DISCOVERY OF 6-HYDROXY-1-AZA-9-OXAFLUORENES AS LEAD STRUCTURES FOR THE DEVELOPMENT OF NOVEL ALZHEIMER THERAPEUTICS

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Introduction: Tau protein hyperphosphorylation leads to NFT formation during AD progression. The role of causative specific kinases is not clear. Moreover, there is no developed therapeutic agent so far for influencing the histopathologic NFT formation.

Aims: The role of specific kinases within the NFT formation shall be investigated by novel specific inhibitors of relevant kinases i.e. glycogen synthase kinase 3 (gsk3) beta and cyclin dependent kinase 5 (cdk5)/p25.

Methods: Lead structure identification was done by screening first inhibitors of the 1-aza-9-oxafluorene type in in vitro kinase inhibition studies. The selectivity of gsk3 beta inhibition was proved by molecular modelling. Neuronal toxicity and gsk3 beta selective inhibition of tau phosphorylation was demonstrated in cellular in vitro studies. Brain activity was demonstrated in in vivo studies using transgenic mice.

Results: The selectivity of gsk3 beta binding was reasoned by additional hydrogen bonding of substituents of the 1-aza-9-oxafluorene scaffold to Thr138 and a deeper location of the molecules within the ATP binding pocket. Demonstrated nontoxic inhibitor concentrations significantly reduce the gsk3 beta selective amino acid hyperphosphorylation of tau protein in in vitro and in vivo studies.

Conclusions: Novel 1-aza-9-oxafluorene lead structures were discovered which proved to effectively reduce the gsk3 beta dependent hyperphosphorylation of tau protein both in vitro and in vivo. Thus, first candidates may help to investigate a gsk3 beta selective influence of the progression of AD in mice models.

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