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Novel coumarin analogues: As new acetylcholinesterase inhibitors

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Background and Aims: Alzheimer's disease (AD), a progressive and degenerative disorder of the brain, is believed to be the most common cause of dementia among the elderly. Up to now most of the drugs approved for AD treatment are acetylcholinesterase (AChE) inhibitors (AChEIs) which can enhance cholinergic neurotransmission by increasing acetylcholine (ACh) availability in the synaptic cleft. Ensaculin composed of a benzopyran with a piperazine substituted moiety has been used clinically as its HCl salt with trade name of KA-672 HCl for treating AD as AChEI for a long time. So ensaculin, a coumarin analogue, was chosen to be the parent compound in this study, and the analogues designed were expected to have anti-AChE activity.
Methods: for the synthesis of target compounds, in the first step 4-hydroxycoumarin was treated with ethylbromo acetate or butyrate and in the next step the latter compounds were treated with several arylpiperazine or piperidine to obtain corresponding amide.
Results: The anticholinesterase activity of synthesized compounds was measured using colorimetric Ellman's method. A significant AChE inhibitory activity was observed for most of these synthesized compounds.
Conclusions: in this work we synthesized novel coumarin analogues with arylpiperazine or piperidine functions as substitution on the positions 4 of coumarin ring were designed and synthesized for studying their potential for treating Alzheimer's disease(AD). Their anticholinesterase activities were assayed according to Ellmann's method against freshly prepared acetylcholinesterase (AChE) from Electrophorus electricus using donepezil as the reference compound. Pharmacological study and preliminary structure–activity relationships showed that good to excellent inhibitory for these compounds.

Keywords: Alzheimer; Ensaculin; Coumarin; Anticholinesterase; Arylpiperazine; Arylpiperidine