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[^{18}F]/^{19}F exchange in fluorine containing compounds for potential use in ^{18}F-labelling strategies

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Exchange of [^{18}F]fluoride with ^{19}F in various organofluorine compounds in concentrations ranging from 0.06 to 56 mM was explored. We aimed to explore whether exchange reactions can be a potential useful labelling strategy, when there are no requirement of high specific radioactivity. Parameters such as solvents, temperature, conventional vs microwave heating, and the degree of fluorine load in some aromatic and alkyl compounds were investigated with regard to radiochemical yield and specific radioactivity. A series of fluorobenzophenones (1–6), 1-(4-fluorophenyl)ethanone (7), various activated and deactivated fluoro benzenes (8–16), *N*-(pentafluorophenyl)benzamide (17), (pentafluorophenyl)formamide (18), (tridecafluorohexyl)benzene (19) and tetradecafluorohexane (20) were subjected to [^{18}F]/^{19}F exchange. To test this strategy to label biologically active molecules containing fluorine atoms in an aryl group, two analogues of WAY-100635 (21–22), Lapatinib (23), 2,5,6,7,8-pentafluoro-3-methylnaphthoquinone (24) and 1-(2,4-difluorophenyl)-3-(4-fluorophenyl)-propan-1-one (25) were investigated. The multi-fluorinated molecules containing an electron-withdrawing group were successfully labelled at room temperature, whereas the monofluorinated, as well as those containing an electron-donating group, required heating for the exchange reaction to take place.

Keywords: nucleophilic ^{18}F-fluorination; halogen exchange; organofluorine compounds; perfluoro compounds

Introduction

Positron emission tomography (PET) is a non-invasive imaging technique allowing *in vivo* measurements and quantification of biological and biochemical processes.[1–3] PET is not only a diagnostic tool in oncology, cardiology, and neurology, but also used in drug development.[4,5] It might also find applications in other fields where there are questions related to response systems, as in plant physiology. There are a number of positron-emitting radionuclides like ^{15}O, ^{13}N, ^{11}C, ^{18}F, ^{76}Br, and ^{124}I, as well as metals including ^{68}Ga and ^{64}Cu with various properties of interest. Radionuclides like ^{11}C and halogens, especially ^{18}F, are of particular interest due to their synthetic potential.[6,7] As time is an important parameter in labelling, we were interested in developing a fluorous[8]-labelling strategy, using polyfluorinated compounds as a way to control reactivity, and facilitate the separation of these fluorous precursors from their non-fluorous products, by using fluorous solid-phase extraction[9] as an efficient technology for fast and reliable purification. We wanted to explore the F-exchange for two reasons: (1) there are already a number of drugs containing one or more fluorine atoms and (2) in some drug-development studies, specific radioactivity is not mandatory, i.e. to perform pharmacokinetic studies, making it possible to use F-exchange as a labelling method. We therefore explored [^{18}F]/^{19}F exchange in a series of fluorobenzophenones (**1–6**), 1-(4-fluorophenyl)ethanone (**7**), various activated and deactivated fluoro benzenes (**8–16**), *N*-(pentafluorophenyl)benzamide (**17**), (pentafluorophenyl)formamide (**18**), (tridecafluorohexyl)benzene (**19**), tetradecafluorohexane (**20**), two analogues of WAY-100635 (**21–22**), Lapatinib (**23**), 2,5,6,7,8-pentafluoro-3-methylnaphthoquinone (**24**) and 1-(2,4-difluorophenyl)-3-(4-fluorophenyl)propan-1-one (**25**).

Results and discussion

Fluorine is a small, highly electronegative atom.[10] Covalently bound fluorine is larger than a hydrogen atom but occupies a smaller van der Waals volume than a methyl, amino, or hydroxyl group.[11] Fluorine substituent effects on pharmacokinetics and pharmacodynamics are often observed.[12,13] The replacement of a hydrogen atom or a hydroxyl group by a fluorine atom is a strategy that is therefore used often by medicinal chemists in drug development.[14] The replacement of a hydrogen atom by a fluorine atom can alter the pK_a, dipole moment, lipophilicity, hydrogen-bonding properties, or chemical reactivity.[15]

Halogen exchange is well known,[16,17] but is rarely been applied in ^{18}F-labelling[18–20] because tracers with high-specific radioactivity are generally desired.[21] Therefore, it was interesting to explore the scope of $^{18/19}$F exchange reactions and its limitations with respect to specific radioactivity. Twenty-two fluorinated compounds were used in these $^{18/19}$F exchange

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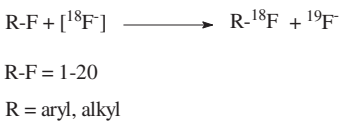
experiments (Scheme 1): (pentafluorophenyl)(phenyl)-methanone (**1**), phenyl(3,4,5-trifluorophenyl)methanone (**2**), (3,4-difluorophenyl)(phenyl)methanone (**3**), (4-fluorophenyl)-(phenyl)methanone (**4**), (3-fluorophenyl)(phenyl)methanone (**5**), (2-fluorophenyl)(phenyl)methanone (**6**), 1-(4-fluorophenyl)ethanone (**7**), hexafluorobenzene (**8**), (trifluoromethyl)benzene (**9**), 1,2,3,4,5-pentafluoro-6-(trifluoromethyl)benzene (**10**), 1, 2, 3, 4, 5-pentafluoro-6-nitrobenzene (**11**), (pentafluorophenyl)amine (**12**), 2,3,4,5,6-pentafluoro-*N*-methylaniline (**13**), pentafluorophenol (**14**), 2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenol (**15**), 1,2,3,4,5-pentafluoro-6-methoxybenzene (**16**), *N*-(pentafluorophenyl) benzamide (**17**), (pentafluorophenyl)formamide (**18**), (tridecafluorohexyl)benzene (**19**) and tetradecafluorohexane (**20**)) (Figure 1). Approximately the same amount of no-carrier-added (n.c.a.) [^{18}F]fluoride (≈0.5 GBq) was used in each experiment.



Scheme 1. General $^{18/19}$F exchange reaction.

The labelling position in the multi-fluorinated compounds was not explored in this study.

The effect of solvent on the fluorine-exchange reaction was investigated. Solutions of (pentafluorophenyl)(phenyl)methanone (**1**; 150 μL, 0.31 mM) were reacted repeatedly with n.c.a. [^{18}F]fluoride at room temperature for 15 min in different solvents or mixtures of solvents. When *N,N*-dimethylformamide (DMF) was used, the incorporation of ^{18}F was 25 ± 1% ($n = 3$). No radiolabelled product was obtained in 1-*n*-butyl-3-methylimidazolium trifluoromethanesulfonate (ionic liquid) or a mixture of ionic liquid/acetonitrile (1:1). In a mixture of acetonitrile and DMF (1:9) or in pure acetonitrile lower incorporation of 17 and 5%, respectively, were observed. The highest incorporation was obtained in dimethyl sulfoxide (DMSO) (97 ± 1% ($n = 4$)).

A series of experiments were set up in DMSO to explore the impact of concentration and temperature on this exchange reaction. The incorporation of [^{18}F]fluoride was approximately 99% when **1** was used at a concentration of 0.46 mM at room temperature (reaction volume 150 μL). When the concentration of **1** was decreased to 0.23 and 0.11 mM, the incorporation decreased to 94 and 90%, respectively, at room temperature. At a lower concentration (0.06 mM), the incorporation at room

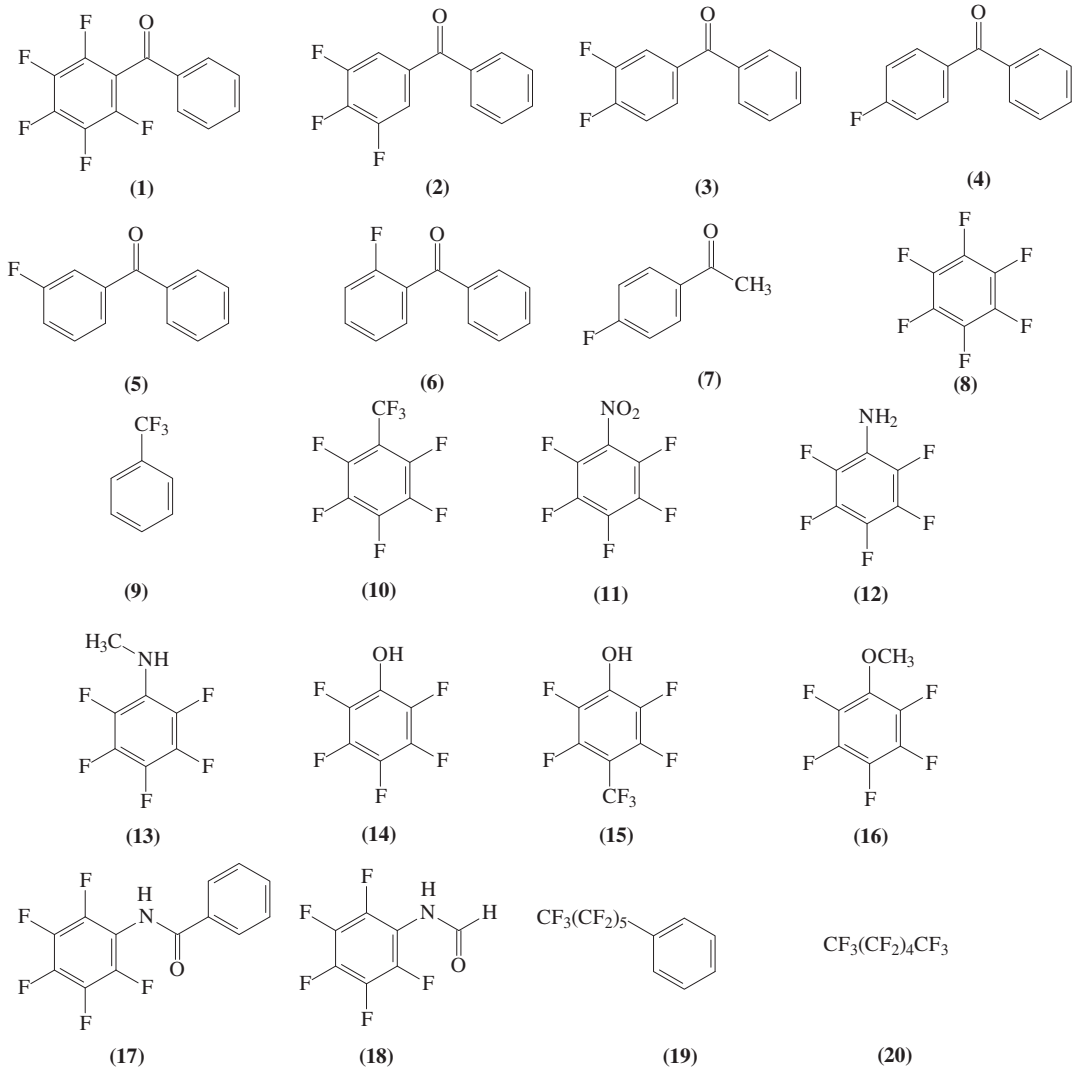


Figure 1. Organofluorine compounds used in this study.

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temperature was decreased to 75%, but heating at 150°C for 15 min decreased the incorporation yield to 40%. Further investigation of this reaction showed that, upon heating and during HPLC purification, one of the fluorine atoms was substituted by a hydroxyl group, (identified by GC-MS).

The impact on incorporation yield of the number of fluorine atoms present and their position in the substrate was explored using compounds **2–7**. The exchange reaction took place in DMSO at room temperature when more than one fluorine atom was present in the molecule (**2** and **3**), as shown in Table 1, but not in the monofluorinated compounds **4–7**. Compound **3** has been evaluated as a binder to the oestrogen receptor by combined quantitative structure–activity relationship models and multilinear regression analyses.[22]

However, the incorporation yield of (4-fluorophenyl)(phenyl)-methanone[23] (**4**), (2-fluorophenyl)(phenyl)methanone (**6**) and 1-(4-fluorophenyl)ethanone[24] (**7**)was increased dramatically when the exchange reaction was performed in DMSO at 150°C (Table 2). The reactivity of these carbonyl-substituted aryl fluorides decreased in the order para > ortho > meta, consistent with an S_{NAr} mechanism.[25]

The scope and limitations of this method were explored further, using the activated and deactivated fluorobenzenes **8–16**. The ^{18}F-labelling syntheses were performed at various concentrations at room temperature, as shown in Table 3.

Table 1. Incorporation yields for the reactions of compounds **2** and **3** with n.c.a. [^{18}F]fluoride[a,b]

Precursor	Conc.[c] (mM)	Incorporation[d](%)
2	0.93	65 ± 3
2	0.46	33 ± 8
3	28	70 ± 5
3	7.5	22 ± 5

[a]All reactions were performed at least in duplicate.
[b]Reaction conditions: 22°C, 150 μL DMSO, 15 min.
[c]Concentration of precursor.
[d]Incorporation yield, determined from HPLC.

Table 2. Incorporation yields for reaction of compounds **4-7** with n.c.a. [^{18}F]fluoride[a,b]

Precursor	Conc.[c] (mM)	Incorporation[d] (%)
4	56	> 99
4	7.5	97 ± 1
4	3.7	90 ± 2
5	56	4 ± 2
6	56	90 ± 1
6	7.5	20 ± 1
7	56	> 99
7	7.5	93 ± 1
7	3.7	91 ± 1

[a]All reactions were performed at least in duplicate.
[b]Reaction conditions: 150°C heating block, 150 μL DMSO, 15 min.
[c]Concentration of precursor.
[d]Incorporation yield, determined from HPLC.

Pentafluorophenyl compounds containing an electron-withdrawing group are susceptible to nucleophilic attack at room temperature, at reaction rates proportional to the electron-withdrawing strength of the group.[26] Moderate incorporation yields of compounds **8**,[27] **10**, and **11**[28,29] were obtained due to their electron-withdrawing substituents. The exchange reaction did not occur with substrate **9**, which has no fluorine atoms on the benzene ring. When 1,2,3,4,5-pentafluoro-6-(trifluoromethyl)benzene (**10**) was used as precursor in the ^{18}F-labelling reaction (3.75 mM), labelled compound **15** was obtained in 13 ± 1% ($n = 2$) yield, in addition to labelled compound **10** (71 ± 2 %, $n = 2$). Compound **15** was identified using co-elution in HPLC. This substitution reaction has previously been published.[30] Compound **15** does not undergo any exchange reaction at room temperature, so the fluorine exchange must take place before the substitution with a hydroxyl group.

As expected, the reaction of [^{18}F]fluoride with compounds **12–15** gave no radiolabelled product at room temperature because of the electron-donating substituents. However, labelled **16** was obtained at room temperature. The impact of microwave vs conventional heating on the incorporation of ^{18}F in compounds **12–16** was explored, as shown in Table 4. The $^{18/19}$F exchange reaction was accelerated by increasing the temperature, using conventional or microwave heating. The incorporation yields were very similar when the exchange of these compounds with electron-donating substituents was performed in either DMF or DMSO, for 15 min with conventional heating or 1–5 min with microwave heating. The data presented in Table 4 are from the reactions in DMF. The hydrogen bond-donating groups present in compounds **12–15** and **17–18** are also well known to reduce the reactivity.[31]

Attempts to perform the labelling reaction at room temperature, using *N*-(pentafluorophenyl)benzamide (**17**), (pentafluorophenyl)formamide (**18**), (tridecafluorohexyl)benzene (**19**) and tetradecafluorohexane (**20**) in DMF were not successful. The incorporation yields of **17** and **18** increased slightly when the reaction was performed at higher temperature, for 15 min with conventional heating or 1–5 min with microwave heating, as shown in Table 5. The labelling reaction of compound **17** was also performed in acetonitrile with microwave heating. This did,

Table 3. Incorporation yields for reaction of compounds **8–16** with n.c.a. [^{18}F]fluoride[a,b]

Precursor	Conc.[c] (mM)	Incorporation[d] (%)
8	0.93	57 ± 2
8	0.47	20 ± 2
9	56	0
10	7.5	91 ± 4
10	3.75	71 ± 2
11	1.86	47 ± 5
12	56	0
13	56	0
14	56	0
15	56	0
16	56	42 ± 8

[a]All reactions were performed at least in duplicate.
[b]Reaction conditions: 22°C, 150 μL DMSO, 15 min.
[c]Concentration of precursor.
[d]Incorporation yield, determined from HPLC.

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Table 4. Incorporation yields for the reaction of compounds **12–16** with n.c.a. [^{18}F]fluoride using a conventional heating block (Con) or microwave heating (MW) at 150°C[a]

Precursor[b]	Heating mode	Time (min)	Conc.[c] (mM)	Incorporation[d] (%)
12 (2)	Con	15	56	9±2
12 (2)	Con	15	42	7±3
12 (2)	MW	1	42	13±1
12 (1)	MW	5	42	20
12 (1)	MW	10	42	20
12 (2)	MW	1	21	7±3
12 (2)	MW	5	21	13±3
13 (2)	Con	15	56	23±2
13 (2)	Con	15	21	8±3
13 (2)	MW	1	21	3±1
13 (1)	MW	5	21	14
14 (2)	Con	15	56	0
14 (1)	MW	1	42	0
14 (1)	MW	5	42	0
15 (2)	Con	15	56	6±1
15 (2)	Con	15	42	2±1
15 (2)	MW	1	42	0
15 (2)	MW	5	42	4±1
16 (2)	Con	15	56	74±1
16 (2)	Con	15	28	67±4
16 (2)	Con	15	7.5	32±4

[a]Reaction conditions: DMF (150 μL and 200 μL when the reaction mixture was heated with conventional heating block and microwave, respectively).
[b]The number in parentheses represents number of experiments.
[c]Concentration of precursor.
[d]Incorporation yield, determined from HPLC.

Table 5. Incorporation yields for the reaction of compounds **17** and **18** with n.c.a. [^{18}F]fluoride using a conventional heating block (Con) or microwave heating (MW) at 150°C[a,b]

Precursor	Heating mode	Time (min)	Conc.[c] (mM)	Incorporation[d] (%)
17	Con	15	56	8±2
17	Con	15	42	4±2
17	MW	1	42	2±1
17	MW	5	42	4
18	Con	15	56	3±1
18	Con	15	42	1±1
18	MW	1	42	1
18	MW	5	42	3

[a]All reactions were performed at least in duplicate.
[b]Reaction conditions: DMF (150 μL and 200 μL when the reaction mixture was heated with conventional heating block and microwave, respectively).
[c]Concentration of precursor.
[d]Incorporation yield, determined from HPLC.

however, not give any ^{18}F incorporation. Solvents such as DMSO or acetonitrile had no impact on the incorporation of **19** and **20**.

Starting with 5 μAh, the specific radioactivity of labelled compounds **3** and **8** were 3±1 (n=2) and 5 (n=1) GBq/μmol, respectively at end-of-synthesis.

As an example of biologically active molecules that can be labelled by using the exchange strategy, two fluorine-containing analogues of WAY-100635, a radioligand for the 5-HT$_{1A}$ receptors for PET analysis in human brain, were used. 4-fluoro-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}-*N*-pyridin-2-ylbenzamide (**21**) and 3,4,5-trifluoro-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]-ethyl}-*N*-pyridin-2-ylbenzamide (**22**) were subjected to $^{18/19}$F exchange. Analogues of WAY-100635 labelled with ^{18}F in different positions on the benzoyl moiety have been prepared previously.[32–35] Nucleophilic aromatic substitution of a nitro group with ^{18}F is one method that has been used for labelling,[32,34] and $^{18/19}$F exchange might be applicable if there is no need for high specific radioactivity. The specific radioactivity is thus lower, and its use is thus restricted (Figure 2).

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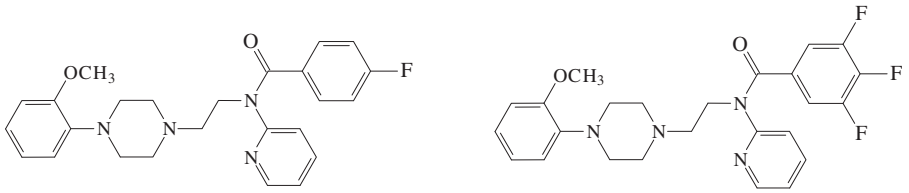


(21) (22)

Figure 2. The two WAY-100635 analogues used in the exchange experiments.

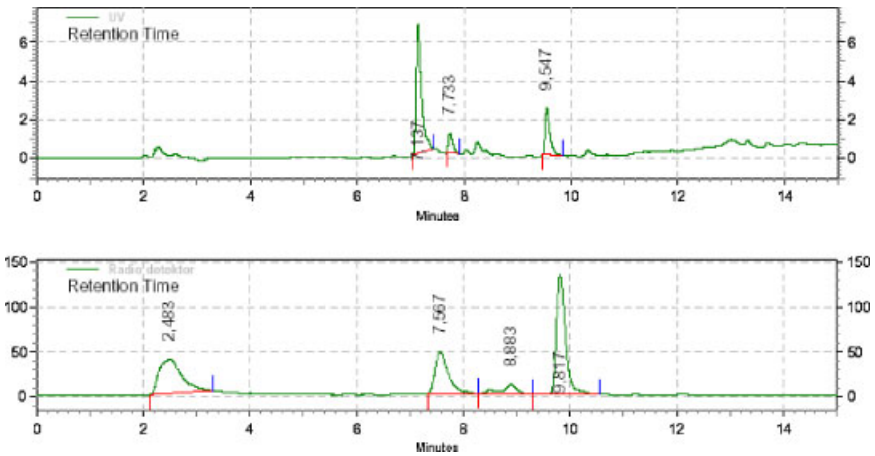
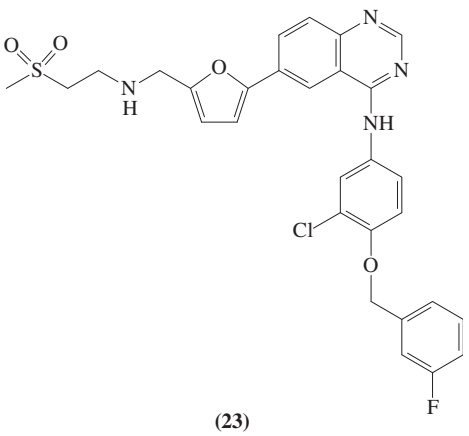


Figure 3. HPLC chromatogram for analysis of compound **22** (UV and radio detector), byproduct at 7.1 min and product at 9.5 min (UV). This figure is available in colour online at www.interscience.wiley.com/journal/jlcr.



(23)

Figure 4. Structure of Lapatinib.

When compound **21** (17.5 mM) was heated together with n.c.a [^{18}F]fluoride (≈0.5 GBq) in DMF (200 μL) at 150°C for 15 min, the incorporation was 8 ± 1% ($n = 2$) and the specific radioactivity was 0.01 GBq/μmol. Performing the labelling reaction using microwave heating in DMF, acetonitrile or DMSO did gave lower incorporation yield (1%) after 15 min reaction time. Compound **22** (10.5 mM) was also reacted with n.c.a [^{18}F]fluoride (≈1 GBq) in DMF (200 μL). The reaction mixture was stirred at room temperature for 15 min and the incorporation yield was 1%. The reaction mixture was heated thereafter at 150°C for 15 min, and the incorporation increased to 35 ± 3% ($n = 2$) yield. Further heating at 150°C for 15 min did not increase the incorporation. The specific radioactivity was 0.58 GBq/μmol.

Another radiolabelled product with lower lipophilicity was formed by substitution of one fluorine atom with a hydroxyl group in the labelling reaction (identified by LC-MS) in 20 ± 5% ($n = 2$) yield (Figure 3). Any attempt to increase the amount of radioactivity or reduce the amount of precursor to increase the specific radioactivity resulted in no labelled product, and consumption of the precursor. This could be due to radiolysis. DMF, acetonitrile and DMSO were used as solvents in microwave reactions. This did not give any differences in product distribution or incorporation yields.

Attempts were also made to label Lapatinib (**23**) (Figure 4), which is a dual inhibitor of EGFR and HER2 tyrosine kinase activity,[36] by $^{18/19}$F exchange. Heating of the monofluorinated compound together with [^{18}F]fluoride at 150°C for 15 min, in either DMF or DMSO, gave no labelled product. This confirms previous observations that meta-substituted monofluorinated compounds are not very reactive in nucleophilic aromatic substitution.

Two other compounds which were labelled are 2,5,6,7,8-pentafluoro-3-methylnaphthoquinone (**24**) and 1-(2,4-difluorophenyl)-3-(4-fluorophenyl)propan-1-one (**25**) (Figure 5). Compound **24** is used as the precursor for a fluorinated analogue of Cpd 5 (2-(2-mercaptoethanol)-3-methyl-1,4-naphthoquinone) predicted to be a cell growth inhibitor by semi-empirical-calculations,[37] and could not be labelled by the exchange procedure in DMSO, even after heating at 150°C. On the other hand, when a mixture of acetonitrile and *tert*-butanol was used as a solvent (with the precursor at a concentration of 14 mM), the incorporation of [^{18}F]fluoride was 8% after 15 min at room temperature. Heating at 110°C for 15 min did not increase the incorporation. Reducing the concentration of **24** to 7.5 mM

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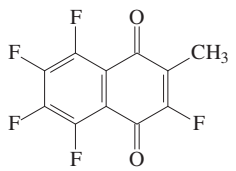

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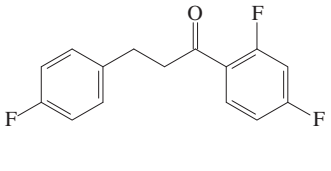

(25)

Figure 5. 2,5,6,7,8-Pentafluoro-3-methylnaphthoquinone (**24**) and 1-(2,4-difluorophenyl)-3-(4-fluorophenyl)propan-1-one (**25**).

Table 6. Incorporation yields for the reactions of compound **25** with n.c.a. [^{18}F]fluoride[a,b]

Precursor	Conc.[c] (mM)	Incorporation[d] (%)
25	28	70 ± 7
25	14	60 ± 5
25	7.5	18 ± 8
25	3.5	5 ± 2

[a]All reactions were performed at least in duplicate.
[b]Reaction conditions: 150°C, 150 mL DMSO, 15 min.
[c]Concentration of precursor.
[d]Incorporation yield, determined from HPLC.

decreased the incorporation to 4%. Compound **25** has inhibitory activity for human 11-β-hydroxysteroid dehydrogenase type 1 enzyme (11βHSD1).[38] It was labelled in DMSO at 150°C, as shown in Table 6. The specific radioactivity was 1 GBq/μmol when 14 mM of the compound was used, and the starting radioactivity was n.c.a. 5.3 GBq [^{18}F]fluoride.

Experimental

Radiosynthesis

General

No-carrier-added [^{18}F]fluoride was produced at Uppsala Imanet on a Scanditronix MC-17 cyclotron by the nuclear reaction ^{18}O(p,n)^{18}F in a target containing water 95% enriched in ^{18}O (Rotem Industries Ltd, Israel or Taiyo Nippon Sanso Corporation). Synthia,[39] an automated synthesis system, was used in the handling of [^{18}F]fluoride. The produced solution of [^{18}F]fluoride in water was transferred from the cyclotron target by an HPLC pump and trapped on a QMA filter (ABX, advanced biochemical compounds, pre-conditioned Sep-PAK®, Light QMA Cartridge with CO_3^{2-} as a counterion, Radeberg), and thereafter released with a 2 mL solution of 96:4 (by volume, total volume 12 mL) acetonitrile–water mixture containing 55.9 mg of Kryptofix 2.2.2 (K2.2.2) and 12.7 mg K_2CO_3. After the eluted ^{18}F-Kryptofix/K_2CO_3 solution was dried under N_2 (g) at 110°C, it was further dried with 2 × 1 mL dry acetonitrile. HPLC analyses of radiolabelled compounds were performed with a VWR Hitachi Pump L-2130 and a VWR Hitachi UV Detector L-2400 UV detector in series with a Bioscan β^+-flow detector. A Discovery® C18, Supelco, 25 cm × 4.6 mm 5 μm HPLC column was used. The following mobile phases were used: 25 mM KH_2PO_4 in water (A), acetonitrile/water 50/7 (B). Program: 60–90 % (B) for 5 min, then 90% for 10 min, flow rate 1.5 mL/min. For semipreparative LC, an ACE 5C18HL 250 × 10 mm 5 μm column was used at a flow rate of 5 mL/min. Acetonitrile (50%) and 0.05 M ammonium formate (50%) were used as the mobile phase. Radioactivity was measured in an ion chamber (Veenstra Instrumenten BV, VDC-202). Microwave heating was performed in a SmithCreator™ monomodal cavity (Biotage AB, Uppsala, Sweden). DMSO was dried over 4 Å molecular sieves.

Retention times on HPLC for compounds 1–25: = (**1**): 7.0 min, (**2**): 6.8 min, (**3**): 6.3 min, (**4**): 5.7 min, (**5**): 5.8 min, (**6**): 5.4 min, (**7**): 4.5 min, (**8**): 5.5 min, (**9**): 5.8 min, (**10**): 5.5 min, (**11**): 5.0 min, (**12**): 5.2 min, (**13**): 6.0 min, (**14**): 3.7 min, (**15**): 3.5 min, (**16**): 6.0 min, (**17**): 5.4 min, (**18**): 3.1 min, (**19**): 12.9 min, (**20**): 9.5 min, (**21**): 9.1 min, (**22**): 9.5 min, (**23**): 11.1 min, (**24**): 6.9 min, (**25**): 6.4 min.

Typical exchange procedure

The dried [K/K2.2.2.]$^+$^{18}F$^-$ was dissolved in dry solvent and added to a solution of the desired amount of precursor in a 1.5 mL pear-shaped vial. After reaction at the specified temperature for the indicated time, the reaction mixture was analysed by HPLC and the incorporation yield determined. In some cases the reaction mixture was purified by semi-preparative HPLC for the determination of specific radioactivity. Microwave experiments were conducted in a 200–1000 μL Smith Process Vial™ microwave vial.

Compound 1 *(byproduct identification)*: Pentafluorophenyl)(phenyl)methanone (**1**) (0.100 g, 0.37 mmol) was dissolved in 5 mL DMSO and tetrabutylammonium fluoride (1.5 mL, 1.5 mmol, 1 M in THF) added and the reaction mixture was heated at 150°C for 1 h. The crude product was purified by semi-preparative HPLC and the more hydrofilic byproduct analysed by GC-MS indicating that one fluorine atom had been substituted by a hydroxyl group (R_t = 5.1 min). EI-MS: *m/z* 270 $[M]^{\bullet+}$.

Compound 10 *(byproduct identification)*: Labelled compound co-eluted on HPLC UV/radio detector with compound 15[30] (R_t = (**10**): 5.5, (**15**) 3.5 min).

Compound 22 *(byproduct identification)*: Compound **22** (0.005 g, 10.6 μmol) was heated at 150°C for 15 min in 0.1 ml DMF with tetrabutylammonium fluoride (0.1 mL, 0.1 mmol, 1 M in THF). The crude product was purified by semi-preparative HPLC and the more hydrofilic byproduct analysed by LC-MS indicating that one fluorine atom had been substituted by a hydroxyl group (R_t = 7.1 min, (**22**) R_t = 9.5 min). ESI-MS: *m/z* 469 $[M+H]^+$.

Chemical synthesis

General

^{1}H NMR, ^{13}C NMR and ^{19}F spectra were recorded on a Varian Unity (^{1}H at 400 MHz, ^{13}C at 100 MHz and ^{19}F at 376 MHz) spectrometer using DMSO-d_6 or $CDCl_3$ as solvent (solvent peak used as reference, except in the case of ^{19}F, when $CFCl_3$ was used as a reference). All NMR experiments were conducted at 25°C. Thin-layer chromatography was performed on Merck silica gel F-254 aluminium plates. Silica gel 60, particle size 0.040–0.063 mm (Merck) was used for column chromatography. Liquid chromatography mass spectrometry (LC-MS) analyses were performed using a Gilson HPLC and Finnigan AQA mass spectrometer, in ESI-mode. Gas chromatography mass spectrometry (GC-MS) analyses were performed using a Finnigan MAT GCQ mass spectrometer, in EI-mode. Melting points were determined using a Bibby Sterlin, Stuart Scientific Melting point apparatus SMP3. All chemicals were obtained from commercial suppliers and used without further

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purification. *N*-{2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl}pyridine-2-amine (WAY-100634) was prepared as described previously.[40] *N*-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methylsulfonyl)ethyl]-amino}methyl)-2-furyl]quinazolin-4-amine (Lapatinib) was supplied by GlaxoSmithKline.

Methyl(pentafluorophenyl)amine[41] *(13)*: Hexafluorobenzene (5.035 g, 27.1 mmol) was dissolved in 40 mL propan-2-ol, and methylamine (2.5 mL, 40% in H_2O) was added. The reaction mixture was heated at 85°C for 56 h, and then distilled under reduced pressure to yield **13** as a colourless liquid (1.403 g, 26%). ^{1}H NMR ($CDCl_3$, 400 MHz, 25°C) $\delta = 3.05$ (*m*, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, 25°C) $\delta = 145.7$ (m), 139.2 (m), 136.8 (m), 134.5 (m), 33.3 (m). ^{19}F NMR (DMSO-d_6, 376 MHz, 25°C) $\delta = -161.5$ (m, 2F), −166.0 (m, 2F), −176.6 (m, 1F). ESI-MS: *m/z* 198 $[M+H]^+$.

N-(Pentafluorophenyl)benzamide[42] *(17)*: Pentafluoroaniline (3.008 g, 16.4 mmol) was dissolved in 15 mL dry CH_2Cl_2 and benzoyl chloride (3.458 g, 24.6 mmol) was added dropwise over 10 min. The mixture was stirred at room temperature for 16 h under a nitrogen atmosphere, and then diluted with $CHCl_3$, washed with H_2O, and concentrated under reduced pressure. The residue was recrystallized from $CHCl_3$/petroleum ether to yield **17** as white crystals (0.280 g, 6%). M.p. 179–180°C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25°C) $\delta = 10.54$ (bs, 1H), 8.03–7.98 (m, 2H), 7.69–7.63 (m, 1H), 7.60–7.54 (m, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25°C) $\delta = 165.4$, 144.2 (m), 141.8 (m), 138.5 (m), 136.0 (m), 132.5, 132.3, 128.7, 127.9. ^{19}F NMR (DMSO-d_6, 376 MHz, 25°C) $\delta = -144.9$ (m, 2F), −157.0 (m, 1F), −163.0 (m, 2F). ESI-MS: *m/z* 288 $[M+H]^+$.

(Pentafluorophenyl)formamide[43] *(18)*: Pentafluoroaniline (3.005 g, 16.41 mmol) was dissolved in 30 mL *p*-xylene and, after addition of 30 mL formic acid, the reaction mixture was heated at 100°C for 67 h. The solvent was removed under reduced pressure and the residue purified by column chromatography (CH_2Cl_2) to yield **18** as white crystals (1.920 g, 56%). M.p. 99–100°C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25°C): $\delta = 10.34$ (bs, 1H), 8.38 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25°C) $\delta = 156.0$, 146.4 (m), 143.8 (m), 139.6 (m), 138.0 (m). ^{19}F NMR (DMSO-d_6, 376 MHz, 25°C) $\delta = -145.4$ (d, $J = 21.3$ Hz, 2F), −158.3 (t, $J = 23.3$ Hz, 1F), −163.7 (m, 2F). EI-MS: *m/z* 211 $[M]^{\bullet+}$, 183.

4-Fluoro-N-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}-N-pyridin-2-ylbenzamide (21): Procedure and spectral data are published elsewhere.[44]

3,4,5-Trifluoro-N-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}-N-pyridin-2-ylbenzamide (22): *N*-{2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl}pyridine-2-amine (0.075 g, 0.24 mmol) was dissolved in 2 mL dry CH_2Cl_2. After cooling to 0°C, triethylamine (0.05 mL, 0.36 mmol) and 3,4,5-trifluorobenzoyl chloride (0.047 mL, 0.36 mmol) was added dropwise. The reaction mixture was heated to room temperature and stirred for 2 h under a nitrogen atmosphere, and thereafter extracted with a 10% aqueous solution of Na_2CO_3 and CH_2Cl_2. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. A colourless oil (0.090 g, 80%) was obtained after purification using column chromatography (CH_2Cl_2/CH_3OH 10:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) $\delta = 8.42$ (ddd, $J = 0.8$, 1.9, 4.9 Hz, 1H), 7.51 (dt, $J = 1.9$, 7.6 Hz, 1H), 7.11-7.07 (m, 1H), 6.99–6.81 (*m*, 7H), 4.22 (*t*, $J = 6.6$ Hz, 2H), 3.83 (s, 3H), 2.91 (*m*, 4H), 2.72 (*t*, $J = 6.6$ Hz, 2H), 2.62 (*m*, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, 25°C) $\delta = 167.2$, 155.8, 152.2, 150.6 (ddd, $J = 3.5$, 10.1, 251.2 Hz), 149.0, 141.3, 140.8 (dt, $J = 15.2$, 256.5 Hz), 137.6, 132.1 (m), 122.8, 122.2, 121.6, 120.9, 118.0, 113.3 (dd, $J = 6.5$, 16.1 Hz), 111.2, 56.1, 55.3, 53.3, 50.6, 45.9. ^{19}F NMR (376 MHz, $CDCl_3$, 25°C) $\delta = -133.6$ (m, 2F), −157.1 (m, 1F). ESI-MS: *m/z* 471 $[M+H]^+$.

Conclusion

$^{18/19}$F Exchange reactions were examined in various organofluorine compounds, and the effect of solvent, temperature, conventional vs microwave heating, degree of fluorine load and the presence of activating and deactivating groups on the radiochemical yield was investigated. This study aimed to understand the impact of fluorinated compounds in choosing a labelling strategy, considering issues such as activated leaving groups, matrix-supported substrates, catalysts, and work-up protocols.

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