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Short Research Article

Integration of a microwave reactor with Synthia to provide a fully automated radiofluorination module†

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Introduction

Microwave technology has been very successfully applied to enhance PET radiolabeling reactions, including one-step nucleophilic radiofluorination reactions with [^{18}F]fluoride ion, so they become faster, cleaner and higher yielding.[1-3] [^{18}F]Fluoride ion is produced as an aqueous solution in a [^{18}O]water target and must be dried to become adequately nucleophilic.[4] However, examples of using microwave reactors for azeotropic drying of the [^{18}F]fluoride ions are rare, and automated radiopharmaceutical production devices that include a microwave reactor are virtually non-existent.[5]

We developed a fully automated radiofluorination module by integrating the Resonance Instrument 521 microwave reactor[6] with a Synthia radiosynthesis device.[7] The microwave reactor provides efficient heating and Synthia provides an automation platform. A process, starting with drying of [^{18}F]fluoride ion in target [^{18}O]water followed by a nucleophilic fluorination, reaction, both under microwave-enhanced conditions, was established. The existing capability of Synthia for HPLC separation, solid phase extraction purification and product formulation were integrated into the process.

Results and discussion

The 521 microwave cavity is securely mounted on the Synthia MKII Lab System (Figure 1(a)). The time and power control is located outside the hotcell and linked to the cavity through a RF coaxial cable. The reaction V-vial (1 ml, Alltech) is equipped with a screw-on cap and septum (Pierce, Tuf-Bond teflon/silicone) and a vent needle that is connected to a glass vial (20 ml) to collect the solvents and a charcoal trap to retain any volatile break away radioactivity (Figure 1(b)). Liquid handling is achieved using the Gilson Aspec auto-injector/dispenser which forms part of the Synthia system. Other operations of the radiosynthesis and purification procedures are controlled by Visual Chemistry based recipe.

The size of V-vial is restricted by the cavity diameter because the curvature of the glass forms part of the focusing mechanism that delivers microwave irradiation. [^{18}F]Fluoride ion in up to 200 µl of target [^{18}O]water can be processed efficiently. During drying the optimal power input is 90 W and it is sufficient to heat each step, 2 minutes in most cases. Heating time and power input are controlled independently and could be adjusted whenever it is necessary. The optimal volume for a reaction is 300–500 µl. The PTFE bonded silicone septum can be easily punctured for delivery of fresh solvent and reagent yet seal effectively so that volatile components of the reaction mixture could be retained.

A general procedure for [^{18}F]fluoride ion drying and reaction under microwaves is as follows: the V-vial containing $^{18}F^-$ in $H_2^{18}O$, K_2CO_3/Kryptofix® 222 (K2.2.2) and CH_3CN is placed in the microwave cavity. Microwave heating at 90 W in 2 min × 3 pulses is applied under N_2 gas flow (200 ml min^{-1}) which speeds up the removal of azeotropic mixture of water and acetonitrile. The heating cycle is repeated twice, and each time fresh CH_3CN (500 µl) is added. Precursor in appropriate solvent is introduced in the V-vial and

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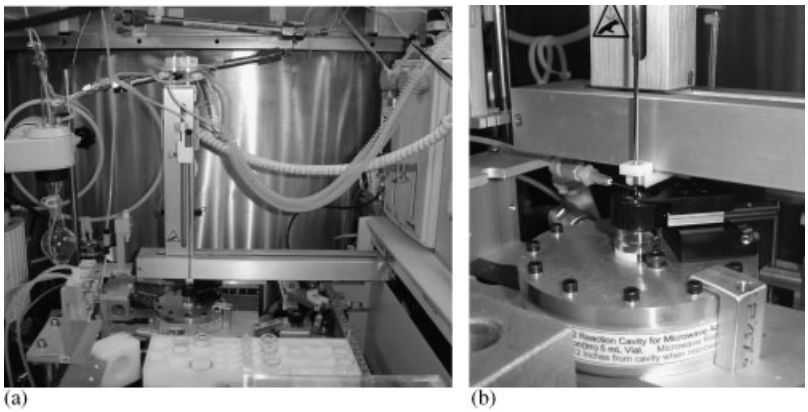
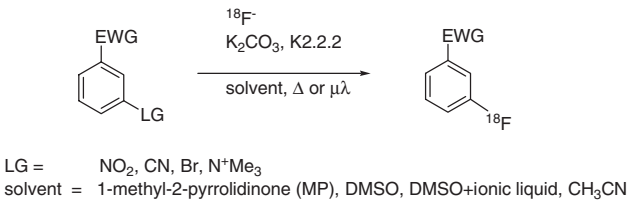
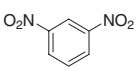
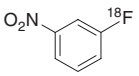
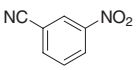
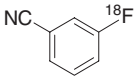
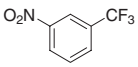
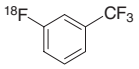
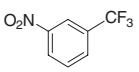
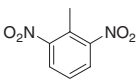
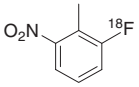
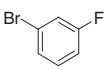
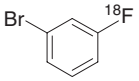
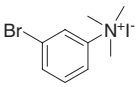
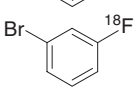
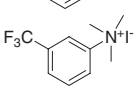
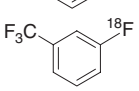
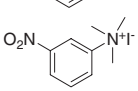
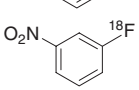


Figure 1 (a) Synthia platform with the 521 microwave cavity (left); and (b) close-up view of the reaction vial with Synthia dilutor needle to deliver liquids and vent needle for azeotropic removal of water (right).



Scheme 1

Table 1 *m*-Fluorination of substituted benzenes with NCA [^{18}F]fluoride ion under microwave-enhanced or thermal conditions*

No	Precursor	Product	RCY# (%, n ≥ 3)	
			Thermal	*Microwave*
1			21	47
2			20	46
3			8	13
			1	4
4			11	41
5			9	19
6			3	17
7			1	12
8			4	8

*Optimal conditions: solvent=1-methyl-2-pyrrolidinone (MP); microwave input=90 W, 3 min; amount of precursor=1.8–2.8 mg (11–19 mmol). Thermal heating=150°C, 10 min. #RCY=radiochemical yield, decay corrected.

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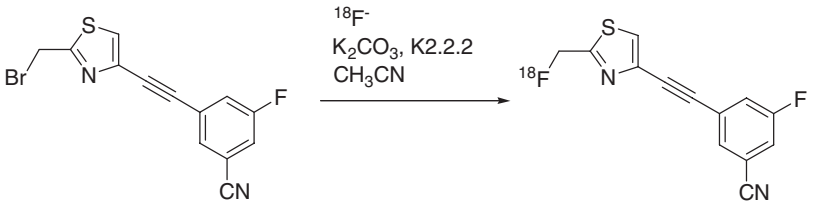

NI box	Thermal drying & reaction	88 °C, 10 min	15-25% (n = 10)
Synthia/521	Microwave drying & reaction	90 W, 2 min	45-50% (n = 6)
Synthia/521	Thermal drying & microwave reaction	90 W, 10 min	80-85% (n = 4)

Scheme 2

heated at a predetermined microwave power input and time. The reaction mixture is diluted with mobile phase (1 ml) and injected onto the HPLC for purification.

Introduction of [^{18}F]fluoride ion into non-activated positions (Scheme 1), such as the *meta*-position of arenes, is difficult under thermal conditions. This is because electron-withdrawing groups (EWG), such as $-NO_2$, have a strong stabilizing effect (*meta* ≪ *ortho* < *para*) on the intermediate anion σ-complexes in S_NAr reactions.[8] Using the microwave-enhanced radiofluorination process, regio-selectively *meta*-[^{18}F]fluorinated benzenes were obtained in moderate to good radiochemical yields (Table 1).

3-Fluoro-5-(2-(2-fluoromethylthiazol-4-yl)ethynyl)-benzonitrile is a high affinity brain metabotropic glutamate subtype 5 (mGluR5) receptor ligand (IC_{50}=0.036 nM, clogP=4.00).[9] An [^{18}F]labelled version (Scheme 2) was produced in this module for monkey studies. RCYs are significantly improved under microwave conditions. The HPLC chromatogram of the reaction mixture also contains fewer impurity peaks. When the volume of [^{18}F]fluoride ion in target [^{18}O]water exceeds 200 μl, the best results are obtained if drying was carried out under thermal conditions, but the radiofluorination carried out under microwave-enhanced conditions.

Better radiochemical yield and chemical purity as well as shorter reaction time were among the advantages compared to an automated conventional heating system.

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