SYNTHESIS OF F-18 FLUOROESTRADIOL USING THE FLEXLAB RADIOSYNTHESIZER

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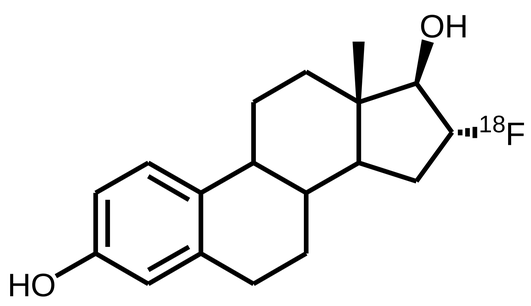
INTRODUCTION

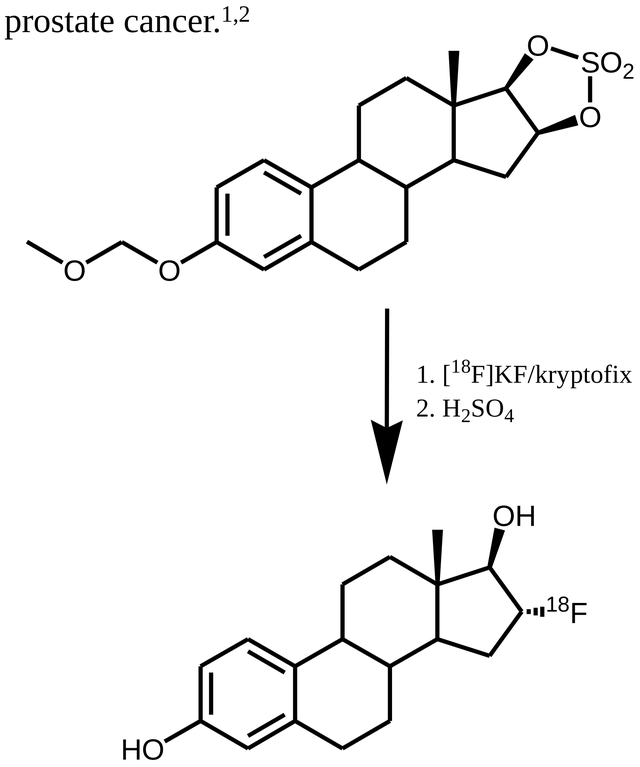
Recent advances in the understanding of the biology of prostate cancer have forced a re-thinking of the role of signalling through sex steroid receptors. New drugs that have agonist or antagonist effects on these receptors are now entering clinical trials. PET imaging using F-18 fluoroestradiol (FES) may help identify patients that can benefit from this treatment.



[^{18}F]Fluoroestradiol

AIM

The aim of this project was to implement the synthesis of F-18 FES on the commercially available FlexLab radiosynthesizer for preclinical evaluation in prostate cancer.[1,2]



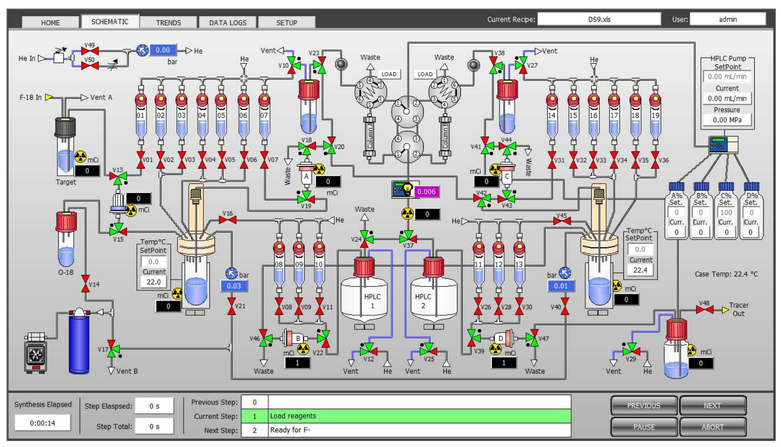
METHODS

GENERAL

The commercially available FlexLab radiosynthesizer (iPHASE technologies) with a quaternary HPLC gradient pump and a Phenomenex Gemini semi-preparative HPLC column was used for the synthesis and purification of FES. The FES precursor MMSE and the FES standard were purchased from ABX. All other solvents and chemicals were purchased from Sigma Aldrich and used without further purification.

RADIOLABELLING

Radiolabelling experiments were performed using the commercially available FlexLab radiosynthesizer. No modifications were made to the module.



No-carrier-added [^{18}F]fluoride was produced by the ^{18}O(p,n)^{18}F nuclear reaction with a 10 MeV proton beam generated by the IBA Cyclone 10/5 cyclotron in a titanium target using [^{18}O]H_2O. After transfer of [^{18}F]fluoride from the cyclotron, the [^{18}F]fluoride ion was isolated from [^{18}O]H_2O by trapping on a QMA cartridge which was preconditioned with K_2CO_3. The cartridge was eluted into reactor 1 using a solution containing 3.45 mg of anhydrous K_2CO_3 (0.025 mmol) and 20 mg of Kryptofix 2.2.2 (0.053 mmol) in 0.4 mL of acetonitrile plus 0.2 mL of water from vial 1. Dry acetonitrile (1 mL) was added to reactor 1 from vial 4 and reactor 1 heated to 90 °C for 10 min to afford the dried [^{18}F]KF/kryptofix complex. 2 mg of MMSE in 1 mL of acetonitrile were then added from vial 4, the reactor vial was sealed and the mixture heated to 110 °C for 8 min. Acetonitrile was then evaporated and 3 mL of 44 mM H_2SO_4 in ethanol were added from vial 3. The reactor vial was sealed and heated to 110 °C for 5 min. 7 mL of water were then added and FES subsequently trapped on a Phenomenex Strata X SPE cartridge. For injection into the HPLC, [^{18}F]FES was eluted from the cartridge with 1 mL of acetonitrile from vial 7 into the HPLC loop loading vial which contained 3.5 mL of 0.1 M ammonium formate.

Semi-preparative HPLC purification of the crude reaction mixture was performed using acetonitrile (A) and aqueous 0.1M ammonium formate (B) as mobile phase. A gradient elution technique was used to elute [^{18}F]FES: 0-20 min: 35-55% A at a flow rate of 4 mL/min. The peak at 14.5 min was diluted with 60 mL of water in HPLC collection vial 2, trapped on a Strata-X SPE cartridge in position D and reformulated in 10% ethanol.

QUALITY CONTROL

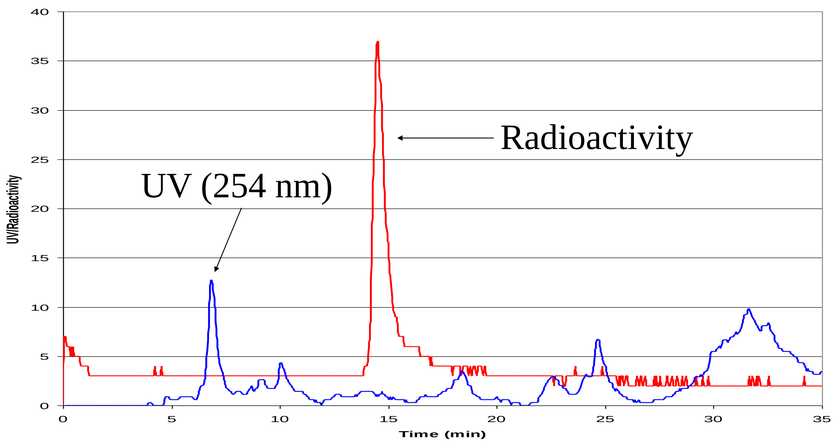
Quality control was performed using a Shimadzu HPLC system with a Bioscan BGO detector and a SPD20A detector at a wavelength of 280 nm.

QUALITY CONTROL (contd.)

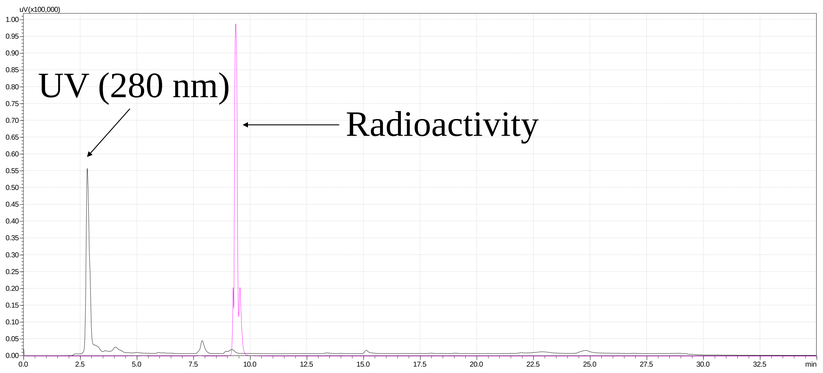
The stationary phase used was a Phenomenex Gemini NX C-18, 5µ RP column, 150×4.6 mm. Acetonitrile (A) and water (B) with 0.1% formic acid were used as the mobile phase. A gradient elution technique was used for analysis: 0-18 min: 5-90% A, 18-30 min: isocratic 90% A at a flow rate of 0.5 mL/min. 20 µL of the reformulated solution was used for quality control and measurement of specific activity.

RESULTS

The semi-preparative purification of [^{18}F]FES shows good separation from non-radioactive chemical impurities:



Quality control of [^{18}F]FES shows that 280 nm wavelength is required for accurate determination of specific activity:



CONCLUSION

[^{18}F]FES was synthesised in overall yield of 23±5% (n=6) with radiochemical purity greater than 95% and specific activity of 1.4±0.2 Ci/µmol. The synthesis time including reformulation was 70 min.

REFERENCES

1. Mori T,, Kasamatsu S, Mosdzianowski C, Welch MJ, Yonekura Y, Fujibayashi Y; Nucl Med Biol **2006** (33):281-286
2. iPHASE technologies Pty Ltd; Website: www.iphase.com.au; email: info@iphase.com.au

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