Design, Synthesis, and Preliminary Pharmacological Evaluation of 1,4-Diazabicyclo[4.3.0]nonan-9-ones as a New Class of Highly Potent Nootropic Agents

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Several 4-substituted 1,4-diazabicyclo[4.3.0]nonan-9-ones have been synthesized and tested in vivo on mouse passive avoidance test, to evaluate their nootropic activity. The results show that they represent a new class of nootropic drugs with a pharmacological profile very similar to that of piracetam, showing much higher potency with respect to the reference. Among the compounds studied, **7** (DM 232) shows outstanding potency, being active at the dose of 0.001 mg kg^{-1} sc.

Introduction

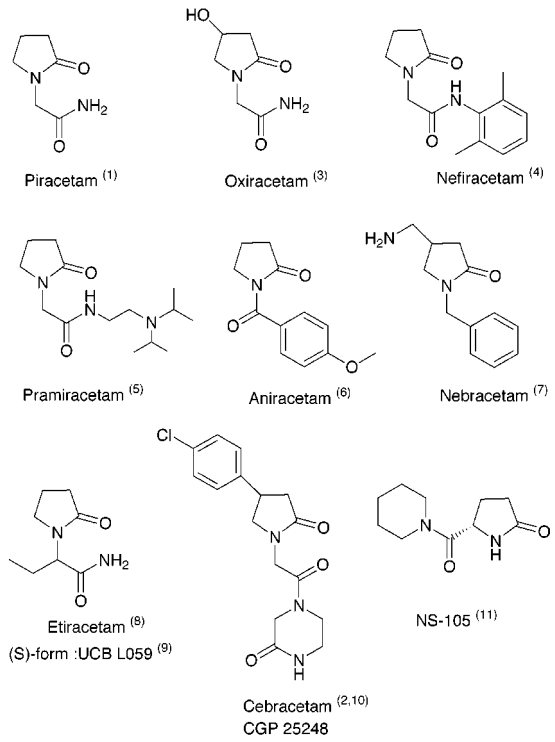
Some 30 years ago the cognition-enhancing properties of piracetam were reported.[1] This discovery stimulated the design and synthesis of a large number of structurally related molecules (see ref 2 for a review), endowed with similar pharmacological action, and few have reached therapeutic utilization, being now on the market as nootropics. Some of the most representative and widely studied compounds of this class are reported in Chart 1.[3−11]

The members of this class share the property of reverting amnesia induced by scopolamine, electroconvulsive shock, and hypoxia, but the mechanism of action of these protective and cognition-enhancing drugs has not yet been elucidated.[12]

As a matter of fact, increased turnover of different neurotransmitters has been observed and the involvement of a cholinergic mechanism has been particularly studied.[13] In general, however, no affinity for the most important central receptors has been found and these drugs, with the exception of nefiracetam, which shows high affinity for the GABA A receptors,[14] do not seem to act on any well-characterized receptor system.[2] Indeed, the effects observed on the cholinergic system might be of secondary origin.[15,16] Modulation of ion fluxes has also been proposed as the mechanism of action of at least some piracetam-like compounds,[2] as seems the case for UCB-L059, the (*S*)-enantiomer of etiracetam.[9] Very recently, modulation of membrane properties has been proposed as a unique mode of action for piracetam.[17] Altogether, it seems that piracetam-like nootropic compounds, through an as yet unidentified mechanism(s) of action, act by increasing neuronal sensitivity toward stimulation.

The lack of a clear mechanism of action has been a major problem in accepting the concept of piracetam-like nootropic agents. Nevertheless, recent data[18,19] suggest that long-term administration of nootropics may lead to a sustained and increased improvement of cognitive functions in patients with mild to moderate Alzheimer's disease, with excellent tolerability and safety.[20]

Chart 1



From a medicinal chemistry point of view, the original structure of piracetam, as can also be seen from the few examples reported in Chart 1, has undergone considerable modifications, and many active compounds lack the 2-oxopyrrolidineacetic acid substructure. However, the vast majority of the active compounds conserve the 2-oxopyrrolidine ring. This ring has been successfully substituted in almost every position, but compounds where the pyrrolidine ring has been condensed with other rings are rare.[21,22]

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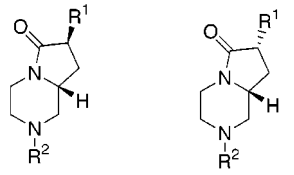
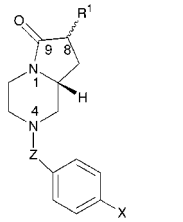
Table 1. Chemical and Physical Characteristics of Compounds **2**−**19**



no.	R^1	R^2	stereo	eluting solvent[a]	mp, °C[b]	anal.[c]
2	H	$SO_2C_6H_5$		A	136−137	$C_{13}H_{16}N_2O_3S$
3	H	$SO_2C_6H_4$-*p*-CH_3		F	179−180	$C_{14}H_{18}N_2O_3S$
4	H	$SO_2C_6H_4$-*p*-OCH_3		H	168−170	$C_{14}H_{18}N_2O_4S$
5	H	$SO_2C_6H_4$-*p*-NO_2		F	238−240	$C_{13}H_{15}N_3O_5S$
6	H	$SO_2C_6H_4$-*p*-Cl		F	209−210	$C_{13}H_{15}ClN_2O_3S$
7	H	$SO_2C_6H_4$-*p*-F		A	157−159	$C_{13}H_{15}FN_2O_3S$
8	H	COC_6H_5		A	134−136	$C_{14}H_{16}N_2O_2$
9	H	COC_6H_4-*p*-CH_3		F	103−105	$C_{15}H_{18}N_2O_2$
10	H	COC_6H_4-*p*-OCH_3		E	130−132	$C_{15}H_{18}N_2O_3$
11	H	COC_6H_4-*p*-NO_2		G	96−98	$C_{14}H_{15}N_3O_4$
12	H	COC_6H_4-*p*-Cl		E	124−126	$C_{14}H_{15}ClN_2O_2$
13	H	COC_6H_4-*p*-F		A	142−143	$C_{14}H_{15}FN_2O_2$
14a	CH_3	$SO_2C_6H_5$	exo	E	115−117	$C_{14}H_{18}N_2O_3S$
14b	CH_3	$SO_2C_6H_5$	endo	B	128−130	$C_{14}H_{18}N_2O_3S$
15a	CH_3	$SO_2C_6H_4$-*p*-F	exo	B	97−99	$C_{14}H_{17}FN_2O_3S$
15b	CH_3	$SO_2C_6H_4$-*p*-F	endo	B	125−127	$C_{14}H_{17}FN_2O_3S$
16a	CH_3	COC_6H_5	exo	E	116−118	$C_{15}H_{18}N_2O_2$
16b	CH_3	COC_6H_5	endo	E	131−132	$C_{15}H_{18}N_2O_2$
17a	CH_3	COC_6H_4-*p*-F	exo	A	142−143	$C_{15}H_{17}FN_2O_2$
17b	CH_3	COC_6H_4-*p*-F	endo	A	135−137	$C_{15}H_{17}FN_2O_2$
18	H	$CH_2C_6H_5$		D	170−172[d]	$C_{14}H_{19}ClN_2O$
19	H	$CH_2C_6H_4$-*p*-F		E	90−92[d]	$C_{14}H_{18}ClFN_2O$

[a] Eluting system for column chromatography: A = $CHCl_3$/MeOH, 90:10; B = $CHCl_3$/MeOH, 97:3; C = $CHCl_3$/anh. EtOH/petroleum ether/NH_4OH, 360:65:60:8; D = cyclohexane/ethyl acetate, 50:50; E = $CHCl_3$/MeOH, 95:5; F = $CHCl_3$/MeOH/hexane, 65:5:30; G = CH_2Cl_2/MeOH, 98:2; H = CH_2Cl_2/MeOH, 95:5. [b] After crystallization from petroleum ether. [c] ^{1}H NMR and IR spectra are in accord with the proposed structures. [d] As hydrochloride.

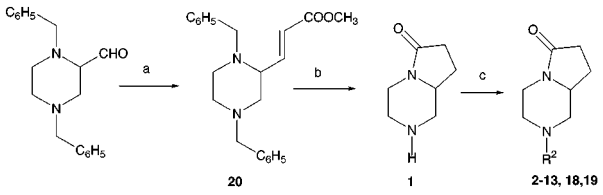
Chart 2



In a preceding study, aimed to identify centrally active nicotinic agonists potentially useful in the treatment of neurodegenerative disorders, we had prepared a series of 8-methyl-1,4-diazabicyclo[4.3.0]nonan-9-ones.[23] In their structure an oxopyrrolidine ring is present, here condensed with a piperazine ring, that, as discussed above, is the constant feature of most nootropic compounds. We reasoned that proper modifications of this structure could produce compounds endowed with nootropic activity that, though with different mechanisms of action, could be used for the same purpose of controlling neurodegenerative pathologies.

On this basis, we designed the series of compounds with the general structure shown in Chart 2. The main modification performed in the new series is the introduction of an aromatic acyl or sulfonyl group on the basic nitrogen of the piperazine ring. The modification was aimed at eliminating the basicity of nitrogen 4, which is connected with nicotinic activity, and at the same time increasing the lipophilicity of the molecules and facilitating brain penetration.

Scheme 1[a]



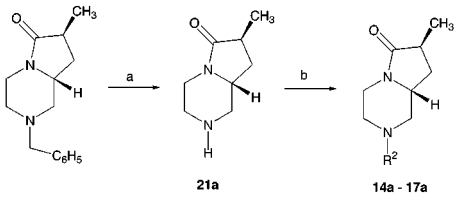
[a] (a) $(C_2H_5O)_2P(O)CH_2COOCH_3$; (b) H_2, Pd/C; (c) acyl and sulfonyl chlorides or benzyl chlorides.

Chemistry

In Scheme 1 is reported the synthetic pathway used to obtain derivatives **2**−**13**. The starting material, 1,4-dibenzyl-2-piperazincarboxaldehyde,[23] was reacted with the ylide obtained from diethyl [1-(methoxycarbonyl)-methyl]phosphonate to give **20** as a cis/trans mixture that was not separated but reduced as such to the corresponding debenzylated alkane, which spontaneously cyclizes to give the 1,4-diazabicyclo[4.3.0]nonan-9-one **1**. Compounds **2**−**13** were obtained by reaction with the corresponding acyl and sulfonyl chlorides; compounds **18** and **19** were obtained by reaction of the corresponding benzyl chlorides.

Compounds **2**−**13**, **18**, and **19** (Table 1) are racemic mixtures that at this stage of the research were not resolved and have been tested as such. The resolution

Scheme 2[a]



[a] (a) H_2, Pd/C; (b) acyl and sulfonyl chlorides. In the same way, the endo isomers **14b**−**17b** were obtained starting from the endo-*N*-benzyl derivative.

of the most interesting racemates is under way and will be reported in due time.

8-Methyl-1,4-diazabicyclo[4.3.0]nonan-9-ones (**14**−**17**) have been synthesized as shown in Scheme 2. They have two stereogenic centers and occur as four optical isomers; unlike their N-substituted analogues,[23] 8-methyl-1,4-diazabicyclo[4.3.0]nonan-9-one (**21**) diastereoisomers cannot be separated by chromatography. Therefore, the two diastereoisomers **21a** (exo) and **21b** (endo) were synthesized by reduction of the previously described[23] exo and endo diastereoisomers of 4-benzyl-8-methyl-1,4-diazabicyclo[4.3.0]nonan-9-one. As observed for the other members of the series,[23] even in this case the bridge-carbon protons of the **a** (exo) series resonate at lower field with respect to the **b** (endo) series (multiplets at $\delta = 3.47-3.56$ and 3.32−3.50 ppm for **21a** and **21b**, respectively). In addition, in the ^{13}C NMR spectra, the CH_2 carbon of the pirrolidinone ring is found at higher field in the exo isomer (**21a**, 32.51 ppm) than in the endo one (**21b**, 34.25 ppm); this rightward shift is more evident in the ^1H NMR spectra, where a multiplet for 2H is found at 1.70−1.78 ppm in the spectrum of **21a** but at lower fields (>2) in that of **21b**. These features of ^{13}C NMR and ^1H NMR spectra are common to all the compounds of this series. Compouds **14a**,**b**−**17a**,**b** were obtained by reaction with the corresponding acyl and sulfonyl chlorides (Scheme 2). Even in this case, at this stage of the research, racemates were not resolved and were tested as such. The resolution of the most interesting racemates is under way and will be reported in due time.

Pharmacology

Since the mechanism of action of piracetam-like cognition enhancers is still under investigation, the search for new drugs in this class generally relies on behavioral tests. Among them, the reversal of scopolamine-induced amnesia in passive avoidance test has been widely used. Therefore, our compounds were tested as cognition enhancers in the mouse passive avoidance test of Jarvik and Kopp, slightly modified by us (see the Experimental Section).[24] In short, mice receive a punishment when entering a dark room in the training session and remember it in the session of the following day, unless their memory is impaired by the amnesic drug. The parameter measured is the entry latency time (expressed in seconds) occurring between the time the mouse is placed in the light and the time it enters the dark room. On the first day there is the training session, while on the second day the mice are placed again in the light and the new latency time is measured on animals treated or untreated with the nootropic drug. Investigated drugs were injected, in a one to 10 dilution sequence, 20 min before the training session, while the amnesic drug was injected immediately after termination of the training session. Scopolamine was used as amnesic drug and piracetam as the reference drug.

Comparison of the latency times of saline-treated animals with those of mice that received both scopolamine and the investigated drug gives a measure of the cognition activity of the compounds tested.

All compounds elicited their antiamnesic effect without changing either gross behavior or motor coordination, as revealed by the rotarod test (data not shown). None of the drugs, at the active doses, increased the number of falls from the rotating rod in comparison with saline-treated mice. The number of falls in the rotarod test progressively decreased, since mice learned how to balance on the rotating rod. The spontaneous motility and inspection activity of mice was unmodified by the administration of the studied compounds, as revealed by the hole-board test in comparison with saline-treated mice (data not shown).

Results

The results obtained by screening the compounds studied on scopolamine-induced amnesia are reported in Table 2. The minimal effective dose for each compound is reported, compared with that of the reference compound, piracetam. Most of the compounds synthesized are active in preventing amnesia. Among them, compound **7** shows an outstanding potency, as it is able to prevent amnesia at doses as low as 0.001 mg kg^{-1} sc, being some 1000 times more potent than the reference compound piracetam. In the same test, piracetam shows a minimum active dose of 30 mg kg^{-1} ip and is totally inactive at the dose of 10 mg kg^{-1} ip. Several other compounds of the series are also active at minimum effective doses below 1 mg kg^{-1} sc, showing that this series represents a new, very potent class of nootropic drugs. In addition to scopolamine (antimuscarinic), the compounds were also able to revert amnesia induced by mecamylamine (nicotinic antagonist), baclofen ($GABA_B$ agonist), and clonidine (α_2 agonist), with a potency pattern similar to that reported for scopolamine (data not shown).

At higher doses, all compounds maintain their antiamnesic activity without any effect on behavior (data not shown). As a matter of fact, rotarod and hole-board tests did not evidence any effect on motor coordination, spontaneous motility, and curiosity of the animal treated. Moreover, the compounds did not elicit any collateral symptoms when injected at a dose a 1000-fold higher than the minimal effective dose preventing amnesia.

Discussion

In the following discussion it must be kept in mind that in vivo tests such as passive avoidance, while obviously speeding up the selection of the compounds with the most promising clinical properties, do not always allow sound structure−activity relationships to be established. In fact, the resulting activity is the consequence of both pharmacokinetic and pharmacodynamic properties that may be differently affected by structural modifications.

Although unsubstituted benzoyl and phenylsulfonyl groups were already able to afford, in both desmethyl-

Table 2. Nootropic Effect of 1,4-Diazabicyclo[4.3.0]nonan-9-ones on Mouse Passive-Avoidance Test, Using Scopolamine (S) as Amnesizing Drug

drug[a] (no. of animals)	minimal effective dose, mg kg^{-1} (sc)	entry latency (s) 1st day	entry latency (s) 2nd day	Δ
saline (13)		15.0 ± 5.9	95.6 ± 8.8	80.6
vehicle§ (10)[b]		20.3 ± 5.3	108.5 ± 10.5	88.2
vehicle (11)[c]		15.7 ± 3.3	101.4 ± 9.6	85.7
scopolamine (6)	1.5[d]	16.6 ± 4.7	44.5 ± 8.3°	27.9
2 (11)[b§]	>10[e]			
3 (9)	1.0	15.1 ± 4.5	95.6 ± 9.4*	80.5
4 (10)	0.1	14.8 ± 5.3	118.3 ± 10.7*	103.5
5 (10)	10	13.8 ± 4.0	89.2 ± 9.7**	75.4
6 (10)	>0.1[e]			
7 (12)	0.001	19.7 ± 5.8	104.4 ± 10.6*	93.8
8 (8)	1.0	16.8 ± 3.7	102.0 ± 11.3*	85.2
9 (10)	1.0	15.6 ± 4.8	100.1 ± 13.5*	84.5
10 (14)[c]	>1.0[e]			
11 (10)[c]	10	18.0 ± 6.1	96.2 ± 11.1*	78.2
12 (10)	10	18.3 ± 5.0	103.7 ± 13.3*	85.4
13 (11)	10	11.7 ± 5.4	88.9 ± 9.7*	77.2
14a (8)	10	18.3 ± 4.5	91.3 ± 9.6*	73.0
14b (10)	1.0	13.6 ± 5.1	94.8 ± 10.2*	78.5
15a (14)	0.1	16.9 ± 6.1	94.9 ± 11.2*	78.0
15b (11)	0.1	21.9 ± 4.7	118.4 ± 10.2*	96.5
16a (9)	1.0	14.3 ± 4.2	99.5 ± 9.2*	85.2
16b (12)	1.0	17.7 ± 4.4	83.5 ± 8.6**	65.8
17a (9)	0.1	21.8 ± 4.8	107.4 ± 10.7*	85.6
17b (9)	0.1	24.0 ± 7.1	104.0 ± 8.6*	80.0
18 (10)	1.0	14.2 ± 4.5	77.4 ± 8.5**	63.2
19 (12)	>10			
piracetam (34)	30[d]	17.6 ± 3.6	108.8 ± 10.4*	91.2

[a] All compounds dissolved in saline unless differently stated. [b] DMSO/H_2O 1:3 used as vehicle, due to insolubility in saline. [c] DMSO/H_2O 1:2 used as vehicle due to insolubility in saline. [d] Intraperitoneally dosed. [e] Dose limited by solubility problems. °$P < 0.01$ with respect to mice treated with saline. *$P < 0.01$; **$P < 0.05$ with respect to mice treated with scopolamine.

and 8-methyl-1,4-diazabicyclo[4.3.0]nonan-9-one series, nootropic compounds with higher potency with respect to the reference (**2**, **8**, **14**, **16**), we extended the synthesis to *p*-substituted compounds to evaluate the importance of substituents with different electronic properties on activity. The more readily available 1,4-diazabicyclo-[4.3.0]nonan-9-one nucleus was chosen for this study (desmethyl series).

This structure−activity relationship study has led to the discovery of **7**, which shows an outstanding potency as a nootropic. It belongs to the desmethyl series and bears a *p*-F substituent on the phenylsulfonyl group. However, the same substitution on the benzoyl moiety (**13**) is definitely detrimental for the activity of **8**. On the contrary, *p*-fluoro substitution, on both benzoyl and phenysulfonyl groups, gives good results in the 8-methyl series (see compounds **15** versus **14** and compounds **17** versus **16**).

In general, there are no clear-cut relationships between the nature of the phenyl substituent and nootropic activity. Also the presence of the methyl in position 8 of the 1,4-diazabicyclo[4.3.0]nonan-9-one nucleus does not seem to be critical, as in some cases it increases (compare compounds **13** and **17**) and in other ones decreases activity (compare compounds **7** and **15**). As mentioned above this lack of structure−activity relationships is most likely due to the in vivo experiments that suffer the influence of pharmacokinetics.

C(6)/C(8) relative stereochemistry does not apparently play an important role in nootropic action, as the diastereoisomers of **15** (**15a** and **15b**), **16** (**16a** and **16b**), and **17** (**17a** and **17b**) show similar potencies, and only in the case of **14**, the exo diastereoisomer **14a** is some 10 times more potent than **14b**. Nothing can be said about enantioselectivity, as the racemates of both the desmethyl and 8-methyl series have not yet been resolved. To clarify this aspect of structure−activity relationships, the resolution of **7** is under way.

To verify the importance of carbonyl and sulfonyl functions, 4-benzyl-1,4-diazabicyclo[4.3.0]nonan-9-one (**18**) and 4-(*p*-F-benzyl)-1,4-diazabicyclo[4.3.0]nonan-9-one (**19**) were also synthesized and tested. The results do not give a consistent indication, as the compounds maintain a potency comparable to that of the corresponding **2**, **8**, **13**, while there is a definite reduction of potency with respect to **7**. Again, the changes introduced into the chemicophysical properties of compounds **18** and **19** (where the 4-nitrogen is basic) may influence pharmacokinetic properties and obscure structure−activity relationships.

For sounder structure−activity relationships, it will be necessary to identify the biological target(s) of our compounds. This will allow in vitro testing and make a reliable study of the pharmacophore possible. Yet, this does not appear to be an easy task, since, as discussed in the Introduction, the mechanism of action of piracetam-like nootropic drugs is still elusive[12] and several, so far inconclusive, different targets have been proposed for them. Notwithstanding the uncertainty on their mechanism of action, pharmacophores for piracetam-like compounds have been proposed.[25,26] It is hoped that the high potency of our compounds will facilitate this search and contribute to elucidating the mechanism of action of piracetam-like nootropic drugs.

Preliminary exploration of the mechanism of action of the compounds reported in the present work shows

that they do not present affinity for muscarinic or nicotinic receptors, nor do they release acetylcholine in the rat brain at 1.0 mg/kg ip (tested on **7**).

In conclusion, our results indicate that 4-substituted 1,4-diazabicyclo[4.3.0]nonan-9-ones represent a new class of nootropic drugs with an in vivo pharmacological profile very similar to that of piracetam, showing much higher potency with respect to the reference. Among the compounds studied, **7** (DM 232) shows outstanding potency, being active at the dose of 0.001 mg kg^{-1} sc. Moreover, this compound, as well as its analogues, did not show any impairment of motor coordination and spontaneous activity, at doses a 1000-fold higher than that active in the passive avoidance test.

Work is in progress to collect more information on the molecular mechanism of action of this class of compounds and to evaluate the effect of other modifications of their chemical structure.

Experimental Section

Chemistry. All melting points were taken on a Büchi apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 681 spectrophotometer in a Nujol mull for solids and neat for liquids. Unless otherwise stated, NMR spectra were recorded on a Gemini 200 spectrometer. Chromatographic separations were performed on a silica gel column by gravity chromatography (Kieselgel 40, 0.063−0.200 mm, Merck) or flash chromatography (Kieselgel 40, 0.040−0.063 mm, Merck). Yields are given after purification, unless otherwise stated. Where analyses are indicated by symbols, the analytical results are within ±0.4% of the theoretical values.

Methyl 1,4-Dibenzyl-2-piperazin-3-acrylate (20). Diethyl [1-(methoxycarbonyl)methyl]phosphonate[27] (0.39 g, 1.85 mmol) was added to NaH (45 mg, 1.85 mmol), washed three times with anhydrous hexane, and then suspended in anhydrous 1,2-dimethoxyethane (DME, 4.6 mL); 1 h later, a solution of 1,4-dibenzyl-2-piperazincarboxaldehyde[23] (0.54 g, 1.85 mmol) in 5 mL of anhydrous DME was added. After 1 h at room temperature, the mixture was washed with water and extracted with Et_2O. Removal of the solvent and purification of the residue by Al_2O_3 column chromatography (cyclohexane/ethyl acetate 50:50) gave the title compound **20** as an oily diasteroisomeric mixture (yield 60%): IR (neat) ν 1720 (C═O), 1620 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10−2.23 (m, 2H, CH), 2.61−2.75 (m, 3H, CH), 3.05−3.15 (m, 2H, CH), 3.45−3.53 (m, 1H, CHPh), 3.49 (s, 3H, CH_3O), 3.73 (s, 2H, CH_2Ph), 3.85−3.94 (m, 1H, CHPh), 5.99−6.07 (m, 1H, CH═), 6.91−7.03 (m, 1H, CH═), 7.20−7.28 (m, 10H, aromatics) ppm. Anal. ($C_{22}H_{26}N_2O_2$) C, H, N.

(±)-1,4-Diazabicyclo[4.3.0]nonan-9-one (1). Compound **20** (0.38 g, 1.10 mmol) was hydrogenated over Pd/C 10% (0.19 g) in absolute ethanol at 50 psi for 8 h. After filtration, the solvent was removed under vacuum to give a residue that was purified by Al_2O_3 column chromatography, using $CHCl_3$/MeOH/hexane 72:8:20 as eluting system, to give **1** (72% yield) as an oil: IR (neat) ν 3200−3500 (NH); 1670 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.49−1.65 (m, 1H, CH), 1.78 (bs, 1H, NH), 2.05−2.27 (m, 1H, CH), 2.29−2.40 (m, 3H, CH,CH_2), 2.50−2.63 (m, 1H, CH), 2.72−2.89 (m, 1H, CH), 2.95−3.02 (m, 1H, CH), 3.10−3.18 (m, 1H, CH), 3.41−3.59 (m, 1H, CH), 3.95−4.02 (m, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$) δ 24.19 (t), 32.29 (t), 42.20 (t), 46.46 (t), 54.44 (t), 57.93 (d), 175.32 (s) ppm. Anal. ($C_7H_{12}N_2O$) C, H, N.

(±)-4-Benzyl-1,4-diazabicyclo[4.3.0]nonan-9-one (18). Benzyl bromide (1 mmol) was added to a solution of **1** (1 mmol) in a few milliliters of $CHCl_3$. After 2 h at room temperature the mixture was made alkaline with $NaHCO_3$, extracted with $CHCl_3$, and dried. Removal of the solvent gave a mixture that was purified by column chromatography using the eluent reported in Table 1: IR (neat) ν 1670 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51−1.72 (m, 2H, CH), 1.92−2.20 (m, 2H, CH), 2.34−2.42 (m, 2H, CH_2CO), 2.80−2.99 (m, 3H, CHN), 3.54 (dd, J = 13.2 Hz, 2H, CH_2Ph), 3.59−3.68 (m, 1H, CHN), 3.94−4.02 (m, 1H, CHN), 7.25−7.38 (m, 5H, aromatics) ppm; ^{13}C NMR ($CDCl_3$) δ 24.10 (t), 32.30 (t), 41.60 (t), 55.10 (d), 57.67 (t), 61.83 (t), 64.75 (t), 129.31 (d), 130.35 (d), 131.04 (d), 139.65 (s), 175.27 (s) ppm. Anal. ($C_{14}H_{19}ClN_2O$) C, H, N.

The oily compound obtained was transformed into the hydrochloride; its chemical and physical characteristics are reported in Table 1.

In the same way **(±)-4-(*p*-fluorobenzyl)-1,4-diazabicyclo-[4.3.0]nonan-9-one (19)** was obtained, using *p*-fluorobenzyl bromide. Its chemical and physical characteristics are reported in Table 1.

exo-(±)-8-Methyl-1,4-diazabicyclo[4.3.0]nonan-9-one (21a). exo-(±)-4-Benzyl-8-methyl-1,4-diazabicyclo[4.3.0]nonan-9-one[23] (notice that in the cited paper the structures of the two isomers have been accidentally inverted; the actual structures are those shown by the X-ray crystallography, reported in the same paper) (0.110 g, 0.45 mmol) was hydrogenated over Pd/C 10% (0.06 g) in absolute ethanol at 47 psi for 12 h. After filtration, the solvent was removed under vacuum to give **21a** (98% yield) as an oil: IR (neat) ν 3300−3500 (NH), 1670 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (d, 3H, CH_3), 1.70−1.78 (m, 2H, CH), 2.24−2.58 (m, 3H, CH), 2.47 (bs, 1H, NH), 2.71−3.08 (m, 3H, CH), 3.47−3.56 (m, 1H, bridge CH), 3.89−3.97 (m, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$) δ 19.26 (q), 32.51 (t), 37.95 (d), 42.81 (t), 46.92 (t), 54.39 (t), 56.74 (d), 178.21 (s) ppm. Anal. ($C_8H_{14}N_2O$) C, H, N.

endo-(±)-8-Methyl-1,4-diazabicyclo[4.3.0]nonan-9-one (21b). endo-(±)-4-Benzyl-8-methyl-1,4-diazabicyclo[4.3.0]-nonan-9-one[23] was hydrogenated under the same conditions described for **21a**, to give **21b**, as an oil, in 95% yield: IR (neat) ν 3300−3500 (NH), 1670 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (d, 3H, CH_3), 2.18 (bs, 1H, NH), 2.23−2.56 (m, 4H, CH), 2.57−2.67 (m, 1H, CH), 2.74−2.92 (m, 1H, CH), 2.98−3.09 (m, 1H, CH), 3.15−3.23 (m, 1H, CH), 3.32−3.50 (m, 1H, bridge CH), 3.85−4.04 (m, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$) δ 18.71 (q), 34.25 (t), 37.85 (d), 42.57 (t), 46.72 (t), 55.27 (t), 56.28 (d), 177.78 (s) ppm. Anal. ($C_8H_{14}N_2O$) C, H, N.

General Procedure for the Synthesis of Acyl and Sulfonyl Derivatives (2−17). Acyl or sulfonyl chlorides (1 mmol) and $N(C_2H_5)_3$ (1.5 mmol) were added to the proper amine (**1**, **21a**, **21b**) dissolved in a few milliliters of anhydrous CH_3CN. After 2 h at room temperature, 50 mL of ether were added and the solution washed with H_2O. Evaporation under reduced pressure of the dried solvent gave solids that were purified by flash chromatography and crystallization from petroleum ether. Yields range from 60 to 95%. Chemical and physical characteristics of the compounds obtained are reported in Table 1. Their IR and ^1H NMR spectra are consistent with the proposed structures.

Pharmacology. Antiamnesic Test (passive-avoidance test). The test was performed according to the step-through method described by Jarvik and Kopp.[24] The apparatus consists of a two-compartment acrylic box with a lighted compartment connected to a darkened one by a guillotine door. In the original method, mice received a punishing electrical shock as soon as they entered the dark compartment, while in our modified method, after entry into the dark compartment, mice receive a nonpainful punishment consisting of a fall (from 40 cm) into a cold water bath (10 °C). For this purpose the dark chamber was constructed with a pitfall floor. The latency times for entering the dark compartment were measured in the training test (first day) and after 24 h in the retention test (second day). Mice who did not enter after 60 s latency were excluded from the experiment. For memory disruption, mice were ip injected with the amnesic drugs (scopolamine, mecamylamine, baclofen, and clonidine). All investigated drugs were injected 20 min before the training session, while amnesic drugs were injected immediately after termination of the training session. The maximum entry latency allowed in the retention session was 120 s. The memory degree of received punishment (fall into cold water)

was expressed as the increase in seconds between training and retention latencies.

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Supporting Information Available: Table 3 with NMR spectra of compounds **2**−**17** and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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