Synthesis, biological evaluation and radiolabelling of a quinolin derivative as a potential imaging agent for the NMDA-receptor

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Introduction: The *N*-methyl-D-aspartate (NMDA) receptor is involved in the majority of neuroexcitatory events and important for neuronal development, functioning and degeneration in the CNS. Its adaptive properties and the presence of numerous regulatory sites could be the basis of its role in learning and memory as well as in neurodegenerative pathologies disorders such as M. Parkinson and Alzheimer's disease. Due to promising results [1] the synthesis of a 3-substituted 4-hydroxy-quinolin-2(1*H*)-one derivative was started, which can be labelled with 2-[^{18}F]fluoroethyltosylate.

Experimental: For affinity determination, the inactive reference compound 7-chloro-3-{3-[4-(2-fluoro-ethoxy)-phenoxy]-phenyl}-4-hydroxy-1*H*-quinolin-2-one was synthesized in a nine step reaction. In parallel, the synthesis of the precursor was done. Radiolabelling was achieved on the terminal phenolic hydroxy group with 2-[^{18}F]fluoroethyltosylate, c.f Figure 1.

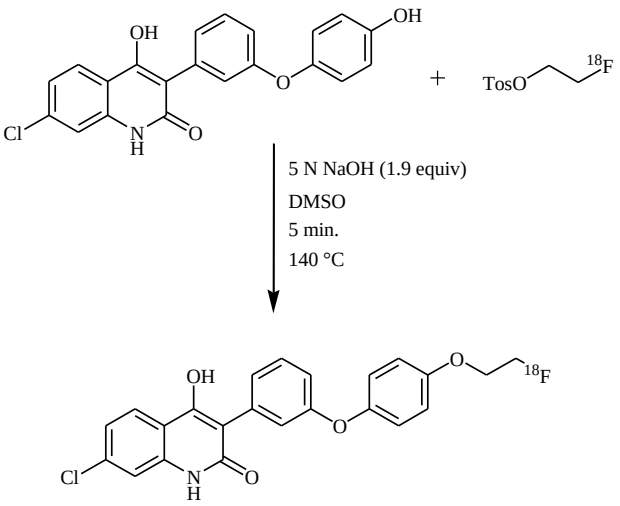

Figure 1. Radiosynthesis of the para-substituted fluoroethoxy-quinolin derivative

Different temperatures and precursor concentrations were used to optimize the reaction to get the desired compound in high radiochemical yields. After 1, 3, 5, 7, 10, 15 and 20 minutes aliquots (0.1 mL) of the reaction mixture were taken and quenched with water (0.1 mL). The reaction yield was determined with radio TLC. The findings of the optimization process are shown in Figure 2. The best results were obtained for 1 minute reaction time at 140 °C, 3 mg of precursor and DMSO as solvent. 2 µL of a 5 N NaOH-solution (1,9 equiv) were used.

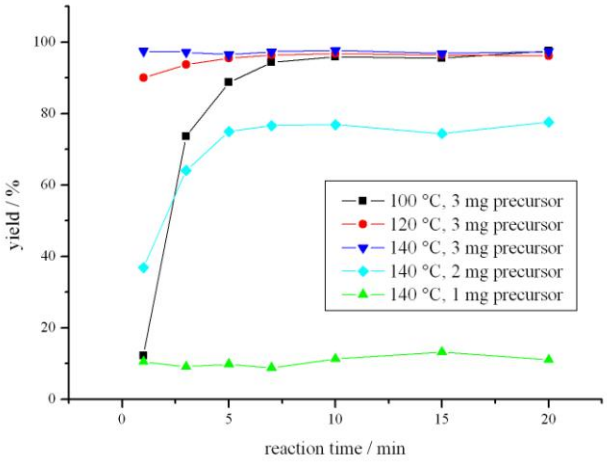

Figure 2. Results of the optimization process

To reduce the tailing effect of the precursor on the HPLC, only 2 mg were used. For separation, the whole reaction mixture was diluted with 1 mL of water and injected into a semipreparative HPLC system, equipped with a Luna PFP (250 x 10 mm) column. After successful separation, the HPLC effluent, containing the labelled compound was fixed on a strata-X cartridge and washed with water. The final compound was completely eluted by the use of ethanol (2.5 mL). Characterisation was done with radio TLC and analytical radio HPLC.

Results: Radiolabelling does succeed with > 95 % RCY within one minute at 140 °C and 3 mg of precursor concentration. For radiosynthesis and separation, 2 mg of precursor were used. Reaction time was extended to 5 minutes. The final product was analysed by analytical HPLC and radio TLC. Due to optimized and practicable reaction parameters, further experiments of the labelled compound are being planned. The log P value and has to be determined. Evaluation of the radioligand and animal studies on the micro PET are planned. The determination of the IC_{50} values of the ^{19}F-inactive compounds, using [^{3}H]MDL-105,519 receptor binding assay [2] is ongoing.

References

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