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Planta Med 2014; 80 - P1L20
DOI: 10.1055/s-0034-1394678

Xanthenedione derivatives, new promising acetylcholinesterase inhibitor agents

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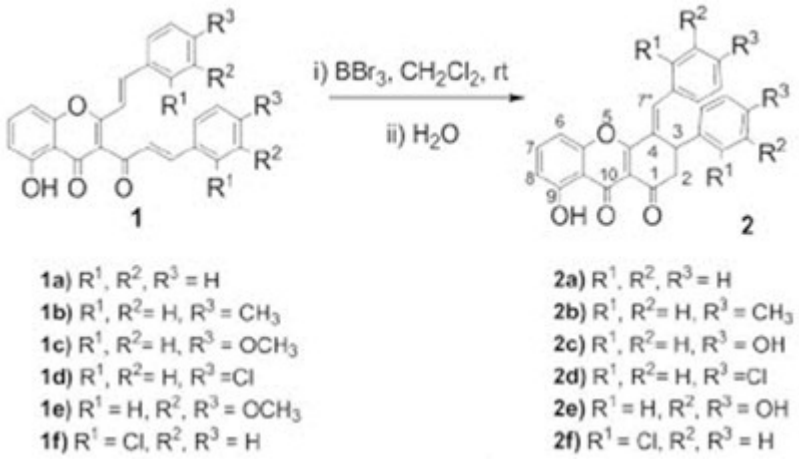
- Congress Abstract

Acetylcholinesterase inhibitors (AChEIs) are employed in medicine mostly for correcting the effects of insufficient levels of acetylcholine [1]. Xanthones are a class of secondary metabolites associated with important pharmacological properties, being some of its derivatives AChEIs [2]. Xanthenedione derivatives are not widely spread in nature but their synthesis and bioactivities evaluation is still a hot topic. Following our interest in the synthesis of biologically active compounds, several xanthene-1,9(2*H*)-diones (*2a*-*2f*) were synthesized by simple and efficient methodologies from (*E*,*E*)-3-cinnamoyl-5-hydroxy-2-styrylchromones (Scheme 1) [3] and their acetylcholinesterase activity evaluated by a modification of the Ellman's method [4]. The results (Table 1) showed that variations in the substitution and hydroxylation pattern seem to be important for their activity, being the xanthenedione bearing a catechol unit the most potent AChEI, even more active than galantamine, an AChEI alkaloid used clinically in early stages of Alzheimer's disease. SAR studies showed that the presence of hydroxyl 3-aryl and 4-benzylidene moieties is essential for the activity. Furthermore xanthenedione *2c* showed a combination of partially competitive and non-competitive inhibition, while xanthenedione *2e* shows an almost pure competitive type inhibition. The most active xanthenediones *2e* and *2c* present zero violations of Lipinski's 'rule of five' and xanthenedione *2c* combine higher AChE activity with good oral bioavailability properties (TPSA < 140 Å2). The results suggest that they may be

excellent templates for drugs to be used in the prevention and treatment of neurodegenerative diseases.



Tab. 1: Acetylcholinesterase inhibitory effect of xanthenediones (2) and some intermediates (1).

Compounds	*Anti-AChE* IC_{50} *(μM ± SD, n = 4)*
1a	> 381
1c	122 ± 2.1
2a	> 381
2b	> 355
2c	41.1 ± 6.1
2 d	> 325
2c	31.0 ± 0.09
2f	> 325
Galanthamine	211.8 ± 9.5

Acknowledgements: Thanks are due to FCT, EU, QREN, FEDER and COMPETE, for funding the QOPNA research unit (project PEst-C/QUI/UI0062/2013; FCOMP-01 – 0124-FEDER-037296) and the Portuguese National NMR Network and also Azores University and FRC/Azores for funding CIRN.

Keywords: Xanthones, xanthene-1,9(2 H)-diones, acetylcholinesterase inhibitors, synthesis

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