New Aβ peptide ligands for the diagnosis and therapy of Alzheimer’s Disease

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Alzheimer’s disease (AD) is a neurodegenerative disorder that affects over 30 million individuals worldwide.¹ A central pathological feature of AD is the accumulation of misfolded Aβ peptides in the form of oligomers and amyloid fibrils in the brain.

Many small molecules that are able to bind Aβ peptides and inhibit their aggregation are already known; most of them are natural compounds bearing aromatic moieties such as Curcumin,² polyphenols derived from red wine,³ apomorphin,⁴ porphirins,⁵ tannic acid⁶ and tetracyclines⁷.

Curcumin derivatives with high chemical stability and improved water solubility have already been synthesized by our group and their ability to bind Aβ peptide oligomers and to efficiently stain Aβ deposits has been demonstrated.⁸

Also tetracycline is particularly attractive for the development of new Aβ ligands. It is known that tetracycline displays anti-amyloidogenic activity against many amyloidogenic proteins both in vivo and in vitro,⁹ and we verified its ability to bind Aβ1-40 and Aβ1-42 oligomers by NMR experiments.¹⁰ Anyway, tetracycline presents some drawbacks, as it suffers from chemical instability, low water solubility and possesses, in this contest, undesired anti-bacterial activity.¹¹ In order to overcome these limitations, and to increase the diversity and derivatisation potential, we developed the synthesis of ductile tricyclic scaffolds presenting the structural requirements allowing the interaction tetracycline-Aβ peptides.

Glycosfused aromatic tricyclic compounds with improved chemical stability and water solubility have been generated, the properties of hydrophilicity/hydrophobicity of which may be easily modulated adding proper substituents on the hydroxyl groups.

The ability of these compounds to bind Aβ oligomers was verified by STD-NMR and trNOESY experiments.

All these compounds were able to bind Aβ peptides but their affinities were modulated by the functional groups present at the aromatic ring.

We demonstrated with molecular dynamic studies that all these molecules have the same 3D-structure and conformation, so the diverse affinity may be only due to the different polarity determined by the aromatic substituents. No influence on the binding was observed for the sugar moiety, which in fact displays only a minor involvement in the interaction with amyloid peptides.