XIV Spanish Drug Discovery Network Meeting

DESIGN AND SYNTHESIS OF NEW CAFFEINE DERIVATIVES AS MULTITARGET AGENTS FOR THE THERAPY OF ALZHEIMER'S DISEASE

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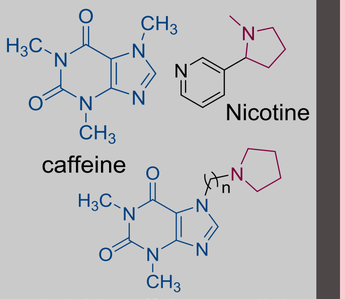
01 INTRODUCTION

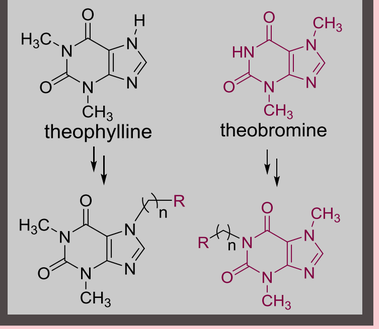
Alzheimer's Disease (AD), the most prevalent neurodegenerative disorder in the elderly, is mainly described by a progressive cognitive decline. Current drugs for the treatment of AD, such as tacrine, donepezil, rivastigmine, and galantamine, are used to inhibit AChE. Unfortunately, these drugs can alleviate the symptoms of AD but are unable to prevent disease progression. For this reason, the search for new drugs is currently going on, focused on molecules with the ability to act on different targets at the same time. Recently, Antollini et al. demonstrated that caffeine (naturally occurring xanthine) is an agonist of nAChRs and also inhibits AChE activity.[1] Subsequently, our group synthesized a series of caffeine-pyrrolidine hybrids that were potent AChE inhibitors and activate both muscle and α7 nAChRs with high potency.[2]



1 C. Fabiani, A. P. Murray, J. Corradi and S. S. Antollini, *Neuropharmacology*, 2018.
2 C. Fabiani, B. Biscussi, J. P. Munafó, A. P. Murray, J. Corradi and S. S. Antollini, *Mol. Pharmacol.*, 2022.

02 OBJECTIVES

Based on the studies mentioned, the aim of this work was to obtain more potent caffeine analogs. Appling once again a simple and efficient methodology developed in our research group[3], a series of new derivatives were synthesized from theophylline and theobromine as starting material, which bears similarity to caffeine, and using different amines. Here we demonstrate that the synthetized compounds behave as AChE inhibitors with greater potency than previously reported caffeine-pyrrolidine hybrids.



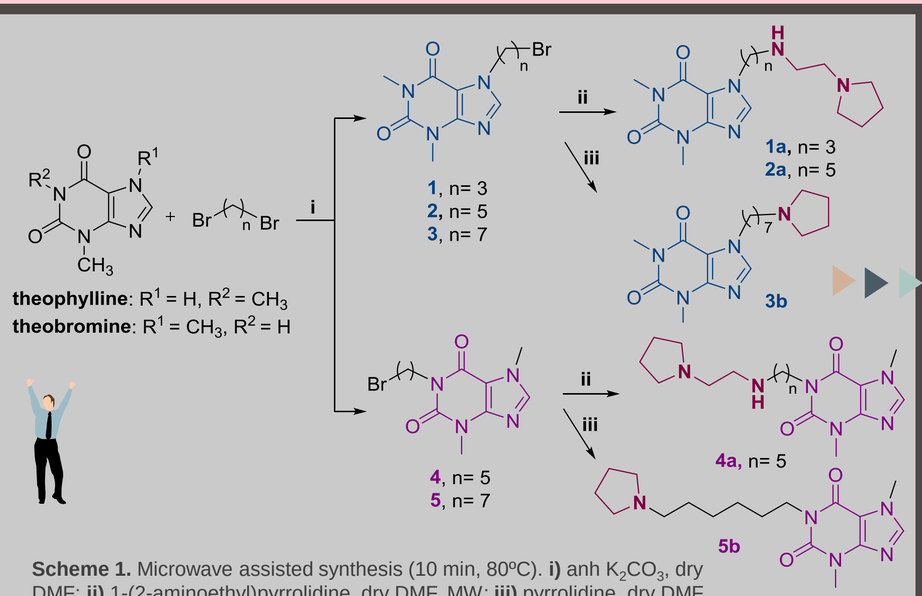
03 RESULTS

Based on the experience of our group, and with the aim of obtaining more potent caffeine hybrids than those previously reported, we decided to synthesize new caffeine analogs by replacing the pyrrolidine fragment with other amino groups. This strategy has proven successful when we have applied it to different molecular scaffolds.[3,4]

The enzymatic inhibition against AChE was evaluated for compounds **1a – 4a**; **5b** and compared to the activity observed for caffeine-pyrrolidine hybrids (**3b**).

The results in Table 1 show that the derivatives **2a** and **4a** (IC_{50} values at nanomolar scale) showed a higher inhibition potency than the already reported caffeine-pyrrolidine hybrids.

3 B. Biscussi, V. Richmond, C. J. Baier, P. Arroyo Mañez and A. P. Murray, *CNS Neurol. Disord. - Drug Targets.*, 2020.
4 B. Biscussi, M. A. Sequeira, V. Richmond, P. Arroyo Mañez and A. P. Murray, *J. Photochem. Photobiol. A Chem.*, 2021.

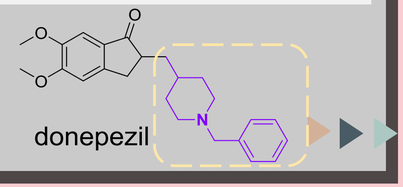


Scheme 1. Microwave assisted synthesis (10 min, 80ºC). **i)** anh K_2CO_3, dry DMF; **ii)** 1-(2-aminoethyl)pyrrolidine, dry DMF, MW; **iii)** pyrrolidine, dry DMF

Table 1. Inhibition of cholinesterase activity by caffeine derivatives

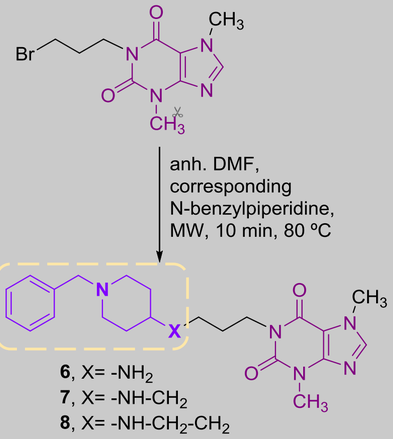
Comp.	n	*ee*AChE IC_{50} (μM)	*h*AChE IC_{50} (μM)
1a	3	1.81	n.d
2a	5	0.046	n.d
4a	5	0.013	0,093
5b	7	0,19	n.d
3b[2]	7	0,22	n.d
donepezil[5]		0.035	0.029

n.d. not determined.
5 F. Li, Z. M. Wang, J. J. Wu, J. Wang, S. S. Xie, J. S. Lan, W. Xu, L. Y. Kong and X. B. Wang, J. *Enzyme Inhib. Med. Chem.*, 2016.



03 MORE DERIVATIVES!

The results were motivating to design and synthesize new products inspired by the structure of donepezil in order to obtain multitargeted hybrids.



These new hybrids are currently being evaluated as inhibitors of AChE, BChE, MAO A and B and BACE-1.

04 CONCLUSIONS

A series of new caffeine derivatives was obtained, in a sequence of efficient microwave assisted reactions. The derivative **4a** (n=5; R= -NH-C_2-pirrolidine) was found to be the most potent AChE inhibitor of the series (*ee*AChE IC_{50} = 13 nM; *h*AChE IC_{50}= 93 nM) even more than the caffeine-pyrrolidine analogs. In addition, three new caffeine - N-benzylpiperidine hybrids were synthesized and studies on their activity against different molecular targets are underway.

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