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New functional caffeine analogs as possible multitarget potentiators of the cholinergic system

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Since cholinergic deficit is characteristic of Alzheimer's disease, two possible molecular targets for its treatment are the acetylcholinesterase (AChE) and the nicotinic acetylcholine receptors (nAChRs). In previous studies of our group, we found that caffeine behaves as an agonist of the nAChRs and confirmed that it inhibits the AChE. We subsequently synthetized hybrid caffeine analogs by connecting a theophylline groupwith a pyrrole group via a carbon linker of different lengths (3 to 7 carbon atoms). All the compounds inhibited the AChE and activated the nAChR with higher potency than caffeine. Some of them conduct the receptor to a desensitized and agonist-refracting state, while others make the receptor quickly return to a resting, agonist-responding state. Based on these results, in this work we synthetized three new hybrid analogsof the synthetic compound with a linker of 5 carbon atoms, which belongs to the desensitizing group, maintaining the theophylline structure but changing the pyrrole group by piperidine, 1-methylpiperazine or dimethylamine. All analogs inhibited the AChE with higher potency than the precursor. Using Crystal violet (CrV) fluorescence probe, an open channel blocker with higher affinity for the desensitized thanfor the resting state of the nAChR, we observed that the compounds with piperidine and 1-methylpiperazinecaused nAChR conformational changes that could be related to a conformational transition corresponding toreceptor activation followed bya stabilization in the desensitized state. In contrast, the compound with the dimethylamine group did not conduct the nAChR to a desensitized state. Our results provide new insights into structure-activity relationship for this group of functional multi-target drugs giving valuable tools to transform the search of new drugs from random screening into a detailed rational drug designof new interventional therapies in neurological diseases.