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Novel carbamate derivatives as selective butyrylcholinesterase inhibitors

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ABSTRACT

Selective butyrylcholinesterase inhibitors could be the promising drug candidates, used in treatment of Alzheimer's disease. The study describes the synthesis and biological activity of novel carbamate derivatives with *N*-phenylpiperazine, *N*-benzylpiperazine and 4-benzylpiperidine moieties. Biological studies revealed that most of these compounds displayed significant activity against BuChE. Compound **16** (3-(4-phenyl-piperazin-1-ylmethyl)-phenyl phenylcarbamate) turned out to be the most active (IC_{50} = 2.00 μM for BuChE). For all synthesized compounds lipophilicity and other physicochemical properties were calculated using computer programs. Relationship between these properties and activity was also checked. Binding mode with enzyme and the ensuing differences in activity were explained by the molecular modeling studies.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder associated with progressive memory loss [1]. One of its most characteristic features is decreased level of the neurotransmitter acetylcholine (ACh) [2]. Cholinergic neurotransmission is terminated by two cholinesterases (ChEs), which play essential role in the hydrolysis of ACh [3]. Acetylcholinesterase (AChE) hydrolyses the acetylcholine in the postsynaptic area. The second enzyme, butyrylcholinesterase (BuChE), called also pseudo-cholinesterase, is able to hydrolyse ACh too but is less substrate specific than AChE. The inhibition of cholinesterases increases the ACh level in the brain and thus has been used in the symptomatic treatment of AD [4]. Currently, cholinesterase inhibitors like rivastigmine (**1**) and donepezil (**2**) are the standard treatment for AD [5]. These drugs belong to a different chemical classes of compounds and they differ from each other in a potency and selectivity towards AChE and BuChE. In spite of limited clinical efficiency of currently used cholinesterase inhibitors, both enzymes are still valuable targets to search for new potential anti-AD agents [6–8]. Many recent studies indicated that BuChE played more important role in the AD brain and selective inhibitors of BuChE could be promising drug candidates [9,10].

Inhibition of acetylcholinesterase and butyrylcholinesterase by carbamates is based on the carbamoylation of serine (SER198 in BuChE) in the catalytic site of the enzyme. Higher persistence of carbamate ester in comparison to acetate ester leads to inhibition of the enzyme (Fig. 1) [11,12]. Non-carbamate part of ligand decides about selectivity, binding dynamics and can increase potency by non-covalent binding inside the active site.

The present study describes the synthesis and preliminary *in vitro* screening of three series of carbamate derivatives designed as potential cholinesterase inhibitors. Considering the structure of rivastigmine which is non-selective cholinesterase inhibitor as well as the structure of cymserine (**3**) - selective butyrylcholinesterase inhibitor, we have designed new structures with different alkyl- and aryl-carbamate moieties (Fig. 2). Our earlier studies [13] demonstrated that among two series of alkyl- and arylcarbamate derivatives with *N*-benzylpiperazine or *N*-benzylpiperidine moiety, compounds of the former series were selective BuChE inhibitors while the further series represented non-selective cholinesterase inhibitors. Two most active agents (**4** and **5**) displayed inhibitory potency against BuChE with IC_{50} in micromolar range (comp. **4** - IC_{50} (BuChE) = 10.0 μM; comp. **5** - IC_{50} (BuChE) = 5.75 μM and 40% AChE inhibition at 100 μM). We assumed that replacement of an amide bond in their structure by amine moiety could improve potency of compounds and change their selectivity towards enzymes. As an amine fragment we selected tertiary amine contained in cyclic derivatives: *N*-phenylpiperazine, *N*-benzylpiperazine and 4-benzylpiperidine.

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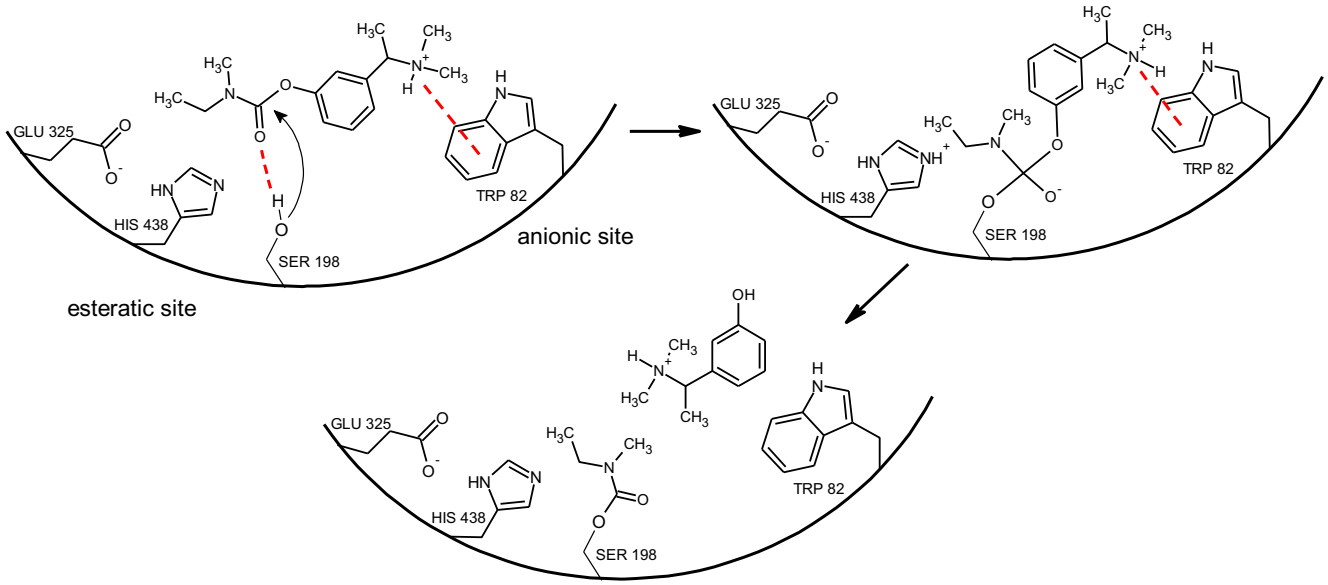

Fig. 1. Mechanism of BuChE carbamoylation by rivastigmine [12]. Numeration according to human BuChE (PDB code: 1P0I).

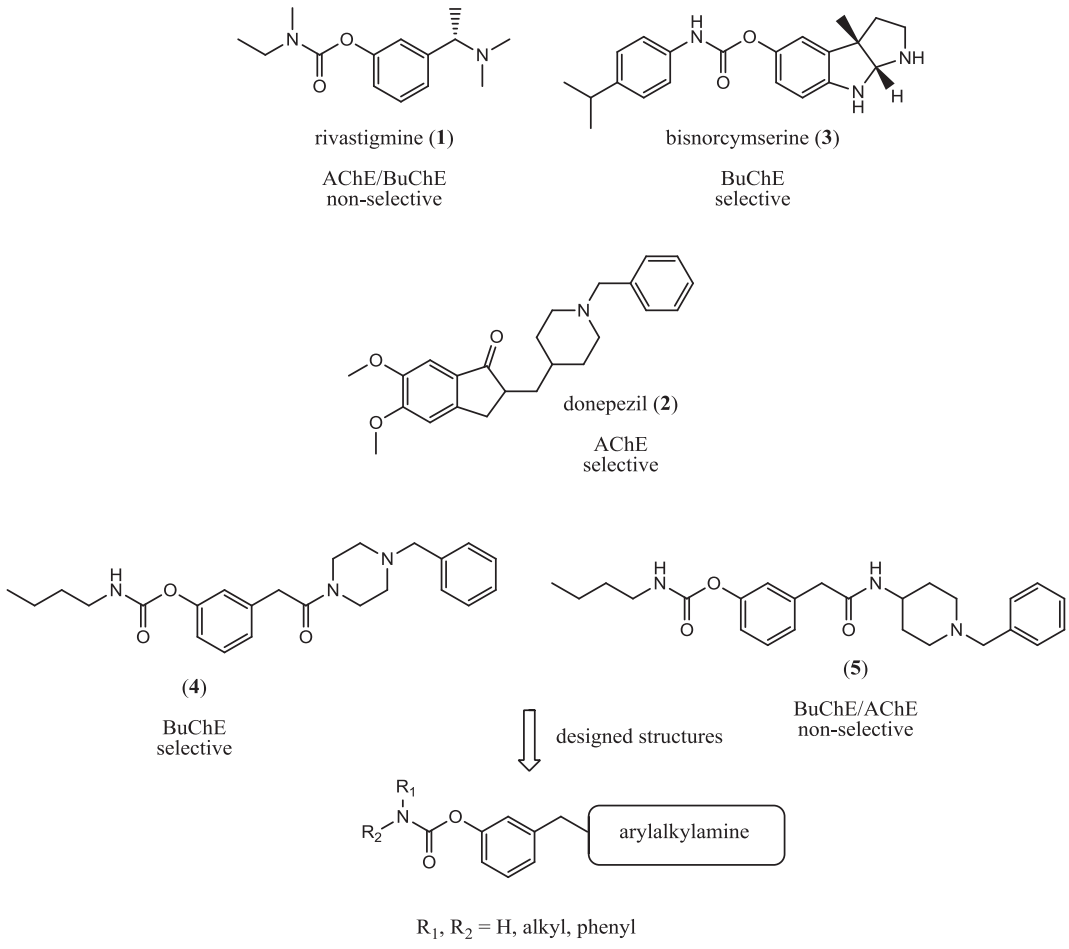

Fig. 2. Structures of selected cholinesterase inhibitors and schematic presentation of designed carbamate derivatives.