^{18}F-Fluorination Reactions and Optimizations using a Parallel Synthesis Reactor

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Objectives

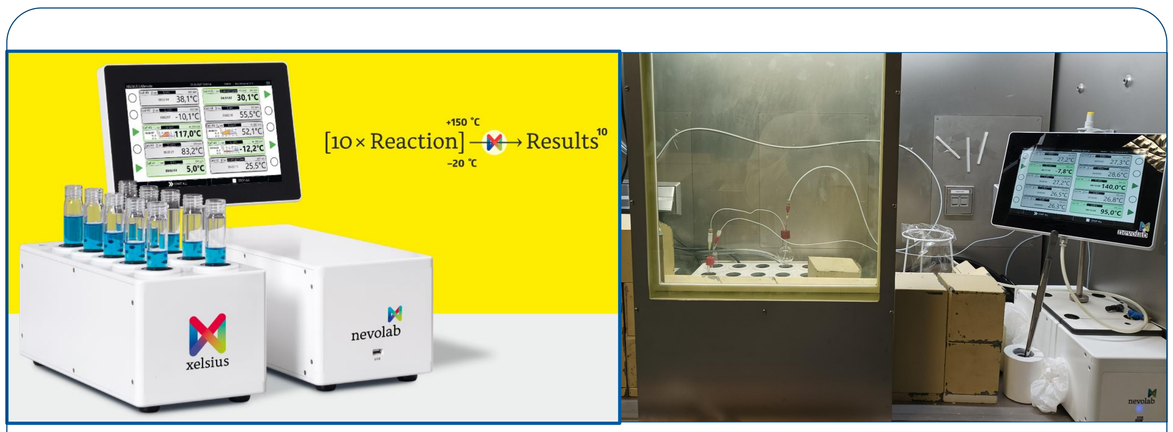

Figure 1: Nevolab's Xelsius® multi-vessel device (left) and its implementation into radionuclide hood (right)

The preparation of ^{18}F-labeled compounds typically requires several time-sensitive processes including azeotropic drying, ^{18}F-fluorination, deprotection as well as purification and formulation steps. Recent advances in late-stage ^{18}F-fluorination approaches, such as copper-mediated radiofluorination (CMRF) chemistry, have paved the way for accelerated development of structurally-diverse PET tracers.[1,2] The multi-faceted and complex processes associated with CMRF require particular attention with respect to reaction optimization in manual radiosyntheses.[3] Herein, the potential of a Xelsius® parallel reactor screening device in manual radiosyntheses and acceleration of CMRF reaction optimizations is disclosed.

AIM OF THIS WORK: Radiolabeling optimization using Nevolab's Xelsius parallel synthesizer for PET tracer development

Methods

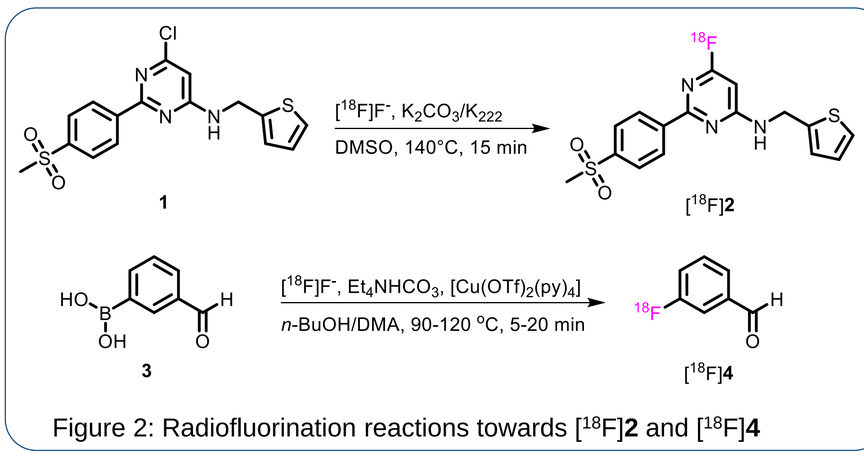

Figure 2: Radiofluorination reactions towards [^{18}F]**2** and [^{18}F]**4**

Two different approaches were tested on the device: 1) Radiosynthesis of a ^{18}F-labeled COX-2 inhibitor [^{18}F]**2**,[4] and 2) A parallel optimization of CMRF on model compound **3** at different temperatures (Figure 2). The preparation of [^{18}F]**2** commenced with azeotropic drying at 95 °C, ^{18}F-fluorination at 140 °C, HPLC and SPE purification, and concentration of the final compound at 70 °C. For the radiofluorination optimization of [^{18}F]**4**; dried [^{18}F]fluoride/ Et_4NHCO_3 was reacted with precursor **3** in DMA/*n*-BuOH (4:1) under CMRF conditions in parallel with stirring for 5-20 min at 90 °C, 100 °C, 110 °C and 120 °C, respectively. The radiochemical conversion (RCC) values were determined for each reaction by taking aliquots from the respective vessels at defined intervals and analyzing their contents by radio-UHPLC.

Radiosyntheses were performed manually using the Xelsius® parallel synthesis reactor (Nevolab, Figure 3) offering ten separately controllable positions to perform reactions between -20 °C and 150 °C. Each heating step was performed at a separate position of the device while one position was cooled at -10 °C to trap contaminated distillates.

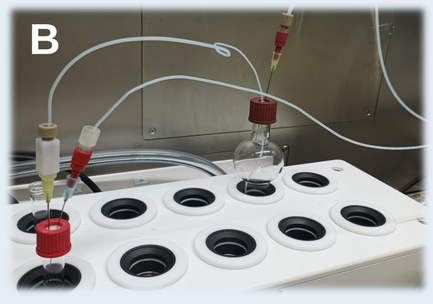

Figure 3 A & B: Xelsius® reaction setup for optimization (left) and azeotropic drying (right)

Results

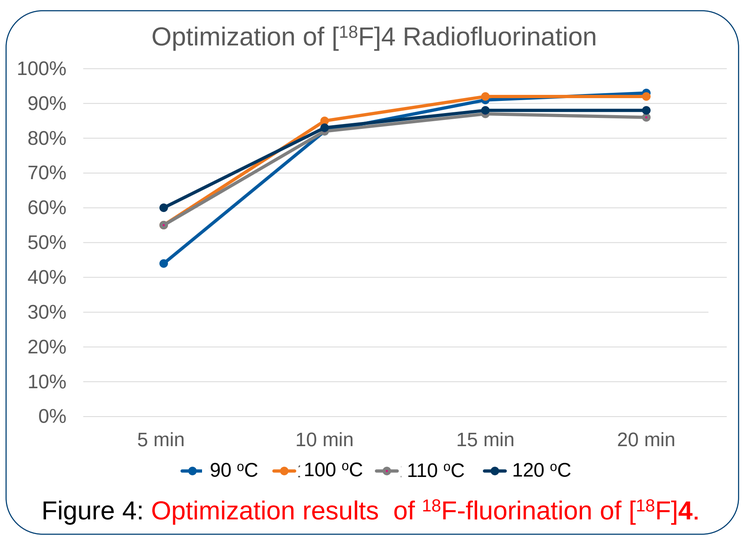

Figure 4: Optimization results of ^{18}F-fluorination of [^{18}F]**4**.

For both approaches, the radiosyntheses were successfully translated to the parallel synthesis reactor. The different heating steps in the multi-step radiosynthesis of [^{18}F]**2** were performed at different positions in the device without the need to wait between the single reaction steps for temperature equilibration.

The CMRF optimization was accelerated by parallel radiosyntheses: The RCC values for [^{18}F]**4** (Figure 4) at the respective timepoints and temperatures ranged between 44 and 93% RCC. The overall duration for the series of four ^{18}F-fluorination reactions took 1 hour. The use of a reaction vessel as a cooling trap to facilitate the evaporation of MeOH was carried out upon attachment of a cooler.

Conclusions & Outlook

- ✓ Using a parallel synthesis reactor can facilitate multi-step radiosyntheses and optimizations in radiochemistry taking into consideration the space-saving construction of the device and the ability to investigate different temperature conditions at a time as well as the ability to fastly switch between different temperatures.
- ✓ The ^{18}F-labeling results were comparable to previous reports in the literature, and facilitated rapid screening of [^{18}F]**4** preparation via CMRF.
- ✓ Notably, for our initial screening only four vessels were simultaneously used; however, it is anticipated that the use of the six additional vessels would further accelerate ^{18}F-fluorination reaction optimization.

References

[1] B. D. Zlatopolskiy et al. Chem. Eur. J. 2015, 21, 5972-5979. [2] C. Hoffmann et al. Chem. Eur. J. 2023, 29, e202202965. [3] G. D. Bowden et al. Sci. Rep. 2019, 9, 11370. [4] M. Y. Cortes-Salva et al. Molecules 2018, 23, 2850.

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