THALESNano

# Radiochemical Synthesis of $^{18}$F-labelled Compounds Using the H-Cube Reactor

**In this application note we demonstrate the first application on flow hydrogenation for the development of a PET radiotracer in a fast, efficient, and reproducible way.**

## INTRODUCTION

Radiochemistry has great importance in research and diagnosis, but working with radioactive materials requires special processes and a high level of safety regulations. Currently, the involvement of PET (positron emission topography) in medical examinations is a generally accepted methodology, which often needs the generation of $^{18}$F-labelled compounds. This isotope has a short, approximately 110 min half-life, which creates a real challenge for chemists when they are trying to provide a suitable compound and synthetic route, which can be easily performed in the shortest time possible.

Harvard Medical School, in cooperation with the Massachusetts General Hospital, has developed an efficient, rapid, and reproducible flow chemistry-based methodology for the synthesis of a radiotracer used in PET scans.

## INSTRUMENTATION

All reactions were carried out in a combined flow-based system containing:

1.) Nanotek® microfluidic device from Advion Inc. for the $^{18}$F-labelling

2.) H-Cube® from ThalesNano for the hydrogenation of labelled compounds. The products were then purified by a semi-preparative HPLC before the formulation for injection by GE TRACElab $FX_{F-N}$.

## MODEL REACTION

Fluorine-18 labelled fluoroanilines, as building blocks of different radiotracers used in PET, were chosen for the model reaction. First, the fluorination of 1,4-dinitrobenzene with [$^{18}$F]$Et_4NF$ was optimized resulting in the $^{18}$F-labelled compound in 92% radiochemical conversion at 180 °C using a flow rate of 80 µL/min and $CH_3CN$ as a solvent. The reaction was carried out in 5 min.

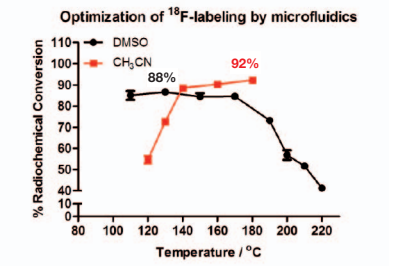


**Figure 1:** Optimization of the fluorination step

During the optimization of the nitro group hydrogenation, all parameters - the solvent, the flow rate, the reaction temperature, and the pressure - were screened (Table 1). A 90% conversion was achieved in 3 min at the optimum conditions using THF as solvent, 1 mL/min flow rate, 20 bar, and 60 °C reaction pressure and temperature respectively. The Pd/C filled cartridges were changed after 15 uses without any degradation observed. Finally, the automated isolation resulted in the final compound in 32 ± 5% (n=3) decay-corrected radiochemical yield with specific activity >1.2 Ci/µmol. The whole process required an overall reaction time of 40 min.

| No | Solvent | Temperature (°C) | $H_2$ pressure (bar) | Radiochemical conversion (%) (n=3) |
|---|---|---|---|---|
| 1 | $CH_3CN$/MeOH (1:1) | 30 | 1 | 64.3 ± 2.0 |
| 4 | $CH_3CN$/MeOH (1:1) | 60 | 1 | 47.1 ± 2.3 |
| 5 | $CH_3CN$ | 50 | 10 | 57.5 ± 1.3 |
| 6 | $CH_3CN$ | 50 | 20 | 61.7 ± 1.2 |
| 7 | THF | 50 | 10 | 86.7 ± 1.5 |
| 8 | THF | 60 | 20 | 90.5 ± 2.9 |
| 10 | THF | 80 | 50 | 84.6 ± 4.7 |

**Table 1:** Reaction conditions and results of hydrogenation using a Pd/C catalyst and 1 mL/min flow rate

## SYNTHESIS OF [$^{18}$F]CABS13

After the model reaction proved the usefulness of applying flow synthesis, the next attempt was the synthesis of [$^{18}$F] CABS13, the radiotracer designed to explore the „metal hypothesis of Alzheimer's disease". Upon performing the same reaction series in batch, 30% yield was achieved. The simplification of the reactions with the combined microfluidic and flow hydrogenation system first required the optimization of the fluorination reaction. Although DMSO resulted in a 90% conversion, acetonitrile was chosen as the solvent so that the final material could be produced in one flow without having to involve and additional solvent exchange step for the hydrogenation. However, it should be noted that ThalesNano does not recommend acetonitrile as a solvent because of its susceptibility to hydrogenation.

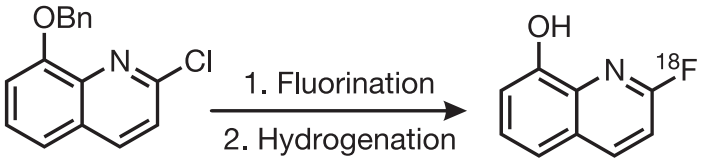


**Figure 2:** Synthesis of [$^{18}$F]CABS13, a PET radiotracer

Applying a 180 °C temperature and 10 µL/min flow rate resulted in the fluorinated compound in 57%. The *O*-debenzylation step was then performed in the H-Cube, and although 10% Pd/C usually provides high yield for this type of transformation, in this case only 50-60% conversion was achieved. The change to 20% $Pd(OH)_2$/C catalyst in THF at 70 °C, 1 mL/min, and 20 bar could improve the hydrogenation step to a near quantitative yield within 3 min. After purification, the final compound was isolated with 12 ± 3% (n=3) decay-corrected radiochemical yield with specific activities >1.4 ci/µmol within 45 min from dried [$^{18}$F]fluoride.

## CONCLUSION

It was demonstrated that hydrogenation is not a limiting factor in radiochemical applications any more. Owing to the advantages of the H-Cube® system, hydrogenation can be used for discovering new radiopharmaceutical labelled compounds with short-lived positron emitting radionuclides.

## REFERENCE

S. Liang, T. Collier, B. Rotstein, R. Lewis, M. Steck, and N. Vasdev.; *Chem. Com.*, **2013**; 49 (78); 8755 – 8757

## LEGAL



For more information on how flow chemistry can benefit you please visit www.thalesnano.com

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