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Synthesis, radiolabelling, in vitro and vivo behaviour of tacrine derivatives

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There are around 36 million people in the world with Alzheimer's disease and up to now here is no cure for this ailment. Alzheimer's disease is the most common form of dementia. One of the drugs used for the treatment of Alzheimer's disease is tacrine - the inhibitor of cholinesterase. The aim of this work was to label with technetium-99m the different analogue of tacrine (containing different number of CH2 groups in the aliphatic chain, n=2÷9) and to select the best one which potentially would be a tool for early diagnosis of Alzheimer's disease.

In the presented work we have synthesized with good yield and purity eight 99mTc-labelling tacrine derivatives. The technetium-99m complex, of type '4+1'used for labelling procedure, contained tetradentate tripodal chelator tris(2-mercaptoethyl)-amine (NS3) and monodentate isocyanide ligand previously coupled with tacrine derivative (CN-tacrine). The synthesized conjugates were isolated from the reaction mixture using semi-preparative HPLC for all physicochemical and biological studies.

The lipophilicity of the conjugates was characterized by the determination of the logarithm of their partition coefficients, log D, in the n-octanol/PBS (pH 7.40) system, which mimics the physiological conditions. Stability of the complexes has been investigated in a function of time, in challenge experiments (by incubation at 37oC with 10 mM solutions of histidine or cysteine) and in human serum. Biological activity of the conjugate characterized by the highest lipophilicity was estimated by means of Ellman's method and preliminary biodistribution studies done in mice.

All conjugates studied showed high stability in all tests. The following distribution coefficients were determined between 0.92- 1.56 (the average values from three independent measurements) depending on the length of the aliphatic chain. The compound having 7 carbon atoms in the aliphatic chain (n=7) have the highest lipophilicity (log D=1.56) and satisfactory biological activity (IC50 = 30.4 nM). Biodistribution studies in mice shoved for this conjugate rapid decrease of radioactivity in blood, the clearance mainly through the hepatic route and, unfortunately, relatively low radioactivity concentration in the brain.

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