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MEETING ABSTRACTS

BRAIN EXPOSURE OF BIS-PYRIDINIUM OXIME KR-26256

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A number of strategies through structural modification of pyridinium oximes have been developed to circumvent the Blood-Brain Barrier (BBB). Some of the attempted examples are (1) enhancement of lipophilicity by introduction of a fluorine atom into pyridinium ring, (2) facilitation of glucose transporters introduction of glucose moiety on the pyridinium nitrogen, (3) use of a prodrug by uncharged dihydropyridyl moiety, etc

One of the strategies that our group tried was the introduction of fluorine atoms into the heterocyclic ring of pyridinium oximes to increase their lipophilicity.[1] In our continuing effort towards the development of new oxime reactivators, we were interested in monoquaternary pyridinium oximes with *N*-alkyl side chains, because oximes with hydrophobic side chains may penetrate the BBB more easily than 2-PAM with an *N*-methyl side chain. We also investigated bis-pyridinium oximes with diethyl ether linker between two pyridine rings.

The synthesized pyridinium oximes were evaluated their inhibitory activities on AChE, as well as their potency to reactivate AChE inhibited by paraoxon organophosphorus agent. The plasma and brain disposition of oximes were evaluated in male ICR mice, and the oximes concentrations in the plasma and brain were measured by LC-MSMS analysis. Therefore, KR-26256 which is a bis-pyridinium oxime showed higher brain concentration as well as better brain/plasma ratio compared with HI-6.

References

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