PREPARATION OF VERSATILE RADIOLABELED PROSTHETIC GROUPS AND THEIR APPLICATION USING A NEWLY DESIGNED AUTOMATED DUAL REACTOR DEVICE

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Background

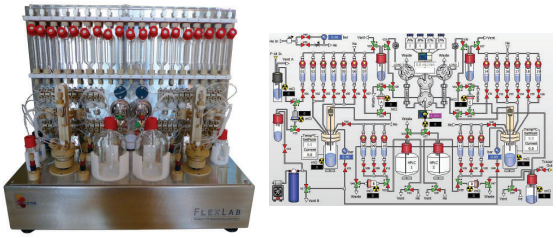
Radiolabeled prosthetic groups are useful tools to introduce radionuclides into molecules that otherwise require indirect labeling. Unfortunately, this approach often requires the use of multiple devices or a degree of manual manipulation. To overcome some of the problems presented by the use of these groups, we have developed a novel automated dual-reactor radiochemistry synthesis module.

The aim of this study was to trial the performance of this device by preparing the common prosthetic groups 2-[^{18}F]fluoropropionic acid 4-nitrophenylester ([^{18}F]FP), 4-[^{18}F]fluorobenzaldehyde ([^{18}F]FBA), N-succinimidyl 4-[^{18}F]fluorobenzoate ([^{18}F]SFB), and subsequently incorporating them into the fully automated syntheses of radiotracers of biological interest. In particular, the preparation of [^{18}F]GalactoRGD is described.

Methods

The FlexLAB Automated Dual Reactor Radiosynthesis Module

The FlexLAB is a fully automated radiosynthesis laboratory designed with the primary aim of simplifying and expediting the radioactive labeling of peptides. Automated operation is via an Excel® time-list which provides control of each device. The time-lists used in this study were prepared from literature procedures[1,2,3]. Any remote manual intervention is by way of the active graphic interface. The module has dual 20 mL glass reactors with heating up to 200°C, compressed air cooling down to approximately 4°C and movable central tube. The product purification system comprises of dual HPLC injection capability with dual HPLC column selection, quaternary HPLC system control and dual HPLC peak reformulation.

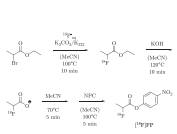


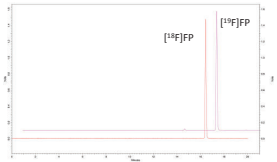
The FlexLAB dual reactor radiosynthesis module and graphic interface used to navigate and control the device.

Results

Synthesis of 2-[^{18}F]Fluoropropionic acid 4-nitrophenylester ([^{18}F]FP)

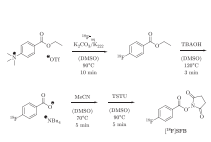
Adopting the procedure described by Lang et al.[1] [^{18}F]FP was prepared, purified by reverse phase HPLC, recovered from mobile phase using solid phase extraction, and transferred to the second reactor where it was concentrated ready for conjugation. [^{18}F]FP was typically transferred to the second reactor in 20 % n.d.c. yield with a radiochemical purity >99 % in a total time of 90 minutes.

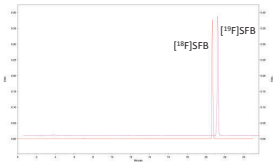




Synthesis of N-Succinimidyl 4-[^{18}F]Fluorobenzoate ([^{18}F]SFB)

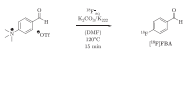
[^{18}F]SFB was prepared in a multi-step single pot process[2] and available in the second reactor in 26 % n.d.c. yield with a radiochemical purity >97 % in a total time of 68 minutes.

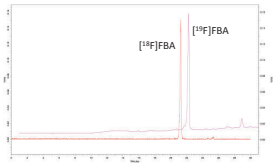




Synthesis of 4-[^{18}F]Fluorobenzaldehyde ([^{18}F]FBA)

Adopting the procedure described by Speranza et al.[3], [^{18}F]FBA was readily prepared for subsequent conjugation reactions. [^{18}F]FBA was typically available in the second reactor in 55 % n.d.c. yield with a radiochemical purity >99 % in a total time of 52 minutes.

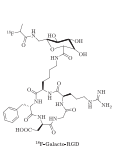


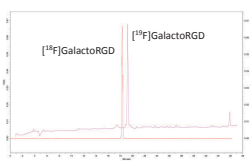


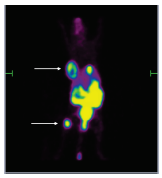
[^{18}F]FBA has been subsequently used in a reductive alkylation capacity to prepare a novel benzamide [^{18}F]MEL054 which is currently being trialled as a melanin imaging agent.

Synthesis of [^{18}F]GalactoRGD

[^{18}F]FP prepared in the first reactor vessel was directly conjugated with carbohydrate modified cyclic RGD peptide c(RGDfK) to yield [^{18}F]GalactoRGD, as previously described by Haubner et al.[4]. The completely automated process yielded [^{18}F]GalactoRGD in 40 % n.d.c. isolated yield from [^{18}F]FP in under 160 minutes.







The structure of [^{18}F]GalactoRGD, its HPLC trace and a MIP image of an in vivo imaging study looking a [^{18}F]GalactoRGD uptake in a 66cl4beta3 tumour bearing mouse with implanted tumour uptake and femoral metastatic lesion uptake indicated with arrows.

Conclusions

The new radiosynthesis module provides a flexible platform for the automated production of a number of commonly used prosthetic groups. The incorporation of [^{18}F]FP into the preparation of [^{18}F]GalactoRGD and its subsequent use in a small animal imaging study exemplifies the utility of this device. Work is ongoing in the application of all three synthons.

Acknowledgements

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References

1. F.T. Chin et al., Mol. Imaging. Biol. 2011, 14, 88-95
2. P.J.H. Scott, X. Shao. J. Label. Compd. Radiopharm. 2010, 53, 586-591
3. A. Speranza et al., Appl. Radiat. Isot. 2009, 67, 1664-1669
4. R. Haubner et al., Bioconjugate Chem. 2004, 15, 61-69