Automated production of [^{18}F] 2-fluoroethyl azide and a thymidine analogue using the Synthera module

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Objectives

The aim of this project was to automate the production of the important click chemistry synthon fluoroethyl azide and investigate the subsequent click chemistry reaction with ethynyl deoxy uridine in a single pot using the Synthera module (Figure 1).

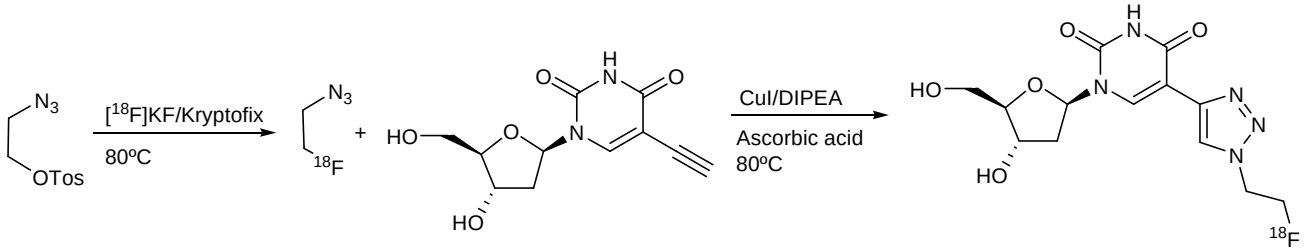

Figure 1: Synthesis of [^{18}F]fluoroethyl azide and a fluoroethyl triazolyl thymidine

Methods

The following catalyst mixture was used for the click chemistry: H_2O (250 µL) was added to CuI (2.5 mg) and ascorbic acid (22.9 mg), followed by diisopropylethylamine (25 µL) and acetonitrile (250 µL). For the semi-preparative HPLC system an Alltech Apollo 250×10mm 5µ C-18 column and the following gradient system were used at a flow rate of 5 mL/min: 0-8 min 100% 21 mM phosphate buffer, pH 8; 8-20 min: 5% ethanol/21 mM phosphate buffer, pH 8; 20-30 min 10% ethanol/21 mM phosphate buffer, pH 8. An IFP nucleophilic was used for the labelling experiments. After drying of the KF kryptofix complex, 2-azidoethyl 4-toluenesulfonate (10 µL in 400 µL of acetonitrile) was added from vial 2 and fluoroethyl azide was prepared by heating to 80°C for 15 min.[1] 2 mg of EDU and the copper (I) catalyst were added from vial 3 and the reaction mixture heated to 80°C for 10 min. Acetonitrile was then evaporated at 100°C, 4 mL of 0.1 N NaOH added and the reaction mixture injected into the HPLC system. The radioactive peak at 25 min was collected and could be used without further reformulation.

Results

The one pot system gave better yields (50%) than our previously developed manual two pot distillation method (32%).[2] The overall synthesis time was also reduced by 20 min using the one pot Synthera method. However, the crude reaction mixture of the one pot method is more difficult to purify and the method is also less reliable due to blockages of transfer lines because of insoluble copper compounds.

Conclusion

We have compared a single-pot Synthera protocol to a manual two pot distillation method for the synthesis of a fluoroethyl triazolyl thymidine analogue. Although giving the highest yields, the single pot method lacked reliability due to the blockage of lines from insoluble copper (I) species. By using soluble Cu(I) catalysts the reliability of the single pot method might be improved. However, due to a difficult separation of our tracer from non-radioactive by-products, the distillation method is still the preferred option. The IFP distillation in combination with a second Synthera module might be the ideal solution for the fully automated production of this radiotracer.

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References

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