EFFICIENT FIVE-STEP SYNTHETIC PATHWAY TOWARD BIOLOGICALLY ACTIVE CARBAMATES

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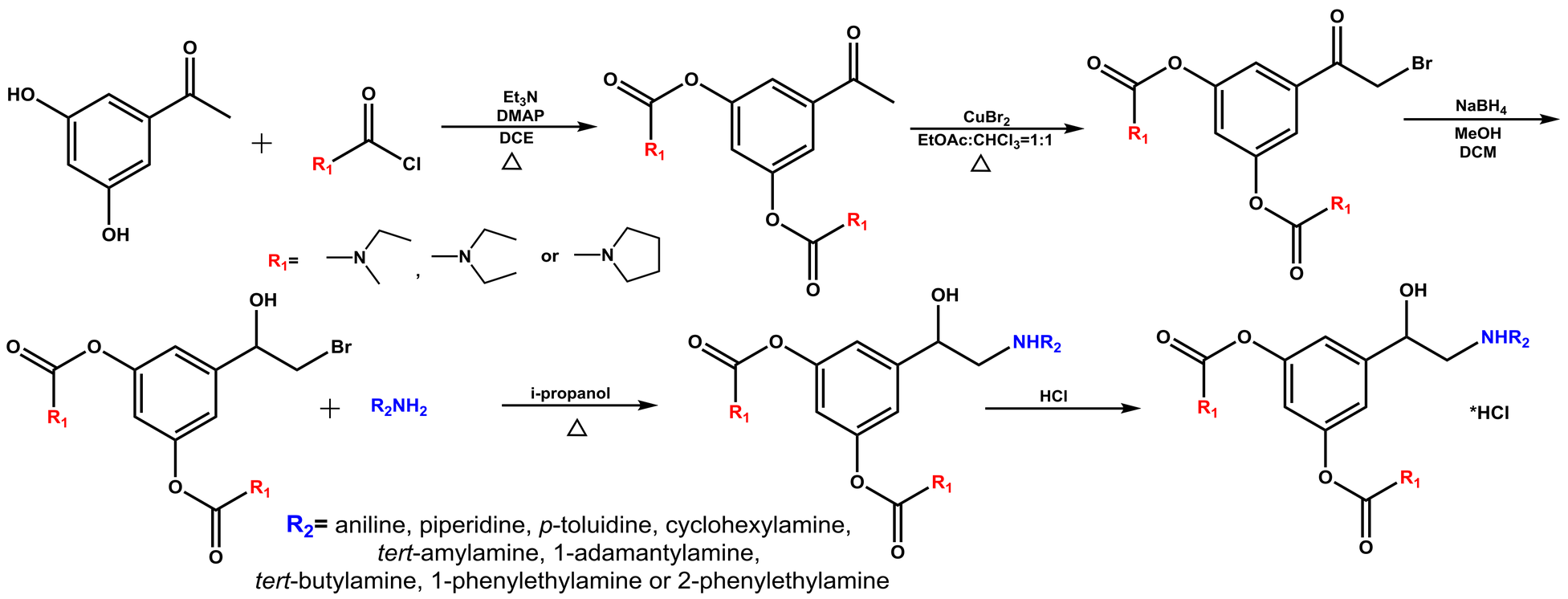
Introduction

The carbamate group is a structural and functional element in many approved and marketed drugs and prodrugs used in the treatment of neurodegenrative disorders (ND), cancer, epilepsy and hepatitis C due to its very good chemical and proteolytic stability, ability to penetrate the cell membranes and resemblance to peptide bonds. The treatment of patients with ND characterized by low concentrations of the neurotransmitter acetylcholine (ACh), as in Alzheimer's disease (AD), is based on restoring ACh levels by inhibiting acetylcholinesterase (AChE) and is successful only in alleviating symptoms. Recent studies have pointed to a related cholinesterase named butyrylcholinesterase (BChE), also capable of hydrolysing ACh, as a new possible target of cholinesterase inhibitors with the potential to be used in the middle and late stages of AD. Carbamates physostigmine, pyridostigmine, rivastigmine and neostigmine are AChE or non selective cholinesterase inhibitors currently in use for the treatment of NDs like AD or *Mystenia gravis.* The aim of this study was to synthesize 27 carbamates with an alkyl chain of different size on the nitrogen atom of a carbamate group and different amine moieties to be tested as human AChE and BChE inhibitors.

Synthesis of carbamates

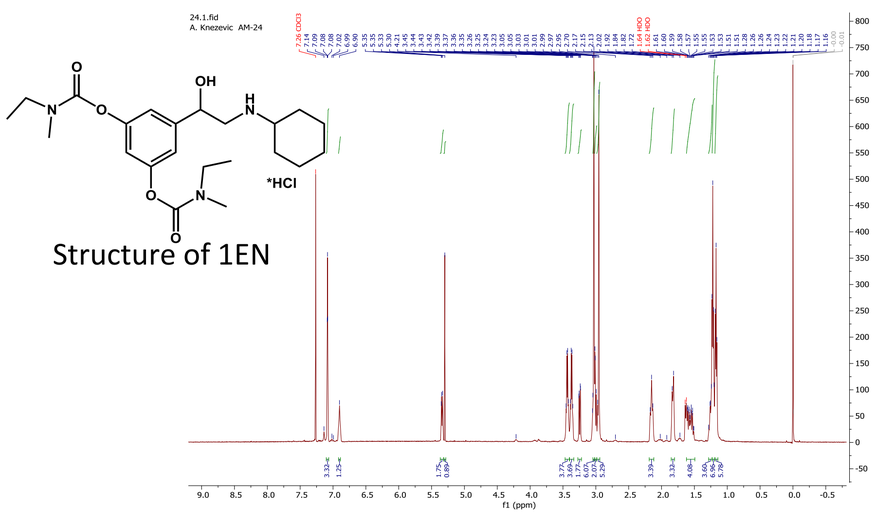
Carbamates were prepared from 3,5-dihydroxyacetophenone, as a starting compound, by five-step reaction pathway



Scheme 1. Reaction pathway for synthesis of carbamates

Characterization

All of the prepared compounds were characterized by ^1H and ^{13}C NMR spectroscopy and HRMS



Structure of 1EN

Figure 1. ^1H spectra of 1EN

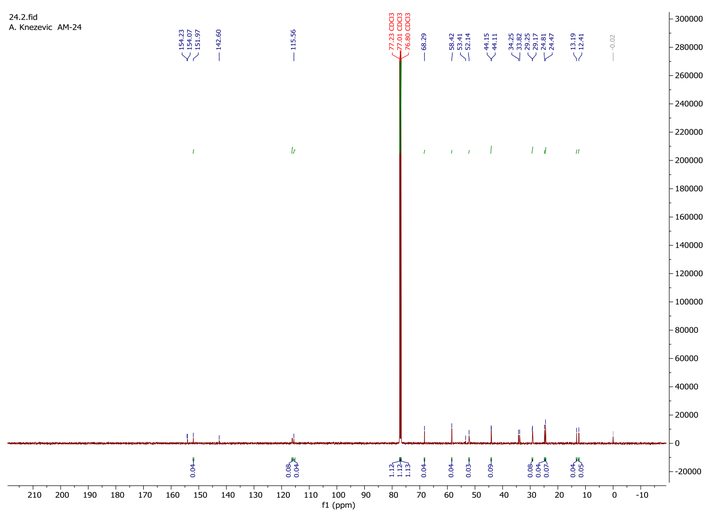


Figure 2. ^{13}C spectra of 1EN

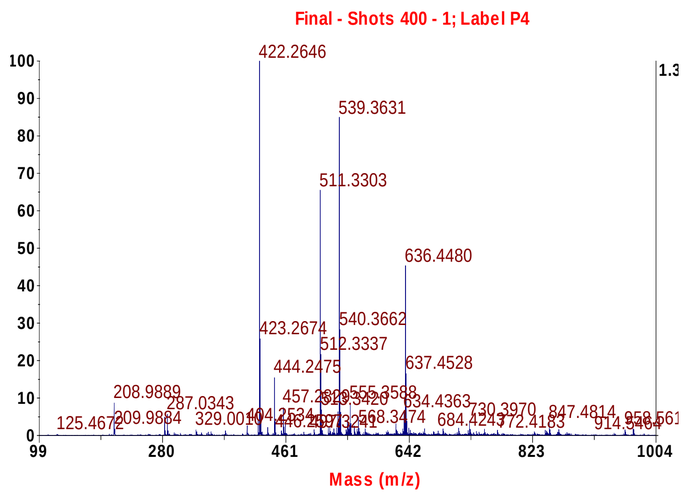


Figure 3. HRMS spectra of 1EN

Conclusion

27 carbamates with differently sized alkyl chains were synthesized in good yields up to 50%

Future work

- Determination of compounds inhibition potency toward human AChE and BChE
- Biological evaluation of compounds (cytotoxicity, metabolic stabillity, oxidative capacity)
- Selection of compound with potential to be used as drug for treatment of NDs

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