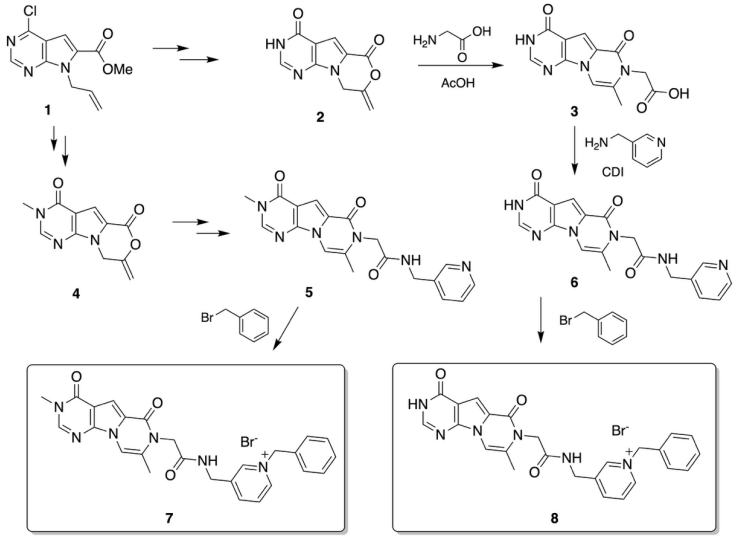
SYNTHESIS OF NEW PYRAZINO[1',2':1,5]PYRROLO[2,3-*d*]PYRIMIDINE-BASED ACETYLCHOLINESTERASE INHIBITORS

Muzychka L. V., Muzychka O. V., Smolii O. B.
V. P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry
of the NAS of Ukraine, Kyiv, Ukraine
liubovmuzychka@gmail.com

Alzheimer's disease is a prevalent type of dementia characterized by progressive memory loss. Inhibition of acetylcholinesterase is crucial for improving cognitive function in patients with Alzheimer's disease. FDA-approved drugs, such as donepezil, that inhibit acetylcholinesterase are used for the symptomatic treatment of Alzheimer's disease.

Considering the previous studies of acetylcholinesterase inhibitors, here we propose the synthesis of new pyrazino[1',2':1,5]pyrrolo[2,3-*d*]pyrimidine-based compounds with benzylpyridinium moiety. The targeted pyrazino[1',2':1,5]pyrrolo[2,3-*d*]pyrimidine derivatives **7** and **8** were obtained by boiling **5** and **6** with benzyl bromide in acetonitrile. The amide **6** was prepared by conversion of the oxazine moiety of **2** into a pyrazine ring (compound **3**), followed by condensation of the acid with 3-(aminomethyl)pyridine. The 3-methyl-substituted analogue **5** was synthesized via a similar route, starting from 8-methylene-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine **4.** The two-step synthesis of **2** and **4** commenced from methyl 7-allylpyrrolo[2,3-*d*]pyrimidine-6-carboxylate **1**.



The new pyrazino[1',2':1,5]pyrrolo[2,3-*d*]pyrimidine derivatives **5-8** were evaluated for their ability to inhibit electric eel acetylcholinesterase. The results showed that pyrazino[1',2':1,5]pyrrolo[2,3-*d*]pyrimidines **7** and **8** containing the *N*-benzylpyridinium moiety were more potent acetylcholinesterase inhibitors than their unsubstituted analogues **5** and **6**. Compounds **7** and **8** inhibited the enzyme activity with IC_{50} values of 0.14 and 0.36 μM, respectively. The obtained data can be used for the development of new acetylcholinesterase inhibitors with the pyrazino[1',2':1,5]pyrrolo[2,3-*d*]pyrimidine scaffold.