SL1

Development of New Acetylcholinesterase Inhibitors: Random Chemistry and Structure-Based Drug Design

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Acetylcholinesterase inhibitors represent the most widely used class of drugs for the therapy of neuromuscular diseases and cognitive disorders. For 20 years, many drugs have been developed for clinical use in the treatment of Alzheimer's disease. Even though their activity was very promising, unfortunately, many of them showed only limited clinical success beside side effects, e.g. observed in the case of tacrine.

The first aim of our study was to develop pyridinium- and bispyridinium-type compounds characterized by oxime ether function which should act as dual inhibitors capable of inhibiting the AChE and of the Aß fibril formation. Using the X-ray analyses of several liganded AChEs our lead compounds were optimized with regard to affinity to the peripheral binding site and the active site.

Additionally, our research objective was to enrich this therapy class by new compounds or lead structures which perform better. Random chemistry represents a new methodology which provides on one the hand compounds of resembling molecular structure and on the other hand also rearranged structures not previously known. The original idea of this technology relies on using the γ-irradiation as an initiator of random free radical recombinations in aqueous or alcohol solution of starting compound(s). The method showed reproducible results.

Via random chemistry we generated a small mixture-based compound library. Bioassay-guided HPLC-fractionation as a deconvolution strategy was employed to search for potent hits. Additionally, the fractions obtained from HPLC were structurally on-line characterized by means of MS^n.

A new potent acetylcholinesterase inhibitor (ATAM) of the acridine-type resulted from this study. The structure of the compound was elucidated by ^1H and ^{13}C NMR spectroscopy, ESI-(tandem)-mass spectrometry and FTIR- spectroscopy. The biological potency of the new anti-Alzheimer candidate was examined by Ellman's test (AChE; E.C.3.1.1.7 from Electric Eel; 0.1 M phosphate buffer, pH 8.0; 20°C) and found to be as active as the potent AChE inhibitor tacrine.