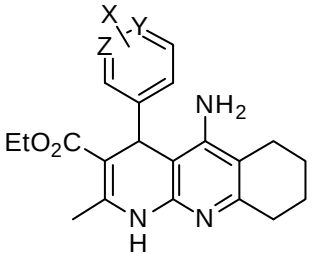
Tacripyrines have been designed by combining an acetylcholinesterase (AChE) inhibitor (**tacrine**) with a **1,4-dihydropyridine** calcium antagonist, such as nimodipine, and are targeted to develop a multitarget therapeutic strategy to confront Alzheimer's disease (AD).



Tacripyrines
(Ethyl 5-amino-4-aryl-2-methyl-1,4,6,7,8,9-hexahydrobenzo[b]
[1,8]naphthyridine-3-carboxylates)

Tacripyrines are selective and potent AChE inhibitors, in the nanomolar range, neuroprotective agents, showing moderate Ca^{2+} channel blocking effect, and cross the blood-brain barrier, emerging as lead candidates for treating AD.
Particularly, the mixed type inhibition of hAChE activity of ***p*-methoxytacripyrine** (IC_{50} = 15 nM) is associated to a 30.7% inhibition of the pro-aggregating action of AChE on the β-amyloid (Aβ) and a moderate inhibition of Aβ self-aggregation (34.9%). The racemate has been separated, and both enantiomers have been investigated for their ChE and Aβ enzymatic activities.
Thus, the (*S*)-enantiomer of ***p*-methoxytacripyrine** has emerged as a new promising drug candidate inhibiting cholinesterase activity, amyloid aggregation and showing significant neuroprotective properties against Aβ- induced cytotoxicity. Molecular modeling indicates that binding of ***p*-methoxytacripyrine** to the AChE PAS mainly involves the (*S*)-enantiomer, which also agrees with the noncompetitive inhibition mechanism exhibited by ***p*-methoxytacripyrine**.

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Prof. José L. Marco-Contelles
Laboratorio de Radicales Libres y Química Computacional
Instituto de Química Orgánica General (CSIC)
3, Juan de la Cierva; 28006-Madrid (Spain)
Tel.: 34 91 562 29 00
FAX: 34 91 564 48 53
e-mail: iqoc21@iqog.csic.es