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Original article

Synthesis and cholinesterase activity of phenylcarbamates related to Rivastigmine, a therapeutic agent for Alzheimer's disease

Carlo Mustazza [a,*], Anna Borioni [a], Maria Rosaria Del Giudice [a], Franco Gatta [a], Rosella Ferretti [a], Annarita Meneguz [b], Maria Teresa Volpe [b], Paola Lorenzini [b]

[a] *Laboratorio di Chimica del Farmaco, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy*
[b] *Laboratorio di Farmacologia, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy*

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Abstract

In order to develop new cholinesterase agents effective against Alzheimer's disease (AD) we synthesized some phenylcarbamates structurally related to Rivastigmine and evaluated their in vitro and in vivo biological activity. Among the compounds which displayed the most significant in vitro activity, 1-[1-(3-dimethylcarbamoyloxyphenyl)ethyl]piperidine (**31b**), in addition to a simple and cheaper synthesis, showed lower toxicity and very similar therapeutic index in comparison with Rivastigmine. © 2002 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

Keywords: acetylcholinesterase inhibitors; Alzheimer's disease; rivastigmine; carbamates

1. Introduction

Alzheimer's disease (AD), one of the most diffuse neurodegenerative pathology among the elderly [1,2], causes a progressive impairment in functional performances and continuous reduction in cognitive activities and memory [3].

The loss of the basal forebrain cholinergic system is one of the most significant aspects of neurodegeneration in the brains of AD patients, and it is thought to play a central role in producing cognitive impairments [4–6].

Therefore, enhancement of cholinergic transmission has been regarded as one of the most promising methods for treating AD patients. Among the following possible strategies: use of acetylcholine precursors such as choline [7], acetylcholine releasing agents such as 4-aminopyridine [8], stimulation of acetylcholine reuptake [9], activation of cholinergic receptors (muscarinic and nicotinic) by synthetical agonists and, finally, lowering acetylcholine metabolic breakdown by inhibition of acetylcholinesterase (AChE), only the last approach was successful as yet to palliative treatment of AD.

The first anticholinesterase drug for AD, Tacrine (Cognex®) [10], suffered from bad though reversible liver toxicity and low bioavailability [11,12], but the new generation AChE inhibitors, Donezepil (Aricept®) [13,14], Rivastigmine (Exelon®) [15] and Galantamine (Reminyl®) [16], are endowed with a better pharmacological profile.

In addition, Rivastigmine showed interesting selectivity in the brain regions more affected by the neuronal degeneration, inhibiting AChE more potently in human cortex and hippocampus than in striatum and pons/medulla [17]. The drug resulted also more effective towards the monomeric form of the enzyme (G1), which is present in relatively higher concentration in these brain areas of AD patients [18,19].

However, Rivastigmine has a short half-life [20] and moreover, it is well known the difficulty of drug's intake in AD patients, so it would be wished to dispose

* Correspondence and reprints.
E-mail address: mustazza@iss.it (C. Mustazza).

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of drugs with longer half-life in order to obtain a better patients compliance.

Considering that Rivastigmine is usually administered to AD patients for long periods, the high cost of the drug is another considerable drawback. This is mainly due to the employment of the very expensive chemical intermediate *N*-ethyl-*N*-methylcarbamoyl chloride in its synthesis.

The template which led to the formulation of Rivastigmine was miotine, an AChE inhibitor which has been used in therapy only as a miotic and which is relatively unstable at physiologic pH [21]. A few carbamates related to miotine and Rivastigmine have been synthesized and their pharmacological properties explored [22,23], but no data are reported about structural modifications of the aminoalkyl moiety of the molecule.

On the basis of these findings and in connection with our present studies directed towards the search of new cholinesterase agents, we here describe the synthesis of some dimethyl, diethyl and *n*-hexylcarbamates related to Rivastigmine, containing a piperidine moiety instead of the dimethylamino group, in order to evaluate their in vitro an in vivo pharmacological properties and to investigate the effects of such structural modifications on activity (Fig. 1).

We chose the carbamic substituents on the basis of literature reports:

(i) dimethylcarbamates of structures related to miotine, are currently in use as AChE inhibitors; for instance pyridostigmine and neostigmine are employed in the treatment of the myasthenia gravis; besides the racemic dimethyl analogue of Rivastigmine is highly active in vitro though short lasting in vivo [23];

(ii) racemic diethylcarbamate analogue of Rivastigmine displays a low toxicity and a good therapeutic ratio [23];

(iii) *n*-hexyl derivatives were prepared as the introduction of a long lipophilic substituent in some AChE inhibiting compounds is reported to enhance their pharmacological properties (heptylphysostigmine [24], octyltacrine [25]).

2. Chemistry

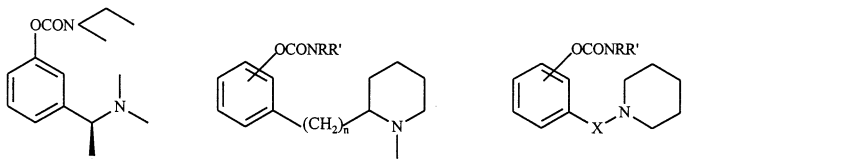
The synthetical pathways to compounds **1** are summarized in Fig. 2.

Compounds **1** ($n = 0$, Fig. 1) were synthesized starting from 6-(2- and 3-methoxyphenyl)-2-piperidones **4**, obtained according to a previously published procedure [26] by heating in formamide at 190–200 °C the corresponding 5-(2- and 3-methoxyphenyl)-5-oxovaleric acids.

Piperidones **4** were methylated by methyl iodide–sodium hydride in anhydrous dimethylformamide and the resulting *N*-methylpiperidones **5** were first reduced by lithium aluminum hydride to *N*-methylpiperidines **6**, then *O*-demethylated by refluxing in 48% hydrobromic acid to afford the 1-methyl-2-(2- and 3-hydroxyphenyl)piperidines **7**. These latter compounds were carbamoylated either by treatment in refluxing benzene with equimolar amount of *n*-hexyl isocyanate, to give compounds **8**, or by reaction with *N*,*N*-dimethyl- (and *N*,*N*-diethyl)-carbamoylchloride in pyridine to give compounds **9** and **10**.

The 2-[(2- and 3-methoxyphenyl)methyl]-pyridines **11**, prepared as reported in the literature [27,28] were the key intermediates for the synthesis of compounds **1** ($n = 1$, Fig. 1). By quaternizing the pyridine moiety with methyl iodide and reducing the corresponding pyridinium salts with sodium borohydride first, then with nickel–aluminum alloy in aq. 1 M potassium hydroxide solution [29], the desired 1-methyl-2-[(2- and 3-methoxyphenyl)methyl]piperidines **12** were obtained. The *O*-demethylation with 48% hydrobromic acid followed by the carbamoylation of the corresponding phenols **13** with *n*-hexyl isocyanate and *N*,*N*-dimethyl- (and *N*,*N*-diethyl)-carbamoylchloride to give compounds **14**, **15** and **16** were respectively accomplished by the procedure previously described.

Finally, the synthesis of compounds **1** ($n = 2$, Fig. 2) was achieved starting from the styrylquaternary salts **17** prepared by condensation of the appropriate anisaldehyde with 2-picoline methiodide [30]. The pyridinium iodides **17** were reduced to 1-methyl-2-[(2- and 3-methoxyphenyl)ethyl]piperidines **18** with sodium



Rivastigmine **1** n = 0,1,2 **2** X= –CH_2–, –$(CH_2)_2$–, –$CH(CH_3)$– R = H, R'= *n*–C_6H_{13}; R = R' = –CH_3; R = R' = –C_2H_5

Fig. 1. Structures of Rivastigmine and of the synthesized compounds.

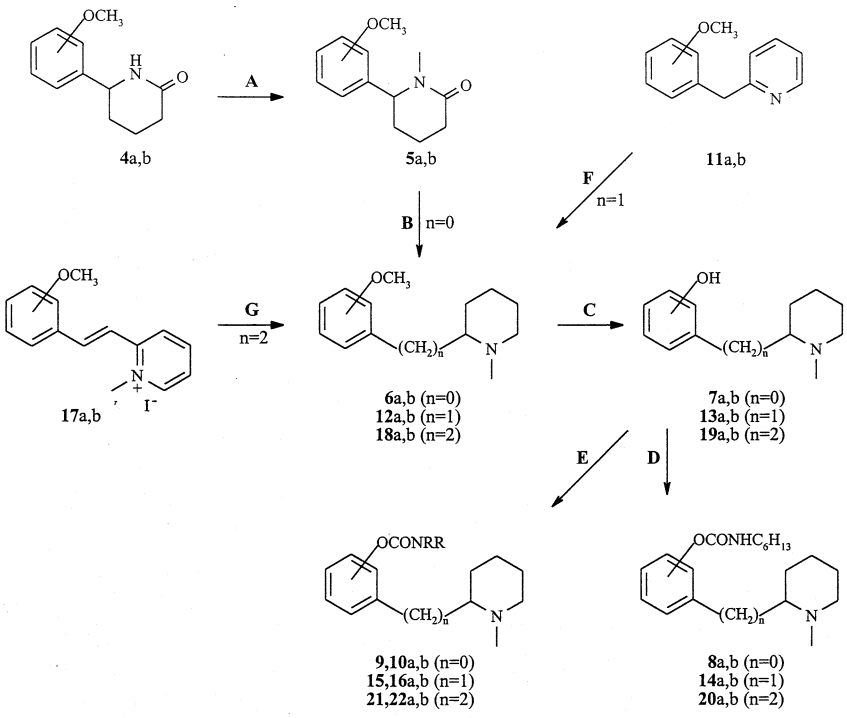


Fig. 2. Synthesis of 2-[(2- and 3-alkylcarbamoyloxyphenyl) and (2- and 3-alkylcarbamoyloxyphenyl)alkyl]-1-methylpiperidines.

borohydride and successively with nickel–aluminum alloy in the same manner as described for compounds **12**. *O*-demethylation and carbamoylation of the resulting phenols **19** proceeded as above described to give compounds **20**, **21** and **22**.

The synthesis of compounds **2** is outlined in Fig. 3.

Compounds **23** (X = –CH_2–) and **28** (X = –$CH(CH_3)$–) were synthesized by reaction of the appropriate benzyl chloride with piperidine, while compounds **33** (X = –$(CH_2)_2$–) were obtained by reduction with lithium aluminum hydride of the corresponding *N*-(phenylacetyl)piperidines. The *O*-demethylation to give phenols **24**, **29** and **34**, followed by their carbamoylation to give compounds **25**–**27**, **30**–**32** and **35**–**37** was accomplished in the same manner as reported for the preparation of compounds **1**.

The unusually low values of ortho spin–spin coupling constants in ^{1}H-NMR spectra values of carbamates **8**–**10a** are probably due to the steric hindrance of the substituents, which may cause a distortion of the benzene ring.

The chiral compounds were in vitro and in vivo tested as racemates. For a pharmacological evaluation of the pure enantiomers, studies are in progress to perform their separation by chiral preparative HPLC.

3. Pharmacology

Synthesized compounds were evaluated for in vitro inhibition of rat brain AChE and rat plasma butyrylcholinesterase (BuChE) by the spectroscopic method of Ellman [31] (Table 1). The approximate LD_{50} of the compounds that showed the most significant activity (IC_{50} for AChE < 100 nM), tested in vivo in mice after oral administration, are reported in Table 2, while the ED_{50} values and the time course of AChE of five

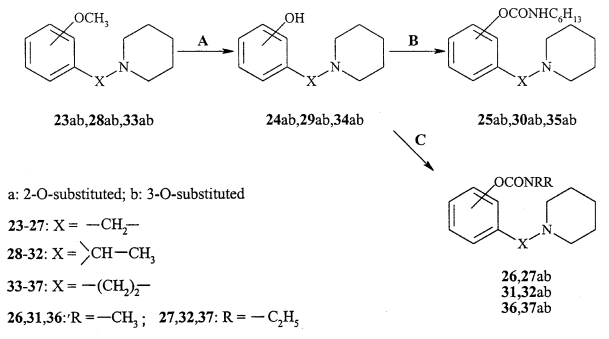
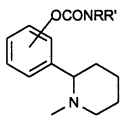
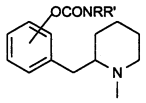
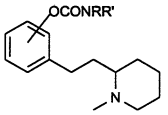
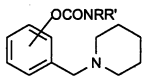
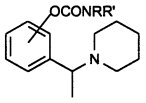
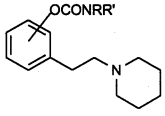


Fig. 3. Synthesis of 1-[(2- and 3-alkylcarbamoyloxyphenyl)alkyl]piperidines.

Table 1
In vitro inhibition of brain AChE and plasma BuChE by hexyl- and dimethylcarbamates

	Compound [a]		IC_{50} for AChE [b] (nM)	IC_{50} for BuChE [b] (nM)	S [c]
	Rivastigmine		>1000	>1000	–
8a		*ortho*	>1000	>1000	–
9a			47	540	11.5
8b		*meta*	>1000	856	1.5
9b			64	438	7.0
14a		*ortho*	970	>1000	–
15a			116	28	0.2
14b		*meta*	47	538	11.4
15b			14	124	8.9
20a		*ortho*	190	>1000	–
21a			102	103	1.0
20b		*meta*	70	232	3.3
21b			50	254	5.1
25a		*ortho*	>1000	>1000	–
26a			10	46	4.6
25b		*meta*	31	45	1.4
26b			32	83	2.6
30a		*ortho*	>1000	>1000	–
31a			16	38	2.4
30b		*meta*	13	16	1.2
31b			7	8	1.1
35a		*ortho*	350	>1000	–
36a			107	82	0.8
35b		*meta*	125	91	0.7
36b			40	93	2.3

[a] **8**, **14**, **20**, **25**, **30**, **35**: R=H, $R_1 = n\text{-}C_6H_{13}$; **9**, **15**, **21**, **26**, **31**, **36**: $R = R_1 = -CH_3$.
[b] Correlation coefficient was in all cases higher than 0.9.
[c] Selectivity calculated as IC50 for BuChE/IC50 for AChE.

selected compounds are reported in Table 3. For the most interesting compound **31b**, besides a BuChE time course, a comparison with Rivastigmine was performed by analysing:

- the time course of AChE inhibition in total brain (Fig. 4);
- the AChE inhibition in three different cerebral regions, cortex, hippocampus and striatum (Fig. 5);
- the in vitro and in vivo properties including effects on brain globular tetrameric (G4) and monomeric (G1) AChE molecular forms (Table 4).

No in vivo AChE inhibition was found for all selected hexylcarbamates.

4. Results and discussion

As it is shown in Table 1, dimethylcarbamates showed IC_{50} values ranging from 7 to 116 nM, unlike hexylcarbamates whose IC_{50} did not result in so sharp range (13 > 1000 nM), and showed a more selective activity for central AChE respect to peripheral BuChE.

None of the diethylcarbamates displayed an IC_{50} lower than 1000 nM and therefore, they were not further investigated.

Dimethylcarbamates showed a high activity for AChE when a methylene bridge was inserted across the piperidine moiety and the aromatic ring (compounds **15**, **26**, **31**); a comparison between the more powerful derivatives **26** and **31** points out that the introduction of a methyl substituent on the methylene bridge resulted in an enhancement of activity on both cholinesterases so that compound **31b**, whose structure is reminiscent of Rivastigmine, was the most potent inhibitor.

Varying the bridge across the piperidine and the aromatic ring reduced activity as it is shown by the IC_{50} of compounds **9** ($n = 0$, Table 1), **21** and **36** ($n = 2$, Table 1).

Hexylcarbamates tended to require the same structural features for activity enhancement as their dimethyl analogues; compound **30b** was indeed the most potent in the hexyl derivatives series with an $IC_{50} = 13$ nM for AChE and 16 nM for BuChE.

Table 2
AChE in vitro inhibition by carbamate derivatives and by Rivastigmine and corresponding approximate LD_{50}

Compound	IC_{50} [a] (nM)	LD_{50} [b] (mg kg^{-1})
9a	47	>25
9b	64	$25 < LD_{50} < 50$
14b	47	>50
15b	14	>50
20b	70	>50
21b	50	>50
25b	13	25
26a	10	>50
26b	31	$1 < LD_{50} < 5$
30b	13	>25
31a	15	>25
31b	7	>50
36b	40	>50
Rivastigmine	>1000	$3 < LD_{50} < 6$

[a] Correlation coefficient was in all cases higher than 0.9.
[b] Approximate LD_{50} was determined using a stepwise procedure. Each dose was administered to five mice.

Table 3
ED_{50} and time course of AChE inhibition by carbamate derivatives and by Rivastigmine

Compound	ED_{50} [a] (mg kg^{-1})	% inhibition [a]			
		0.5 h	1 h	2 h	3 h
9a	5.3 ± 0.3	60 ± 7.8	42.3 ± 8.4	8.3 ± 4.9	0
9b	8.0 ± 1.1	41.0 ± 12.5	40.3 ± 9.0	16.5 ± 4.9	9.0 ± 9.0
15b	9.5 ± 0.9	49.3 ± 5.5	44.7 ± 12.5	16.3 ± 4.0	2.0 ± 2.6
31a	11.6 ± 1.7	55.6 ± 5.5	53.0 ± 0.6	19.0 ± 5.7	7.0 ± 5.7
31b	6.5 ± 0.6	56.6 ± 8.2	43.0 ± 2.6	32.3 ± 4.6	14.7 ± 1.5
Rivastigmine	1.0 [b]	47.5 ± 3.1	54.0 ± 4.4	32.2 ± 7.6	13.8 ± 4.0

[a] The values are means ± SD of three independent experiments.
[b] Lit. [23].

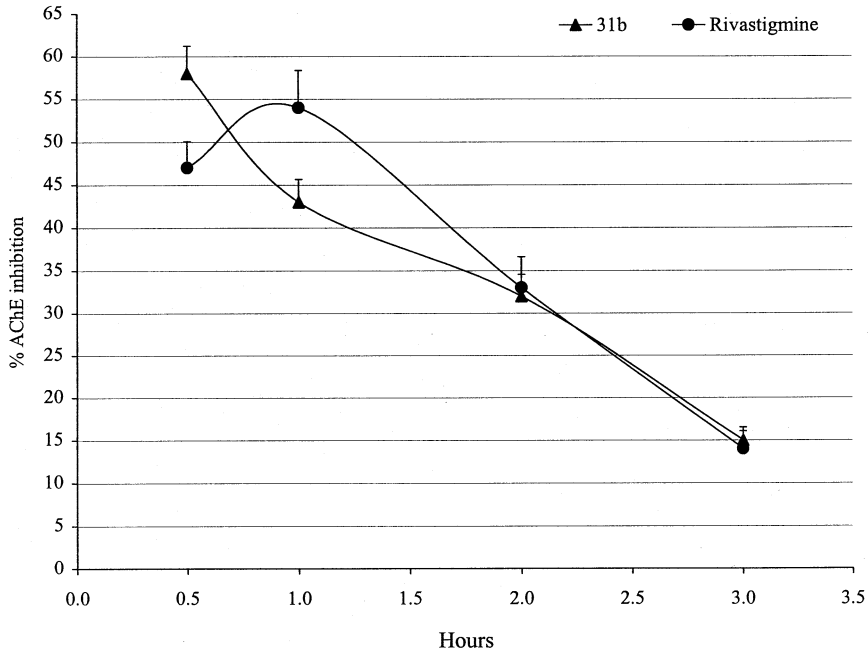


Fig. 4. Plot of observed time course of in vivo AChE inhibition.

The activity of long-chain carbamates strictly depends on the molecular shape and on the ability to reach a suitable conformation for inhibition. So, compact structures as **8a**,**b**, **14a**, **25a** and **30a** displayed a marked decrease of potency in comparison with the more flexible **20a**,**b**, **35a**,**b** derivatives and the less hindered **14b**, **25b** and **30b** compounds (Table 1).

The in vitro activity of carbamates seems to be related to the spatial distance between carbamic carbon and piperidine nitrogen atoms (C–N). For AChE interaction, such a distance is considered a characteristic parameter of each molecular structure depending on the conformational features.

In order to evaluate this geometric parameter, a conformational analysis has been performed on a HP computer with Chem-X (Chemical Design Ltd., July 97 version) molecular modelling software. Minimum energy conformations were determined by performing a systematic conformational search about rotable bonds at increment of 30° using MME calculations. Spatial C–N distances of the lowest energy conformations were related to IC_{50} values for dimethylcarbamates (Fig. 6), and hexylcarbamates (Fig. 7).

In the series of dimethyl derivatives the best activity was found when C–N distance values were 4.3 and 4.5 Å (compounds **31a** and **26a**) and 6.6 Å (compounds **15b** and **31b**).

Hexylcarbamates showed an optimum at 5.8 Å (**30b**), a strong decrease of potency for shorter and a gradual decrease of potency for longer C–N distances.

It should also be noted that similar activities correspond to different ranges of distances. This multiplicity suggests that our compounds inhibit the enzyme through a covalent or non-covalent mechanism which involves different binding sites [32]; moreover, in the case of ligands interacting with the esteratic site, it is

also possible that the inhibitor–enzyme adduct is stabilized by aminoacids situated at different distances from the esteratic serine [33].

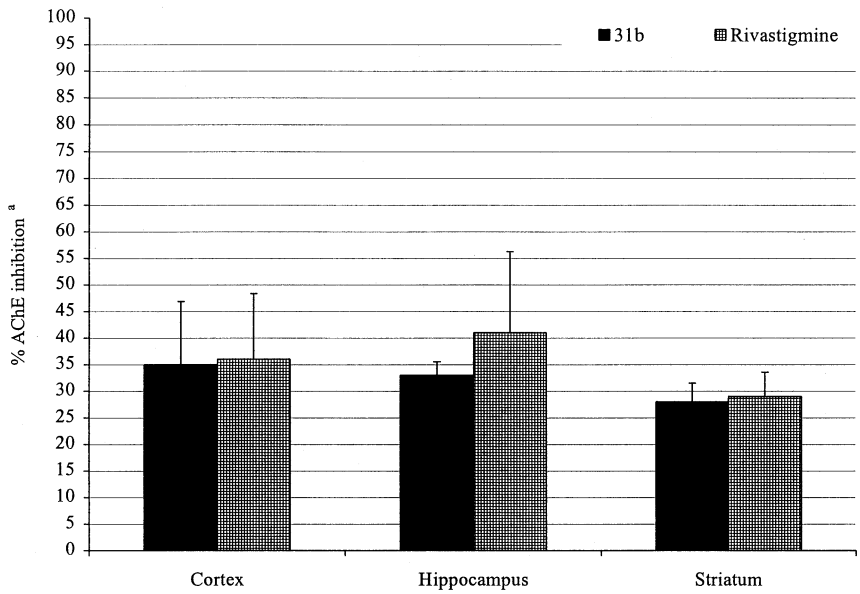
Compounds **31a** and **26a** whose C–N distances are 4.3 and 4.5 Å, could undergo a mechanism similar to that of acetylcholine, whose calculated C–N distance in the trans active conformation is 4.4 Å. These compounds may interact by the carbamic portion with serine esteratic locus (ES) and by the protonated aminic portion with the anionic locus (AS), 4.7 Å far from the esteratic site. Compounds **15b** and **31b**, binding the esteratic serine site, may instead extend towards the hydrophobic region which is at about 7 Å from ES [33].

On the contrary, C–N distance seems not to be a critical parameter for activity of hexylcarbamates; in vivo observation of typical symptoms of central cholinergic inhibition was not associated with enzyme inhibition in vivo tests. Therefore, we suppose that these compounds bind by a non-covalent interaction with AChE, as reported for similar structures attaching to the peripheral anionic site (PAS) of the enzyme about 20 Å far from ES [34]. This interaction could be easily lost during enzyme extraction from rat brain as reported previously for other reversible inhibitors [35,36].

On the basis of the affinity for AChE, selectivity and results of a preliminary screening, five compounds (**9a**, **9b**, **15b**, **31a**, and **31b**) were selected for in vivo activity studies.

As reported in Table 2, in comparison with Rivastigmine, their acute toxicity evaluated in mice, resulted relatively lower. Death of animals occurred from 30 min to a maximum of 3 h after dosing, and the observed clinical signs as mydriasis, tremor and fasciculation, were indicative of a cholinergic system alteration. However, peripheral cholinergic signs as sweating and salivation, were less evident or minimal, indicating a selective action on central nervous system.

The ED_{50} values for the five compounds range from 5.3 to 11.6 mg kg^{-1}, in comparison to 1 mg kg^{-1} for Rivastigmine [23], and the time course analysis of



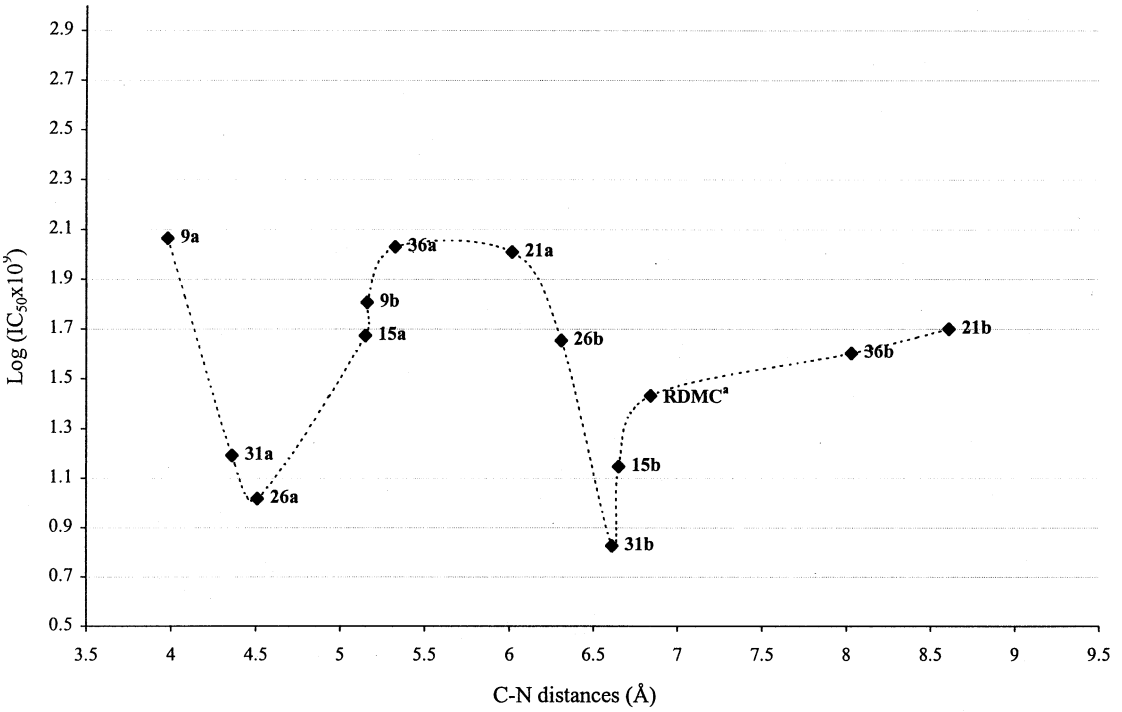
[a] The values are MEANS ± SD of four independent experiments.

Fig. 5. Inhibition of AChE activity by **31b** and Rivastigmine in different regions of mouse brain.

Table 4
Comparison of in vitro and in vivo data of **31b** and Rivastigmine

	IC_{50} [a] (nM)	G1 form IC_{50}[a] (μM)	G4 form IC_{50}[a] (μM)	G1/G4	LD_{50}[b] (mg kg^{-1})	ED_{50}[c] (mg kg^{-1})	T.I. LD_{50}/ED_{50}
31b	7	0.4 ± 0.1	0.2 ± 0.1	2	$25 < DL_{50} < 50$	6.5 ± 0.6	4–8
Rivastigmine	>1000	34 ± 0.5	3 ± 0.5	11	$3 < DL_{50} < 6$	1.0 [d]	3–6

[a] Correlation coefficient was in all cases higher than 0.9.
[b] Approximate LD_{50} was determined using a stepwise procedure. Each dose was administered to five mice.
[c] The values are means ± SD of three independent experiments.
[d] Lit. [23].



[a] The IC_{50} of racemic Rivastigmine analogue N,N-dimethyl-N-[1-(3-dimethylcarbamoyloxyphenyl)ethyl]amine (**RDMC**) is reported in the lit. [23].

Fig. 6. Inhibitory activity of *N*,*N*-dimethyl carbamates related to spatial C–N distance of the lowest energy conformation.

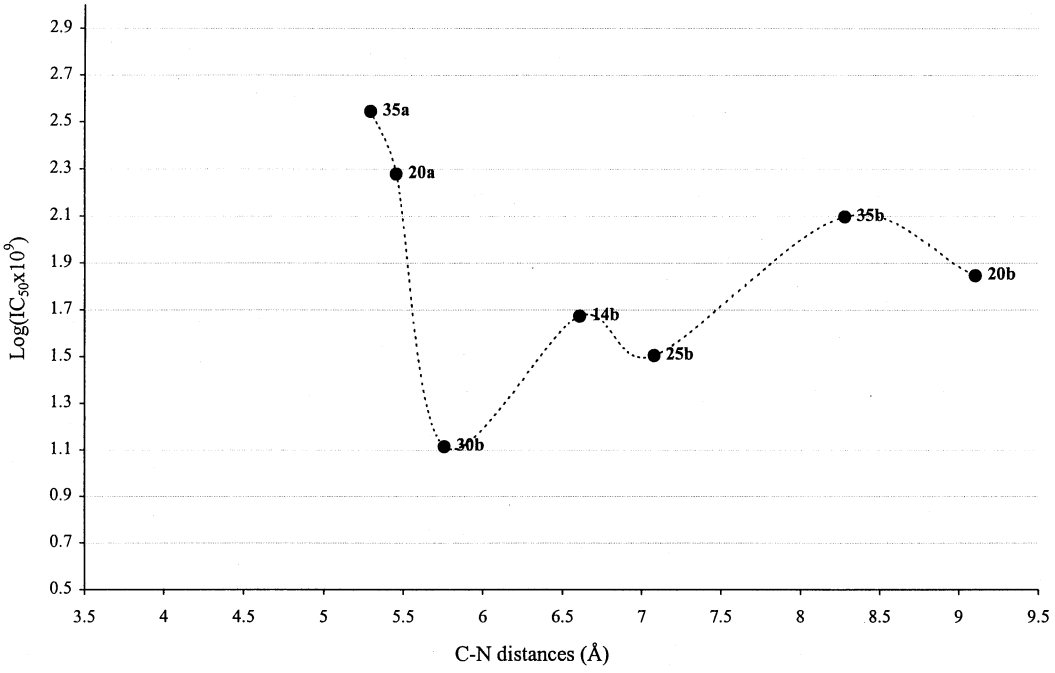


Fig. 7. Inhibitory activity of *n*-hexyl carbamates related to spatial C–N distance of the lowest energy conformation.

AChE inhibition, illustrated in Table 3, indicated a good absorption after oral administration with a maximum effect already present half an hour after treatment for all compounds. Compound **31b**, the most interesting synthesized derivative, like Rivastigmine, displayed significant AChE inhibition 2 h after dosing (about 30%) and 3 h after treatment still showed activity. The time course of BuChE inhibition was analyzed in mice

treated with **31b** at ED_{50} dose for brain AChE. BuChE inhibition resulted lower than AChE inhibition with a maximum effect (35%) at 0.5 h and a gradual decrease to 13%, 3 h after administration. These data seem to confirm a preferential activity of compound **31b** on the central nervous system.

Fig. 4 shows the AChE inhibition time course for **31b** and Rivastigmine at ED_{50} dose: half an hour after treatment the latter compound induced the highest inhibitory effect ($P < 0.05$) while Rivastigmine increased its effect during the first hour followed by a slower decrease of anticholinesterase activity.

Fig. 5 reports the values of in vivo AChE inhibition in cerebral cortex, hippocampus and striatum after oral **31b** and Rivastigmine administration in mouse. Both compounds caused a significant ($P < 0.01$) reduction of AChE activity in the three regions in treated animals, especially in cortex and hippocampus, while no anticholinesterasic effect was seen in cerebellum, a non-cholinergic region, (data not shown). There was a trend, but not statistically significant, of a more pronounced effect of Rivastigmine on hippocampus AChE. On the basis of these results **31b**, as already reported for Rivastigmine [19], seems to be able to induce a preferential inhibition of AChE in regions particularly relevant in situation of cholinergic impairment like AD.

It is well known that AChE can be separated into multiple molecular forms by means of their sedimentation coefficient in rodent and human brain [37–39], in which the bulk of AChE is the G4 (10S) and G1 (4S) forms. The evaluation of in vivo AChE molecular form patterns in the three cerebral regions of mice treated with **31b** and Rivastigmine, indicated that G4 and G1 profiles are the same in control and treated animals (data not shown). This result is not due to the lack of binding to AChE G4 and G1 active sites, but probably depends on the strength of the binding or on technical dilution problems. Enzyme dilution in connection with the time required for the separation (18 h), restores almost completely the anticholinesterase activity. These data are in agreement with those already published for Tacrine [35] and confirm that **31b** is a reversible inhibitor of AChE and interacts with active catalytic sites by weak bindings. This phenomenon was never observed using irreversible anticholinesterase compounds like diisopropylfluorophosphate [38].

Finally Table 4 illustrates the in vitro affinity of **31b** and Rivastigmine for AChE G1 and G4 molecular forms from mouse brain, and summarizes the comparison between the two compounds. Compound **31b**, like physostigmine [39], shows no significant differences in IC_{50} between G4 and G1 forms while Rivastigmine seems to induce a selective effect on G4 form. This result is different from published data which were obtained from experiments carried out on human brain AChE [17,19].

5. Conclusions

In summary, in vitro and in vivo studies have demonstrated that **31b** possesses a high affinity for brain AChE, a relatively low acute toxicity, an ED_{50} of 6.5 mg kg^{-1} and a therapeutic index (T.I. LD_{50}/ED_{50}) ranging from 4 to 8. Moreover, it is well absorbed after oral administration and produces a consistent and selective inhibition of AChE in brain areas where the cholinergic impairment is particularly evident in AD. Finally **31b** binds to both AChE molecular forms, though in a non-selective manner, and at the ED_{50} dose produces minimal peripheral cholinesterase inhibition and clinical signs.

So far, **31b** appears a suitable anticholinesterase agent for further pharmacological investigations in order to test its ability to improve memory and cognitive functions, especially taking into account that its synthesis is very simple and cheap, aspect particularly relevant for the treatment of AD very often associated with a considerable cost burden [40].

6. Experimental

6.1. Chemistry

Melting point (m.p.) were taken on a Köfler hot stage apparatus and are uncorrected. The ^{1}H-NMR spectra were obtained on a Varian Gemini 200 MHz instrument; all values were reported in ppm (δ) and standard abbreviations were used (a, apparent; b, broad; d, doublet; dd, doublet of doublets; m, multiplet; q, quadruplet; s, singlet; t, triplet); assignments were also based on ^{1}H-COSY experiments; electron ionization mass spectra were recorded on a HP 59980 B spectrometer operating at 70 eV.

Column chromatographic separations were accomplished on Merck silica gel (70–230 mesh) or on Merck aluminium oxide 90.

The purity of each compound was checked on silica gel C. Erba 60 F_{254} or Merck aluminium oxide 60 F_{254} (type E) plates and spots were located by UV light. Sodium sulphate was used to dry organic solutions.

Analyses indicated by the symbols of the elements were within $\pm 0.4\%$ of the theoretical values.

The synthesis of **11a** [27], **11b** [28], **23a** and **23b** [41], has been reported elsewhere.

6.1.1. General procedure for the preparation of 6-(2- and 3-methoxyphenyl)-2-piperidones (4)

These compounds were prepared starting from ethyl 3-(2- and 3-methoxyphenyl)-3-oxopropionates. The 2-methoxy derivative was obtained in the same manner as the known 3-methoxy compound [42], and had b.p. = 121–122 °C/0.3 Torr, 72%. Anal. $C_{12}H_{14}O_4$ (C, H)

Ketoesters were monocyanoethylated as reported in the literature [43] to afford the ethyl 2-(2-cyanoethyl)-3-(2-methoxyphenyl)-3-oxopropionate (oil, 55%) and the corresponding 3-methoxyphenyl derivative (oil, 88%), which were purified by silica gel column chromatography, by eluting with a 1:3 EtOAc–n-C_6H_{14} mixture. The latter compounds were hydrolyzed in a 1:3:1 sulphuric acid–acetic acid–water mixture according to a literature method [43], to afford the 5-(2-methoxyphenyl)-5-oxovaleric acid (m.p. = 63–65 °C, EtOAc, 84%. Anal. $C_{12}H_{14}O_4$ (C, H)) and the 5-(3-methoxyphenyl)-5-oxovaleric acid (m.p. = 87–89 °C, EtOAc, 63%. Anal. $C_{12}H_{14}O_4$ (C, H)), respectively. Cyclization to 2-piperidones **4** was carried out by heating the oxoacids in formamide at 190–200 °C, according to a previously described procedure [26].

*6.1.1.1. 6-(2-Methoxyphenyl)-2-piperidone (**4a**).* Compound **4a** was obtained in 80% yield, m.p. 165–167 °C (EtOAc) (lit. [26] m.p. 148–155 °C). ^{1}H-NMR ($CDCl_3$): δ 7.26 (d, 1H, H-6′, $J_{ortho} = 7.6$ Hz), 7.24 (t, 1H, H-4′, $J_{ortho} = 7.4$ Hz), 6.94 (t, 1H, H-5′, $J_{ortho} = 7.4$ Hz), 6.85 (d, 1H, H-3′, $J_{ortho} = 7.5$ Hz), 5.97 (s, 1H, NH), 4.92 (bt, 1H, H-6, $J_{vic} = 6.0$ Hz), 3.81 (s, 3H, OCH_3), 2.40 (t, 2H, H-3, $J_{vic} = 6.5$ Hz), 2.07 (m, 1H, H-5_{eq}), 1.84–1.58 (m, 3H, H-4 and H-5_{ax}); MS: m/z: 205 [M^+], 177, 146, 134. Anal. $C_{12}H_{15}NO_2$ (C, H, N).

*6.1.1.2. 6-(3-Methoxyphenyl)-2-piperidone (**4b**).* Compound **4b** was obtained in 76% yield, m.p. 105–107 °C (EtOAc); ^{1}H-NMR (DMSO-d_6): δ 7.73 (s, 1H, NH), 7.25 (t, 1H, H-5′, $J_{ortho} = 7.5$ Hz), 6.83 (overlapped doublets, 2H, H-4′ and H-6′, $J_{ortho} = 7.5$ Hz), 6.81 (d, 1H, H-2′, $J_{meta} = 3.1$ Hz), 4.46 (bt, 1H, H-6, $J_{vic} = 6.0$ Hz), 3.74 (s, 3H, OCH_3), 2.20 (bt, 2H, H-3, $J_{vic} = 6.7$ Hz), 1.95 (m, 1H, H-5eq), 1.61 (m, 3H, H-4 and H-5ax); MS: m/z 205 [M^+], 174, 149, 134. Anal. $C_{12}H_{15}NO_2$ (C, H, N).

*6.1.2. General procedure for the preparation of 6-(2- and 3-methoxyphenyl)-1-methyl-2-piperidones (**5**)*

To a stirred suspension of NaH (2.5 g of 60% oil dispersion, 50 mmol) in anhydrous dimethylformamide (100 mL) each compound **4** (8.0 g, 42 mmol) was added in several portions. After 1 h stirring at room temperature (r.t.), MeI (3.2 mL, 51 mmol) was dropwise added and the reaction mixture stirred for 1 h at r.t. The inorganic salts were then filtered, the filtrate evaporated to dryness and the residue purified by column chromatography on silica gel, by eluting with EtOAc.

*6.1.2.1. 6-(2-Methoxyphenyl)-1-methyl-2-piperidone (**5a**).* Compound **5a** was obtained as an oil in 94% yield, ^{1}H-NMR ($CDCl_3$): δ 7.24 (dt, 1H, H-4′, $J_{ortho} = 8.0$ Hz, $J_{meta} = 2.5$ Hz), 6.96 (m, 2H, H-5′ and H-6′), 6.87 (d, 1H, H-3′, $J_{ortho} = 8.0$ Hz), 4.88 (q, 1H, H-6, $J_{5ax,6} = 5.6$ Hz, $J_{5eq,6} = 3.7$ Hz), 3.83 (s, 3H, OCH_3), 2.78 (s, 3H, N–CH_3), 2.44 (m, 2H, H-3), 2.02 (m, 1H, H-5eq), 1.90 (m, 1H, H-5ax), 1.63 (m, 2H, H-4); MS: m/z 219 [M^+], 204, 190, 148. Anal. $C_{13}H_{17}NO_2$ (C, H, N).

*6.1.2.2. 6-(3-Methoxyphenyl)-1-methyl-2-piperidone (**5b**).* Compound **5b** was obtained in 94% yield, m.p. 60–62 °C (C_6H_6–n-C_6H_{14}); ^{1}H-NMR (DMSO-d_6): δ 7.28 (t, 1H, H-5′, $J_{ortho} = 8.1$ Hz), 6.84 (dd, 1H, H-4′, $J_{ortho} = 8.1$ Hz, $J_{meta} = 2.2$ Hz), 6.73 (d, 1H, H-6′, $J_{ortho} = 8.1$ Hz), 6.70 (d, 1H, H-2′, $J_{meta} = 2.2$ Hz), 4.55 (t, 1H, H-6, $J_{vic} = 5.2$ Hz), 3.74 (s, 3H, OCH_3), 2.62 (s, 3H, N–CH_3), 2.33 (m, 2H, H-3), 2.07 (m, 1H, H-5eq), 1.74 (m, 1H, H-5ax), 1.56 (m, 2H, H-4); MS: m/z 219 [M^+], 204, 190, 148, 112. Anal. $C_{13}H_{17}NO_2$ (C, H, N).

*6.1.3. General procedure for the preparation of 2-(2- and 3-methoxyphenyl)-1-methylpiperidines (**6**)*

A solution of each compound **5** (8.0 g, 39 mmol) in anhydrous Et_2O (80 mL) was added dropwise under stirring and at r.t. to a suspension of $LiAlH_4$ (2.0 g, 53 mmol) in anhydrous Et_2O (60 mL). The mixture was allowed to react for 2 h, then cooled in an ice–water bath and treated with 20% aq. NaOH (5 mL). The precipitated hydroxides were removed by filtration and rinsed thoroughly with Et_2O. The solvent was evaporated to dryness and the crude products **6** were purified by column chromatography on Al_2O_3 by eluting with EtOAc.

*6.1.3.1. 2-(2-Methoxyphenyl)-1-methylpiperidine (**6a**).* Compound **6a** was obtained as an oil in 64% yield, b.p. 120–123 °C/0.3 Torr (hydrochloride lit. [44] m.p. 147 °C); ^{1}H-NMR ($CDCl_3$): δ 7.45 (dd, 1H, H-6′, $J_{ortho} = 7.5$ Hz, $J_{meta} = 1.7$ Hz), 7.19 (dt, 1H, H-4′, $J_{ortho} = 7.5$ Hz, $J_{meta} = 1.8$ Hz), 6.96 (t, 1H, H-5′, $J_{ortho} = 7.5$ Hz), 6.86 (d, 1H, H-3′, $J_{ortho} = 7.8$ Hz), 3.82 (s, 3H, OCH_3), 3.38 (dd, 1H, H-2, $J_{2,3ax} = 10.4$ Hz, $J_{2,3eq} = 2,4$ Hz), 3.05 (dt, 1H, H-6eq, $J_{gem} = 10.0$ Hz), 2.15 (m, 1H, H-6ax), 2.02 (s, 3H, N–CH_3), 1.74 (m, 4H, H-5 and H-4), 1.47 (m, 2H, H-3); MS: m/z 205 [M^+], 174, 167, 149. Anal. $C_{13}H_{19}NO$ (C, H, N).

*6.1.3.2. 2-(3-Methoxyphenyl)-1-methylpiperidine (**6b**).* Compound **6b** was obtained as an oil in 75% yield, b.p. 140–143 °C/0.3 Torr; ^{1}H-NMR ($CDCl_3$): δ 7.20 (t, 1H, H-5′, $J_{ortho} = 8.2$ Hz), 6.88 (d, 1H, H-6′, $J_{ortho} = 8.0$ Hz), 6.86 (s, 1H, H-2′), 6.75 (d, 1H, H-4′, $J_{ortho} = 8.2$ Hz), 3.79 (s, 3H, OCH_3), 3.01 (ad, 1H, H-6eq, $J_{gem} =$ 11.3 Hz), 2.71 (dd, 1H, H-2, $J_{2,3ax} = 10.4$ Hz, $J_{2,3eq} =$ 3.1 Hz), 2.08 (m, 1H, H-6ax), 1.99 (s, 3H, N–CH_3), 1.69 (m, 4H, H-3eq, H-4eq and H-5), 1.53 (m, 1H, H-3ax), 1.36 (m, 1H, H-4ax); MS: m/z 205 [M^+], 190, 164, 150, 134, 98. Anal. $C_{13}H_{19}NO$ (C, H, N).

*6.1.4. General procedure for the preparation of 2-[(2-and 3-methoxyphenyl)methyl]-1-methylpiperidines (**12**)*

A solution of each compound **11** [27,28] (9.9 g, 50 mmol) and MeI (9.3 mL, 149 mmol) in MeOH (50 mL) was heated to reflux for 3 h. The solvent was evaporated in vacuo and the residue, dissolved in water (200 mL), was treated with $NaBH_4$ (2.0 g, 53 mmol) added in small portions at r.t. The reaction mixture, monitored by TLC on Al_2O_3 (1:2 EtOAc–*n*-C_6H_{14} mixture), was stirred at r.t. for about 2 h, then cooled in an ice–water bath. Potassium hydroxide in pellets (11 g. 196 mmol) was carefully added, then the mixture was heated while stirring at 60 °C. Nickel–Al alloy (20 g) was added in portions over 1 h. After about 3 h at 60 °C, TLC showed that the reaction had gone to completion so the mixture was filtered. The inorganic solid residue and the filtrate were thoroughly extracted with EtOAc. The organic phase was separated, washed with water, dried and concentrated to afford a yellow–brown oil, which was distilled.

*6.1.4.1. 2-[(2-Methoxyphenyl)methyl]-1-methylpiperidine (**12a**).* Compound **12a** was obtained as an oil in 70% yield; b.p. 110–112 °C/0.01 Torr; ^{1}H-NMR ($CDCl_3$): δ 7.17 (dt, 1H, H-4′, $J_{ortho} = 7.6$ Hz, $J_{meta} = 1.6$ Hz), 7.08 (dd, 1H, H-6′, $J_{ortho} = 7.5$ Hz, $J_{meta} = 1.6$ Hz), 6.84 (t and d, 2H, H-5′, $J_{ortho} = 7.4$ Hz and H-3′, $J_{ortho} = 8.4$ Hz), 3.79 (s, 3H, OCH_3), 3.23 (dd, 1H, benzylic CH_2, $J_{gem} = 12.4$ Hz, $J_{vic} = 3.4$ Hz), 2.83 (bd, 1H, H-6eq, $J_{gem} = 10.5$ Hz), 2.41 (s, 3H, N–CH_3), 2.34 (dd, 1H, benzylic CH_2, $J_{gem} = 12.5$ Hz, $J_{vic} = 2.4$ Hz), 2.13 (m, 2H, H-2 and H-6ax), 1.70–1.00 (m, 6H, H-3, H-5 and H-4); MS: *m*/*z* 219 [M^+], 198, 183, 167, 154, 121. Anal. $C_{14}H_{21}NO$ (C, H, N).

*6.1.4.2. 2-[(3-Methoxyphenyl)methyl]-1-methylpiperidine (**12b**).* Compound **12b** was obtained in 68% yield, b.p. 95–98 °C/0.01 Torr (lit. [28]: 102 °C/0.04 Torr); ^{1}H-NMR ($CDCl_3$): δ 7.17 (t, 1H, H-5′, $J_{ortho} = 7.6$ Hz), 6.73 (d, 1H, H-4′, $J_{ortho} = 7.6$ Hz), 6.72 (d, 1H, H-6′, $J_{ortho} = 7.6$ Hz), 6.69 (s, 1H, H-2′), 3.77 (s, 3H, OCH_3), 3.15 (dd, 1H, benzylic CH_2, $J_{gem} = 12.9$ Hz, $J_{vic} = 3.9$ Hz), 2.83 (bd, 1H, H-6eq, $J_{gem} = 10.5$ Hz), 2.38 (s, 3H, N–CH_3), 2.29 (dd, 1H, benzylic CH_2, $J_{gem} = 12.9$ Hz, $J_{vic} = 3.1$ Hz), 2.12 (m, 2H, H-2 and H-6ax), 1.70–1.00 (m, 6H, H-3, H-5 and H-4); MS: *m*/*z* 219 [M^+], 218, 198, 183, 154, 121. Anal. $C_{14}H_{21}NO$ (C, H, N).

*6.1.5. General procedure for the preparation of 2-[2-(2-and 3-methoxyphenyl)ethenyl]pyridine methiodides (**17**)*

These compounds were synthesized according to a method reported in the lit. [30].

*6.1.5.1. 2-[2-(2-Methoxyphenyl)ethenyl]pyridine methiodide (**17a**).* Compound **17a** was obtained in 74% yield, m.p. 212–214 °C (dimethylformamide); MS: *m*/*z* 226 [$M^+ - 127$], 211, 180, 127. Anal. $C_{15}H_{16}INO$ (C, H, N).

*6.1.5.2. 2-[2-(3-Methoxyphenyl)ethenyl]pyridine methiodide (**17b**).* Compound **17b** was obtained in 69% yield, m.p. 256–257 °C (dimethylformamide); MS: *m*/*z* 226 [$M^+ - 127$], 211, 180, 142, 127. Anal. $C_{15}H_{16}INO$ (C, H, N).

*6.1.6. General procedure for the preparation of 2-[2-(2-and 3-methoxyphenyl)ethyl]-1-methylpiperidines (**18**)*

To a suspension of each compound **17** (10 g, 28 mmol) in MeOH (80 mL), $NaBH_4$ (1.1 g, 29 mmol) was added in portions while stirring at 0–5 °C, then the mixture was stirred for 2 h at 50–60 °C. After cooling, water (200 mL) was added and the mixture extracted with EtOAc. Removal of the solvent gave an oil which was dissolved in a 1:1 mixture of EtOH and 1 M aq. KOH (200 mL) heated at 60 °C. Nickel–Al alloy (20 g) was carefully added in portions during 1 h. The reaction mixture was then stirred overnight at 60 °C, whereupon TLC on Al_2O_3 (1:1 EtOAc–*n*-C_6H_{14} mixture) indicated that the reduction was complete. The suspension was filtered while still hot and the inorganic solid was rinsed with hot EtOH. Ethanol was evaporated from the mixture under reduced pressure and the resulting aq. suspension was extracted with CH_2Cl_2. Removal of the solvent afforded an oily residue which was distilled.

*6.1.6.1. 2-[2-(2-Methoxyphenyl)ethyl]-1-methylpiperidine (**18a**).* Compound **18a** was obtained in 72% yield, b.p. 111–114 °C/0.01 Torr (lit. [45] hydroiodide m.p. 146–147 °C); ^{1}H-NMR ($CDCl_3$): δ 7.15 (t, 1H, H-4′, $J_{ortho} = 7.7$ Hz), 7.13 (d, 1H, H-6′, $J_{ortho} = 7.7$ Hz), 6.86 (t, 1H, H-5′, $J_{ortho} = 7.8$ Hz), 6.82 (d, 1H, H-3′, $J_{ortho} = 7.8$ Hz), 3.80 (s, 3H, OCH_3), 2.85 (bd, 1H, H-6eq, $J_{gem} = 10.6$ Hz), 2.63 (m, 2H, benzylic CH_2), 2.28 (s, 3H, N–CH_3), 2.06 (m, 1H, H-6ax), 1.82 (m, 2H, piperidine–CH_2), 1.80–1.10 (m, 7H, H-2, H-5, H-3 and H-4); MS: *m*/*z* 233 [M^+], 218. Anal. $C_{15}H_{23}NO$ (C, H, N).

*6.1.6.2. 2-[2-(3-Methoxyphenyl)ethyl]-1-methylpiperidine (**18b**).* Compound **18b** was obtained in 66% yield, b.p. 125–127 °C/0.01 Torr; ^{1}H-NMR ($CDCl_3$): δ 7.18 (t, 1H, H-5′, $J_{ortho} = 7.8$ Hz), 6.76 (d, 1H, H-4′, $J_{ortho} = 7.8$ Hz), 6.73 (s, 1H, H-2′), 6.70 (d, 1H, H-6′, $J_{ortho} = 7.8$ Hz), 3.76 (s, 3H, OCH_3), 2.84 (bd, 1H, H-6eq, $J_{gem} = 10.7$ Hz), 2.60 (m, 2H, benzylic CH_2), 2.26 (s, 3H, N–CH_3), 2.06 (m, 1H, H-6ax), 1.80 (m, 2H, piperidine–CH_2), 1.80–1.10 (m, 7H, H-2, H-3, H-4 and H-5); MS: *m*/*z* 233 [M^+], 218. Anal. $C_{15}H_{23}NO$ (C, H, N).

*6.1.7. General procedure for the preparation of 1-[1-(2- and 3-methoxyphenyl)ethyl]piperidines (**28**)*

These compounds were synthesized by heating at 50 °C overnight a mixture of piperidine (9.9 mL, 100 mmol) and 1-chloro-1-(2-methoxyphenyl)ethane [46] (to obtain **28a**) or 1-chloro-1-(3-methoxyphenyl)ethane [47] (to obtain **28b**) (50 mmol). The reaction mixture was treated with 1 M HCl and Et_2O, shacked, the aq. layer separated, alkalinized with K_2CO_3, then extracted with Et_2O. The solvent was evaporated and the residue distilled.

*6.1.7.1. 1-[1-(2-Methoxyphenyl)ethyl]piperidine (**28a**).* Compound **28a** was obtained in 41% yield, b.p. 90–92 °C/0.01 Torr; ^{1}H-NMR ($CDCl_3$): δ 7.16 (t, 1H, H-4′, $J_{ortho} = 7.5$ Hz), 7.11 (d, 1H, H-6′, $J_{ortho} = 7.6$ Hz), 6.85 (t, 1H, H-5′, $J_{ortho} = 7.6$ Hz), 6.81 (d, 1H, H-3′, $J_{ortho} = 7.5$ Hz), 3.79 (s, 3H, OCH_3), 3.57 (q, 1H, C*H*–CH_3, $J_{vic} = 6.9$ Hz), 2.32 (m, 4H, H-2 and H-6), 1.47 (m, 4H, H-3 and H-5), 1.37 (m, 2H, H-4), 1.33 (d, 3H, CH–C*H*$_3$, $J_{vic} = 6.9$ Hz); MS: m/z 219 [M^+], 204. Anal. $C_{14}H_{21}NO$ (C, H, N).

*6.1.7.2. 1-[1-(3-Methoxyphenyl)ethyl]piperidine (**28b**).* Compound **28b** was obtained in 70% yield, b.p. 110–112 °C/0.01 Torr; ^{1}H-NMR ($CDCl_3$): δ 7.19 (t, 1H, H-5′, $J_{ortho} = 7.8$ Hz), 6.78 (d, 1H, H-4′, $J_{ortho} = 7.8$ Hz), 6.73 (s, 1H, H-2′), 6.69 (d, 1H, H-6′, $J_{ortho} = 7.8$ Hz), 3.77 (s, 3H, OCH_3), 3.37 (q, 1H, C*H*–CH_3, $J_{vic} = 6.9$ Hz), 2.35 (m, 4H, H-2 and H-6), 1.52 (m, 4H, H-3 and H-5), 1.40 (m, 2H, H-4), 1.33 (d, 3H, CH–C*H*$_3$, $J_{vic} = 6.9$ Hz); MS: m/z 219 [M^+], 204. Anal. $C_{14}H_{21}NO$ (C, H, N).

*6.1.8. General procedure for the preparation of 1-[2-(2- and 3-methoxyphenyl)ethyl]piperidines (**33**)*

The *N*-(2- and 3-methoxyphenylacetyl)piperidines were obtained by adding dropwise a solution of the corresponding phenylacetyl chloride (10 g, 55 mmol) in anhydrous Et_2O (50 mL) to a cooled and stirred solution of piperidine (12 mL, 120 mmol) in anhydrous Et_2O (50 mL). After 6 h stirring at r.t., water was added. The organic phase was separated, washed with diluted HCl and water, then evaporated and the residue distilled.

N-(2-Methoxyphenylacetyl)piperidine was obtained in 79% yield, b.p. 140–142 °C/0.01 Torr. Anal. $C_{14}H_{19}NO_2$ (C, H, N).

N-(3-Methoxyphenylacetyl)piperidine was obtained in 56% yield, b.p. 133–135 °C/0.01 Torr (lit. [48] 166–168 °C/0.2 Torr). Anal. $C_{14}H_{19}NO_2$ (C, H, N).

The above amides were reduced with $LiAlH_4$ according to the procedure described for compounds **6**.

*6.1.8.1. 1-[2-(2-methoxyphenyl)ethyl]piperidine (**33a**).* Compound **33a** was obtained in 80% yield, b.p. 110–115 °C/0.01 Torr; ^{1}H-NMR ($CDCl_3$): δ 7.16 (m, 2H, H-4′ and H-6′), 6.85 (m, 2H, H-5′ and H-3′), 3.80 (s, 3H, OCH_3), 2.86–2.77 (m, 2H, benzylic CH_2), 2.53–2.44 (m, 6H, piperidine–CH_2, H-2 and H-6), 1.61 (m, 4H, H-3 and H-5), 1.44 (m, 2H, H-4); MS: m/z 219 [M^+], 217, 190, 134, 121. Anal. $C_{14}H_{21}NO$ (C, H, N).

*6.1.8.2. 1-[2-(3-Methoxyphenyl)ethyl]piperidine (**33b**).* Compound **33b** was obtained in 80% yield, b.p. 105–110/0.01 Torr; ^{1}H-NMR ($CDCl_3$): δ 7.10 (t, 1H, H-5′ $J_{ortho} = 7.6$ Hz), 6.76 (d, 1H, H-4′, $J_{ortho} = 7.6$ Hz), 6.73 (s, 1H, H-2′), 6.70 (d, 1H, H-6′, $J_{ortho} = 7.6$ Hz), 3.78 (s, 3H, OCH_3), 2.77 (m, 2H, benzylic CH_2), 2.53 (m, 2H, piperidine–CH_2), 2.43 (m, 4H, H-2 and H-6), 1.59 (m, 4H, H-3 and H-5), 1.43 (m, 2H, H-4); MS: m/z 219 [M^+], 190, 152, 134, 121. Anal. $C_{14}H_{21}NO$ (C, H, N).

*6.1.9. General procedure for the preparation of phenol derivatives **7**, **13**, **19**, **24**, **29**,**34***

A solution of each methoxyderivative **6**, **12**, **18**, **23**, **28** **33** (10 g) in 48% hydrobromic acid (80 mL), was heated at 125 °C for 3 h. The hydrobromic acid was evaporated at reduced pressure and the residue, made alkaline with aq. K_2CO_3 solution, was extracted with EtOAc. Removal of the solvent gave a residue, which upon chromatography over Al_2O_3 (EtOAc) afforded the pure title compounds.

*6.1.9.1. 2-(2-Hydroxyphenyl)-1-methylpiperidine (**7a**).* Compound **7a** was obtained as an oil in 75% yield; ^{1}H-NMR ($CDCl_3$): δ 11.00 (bs, 1H, OH), 7.14 (dt, 1H, H-4′, $J_{ortho} = 8.0$ Hz, $J_{meta} = 1.8$ Hz), 6.91 (dd, 1H, H-6′, $J_{ortho} = 7.4$ Hz, $J_{meta} = 1.8$ Hz), 6.77 (m, 2H, H-3′ and H-5′), 3.03 (m, 2H, H-2 and H-6eq), 2.19 (s, 3H, N–CH_3), 2.09 (m, 1H, H-6ax), 1.73 (m, 5H, H-4, H-5 and H-3eq), 1.30 (m, 1H, H-3ax); MS: m/z 191 [M^+], 162, 148, 134, 120, 98. Anal. $C_{12}H_{17}NO$ (C, H, N).

*6.1.9.2. 2-(3-Hydroxyphenyl)-1-methylpiperidine (**7b**).* Compound **7b** was obtained in 80% yield, m.p. 144–145 °C (EtOAc); (lit. [39] hydrobromide hemihydrate m.p. 60 °C); ^{1}H-NMR ($CDCl_3$): δ 7.32 (bs, 1H, OH), 7.13 (t, 1H, H-5′, $J_{ortho} = 7.9$ Hz), 6.97 (s, 1H, H-2′), 6.77 (d, 1H, H-6′, $J_{ortho} = 7.9$ Hz), 6.76 (d, 1H, H-4′, $J_{ortho} = 8.0$ Hz), 3.10 (bd, 1H, H-6eq, $J_{gem} = 11.5$ Hz), 2.84 (t, 1H, H-2, $J_{vic} = 6.9$ Hz), 2.18 (dt, 1H, H-6ax, $J_{gem} = 11.5$ Hz, $J_{6ax,5ax} = 11.0$ Hz, $J_{6ax,5eq} = 2.8$ Hz), 2.05 (s, 3H, N–CH_3), 1.70 (m, 5H, H-3, H-4eq and H-5), 1.41 (m, 1H, H-4ax); MS: m/z 191 [M^+], 162, 148, 134, 98. Anal. $C_{12}H_{17}NO$ (C, H, N).

*6.1.9.3. 2-[(2-Hydroxyphenyl)methyl]-1-methylpiperidine (**13a**).* Compound **13a** was obtained in 71% yield, m.p. 109–110 °C (EtOAc); ^{1}H-NMR ($CDCl_3$): δ 7.34 (bs, 1H, OH), 7.15 (t, 1H, H-4′, $J_{ortho} = 7.6$ Hz), 6.90 (d, 1H, H-6′, $J_{ortho} = 7.5$ Hz), 6.81 (d, 1H, H-3′, $J_{ortho} = 7.6$

Hz), 6.68 (t, 1H, H-5′, $J_{ortho} = 7.5$ Hz), 2.65 (dd, 1H, benzylic CH_2, $J_{gem} = 12.4$ Hz, $J_{vic} = 3.3$ Hz), 2.57 (bd, 1H, H-6eq, $J_{gem} = 10.5$ Hz), 2.46 (s, 3H, N–CH_3), 2.44 (dd, 1H, benzylic CH_2, $J_{gem} = 12.4$ Hz, $J_{vic} = 2.5$ Hz), 2.25 (m, 2H, H-2 and H-6ax), 1.70–1.00 (m, 6H, H-3, H-5 and H-4); MS: *m/z* 205 [M^+], 184, 160, 146, 133. Anal. $C_{13}H_{19}NO$ (C, H, N).

6.1.9.4. 2-[(3-Hydroxyphenyl)methyl]-1-methylpiperidine ***(13b)***. Compound **13b** was obtained as an oil in 82% yield (lit. [27] hydrobromide m.p. 78–79 °C); ^{1}H-NMR ($CDCl_3$): δ 7.20 (bs, 1H, OH), 7.10 (t, 1H, H-5′, $J_{ortho} = 7.6$ Hz), 6.68 (s, 1H, H-2′), 6.64 (overlapped doublets, 2H, H-4′, $J_{ortho} = 7.6$ Hz and H-6′, $J_{ortho} = 7.5$ Hz), 3.12 (dd, 1H, benzylic CH_2, $J_{gem} = 12.8$ Hz, $J_{vic} = 3.9$ Hz), 2.89 (bd, 1H, H-6eq, $J_{gem} = 11.7$ Hz), 2.40 (s, 3H, N–CH_3), 2.39 (dd, 1H, benzylic CH_2, $J_{gem} = 12.8$ Hz, $J_{vic} = 3.1$ Hz), 2.26 (m, 2H, H-2 and H-6ax), 1.70–1.00 (m, 6H, H-3, H-5 and H-4); MS: *m/z* 204 [$M^+ - 1$], 184, 167, 160, 133. Anal. $C_{13}H_{19}NO$ (C, H, N).

6.1.9.5. 2-[2-(2-Hydroxyphenyl)ethyl]-1-methylpiperidine ***(19a)***. Compound **19a** was obtained as an oil in 61% yield; ^{1}H-NMR ($CDCl_3$): δ 7.25 (s, 1H, OH), 7.09 (t, 1H, H-4′, $J_{ortho} = 7.7$ Hz), 7.04 (d, 1H, H-6′, $J_{ortho} = 7.7$ Hz), 6.86 (d, 1H, H-3′, $J_{ortho} = 7.7$ Hz), 6.79 (t, 1H, H-5′, $J_{ortho} = 7.7$ Hz), 2.94 (bd, 1H, H-6eq, $J_{gem} = 10.6$ Hz), 2.73 (m, 1H, benzylic CH_2), 2.59 (m, 1H, benzylic CH_2), 2.34 (overlapped m and s, 4H, H-6ax and N–CH_3), 1.90–1.10 (m, 9H, piperidine–CH_2, H-2, H-3, H-4 and H-5); MS: *m/z* 219 [M^+], 190, 162, 146, 131, 107. Anal. $C_{14}H_{21}NO$ (C, H, N).

6.1.9.6. 2-[2-(3-Hydroxyphenyl)ethyl]-1-methylpiperidine ***(19b)***. Compound **19b** was obtained as an oil in 69% yield; ^{1}H-NMR ($CDCl_3$): δ 7.66 (bs, 1H, OH), 7.09 (t, 1H, H-5′, $J_{ortho} = 7.8$ Hz), 6.62 (overlapped d and s, 3H, H-4′, H-6′ and H-2′), 2.89 (bd, 1H, H-6eq, $J_{gem} = 11.9$ Hz), 2.55 (m, 2H, benzylic CH_2), 2.29 (s, 3H, N–CH_3), 2.17 (m, 1H, H-6ax), 1.98 (m, 2H, piperidine–CH_2), 1.85–1.10 (m, 7H, H-2, H-3, H-4 and H-5); MS: *m/z* 219 [M^+], 190, 162, 148, 133, 107. Anal. $C_{14}H_{21}NO$ (C, H, N).

6.1.9.7. 1-[(2-Hydroxyphenyl)methyl]piperidine ***(24a)***. Compound **24a** was obtained as an oil in 74% yield; ^{1}H-NMR: δ 9.20 (bs, 1H, OH), 7.13 (t, 1H, H-4′, $J_{ortho} = 7.3$ Hz), 6.93 (d,1H, H-6′, $J_{ortho} = 7.3$ Hz), 6.77 (partially overlapped d and t, 2H, H-3′ and H-5′, $J_{ortho} = 7.3$ Hz), 3.64 (s, 2H, benzylic CH_2), 2.47 (m, 4H, H-2 and H-6), 1.62 (m, 4H, H-3 and H-5), 1.48 (m, 2H, H-4); MS: *m/z* 191 [M^+]. Anal. $C_{12}H_{17}NO$ (C, H, N).

6.1.9.8. 1-[(3-Hydroxyphenyl)methyl]piperidine ***(24b)***. Compound **24b** was obtained in 90% yield, m.p. 135–137 °C (EtOH); (lit. [49] m.p. 136–137 °C); ^{1}H-NMR ($CDCl_3$): δ 7.84 (bs, 1H, OH), 7.09 (t, 1H, H-5′, $J_{ortho} = 7.6$ Hz), 6.75 (d, 1H, H-4′, $J_{ortho} = 7.6$ Hz), 6.71–6.67 (m, 2H, H-2′ and H-6′), 3.43 (s, 2H, benzylic CH_2), 2.46 (t, 4H, H-2 and H-6), 1.59 (m, 4H, H-3 and H-5), 1.41 (m, 2H, H-4); MS: *m/z* 191 [M^+], 190, 162, 148, 134, 107. Anal. $C_{12}H_{17}NO$ (C, H, N).

6.1.9.9. 1-[1-(2-Hydroxyphenyl)ethyl]piperidine ***(29a)***. Compound **29a** was obtained as an oil in 75% yield; ^{1}H-NMR ($CDCl_3$): δ 7.12 (dt, 1H, H-4′, $J_{ortho} = 7.0$ Hz, $J_{meta} = 1.7$ Hz), 6.95 (dd, 1H, H-6′, $J_{ortho} = 7.2$ Hz, $J_{meta} = 0.9$ Hz), 6.77 (dd, 1H, H-3′, $J_{ortho} = 7.3$ Hz, $J_{meta} = 1.2$ Hz), 6.75 (dt, 1H, H-5′, $J_{ortho} = 7.3$ Hz, $J_{meta} = 1.2$ Hz), 3.65 (q, 1H, C*H*–CH_3, $J_{vic} = 6.8$ Hz), 2.54 (m, 4H, H-2 and H-6), 1.61 (m, 4H, H-5 and H-3), 1.47 (m, 2H, H-4), 1.35 (d, 3H, CH–C*H*$_3$, $J_{vic} = 6.8$ Hz); MS: *m/z* 205 [M^+], 190, 122, 107. Anal. $C_{13}H_{19}NO$ (C, H, N).

6.1.9.10. 1-[1-(3-Hydroxyphenyl)ethyl]piperidine ***(29b)***. Compound **29b** was obtained in 92% yield, m.p. 143–145 °C (EtOAc) (lit. [50] m.p. 142–143 °C) ^{1}H-NMR ($CDCl_3$): δ 7.97 (bs, 1H, OH), 7.10 (t, 1H, H-5′, $J_{ortho} = 8.1$ Hz), 6.86 (s, 1H, H-2′), 6.72 (two overlapped d, 2H, H-4′ and H-6′, $J_{ortho} = 8.2$ Hz), 3.50 (q, 1H, C*H*–CH_3, $J_{vic} = 6.9$ Hz), 2.51 (m, 4H, H-2 and H-6), 1.57 (m, 4H, H-3 and H-5), 1.41 (d, 3H, CH–C*H*$_3$, $J_{vic} = 6.9$ Hz), 1.34 (m, 2H, H-4); MS: *m/z* 205 [M^+], 190, 112, 107. Anal. $C_{13}H_{19}NO$ (C, H, N).

6.1.9.11. 1-[2-(2-Hydroxyphenyl)ethyl]piperidine ***(34a)***. Compound **34a** was obtained in 70% yield, hydrobromide m.p. 225–228 °C (EtOH); ^{1}H-NMR ($CDCl_3$): δ 13.27 (bs, 1H, OH), 7.10 (dt, 1H, H-4′, $J_{ortho} = 7.8$ Hz, $J_{meta} = 1.5$ Hz), 6.97 (dd, 1H, H-6′, $J_{ortho} = 7.4$ Hz, $J_{meta} = 1.5$ Hz), 6.86 (dd, 1H, H-3′, $J_{ortho} = 7.8$ Hz, $J_{meta} = 1.2$ Hz), 6.71 (dt, 1H, H-5′, $J_{ortho} = 7.5$ Hz, $J_{meta} = 1.3$ Hz), 2.80 (m, 2H, benzylic CH_2), 2.63 (m, 6H, piperidine–CH_2, H-2 and H-6), 1.69 (m, 4H, H-3 and H-5), 1.51 (m, 2H, H-4); MS: *m/z* 205 [M^+], 190, 174, 146, 121. Anal. $C_{13}H_{19}NO$ (C, H, N).

6.1.9.12. 1-[2-(3-Hydroxyphenyl)ethyl]piperidine ***(34b)***. Compound **34b** was obtained in 88% yield, m.p. 134–135 °C (EtOAc); ^{1}H-NMR ($CDCl_3$): δ 7.12 (t, 1H, H-5′, $J_{ortho} = 7.9$ Hz), 6.80 (bs, 1H, OH), 6.69 (s, 1H, H-2′), 6.65 (m, 2H, H-4′ and H-6′), 2.78 (m, 2H, benzylic CH_2), 2.69 (m, 2H, piperidine–CH_2), 2.56 (m, 4H, H-2 and H-6), 1.68 (m, 4H, H-3 and H-5), 1.47 (m, 2H, H-4). MS: *m/z* 205 [M^+], 204, 190, 146, 121. Anal. $C_{13}H_{19}NO$ (C, H, N).

*6.1.10. General procedure for the preparation of n-hexylcarbamoyloxyphenyl derivatives **8**, **14**, **20**, **25**, **30**, **35***

Each compound **7**, **13**, **19**, **24**, **29**, **34** (20 mmol) was added to a stirred solution of *n*-hexylisocyanate (20 mmol), prepared in situ from heptanoyl azide by Curtius rearrangement in refluxing C_6H_6 [51]. The mixture was refluxed for 2 h, the solvent was evaporated and the residue purified by column chromatography on Al_2O_3 by eluting with an 1:2 EtOAc–*n*-C_6H_{14} mixture.

*6.1.10.1. 2-(2-n-Hexylcarbamoyloxyphenyl)-1-methylpiperidine (**8a**).* Compound **8a** was obtained as an oil in 30% yield; ^{1}H-NMR ($CDCl_3$): δ 7.52 (dt, 1H, H-4′, $J_{ortho} = 5.9$ Hz, $J_{meta} = 3.6$ Hz), 7.28 (t, 1H, NH, $J_{vic} = 6.7$ Hz), 7.23 (d, 1H, H-3′, $J_{ortho} = 5.9$ Hz), 7.20 (d, 1H, H-6′, $J_{ortho} = 5.9$ Hz), 6.94 (dt, 1H, H-5′ $J_{ortho} = 5.9$ Hz), 3.01 (bd, 1H, H-6eq, $J_{gem} = 11.4$ Hz), 2.91 (dd, 1H, H-2, $J_{2,3ax} = 10.7$ Hz, $J_{2,3eq} = 3.0$ Hz), 2.58 (t, 2H, carbamic H-1, $J_{vic} = 7.3$ Hz), 2.03 (m, 1H, H-6ax), 1.94 (s, 3H, N–CH_3), 1.68 (m, 6H, H-3, H-4 and H-5), 1.36 (m, 8H, carbamic H-2–H-5), 0.90 (t, 3H, carbamic H-6); MS: *m*/*z* 318 [M^+], 303, 288, 190, 168, 134. Anal. $C_{19}H_{30}N_2O_2$ (C, H, N).

*6.1.10.2. 2-(3-n-Hexylcarbamoyloxyphenyl)-1-methylpiperidine (**8b**).* Compound **8b** was obtained as an oil in 35% yield; ^{1}H-NMR ($CDCl_3$): δ 7.26 (t, 1H, H-5′, $J_{ortho} = 7.7$ Hz), 7.11 (d, 1H, H-4′, $J_{ortho} = 7.8$ Hz), 7.08 (s, 1H, H-2′), 6.98 (d, 1H, H-6′ $J_{ortho} = 8.0$ Hz), 5.01 (t, 1H, NH, $J_{vic} = 6.6$ Hz), 3.23 (q, 2H, carbamic H-1, $J_{vic} = 6.7$ Hz), 2.99 (bd, 1H, H-6eq, $J_{gem} = 11.4$ Hz), 2.72 (dd, 1H, H-2, $J_{2,3ax} = 10.6$ Hz, $J_{2,3eq} = 2.6$ Hz), 2.08 (m, 1H, H-6ax), 1.98 (s, 3H, N–CH_3), 1.79–1.51 (m, 6H, H-3, H-4 and H-5), 1.30 (bs, 8H, carbamic H-2–H-5), 0.88 (t, 3H, carbamic H-6); MS: *m*/*z* 318 [M^+], 191, 162, 134, 120. Anal. $C_{19}H_{30}N_2O_2$ (C, H, N).

*6.1.10.3. 2-[(2-n-Hexylcarbamoyloxyphenyl)methyl]-1-methylpiperidine (**14a**).* Compound **14a** was obtained as an oil in 49% yield; ^{1}H-NMR ($CDCl_3$): δ 7.20–7.05 (m, 4H, phenyl protons), 5.04 (bt, 1H, NH, $J_{vic} = 6.7$ Hz), 3.24 (q, 2H, carbamic H-1, $J_{vic} = 6.7$ Hz), 3.13 (dd, 1H, benzylic CH_2, $J_{gem} = 12.9$ Hz, $J_{vic} = 3.5$ Hz), 2.83 (bd, 1H, H-6eq, $J_{gem} = 11.5$ Hz), 2.38 (s, 3H, N–CH_3), 2.33 (d, 1H, benzylic CH_2, $J_{gem} = 12.9$ Hz), 2.09 (m, 2H, H-2 and H-6ax), 1.70–1.00 (m, 14H, H-3, H-4, H-5 and carbamic H-2–H-5), 0.88 (bt, 3H, carbamic H-6); MS: *m*/*z* 333 [$M^+ + 1$], 228, 206, 168. Anal. $C_{20}H_{32}N_2O_2$ (C, H, N).

*6.1.10.4. 2-[(3-n-Hexylcarbamoyloxyphenyl)methyl]-1-methylpiperidine (**14b**).* Compound **14b** was obtained as an oil in 75% yield; ^{1}H-NMR ($CDCl_3$): δ 7.22 (t, 1H, H-5′, $J_{ortho} = 7.6$ Hz), 6.97 (d, 1H, H-4′, $J_{ortho} = 7.6$ Hz), 6.93 (d, 1H, H-6′, $J_{ortho} = 7.5$ Hz), 6.91 (s, 1H, H-2′), 4.98 (t, 1H, NH, $J_{vic} = 6.7$ Hz), 3.24 (q, 2H, carbamic H-1, $J_{vic} = 6.7$ Hz), 3.17 (dd, 1H, benzylic CH_2, $J_{gem} = 12.8$ Hz, $J_{vic} = 3.9$ Hz), 2.84 (bd, 1H, H-6eq, $J_{gem} = 11.5$ Hz), 2.37 (s, 3H, N–CH_3), 2.33 (d, 1H, benzylic CH_2, $J_{gem} = 12.8$ Hz), 2.10 (m, 2H, H-2 and H-6ax), 1.70–1.00 (m, 14H, H-3, H-4, H-5 and carbamic H-2–H-5), 0.88 (bt, 3H, carbamic H-6); MS: *m*/*z* 333 [$M^+ + 1$], 228, 199, 185. Anal. $C_{20}H_{32}N_2O_2$ (C, H, N).

*6.1.10.5. 2-[2-(2-n-Hexylcarbamoyloxyphenyl)ethyl]-1-methylpiperidine (**20a**).* Compound **20a** was obtained as an oil in 63% yield; ^{1}H-NMR ($CDCl_3$): δ 7.20–7.02 (overlapped d and t, 4H, phenyl protons), 5.10 (bt, 1H, NH, $J_{vic} = 6.7$ Hz), 3.22 (bq, 2H, carbamic H-1, $J_{vic} = 6.7$ Hz), 2.82 (bd, 1H, H-6eq, $J_{gem} = 10.6$ Hz), 2.55 (m, 2H, benzylic CH_2), 2.23 (s, 3H, N–CH_3), 2.05 (m, 1H, H-6ax), 1.90–1.35 (m, 9H, piperidine–CH_2, H-2, H-3, H-4 and H-5), 1.29 (bs, 8H, carbamic H-2-H-5), 0.87 (bt, 3H, carbamic H-6); MS: *m*/*z* 347 [$M^+ + 1$], 275, 219, 190, 112, 107. Anal. $C_{21}H_{34}N_2O_2$ (C, H, N).

*6.1.10.6. 2-[2-(3-n-Hexylcarbamoyloxyphenyl)ethyl]-1-methylpiperidine (**20b**).* Compound **20b** was obtained as an oil in 52% yield; ^{1}H-NMR ($CDCl_3$): δ 7.19 (t, 1H, H-5′, $J_{ortho} = 7.6$ Hz), 6.95 (d, 1H, H-4′, $J_{ortho} = 7.6$ Hz), 6.91 (s, 1H, H-2′), 6.88 (d, 1H, H-6′, $J_{ortho} = 7.6$ Hz), 5.30 (t, 1H, NH, $J_{vic} = 6.4$ Hz), 3.17 (bq, 2H, carbamic H-1, $J_{vic} = 6.4$ Hz), 2.79 (bd, 1H, H-6eq, $J_{gem} = 11.2$ Hz), 2.59 (m, 2H, benzylic CH_2), 2.22 (s, 3H, N–CH_3), 2.03 (m, 1H, H-6ax), 1.90–1.35 (m, 9H, piperidine–CH_2, H-2, H-3, H-4 and H-5), 1.26 (bs, 8H, carbamic H-2–H-5), 0.85 (bt, 3H, carbamic H-6); MS: *m*/*z* 347 [$M^+ + 1$], 275, 218, 190, 162, 120,107. Anal. $C_{21}H_{34}N_2O_2$ (C, H, N).

*6.1.10.7. 1-[(2-n-Hexylcarbamoyloxyphenyl)methyl]piperidine (**25a**).* Compound **25a** was obtained as an oil in 46% yield; ^{1}H-NMR ($CDCl_3$): δ 7.39 (dd, 1H, H-3′, $J_{ortho} = 7.3$ Hz, $J_{meta} = 2.0$ Hz), 7.27 (t, 1H, NH), 7.25–7.16 (overlapped 2 dt, 2H, H-4′ and H-5′, $J_{ortho} = 7.3$ Hz, $J_{meta} = 1.6$ Hz), 6.98 (dd, 1H, H-6′, $J_{ortho} = 7.4$ Hz, $J_{meta} = 1.6$ Hz), 3.35 (s, 2H, benzylic CH_2), 2.55 (t, 2H, carbamic H-1, $J_{vic} = 7.3$ Hz), 2.31 (m, 4H, H-2 and H-6), 1.74 (m, 2H, carbamic H-2), 1.48 (m, 4H, H-3 and H-5), 1.42–1.24 (m, 8H, H-4, carbamic H-3–H-5), 0.88 (t, 3H, carbamic H-6); MS: *m*/*z* 318 [M^+], 261, 247, 190, 162, 134. Anal. $C_{19}H_{30}N_2O_2$ (C, H, N).

*6.1.10.8. 1-[(3-n-Hexylcarbamoyloxyphenyl)methyl]piperidine (**25b**).* Compound **25b** was obtained as an oil in 60% yield; ^{1}H-NMR ($CDCl_3$): δ 7.25 (t, 1H, H-5′, $J_{ortho} = 7.6$ Hz), 7.11 (overlapped d and s, 2H, H-4′, $J_{ortho} = 7.6$ Hz and H-2′), 6.98 (d, 1H, H-6′, $J_{ortho} = 7.6$ Hz), 5.04 (bt, 1H, NH, $J_{vic} = 6.7$ Hz), 3.43 (s, 2H, benzylic CH_2), 3.23 (q, 2H, carbamic H-1, $J_{vic} = 6.7$

Hz), 2.33 (m, 4H, H-2 and H-6), 1.54 (m, 6H, H-3, H-5 and carbamic H-2), 1.29 (m, 8H, H-4 and carbamic H-3–H-5), 0.88 (t, 3H, carbamic H-6) MS: *m/z* 318 [M^+], 261, 247, 216, 190, 162, 134. Anal. $C_{19}H_{30}N_2O_2$ (C, H, N).

*6.1.10.9. 1-[1-(2-n-Hexylcarbamoyloxyphenyl)ethyl]piperidine (**30a**).* Compound **30a** was obtained as an oil in 55% yield; ^{1}H-NMR ($CDCl_3$): δ 7.44 (dd, 1H, H-3′, $J_{ortho} = 6.7$ Hz, $J_{meta} = 2.7$ Hz), 7.24–7.17 (three partially overlapped t, 3H, NH, H-4′ and H-5′, $J_{ortho} = 6.8$ Hz, $J_{meta} = 2.7$ Hz), 6.97 (dd, 1H, H-6′, $J_{ortho} = 6.9$ Hz, $J_{meta} = 2.4$ Hz), 3.47 (q, 1H, C*H*–CH_3, $J_{vic} = 6.7$ Hz), 2.56 (t, 2H, carbamic H-1, $J_{vic} = 7.3$ Hz), 2.28 (m, 4H, H-2 and H-6), 1.76 (m, 2H, carbamic H-2), 1.49 (m, 4H, H-3 and H-5), 1.35–1.24 (m, 8H, H-4 and carbamic H-3–H-5), 1.29 (d, 3H, CH–C*H*$_3$, $J_{vic} = 6.7$ Hz), 0.90 (t, 3H, carbamic H-6); MS: *m/z* 317 [$M^+ - 15$], 302, 190, 149, 121. Anal. $C_{20}H_{32}N_2O_2$ (C, H, N).

*6.1.10.10. 1-[1-(3-n-Hexylcarbamoyloxyphenyl)ethyl]piperidine (**30b**).* Compound **30b** was obtained as an oil in 68% yield; ^{1}H-NMR ($CDCl_3$): δ 7.25 (t, 1H, H-5′, $J_{ortho} = 7.6$ Hz), 7.07 (d, 1H, H-4′, $J_{ortho} = 7.6$ Hz), 7.04 (s, 1H, H-2′), 6.97 (d, 1H, H-6′, $J_{ortho} = 7.6$ Hz), 5.03 (bs, 1H, NH), 3.37 (q, 1H, C*H*–CH_3, $J_{vic} = 6.9$ Hz), 3.22 (q, 2H, carbamic H-1, $J_{vic} = 6.9$ Hz), 2.32 (m, 4H, H-2 and H-6), 1.49 (m, 6H, H-3, H-5 and carbamic H-2), 1.34 (d, 3H, CH–C*H*$_3$, $J_{vic} = 6.9$ Hz), 1.32 (m, 8H, H-4 and carbamic H-3–H-5), 0.87 (t, 3H, carbamic H-6); MS: *m/z* 332 [M^+], 317, 261, 205, 190, 112. Anal. $C_{20}H_{32}N_2O_2$ (C, H, N).

*6.1.10.11. 1-[2-(2-n-Hexylcarbamoyloxyphenyl)ethyl]piperidine (**35a**).* Compound **35a** was obtained as an oil in 63% yield; ^{1}H-NMR ($CDCl_3$): δ 7.24–7.11 (m, 4H, phenyl protons), 5.23 (t, 1H, NH, $J_{vic} = 6.1$ Hz), 3.23 (q, 2H, carbamic H-1, $J_{vic} = 6.1$ Hz), 2.75 (m, 2H, piperidine–CH_2), 2.51 (m, 2H, benzylic CH_2), 2.45 (t, 4H, H-2 and H-6), 1.59 (m, 6H, H-3, H-5 and carbamic H-2), 1.43 (m, 2H, H-4), 1.30 (m, 6H, carbamic H-3–H-5), 0.88 (t, 3H, carbamic H-6); MS: *m/z* 333 [$M^+ + 1$], 289, 261, 228, 205, 190, 133, 121, 112, 107. Anal. $C_{20}H_{32}N_2O_2$ (C, H, N).

*6.1.10.12. 1-[2-(3-n-Hexylcarbamoyloxyphenyl)ethyl]piperidine (**35b**).* Compound **35b** was obtained as an oil in 72% yield; ^{1}H-NMR ($CDCl_3$): δ 7.24 (t, 1H, H-5′, $J_{ortho} = 7.8$ Hz), 7.00 (d, 2H, H-4′, $J_{ortho} = 7.8$ Hz), 6.95 (s, 1H, H-2′), 6.93 (d, 1H, H-6′, $J_{ortho} = 7.8$ Hz), 5.01 (t, 1H, NH, $J_{vic} = 6.1$ Hz), 3.25 (q, 2H, carbamic H-1, $J_{vic} = 6.1$ Hz), 2.74 (m, 2H, benzylic CH_2), 2.55 (m, 2H, piperidine–CH_2), 2.44 (m, 4H, H-2 and H-6), 1.59 (m, 6H, H-3, H-5 and carbamic H-2), 1.43 (m, 2H, H-4), 1.29 (m, 6H, carbamic H-3–H-5), 0.87 (t, 3H, carbamic H-6); MS: *m/z* 332 [M^+], 261, 204, 112. Anal. $C_{20}H_{32}N_2O_2$ (C, H, N).

*6.1.11. General procedure for the preparation of N,N-dimethyl- and N,N-diethylcarbamoyloxyderivatives **9**, **15**, **21**, **26**, **31**, **36** and **10**, **16**, **22**, **27**, **32**, **37***

To a cooled and stirred solution of each compound **7**, **13**, **19**, **24**, **29**, **34** (20 mmol) in a mixture of anhydrous pyridine (50 mL) and triethylamine (3.5 mL, 25 mmol), *N*,*N*-dimethyl- or *N*,*N*-diethylcarbamoyl chloride [52] (25 mmol) was dropwise added. The mixture was stirred overnight at r.t., then evaporated to dryness under reduced pressure (maximum bath temperature 40 °C). After addition of water, the mixture was extracted with EtOAc, the solvent removed and the residue chromatographed on Al_2O_3 by eluting with an 1:2 EtOAc–*n*-C_6H_{14} mixture.

*6.1.11.1. 2-(2-Dimethylcarbamoyloxyphenyl)-1-methylpiperidine (**9a**).* Compound **9a** was obtained as an oil in 73% yield; ^{1}H-NMR ($CDCl_3$): δ 7.51 (t, 1H, H-4′, $J_{ortho} = 5.1$ Hz), 7.20 (partially overlapped doublets, 2H, H-3′ and H-6′, $J_{ortho} = 5.1$ Hz), 7.02 (t, 1H, H-5′, $J_{ortho} = 5.1$ Hz), 3.12 (s, 3H, carbamic N–CH_3), 3.01 (bs, 5H, carbamic N–CH_3, H-6eq and H-2), 2.06 (m, 1H, H-6ax), 1.99 (s, 3H, piperidine N–CH_3), 1.85–1.18 (m, 6H, H-3, H-4 and H-5); MS: *m/z* 262 [M^+], 247, 202, 174, 134. Anal. $C_{15}H_{22}N_2O_2$ (C, H, N).

*6.1.11.2. 2-(3-Dimethylcarbamoyloxyphenyl)-1-methylpiperidine (**9b**).* Compound **9b** was obtained as an oil in 45% yield; ^{1}H-NMR ($CDCl_3$): δ 7.27 (t, 1H, H-5′, $J_{ortho} = 7.9$ Hz), 7.12 (d, 1H, H-4′, $J_{ortho} = 7.8$ Hz), 7.08 (s, 1H, H-2′), 6.99 (d, 1H, H-6′, $J_{ortho} = 7.8$ Hz), 3.07 (bs, 4H, carbamic N–CH_3 and H-6eq), 2.99 (s, 3H, carbamic N–CH_3), 2.77 (dd, 1H, H-2, $J_{2,3ax} = 10.4$ Hz, $J_{2,3eq} = 2.8$ Hz), 2.11 (m, 1H, H-6ax), 2.01 (s, 3H, piperidine N–CH_3), 1.88–1.20 (m, 6H, H-3, H-4 and H-5); MS: *m/z* 262 [M^+], 247, 205, 190, 134. Anal. $C_{15}H_{22}N_2O_2$ (C, H, N).

*6.1.11.3. 2-(2-Diethylcarbamoyloxyphenyl)-1-methylpiperidine (**10a**).* Compound **10a** was obtained as an oil in 53% yield; ^{1}H-NMR ($CDCl_3$): δ 7.51 (t, 1H, H-4′, $J_{ortho} = 5.0$ Hz), 7.21 (partially overlapped doublets, 2H, H-3′ and H-6′, $J_{ortho} = 5.0$ Hz), 7.02 (t, 1H, H-5′, $J_{ortho} = 5.0$ Hz), 3.42 (partially overlapped quartets, 4H, carbamic N–CH_2), 3.00 (overlapped dd and m, 2H, H-2, $J_{2,3ax} = 10.6$ Hz, $J_{2,3eq} = 2.5$ Hz and H-6eq), 2.05 (m, 1H, H-6ax), 1.97 (s, 3H, N–CH_3), 1.70 (m, 5H, H-4, H-5 and H-3eq), 1.50 (m, 1H, H-3ax), 1.23 (partially overlapped triplets, 6H, carbamic CH_3); MS: *m/z* 290 [M^+], 275, 202, 174, 134. Anal. $C_{17}H_{26}N_2O_2$ (C, H, N).

*6.1.11.4. 2-(3-Diethylcarbamoyloxyphenyl)-1-methylpiperidine (**10b**).* Compound **10b** was obtained as an oil in 48% yield; ^{1}H-NMR ($CDCl_3$): δ 7.26 (t, 1H, H-5′, $J_{ortho} = 7.8$ Hz), 7.10 (d, 1H, H-4′, $J_{ortho} = 7.9$ Hz), 7.08 (s, 1H, H-2′), 6.99 (d, 1H, H-6′, $J_{ortho} = 7.9$ Hz), 3.38 (partially overlapped quartets, 4H, carbamic N–CH_2), 3.01 (bd, 1H, H-6eq, $J_{gem} = 10.3$ Hz), 2.74 (dd, 1H, H-2, $J_{2,3ax} = 10.5$ Hz, $J_{2,3eq} = 2.8$ Hz), 2.08 (m, 1H, H-6ax), 1.99 (s, 3H, N–CH_3), 1.85–1.25 (m, 6H, H-3, H-4 and H-5), 1.19 (partially overlapped triplets, 6H, carbamic CH_3); MS: m/z 290 [M^+], 275, 233, 190, 162. Anal. $C_{17}H_{26}N_2O_2$ (C, H, N).

*6.1.11.5. 2-[(2-Dimethylcarbamoyloxyphenyl)methyl]-1-methylpiperidine (**15a**).* Compound **15a** was obtained as an oil in 89% yield; ^{1}H-NMR ($CDCl_3$): δ 7.20–7.02 (m, 3H, H-3′, H-4′ and H-5′), 7.03 (d, 1H, H-6′, $J_{ortho} = 7.5$ Hz), 3.15 (dd, 1H, benzylic CH_2, $J_{gem} = 13.1$ Hz, $J_{vic} = 3.7$ Hz), 3.12 (s, 3H, carbamic N–CH_3), 2.99 (s, 3H, carbamic N–CH_3), 2.85 (bd, 1H, H-6eq, $J_{gem} = 11.5$ Hz), 2.38 (s, 3H, piperidine N–CH_3), 2.33 (d, 1H, benzylic CH_2, $J_{gem} = 13.1$ Hz), 2.10 (m, 2H, H-2 and H-6ax), 1.80–1.10 (m, 6H, H-3, H-4 and H-5); MS: m/z 277 [$M^+ + 1$], 275 [$M^+ - 1$], 230, 186, 132, 107. Anal. $C_{16}H_{24}N_2O_2$ (C, H, N).

*6.1.11.6. 2-[(3-Dimethylcarbamoyloxyphenyl)methyl]-1-methylpiperidine (**15b**).* Compound **15b** was obtained as an oil in 62% yield; ^{1}H-NMR ($CDCl_3$): δ 7.19 (t, 1H, H-5′, $J_{ortho} = 7.9$ Hz), 6.93 (d, 1H, H-4′, $J_{ortho} = 7.9$ Hz), 6.88 (d, 1H, H-6′, $J_{ortho} = 8.0$ Hz), 6.86 (s, 1H, H-2′), 3.13 (dd, 1H, benzylic CH_2, $J_{gem} = 13.1$ Hz, $J_{vic} = 3.9$ Hz), 3.03 (s, 3H, carbamic N–CH_3), 2.94 (s, 3H, carbamic N–CH_3), 2.78 (bd, 1H, H-6eq, $J_{gem} = 11.7$ Hz), 2.33 (s, 3H, piperidine N–CH_3), 2.30 (d, 1H, benzylic CH_2, $J_{gem} = 13.1$ Hz), 2.09 (m, 2H, H-2 and H-6ax), 1.53 (m, 4H, H-5, H-3eq and H-4eq), 1.10 (m, 2H, H-3ax and H-4ax); MS: m/z 275 [$M^+ - 1$], 233, 188, 160, 147, 133, 111. Anal. $C_{16}H_{24}N_2O_2$ (C, H, N).

*6.1.11.7. 2-[(2-Diethylcarbamoyloxyphenyl)methyl]-1-methylpiperidine (**16a**).* Compound **16a** was obtained as an oil in 72% yield; ^{1}H-NMR ($CDCl_3$): δ 7.16 (overlapped d and t, 4H, phenyl protons), 3.42 (partially overlapped quartets, 4H, carbamic N–CH_2), 3.18 (dd, 1H, benzylic CH_2, $J_{gem} = 13.1$ Hz, $J_{vic} = 3.9$ Hz), 2.85 (bd, 1H, H-6eq, $J_{gem} = 11.7$ Hz), 2.38 (s, 3H, N–CH_3), 2.35 (d, 1H, benzylic CH_2, $J_{gem} = 13.1$ Hz), 2.13 (m, 2H, H-2 and H-6ax), 1.70–1.10 (m, 6H, H-3, H-5 and H-4), 1.24 (partially overlapped triplets, 6H, carbamic CH_3); MS: m/z 304 [M^+], 289, 232, 190, 168, 107. Anal. $C_{18}H_{28}N_2O_2$ (C, H, N).

*6.1.11.8. 2-[(3-Diethylcarbamoyloxyphenyl)methyl]-1-methylpiperidine (**16b**).* Compound **16b** was obtained as an oil in 67% yield; ^{1}H-NMR ($CDCl_3$): δ 7.24 (t, 1H, H-5′, $J_{ortho} = 7.6$ Hz), 6.97 (d, 1H, H-4′, $J_{ortho} = 7.6$ Hz), 6.93 (d, 1H, H-6′, $J_{ortho} = 7.6$ Hz), 6.91 (s, 1H, H-2′), 3.39 (partially overlapped quartets, 4H, carbamic N–CH_2), 3.19 (dd, 1H, benzylic CH_2, $J_{gem} = 13.1$ Hz, $J_{vic} = 3.7$ Hz), 2.84 (bd, 1H, H-6eq, $J_{gem} = 11.7$ Hz), 2.39 (t, 3H, N–CH_3), 2.33 (dd, 1H, benzylic CH_2, $J_{gem} = 13.1$ Hz, $J_{vic} = 3.4$ Hz), 2.11 (m, 2H, H-2 and H-6ax), 1.80–1.10 (m, 6H, H-3, H-5 and H-4), 1.22 (partially overlapped triplets, 6H, carbamic CH_3); MS: m/z 304 [M^+], 277, 220, 192, 107. Anal. $C_{18}H_{28}N_2O_2$ (C, H, N).

*6.1.11.9. 2-[2-(2-Dimethylcarbamoyloxyphenyl)ethyl]-1-methylpiperidine (**21a**).* Compound **21a** was obtained as an oil in 50% yield; ^{1}H-NMR ($CDCl_3$): δ 7.21–7.02 (overlapped d and t, 4H, phenyl protons), 3.11 (s, 3H, carbamic N–CH_3), 3.00 (s, 3H, carbamic N–CH_3), 2.83 (bd, 1H, H-6eq, $J_{gem} = 10.4$ Hz), 2.56 (m, 2H, benzylic CH_2), 2.24 (s, 3H, piperidine N–CH_3), 2.05 (m, 1H, H-6ax), 1.95–1.10 (m, 9H, piperidine–CH_2, H-2, H-3, H-4 and H-5); MS: m/z 291 [$M^+ + 1$], 275, 261, 218, 162, 146, 124, 112, 107. Anal. $C_{17}H_{26}N_2O_2$ (C, H, N).

*6.1.11.10. 2-[2-(3-Dimethylcarbamoyloxyphenyl)ethyl]-1-methylpiperidine (**21b**).* Compound **21b** was obtained as an oil in 55% yield; ^{1}H-NMR ($CDCl_3$): δ 7.23 (t, 1H, H-5′, $J_{ortho} = 7.6$ Hz), 7.00 (d, 1H, H-4′, $J_{ortho} = 7.6$ Hz), 6.93 (s, 1H, H-2′), 6.90 (d, 1H, H-6′, $J_{ortho} = 7.6$ Hz), 3.08 (s, 3H, carbamic N–CH_3), 2.99 (s, 3H, carbamic N–CH_3), 2.83 (bd, 1H, H-6eq, $J_{gem} = 11.5$ Hz), 2.62 (m, 2H, benzylic CH_2), 2.25 (s, 3H, piperidine N–CH_3), 2.05 (m, 1H, H-6ax), 1.95–1.10 (m, 9H, piperidine–CH_2, H-2, H-3, H-4 and H-5); MS: m/z 291 [$M^+ + 1$], 290 [M^+], 289 [$M^+ - 1$], 273, 247, 218, 178, 132, 126, 111. Anal. $C_{17}H_{26}N_2O_2$ (C, H, N).

*6.1.11.11. 2-[2-(2-Diethylcarbamoyloxyphenyl)ethyl]-1-methylpiperidine (**22a**).* Compound **22a** was obtained as an oil in 60% yield; ^{1}H-NMR ($CDCl_3$): δ 7.22–7.01 (overlapped d and t, 4H, phenyl protons), 3.40 (partially overlapped quartets, 4H, carbamic N–CH_2, $J_{vic} = 7.3$ Hz), 2.80 (bd, 1H, H-6eq, $J_{gem} = 11.5$ Hz), 2.55 (m, 2H, benzylic CH_2), 2.23 (s, 3H, N–CH_3), 2.05 (m, 1H, H-6ax), 1.90–1.20 (m, 9H, piperidine–CH_2, H-2, H-3, H-4 and H-5), 1.21 (partially overlapped triplets, 6H, carbamic CH_3, $J_{vic} = 7.3$ Hz); MS: m/z 319 [$M^+ + 1$], 303, 219, 200, 190, 112. Anal. $C_{19}H_{30}N_2O_2$ (C, H, N).

*6.1.11.12. 2-[2-(3-Diethylcarbamoyloxyphenyl)ethyl]-1-methylpiperidine (**22b**).* Compound **22b** was obtained as an oil in 49% yield; ^{1}H-NMR ($CDCl_3$): δ 7.19 (t, 1H, H-5′, $J_{ortho} = 7.1$ Hz), 6.99 (d, 1H, H-4′, $J_{ortho} = 7.1$ Hz), 6.94 (s, 1H, H-2′), 6.91 (d, 1H, H-6′, $J_{ortho} = 7.1$ Hz), 3.39 (partially overlapped quartets, 4H, carbamic N–CH_2, $J_{vic} = 7.6$ Hz), 2.85 (bd, 1H, H-6eq, $J_{gem} = 11.4$ Hz), 2.62 (m, 2H, benzylic CH_2), 2.27 (s, 3H, N–CH_3), 2.08 (m, 1H, H-6ax), 2.00–1.20 (m, 9H,

piperidine–CH_2, H-2, H-3, H-4 and H-5), 1.20 (partially overlapped triplets, 6H, carbamic CH_3, $J_{vic} = 7.6$ Hz); MS: m/z 318 [M^+], 290, 258, 204, 174, 126. Anal. $C_{19}H_{30}N_2O_2$ (C, H, N).

*6.1.11.13. 1-[(2-Dimethylcarbamoyloxyphenyl)methyl]piperidine (**26a**).* Compound **26a** was obtained as an oil in 90% yield; ^{1}H-NMR ($CDCl_3$): δ 7.37 (dd, 1H, H-3′, $J_{ortho} = 7.3$ Hz, $J_{meta} = 1.9$ Hz), 7.24 (dt, 1H, H-5′, $J_{ortho} = 7.3$ Hz, $J_{meta} = 2.1$ Hz), 7.13 (dt, 1H, H-4′, $J_{ortho} = 7.3$ Hz, $J_{meta} = 1.5$ Hz), 7.07 (dd, 1H, H-6′, $J_{ortho} = 7.3$ Hz, $J_{meta} = 1.5$ Hz), 3.41 (s, 2H, benzylic CH_2), 3.10 (s, 3H, carbamic N–CH_3), 2.99 (s, 3H, carbamic N–CH_3), 2.33 (t, 4H, H-2 and H-6), 1.52 (m, 4H, H-3 and H-5), 1.43 (m, 2H, H-4); MS: m/z 262 [M^+], 233, 219, 190, 174, 144. Anal. $C_{15}H_{22}N_2O_2$ (C, H, N).

*6.1.11.14. 1-[(3-Dimethylcarbamoyloxyphenyl)methyl]piperidine (**26b**).* Compound **26b** was obtained as an oil in 80% yield; ^{1}H-NMR ($CDCl_3$): δ 7.26 (t, 1H, H-5′, $J_{ortho} = 7.6$ Hz), 7.11 (d, 1H, H-4′, $J_{ortho} = 7.6$ Hz), 7.06 (s, 1H, H-2′), 6.97 (d, 1H, H-6′, $J_{ortho} = 7.6$ Hz), 3.43 (s, 2H, benzylic CH_2), 3.07 (s, 3H, carbamic N–CH_3), 2.99 (s, 3H, carbamic N–CH_3), 2.35 (t, 4H, H-2 and H-6), 1.54 (t, 4H, H-3 and H-5), 1.40 (m, 2H, H-4); MS: m/z 262 [M^+], 261, 233, 219, 178, 135, 107. Anal. $C_{15}H_{22}N_2O_2$ (C, H, N).

*6.1.11.15. 1-[(2-Diethylcarbamoyloxyphenyl)methyl]piperidine (**27a**).* Compound **27a** was obtained as an oil in 86% yield; ^{1}H-NMR ($CDCl_3$): δ 7.39 (dd, 1H, H-3′, $J_{ortho} = 7.2$ Hz, $J_{meta} = 1.9$ Hz), 7.23 (dt, 1H, H-5′, $J_{ortho} = 7.3$ Hz, $J_{meta} = 2.0$ Hz), 7.13 (dt, 1H, H-4′, $J_{ortho} = 7.3$ Hz, $J_{meta} = 1.7$ Hz), 7.05 (dd, 1H, H-6′, $J_{ortho} = 7.3$ Hz, $J_{meta} = 1.7$ Hz), 3.41 (m, 6H, benzylic CH_2 and carbamic N–CH_2), 2.33 (t, 4H, H-2 and H-6, $J_{vic} = 4.4$ Hz), 1.52 (m, 4H, H-3 and H-5), 1.40 (m, 2H, H-4), 1.22 (m, 6H, carbamic CH_3); MS: m/z 290 [M^+], 206, 190, 174, 146. Anal. $C_{17}H_{26}N_2O_2$ (C, H, N).

*6.1.11.16. 1-[(3-Diethylcarbamoyloxyphenyl)methyl]piperidine (**27b**).* Compound **27b** was obtained as an oil in 60% yield; ^{1}H-NMR ($CDCl_3$): δ 7.28 (t, 1H, H-5′, $J_{ortho} = 7.8$ Hz), 7.09 (overlapped d and s, 2H, H-4′, $J_{ortho} = 7.6$ Hz and H-2′), 7.00 (d, 1H, H-6′, $J_{ortho} = 7.9$ Hz), 3.44 (s, 2H, benzylic CH_2), 3.39 (m, 4H, carbamic N–CH_2), 2.35 (t, 4H, H-2 and H-6, $J_{vic} = 5.3$ Hz), 1.58 (m, 4H, H-3 and H-5), 1.41 (m, 2H, H-4), 1.23 (m, 6H, carbamic CH_3); MS: m/z 290 [M^+], 263, 234, 207, 192. Anal. $C_{17}H_{26}N_2O_2$ (C, H, N).

*6.1.11.17. 1-[1-(2-Dimethylcarbamoyloxyphenyl)ethyl]piperidine (**31a**).* Compound **31a** was obtained as an oil in 59% yield; ^{1}H-NMR ($CDCl_3$): δ 7.41 (dd, 1H, H-3′, $J_{ortho} = 7.9$ Hz, $J_{meta} = 2.5$ Hz), 7.24–7.14 (two partially overlapped dt, 2H, H-4′ and H-5′, $J_{ortho} = 7.8$ Hz, $J_{meta} = 2.2$ Hz), 7.04 (dd, 1H, H-6′, $J_{ortho} = 7.8$ Hz, $J_{meta} = 2.2$ Hz), 3.57 (q, 1H, C*H*–CH_3, $J_{vic} = 6.7$ Hz), 3.10 (s, 3H, carbamic N–CH_3), 2.99 (s, 3H, carbamic N–CH_3), 2.32 (m, 4H, H-2 and H-6), 1.47 (m, 4H, H-3 and H-5), 1.37 (m, 2H, H-4), 1.33 (d, 3H, CH–*C*H_3, $J_{vic} = 6.7$ Hz); MS: m/z 276 [M^+], 261, 233, 204, 188. Anal. $C_{16}H_{24}N_2O_2$ (C, H, N).

*6.1.11.18. 1-[1-(3-Dimethylcarbamoyloxyphenyl)ethyl]piperidine (**31b**).* Compound **31b** was obtained as an oil in 64% yield; ^{1}H-NMR ($CDCl_3$): δ 7.26 (t, 1H, H-5′, $J_{ortho} = 7.7$ Hz), 7.05 (d, 1H, H-4′, $J_{ortho} = 7.7$ Hz), 7.03 (s, 1H, H-2′), 6.97 (d, 1H, H-6′, $J_{ortho} = 7.8$ Hz), 3.37 (q, 1H, C*H*–CH_3, $J_{vic} = 6.7$ Hz), 3.08 (s, 3H, carbamic N–CH_3), 2.99 (s, 3H, carbamic N–CH_3), 2.35 (m, 4H, H-2 and H-6), 1.52 (m, 4H, H-3 and H-5), 1.40 (m, 2H, H-4), 1.33 (d, 3H, CH–*C*H_3, $J_{vic} = 6.7$ Hz); MS: m/z 276 [M^+], 261, 193, 178, 134, 112. Anal. $C_{16}H_{24}N_2O_2$ (C, H, N).

*6.1.11.19. 1-[1-(2-Diethylcarbamoyloxyphenyl)ethyl]piperidine (**32a**).* Compound **32a** was obtained as an oil in 54% yield; ^{1}H-NMR ($CDCl_3$): δ 7.43 (dd, 1H, H-3′, $J_{ortho} = 6.7$ Hz, $J_{meta} = 2.7$ Hz), 7.17 (two partially overlapped dd, 2H, H-4′ and H-5′, $J_{ortho} = 6.8$ Hz, $J_{meta} = 2.7$ Hz), 7.03 (dd, 1H, H-6′, $J_{ortho} = 6.9$ Hz, $J_{meta} = 2.6$ Hz), 3.56 (q, 1H, C*H*–CH_3, $J_{vic} = 6.7$ Hz), 3.39 (m, 4H, carbamic N–CH_2), 2.33 (m, 4H, H-2 and H-6), 1.50 (m, 4H, H-3 and H-5), 1.28 (m, 11H, H-4, CH–CH_3 and carbamic CH_3); MS: m/z 304 [M^+], 289, 261, 204, 188, 112. Anal. $C_{18}H_{28}N_2O_2$ (C, H, N).

*6.1.11.20. 1-[1-(3-Diethylcarbamoyloxyphenyl)ethyl]piperidine (**32b**).* Compound **32b** was obtained as an oil in 68% yield; ^{1}H-NMR ($CDCl_3$): δ 7.26 (t, 1H, H-5′, $J_{ortho} = 7.6$ Hz), 7.22 (d, 1H, H-4′, $J_{ortho} = 7.6$ Hz), 7.03 (s, 1H, H-2′), 6.95 (d, 1H, H-6′, $J_{ortho} = 7.6$ Hz), 3.38 (m, 5H, *CH*–CH_3 and carbamic N–CH_2), 2.34 (m, 4H, H-2 and H-6), 1.53 (m, 4H, H-3 and H-5), 1.33 (m, 5H, H-4 and CH–CH_3), 1.24 (m, 6H, carbamic CH_3), MS: m/z 304 [M^+], 289, 248, 220, 185, 154. Anal. $C_{18}H_{28}N_2O_2$ (C, H, N).

*6.1.11.21. 1-[2-(2-Dimethylcarbamoyloxyphenyl)ethyl]piperidine (**36a**).* Compound **36a** was obtained as an oil in 74% yield;^{1}H-NMR ($CDCl_3$): δ 7.20 (overlapped t and d, 2H, H-4′ and H-6′, $J_{ortho} = 7.3$ Hz), 7.16 (d, 1H, H-3′, $J_{ortho} = 7.3$ Hz), 7.06 (t, 1H, H-5′, $J_{ortho} = 7.2$ Hz), 3.11 (s, 3H, carbamic N–CH_3), 3.00 (s, 3H, carbamic N–CH_3), 2.76 (m, 2H, piperidine–CH_2), 2.53 (m, 2H, benzylic CH_2), 2.46 (m, 4H, H-2 and H-6), 1.60 (m, 4H, H-3 and H-5), 1.44 (m, 2H, H-4); MS: m/z 277 [$M^+ + 1$], 276 [M^+], 230, 192, 132, 118. Anal. $C_{16}H_{24}N_2O_2$ (C, H, N).

*6.1.11.22. 1-[2-(3-Dimethylcarbamoyloxyphenyl)ethyl]-piperidine (**36b**).* Compound **36b** was obtained as an oil in 70% yield; ^{1}H-NMR ($CDCl_3$): δ 7.24 (t, 1H, H-5′, J_{ortho}, = 7.8 Hz), 7.00 (d, 1H, H-4′, J_{ortho} = 7.8 Hz), 6.93 (overlapped s and d, 2H, H-2′ and H-6′), 3.08 (s, 3H, carbamic N–CH_3), 2.99 (s, 3H, carbamic N–CH_3), 2.77 (m, 2H, benzylic CH_2), 2.53 (m, 2H, piperidine–CH_2), 2.43 (t, 4H, H-2 and H-6), 1.59 (m, 4H, H-3 and H-5), 1.43 (m, 2H, H-4), MS: m/z 277 [$M^+ + 1$], 276 [M^+], 275 [$M^+ - 1$], 247, 204, 174, 132, 121. Anal. $C_{16}H_{24}N_2O_2$ (C, H, N).

*6.1.11.23. 1-[2-(2-Diethylcarbamoyloxyphenyl)ethyl]-piperidine (**37a**).* Compound **37a** was obtained as an oil in 58% yield; ^{1}H-NMR ($CDCl_3$): δ 7.24–7.04 (m, 4H, phenyl protons), 3.43 (m, 4H, carbamic N–CH_2), 2.75 (m, 2H, benzylic CH_2), 2.51 (m, 2H, piperidine–CH_2), 2.43 (t, 4H, H-2 and H-6), 1.59 (m, 4H, H-3 and H-5), 1.42 (m, 2H, H-4), 1.24 (m, 6H, carbamic CH_3); MS: m/z 304 [M^+], 277, 232, 220, 192, 130, 112. Anal. $C_{18}H_{28}N_2O_2$ (C, H, N).

*6.1.11.24. 1-[2-(3-Diethylcarbamoyloxyphenyl)ethyl]-piperidine (**37b**).* Compound **37b** was obtained as an oil in 58% yield; ^{1}H-NMR ($CDCl_3$): δ 7.24 (t, 1H, H-5′, J_{ortho} = 7.4 Hz), 7.02 (d, 1H, H-4′, J_{ortho} = 7.5 Hz), 6.95 (s, 1H, H-2′), 6.94 (d, 1H, H-6′, J_{ortho} = 7.4 Hz), 3.39 (m, 4H, carbamic N–CH_2), 2.79 (m, 2H, benzylic CH_2), 2.55 (m, 2H, piperidine–CH_2), 2.44 (m, 4H, H-2 and H-6), 1.60 (m, 4H, H-3 and H-5), 1.44 (m, 2H, H-4), 1.20 (m, 6H, carbamic CH_3); MS: m/z 304 [M^+], 277, 220, 192, 112. Anal. $C_{18}H_{28}N_2O_2$ (C, H, N).

6.2. Pharmacology

6.2.1. In vitro assays on total brain AChE and on blood BuChE

Sprague–Dawley male rats (200–250 g body weight from Charles River Calco, Como, Italy), were housed on polypropylene cages at 22 °C and 50% humidity, with lighting from 7:00 to 22:00 h and were given standard chow and drinking water ad libitum. Rats were killed by decapitation, the whole brain minus cerebellum rapidly removed, weighted and homogenized in 10 volumes of cold 0.038 M Tris–HCl buffer, pH 8.5, containing 0.25% Triton X-100 using a Braun Potter S for 2 min. The homogenates were then centrifuged at 100,000 × g for 1 h in a Centrikon T-1055 (Kontron) ultracentrifuge, and supernatant used as AChE source divided into aliquots and stored at −20 °C. The same animals supplied blood as butyrylcholinesterase (BuChE) source.

Inhibition of AChE and BuChE was determined by Ellman's spectrophotometric method using acetylthiocholine (AcThCh) and butyrylthiocholine (BuThCh) as already described [37,38]. Results are expressed as nmoles of AcThCh and BuThCh per hydrolyzed min^{-1} g^{-1} of tissue and the IC_{50} values were determined graphically from log concentration–inhibition curve from 20 to 80%. Correlation coefficients were in all cases greater that 0.95.

6.2.2. In vivo inhibition of AChE from different brain regions

White Swiss male mice (20–25 g body weight from Charles River Calco, Como, Italy), were housed on polypropylene cages at 22 °C and 50% humidity, with lighting from 7:00 to 22:00 h and were given standard chow and drinking water ad libitum. Mice were killed by decapitation, the cerebral cortex, hippocampus and striatum were dissected [53] and were treated separately according to the procedure described for total brain AChE.

6.2.3. In vitro inhibition of AChE G1 and G4 molecular forms

AChE was extracted from control mouse brains following the same procedure already described for the in vitro assay. The molecular forms of AChE were separated by ultracentrifugation in sucrose gradient as previously described [54]. Briefly, 200 μL of a fresh 100,000 g supernatant were layered on 4.8 mL of 5–20% linear sucrose gradient and centrifuged at 38,000 rpm in a SW55B rotor in a Centrikon T-1055 (Kontron) ultracentrifuge for 18 h. In some experiments, catalase (11.3 S) and bovine serum albumin (4.3 S) were used as sedimentation standards. Ten drops fractions were collected from the bottom of each centrifuge tube and AChE determined in each fraction. The distribution profiles of individual molecular forms were evaluated. In vitro inhibition of AChE forms G4 and G1 was determined by Ellman's spectrophotometric method using acetylthiocholine (AcThCh) as already described for the in vitro assay. Results are expressed as nmol of AcThCh per hydrolyzed min^{-1} g^{-1} of tissue and the IC_{50} values were determined graphically from log concentration–inhibition curve from 20 to 80%. Correlation coefficients were in all cases greater that 0.95.

6.2.4. Acute toxicity study

Acute toxicity was evaluated in male mice (20–25 g body weight from Charles River Calco, Como, Italy) which were housed on polypropylene cages at 22 °C and 50% humidity, with lighting from 7:00 to 22:00 h and were given standard chow and drinking water ad libitum.

The method used was a stepwise procedure, similar to OCSE guideline no. 423, and is not intended to allow the calculation of a precise LD_{50} value, but to afford the determination of a range of exposure where lethality is expected. According to our National rules on behalf of laboratory animals, as little as possible number of animals was used to give acceptable data.

Moreover, taking into account that anticholinesterase compounds are known to cause signs of severe and enduring distress to animals, the maximum dose used in all tests was 50 mg kg^{-1}.

Each compound dissolved in a 1:10 propylene glycol–water mixture was orally administered to a group of five animals at the starting dose of 50 mg kg^{-1}. The dose was lowered to 25, 10 and 5 mg kg^{-1} if necessary in the case of death of animals.

6.2.5. In vivo study: ED_{50} calculation

Groups of three mice were orally treated with a 1:10 propylene glycol–water solution of the tested compounds.

The doses administered ranged from 1 to 15 mg kg^{-1}. In order to exclude possible food interference and to obtain a rapid and complete absorption, the mice were not given the standard chow during the night before the test.

Preliminary experiments showed maximum in vivo AChE inhibition at about 30 min after the treatment so this time was chosen for the sacrifice.

The brains were removed as reported for in vitro assay and homogenized in 10 volumes of cold 0.32 M sucrose. Inhibition of AChE was determined according to Ellman's spectrophotometric method and the $ED_{50} \pm SD$ determined using a linear regression.

6.2.6. Time course of inhibition of cerebral AChE and BuChE

Groups of three mice were treated as described in Section 6.2.3, with doses of the tested compounds ca. equivalent to ED_{50} and killed at different times (0.5, 1, 2 and 3 h after the treatment). The same experiment was performed in order to evaluate the time course of the cerebral BuChE inhibition only for **31b**. AChE and BuChE inhibition was measured according to Ellman's method in cerebral homogenates.

The principle set forth in the Directive of the Council of European Communities (86/609/EEC) on animal care and use, were followed.

6.2.7. Statistical analysis

Depending on the experiment, statistical analysis was carried out either by Student's *t*-test or by ANOVA. Student's *t*-test was used for comparison of two groups, whereas ANOVA in case of multiple comparisons.

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