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Synthesis and Structure–Activity Relationships of Open D-Ring Galanthamine Analogues

Denyse Herlem, Marie-Thérèse Martin, Claude Thal and Catherine Guillou*

Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette Cedex, France

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Abstract—Open D-ring galanthamine analogues were prepared using ring-opening reactions of the quaternarized urethane or oxazolidine functions and were evaluated for their acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibition potency.

(−)-Galanthamine **1**,[1] a tertiary alkaloid isolated from *Amaryllidaceae*, is a centrally acting, competitive and reversible inhibitor of acetylcholinesterase that enhances cognitive functions in Alzheimer's patients.[2] This drug is commercially available in Austria, and is the most recently approved acetylcholinesterase inhibitor for use in the United States and Europe.

A variety of synthetic galanthamine derivatives has been previously described including C-ring[3] and D-ring derivatives,[4] quaternary ammonium derivatives,[5] esters and carbamates of 6-*O*-demethylgalanthamine[5] and bis-interacting ligands.[6]

In continuation of our work in the galanthamine series, we report the synthesis of new optically pure open D-ring galanthamine analogues **2** and **3** which could also be the starting compounds for the synthesis of new bis-interacting ligands of type **4** (Fig. 1). Furthermore, galanthamine being also a nicotinic allosteric potentiating ligand, open D-ring galanthamine analogues will be tested for this other activity.[7]

Cleavage of the C9N10 bond of galanthamine **1** was based on D-ring opening reactions of galanthamine or oxazocine **10** with ethyl chloroformate. The benzylic cleavage of phthalidisoquinoline alkaloids by ethyl chloroformate has been previously described.[8]

Treatment of galanthamine **1** with ethyl chloroformate at room temperature afforded **5** and **6** as an inseparable mixture (80/20, respectively) in 80% yield together with the *o*-chloromethyl substituted tertiary urethane **7** (5%). Compound **7** results from a nucleophilic attack of Cl^- at the benzylic position of the quaternary urethane **5**. Subsequent heating of the **5**/**6** mixture in water and acetone yielded **8** (50%) and **6** (23%) (Scheme 1).

The second route to access open D-ring galanthamine analogues was based on degradation of the oxazocine **10** with ethyl chloroformate.

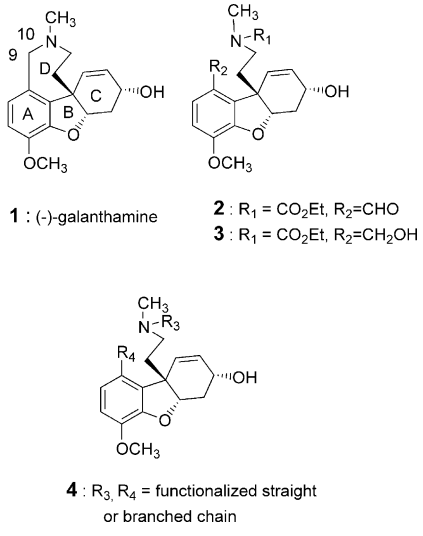

Figure 1.

*Corresponding author. fax: +33-1-6907-7247; e-mail: guillou@icsn.cnrs-gif.fr

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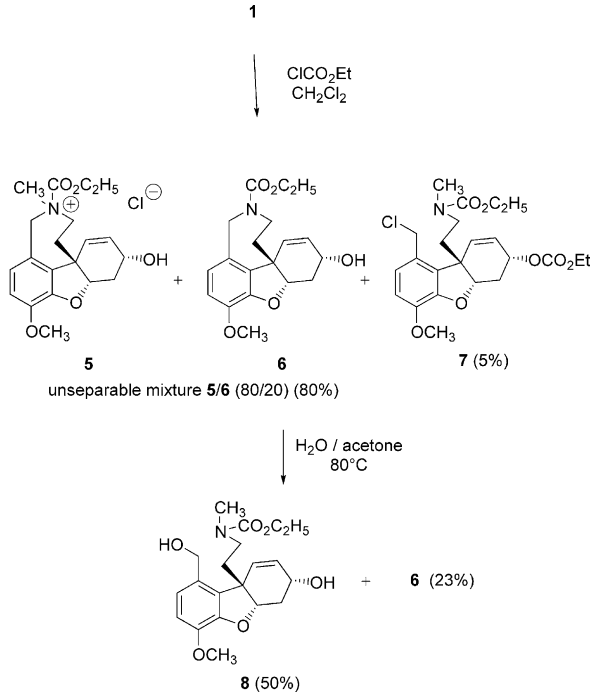
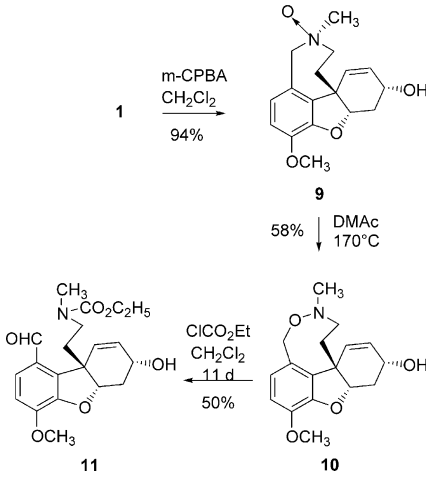


Scheme 1.

Galanthamine **1** was quantitatively converted into its *N*-oxide **9** by oxidation with *m*-chloroperbenzoic acid in dichloromethane at room temperature.[9] The heating of *N*-oxide **9** at 170 °C in *N*,*N*-dimethylacetamide afforded the corresponding undescribed Meisenheimer rearrangement[10] product **10**. It was not possible to cleave the *N–O* bond of **10** by reduction (under the following conditions: Na/NH_3; $NiCl_2{\cdot}6H_2O$; $NaBH_4$; $TiCl_3$ ethanol; $Li/EtNH_2$; SmI_2, Zn/Ac_2O) or by quaternization with dimethyl sulfate in satisfactory yield. However, reaction of **10** with ethyl chloroformate during 11 days afforded **11** in 58% yield (Scheme 2).

This reactivity may be explained by the structure of **10**, in which the nitrogen atom is not easily accessible. In particular it was found in the NMR spectrum (C_6D_6) that the *N*-methyl group showed strong NOE interactions with H9 and H12α suggesting that the methyl group is α oriented. In addition, there is a strong interaction between H1 and H12α, which hinders the α face of the molecule, where the nitrogen atom is localized (Fig. 2).



Scheme 2.

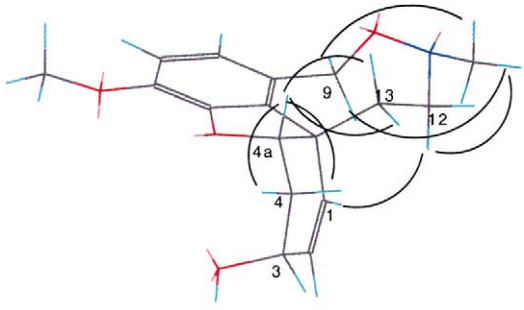
Biological Evaluation and Discussion

Newly synthesized compounds were assayed for AChE (*Electrophorus electricus*) and BChE (*Human serum*) inhibition potency by the Ellman method.[11] The results are summarized in Table 1.

As shown in Table 1, replacement of the *N*-methyl group of galanthamine **1** by a CO_2Et group (i.e., compound **6**) decreases the AChE inhibition. This could be explained by the loss of a non-conventional hydrogen bond between the *N*-methyl group of galanthamine and aspartate 72 of AChE.[12]

The potency of acetylcholinesterase inhibition decreases when the size of the D-ring increases (i.e., **10**) as well as when the D-ring is opened (i.e., **7**, **8** and **11**). The presence of an electron withdrawing group on the A-ring of galanthamine enhances the BChE inhibition potency (i.e., **11**) compared to the other analogues.

The marked BChE/AChE selectivity of compounds **8**, **10**, **11** could be explained by the fact BChE seems to be better able than AChE to accommodate steric bulk around the catalytic site.



10

Figure 2. Principal observed NOESY correlations.

Table 1. In vitro inhibition of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE)

Compd	AChE[a]	BChE[b]	Selectivity[c]	
	IC_{50} (μM)	IC_{50} (μM)	AChE	BChE
6	67±8	300±10	4.5	
7	650±30	790±40	1.2	
8	580±50	216±30		2.7
10	9900±100	960±30		10
11	1000±400	155±3		6.5
1	0,35	18,6	53	
Tacrine	16±2 nM	0.9±0.01 nM		17.7

[a]The source of AChE was *Electrophorus electricus*.
[b]The source of BChE was *Human serum*.
[c]The selectivity is defined as: selectivity for AChE = IC_{50}(BChE)/IC_{50}(AChE), and selectivity for BChE = IC_{50}(AChE)/IC_{50}(BChE).

In summary, open D-ring galanthamine analogues **7**, **8**, **11** have been prepared. These compounds are less active than the parent compound galanthamine. It my be possible to increase the inhibitory potency of these compounds by functionalization of the nitrogen atom with straight or branched chain in order to permit interaction with tryptophan 279 located at the peripheral site of AChE. Bis interacting ligands have been shown to be more potent than galanthamine.[6] Alternatively, these compounds could perhaps help prevent the formation of β-amyloid plaques. According to recent investigations, the peripheral site of AChE promotes aggregation of β-amyloid peptides,[13] which causes plaque formation known to play an essential role in the development of Alzheimer's dementia.[14] This possibility is presently being investigated.

Acknowledgements

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