PHARMACOLOGICAL EVALUATION OF NEW ANTICHOLINESTERASIC DRUGS HUPRINE-TACRINE HETERODIMERS WITH DUAL ACTION ON CATALYTIC AND PERIPHERAL SITE OF ACETYLCHOLINESTERASE

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Connection of huprine Y with tacrine through a linker to allow simultaneous interaction with catalytic and peripheral sites of Acetylcholinesterase (AChE) has generated a series of dual heterodimers.

The aim was to analyze the ability of HUP9TH, HUP9TCI, HUP10TH, HUP10TCI: i) to inhibit the catalytic human recombinant AChE (hAChEr) and human Butyrylcholinesterase (hBChE) activities; ii) to block the peripheral site of AChE and iii) to modify the cellular viability.

To reach these goals Ellman's test, prion PrP106-126 aggregation induced by AChE and MTT test on SHSY5Y cells viability against H₂O₂ insult, were used.

All compounds were clearly more active as AChE than hBChE inhibitors. IC50 values obtained after analyzing the interaction of drugs with hAChEr were at nanomolar range (from 3,26 nM to 9,1 nM) while the inhibitory activity against hBChE was about 10-15 times lower compared to hAChEr. All compounds showed a potent inhibitory effect on the PrP106-126 aggregation induced by AChE, with percentages of inhibition between 80%-90%. Viability studies showed that only heterodimers HUP10TH, HUP10TCI, in a wide range of concentrations, protected SHSY5Y cells against H₂O₂ (>20%).

In summary, all huprine-tacrine derivatives inhibit AChE activity at nanomolar range, being less potent as BChE inhibitors. They also showed high capacity to inhibit the peripheral site of AChE and HUP10TH, HUP10TCI showed a protective activity in cell culture, suggesting that these compounds can be considered as promising candidates against amyloidogenic and neurodegenerative diseases.

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