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New caffeine analogs as promising multitarget drugs for cholinergic deficiency

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Previously, we found that caffeine acts as a partial agonist of both muscle and neuronal nicotinic acetylcholine receptors (nAChR) and confirmed that it also inhibits acetylcholinesterase (AChE). Cholinergic deficiency is a characteristic feature of several pathologies, such as myasthenia gravis, certain types of congenital myasthenic syndromes and Alzheimer's disease whereas AChE and nAChR are the two main molecular targets for its treatment. Thus, caffeine becomes a promising new multitarget leader for both molecular targets. In this study, we synthesized novel bifunctional caffeine derivatives. All of them were more potent AChE inhibitors than caffeine. By electrophysiological and fluorescence spectroscopy studies, we observed that some of them also behaved as partial agonists of muscle nAChR, but not all stabilized the nAChR in a desensitized state. *In silico* studies were performed to understand the molecular mechanism underlying these results. Taken together, all these results give valuable information about the necessary pharmacophoric chemical properties for both nAChR and AChE molecular targets and provide knowledge about the mechanisms of modulation of these both pharmacological targets which may have implications for the design of new therapeutic strategies in neurological disorders.

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