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Perfluorinated markers for hypoxia detection: synthesis of sulfur-containing precursors and [^{18}F]-labelling

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Abstract—Synthetic pathways of two novel sulfurated precursors for [^{18}F]-labelling by oxidative fluorodesulfurization reaction are described. A three-step sequence starting from *N*-phthalimido-β-alanine allows the preparation of a new trithioorthoester as valuable precursor of the synthesis of [^{18}F]-3,3,3-trifluoropropylamine, a convenient radiolabelled intermediate for [^{18}F]-EF3. A five-step sequence for the preparation of methyl 4-phthalimido-2,2-difluoropropanedithioate from ethyl 2,2-difluoropropanoate, via the key conversion step of α,α′-difluorothioamidate to the corresponding α,α′-difluorodithioester, and the first results of its use as precursor for oxidative fluorodesulfurization in [^{18}F]-radiochemistry are also presented.

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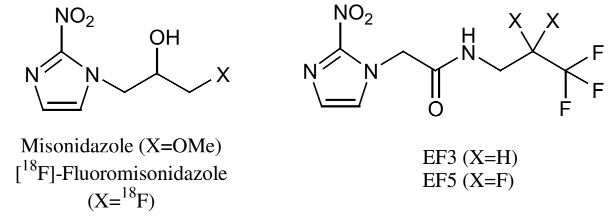
1. Introduction

Hypoxia, that is, low tissue oxygen concentration, is a typical feature in various pathological states such as malignant tumour development, heart disease, stroke, diabetes and wound healing. In solid tumours, experimental and clinical evidences have shown that the hypoxic fraction may influence the malignant phenotype, the growth rate and the metastatic potential. Cellular hypoxia is also known to reduce the sensitivity to radiation therapy and to confer some resistance to chemotherapy.[1] For these reasons, markers of hypoxia are important prognostic tools in medicine. Nitroimidazole derivatives constitute actually a major class of chemical markers from which a few representatives (misonidazole for instance; Scheme 1) have been radiolabelled with [^{18}F]-fluorine, thus making possible the in vivo detection of hypoxia by a non-invasive imaging technique, namely the positron emission tomography (PET).[2–4] The most lipophilic nitroimidazole derivatives, such as EF3 [2-(2-nitroimidazol-1-yl)-*N*-(3,3,3)-trifluoropropyl)-acetamide] and EF5 [2-(2-nitroimidazol-1-yl)-*N*-(2,2,3,3,3)-pentafluoropropyl)-acetamide] (Scheme 1), allowed biodistribution to all organs, including the brain.[1,5] The [^{18}F]-fluorine radiolabelling of such hypoxia-detection agents appears of great interest because the same molecules could be measured both invasively and non-invasively (the cold drug being the carrier of the radioactive agent), in the same tumours.[3,4]



Scheme 1. Hypoxia-binding chemical markers.

The radiolabelling of perfluorinated motifs (CF_3, C_2F_5) is scarcely described in the literature. The methods are based on isotopic exchange[6,7] and nucleophilic

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Keywords: Hypoxia detection; [^{18}F]-labelling; Trithioorthoester; α,α′-difluorodithioester.

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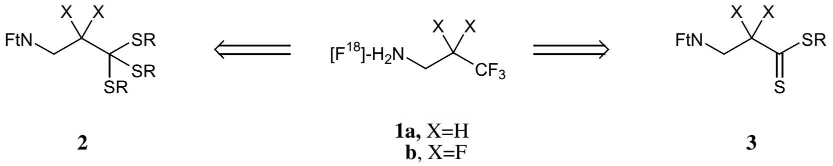


Scheme 2. Sulfur-containing precursors of $[^{18}F]$-labelled trifluoro- and pentafluoropropylamines.

substitution,[8–11] from particular precursors, by using $[^{18}F]$–KF/[2,2,2]-kryptofix. Electrophilic fluorination with $[^{18}F]$–F_2 has been mentioned in two cases: the preparation of $[^{18}F]$-EF5[12] from *N*-(2,3,3-trifluoroallyl)-acetamide precursor, and the synthesis of $[^{18}F]$-trifluoromethyl ketones[13] from the corresponding 2,2-difluorosilylenol ethers.

Recently, we considered the oxidative fluorodesulfurization reaction[14,15] as a useful strategy for $[^{18}F]$-radiolabelling of the C_nF_{2n+1} motifs found in the hypoxia markers EF3 and EF5. For that purpose, we developed $[^{18}F]$–HF·pyridine[16] as labelling reagent for the transformation of dithioesters into $[^{18}F]$–CF_3 moieties, in the presence of DBH (1,3-dibromo-5,5-dimethylhydantoin) as source of Br^+ ion. The method was successfully applied to the preparation of $[^{18}F]$-EF3 (Scheme 1);[17] the key intermediate was $[^{18}F]$-3,3,3-trifluoropropylamine **1a** obtained by the radiolabelling of ethyl 3-phthalimidopropanedithioate **3a** (Scheme 2).[18]

In continuation of our previous work, we report now the preparation of novel sulfur-containing precursors (trithioorthoester **2** and dithioester **3**; Scheme 2) for the oxidative fluorodesulfurization reaction with $[^{18}F]$–HF·pyridine and DBH. The aim was to optimalize our former synthesis of $[^{18}F]$-EF3[19] and to propose an alternative route towards $[^{18}F]$-EF5[20] regarding the electrophilic method of Koch and co-workers[12] based on $[^{18}F]$–F_2, a labelling reagent much less practical than $[^{18}F]$–HF·pyridine.

2. Results and discussion

The hypoxia-markers EF3 and EF5 could be easily prepared by coupling the tetrafluorophenyl ester of 2-(2-nitroimidazol-1-yl) acetic acid[21,22] with 3,3,3-trifluoropropylamine **1a**[17] and 2,2,3,3,3-pentafluoropropylamine **1b**,[23] respectively. We have previously shown that the experimental conditions of this reaction (reaction time, temperature, solvent, purification) are compatible with the radiolabelling requirements when using $[^{18}F]$-**1a** as reagent.[19] We have also established the advantages of the phthalimido *N*-protective group: (i) this group is stable under the drastic conditions of oxidative fluorodesulfurization; (ii) this group is rapidly cleaved with aqueous hydrazine at 85 °C; (iii) the resulting amine, thus obtained 'acid free', is readily purified by distillation from the aqueous mixture under an argon stream.[17] Accordingly, our synthetic targets are the *N*-phthalimido-trithioorthoesters **2a**,**b** and dithioester **3b** (Scheme 2).

2.1. Synthesis of trithioorthoesters

Only punctual examples of oxidative fluorodesulfurization applied to trithioorthoester precursors are mentioned in the previous literature.[24–26] We decided yet to evaluate this synthetic route because, in the case of success, this would be the shortest one towards **1a**,**b**.

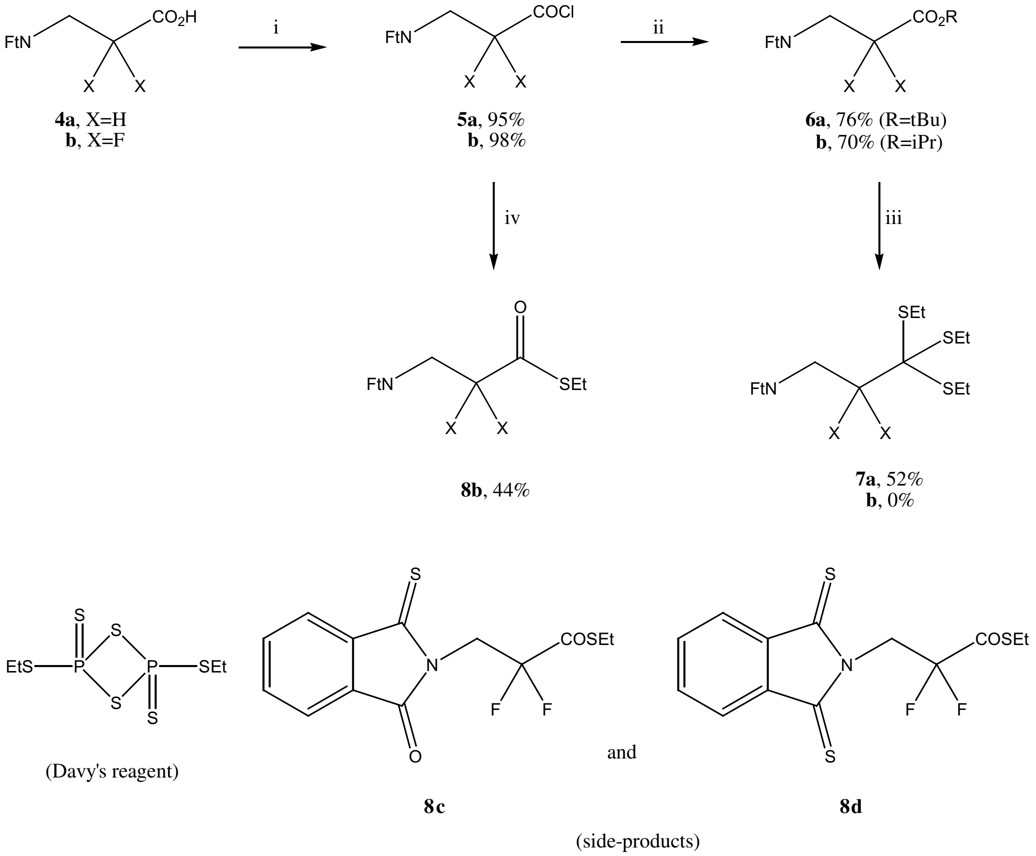
The one-step transformation of an ester function into a trithioorthoester function has been recently described by using an excess of trimethylaluminium (10 equiv) and a large excess of alkane thiol (30 equiv); the process was developed in α-aminoacid and peptide series.[27,28] Starting from *N*-phthalimido-β-alanine (**4a**), we prepared the corresponding acid chloride (**5a**) and then the *t*-butyl ester **6a** in 72% yield, which treatment with $AlMe_3$/EtSH gave the expected trithioethyl orthoester **7a** in 52% yield after several purifications by column chromatography (Scheme 3). Indeed, the main side product was the corresponding dithioethyl keteneacetal resulting from EtSH elimination (olefinic proton at $\delta = 6.0$ ppm). The quaternary carbon of the orthoester function (**7a**) gave a typical line at $\delta = 69.9$ ppm in ^{13}C NMR.

Disappointingly, the same sequence of reactions performed with *N*-phthalimido-α,α′-difluoro-β-alanine (**4b**)[29] did not furnish the desired product **7b**; extensive HF elimination and degradation occurred.

Having in hand the acid chloride **5b**, we tested the possible direct formation of dithioester **3b** (R = Et) by reaction with the Davy's reagent.[30] We recovered the thiolester **8b** (44% isolated yield) and side products **8c** and **8d** corresponding to the thionation of the phthalimide protecting group (monothionation **8c**: C═S at $\delta = 196.6$ ppm and dithionation **8d**: C═S at $\delta = 197.3$ ppm), but no traces of the dithioester could be identified.

2.2. Synthesis of dithioesters (Scheme 4)

We already prepared dithioester **16a**, precursor of $[^{18}F]$-EF3, in six steps with an overall yield of 21% from *N*-Boc-β-alanine.[17,18] We thus applied the same synthetic scheme for the preparation of dithioester **16b** from ethyl α,α′-difluoro-β-alanine (**9b**),[29] with a minor modification in the synthesis of the amide **11b**. Indeed, due to the activating effect of the CF_2 group, which increases the electrophilic character of the carbonyl function, **11b** could be quantitatively obtained by simple aminolysis of the ethyl ester **10b**. In the non-fluorinated series, the corresponding amide **11a** resulted from the coupling of *N*-Boc-β-alanine with ammonium bicarbonate in the



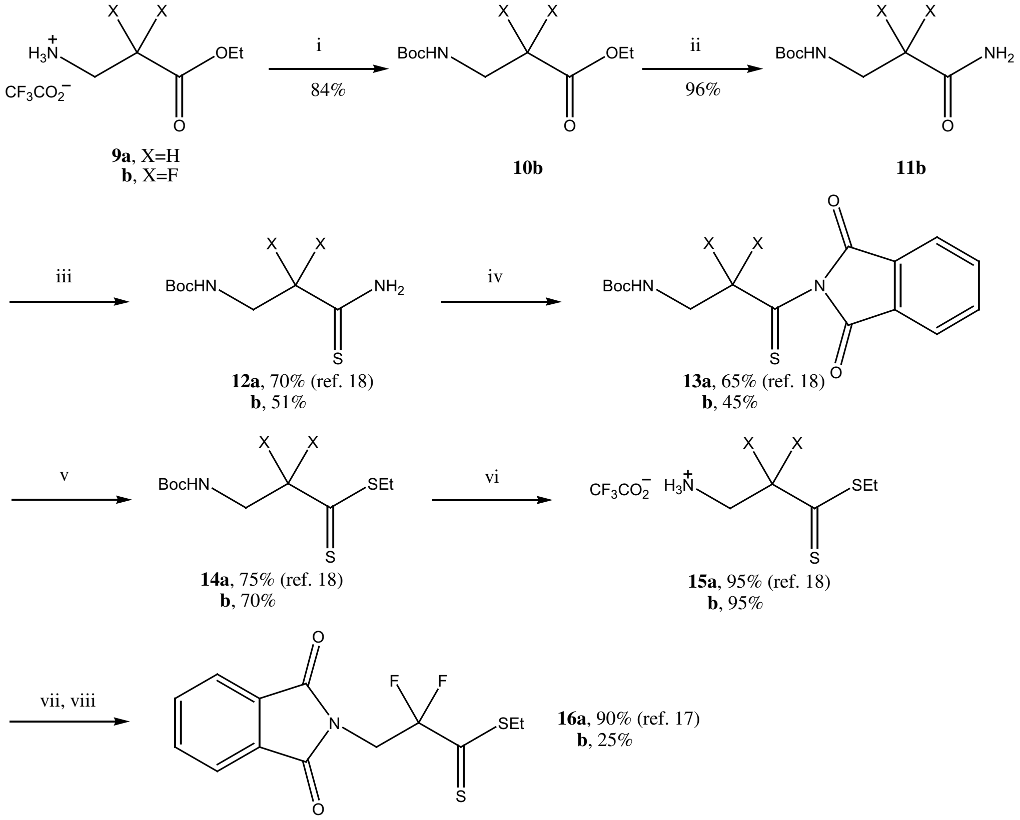
Scheme 3. Synthesis of trithioorthoester. Reagents and conditions: (i) $(COCl)_2$, DMF catal., $CHCl_3$; (ii) R–OH, $CHCl_3$; (iii) $AlMe_3$ (10 equiv), EtSH (30 equiv), CH_2Cl_2, 0–20 °C; (iv) Davy's reagent, THF, reflux, 18 h; then toluene reflux, 18 h.

presence of EEDQ (2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline) as activating agent.[18] The next step was the thionation of **11b** with the Lawesson's reagent[31] to furnish the thioamide **12b** in moderate yield after chromatography. Activation of the thioamide **12b** by transformation into the corresponding thioacyl-*N*-phthalimide[32] (**13b**) was less efficient compared to the non-fluorinated analogue (**13a**). In this reaction with phthaloyl dichloride, the thioamide function of **12b** acts as the nucleophilic partner, and thus the neighbouring CF_2 motif exercises a deactivating effect. Further treatment of **13b** with an excess of ethanethiol in the presence of triethylamine gave the ethyl dithioester **14b** in 70% yield after chromatography. The following steps were, as previously, the Boc deprotection with trifluoroacetic acid and the two-step introduction of the phthalimido protective group,[33] transforming **15b** into the target **16b**, namely ethyl 3-phthalimido-2,2-difluoropropane dithioate. Unfortunately, due to an arduous purification, the yield of pure **16b** was rather low (25%). As a consequence, the overall yield of **16b** from **9b** is only 3%, for seven steps.

All compounds were characterized by the usual spectroscopies (see experimental). Typical ^{13}C NMR features are summarized in Table 1; the shielding effect of the neighbouring CF_2 motif can be pointed out (**b** series of compounds).

2.3. Synthetic improvement (Scheme 5)

Since the synthesis of **16b** outlined in Scheme 4 was not satisfactory, we examined a modified route based on the thiolysis of thioamidium salt. This method was originally developed by Viehe and co-workers[34,35] for the preparation of methyl trifluorodithioacetate. *N*,*N*-dimethylamide **17b** was quantitatively formed by treatment of ethyl ester **10b** with dimethylamine in methanol. Thionation with the Lawesson's reagent[31] gave thioamide **18b**, which Boc protective group was cleaved with TFA and replaced by the phthalimido group as previously described. The resulting compound **20b** was treated with methyl triflate to furnish the reactive intermediate **21b** resulting from S-alkylation of the thioamide function. The thioamidium salt was not isolated, but directly reacted with H_2S to give the dithioester **22b**. The target compound was contaminated with variable amounts of thiolester **23b**, depending on the presence of moisture in the reaction medium. However, **22b** could be separated from **23b** by column chromatography and the isolated yields were around 60%. Compounds **17b** to **23b** (Scheme 5) were characterized by the usual spectroscopies (see Experimental); ^{13}C NMR chemical shifts of carbonyl and thiocarbonyl carbons are presented in Table 1. Our improved synthetic route allowed thus to obtain methyl 3-phthalimido-2,2-difluoropropanedithioate (**22b**) from **10b** in five steps, with an overall yield of 18.5%.



Scheme 4. Synthesis of dithioester (first method). Reagents and conditions: (i) $(Boc)_2O$, py, CH_2Cl_2; (ii) NH_3, MeOH; (iii) Lawesson's reagent; (iv) phthaloyl dichloride, py; (v) EtSH, Et_3N; (vi) TFA; (vii) 2-(methoxycarbonyl)benzoic acid, PyBOP; (viii) *p*-TsOH.

Table 1. ^{13}C NMR chemical shifts (ppm) in $CDCl_3$

Compd	O=C–OEt	O=C–SR	O=C–NR$_2$		S=C–NR$_2$		S=C–SR
	10	**8**; **23**	**11**; **17**		**12**; **18**		**14**; **15**; **16**; **22**
a	—	—	174.1 (R = H)	—	207.6 (R = H)	—	235.6; 235.4; 233.0
b	163.2	191.75 (R = Et), 192.33 (R = Me)	167.8[a] (R = H)	162.8 (R = Me)	195.4 (R = H)	188.9 (R = Me)	222.5 (R = Me)

[a] Solvent CD_3OD.

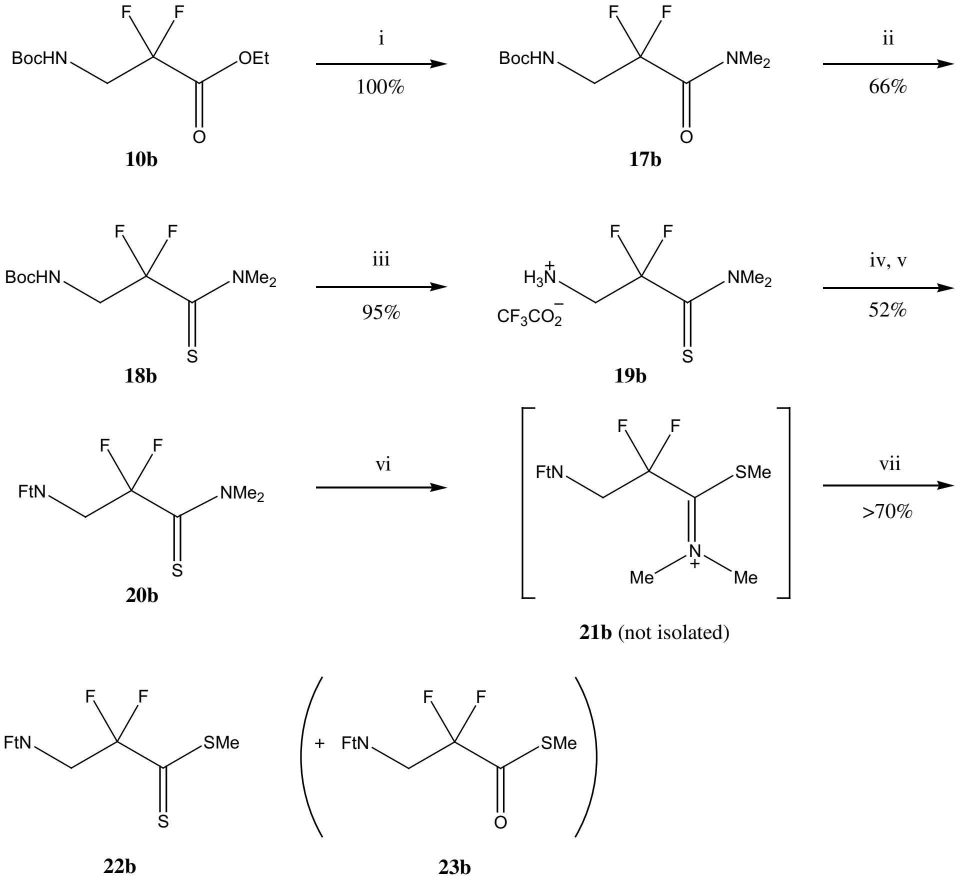
2.4. [^{18}F]-radiolabelling

[^{18}F]–HF·pyridine was prepared from dry [^{18}F]–KF and HF·pyridine, as previously described.[17] By using the radiolabelling process of **3a**,[17] that is, the preparation of a [^{18}F]-labelled intermediate **24** resulting from the substitution of one ethylthioxy group by [^{18}F]-fluoride under DBH activation followed by the substitution of the remaining ethylthioxy groups by a large excess of unlabelled fluoride (Scheme 6), we could obtain [^{18}F]-*N*-phthalimido-3,3,3-trifluoropropylamine (**25a**) from the precursor trithioorthoester **7a**.

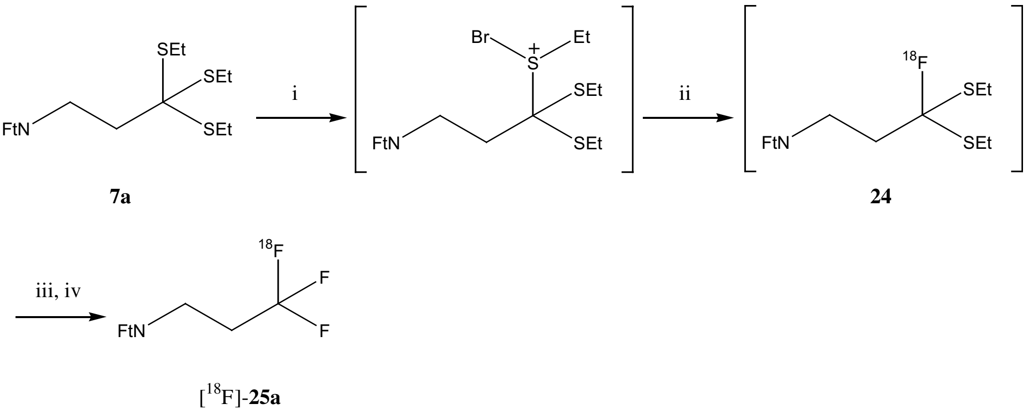
The labelled compound was identified by HPLC (UV and radiodetection) and mass spectrometry, by comparison with an authentical sample. The reaction time was less than 25 min and the radiochemical yield was around 1.6% (decay corrected) ($\leqslant$0.01 mmol of precursor **7a**).

We similarly conducted the [^{18}F]-labelling of methyl *N*-phthalimido-2,2-difluoro-propanedithioate (**22b**) (Scheme 7).

We recovered [^{18}F]-*N*-phthalimido-2,2,3,3-tetrafluoro-3-methylthioxy-propylamine (**26**) as the main product and variable amounts of the corresponding HF-elimination product **27**, depending on the reaction time in the excess of HF·pyridine used (analysis of the crude mixtures by HPLC with double detection and mass spectrometry). It appears thus that the creation of the CF_3 motif next to a pre-existing CF_2 motif by S/F nucleophilic exchange is rather difficult: the reaction stopped after the introduction of two fluorine atoms.[36] Even after addition of a large excess of a silver or mercury salt and prolonged reaction time (total reaction time: 40 min), we found that the reluctant methylthioxy group could not be satisfactorily substituted by HF·pyridine. The expected [^{18}F]-



Scheme 5. Synthesis of dithioester (second method). Reagents and conditions: (i) $HNMe_2$, MeOH, 1 h, 0 °C; (ii) Lawesson's reagent, toluene, 2 h, 100 °C; (iii) TFA–CH_2Cl_2 (1:1), 1 h, 0 °C; (iv) and (v): see Scheme 4; (vi) CF_3SO_3Me, CH_2Cl_2, 2 h, rt; (vii) H_2S, CH_2Cl_2, 0 °C, 1 h.

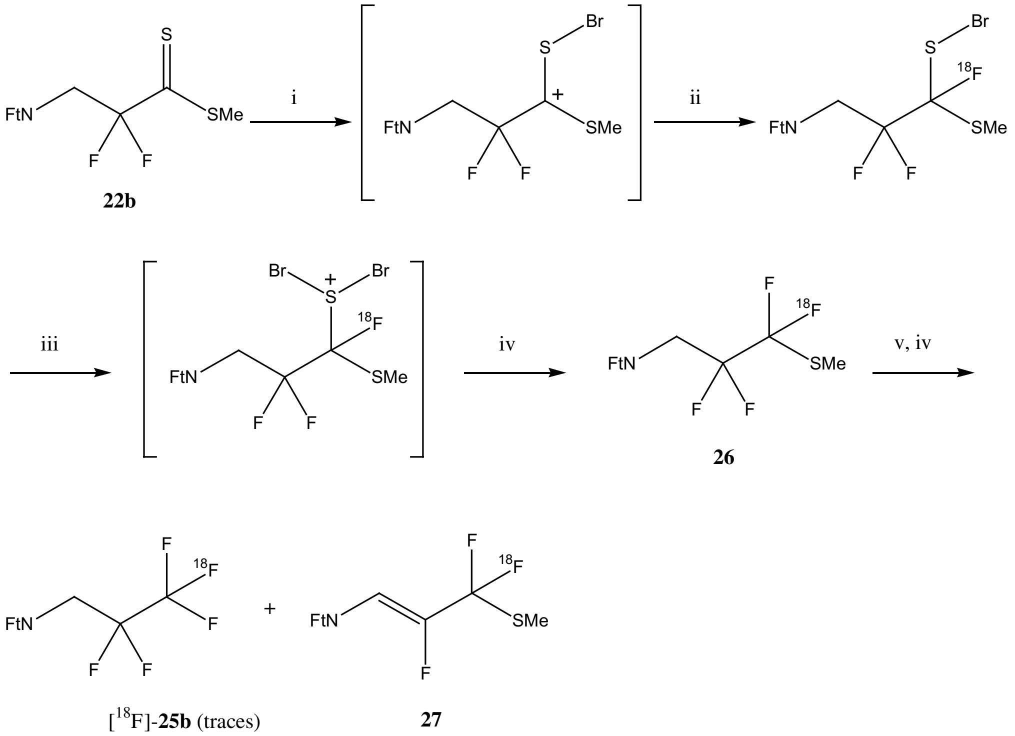


Scheme 6. [^{18}F]-radiolabelling of trithioorthoester. Reagents and conditions: (i) DBH (2 equiv); (ii) [^{18}F]–HF·pyridine (7 equiv of fluoride), CH_2Cl_2, 20 °C, 10 min; (iii) DBH (4 equiv); (iv) HF·pyridine (140 equiv of fluoride), 20 °C, 10 min.

N-phthalimido-2,2,3,3,3-pentafluoropropylamine (**25b**) was identified only as traces in HPLC by comparison with an authentical sample. Optimalization of the production of [^{18}F]-**25b** is still under investigation. An alternative strategy is currently examined, that is, the radiolabelling of dithioketal or oxime derivatives of the *N*-(phthalimido)methyl trifluoromethyl ketone precursor (CF_2 labelling instead of CF_3 labelling).

3. Conclusion

The [^{18}F]-labelled precursors **25a** and **25b** of the hypoxia markers [^{18}F]-EF3 and [^{18}F]-EF5 (see Schemes 1 and 2) have been prepared from novel sulfur-containing compounds, respectively *N*-phthalimido-3,3,3-(triethylthioxy)propylamine (**7a**, see Scheme 6) and methyl *N*-phthalimido-2,2-difluoropropanedithioate (**22b**, see



Scheme 7. [18F]-radiolabelling of α,α′-difluorodithioester **22b**. Reagents and conditions: (i) DBH (3equiv); (ii) [18F]–HF·pyridine (7equiv of fluoride), CH_2Cl_2, 20°C, 15min; (iii) DBH (6equiv), (iv) HF·pyridine (240equiv of fluoride), 20°C, 15min; (v) $HgCl_2$ (20equiv) or AgX.

Scheme 7). The preparation of [18F]-**25a** works, while the similar synthesis of [18F]-**25b** remains to be confirmed. This work represents the first example of the [18F]-labelling of the CF_3 motif by oxidative fluorodesulfurization reaction of a trithioorthoester precursor, and constitutes a significant improvement of the [18F]-EF3 preparation since the radiolabelling precursor is now directly available from *t*-butyl *N*-phthalimido-β-alaninate **6a** (see Scheme 3).

For the [18F]-labelling of the C_2F_5 motif of EF5, we selected a α,α′-difluoro-dithioester precursor. This class of compounds is scarcely described in the literature,[37–40] comparatively to the simple dithioesters.[41–43] The lack of convenient methods of preparation, compatible with *N*-functionalized aliphatic starting materials, led us to propose the route outlined in Scheme 5, and applicable to α,α′-difluoro-β-amino-esters, a class of compounds now readily accessible.[44,45] Our method relies upon: (i) the transformation of the ester function into *N*,*N*-dimethyl-thioamide; (ii) the S-alkylation with methyl triflate followed by the in situ thiolysis.

Having in hand the α,α′-difluoro-dithioester precursor **22b**, we investigated the feasibility of the [18F]-labelling of a C_2F_5 motif by S/F nucleophilic displacement activated with DBH as oxidant. We found that the tetrafluoro derivative [18F]-**26** was readily and nearly quantatively obtained; the radiolabelling of a tetrafluorinated motif has not been reported yet. However, the required [18F]-pentafluorinated compound **25b**, resulting from a forced substitution of the last alkylthio group in the presence of a strong thiophilic Lewis acid, could not be obtained at the preparative scale since competitive elimination of HF occurred to furnish [18F]-**27** as the major product. Thus other routes towards [18F]-**25b** have to be explored.

4. Experimental

Solvents were dried before use. Reagents (from Acros, Fluka or Aldrich) were used as purchased. Melting points (uncorrected) were recorded on an Electrothermal apparatus. ^{1}H (200MHz) and ^{13}C (50MHz) NMR spectra were recorded on Varian Gemini 200 spectrometer; ^{13}C (125MHz) NMR spectra were recorded on Bruker AM-500 apparatus and ^{19}F (282MHz) on Varian Gemini 300 spectrometer. Chemical shifts are reported as δ values (ppm) downfield from TMS. Mass spectra were obtained on a Finnigan-MAT TSQ-70 instrument at 70eV. HRMS was recorded at the University of Mons, Belgium (Prof. R. Flammang). TLC were carried out using silicagel 60 F_{254} (0.2mm, Merck) and spots were visualized by UV. Silica gel 60, mesh size 0.04–0.063mm (Merck), was used for column chromatography.

4.1. 3-Phthalimido-propanoyl chloride (5a)

To a cold (0°C) solution of *N*-phthalimido-β-Ala–OH **4a** (2.5g, 11.41mmol) in ethanol-free chloroform (12mL) and with a catalytic amount of DMF, was added oxalyl chloride (2.9g, 2mL, 22.82mmol), dropwise and under vigorous stirring. After 10min at 0°C, and progressive return at room temperature, completion of the reaction was observed with the end of CO_2 release. Concentration of the solvent under reduced pressure gave crude **5a** as a yellow solid directly used in the following step. Yield: 95% (2.58g); ^{1}H NMR (200MHz, $CDCl_3$): $\delta = 3.34$ (t, 2H, $J = 7$Hz, CH_2), 4.03 (t, 2H, $J = 7$Hz, CH_2), 7.71–7.88 (m, 4H, C_6H_4).

4.2. 3-Phthalimido-2,2-difluoropropanoyl chloride (5b)

To a cold (0°C) solution of 3-phthalimido-2,2-difluoropropanoic acid **4b** (0.30g, 1.18mmol) in ethanol-free chloroform (10mL) and with a catalytic amount of DMF, was added oxalyl chloride (0.3g, 0.21mL, 2.365mmol), dropwise and under vigorous stirring. After 10min at 0°C, and progressive return at room temperature, completion of the reaction was observed with the end of CO_2 release. Concentration of the solvent under reduced pressure gave crude **5b** as a yellow solid directly used in the following step. Yield: 100% (0.325g); ^{1}H NMR (200MHz, $CDCl_3$): $\delta = 4.41$ (t, 2H, $J_{HF} = 7$Hz, CH_2), 7.78–7.96 (m, 4H, C_6H_4); ^{19}F NMR (282MHz, $CDCl_3/CFCl_3$): $\delta = -104.96$ (t, $J_{F-H} = 12.7$Hz, CH_2CF_2).

4.3. *tert*-Butyl 3-phthalimido-propanoate (6a)

To a crude solution of **5a** (2.58g, 10.84mmol) in ethanol-free chloroform (12mL) was added a large excess of *t*BuOH (3mL). After stirring for 24h and concentration of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane: 20/80 ($R_f = 0.42$)) to afford **6a** as a white solid. Overall yield for the two steps: 72% (2.26g); mp = 112–113°C; ^{1}H NMR (200MHz, $CDCl_3$): $\delta = 1.41$ (s, 9H, CH_3), 2.65 (t, 2H, $J = 7.3$Hz, CH_2), 3.96 (t, 2H, $J = 7.3$Hz, CH_2), 7.70–7.88 (m, 4H, C_6H_4); ^{13}C NMR (50MHz, $CDCl_3$): $\delta = 28.18$ (CH_3), 34.17 (CH_2), 34.41 (CH_2), 81.23 (C), 123.44, 132.33, 134.13 arom., 168.15 (N–C=O), 170.10 (C=O); MS (+c CI, CH_4–NO_2): $m/z = 276.1$ (M+1), $C_{15}H_{17}NO_4$.

4.4. *iso*-Propyl 3-phthalimido-2,2-difluoropropanoate (6b)

To a crude solution of **5b** (0.1g, 0.39mmol) was added a large excess of *i*-PrOH (3mL). After stirring for 24h and concentration of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane: 20/80, ($R_f = 0.75$)) to afford **6b** as a brown oil, which solidified slowly. Overall yield for the two steps: 78% (0.09g); ^{1}H NMR (200MHz, $CDCl_3$): $\delta = 1.22$ (d, 6H, $J = 5.1$Hz, CH_3), 4.05 (sept, 1H, $J = 5.1$Hz, CH), 4.31 (t, 2H, $J_{HF} = 13.6$Hz, CH_2), 7.74–7.94 (m, 4H, C_6H_4); ^{19}F NMR (282MHz, $CDCl_3/CFCl_3$): $\delta = -109.83$ (t, $J_{FH} = 12.7$Hz, CH_2CF_2); ^{13}C NMR (50MHz, $CDCl_3$): $\delta = 21.60$ (CH_3), 40.30 (t, $J_{C-F} = 29.5$Hz, CH_2CF_2), 72.22 (CH), 117.86 (t, $J_{C-F} = 254$Hz, CF_2), 123.90, 131.94, 134.58 arom., 162.27 (t, $J_{C-F} = 31$Hz, C=O), 167.21 (s, N–C=O).

4.5. 3-Phthalimido-propyl trithioethyl orthoester (7a)

To a cold (0°C) solution of $AlMe_3$ (2.0M in heptane, 36.36mL, 72.72mmol) in ethanol-free chloroform (140mL) was added dropwise EtSH (16.12mL, 2.18mol). After 15min of stirring, a solution of **6a** (2g, 7.27mmol) in chloroform (34mL) was added and the cold bath was removed. After 24h stirring at room temperature, the solution was poured in ice (140g) and after the end of gas release, extracted with chloroform (3 × 140mL). The organic phase was dried ($MgSO_4$) and concentrated to afford a pale yellow oil, which was purified by flash chromatography on silica gel (ethyl acetate/hexane: 2/98, (ethyl acetate/hexane: 20/80, $R_f = 0.67$)) to afford **7a** as a colourless oil. Yield: 52% (1.39g); ^{1}H NMR (200MHz, $CDCl_3$): $\delta = 1.29$ (t, 9H, $J = 7.5$Hz, CH_3), 2.25 (m, 2H, CH_2), 2.81 (q, 2H, $J = 7.5$Hz, CH_2), 4.11 (m, 2H, CH_2), 7.70–7.87 (m, 4H, C_6H_4); ^{13}C NMR (50MHz, $CDCl_3$): $\delta = 13.82$ (CH_3), 24.65 (SCH_2), 34.17 (CH_2), 34.41 (CH_2), 69.87 (C), 123.30, 132.38, 134.06 arom., 168.29 (N–C=O); MS (−c CI, CH_4–NO_2): $m/z = 369.2$ (M−1), $C_{17}H_{23}NO_2S_3$.

4.6. Ethyl 3-phthalimido-2,2-difluoropropanethioate (8b)

To a solution of **5b** (0.238g, 0.87mmol) in THF (5mL) was added Davy's reagent (0.272g, 0.87mmol). The mixture was heated to reflux during 18h. After cooling to room temperature and concentration of the solvent under reduced pressure, purification by flash chromatography on silica gel (ether/petroleum ether: 3/17 ($R_f = 0.11$)) afforded **8b** as an orange solid. Yield: 44% (0.114g); mp = 121–122°C; ^{1}H NMR (200MHz, $CDCl_3$): $\delta = 1.31$ (t, 3H, $J = 7.3$Hz, CH_3), 3.00 (q, 2H, $J = 7.3$Hz, CH_2S), 4.31 (t, 2H, $J_{HF} = 13.6$Hz, CH_2CF_2), 7.78–7.95 (m, 4H, C_6H_4); ^{19}F NMR (282MHz, $CDCl_3/CFCl_3$): $\delta = -107.71$ (t, $J_{F-H} = 13.8$Hz, CH_2CF_2); ^{13}C NMR (125MHz, $CDCl_3$): $\delta = 13.93$ (CH_3), 23.52 (CH_2), 39.77 (t, $J_{C-F} = 32$Hz, CH_2CF_2), 114.36 (t, $J_{C-F} = 258$Hz, CF_2), 123.76, 131.74, 134.56 arom., 167.07 (s, N–C=O), 191.75 (t, $J_{C-F} = 32$Hz, C=O); MS (+c APCI, CH_4–NO_2): $m/z = 299.9$ (M+1), $C_{13}H_{11}F_2NO_3S$.

4.7. Ethyl 3-thiophthalimido-2,2-difluoropropanethioate 8c and ethyl 3-dithiophthalimido-2,2-difluoropropanethioate 8d

To a suspension of **8b** (0.074g, 0.2.47mmol) in toluene (10mL) was added Davy's reagent (0.042g, 0.136mmol). The mixture was heated to reflux over night. After cooling to room temperature and concentration of the solvent under reduced pressure, separation by flash chromatography on silica gel (ether/petroleum ether: 3/17 (**8c** $R_f = 0.58$ and **8d** $R_f = 0.31$)) afforded **8c** as a pink oil, which crystallizes slowly, and **8d** as a red oil. Compound **8c** yield: 32% (0.025g); **8d** yield: 63% (0.052g):

Compound **8c** ^{1}H NMR (200MHz, $CDCl_3$): $\delta = 1.31$ (t, 3H, $J = 7.4$Hz, CH_3), 3.00 (q, 2H, $J = 7.4$Hz, CH_2S), 4.73 (t, 2H, $J_{HF} = 13.36$Hz, CH_2CF_2), 7.72–8.06 (m, 2H, 1H, 1H, C_6H_4); ^{19}F NMR (282MHz, $CDCl_3/CFCl_3$): $\delta = -106.02$ (t, $J_{F-H} = 13.8$Hz, CH_2CF_2); ^{13}C NMR (125MHz, $CDCl_3$): $\delta = 14.00$ (CH_3), 23.68 (CH_2), 42.26 (t, $J_{C-F} = 28.2$Hz, CH_2CF_2), 114.61 (t, $J_{C-F} = 258.4$Hz, CF_2), 123.38, 124.54, 126.95, 133.80, 134.65, 137.32 arom., 168.97 (s, N–C=O), 192.02 (t,

$J_{\mathrm{C-F}} = 31.9$ Hz, *C*═O), 196.64 (s, N–*C*=S); MS (+c APCI, CH_4–NO_2): *m*/*z* = 315.9 (M+1), $C_{13}H_{11}F_2NO_2S_2$.

Compound **8d** ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.31$ (t, 3H, $J = 7.5$ Hz, C*H*$_3$), 2.98 (q, 2H, $J = 7.5$ Hz, C*H*$_2$S), 5.19 (t, 2H, $J_{\mathrm{HF}} = 13.3$ Hz, C*H*$_2$CF$_2$), 7.72–7.95 (m, 2H, 2H, C_6H_4); ^{19}F NMR (282 MHz, $CDCl_3/CFCl_3$): $\delta = -103.85$ (t, $J_{\mathrm{F-H}} = 12.83$ Hz, CH$_2$C*F*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 14.00$ (*C*H$_3$), 23.69 (*C*H$_2$), 44.47 (t, $J_{\mathrm{C-F}} = 27.3$ Hz, *CH*$_2$CF$_2$), 114.77 (t, $J_{\mathrm{C-F}} = 259.3$ Hz, *C*F$_2$), 123.90, 133.70, 134.65, 134.96 arom., 192.22 (t, $J_{\mathrm{C-F}} = 31.9$ Hz, *C*═O), 197.35 (s, N–*C*=S); MS (–c APCI, CH_4–NO_2): *m*/*z* = 331.0 (M–1), $C_{13}H_{11}F_2NOS_3$.

4.8. Ethyl (*N*-*tert*-butoxycarbonyl)-3-amino-2,2-difluoropropanoate (10b)

To a solution of **9b** (4.18 g, 15.68 mmol) in dichloromethane (10 mL) and pyridine (5 mL), cooled at 0 °C and under stirring for 10 min, was added dropwise a solution of di-*tert*-butyl-dicarbonate (3.42 g, 15.68 mmol) in dichloromethane (5 mL). After the addition was complete, the mixture was further stirred for 15 h at 20 °C, then poured into H_2O (10 mL) and extracted with dichloromethane (2 × 15 mL). Drying ($MgSO_4$) and concentration of the solvent gave **10b** as colourless oil. Yield: 84% (3.31 g); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.36$ (t, 3H, $J = 7.1$ Hz, C*H*$_3$), 1.44 (s, 9H, C*H*$_3$), 3.76 (dt, 2H, $J_{\mathrm{HF}} = 13.4$ Hz, $J_{\mathrm{HH}} = 6.7$ Hz, C*H*$_2$CF$_2$), 4.33 (q, 2H, $J = 7.16$ Hz, C*H*$_2$O); ^{19}F NMR (282 MHz, $CDCl_3/CFCl_3$): $\delta = -111.66$ (t, $J_{\mathrm{F-H}} = 13$ Hz, CH$_2$C*F*$_2$); *^{13}C NMR (50 MHz, $CDCl_3$):* $\delta = 13.91$ (*C*H$_3$), 28.29 (*C*H$_3$), 43.71 (t, $J_{\mathrm{C-F}} = 28.3$ Hz, *CH*$_2$CF$_2$), 63.26 (*CH*$_2$O), 80.50 (*C*), 113.46 (t, $J_{\mathrm{C-F}} = 251$ Hz, *C*F$_2$), 155.50 (s, N–*C*═O), 163.19 (t, $J_{\mathrm{C-F}} = 31.5$ Hz, *C*═O); MS (APCI, CH_4–NO_2): *m*/*z* = 254.2 (M+1), $C_{10}H_{17}F_2NO_4$.

4.9. (*N*-*tert*-Butoxycarbonyl)-3-amino-2,2-difluoropropanamide (11b)

Compound **10b** (7.58 g, 29.94 mmol) was added to a solution of ammonia 7N in methanol (20 mL) cooled at 0 °C and the mixture was stirred for 2 h at room temperature. Concentration of the solvent under reduced pressure gave **11b** as a yellow solid. Yield: 98% (6.53 g); mp = 124–125 °C; ^{1}H NMR (200 MHz, CD_3OD): $\delta = 1.43$ (s, 9H, C*H*$_3$), 3.67 (t, 2H, $J_{\mathrm{HF}} = 19.9$ Hz, C*H*$_2$CF$_2$); ^{19}F NMR (282 MHz, CD_3OD): $\delta = -111.47$ (t, $J_{\mathrm{F-H}} = 15$ Hz, CH$_2$C*F*$_2$); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 28.63$ (*C*H$_3$), 43.84 (t, $J_{\mathrm{C-F}} = 27.5$ Hz, *CH*$_2$CF$_2$), 80.75 (*C*), 116.44 (t, $J_{\mathrm{C-F}} = 251.5$ Hz, *C*F$_2$), 158.11 (s, N–*C*═O), 167.76 (t, $J_{\mathrm{C-F}} = 28.4$ Hz, *C*═O); MS (+c APCI, CH_4–NO_2): *m*/*z* = 225.0 (M+1), $C_8H_{14}F_2N_2O_3$.

4.10. (*N*-*tert*-Butoxycarbonyl)-3-amino-2,2-difluoropropanethioamide (12b)

Compound **11b** (6.52 g, 29.12 mmol) and Lawesson's Reagent (7.06 g, 12.47 mmol) in THF (100 mL) were stirred at room temperature for 24 h. After concentration, the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate: 80/20 ($R_f = 0.18$)) to afford (**12b**) as a white solid. Yield: 69% (4.80 g); mp = 131–132 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.46$ (s, 9H, C*H*$_3$), 3.97 (dt, 2H, $J_{\mathrm{HF}} = 14$ Hz, $J_{\mathrm{HH}} = 6.9$ Hz, C*H*$_2$CF$_2$), 4.89 (s, 1H, NH), 7.63 (s, 2H, NH$_2$); ^{19}F NMR (282 MHz, $CDCl_3/CFCl_3$): $\delta = -105.68$ (t, $J_{\mathrm{F-H}} = 15$ Hz, CH$_2$C*F*$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 28.46$ (*C*H$_3$), 45.05 (t, $J_{\mathrm{C-F}} = 25.6$ Hz, *CH*$_2$CF$_2$), 80.8 (*C*), 117.51 (t, $J_{\mathrm{C-F}} = 254$ Hz, *C*F$_2$), 155.74 (s, N–*C*═O), 195.37 (t, $J_{\mathrm{C-F}} = 26$ Hz, *C*=S); MS (+c CI, CH_4–NO_2): *m*/*z* = 241.0 (M+1), $C_8H_{14}F_2N_2O_2S$.

4.11. (*N*-*tert*-Butoxycarbonyl) 3-amino-2,2-difluoropropanethioacyl *N*-phthalimide (13b)

To a mixture of thioamide **12b** (0.439 g, 1.83 mmol) and pyridine (0.588 mL, 0.578 g, 7.32 mmol) in dichloromethane (15 mL), cooled a 0 °C, was added dropwise (within 4 h and stirring under argon atmosphere) a solution of phthaloyl dichloride (0.316 mL, 0.446 g, 2.196 mmol) in dichloromethane (15 mL). After completion of the addition, the mixture was further stirred over night at 20 °C, then poured into water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phase was dried ($MgSO_4$), concentrated and purified by chromatography on silica gel (hexane/ethyl acetate: 80/20 ($R_f = 0.28$)) to afford **13b** as a colourless oil, which crystallizes slowly. Yield: 24% (0.165 g); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.45$ (s, 9H, C*H*$_3$), 3.97 (dt, 2H, $J_{\mathrm{HF}} = 14$ Hz, $J_{\mathrm{HH}} = 6.9$ Hz, C*H*$_2$CF$_2$), 4.95 (s, 1H, NH), 7.74–7.91 (m, 4H, C_6H_4); ^{19}F NMR (282 MHz, $CDCl_3/CFCl_3$): $\delta = -106.08$ (t, $J_{\mathrm{F-H}} = 12.7$ Hz, CH$_2$C*F*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 28.36$ (*C*H$_3$), 44.78 (t, $J_{\mathrm{C-F}} = 28.3$ Hz, *CH*$_2$CF$_2$), 80.7 (*C*), 117.4 (t, $J_{\mathrm{C-F}} = 253$ Hz, *C*F$_2$), 124.21, 131.58, 134.761, 155.85 (s, N–*C*═O), 195.17 (t, $J_{\mathrm{C-F}} = 25.5$ Hz, *C*=S).

4.12. Ethyl 3-phthalimido-2,2-difluoropropane dithioate (16b)

To a cold (0 °C) solution under argon atmosphere of **13b** (0.25 g, 0.676 mmol) in chloroform (3 mL) were added successively ethanethiol (0.25 mL, 0.209 g, 3.38 mmol) and dropwise triethylamine (0.094 mL, 0.069 g, 0.676 mmol). The solution was allowed to reach room temperature within 1 h and left for another 1 h at 20 °C. After addition of 4N NaOH (3 mL), the mixture was rapidly extracted with chloroform (3 × 3 mL), dried over $MgSO_4$ and concentrated under vaccum. Purification by flash chromatography on silica gel (hexane/ethyl acetate: 70/30 ($R_f = 0.39$)) afforded **14b** as a yellow solid. Yield: 70% (0.134 g). Compound **14b** (0.134 g, 0.47 mmol) was dissolved under argon atmosphere in cold (0 °C) trifluoroacetic acid (5 mL) and left 1 h under stirring. Evaporation under vaccum to remove the excess of trifluoroacetic acid afforded pure **15b** as a yellow oil. Yield: 95% (0.133 g). To a suspension of PyBOP (0.255 g, 0.49 mmol) in THF (1 mL) was added a solution of 2-(methoxycarbonyl)benzoic acid (0.095 g, 0.49 mmol) in THF (1 mL) and pyridine (0.053 mL, 0.052 g, 0.66 mmol). The mixture was stirred at room temperature for 45 min. Compound **15b** (0.113 g, 0.45 mmol) in THF (1 mL) was introduced in one portion followed by slow addition of pyridine (0.106 mL, 0.104 g, 1.32 mmol). After stirring at room temperature for 6 h, a catalytic amount of *p*-TsOH was added before refluxing for 48 h. After cooling at room temperature, the solution was poured on aqueous 10% $NaHCO_3$ (2 mL) and extracted with ethyl acetate (3 × 5 mL). The organic layer was dried ($MgSO_4$) and concentrated before purification by flash chromatography on silica gel (ethyl acetate/hexane: 40/60 ($R_f = 0.68$)) to afford **16b** as an orange solid. Yield: 25% (0.033 g); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.36$ (t, 3H, $J = 7.4$ Hz, CH_3), 3.19 (t, 2H, $J = 7.4$ Hz, CH_2CF_2), 4.57 (q, 2H, $J = 13.4$ Hz, CH_2), 7.74–7.93 (m, 4H$_{arom.}$); ^{19}F NMR (282 MHz, $CDCl_3/CFCl_3$): $\delta = -104.43$ (t, $J_{F-H} = 12.7$ Hz, CH_2CF_2); MS (−c CI, CH_4–NO_2): $m/z = 314.0$, $C_{13}H_{11}F_2NO_2S_2$.

4.13. (*N-tert*-Butoxycarbonyl)-3-amino-2,2-difluoropropane *N*,*N*-dimethylamide (17b)

Compound **10b** (1.50 g, 12.53 mmol) was added to a solution of dimethylamine 33% in ethanol (20 mL) cooled at 0 °C and the mixture was stirred for 1 h at room temperature. Concentration of the solvent under reduced pressure gave **17b** as an orange oil. Yield: 100% (1.5 g); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.43$ (s, 9H, CH_3), 2.99 (s, 3H, N–CH_3), 3.18 (t, 3H, $J_{HF} = 2.0$ Hz, N–CH_3), 3.79 (dt, 2H, $J_{HF} = 13.5$ Hz, $J_{HH} = 6.7$ Hz, CH_2CF_2); ^{19}F NMR (282 MHz, $CDCl_3/CFCl_3$): $\delta = -106.40$ (t, $J_{F-H} = 13$ Hz, CH_2CF_2); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 28.29$ (CH_3), 35.58 (CH_3), 43.76 (t, $J_{C-F} = 21$ Hz, CH_2CF_2), 79.84 (*C*quaternaire), 116.42 (t, $J_{C-F} = 257$ Hz, CF_2), 155.81 (s, N–$C{=}O$), 162.77 (t, $J_{C-F} = 28$ Hz, $C{=}O$); MS (+c CI, CH_4–NO_2): $m/z = 253.0$ (M+1), $C_{10}H_{18}F_2N_2O_3$.

4.14. (*N-tert*-Butoxycarbonyl)-3-amino-2,2-difluoropropane *N*,*N*-dimethylthioamide (18b)

Compound **17b** (1.54 g, 6.24 mmol) and Lawesson's reagent (1.514 g, 3.74 mmol) in toluene (50 mL) were stirred at reflux for 3 h. After concentration, the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane: 20/80 ($R_f = 0.38$)) to afford **18b** as a yellow solid. Yield: 66% (1.092 g); mp = 95–96 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.45$ (s, 9H, CH_3), 3.46 (s, 3H, N–CH_3), 3.52 (t, 3H, $J_{HF} = 2.0$ Hz, N–CH_3), 4.07 (dt, 2H, $J_{HF} = 13.5$ Hz, $J_{HH} = 6.9$ Hz, CH_2CF_2); ^{19}F NMR (282 MHz, $CDCl_3/CFCl_3$): $\delta = -100.95$ (t, $J_{F-H} = 13$ Hz, CH_2CF_2); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 28.30$ (CH_3), 45.93 (CH_3), 46.08 (t, $J_{C-F} = 30$ Hz, CH_2CF_2), 79.92 (*C*quaternaire), 117.86 (t, $J_{C-F} = 257$ Hz, CF_2), 155.87 (s, N–$C{=}O$), 188.68 (t, $J_{C-F} = 24$ Hz, $C{=}S$); MS (+c CI, CH_4–NO_2): $m/z = 268.7$ (M+1), $C_{10}H_{18}F_2N_2O_2S$.

4.15. 3-Phthalimido-2,2-difluoropropane *N*,*N*-dimethylthioamide (20b)

Compound **18b** (1.092 g, 4.075 mmol) was dissolved in a cold (0 °C) solution of trifluoroacetic acid (5 mL) in dichloromethane (5 mL) and left 1 h stirring under argon atmosphere. Evaporation under vacuum to remove the solvent and the excess of trifluoroacetic acid gave crude **19b** as yellow oil, which crystallizes slowly. To a suspension of PyBOP (1.067 g, 2.05 mmol) in THF (10 mL) was added a solution of 2-(methoxycarbonyl)benzoic acid (0.369 g, 2.05 mmol) in THF (10 mL) and pyridine (0.247 mL, 0.243 g, 3.08 mmol). The mixture was stirred at room temperature for 45 min. Compound **19b** (0.526 g, 1.86 mmol) in THF (2 mL) was introduced in one portion followed by slow addition of pyridine (0.748 mL, 0.735 g, 9.3 mmol). After stirring at room temperature for 4 h, the mixture was poured into 10% $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was dissolved in anhydrous toluene (40 mL) and a catalytic amount of *p*-TsOH was added before refluxing for 48 h. After cooling at room temperature, the solution was poured on aqueous 10% $NaHCO_3$ (10 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried ($MgSO_4$) before purification by flash chromatography on silica gel (hexane/ethyl acetate: 70/30 ($R_f = 0.36$)) to afford **20b** as a yellow solid. Yield: 52% (0.287 g); mp = 113–114 °C.

Compound **19b** ^{1}H NMR (200 MHz, D_2O): $\delta = 3.45$ (s, 3H, NCH_3), 3.54 (s, 3H, NCH_3), 4.06 (t, 2H, $J_{HF} = 14.8$ Hz, CH_2CF_2); ^{19}F NMR (282 MHz, $CDCl_3/CFCl_3$): $\delta = -76.07$ (q, $J_{F-H} = 8.6$ Hz, CF_3), 100.52 (t, $J_{F-H} = 15$ Hz, CH_2CF_2).

Compound **20b** ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 3.47$ (s, 3H, N–CH_3), 3.50 (t, 3H, $J_{HF} = 2.0$ Hz, N–CH_3), 4.74 (t, 2H, $J_{HF} = 16.6$ Hz, CH_2CF_2), 7.73–7.94 (m, 4H, C_6H_4); ^{19}F NMR (282 MHz, $CDCl_3/CFCl_3$): $\delta = -106.08$ (t, $J_{F-H} = 15$ Hz, CH_2CF_2); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 43.12$ (t, $J_{C-F} = 29$ Hz, CH_2CF_2), 45.89 (CH_3), 45.95 (CH_3), 116.61 (t, $J_{C-F} = 258$ Hz, CF_2), 123.74, 132.30, 134.35, 167.65 (s, N–$C{=}O$), 188.91 (t, $J_{C-F} = 24$ Hz, $C{=}S$); MS (APCI, CH_4–NO_2): $m/z = 299.0$ (M+1), $C_{13}H_{12}F_2N_2O_2S$.

4.16. Methyl 3-phthalimido-2,2-difluoropropanedithioate (22b)

Freshly distillated methyl triflate (0.073 mL, 0.109 g, 0.664 mmol) in dry and ethanol-free dichloromethane (1 mL) was added to a solution of **20b** (0.180 g, 0.604 mmol) in dry and ethanol-free dichloromethane (1 mL) via a syringe and under argon. The mixture was stirred at room temperature until reaction was complete (2 h) and ethanol-free dichloromethane (3.2 mL) was added to the solution. The solution of aminidium salt **21b** was cooled to 0 °C and a stream of H_2S was bubbled through the solution until an orange colour appeared. The mixture was stirred for 25 min at room temperature and the solution was washed with HCl (10%, 3 mL), brine and water. The organic layer was dried ($MgSO_4$) and concentrated. Purification by flash chromatography on silica gel (hexane/ethyl acetate: 80/20) allowed to separate **23b** ($R_f = 0.25$) and **22b** ($R_f = 0.31$) isolated as an orange solid. Compound **22b** yield: 57% (0.114 g); mp = 154–155 °C.

Compound **22b** ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.68$ (s, 3H, $C\mathit{H}_3$), 4.48 (t, 2H, $J_{HF} = 13.8$ Hz, $C\mathit{H}_2CF_2$), 7.75–7.95 (m, 4H, C_6H_4); ^{19}F NMR (282 MHz, $CDCl_3/CFCl_3$): $\delta = -95.95$ (t, $J_{F-H} = 15$ Hz, $CH_2C\mathit{F}_2$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 19.53$ ($\mathit{C}H_3$), 42.64 (t, $J_{C-F} = 28.5$ Hz, $\mathit{C}H_2CF_2$), 118.43 (t, $J_{C-F} = 253$ Hz, $\mathit{C}F_2$), 123.85, 131.85, 134.51 (arom.), 167.24 (s, N–C=O), 222.47 (t, $J_{C-F} = 25.6$ Hz, C=S); MS (EI, CH_4–NO_2): $m/z = 300.9$ (M+·); HRMS (M+1) m/z = calcd for $C_{12}H_9F_2NO_2S_2$ 301.004279, found: 301.005433.

Compound **23b** ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.42$ (s, 3H, $C\mathit{H}_3$), 4.32 (t, 2H, $J_{HF} = 13.5$ Hz, $C\mathit{H}_2CF_2$), 7.76–7.93 (m, 4H, C_6H_4); ^{19}F NMR (282 MHz, $CDCl_3/CFCl_3$): $\delta = -107.85$ (t, $J_{F-H} = 12.7$ Hz, $CH_2C\mathit{F}_2$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 11.66$ ($\mathit{C}H_3$), 40.15 (t, $J_{C-F} = 28.2$ Hz, $\mathit{C}H_2CF_2$), 115.17 (t, $J_{C-F} = 259$ Hz, $\mathit{C}F_2$), 124.00, 131.86, 134.64 (arom.), 167.23 (s, N–C=O), 192.33 (t, $J_{C-F} = 32.13$ Hz, C=O); MS (+c APCI, CH_4–NO_2): $m/z = 286.7$ (M+1), $C_{12}H_9F_2NO_3S$.

4.17. [^{18}F]-*N*-(3,3,3-Trifluoropropyl)phthalimide (25a)

Radiolabelling procedure: in polypropylene vessel dried under argon containing DBH (0.030 g, 0.11 mmol) in suspension in dichloromethane (300 μL), [^{18}F]–KF and [^{18}F]–$(HF)_n$·pyridinium (10 μL, 7 equiv of fluoride) (overall activity = 274 mCi) was added **7a** (0.018 g, 0.05 mmol) in one portion and the mixture was stirred for 10 min at 20 °C. Then DBH (0.060 g, 0.22 mmol) and 'cold' $(HF)_n$·pyridinium (200 μL, 140 equiv of fluoride) were introduced and the stirring was continued for additional 5 min. The crude mixture was filtered on neutral alumina and eluted with dichloromethane to give the crude product. Analysis by HPLC using SiO_2 column (rt = 19.8 min; hexane/ethyl acetate: 95/5) allowed to identify [^{18}F]-**25a** with 1.06% radiochemical yield (decay corrected) (4.058 mCi, radiochemical purity: 24%).

4.18. [^{18}F]-*N*-(2,2,3,3-Tetrafluoro-3-methylthioxypropyl)phthalimide (26)

Radiolabelling procedure:[46] in polypropylene vessel dried under argon containing DBH (0.041 g, 0.15 mmol) in suspension in dichloromethane (300 μL), [^{18}F]–KF and [^{18}F]–$(HF)_n$·pyridinium (10 μL, 7 equiv of fluoride) (overall activity = 904 mCi) was added **22b** (0.015 g, 0.05 mmol) in one portion and the mixture was stirred for 15 min at 20 °C. Then DBH (0.081 g, 0.30 mmol) and 'cold' $(HF)_n$·pyridinium (400 μL, 280 equiv of fluoride) were introduced and the stirring was continued for additional 15 min. Then $HgCl_2$ (0.27 g, 1 mmol) was introduced and the stirring was continued for additional 10 min. The crude mixture was filtered on neutral alumina and eluted with dichloromethane to give the crude product. Analysis by HPLC using SiO_2 column (rt = 7.5 min; hexane/ethyl acetate: 85/15) allowed to identify [^{18}F]-**26**, with 1.07% radiochemical yield (decay corrected) (MS (−c CI, CH_4–NO_2): $m/z = 306.9$ (M−1), $C_{12}H_9F_4NO_2S$, 5.148 mCi, radiochemical purity: 78%). Other compounds, [^{18}F]-**25b** (rt = 6.9 min; hexane/ethyl acetate: 85/15) and [^{18}F]-**27** (rt = 7.3 min; hexane/ethyl acetate: 85/15) have been identified by mass spectrometry (coupled to HPLC): MS (+c CI, CH_4–NO_2): $m/z = 280.0$ (M+1), $C_{11}H_6F_5NO_2$ and $m/z = 288.0$ (M+1), $C_{12}H_8F_3NO_2S$, respectively.

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References and notes

1. Evans, S. M.; Koch, C. J. *Cancer Lett.* **2003**, *195*, 1–16.
2. Ballinger, J. R. *Sem. Nucl. Med.* **2001**, *31*, 321–329.
3. Mahy, P.; DeBast, M.; Gallez, B.; Gueulette, J.; Koch, C. J.; Scaillet, P.; Grégoire, V. *Radiother. Oncol.* **2003**, *67*, 53–61, and references cited therein.
4. Ziemer, L. S.; Evans, S. M.; Kachur, A. V.; Shuman, A. L.; Cardi, C. A.; Jenkins, W. T.; Karp, J. S.; Alavi, A.; Dolbier, W. R., Jr.; Koch, C. J. *Eur. J. Nucl. Med. Mol. Imaging* **2003**, *30*, 259–266.
5. Mahy, P.; DeBast, M.; Labar, D.; Levêque, P.; Marchand-Brynaert, J.; Grégoire, V. *Radiother. Oncol.* **2002**, *64*(Suppl. 1), S189.
6. Satter, M. R.; Martin, C. C.; Oakes, T. R.; Christian, B. F.; Nickles, R. J. *Appl. Radiat. Isot.* **1994**, *45*, 1093–1100.
7. Taylor, M. D.; Nickles, R. J. *J. Labelled. Compd. Radiopharm.* **1997**, *40*, 11–13.
8. Johnström, P.; Stone-Elander, S. *J. Labelled Compd. Radiopharm.* **1995**, *36*, 537–545.
9. Johnström, P.; Stone-Elander, S. *Appl. Radiat. Isot.* **1996**, *47*, 401–407.
10. Das, M. K.; Mukherjee, J. *Appl. Radiat. Isot.* **1993**, *44*, 835–842.
11. Koolen, C. L.; Herscheid, J. D. M. *J. Labelled Compd. Radiopharm.* **2001**, *44*(Suppl. 1), S993–S994.
12. Dolbier, W. R., Jr.; Li, A.-R.; Koch, C. J.; Shiue, C.-Y.; Kachur, A. V. *Appl. Radiat. Isot.* **2001**, *54*, 73–80.
13. Prakash, G. S. K.; Hu, J.; Alauddin, M. M.; Conti, P. S.; Olah, G. A. *J. Fluorine Chem.* **2003**, *121*, 239–243.
14. Kollonitsch, J.; Marburg, S.; Perkins, L. M. *J. Org. Chem.* **1976**, *41*, 3107–3111.
15. Kurboshi, M.; Kanie, K.; Hiyama, T. *Adv. Synth. Catal.* **2001**, *343*, 235–250.
16. Josse, O.; Labar, D.; Marchand-Brynaert, J. *J. Labelled Compd. Radiopharm.* **2000**, *42*, 315–317.
17. Josse, O.; Labar, D.; Georges, B.; Grégoire, V.; Marchand-Brynaert *J. Bioorg. Med. Chem.* **2001**, *9*, 665–675.
18. Josse, O.; Labar, D.; Marchand-Brynaert, J. *Synthesis* **1999**, 404–406.
19. Marchand-Brynaert, J.; Josse, O.; Labar, D.; Grégoire, V. European Patent, 99 87 01 72.6, 1999.
20. Dolbier, W. R.; Koch, C. J.; Li A.-R.; Kachur, A. V. US Patent, 40437, WO01/07414, 2000.
21. Tewson, T. J. *Nucl. Med. Biol.* **1997**, *24*, 755–760.
22. Gamper, H. B.; Reed, M. W.; Cox, T.; Virosco, J. S.; Adams, A. D.; Gall, A. A.; Scoller, J. K.; Meyer, R. B., Jr. *Nucleic Acids Res.* **1993**, *21*, 145–150.
23. Commercially available from Fluorochem Ltd, RN 422-03-07, Order Number 006985.
24. Kim, K. I.; McCarthy, J. R. *Tetrahedron Lett.* **1996**, *37*, 3223–3226.

25. Furuta, S.; Hiyama, T. *Tetrahedron Lett.* **1996**, *37*, 7983–7986.
26. Patrick, T. B.; Hudson, C. M. *Heteroat. Chem.* **1999**, *10*, 31–34.
27. Swinnen, D.; Hilvert, D. *Org. Lett.* **2000**, *2*, 2439–2442.
28. Brask, J.; Albericio, F.; Jensen, K. J. *Org. Lett.* **2003**, *5*, 2951–2953.
29. Cheguillaume, A.; Lacroix, S.; Marchand-Brynaert, J. *Tetrahedron Lett.* **2003**, *44*, 2375–2377.
30. Davy, H.; Metzner, P. *J. Chem. Res. (M)* **1985**, 2701–2712.
31. Jesberger, M.; Davis, T. P.; Barner, L. *Synthesis* **2003**, 1929–1958.
32. Brain, C. T.; Hallet, A.; Ko, S. Y. *J. Org. Chem.* **1997**, *62*, 3808–3809.
33. Aguilar, N.; Moyano, A.; Pericas, M. A.; Riera, A. *Synthesis* **1998**, 313–316.
34. Laduron, F.; Nyns, C.; Janousek, Z.; Viehe, H. G. *J. Prakt. Chem.* **1997**, *339*, 697–707.
35. Laduron, F.; Atès, C.; Viehe, H. G. *Tetrahedron Lett.* **1996**, *31*, 5515–5518.
36. Kiss, L. E.; Rabai, J.; Varga, L.; Kövesdi, I. *Synlett* **1998**, 1243–1245.
37. Brown, H. C.; Pater, R. *J. Org. Chem.* **1962**, *27*, 2858–2863.
38. Shermolovich, Y. G.; Slusarenko, Y. I.; Timoshenko, V. M.; Rozhenko, A. B.; Markovski, L. N. *J. Fluorine Chem.* **1991**, *55*, 329–333.
39. Portella, C.; Shermolovich, Y. G.; Tschenn, O. *Bull. Soc. Chim. Fr.* **1997**, *134*, 697–702.
40. Pfund, E.; Lequeux, T.; Masson, S.; Vazeux, M. *Org. Lett.* **2002**, *4*, 843–846.
41. Bonnans-Plaisance, C.; Gressier, J.-C.; Levesque, G.; Mahjoub, A. *Bull. Soc. Chim. Fr.* **1985**, 891–899.
42. Neugebauer, W.; Pinet, E.; Kim, M.; Carey, P. R. *Can. J. Chem.* **1996**, *74*, 341–343.
43. Alberti, A.; Benaglia, M.; Laus, M.; Sparnacci, K. *J. Org. Chem.* **2002**, *67*, 7911–7914.
44. Sorochinsky, A.; Voloshin, N.; Markovsky, A.; Belik, M.; Yasuda, N.; Uekusa, H.; Ono, T.; Bernasov, D. O.; Solonshonok, V. A. *J. Org. Chem.* **2003**, *68*, 7448–7454.
45. Lacroix, S.; Cheguillaume, A.; Gérard, S.; Marchand-Brynaert, J. *Synthesis* **2003**, 2483–2486.
46. In this procedure, HF·pyridine could be replaced with HF·melamine.