹H NMR (DMSO-d_6): δ 2.45–2.70 (m, 2H), 2.90 (s, 3H), 3.10–3.50 (m, 2H), 3.60 (t, 1H), 3.85–4.20 (m, 2H), 5.35 (d, 2H), 6.55–6.65 (m, 1H), 8.15 (s, 1H). Anal. ($C_{11}H_{14}N_4 \cdot HCl$) C, H, N.

General Method for the Preparation of Tetrazoles According to Scheme 1. 2-Butyl-5-(1-methyl-1,2,3,6-tetrahydro-5-pyridyl)-2H-tetrazole Oxalate (12e). A mixture of 5-(3-pyridyl)-1H-tetrazole[46] (20 g, 0.14 mol), potassium carbonate (24 g, 0.18 mol), and n-butyl bromide (24 g, 0.18 mol) in acetone (200 mL) was stirred for 14 h at 40 °C. Filtration and removal of solvnt *in vacuo* gave an oil, which was dissolved in dichloromethane and washed with brine. Standard workup gave crude 2-butyl-5-(3-pyridyl)-2H-tetrazole as an oil (22 g, 77%), which was sufficiently pure for further reaction. ¹H NMR (CDCl₃): δ 1.00 (t, 3H), 1.45 (sx, 2H), 2.05 (qui, 2H), 4.70 (t, 2H), 7.45 (dd, 1H), 8.40 (dt, 1H), 8.70 (dd, 1H), 9.35 (d, 1H). This product (17 g, 0.086 mol) and methyl iodide (18 g, 0.13 mol) were refluxed for 6 h in 1,2-dimethoxyethane (190 mL). Cooling and filtration gave the methylpyridinium iodide (25.0 g, 73 mmol, 85%), which was suspended in water (90 mL) and added with cooling to a solution of sodium borohydride (3.9 g, 0.10 mol) in ethanol (90 mL) at 10 °C. After stirring for 3 h the solvent was removed *in vacuo*, and saturated ammonium chloride solution (50 mL) was added followed by standard workup with ether. The crude product was dissolved in dilute hydrochloric acid (50 mL) and was extracted with ether (3 × 50 mL). The aqueous phase was made alkaline with 25% sodium hydroxide solution. Standard workup with ether gave the free base of **12e** (10 g, 65%) as an oil. Crystalline **12e** was prepared from free base (3.5 g) and oxalic acid (1.4 g) in acetone. Yield of **12e**: 3.6 g (73%). Mp: 128–29 °C. ¹H NMR (DMSO-d_6): δ 0.90 (t, 3H), 1.25 (sx, 2H), 1.90 (qui, 2H), 2.50–2.60 (m, 2H), 2.80 (s, 3H), 3.10–3.20 (m, 2H), 3.90–4.00 (m, 2H), 4.70 (t, 2H), 6.90–7.00 (m, 1H). Anal. ($C_{11}H_{19}N_5 \cdot C_2H_2O_4$) C, H, N.

In a similar manner and in similar yields the following tetrazole derivatives were prepared.

2-Ethyl-5-(1-ethyl-1,2,3,6-tetrahydro-5-pyridyl)-2H-tetrazole Hydrochloride (9b). Mp: 151–53 °C (acetone/ether). ¹H NMR (DMSO-d_6): δ 1.35 (t, 3H), 1.50 (t, 3H), 2.50–2.65 (m, 1H), 2.65–2.90 (m, 1H), 3.00–3.35 (m, 3H), 3.50–3.70 (m, 1H), 3.85–4.05 (m, 1H), 4.05–4.25 (m, 1H), 4.75 (q, 2H), 6.90–7.00 (m, 1H). Anal. ($C_{10}H_{17}N_5 \cdot HCl$) C, H; N: calcd, 28.73; found, 27.90.

2-Ethyl-5-(1-propyl-1,2,3,6-tetrahydro-5-pyridyl)-2H-tetrazole Hydrochloride (9c). Mp: 171–75 °C (acetone/ether). ¹H NMR (DMSO-d_6): δ 0.95 (t, 3H), 1.60 (t, 3H), 1.85 (sx, 2H), 2.50–2.70 (m, 1H), 2.70–2.90 (m, 1H), 3.00–3.30 (m, 3H), 3.45–3.65 (m, 1H), 3.90–4.30 (m, 2H), 4.70 (q, 2H), 6.90–7.00 (m, 1H). Anal. ($C_{11}H_{19}N_5 \cdot HCl$) C, H, N.

2-Ethyl-5-(1-isopropyl-1,2,3,6-tetrahydro-5-pyridyl)-2H-tetrazole Hydroiodide (9d). Mp: 157–59 °C (acetone). ¹H NMR (DMSO-d_6): 1.35 (d, 6H), 1.55 (t, 3H), 2.55–2.75 (m, 2H), 3.00–3.25 (m, 1H), 3.55–3.65 (m, 1H), 3.75 (h, 1H), 4.10–4.20 (m, 2H), 4.70 (q, 2H), 6.90–7.00 (m, 1H). Anal. ($C_{11}H_{19}N_5 \cdot HI$) C, H, N.

5-(1-Butyl-1,2,3,6-tetrahydro-5-pyridyl)-2-ethyl-2H-tetrazole Oxalate (9e). Mp: 147–149 °C (acetone). ¹H NMR (DMSO-d_6): δ 0.95 (t, 3H), 1.35 (sx, 2H), 1.50 (t, 3H), 1.70 (qui, 2H), 2.50–2.70 (m, 2H), 3.00–3.15 (m, 2H), 3.25 (t, 2H), 3.95–4.05 (m, 2H), 4.70 (q, 2H), 6.90–7.00 (m, 1H). Anal. ($C_{12}H_{21}N_5 \cdot C_2H_2O_4$) C, H, N.

2-Ethyl-5-(1-methyl-1,2,3,6-tetrahydro-5-pyridyl)-2H-tetrazole L-(+)-Tartrate (12b). Mp: 143–45 °C (ethanol). ¹H NMR (DMSO-d_6): δ 1.50 (t, 3H), 2.40–2.50 (m, 2H), 2.55 (s, 3H), 2.80 (t, 2H), 3.50–3.60 (m, 2H), 4.20 (s, 2H), 4.70 (q, 2H), 6.85–6.95 (m, 1H). Anal. ($C_9H_{15}N_5 \cdot C_4H_6O_6$) C, H, N.

5-(1-Methyl-1,2,3,6-tetrahydro-5-pyridyl)-2-propyl-2H-tetrazole Maleate (12c). Mp: 143–45 °C (1,2-dimethoxyethane). ¹H NMR (DMSO-d_6): δ 0.85 (t, 3H), 1.95 (sx, 2H), 2.55–2.70 (m, 2H), 2.95 (s, 3H), 3.35 (t, 2H), 4.10–4.20 (m, 2H), 4.65 (t, 2H), 6.05 (s, 2H), 6.95–7.05 (m, 1H). Anal. ($C_{10}H_{17}N_5 \cdot C_4H_4O_4$) C, H, N.

2-Isopropyl-5-(1-methyl-1,2,3,6-tetrahydro-5-pyridyl)-2H-tetrazole Fumarate (12d). Mp: 107–8 °C (acetone). ¹H NMR (DMSO-d_6, 80 MHz): δ 1.60 (d, 6H), 2.40–2.50 (m, 2H), 2.55 (s, 3H), 2.60–2.90 (m, 2H), 3.45–3.60 (m, 2H), 5.20 (qui, 1H), 6.65 (s, 2H), 6.90–7.00 (m, 1H). Anal. ($C_{10}H_{17}N_5 \cdot C_4H_4O_4$) C, H; N: calcd, 21.66; found, 21.22.

5-(1-Methyl-1,2,3,6-tetrahydro-5-pyridyl)-2-pentyl-2H-tetrazole Oxalate (12f). Mp: 159–60 °C (acetone). ¹H NMR (DMSO-d_6): δ 0.85 (t, 3H), 1.10–1.40 (m, 4H), 1.90 (qui, 2H), 2.50–2.60 (m, 2H), 2.85 (s, 3H), 3.20 (t, 2H), 3.95–4.00 (m, 2H), 4.70 (t, 2H), 6.90–7.00 (m, 1H). Anal. ($C_{12}H_{21}N_5 \cdot C_2H_2O_4$) C, H; N: calcd, 21.53; found, 21.11.

2-Hexyl-5-(1-methyl-1,2,3,6-tetrahydro-5-pyridyl)-2H-tetrazole Oxalate (12g). Mp: 140–42 °C (acetone). ¹H NMR (DMSO-d_6): δ 0.85 (t, 3H), 1.10–1.35 (m, 6H), 1.90 (qui, 2H), 2.50–2.60 (m, 2H), 2.80 (s, 3H), 3.20 (t, 2H), 3.95–4.05 (m, 2H), 4.65 (t, 2H), 6.90–7.00 (m, 1H). Anal. ($C_{13}H_{23}N_5 \cdot C_2H_2O_4$) C, H; N: calcd, 20.64; found, 20.14.

2-Heptyl-5-(1-methyl-1,2,3,6-tetrahydro-5-pyridyl)-2H-tetrazole Oxalate (12h). Mp: 143–45 °C (acetone). ¹H NMR (DMSO-d_6): δ 0.90 (t, 3H), 1.15–1.40 (m, 8H), 2.00 (qui, 2H), 2.65–2.85 (m, 2H), 3.00 (s, 3H), 3.30–3.50 (m, 2H), 4.05–4.25 (m, 2H), 4.60 (t, 2H), 7.05 (h, 1H). Anal. ($C_{14}H_{25}N_5 \cdot C_2H_2O_4$) C, H, N.

5-(1-Methyl-1,2,3,6-tetrahydro-5-pyridyl)-2-octyl-2H-tetrazole Oxalate (12i). Mp: 141–42 °C (acetone). ¹H NMR (DMSO-d_6): δ 0.90 (t, 3H), 1.15–1.40 (m, 10H), 2.00 (qui, 2H), 2.65–2.75 (m, 2H), 3.00 (s, 3H), 3.40 (t, 2H), 4.05–4.25 (m, 2H), 4.60 (t, 2H), 7.05–7.15 (m, 1H). Anal. ($C_{15}H_{27}N_5 \cdot C_2H_2O_4$) C, H, N.

5-(1-Methyl-1,2,3,6-tetrahydro-5-pyridyl)-2-propargyl-2H-tetrazole Oxalate (13f). Mp: 143–45 °C (acetone). ¹H NMR (DMSO-d_6): δ 2.50–2.65 (m, 2H), 2.85 (s, 3H), 3.25 (t, 2H), 3.70 (t, 1H), 3.95–4.05 (m, 2H), 5.75 (d, 2H), 6.95–7.05 (m, 1H). Anal. ($C_{10}H_{13}N_5 \cdot C_2H_2O_4$) C, H, N.

General Method for the N-Demethylation of 1-Methyl-1,2,3,6-tetrahydropyridine Derivatives. 2-Ethyl-4-(1,2,3,6-tetrahydro-5-pyridyl)-1,2,3-triazole Hydrobromide (10b). A solution of 2-ethyl-4-(1-methyl-1,2,3,6-tetrahydro-5-pyridyl)-1,2,3-triazole, **11b**, (2.0 g, 20 mmol) in 1,1,1-trichloroethane

(25 mL) was added dropwise to neat ethyl chloroformate (25 mL) at reflux temperature. After reflux for 1 h the solution was cooled, filtered, and concentrated *in vacuo*. Filtration through silica gel with ethyl acetate and removal of solvent *in vacuo* gave 4-[1-(ethoxycarbonyl)-1,2,3,6-tetrahydro-5-pyridyl]-2-ethyl-1,2,3-triazole (2.3 g, 46%) as a yellow oil. ^{1}H NMR (CDCl₃): δ 1.30 (t, 3H), 1.55 (t, 3H), 2.20—2.40 (m, 2H), 3.60 (t, 2H), 4.20 (q, 2H), 4.25—4.40 (m, 2H), 4.45 (q, 2H), 6.35—6.50 (m, 1H), 7.60 (s, 1H). The oil was dissolved in 38% HBr/AcOH (25 mL) and allowed to stand for 20 h at room temperature. Concentration *in vacuo* and trituration with acetone gave **10b** as a crystalline solid (0.9 g, 38%). Mp: 195—200 °C. ^{1}H NMR (DMSO-d_6): δ 1.45 (t, 3H), 2.40—2.55 (m, 2H), 3.20—3.30 (m, 2H), 3.90—4.00 (m, 2H), 4.40 (q, 2H), 6.55 (h, 1H), 8.05 (s, 1H). Anal. ($C_9H_{14}N_4\cdot HBr$) C, H; N: calcd, 21.62; found, 20.95.

In a similar manner and in similar yields the following 1,2,3-triazoles were prepared.

2-Methyl-4-(1,2,3,6-tetrahydro-5-pyridyl)-1,2,3-triazole Fumarate (10a). The fumarate salt was obtained by addition of fumaric acid to an acetone solution of the free base of 10a. The free base was obtained from crude hydrobromide. Mp: 126—27 °C (acetone). ^{1}H NMR (DMSO-d_6, 80 MHz): δ 2.25—2.55 (m, 2H), 3.10 (t, 2H), 3.75—3.90 (m, 2H), 4.10 (s, 3H), 6.50 (s, 2H), 8.00 (s, 1H). Anal. ($C_8H_{12}N_4\cdot C_4H_4O_4$) C, H, N.

2-Propyl-4-(1,2,3,6-tetrahydro-5-pyridyl)-1,2,3-triazole Hydrobromide (10c). Mp: 124—30 °C (ether/acetone). ^{1}H NMR (DMSO-d_6): δ 0.85 (t, 3H), 1.90 (sx, 2H), 2.40—2.55 (m, 2H), 2.70—2.85 (m, 2H), 3.90—4.00 (m, 2H), 4.35 (t, 2H), 6.50—6.60 (m, 1H), 8.05 (s, 1H). Anal. ($C_{10}H_{16}N_4\cdot HBr$) C, H; N: calcd 20.51; found, 20.09.

2-Butyl-4-(1,2,3,6-tetrahydro-5-pyridyl)-1,2,3-triazole Hydrobromide (10d). Mp: 116—20 °C (ether/acetone). ^{1}H NMR (DMSO-d_6): δ 0.90 (t, 3H), 1.25 (sx, 2H), 1.80 (qui, 2H), 2.40—2.50 (m, 2H), 3.20—3.35 (m, 2H), 3.90—4.00 (m, 2H), 4.40 (t, 2H), 6.50—6.60 (m, 1H), 8.05 (s, 1H). Anal. ($C_{11}H_{18}N_4\cdot HBr$) C, H; N: calcd, 19.51; found, 19.07.

General Procedure for Eschweiler–Clarke Methylations. 2-Methyl-5-(1-methyl-1,2,3,6-tetrahydro-5-pyridyl)-2H-tetrazole (12a). A solution of 2-methyl-5-(1,2,3,6-tetrahydro-5-pyridyl)-2H-tetrazole, 7a (0.70 g, 2.8 mmol), in formic acid (20 mL) and 35% aqueous formaldehyde (7 mL) was refluxed for 16 h. The mixture was concentrated *in vacuo*, and the remaining oil was dissolved in a mixture of 2 M sodium hydroxide solution (50 mL) and dichloromethane (100 mL). Standard workup gave crude **12a** (0.6 g), which was crystallized from ether/pentane (0.25 g, 50%). Mp: 91—92 °C. ^{1}H NMR (CDCl₃, 80 MHz): δ 2.20—2.60 (m, 4H), 2.30 (s, 3H), 3.20—3.40 (m, 2H), 4.20 (s, 3H), 6.80 (h, 1H). Anal. ($C_8H_{13}N_5$) C, H; N: calcd, 39.08; found, 39.67.

In a similar manner the following derivatives were prepared.

1-Methyl-5-(1-methyl-1,2,3,6-tetrahydro-5-pyridyl)-1H-tetrazole Fumarate (8c). Mp: 148—50 °C (ethanol). ^{1}H NMR (DMSO-d_6): δ 2.40 (s, 3H), 2.35—2.50 (m, 2H), 2.65 (t, 2H), 3.30—3.40 (m, 2H), 4.10 (s, 3H), 6.50—6.60 (h, 1H), 6.60 (s, 2H). Anal. ($C_8H_{13}N_5\cdot C_4H_4O_4$) C, H, N.

2-Allyl-5-(1-methyl-1,2,3,6-tetrahydro-5-pyridyl)-2H-tetrazole Oxalate (13e). Mp: 148—50 °C (2-propanol). ^{1}H NMR (DMSO-d_6): δ 2.50—2.65 (m, 2H), 2.80 (s, 3H), 3.20 (t, 2H), 3.95—4.05 (m, 2H), 5.35 (d, 4H), 5.95—6.20 (m, 1H), 6.90—7.00 (m, 1H). Anal. ($C_{10}H_{15}N_5\cdot C_2H_2O_4$) C, H, N.

2-Methyl-5-(1-methyl-3-piperidyl)-2H-tetrazole Oxalate [(±)-14a]. Mp: 113—15 °C (acetone). ^{1}H NMR (DMSO-d_6): δ 1.50—1.70 (m, 1H), 1.80—1.95 (m, 2H), 2.15 (d, 1H), 2.75 (s, 3H), 2.80—2.95 (m, 1H), 3.10 (t, 1H), 3.35 (d, 2H), 3.50 (tt, 1H), 3.60 (d, 1H), 4.35 (s, 3H). Anal. ($C_8H_{15}N_5\cdot C_2H_2O_4\cdot 0.17H_2O$) C, H, N.

2-Methyl-5-(1,2,3,6-tetrahydro-5-pyridyl)-2H-tetrazole Hydrobromide (7a). A solution of 3-cyanopyridine (69 g, 0.67 mol) and methyl iodide (142 g, 1.0 mol) in acetone (500 mL) was stirred with gentle reflux for 16 h. After cooling to room temperature, filtration and drying *in vacuo* gave 3-cyano-1-methylpyridinium iodide (133 g, 81%) as a solid. The product was dissolved in methanol (1 L) and water (200 mL). Sodium

borohydride (pellets, 41.0 g, 1.1 mol) was added at 28 °C with stirring and cooling. After addition the mixture was stirred for 1 h at room temperature. The solvent was removed *in vacuo*, saturated ammonium chloride solution (200 mL) was added followed by extraction with ether (3 × 200 mL). The combined etheral phases were extracted with 4 M hydrochloric acid (3 × 200 mL). The combined aqueous phases were washed with ether (3 × 100 mL) and were then made alkaline with 25% sodium hydroxide solution. Standard workup with ether gave 5-cyano-1-methyl-1,2,3,6-tetrahydropyridine (17.4 g, 26%) as a red oil. ^{1}H NMR (CDCl₃, 80 MHz): δ 2.20—2.60 (m, 2H), 2.35 (s, 3H), 3.00 (q, 2H), 6.50—6.75 (m, 1H). The oil was dissolved in 1,1,1-trichloroethane (75 mL), and ethyl chloroformate (18 mL) was added. The resulting solution was heated to reflux for 16 h. After cooling to room temperature the solution was washed with 4 M hydrochloric acid (3 × 50 mL). Standard workup gave 5-cyano-1-(ethoxycarbonyl)-1,2,3,6-tetrahydropyridine (20, 11 g, 42%) as an oil. ^{1}H NMR (CDCl₃, 80 MHz): δ 1.25 (t, 3H), 2.20—2.40 (m, 2H), 3.50 (t, 2H), 4.00—4.10 (m, 2H), 4.10 (q, 2H), 6.70 (h, 1H).

A mixture of **20** (14 g, 79 mmol), sodium azide (24 g, 0.37 mol), and anhydrous aluminum trichloride (11.0 g, 83 mmol) in tetrahydrofuran (175 mL) was stirred under reflux for 16 h. The reaction mixture was cooled in an ice bath followed by addition of ice-cold 6 M hydrochloric acid (150 mL). The phases were separated, and the aqueous phase was extracted with ether (3 × 100 mL). The combined organic phases were washed with brine (3 × 100 mL). Standard workup gave 5-[1-(ethoxycarbonyl)-1,2,3,6-tetrahydro-5-pyridyl]-1H-tetrazole (21, 13 g 72%) as a solid. Mp: 113—16 °C (ethanol). ^{1}H NMR (CDCl₃, 80 MHz): δ 1.35 (t, 3H), 2.40—2.60 (m, 2H), 3.70 (t, 2H), 4.35 (q, 2H), 4.45—4.65 (m, 2H), 7.10—7.25 (m, 1H).

A mixture of **21** (7.0 g, 31 mmol), sodium hydroxide (1.5 g, 37 mmol), and methyl iodide (4 mL, 64 mmol) in acetone (60 mL) and water (15 mL) was heated to gentle reflux for 4 h. After cooling the mixture was filtered and the solvent removed *in vacuo*. Standard workup with ether gave 8.3 g of an oil, which was applied to flash chromatography (eluent: ethyl acetate/heptane, 1:3), giving 5-[1-(ethoxycarbonyl)-1,2,3,6-tetrahydro-5-pyridyl]-2-methyl-2H-tetrazole (3.8 g, 51%). Mp: 92—94 °C. ^{1}H NMR (CDCl₃, 80 MHz): δ 1.15 (t, 3H), 2.05—2.40 (m, 2H), 3.50 (t, 2H), 4.05 (q, 2H), 4.20—4.30 (m, 3H), 4.25 (s, 2H), 6.75—7.00 (m, 1H). Further elution of the flash column with ethyl acetate gave 5-[1-(ethoxycarbonyl)-1,2,3,6-tetrahydro-5-pyridyl]-1-methyl-1H-tetrazole (1.80 g, 24%). Mp: 85—90 °C. ^{1}H NMR (CDCl₃, 80 MHz): δ 1.25 (t, 3H), 2.30—2.55 (m, 2H), 3.65 (t, 2H), 4.10 (s, 3H), 4.15 (q, 2H), 4.30—4.50 (m, 2H), 6.50 (h, 1H). The 2-methyltetrazole (2.2 g, 9 mmol) was dissolved in 30% HBr/AcOH (50 mL) followed by stirring for 72 h. The solvent was removed *in vacuo*, and the remaining oil was crystallized from ethanol. Recrystallization from ethanol gave 7a (1.5 g, 71%). Mp: 203—5 °C. ^{1}H NMR (DMSO-d_6, 80 MHz): δ 2.40—2.65 (m, 2H), 3.35 (t, 2H), 3.95—4.10 (m, 2H), 4.40 (s, 3H), 6.80—7.00 (m, 1H). Anal. ($C_7H_{11}N_5\cdot HBr$) C, H, N.

In a similar manner the following derivative was prepared.

2-Ethyl-5-(1,2,3,6-tetrahydro-5-pyridyl)-2H-tetrazole Hydrobromide (9a). Mp: 160—62 °C (ethanol). ^{1}H NMR (DMSO-d_6): δ 1.5 (t, 3H), 2.50 (m, 2H), 3.15—3.35 (m, 2H), 4.00—4.10 (m, 2H), 4.70 (q, 2H), 6.90—7.00 (m, 1H). Anal. ($C_8H_{13}N_5\cdot HBr$) C, H; N: calcd, 26.92; found, 26.06.

2-Methyl-5-(2-methyl-1,2,3,6-tetrahydro-5-pyridyl)-2H-tetrazole Hydrobromide (7b). Methyl 6-methylnicotinate (120 g, 0.79 mol) was heated to 80 °C with ethanol (120 mL) and liquid ammonia (120 mL) in an autoclave for 72 h. After cooling crude 6-methylnicotinic amide was isolated by filtration (81.5 g, 91%). ^{1}H NMR (CDCl₃, 80 MHz): δ 2.50 (s, 3H), 7.30 (d, 1H), 7.45 (broad, 2H), 8.05 (dd, 1H), 8.95 (d, 1H). Crude amide (97 g, 0.72 mol) was dissolved in ethanol (200 mL) with heating. Acetone (400 mL) and benzyl bromide (150 g, 0.88 mol) were added followed by reflux for 16 h. Cooling, filtration, and drying *in vacuo* gave 1-benzyl-3-carboxamido-6-methylpyridinium bromide (201 g, 92%). Mp: 170—73 °C. The product was treated with sodium borohydride as described in the preparation of 7a, giving 1-benzyl-5-carboxamido-2-methyl-1,2,3,6-tetrahydropyridine (32, 44 g, 29%) as an oil. A portion

of **32** (10 g, 44 mmol) was dissolved in dichloromethane (50 mL) and triethylamine (7 mL). The solution was cooled in an ice bath, and a solution of trichloroacetyl chloride (8.5 g, 47 mmol) in dichloromethane (40 mL) was added dropwise at 5 °C followed by stirring for 30 min at room temperature. Saturated sodium carbonate solution (50 mL) was added, and standard workup up gave 1-benzyl-2-methyl-5-cyano-1,2,3,6-tetrahydropyridine (10 g, 100%), which was dissolved in 1,1,1-trichloroethane (40 mL). Methyl chloroformate (6.1 g, 65 mmol) was added, and the mixture was heated to reflux for 1 h. After cooling, the solvent was removed *in vacuo* giving crude 1-(methoxycarbonyl)-5-cyano-2-methyl-1,2,3,6-tetrahydropyridine (**33**, 14 g, 93%) as an oil. Crude **33** (44 g, 0.23 mol) was converted to **7b** by a series of steps similar to those described in the preparation of **7a**. Mp: 193–96 °C (2-propanol). ¹H NMR (DMSO-*d₆*, 80 MHz): δ 1.40 (d, 3H), 2.40–2.60 (m, 2H), 3.20–3.80 (m, 1H), 4.00–4.20 (m, 2H), 4.45 (s, 3H), 6.90–7.05 (m, 1H). Anal. (C₈H₁₃N₅·HBr·0.30H₂O) C, H; N: calcd, 26.39; found, 25.69.

2-Methyl-5-(3-methyl-1,2,3,6-tetrahydro-5-pyridyl)-2*H*-tetrazole Hydrobromide (7c). A solution of 3-cyano-1-(methoxycarbonyl)-5-methyl-4-oxopiperidine (**36**)[75] (40 g, 0.19 mol) in toluene (250 mL) was added to a refluxing solution of triphenylphosphine (32 g, 0.12 mol) in tetrachloromethane (120 mL). After reflux for 6 h, additional triphenylphosphine (32 g, 0.12 mol) was added and reflux continued for 16 h. The mixture was cooled and filtered, and the solvent was removed *in vacuo*. Triphenylphosphine oxide and excess triphenylphosphine was crystallized from ethyl acetate leaving an oil (45 g), which was applied to flash chromatography (eluent: ethyl acetate/heptane, 3:1), giving 4-chloro-5-cyano-1-(methoxycarbonyl)-3-methyl-1,2,3,6-tetrahydropyridine (**37**, 24.0 g, 55%) as an oil. ¹H NMR (CDCl₃, 80 MHz): δ 1.25 (d, 3H), 2.50–2.75 (m, 1H), 3.45–3.70 (m, 2H), 3.80 (s, 3H), 4.20 (dd, 2H). The product was dissolved in toluene (400 mL) and α,α′-azobisisobutyronitrile (1 g, 7 mmol), and tri-*n*-butyltin hydride (38 g, 0.12 mol) was added followed by reflux for 16 h. After removal of the solvent *in vacuo*, the remaining oil was applied to flash chromatography (eluent: ethyl acetate/heptane, 1:2) to give 5-cyano-1-(methoxycarbonyl)-3-methyl-1,2,3,6-tetrahydropyridine (10 g, 51%) as an oil. ¹H NMR (CDCl₃, 80 MHz): 1.05 (d, 3H), 2.30–2.70 (m, 1H), 3.50–3.60 (m, 2H), 3.75 (s, 3H), 3.90–4.10 (m, 2H), 6.50–6.70 (m, 1H). From this nitrile **7c** was prepared following the procedure described for the preparation of **7a**. Mp: 157–59 °C (2-propanol). ¹H NMR (DMSO-*d₆*, 80 MHz): δ 1.10 (d, 3H), 2.70–3.05 (m, 2H), 3.25–3.50 (m, 2H), 3.90–4.10 (m, 2H), 4.40 (s, 3H), 6.75–6.90 (m, 1H). Anal. (C₈H₁₃N₅·HBr) C, H; N: calcd, 26.92; found, 26.48.

4-(3-Methyl-1,2,3,6-tetrahydro-5-pyridyl)-2-propargyl-1,2,3-triazole Hydrochloride (7d). A mixture of methyl 1-(methoxycarbonyl)-5-methyl-4-piperidone-3-carboxylate, **39**, (320 g, 1.4 mol, prepared by a method analogous to the method described by Moos *et al.*[61]) and PtO₂ (5 g) in ethanol (1.3 L) was hydrogenated at 3 atm of hydrogen pressure in a Parr apparatus for 16 h. Filtration and removal of solvent gave methyl 4-hydroxy-1-(methoxycarbonyl)-5-methylpiperidine-3-carboxylate (270 g, 85%) as a viscous oil. The oil was dissolved in acetic acid anhydride (1.2 L), and sodium acetate (41 g, 0.5 mol) was added followed by reflux for 10 h. Concentration of the reaction mixture *in vacuo* followed by addition of 6 M ammonia and standard workup with ether gave crude **40** (213 g, 85%) as an orange oil, which was sufficiently pure for further synthesis. The oil was suspended in 2 M NaOH (800 mL) and refluxed for 1.5 h. Acidification with concentrated hydrochloric acid followed by standard workup with dichloromethane gave 1-(methoxycarbonyl)-3-methyl-1,2,3,6-tetrahydropyridine-3-carboxylic acid (157 g, 79%) as an oil, which was treated with thionyl chloride (240 g, 2 mol) in toluene (500 mL) at 80 °C for 2.5 h. Removal of volatiles *in vacuo* gave crude 1-(methoxycarbonyl)-3-methyl-1,2,3,6-tetrahydropyridine-3-carboxylic acid chloride (145 g, 85%) as a brown oil. ¹H NMR (CDCl₃, 80 MHz): δ 1.25 (d, 3H), 2.50–2.80 (m, 1H), 3.75 (s, 3H), 3.80–4.05 (m, 2H), 4.20 (dd, 1H), 4.30 (t, 1H), 7.25–7.50 (m, 1H). A portion of the acid chloride (22 g, 100 mmol) was dissolved in diglyme (50 mL) under a nitrogen atmosphere and cooled to −78 °C. A solution of Li(*t*-BuO)₃AlH (25 g, 100 mmol) in

diglyme (100 mL) was added dropwise at −78 °C. The reaction mixture was allowed to warm to room temperature followed by addition of water (1 L) and standard workup with ether to give the aldehyde **41** (14 g, 75%) as a brown oil. ¹H NMR (CDCl₃, 80 MHz): δ 1.20 (d, 3H), 2.40–2.80 (m, 1H), 3.50–3.70 (m, 1H), 3.75 (s, 3H), 3.75–3.95 (m, 1H), 4.05 (dd, 1H), 4.25 (t, 1H), 6.70–6.85 (m, 1H), 9.50 (s, 1H). A solution of **41** (14 g, 78 mmol) and triphenylphosphine (118 g, 450 mmol) in dichloromethane (500 mL) was cooled to −10 °C and treated dropwise with tetrabromomethane. After stirring for 1 h at 0 °C and 1 h at room temperature, saturated aqueous bicarbonate (500 mL) was added followed by standard workup with dichloromethane. Addition of ether (500 mL) to the remaining oil resulted in precipitation of most of the triphenylphosphine oxide formed. Filtration and removal of solvent *in vacuo* gave an oil, which was applied to flash chromatography (eluent: ether), giving 5-(2,2-dibromovinyl)-1-(methoxycarbonyl)-3-methyl-1,2,3,6-tetrahydropyridine (18 g, 71%) as a yellow oil. ¹H NMR (CDCl₃, 80 MHz): δ 1.05 (d, 3H), 2.20–2.60 (m, 1H), 3.75 (s, 3H), 3.75–4.00 (m, 2H), 4.15 (t, 1H), 4.30 (t, 1H), 5.90–6.00 (m, 1H), 6.95–7.00 (m, 1H). The oil was dissolved in tetrahydrofuran (400 mL) and cooled to −78 °C under a nitrogen atmosphere. A 2 M solution of butyllithium in cyclohexane (110 mL, 0.22 mol BuLi) was added dropwise at −70 °C. After stirring for 1 h at −70 °C, saturated aqueous bicarbonate (500 mL) was carefully added followed by slowly warming to room temperature. Standard workup with ethyl acetate gave a red oil, which was dissolved in tetrahydrofuran (100 mL) followed by addition of di-*tert*-butyl dicarbonate (22 g, 100 mmol) and water (50 mL). Stirring for 16 h at room temperature followed by standard workup gave an oil, which was separated by column chromatography (eluent: ethyl acetate/heptane, 1:9), giving **42** (2.9 g, 27%) as a colorless oil. ¹H NMR (CDCl₃, 80 MHz): δ 1.00 (d, 3H), 1.50 (s, 9H), 2.25–2.60 (m, 1H), 2.90 (s, 1H), 3.50–4.10 (m, 4H), 6.10–6.25 (m, 1H). A mixture of **42** (2.4 g, 12 mmol) and trimethylsilyl azide (5 mL, 42 mmol) was heated in a sealed tube to 140 °C for 24 h. Cooling and addition of brine (75 mL) followed by standard workup with ether gave a red oil, which was applied to column chromatography (eluent: ether), giving **43** (1.4 g, 44%) as a colorless oil. ¹H NMR (CDCl₃, 80 MHz): δ 1.10 (d, 3H), 1.50 (s, 9H), 2.30–2.75 (m, 1H), 3.60–4.10 (m, 2H), 4.25–4.50 (m, 2H), 6.30–6.50 (m, 1H), 7.90 (s, 1H).

Alkylation of **43** with propargyl bromide and deprotection by the method described in the synthesis of (±)-**15b** gave **7d**. Mp: 217–19 °C (acetone). ¹H NMR (DMSO-*d₆*, 80 MHz): δ 1.10 (d, 3H), 2.60–3.00 (m, 2H), 3.25–3.50 (m, 1H), 3.60 (t, 1H), 3.75–4.00 (m, 1H), 5.40 (d, 2H), 6.45–6.60 (m, 1H), 8.10 (s, 1H). Anal. (C₁₁H₁₄N₄·HCl·0.47H₂O) C, H, N.

2-Methyl-5-(4-methyl-1,2,3,6-tetrahydro-5-pyridyl)-2*H*-tetrazole Oxalate (7e). A solution of 3-bromo-4-methylpyridine[76] (54 g, 0.28 mol) and copper(I) cyanide (50 g, 0.56 mol) in dimethylformamide (50 mL) was heated to reflux for 3 h. After cooling, sodium cyanide (50 g, 1.0 mol) in water (200 mL) was added followed by heating on a steam bath for 2 h. Cooling and standard workup with ethyl acetate gave an oil. 4-Picoline, which was formed as a byproduct, was removed at 0.1 Torr, and addition of ether/heptane to the residue gave crystalline 3-cyano-4-methylpyridine (**34**, 10 g, 30%). Mp: 43–44 °C. A solution of **34** (5.9 g, 50 mmol), sodium azide (3.9 g, 60 mmol), and ammonium chloride (3.2 g, 60 mmol) in DMF (50 mL) was heated to 130 °C with stirring for 48 h. After cooling, the mixture was filtered and the solvent was removed *in vacuo*. Addition of water to the remaining oil gave crystalline 5-(4-methyl-3-pyridyl)-1*H*-tetrazole (**35**, 3.7 g, 47%). Mp: 209–13 °C. ¹H NMR (DMSO-*d₆*, 80 MHz): δ 2.55 (s, 3H), 7.50 (d, 1H), 8.60 (d, 1H), 8.90 (s, 1H). Using the procedure described in the preparation of **12e**, compound **35** was converted to 5-(1,4-dimethyl-1,2,3,6-tetrahydro-5-pyridyl)-2-methyl-2*H*-tetrazole. This *N*-methyl derivative was then demethylated by the procedure described in the synthesis of **10b** to give **7e**. Mp: 212–14 °C. ¹H NMR (DMSO-*d₆*, 80 MHz): δ 2.05 (s, 3H), 2.25–2.50 (m, 2H), 3.10 (t, 2H), 3.70–3.90 (m, 2H), 4.35 (s, 3H). Anal. (C₈H₁₃N₅·0.5C₂H₂O₄·0.12H₂O) C, H; N: calcd, 30.93; found, 30.17.

4-(1-Methyl-1,2,3,6-tetrahydro-5-pyridyl)-2-vinyl-1,2,3-

triazole Hydrochloride (13a). Alkylation of 4-(3-pyridyl)-1,2,3-triazole, **16** (11 g, 72 mmol), with 1-bromo-2-chloroethane (11 g, 77 mmol), according to the method described in the synthesis of **8a**, gave 2-(2-chloroethyl)-4-(3-pyridyl)-1,2,3-triazole (9.9 g, 66%) as an oil. A portion of the oil (5.9 g, 29 mmol) was dissolved in toluene (25 mL) and added dropwise to a solution of potassium *tert*-butoxide (8.4 g, 75 mmol) in toluene (75 mL) at 90 °C. After stirring for 10 min at 90 °C, the reaction mixture was cooled and water was added. Standard workup with toluene gave a yellow oil, which was dissolved in ether and stirred with charcoal. Filtration and removal of solvent *in vacuo* gave 4-(3-pyridyl)-2-vinyl-1,2,3-triazole (4.7 g, 94%) as a colorless oil. This pyridine derivative was converted to **13a** by the general procedure described above in the synthesis of **8a**. Mp: 205–7 °C (acetone). ^{1}H NMR (DMSO-d_6: δ 2.50–2.75 (m, 2H), 2.90 (s, 3H), 3.15–3.50 (m, 2H), 3.90–4.20 (m, 2H), 5.15 (d, 1H), 5.80 (d, 1H), 6.65–6.75 (m, 1H), 7.45 (dd, 1H), 8.35 (s, 1H). Anal. ($C_{10}H_{14}N_4$·HCl·0.46-H_2O) C, H, N.

In the same manner the corresponding vinyltetrazole was prepared:

5-(1-Methyl-1,2,3,6-tetrahydro-5-pyridyl)-2-vinyl-2H-tetrazole Hydrochloride (13d). Mp: 202–4 °C (ether/acetone). ^{1}H NMR (DMSO-d_6): δ 2.60–2.80 (m, 2H), 2.90 (s, 3H), 3.30–3.50 (m, 2H), 4.05–4.25 (m, 2H), 5.05 (dd, 1H), 6.15 (dd, 1H), 7.05–7.15 (m, 1H), 7.90 (dd, 1H). Anal. (C_8H_{13}-N_5·HCl·0.13H_2O) C, H; N: calcd, 30.45; found, 29.70.

2-Methyl-5-(3-piperidyl)-2H-tetrazole Hydrochloride [(±)-14b]. To a solution of 2-methyl-5-(1,2,3,6-tetrahydro-5-pyridyl)-2H-tetrazole, **7a** (0.50 g, 2 mmol), in ethanol, was added PtO$_2$ (10 mg), and the resulting mixture was hydrogenated at 3.5 atm of hydrogen pressure in a Parr apparatus for 2 h. Filtration and removal of solvent *in vacuo* gave an oil, which was dissolved in 2 M sodium hydroxide solution (25 mL) and dichloromethane (50 mL). Standard workup gave an oil (0.35 g), which crystallized on treatment with dry hydrogen chloride in ether. Recrystallization from 2-propanol gave (±)-**14b** (0.15 g, 26%). Mp: 167–68 °C (2-propanol). ^{1}H NMR (DMSO-d_6): δ 1.60–2.00 (m, 3H), 2.05–2.20 (m, 1H), 2.80–2.95 (m, 1H), 3.10 (t, 1H), 3.25 (d, 1H), 3.40–3.60 (m, 2H), 4.35 (s, 3H). Anal. ($C_7H_{13}N_5$·HCl·0.17H_2O) C, H; N: calcd, 34.03; found, 33.58.

In a similar manner (±)-**15a** was prepared.

2-Ethyl-4-(3-piperidyl)-1,2,3-triazole Hydrobromide [(±)-15a]. Mp: 149–52 °C (acetone). ^{1}H NMR (DMSO-d_6): δ 1.40 (t, 3H), 1.55–1.95 (m, 3H), 1.95–2.10 (m, 1H), 2.75–3.10 (m, 2H), 3.15 (tt, 1H), 3.25–3.40 (m, 1H), 3.40–3.55 (m, 1H), 4.40 (q, 2H), 7.70 (s, 1H). Anal. ($C_9H_{16}N_4$·HBr) C, H, N.

2-Ethyl-5-(3-piperidyl)-2H-tetrazole Fumarate [(±)-14c]. To a solution of 2-ethyl-5-(3-pyridyl)-2H-tetrazole (4.0 g, 23 mmol, from the preparation of **12b**) in acetic acid (100 mL), was added PtO$_2$ (0.20 g, 0.9 mmol), followed by hydrogenation at 3.5 atm of hydrogen pressure for 16 h in a Parr apparatus. After filtration and removal of the solvent *in vacuo*, the remaining oil was dissolved in 2 M sodium hydroxide solution (50 mL), and standard workup with dichloromethane was performed giving an oil (2.0 g, 0.11 mol, 48%), which crystallized as the fumarate salt, (±)-**14c**, from acetone (1.6 g, 23%). Mp: 122–25 °C. ^{1}H NMR (DMSO-d_6): δ 1.50 (t, 3H), 1.65–1.90 (m, 3H), 2.05–2.20 (m, 1H), 2.85 (tt, 1H), 3.00 (t, 1H), 3.10–3.25 (m, 1H), 3.25–3.45 (m, 1H), 3.50 (dd, 1H), 4.65 (q, 2H), 6.45 (s, 2H). Anal. ($C_8H_{15}N_5$·$C_4H_4O_4$) C, H; N: calcd, 23.56; found, 23.05.

5-(3-Piperidyl)-2-propargyl-2H-tetrazole [(±)-14d]. To a solution of 5-[1-(ethoxycarbonyl)-1,2,3,6-tetrahydro-5-pyridyl]-2H-tetrazole, **21**, (15 g, 78 mmol) in ethyl acetate (25 mL) and acetic acid (25 mL) was added 5% palladium on charcoal (1.3 g), and the mixture was hydrogenated at 3.5 atm of hydrogen pressure for 5 days in a Parr apparatus. Filtration and removal of the solvent *in vacuo* gave an oil (12 g) from which remaining starting material crystallized by addition of ethyl acetate. The filtrate was concentrated to an oil (6.6 g), which was dissolved in 30% HBr/AcOH (100 mL) and left for 72 h at room temperature. The solvent was removed *in vacuo*, and the remaining oil was dissolved in water (50 mL). The aqueous phase was extracted with ether (3 × 50 mL), and the

aqueous phase containing 5-(3-piperidyl)-1H-tetrazole (**25**) was treated with 25% sodium hydroxide solution to pH 8. Potassium carbonate (7.5 g, 54 mmol) was added together with a solution of di-*tert*-butyl dicarbonate (8 g, 37 mmol) in tetrahydrofuran (50 mL). After stirring for 16 h the tetrahydrofuran was removed *in vacuo*, and the remaining aqueous phase was carefully acidified to pH 6 with 2 M hydrochloric acid. Standard workup with dichloromethane gave 5-[1-(*tert*-butoxycarbonyl)-3-piperidyl]-1H-tetrazole (**26**, 7.8 g, 45% from **21**) as an oil. ^{1}H NMR (CDCl$_3$): δ 1.45 (s, 9H), 1.50–1.70 (m, 2H), 2.00–2.40 (m, 2H), 3.35 (qui, 2H), 3.35–4.05 (m, 3H). This product was dissolved in acetone (100 mL) followed by addition of potassium carbonate (7.5 g, 54 mmol) and propargyl bromide (4.8 mL, 53 mmol). The mixture was refluxed for 6 h. After cooling and filtration, the solvent was removed *in vacuo* followed by standard workup with ether giving an oil (7.1 g), which was applied to flash chromatography (eluent: ethyl acetate/heptane, 1:1). The free base of (±)-**14d** (2.1 g) was obtained as an oil, which was treated with a solution of dry hydrogen chloride in ether giving (±)-**14d** as a crystalline material (1.1 g, 6% from **21**). Mp: 162–64 °C. ^{1}H NMR (DMSO-d_6): δ 1.60–1.95 (m, 2H), 2.10–2.25 (m, 1H), 2.85–3.00 (m, 1H), 3.05 (t, 1H), 3.20–3.40 (m, 1H), 3.45–3.60 (m, 2H), 3.75 (t, 1H), 5.70 (d, 2H). Anal. ($C_9H_{13}N_5$·HCl) C, H; N: calcd, 30.75; found, 31.16.

2-Allyl-4-(3-piperidyl)-1,2,3-triazole Hydrochloride [(±)-15b]. A mixture of 4-(3-pyridyl)-1,2,3-triazole, **16** (10 g, 68 mmol), PtO$_2$ (0.5 g), and 4 M hydrochloric acid (10 mL) in ethanol (200 mL) was hydrogenated at 3 atm of hydrogen pressure in a Parr apparatus for 24 h. Filtration and removal of solvent *in vacuo* gave the crude hydrochloride of **28** as a red oil (13 g). The oil was dissolved in a mixture of water (100 mL) and tetrahydrofuran (150 mL). Potassium carbonate (20 g, 140 mmol) and di-*tert*-butyl dicarbonate (16 g, 73 mmol) were added followed by stirring for 24 h at room temperature. The phases were separated, and the aqueous phase was extracted with ether. The combined organic phases were concentrated *in vacuo*, leaving a viscous oil, which according to NMR consisted of a mixture of **29** and BOC-protected **29**. The mixture was dissolved in a 1% solution of potassium carbonate in methanol (100 mL) and stirred for 2 h at room temperature. Removal of solvent *in vacuo* followed by addition of brine (100 mL) and standard workup with dichloromethane gave neat **29** (13.5 g, 78%) as a colorless oil. ^{1}H NMR (CDCl$_3$): δ 1.50 (s, 9H), 1.55–1.85 (m, 3H), 2.10–2.15 (m, 1H), 2.90–3.15 (m, 3H), 3.85–4.05 (m, 1H), 4.10–4.30 (m, 1H), 7.60 (s, 1H).

A mixture of **29** (2.2 g, 8.7 mmol), allyl bromide (1.8 g, 15 mmol), and potassium carbonate (7 g, 50 mmol) in acetone (75 mL) was refluxed for 20 h. Filtration and removal of solvent *in vacuo* gave an oil, which was applied to flash chromatography (eluent: ethyl acetate/heptane, 1:1), giving 2-allyl-4-[1-(*tert*-butoxycarbonyl)-3-piperidyl]-1,2,3-triazole (0.9 g, 35%) as a colorless oil. The oil was dissolved in acetone (10 mL), and a saturated solution of dry HCl in ether (3 mL) was added followed by stirring for 20 h. Filtration and drying *in vacuo* gave (±)-**15b** as a crystalline solid. Yield: 0.5 g. Mp: 126–28 °C. ^{1}H NMR (DMSO-d_6): δ 1.50–1.70 (m, 1H), 1.75–1.90 (m, 2H), 2.00–2.15 (m, 1H), 2.75–2.95 (m, 1H), 2.95 (t, 1H), 3.15–3.50 (m, 3H), 5.00 (d, 2H), 5.15 (d, 1H), 5.20 (d, 1H), 5.95–6.15 (m, 1H), 7.75 (s, 1H). Anal. ($C_{10}H_{16}N_4$·HCl) C, H, N.

By using propargyl bromide instead of allyl bromide in the above described procedure, **4-(3-piperidyl)-2-propargyl-1,2,3-triazole hydrochloride,** (±)-**15c**, was obtained as a crystalline solid from acetone. Mp: 187–90 °C. ^{1}H NMR (DMSO-d_6): δ 1.50–1.70 (m, 1H), 1.75–1.90 (m, 2H), 2.00–2.15 (m, 1H), 2.70–3.05 (m, 2H), 3.15–3.50 (m, 3H), 3.55 (t, 1H), 5.30 (d, 2H), 7.80 (s, 1H). Anal. ($C_{10}H_{14}N_4$·HCl) C, H; N: calcd, 24.71; found, 24.24.

(+)- and (−)-2-Allyl-4-(3-piperidyl)-1,2,3-triazole Fumarate [(+)-15b and (−)-15b]. A solution of 4-(3-pyridyl)-1,2,3-triazole, **16** (40 g, 0.27 mol), dimethoxymethane (160 mL, 1.8 mol), and TsOH (92 g, 0.47 mol) in dichloromethane (1.4 L) was refluxed in a Soxleth apparatus with molecular sieves (3 Å, 70 g) for 26 h. After cooling, the reaction mixture was

washed with 2 M sodium hydroxide followed by standard workup with dichloromethane giving a mixture of 1-, 2-, and 3-(methoxymethyl)-4-(3-pyridyl)-1,2,3-triazole (48 g) as an oil. The oil was dissolved in ethanol (550 mL), and PtO_2 (5.0 g) and conc. hydrochloric acid (20 mL) were added followed by hydrogenation at 3 atm of hydrogen pressure in a Parr apparatus for 72 h. Filtration and removal of solvent *in vacuo* gave a mixture of 1-, 2-, and 3-(methoxymethyl)-4-(3-piperidyl)-1,2,3-triazole (49 g, 0.25 mol) as an oil. The mixture was dissolved in dimethylformamide (400 mL), and potassium carbonate (54 g, 0.39 mol) was added. A solution of benzyl bromide (43 g, 0.25 mol) in dimethylformamide (40 mL) was added dropwise at 10 °C followed by stirring for 16 h at room temperature. Addition of water followed by standard workup with dichloromethane gave a viscous oil, which was applied to flash chromatography. The first main fraction, 4-(1-benzyl-3-piperidyl)-2-(methoxymethyl)-1,2,3-triazole, **30**, was isolated (48 g, 67%) as an oil. ^1H NMR (CDCl$_3$): δ 1.40–1.60 (m, 1H), 1.60–1.80 (m, 2H), 1.90–2.15 (m, 2H), 2.20 (t, 1H), 2.75–2.85 (m, 1H), 2.95–3.10 (m, 2H), 3.35 (s, 3H), 3.55 (s, 2H), 5.55 (s, 2H), 7.15–7.35 (m, 5H), 7.50 (s, 1H). ^1H NMR spectroscopy at 250 MHz of a sample consisting of **30** (5 mg, 0.018 mmol) and the shift reagent (R)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (50 mg, 0.18 mmol) in 0.5 mL of CDCl$_3$ resulted in splittings of several signals. The observed base-line splitting of the signal at 5.55 ppm (CH$_2$ group in methoxymethyl side chain) was used for determination of enantiomeric purity in the following resolution.

(−)-BNPA^{50} (28 g, 87 mmol) was dissolved in warm ethanol (1.2 L), and **30** (48 g, 170 mmol), dissolved in ethanol (150 mL), was added. The mixture was kept at 5 °C for 16 h. The crystalline material formed was isolated by filtration and dried *in vacuo*.

Concentration of the filtrate *in vacuo* folllowed by addition of 250 mL of ether and 50 mL of ethanol gave a second crop of crystals, which were recrystallized from 500 mL of ethanol. The two crystal fractions (mp 260–64 °C) were combined, and 2 M NaOH was added followed by standard workup giving 19 g (78%) of a colorless oil, **30a**. The ^1H NMR spectrum was identical to the spectrum of racemic **30** and ^1H NMR spectroscopy with shift reagent as described above showed an enantiomeric purity of >98%.

The combined filtrates from the crystallizations were combined and concentrated *in vacuo* followed by addition of 2 M sodium hydroxide. Standard workup gave an oil, which was dissolved in ethanol (150 mL) and added to a warm solution of (+)-BNPA^{50} (28 g, 85 mmol) in ethanol (1.2 L). The mixture was kept at 5 °C for 20 h, giving a crystalline precipitate, which was collected by filtration. Concentration of the filtrate gave a second crop of crystals. The combined crystal fractions (mp 260–64 °C) were treated with 2 M sodium hydroxide, as described above, giving 20 g (85%) of a colorless oil, **30b**. ^1H NMR spectroscopy showed an enantiomeric purity of >98%.

A mixture of **30a** (19 g, 65 mmol), 5% palladium on carbon (4 g), and ethanol (400 mL) was hydrogenated at 4 atm of hydrogen pressure in a Parr apparatus for 16 h. Addition of 25 mL of 2 M hydrochloric acid followed by removal of solvents *in vacuo* gave crude 2-(methoxymethyl)-4-(3-piperidyl)-1,2,3-triazole hydrochloride, which was dissolved in 1 M hydrochloric acid (200 mL). Reflux for 1.5 h resulted in complete removal of the methoxymethyl group. The solution was treated directly with potassium carbonate and di-*tert*-butoxydicarbonyl by a procedure similar to the procedure described above in the synthesis of (±)-**15b** giving **31a** as a colorless oil (11 g, 66% overal yield from **30a**). The ^1H NMR spectrum was identical to the ^1H NMR spectrum of **29**. By a similar procedure **31b** was obtained as a colorless oil in 73% overall yield from **30b**.

Both **31a** and **31b** were alkylated with allyl bromide and deprotected by the method described in the synthesis of (±)-**15b**. The free bases of (+)-**15b** and (−)-**15b** were obtained by treatment with 1 M sodium hydroxide followed by standard workup with dichloromethane. The fumarates, (+)-**15b** and (−)-**15b**, were obtained from acetone by addition of fumaric acid.

(+)-**15b**. Mp: 101–3 °C. [α]$_D$: +3.3° (c = 1, MeOH). The ^1H NMR spectrum in DMSO-d$_6$ was identical to the ^1H NMR

spectrum of (±)-**15b**. ^1H NMR spectroscopy ((+)-**15b** (4.5 mg) and (R)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (60 mg) in benzene-d$_6$ (0.5 mL) revealed only one peak corresponding to pure (+)-**15b**. On the basis of the signal to noise ratio of the NMR spectrum, the enantiomeric excess could be estimated to be >98%. To ensure that the observed signal corresponded to the pure enantiomer 2 w/w % of the antipode (−)-**15b** were added, and a peak corresponding to the added amount of antipode could be observed in the NMR spectrum and quantified correctly by integration. Anal. (C$_{10}$H$_{16}$N$_4$·C$_4$H$_4$O$_4$), C, H, N.

(−)-**15b**. Mp: 103–4 °C. [α]$_D$: −2.7° (c = 1, MeOH). The ^1H NMR spectrum in DMSO-d$_6$ was identical to the spectrum of (±)-**15b**. ^1H NMR spectroscopy with shift reagent (same conditions as for (+)-**15b**) showed an enantiomeric purity of >98%. Anal. (C$_{10}$H$_{16}$N$_4$·C$_4$H$_4$O$_4$) C, H, N.

In a similar procedure using propargyl bromide instead of allyl bromide (+)-**15c** and (−)-**15c** were obtained.

(+)-**2-Propargyl-4-(3-piperidyl)-1,2,3-triazole Hydrochloride** [(+)-**15c**]. Mp: 190–93 °C (acetone). [α]$_D$: +1.9° (c = 1, MeOH). The ^1H NMR spectrum in DMSO-d$_6$ was identical to the ^1H NMR spectrum of (±)-**15c**. ^1H NMR spectroscopy with shift reagent (same conditions as for (+)-**15b**) showed an enantiomeric purity of >98%. Anal. (C$_{10}$H$_{14}$-N$_4$·HCl) C, H; N: calcd, 24.71; found, 24.12.

(−)-**2-Propargyl-4-(3-piperidyl)-1,2,3-triazole Hydrochloride** [(−)-**15c**]. Mp: 190–93 °C (acetone). [α]$_D$: −1.7° (c = 1, MeOH). The ^1H NMR spectrum in DMSO-d$_6$ was identical to the ^1H NMR spectrum of (±)-**15c**. ^1H NMR spectroscopy with shift reagent (same conditions as for (+)-**15b**) showed an enantiomeric purity of >98%. Anal. (C$_{10}$H$_{14}$-N$_4$·HCl), C, H; N: calcd, 24.71; found, 24.14.

Pharmacological Test Methods. Animals. Male Wistar rats (Mol:Wist strain, Møllegaard, Denmark, 150–250 g), guinea pigs of both sexes (Dunkin Hartley, 300–500 g), and male mice (NMRI/BOM, SPF, 20–25 g) were used. The handling procedures have recently been described in detail.^{26,27}

Receptor Binding. The affinity of the compounds for muscarinic receptors were estimated by their ability to displace [^{3}H]oxotremorine-M (0.20 nM) from whole rat brain homogenate, [^{3}H]pirenzepine (1.0 nM) from whole rat brain homogenate, and [^{3}H]quinuclidinyl benzilate (0.12 nM) from whole rat brain homogenate and from rat brainstem homogenate, respectively. Details have been described previously.^{77} Inhibitory constants (K_i values) were estimated from IC$_{50}$ values using the Cheng–Prusoff^{78} equation: $K_i = IC_{50}/(1 + s/K_D)$, where s is the fixed concentration and K_D the dissociation constant of the labeled ligand. The following K_D constants were derived from computer-assisted Scatchard analyses of binding experiments: [^{3}H]oxotremorine-M, 0.48 ± 0.03 nM; [^{3}H]pirenzepine, 1.8 ± 1.0 nM; [^{3}H]quinuclidinyl benzilate to homogenate brain, 13.7 ± 0.9 pM; [^{3}H]quinuclidinyl benzilate to homogenate brain stem, 9.7 ± 0.8 pM. Two complete concentration–response curves were determined using five concentrations of test drug in triplicate (covering 3 decades). IC$_{50}$ values were estimated from handdrawn log concentration–response curves.

In a series of n determinations the variance of the log ratio (Var$_R$) between the double determinations was determined according to: Var$_R = (1/2n)\sum(\log R_i)^2$, where R_i is the ith ratio and n is the number of observations. The Var$_R$ is equivalent to the square of the standard deviation of the log ratio (SD$_R^2$). The following standard deviations were obtained: [^{3}H]oxo-M, 1.5 (n = 100); [^{3}H]PZ, 1.6 (n = 100); [^{3}H]QNB, 1.5 (n = 100).

Functional Assays. The ability of the compounds to depolarize isolated rat superior cervical ganglion was used to estimate their M$_1$ agonistic effect and efficacy. Details have been described previously.^{77} The potency of the agonists are expressed by their **EC$_{50}$** values, *i.e.*, the concentrations, which have effects equal to 50% of the individual maximum effects. All EC$_{50}$ values estimated for the ganglion are expressed as equal to or greater than the values calculated because the concentration–response curve is biphasic. The apparent efficacy of the agonists was expressed by their RM value, *i.e,* the maximum effect of agonists relative to the maximum effect of muscarine determined on separate ganglia.

The ability of the compounds to depress the electrically stimulated contraction of isolated guinea pig left atrium was used to estimate their M_2 agonistic effect and efficacy. Details have been described previously.[77] The potencies of the agonists were expressed by their EC_{50} values. The apparent efficacy was estimated by the RM value, *i.e.*, the maximum depression of agonist relative to the maximum depression of carbachol measured on the same atrium.

The ability of the compounds to contract isolated guinea pig ileum was used to estimate their M_2/M_3 agonistic effect and efficacy. Details have been described previously.[77] The potencies of the agonists were expressed by their EC_{50} values. The apparent efficacy was estimated by the RM value, *i.e.*, the maximum effect of the agonist relative to the maximum effect of carbachol measured on the same ileum strip.

In Vivo **Studies.** The side effect liabilities of the compounds were estimated by their ability to induce hypothermia, tremor, and salivation in male mice. Details have been described previously.[26] Agonist-induced hypothermia was defined as the maximum decrease in core body temperature relative to a control group. The temperature was recorded 30, 60, 120, and 180 min after subcutaneous administration of agonist. At the same times, salivation and tremor were scored as present or not present. Salivation was scored as present if mouth surroundings were wet, while tremor was scored by estimation of intensity of tremor provoked by handling.

The hypothermia, tremor, and salivation inducing potencies are expressed as ED_{50} values. The maximum decreases of body temperature are expressed as percent of the maximum decrease of temperature obtained in a parallel control group treated with oxotremorine (1.7 μmol/kg, sc). ED_{50} is calculated by means of log probit analysis.

References

(1) Davies, P.; Maloney, A. J. F. Selective loss of central cholinergic neurons in Alzheimer's disease. *Lancet* **1976**, No. 2, 1403.

(2) Bartus, R. T.; Dean, R. L., III; Beer, B.; Lippa, A. S. The cholinergic hypothesis of geriatric memory dysfunction. *Science* **1982**, *217*, 408–417.

(3) DeFeudis, F. V. Cholinergic systems and Alzheimer's disease. *Drug Dev. Res.* **1988**, *14*, 95–109.

(4) Street, L. J.; Baker, R.; Book, T.; Reeve, A. J.; Saunders, J.; Willson, T.; Marwood, R. S.; Patel, S.; Freedman, S. B. Synthesis and muscarinic activity of quinuclidinyl- and (1-azanorbornyl)-pyrazine derivatives. *J. Med. Chem.* **1992**, *35*, 295–305.

(5) Fibiger, H. C. Cholinergic mechanisms in learning, memory and dementia: a review of recent evidence. *Trends Neurosci.* **1991**, *14*, 220–223.

(6) Holttum, J. R.; Gershon, S. The cholinergic model of dementia, Alzheimer type: progression from the unitary transmitter concept. *Dementia* **1992**, *3*, 174–185.

(7) Palacios, J. M.; Spiegel, R. Muscarinic cholinergic agonists: pharmacological and clinical perspectives. *Prog. Brain Res.* **1986**, *70*, 485–498.

(8) Hollander, E.; Davidson, M.; Mohs, R. C.; Horvath, T. B.; Davis, B. M.; Zemishlany, Z.; Davis, K. L. RS 86 in the treatment of Alzheimer's disease: Cognitive and biological effects. *Biol. Psych.* **1987**, *22*, 1067–1078.

(9) Baker, R.; MacLeod, A. M. Muscarinic agonists for the central nervous system. In *Drug design for neuroscience*; Kozikowski, A. P., Ed.; Raven Press: New York, 1993; pp 61–85.

(10) Gottfries, C. G. Clinical and neurochemical aspects of diseases with cognitive impairment. *Rev. Neurosci.* **1992**, *3*, 191–206.

(11) Marchbanks, R. M. Biochemistry of Alzheimer's dementia. *J. Neurochem.* **1982**, *39*, 9–15.

(12) Kan, J. P. Current and future approaches to therapy of Alzheimer's disease. *Eur. J. Med. Chem.* **1992**, *27*, 565–570.

(13) Mei, L.; Roeske, W. R.; Yamamura, H. I. Molecular pharmacology of muscarinic receptor heterogeneity. *Life Sci.* **1989**, *45*, 1831–1851.

(14) Watson, S.; Girdlestone, D. TIPS receptor nomenclature supplement, 4. Ed. *Trends Pharmacol. Sci.* **1993**, March 1993 Suppl.

(15) Bonner, T. I. The molecular basis of muscarinic receptor diversity. *Trends Neurosci.* **1989**, *12*, 148–151.

(16) Waelbroeck, M.; Tastenoy, M.; Camus, J.; Christophe, J. Binding of selective antagonists to four muscarinic receptors (M_1 to M_4) in rat forebrain. *Mol. Pharmacol.* **1990**, *38*, 267–273.

(17) Hulme, E. C.; Birdsall, N. J. M.; Buckley, N. J. Muscarinic receptor subtypes. *Annu. Rev. Pharmacol. Toxicol.* **1990**, *30*, 633–673.

(18) Vanderheyden, P.; Gies, J.-P.; Ebinger, G.; De Keyser, J.; Landry, Y.; Vauquelin, G. Human M_1-, M_2-, and M_3-muscarinic cholinergic receptors: Binding characteristics of agonists and antagonists. *J. Neurol. Sci.* **1990**, *97*, 67–80.

(19) Levey, A. I. Immunological localization of m1-m5 muscarinic acetylcholine receptors in peripheral tissues and brain. *Life Sci.* **1993**, *52*, 441–448.

(20) Caulfield, M. P.; Higgens, G. A.; Straughan, D. W. Central administration of the muscarinic receptor subtype-selective antagonist pirenzepine selectively impairs passive avoidance learning in the mouse. *J. Pharm. Pharmacol.* **1983**, *35*, 131–132.

(21) Hagan, J. J.; Jansen, J. H. M.; Broekkamp, C. L. E. Blockade of spatial learning by the M_1 muscarinic antagonist pirenzepine. *Pyschopharmacology* **1987**, *93*, 470–476.

(22) Messer, W. S., Jr.; Bohnett, M.; Stibbe, J. Evidence for a preferential involvement of M_1 muscarinic receptors in representational memory. *Neurosci. Lett.* **1990**, *116*, 184–189.

(23) Araujo, D. M.; Lapchak, P. A.; Robitaille, Y.; Gauthier, S.; Quirion, R. Differential alteration of various cholinergic markers in cortical and subcortical regions of human brain in Alzheimer's disease. *J. Neurochem.* **1988**, *50*, 1914–1923.

(24) McKinney, M.; Miller, J. H.; Aagaard, P. J. Pharmacological characterization of the rat hippocampal muscarinic autoreceptor. *J. Pharm. Exp. Ther.* **1993**, *264*, 74–78.

(25) Richards, M. H. Rat hippocampal muscarinic autoreceptors are similar to the M_2 (cardiac) subtype: Comparison with hippocampal M_1, atrial M_2, and ileal M_3 receptors. *Br. J. Pharmacol.* **1990**, *99*, 753–761.

(26) Sánchez, C.; Meier, E. Central and peripheral mediation of hypothermia, tremor and salivation induced by muscarinic agonists in mice. *Pharmacol. Toxicol.* **1993**, *72*, 262–267.

(27) Sánchez, C.; Lembøl, H. L. The involvement of muscarinic receptor subtypes in the mediation of hypothermia, tremor, and salivation in male mice. *Pharmacol. Toxicol.* **1994**, *74*, 35–39.

(28) Freedman, S. B.; Dawson, G. R.; Iversen, L. L.; Baker, R.; Hargreaves, R. J. The design of novel muscarinic partial agonists that have functional selectivity in pharmacological preparations in vitro and reduced side-effect profile in vivo. *Life Sci.* **1993**, *52*, 489–495.

(29) Arjungi, K. N. Areca nut. *Drug Res.* **1976**, *26*, 951–956.

(30) Floersheim, P.; Pompo-Villar, E.; Shapiro, G. Isosterism and bioisosterism case studies with muscarinic agonists. *Chimia* **1992**, *46*, 323–334.

(31) Saunders, J.; Cassidy, M.; Freedman, S. B.; Harley, E. A.; Iversen, L. L.; Kneen, C.; MacLeod, A. M.; Merchant, K. J.; Snow, R. J.; Baker, R. Novel quinuclidine-based ligands for the muscarinic cholinergic receptor. *J. Med. Chem.* **1990**, *33*, 1128–1138.

(32) Street, L. J.; Baker, R.; Book, T.; Kneen, C. O.; MacLeod, A. M.; Merchant, K. J.; Showell, G. A.; Saunders, J.; Herbert, R. H.; Freedman, S. B.; Harley, E. A. Synthesis and biological activity of 1,2,4-oxadiazole derivatives: Highly potent and efficacious agonists for cortical muscarinic receptors. *J. Med. Chem.* **1990**, *33*, 2690–2697.

(33) Freedman, S. B.; Harley, E. A.; Patel, S.; Newberry, N. R.; Gilbert, M. J.; McKnight, A. T.; Tang, J. K.; Maguire, J. J.; Mudunkotuwa, N. T.; Baker, R.; Street, L. J.; MacLeod, A. M.; Saunders, J.; Iversen, L. L. A novel series of non-quaternary oxadiazoles acting as full agonists at muscarinic receptors. *Br. J. Pharmacol.* **1990**, *101*, 575–580.

(34) Freedman, S. B.; Harley, E. A.; Marwood, R. S.; Patel, S. In vivo characterization of novel efficacious muscarinic receptor agonists. *Eur. J. Pharm.* **1990**, *187*, 193–199.

(35) Eglen, R. M.; Harris, G. C.; Ford, A. P. D. W.; Wong, E. H. F.; Pfister, J. R.; Whiting, R. L. The action of (±)L-660,863 [(±)3-(3-amino-1,2,4-oxadiazole-5-yl)-quinuclidine] at muscarinic receptor subtypes in vitro. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1992**, *345*, 375–381.

(36) *Drug News Perspect.* **1993**, *6*, 559. See also abstracts and proceedings from the Third International Conference on Alzheimer's and Parkinson's Diseases, 1–6 November, 1993, Chicago, IL.

(37) Sauerberg, P.; Olesen, P. H.; Nielsen, S.; Treppendahl, S.; Sheardown, M. J.; Honoré, T.; Mitch, C. H.; Ward, J. S.; Pike, A. J.; Bymaster, F. P.; Sawyer, B. D.; Shannon, H. E. Novel functional M_1 selective muscarinic agonists. Synthesis and structure-activity relationships of 3-(1,2,5-thiadiazolyl)-1,2,5,6-tetrahydro-1-methylpyridines. *J. Med. Chem.* **1992**, *35*, 2274–2283.

(38) Sauerberg, P.; Olesen, P. H.; Suzdak, P. D.; Sheardown, M. J.; Mitch, C. H.; Quimby, S. J.; Ward, J. S.; Bymaster, F. P.; Sawyer, B. D.; Shannon, H. E. Synthesis and structure-activity relationships of heterocyclic analogues of the functional M₁ selective muscarinic agonist hexyloxy-TZTP. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 809–814.

(39) Ngur, D. O.; Roknich, S.; Mitch, C. H.; Quimby, S. J.; Ward, J. S.; Merritt, L.; Sauerberg, P.; Messer, W. S., Jr.; Hoss, W. Steric and electronic requirements for muscarinic receptor-stimulated phosphoinositide turnover in the CNS in a series of arecoline bioisosteres. *Biochem. Biophys. Res. Commun.* **1992**, *187*, 1389–1394.

(40) Hargreaves, R. J.; McKnight, A. T.; Scholey, K.; Newberry, N. R.; Street, L. J.; Hutson, P. H.; Semark, J. E.; Harley, E. A.; Patel, S.; Freedman, S. B. L-689,660, a novel cholinomimetic with functional selectivity for M₁ and M₃ receptors. *Br. J. Pharmacol.* **1992**, *107*, 494–501.

(41) Bøgesø, K. P.; Jensen, K. G.; Moltzen, E. K.; Pedersen, H. Eur. Pat. Appl. EP 296721 A2; *Chem. Abstr.* **1992**, *110*, 192831.

(42) Wadsworth, H. J.; Jenkins, S. M.; Orlek, B. S.; Cassidy, F.; Clark, M. S. G.; Brown, F.; Riley, G. J.; Graves, D.; Hawkins, J.; Naylor, C. B. Synthesis and muscarinic activities of quinuclidin-3-yltriazole and -tetrazole derivatives. *J. Med. Chem.* **1992**, *35*, 1280–1290.

(43) Jenkins, S. M.; Wadsworth, H. J.; Bromidge, S.; Orlek, B. S.; Wyman, P. A.; Riley, G. J.; Hawkins, J. Substituent variation in azabicyclic triazole- and tetrazole-based muscarinic receptor ligands. *J. Med. Chem.* **1992**, *35*, 2392–2406.

(44) Birkofer, L.; Wegner, P. 1,3-Cycloadditionen mit Trimethylsilyl-azid; über isomere N-Acetyl-1,2,3-triazole. (1,3-Cycloadditions with Trimethylsilylazide: On Isomeric *N*-acetyl-1,2,3-triazole.) *Chem. Ber.* **1966**, *99*, 2512–2517.

(45) Butler, R. N. Tetrazoles. In *Comprehensive heterocyclic chemistry, Vol. 5*; Potts, K. T., Ed.; Pergamon Press: Oxford, 1984; pp 828–834.

(46) McManus, J. M.; Herbst, R. M. Tetrazole analogs of pyridine-carboxylic acid. *J. Org. Chem.* **1959**, *24*, 1462–1464.

(47) Holik, M.; Ferles, M. Pyridine Series. XX. The aluminium hydride reduction of quaternary pyridinium salts. *Collect. Czech. Chem. Commun.* **1967**, *32X*, 3067–3070.

(48) Cooley, J. H.; Evain, E. J. Amine dealkylations with acyl chlorides. *Synthesis* **1989**, 1–7.

(49) Meyers, A. I.; Tomioka, K.; Roland, D. M.; Comins, D. Progress toward the total synthesis of maytansinoids. An efficient route to two major precursors (western-southern zone). *Tetrahedron Lett.* **1988**, *29*, 1375–1378.

(50) Jacques, J.; Fouquey, C. Enantiomeric (S)-(+)- and (R)-(−)-1,1′-binaphtyl-2,2′-diyl hydrogen phosphate. *Org. Synth.* **1989**, *67*, 1–18.

(51) Bøgesø, K.; Liljefors, T.; Arnt, J.; Hyttel, J.; Pedersen, H. Octoclothepin enantiomers. A reinvestigation of their biochemical and pharmacological activity in relation to a new receptor-interaction model for dopamine D-2 receptor antagonists. *J. Med. Chem.* **1991**, *34*, 2023–2030.

(52) Saednya, A. Conversion of carboxamides to nitriles using trichloroacetyl chloride/triethylamine as a mild dehydrating agent. *Synthesis* **1985**, 184–185.

(53) Kozikowski, A. P.; Okita, M.; Kobayashi, M.; Floss, H. G. Probing ergot alkaloid biosynthesis: Synthesis and feeding of a proposed intermediate along the biosynthetic pathway. A new amidomalonate for tryptophan elaboration. *J. Org. Chem.* **1988**, *53*, 863–869.

(54) Freedman, S. B.; Harley, E. A.; Iversen, L. L. Relative affinities of drugs acting at cholinoceptors in displacing agonist and antagonist radioligands: The NMS/Oxo-M ratio as an index of efficacy at cortical muscarinic receptors. *Br. J. Pharmacol.* **1988**, *93*, 437–445.

(55) Krogsgaard-Larsen, P.; Falch, E.; Sauerberg, P.; Freedman, S. B.; Lembøl, H. L.; Meier, E. Bioisosteres of arecoline as novel CNS-active muscarinic agonists. *Trends Pharmacol. Sci.* **1988**, suppl., 69–74.

(56) Boddeke, H. W. G. M. Different effects of muscarinic agonists in rat superior cervical ganglion and hippocampal slices. *Eur. J. Pharmacol.* **1991**, *201*, 191–197.

(57) Freedman, S. B.; Beer, M. S.; Harley, E. A. Muscarinic M₁, M₂ receptor binding. Relationship with functional efficacy. *Eur. J. Pharm.* **1988**, *156*, 133–142.

(58) Hu, J.; Wang, S.-Z.; El-Fakahany, E. E. Effects of agonist efficacy on desensitization of phosphoinositide hydrolysis mediated by m1 and m3 muscarinic receptors expressed in chinese hamster ovary cells. *J. Pharm. Exp. Ther.* **1991**, *257*, 938–945.

(59) McKinney, M.; Anderson, D. J.; Vella–Rountree, L.; Connolly, T.; Miller, J. H. Pharmacological profiles for rat cortical M₁ and M₂ muscarinic receptors using selective antagonists: Comparison with N1E-115 muscarinic receptors. *J. Pharm. Exp. Ther.* **1991**, *257*, 1121–1129.

(60) Mei, L.; Lai, J.; Yamamura, H. I.; Roeske, W. R. Pharmacologic comparison of selected agonists for the M₁ muscarinic receptor in transfected murine fibroblast cells (B82). *J. Pharm. Exp. Ther.* **1991**, *256*, 689–694.

(61) Moos, W. H.; Bergmeier, S. C.; Coughenour, L. L.; Davis, R. E.; Hershenson, F. M.; Kester, J. A.; McKee, J. S.; Marriott, J. G.; Schwarz, R. D.; Tecle, H.; Thomas, A. J. Cholinergic agents: Effect of methyl substitution in a series of arecoline derivatives on binding to muscarinic acetylcholine receptors. *J. Pharm. Sci.* **1992**, *81*, 1015–1019.

(62) Sauerberg, P.; Kindtler, J. W.; Nielsen, L.; Sheardown, M. J.; Honoré, T. Muscarinic cholinergic agonists and antagonists of the 3-(3-alkyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine type. Synthesis and structure-activity relationships. *J. Med. Chem.* **1991**, *34*, 687–692.

(63) Showell, G. A.; Gibbons, T. L.; Kneen, C. O.; MacLeod, A. M.; Merchant, K. J.; Saunders, J.; Freedman, S. B.; Patel, S.; Baker, R. Tetrahydropyridyloxadiazoles: Semirigid muscarinic ligands. *J. Med. Chem.* **1991**, *34*, 1086–1094.

(64) Tecle, H.; Lauffer, D. J.; Mirzadegan, T.; Moos, W. H.; Moreland, D. W.; Pavia, M. R.; Schwartz, R. D.; Davis, R. E. A rationale for the design and synthesis of m1 selective muscarinic agonists. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 821–826.

(65) Toja, E.; Bonetti, C.; Butti, A.; Hunt, P.; Fortin, M.; Barzaghi, F.; Formento, M. L.; Maggioni, A.; Nencioni, A.; Galliani, G. 1-Substituted-1,2,5,6-tetrahydropyridine-3-carboxaldehyde-O-alkyl oximes as novel orally active and long-lasting muscarinic cholinergic agonists. *Eur. J. Med. Chem.* **1992**, *27*, 519–526.

(66) Wolf-Pflugmann, M.; Lambrecht, G.; Wess, J.; Mutschler, E. Synthesis and muscarinic activity of a series of tertiary and quaternary N-substituted guvacine esters structurally related to arecoline and arecaidine propargyl ester. *Drug Res.* **1989**, *39*, 539–544.

(67) Moser, U.; Lambrecht, G.; Wagner, M.; Wess, J.; Mutschler, E. Structure-activity relationships of new analogues of arecaidine propargyl ester at muscarinic M₁ and M₂ receptor subtypes. *Br. J. Pharmacol.* **1989**, *96*, 319–324.

(68) Wess, J.; Lambrecht, G.; Moser, U.; Mutschler, E. Stimulation of ganglionic muscarinic M₁ receptors by a series of tertiary arecaidine and isoarecaidine esters in the pithed rat. *Eur. J. Pharm.* **1987**, *134*, 61–67.

(69) De Amici, M.; Dallanoce, C.; De Micheli, C.; Grana, E.; Dondi, G.; Ladinsky, H.; Schiavi, G. B.; Zonta, F. Synthesis and pharmacological investigation of stereoisomeric muscarines. *Chirality* **1992**, *4*, 230–239.

(70) Angeli, P.; Brasili, L.; Giannella, M.; Gualtieri, F.; Picchio, M. T.; Teodori, E. Chiral muscarinic agonists possessing a 1,3-oxathiolane nucleus: enantio- and tissue-selectivity on isolated preparations of guinea-pig ileum and atria and of rat urinary bladder. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1988**, *337*, 241–245.

(71) Saunders, J.; Showell, G. A.; Baker, R.; Freedman, S. B.; Hill, D.; McKnight, A.; Newberry, N.; Salamone, J. D.; Hirshfield, J.; Springer, J. P. Synthesis and characterization of all four isomers of the muscarinic agonist 2′-methyl-spiro[1-azabicyclo[2.2.2]-octane-3,4′-[1,3]dioxolane]. *J. Med. Chem.* **1987**, *30*, 969–975.

(72) Wei, H.; Roeske, W. R.; Lai, J.; Wanibuchi, F.; Hidaka, K.; Usuda, S.; Yamamura, H. I. Pharmacological characterization of a novel muscarinic partial agonist, YM796, in transfected cells expressing the m1 or m2 muscarinic receptor gene. *Life Sci.* **1992**, *50*, 355–363.

(73) Messer, W. S., Jr.; Ngur, D. O.; Abuh, Y. F.; Dokas, L. A.; Ting, S.-M.; Hacksell, U.; Nilsson, B. M.; Dunbar, P. G.; Hoss, W. Stereoselective binding and activity of oxotremorine analogs at muscarinic receptors in rat brain. *Chirality* **1992**, *4*, 463–468.

(74) Haug, U.; Fürst, H. Darstellung und Eigenschaften der Pyridyl- und Chinolyl-acetylene. (Synthesis and Properties of Pyridyl- and Chinolylactylene.) *Chem. Ber.* **1960**, *93*, 593–598.

(75) Krogsgaard-Larsen, P.; Pedersen, H.; Falch, E. Eur. Pat. Appl. EP 336555; *Chem. Abstr.* **1990**, *112*, 198366.

(76) Pearson, D. E.; Hargrove, W. W.; Chow, J. K. T.; Suthers, B. R. The swamping catalyst effect. III. The halogenation of pyridine and picolines. *J. Org. Chem.* **1961**, *26*, 789–792.

(77) Arnt, J.; Lembøl, H. L.; Meier, E.; Pedersen, H. Discriminative stimulus properties of the muscarinic receptor agonists Lu 26-046 and O-Me-THPO in rats: evidence for involvement of different muscarinic receptor subtypes. *Eur. J. Pharm.* **1992**, *218*, 159–169.

(78) Cheng, K.-C.; Prusoff, W. H. Relationship between the inhibition constant (K₁) and the concentration of inhibitor which causes 50 per cent inhibition (IC₅₀) of an enzymatic reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099–3090.