SYNTHESIS OF NEW DONEPEZIL ANALOGS AS ACETYLCHOLINESTERASE INHIBITORS

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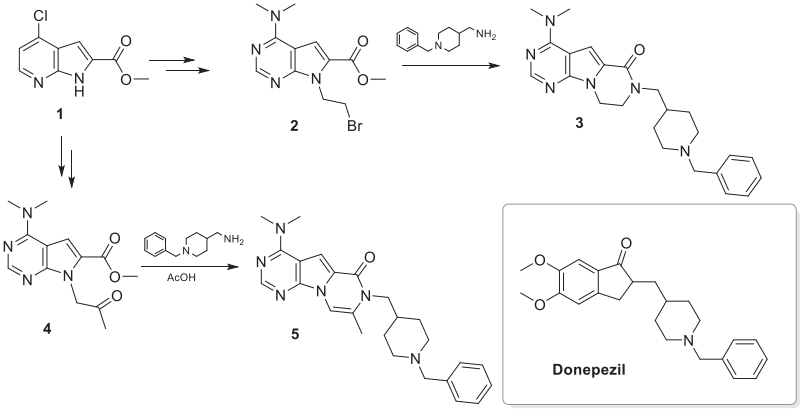
Alzheimer's disease is a progressive neurodegenerative disorder associated with dysfunction of the cholinergic system. The inhibition of acetylcholinesterase, the enzyme that catalyzes the hydrolysis of acetylcholine, is one of the approaches for the symptomatic treatment of Alzheimer's disease. Among the acetylcholinesterase inhibitors, donepezil is a drug approved by the FDA.

Taking into account the previous studies of acetylcholinesterase inhibitors as structural analogs of donepezil, here we propose the synthesis of new pyrazino[1',2':1,5]pyrrolo[2,3-*d*]-pyrimidine derivatives with a benzylpiperidine moiety.



The target pyrazino[1',2':1,5]pyrrolo[2,3-*d*]pyrimidine derivatives **3** and **5** were obtained by refluxing carboxylate **2** with excess [(1-benzylpiperidin-4-yl)methyl]amine or by heating compound **4** with *in situ* amine acetate. The two-step synthesis of 7-alkyl- pyrrolo[2,3-*d*]pyrimidine-6-carboxylates **2** and **4** was started from methyl 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate **1**. The structures of the synthesized compounds were confirmed by elemental analysis, ^{1}H NMR, ^{13}C NMR and MS spectral data.

The new pyrazino[1',2':1,5]pyrrolo[2,3-*d*]pyrimidine derivatives **3** and **5** were evaluated for their ability to inhibit acetylcholinesterase from Electric eel. It was found that the presence of a hydropyrazine moiety in the structure of inhibitor **3** led to a decrease in inhibitory activity towards the enzyme compared to compound **5**. Compounds **3** and **5** inhibited enzyme activity with an IC_{50} value of 10.09 and 0.46 μM respectively. The obtained data can be used for the development of potent acetylcholinesterase inhibitors with a pyrazino[1',2':1,5]pyrrolo[2,3-*d*]-pyrimidine scaffold.