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Iminosugars as a new class of cholinesterase inhibitors

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ABSTRACT

To further extend the scope of iminosugar biological activity, a systematic structure–activity relationship investigation has been performed by synthesizing and evaluating as cholinesterase inhibitors a library of twenty-three iminoalditols with different substitutions and stereochemistry patterns. These compounds have been evaluated in vitro for the inhibition of cholinesterases (different sources of acetylcholinesterase and butyrylcholinesterase). Some compounds have IC_{50} values in the micromolar range and display significant inhibition selectivity for butyrylcholinesterase over acetylcholinesterase. These are the first examples of iminosugar-based inhibitors of cholinesterases.

Alzheimer disease (AD) is a progressive neurodegenerative disorder of the central nervous system (CNS) that affects mainly aged population. AD is characterized by profound memory impairments, emotional disturbance, and also personality changes. The main pathological changes in the AD brain are extracellular amyloid plaques,[1] intracellular neurofibrillary tangles containing abnormally hyperphosphorylated tau protein,[2] and loss of neurons in the nucleus basalis of Meynert and the hippocampus. AD is characterized by a pronounced alteration of the cholinergic system and other neurotransmitter systems (glutamate and serotonine). The cholinergic hypothesis postulates that memory impairments in patients with AD result from a deficit of cholinergic function in the brain.[3] Most currently prescribed AD drugs aim to increase the level of acetylcholine (ACh) in the brain by inhibiting acetylcholinesterase (AChE). However, clinical use of AChE inhibitors is sometimes limited mainly due to their adverse effects and modest benefits to AD patients. Therefore, novel more effective therapies, including AChE inhibitors, need to be developed. In addition to its catalytic activity, AChE exerts secondary non-cholinergic functions related to its peripheral binding site on differentiation, cell adhesion, in mediating the processing and deposition of β-amyloid peptide (Aβ).[2] It was postulated that AChE binds through its peripheral site to the non-amyloidogenic form of β-amyloid protein acting as a chaperone protein and inducing conformational change to the amyloidogenic form with the subsequent amyloid fibril formation. Moreover, it has been shown that molecules which are able to interact with both the active and peripheral sites of AChE could prevent the aggregating activity of AChE towards Aβ besides the inhibitory activity.[3–5] Therefore, inhibitors with dual binding to AChE represent a new therapeutic strategic option.[6–8] The cholinergic neurotransmission could also be enhanced by inhibiting butyrylcholinesterase (BuChE). BuChE has a key role that can partly compensate for the action of AChE.[9] AChE activity decreases progressively in certain brain regions from mild to severe stages of AD to reach 10–15% of normal values, whereas BuChE levels are unchanged or rise with disease progression.[10] The ratio of BuChE to AChE changes enormously in cortical regions affected by AD from 0.2 to 11.[11] Furthermore, BuChE may also have a role in the aggregation of Aβ besides the AChE.[12]

In continuation of our on-going research on new AChE inhibitors,[13,14] we present herein the first examples of iminosugar-based acetylcholinesterase inhibitors. Iminosugars, which are sugar mimetics with a nitrogen atom replacing the endocyclic oxygen,[15] are known as potent glycosidase inhibitors since the 70s.[16] From the early 90s, the scope of their biological activity has been extended to the inhibition of a number of enzymes of therapeutic interest such as glycosyltranferases,[17,18] glycogen

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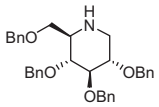
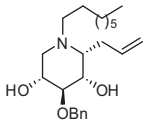
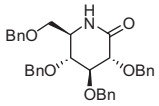
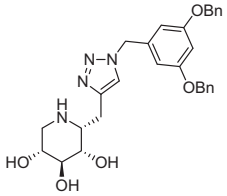
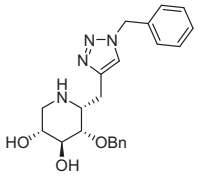
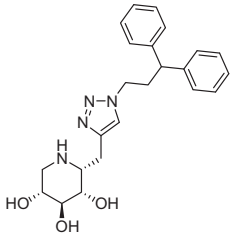
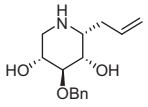
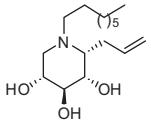
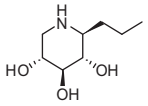
Table 1
AChE and BuChE inhibitory activities of tacrine (**1**) and iminosugars **2–10**[a]

Compound		IC_{50} (μM)			
		*Ee*AChE	*h*AChE	*h*BuChE	*h*AChE/*h*BuChE selectivity[b]
2		3.0 ± 0.6	60 ± 9	2.0 ± 0.1	30.0
3		63 ± 10	22.0 ± 1.2	3.0 ± 0.1	7.3
4		2.0 ± 0.8	46.0 ± 1.8	4.0 ± 0.4	11.5
5		n.i.[c]	n.i.[c]	1.2 ± 0.1	n.d.[d]
6		n.i.[c]	n.i.[c]	7.0 ± 0.1	n.d.[d]
7		n.i.[c]	n.i.[c]	15.0 ± 0.5	n.d.[d]
8		n.i.[c]	n.i.[c]	61.0 ± 1.6	n.d.[d]
9		n.i.[c]	n.i.[c]	161 ± 29	n.d.[d]
10		n.i.[c]	n.i.[c]	210 ± 13	n.d.[d]
Tacrine (**1**)		0.136 ± 0.01	0.484 ± 0.004	0.073 ± 0.07	6.6

[a] Values are expressed as the mean of three experiments ± standard error. IC_{50} inhibitory concentration (μM) of AChE from *Electrophorus electricus* (*Ee*AChE) or human recombinant (*h*AChE) or BuChE from human serum (*h*BuChE).
[b] IC_{50} (*h*AChE)/IC_{50} (*h*BuChE).
[c] n.i.: no inhibition (less than 50% inhibition at 250 μM).
[d] n.d.: not determined.

phosphorylases,[19,20] nucleoside-processing enzymes[21] and very recently protein kinases.[22] In 2004, based on their study on metalloproteinase inhibitors, the group of Nishimura reported the first example of a family of enzymes using non-sugar substrates that are inhibited by iminosugars.[23] As a consequence of their wide inhibitory spectrum, iminosugar derivatives are now lead compounds for the treatment of a variety of diseases including diabetes,[24] cancer,[25] viral infections,[26,27] cystic fibrosis[28] and lysosomal diseases.[29,30] To further extend the biological relevance of iminosugars, we have performed a systematic structure–activity relationship investigation by synthesizing and evaluating as cholinesterase inhibitors a library of iminoalditols. These compounds may be seen as constrained choline mimetics thanks to their ability to become protonated in physiological media,[15,16] thus generating