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 ^{18}F -labelling of nitrogen-containing aryl boronates – anti-cancer drug melflufen as a case study†Kevin Bajerke,^a Fredrik Lehmann,^b Gunnar Antoni^c and Kálmán J. Szabó^{*a}

^{18}F -labelling of nitrogen-containing arenes *via* copper-mediated radiofluorination (CMRF) was investigated. The studies targeted the analogues of the anti-cancer drug melflufen with an alkylating bis(2-chloroethyl)amino pharmacophore. Studies of the melflufen analogues and various model compounds indicated that the copper mediated boron–fluorine-18 exchange reaction is affected differently by the three nitrogen-containing groups in the target compound. The largest inhibitory effects on the fluorine labelling process were exerted by the tertiary amine based bis(2-chloroethyl)amino pharmacophore. The best results were achieved by applying bipyridyl ligands for the copper mediator.

Introduction

Positron emission tomography (PET) is a non-invasive, versatile diagnostic tool for preclinical and clinical research, as well as for studies on drug delivery and metabolism.¹ Fluorine-18 labelled small-molecules are the most widely used PET tracers due to the beneficial physical and nuclear properties of the short-lived positron-emitting radionuclide fluorine-18.^{1,2} As a result, currently, there is great interest in the development of new radiochemical methods for the selective synthesis of ^{18}F -labelled small-molecules. However, translating modern synthetic methods into ^{18}F -labelling techniques is still challenging.³ These challenges involve downscaling of the methods reported for the naturally occurring isotope of fluorine as well as overcoming the short half-life of fluorine-18 (110 min), which requires on-site generation of radio-isotopes and rapid late-stage fluoro-functionalization of the small molecules.³ In addition, synthetic fluorination and the corresponding ^{18}F -labelling methods may be mechanistically different due to the very different stoichiometric relationships with nanomole amounts of the ^{18}F -reagent.

One of the most important pharmacophores are fluoroaromatics, characterized by a metabolically stable, strong $\text{C}(\text{sp}^2)\text{--}\text{F}$ bond. Studies by the Gouverneur,⁴ Sanford⁵ and other groups⁶ have led to an efficient labelling technique of aromatic substrates based on boron– ^{18}F exchange. The copper mediated version of the reaction has become a standard synthetic

method for ^{18}F -labelling.^{2a,5b} Copper-mediated radiofluorination (CMRF) has been employed for the development of PET tracers for a wide range of drug-like substances.⁷ However, the radiochemical conversion⁸ (RCC) strongly varies depending on the substrate and the applied reaction conditions.^{4,7a} There are several reasons for this issue. A general problem in transition metal-catalysed fluorination reactions is the high activation barrier involved in the reductive elimination of the metal–fluorine bond to form the fluorine–carbon bond (Fig. 1a).⁹ Another potential problem is the formation of fluoro-boronate type by-products, as the boron–fluorine bond is much stronger than the carbon–boron bond (Fig. 1b).^{6b}

The sensitivity of the reaction toward nitrogen-containing functional groups is a well-known problem (Fig. 1c).⁴ In a pioneering study on CMRF reactions, Gouverneur and co-workers^{2a} pointed out that amino groups sometimes require double Boc-protection to accomplish the copper-mediated boron to fluorine exchange with acceptable RCC. Mechanistic studies with copper-mediated/catalysed fluorination of organoboronates^{2a} indicate that the reaction probably follows a Chan–Lam mechanism.¹⁰ Thus, the sensitivity of the CMRF reactions toward nitrogen-containing functional groups (Fig. 1c) is not

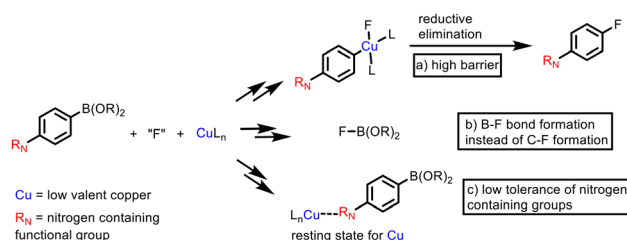


Fig. 1 Main issues with copper-catalysed/mediated boron–fluorine exchange.

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surprising, as the Chan–Lam coupling was originally developed for amination of organoboron substrates.¹⁰ However, nitrogen-containing groups are highly abundant functionalities in bioactive small molecules. Sometimes, several nitrogen-containing groups may occur in the same molecule. In this case, the deprotection of the nitrogens following ¹⁸F-labelling elongates the reaction time of the synthesis, which leads to additional decay of fluorine-18 introduced into the molecule. Probably, the most problematic groups are tertiary amines, which are relatively difficult to protect in radiosynthesis. As a part of our program in radiofluorine chemistry,¹¹ we decided to study the effects and handling of nitrogen substituents of alkylating agents in CMRF reactions.

Results and discussion

Model reactions for ¹⁸F-labelling of the anti-cancer drug melflufen

As a case study, we investigated the radiosynthesis of [¹⁸F]1a, which contains three different types of nitrogen-based substituents (Fig. 2). The structure of compound 1a is based on the anti-cancer drug melflufen 1b (Fig. 2).¹² Melflufen 1b is currently being introduced in several countries as a promising alkylating agent for the treatment of the haematological disease multiple myeloma.¹³ Compound 1 is based on an aminopeptide backbone containing two nitrogen atoms. In addition, the main pharmacophore is a bis(2-chloroethyl) amino alkylating group embracing a tertiary amine structure. Our studies were directed to investigate the possibilities to obtain [¹⁸F]1a via a copper mediated boron to ¹⁸F-exchange in the presence of these three nitrogen-containing groups. Our approach involved systematic studies of each nitrogen-containing group in 1a. To this end, we prepared organoboron precursors for labelling of various model compounds. The first model compound was 2a containing a Boc-protected amino group (Table 1), which was labelled to form [¹⁸F]2b. The initial labelling studies were conducted under conditions similar to those reported by the Gouverneur group in their method development paper^{4a} (Table 1, entry 1). Thus, sub-stoichiometric amounts of [Cu(OTf)₂(py)₄] and [¹⁸F]KF/K₂₂₂ were reacted with 2a in DMF under inert conditions (N₂) for 20 min. The reaction resulted in the desired labelled product [¹⁸F]2b, albeit with a poor RCC (16%). Increasing the amount of the copper mediator to a stoichiometric amount did not alter the RCC (entry 2). A slight improvement in the RCC (22%) occurred upon elongation of the reaction time to 40 min (entry 3).

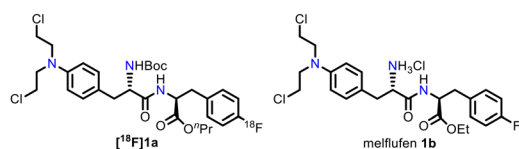


Fig. 2 Targeted radiotracer [¹⁸F]1a, analogue of the anti-cancer drug melflufen 1b.

Table 1 ¹⁸F-labelling of the model substrate 2a^a

Entry	<i>t</i> [min]	Change	RCC ^b [%]
1	20	—	16
2	20	1.0 equiv. Cu	16
3	40	—	22
4	20	Under air	85 ± 12 (<i>n</i> = 2)

^a To 2a (30 μmol, 1.0 equiv.) and [Cu(OTf)₂(py)₄] (9 μmol, 0.3 equiv.) in DMF (150 μL) was added [¹⁸F]KF/K₂₂₂ (in ~30 μL MeCN) under N₂.
^b RCC: radiochemical conversion.

Several studies⁴ indicated that the CMRF reactions under air often give higher RCCs than under inert conditions. Indeed, conducting the reaction under air (entry 4) resulted in a significantly higher RCC (85%).

Labelling of model substrate 2a in the presence of additives

Based on the above results, we conclude that upon conducting the labelling under the standard conditions and air, the mono-Boc-protected amino group in the amino acid model substrate 2a does not significantly affect the CMRF reaction. Keeping this in mind, the 2a → [¹⁸F]2b transformation was performed in the presence of various melflufen analogues 1a and 1c–f as additives (Fig. 3).

The aim of these studies was to assess the possible adverse effects of the different types of nitrogen-containing groups on the 2a → [¹⁸F]2b transformation. In the presence of the bis(2-chloroethyl)amino moiety containing 1a, the formation of [¹⁸F]2b from 2a was not observed at all. This finding indicates a major inhibitory effect of the bis(2-chloroethyl)amino moiety under the standard CMRF reaction conditions. In further studies, we assessed the effects of the different components of this pharmacophore. In the aniline derivative 1c, the nitrogen bis(2-chloroethyl)amino moiety was replaced by an amino

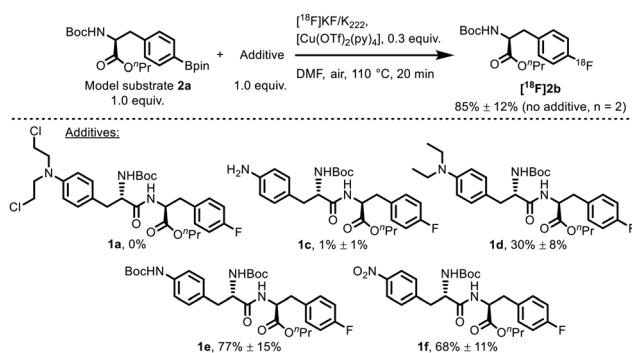


Fig. 3 The 2a → [¹⁸F]2b transformation was conducted in the presence of additives 1a–f. To 2a (30 μmol, 1.0 equiv.) and [Cu(OTf)₂(py)₄] (9 μmol, 0.3 equiv.) in DMF (150 μL) was added [¹⁸F]KF/K₂₂₂ (in ~30 μL MeCN). Under air at 110 °C for 20 min. Carried out twice (*n* = 2).



group. Even this compound exerted a strong inhibition on the $2\mathbf{a} \rightarrow [^{18}\mathbf{F}]\mathbf{2b}$ transformation. This result was not surprising in view of the fact that CMRF reactions under standard conditions are known to have poor tolerance toward aniline groups.^{4a} Subsequently, we conducted the $2\mathbf{a} \rightarrow [^{18}\mathbf{F}]\mathbf{2b}$ transformation in the presence of $\mathbf{1d}$. This compound ($\mathbf{1d}$) contains a diethyl aniline moiety instead of a bis(2-chloroethyl)amino group in $\mathbf{1a}$, *i.e.* the chloromethyl groups are replaced with ethyl groups. Unlike with $\mathbf{1a}$, on using $\mathbf{1d}$ as an additive, the formation of $[^{18}\mathbf{F}]\mathbf{2b}$ could be detected, albeit with a poor RCC (30%). This result indicates that under standard conditions, the tertiary amine and the chloro-ethyl groups synergistically inhibit the CMRF reaction, while the adverse effect of the diethyl aniline moiety alone is less pronounced. Further confirmation of these results was obtained by performing the $2\mathbf{a} \rightarrow [^{18}\mathbf{F}]\mathbf{2b}$ transformation in the presence of Boc-aniline ($\mathbf{1e}$) and nitro ($\mathbf{1f}$) substituents in place of the bis(2-chloroethyl)amino group ($\mathbf{1a}$) in the additives. In both cases, the formation of $[^{18}\mathbf{F}]\mathbf{2b}$ was only slightly affected (Fig. 3). These results confirm our hypothesis that out of the three nitrogen-containing substituents in $\mathbf{1}$, the bis(2-chloroethyl)amino pharmacophore presents the greatest challenge for $^{18}\mathbf{F}$ -labelling.

$^{18}\mathbf{F}$ -labelling of melflufen analogues with various nitrogen-containing groups

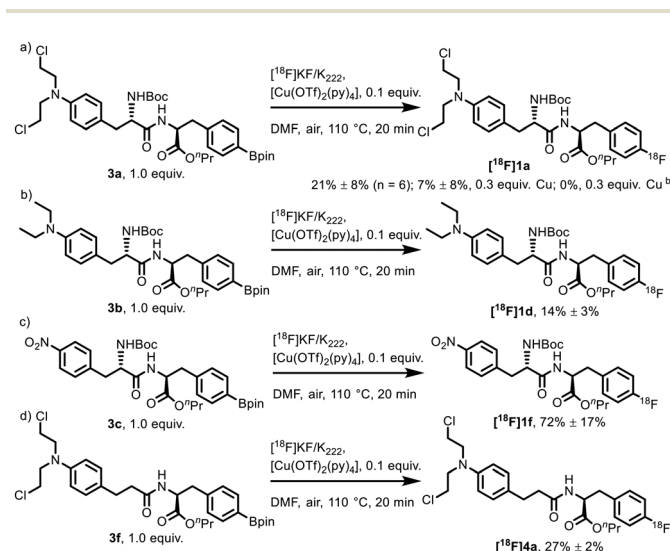
Subsequently, we attempted the radiosynthesis of $[^{18}\mathbf{F}]\mathbf{1a}$ from aryl boronate $\mathbf{3a}$ (Scheme 1a) under the same conditions as those used for the $2\mathbf{a} \rightarrow [^{18}\mathbf{F}]\mathbf{2b}$ transformation (Fig. 3). We were able to detect the formation of $[^{18}\mathbf{F}]\mathbf{1a}$ with a poor RCC of 7%. We found that further reduction of the amount of $[\text{Cu}(\text{OTf})_2(\text{py})_4]$ to 0.1 equiv./10 mol% with respect to $\mathbf{3a}$ improved the RCC to 21%. We employed this ratio for the copper

mediator (10 mol%) in the subsequent studies. In some CMRF studies, the application of DMA in place of DMF proved to be beneficial.^{4a} However, when we used DMA as the solvent, the reaction did not result in the formation of $[^{18}\mathbf{F}]\mathbf{1a}$ (Scheme 1a). According to the inhibition experiments (Fig. 3) using $\mathbf{1d}$, we expected that the diethyl moiety at the aniline group would exert a milder effect on the outcome of the reaction than the bis(2-chloroethyl)amino moiety.

However, the RCC was about as low for labelling $\mathbf{3b}$ (14%) as for $\mathbf{3a}$ (21%) under the same conditions (Scheme 1b). When the alkylamino groups ($\mathbf{3a}$ and $\mathbf{3b}$) were replaced with a nitro group ($\mathbf{3c}$), the labelling proceeded with a high RCC (72%, Scheme 1c). This result was also expected on the basis of the inhibition experiments (Fig. 3) using $\mathbf{1f}$. As mentioned above, previous publications^{4a} indicated that primary amines may require double Boc protection to obtain satisfactory RCCs in CMRF reactions. Thus, we performed the labelling of the melflufen analogue $\mathbf{3f}$, which does not bear any primary amino functionality (Scheme 1d). We found that under the same conditions, the $\mathbf{3f} \rightarrow [^{18}\mathbf{F}]\mathbf{4a}$ (Scheme 1d) and $\mathbf{3a} \rightarrow [^{18}\mathbf{F}]\mathbf{1a}$ (Scheme 1a) labelling reactions could be performed with about the same (poor) RCC of 27% and 21%, respectively. Our conclusion from the above studies was that the amino-peptide nitrogen atoms and the mono-Boc-protected primary amine have a relatively small effect on the labelling reaction under the optimized conditions (*i.e.* conducting the reaction under air in the presence of 0.1 equiv. of the copper mediator).

Effects of nitrogen-containing ligands on the $^{18}\mathbf{F}$ -labelling

The next step was finding a solution for the suppression of the adverse effects of the bis(2-chloroethyl)amino pharmacophore on the CMRF reaction to improve the RCC for the formation of $[^{18}\mathbf{F}]\mathbf{1a}$. We surmised that the bis(2-chloroethyl)amino moiety of the substrate is able to coordinate to the copper mediator, bringing it to a resting state. However, the presence of a nitrogen or σ -donor ligand coordinated to copper may have beneficial effects.^{6d,7b,14} As mentioned above, the reductive elimination from low-valent metal fluoride complexes is sluggish (Fig. 1a).^{9a-c} Increase of the oxidation state of the metal centre leads to a facile reductive elimination.¹⁵ Application of σ -donor ligands, such as nitrogen-containing species, is a common approach for facilitating the oxidation of the metal atom, and thus accelerating the reductive elimination of metal fluorides. This approach was used in many applications including $^{18}\mathbf{F}$ -labelling studies.^{4b,7b,9b,14} Thus, we reasoned that certain appropriate nitrogen-containing additives, which are potential ligands for the copper mediator, may improve the RCC in the $\mathbf{3a} \rightarrow [^{18}\mathbf{F}]\mathbf{1a}$ process. Moreover, we expected that by addition of certain types of external nitrogen ligands, the coordination of the nitrogen atom in the bis(2-chloroethyl)amino moiety can be avoided, and in addition, the oxidation of copper can be facilitated. Thus, we performed the $^{18}\mathbf{F}$ -labelling of $\mathbf{3a}$ in the presence of potential nitrogen-type ligands for copper, $\mathbf{5a-e}$ (Fig. 4). Pyridine ($\mathbf{5a}$) is present in $[\text{Cu}(\text{OTf})_2(\text{py})_4]$, but addition of 1 equiv. of $\mathbf{5a}$ did not improve the RCC (Fig. 4a), suggesting that more sophisticated nitrogen ligands are



Scheme 1 $^{18}\mathbf{F}$ -labelling of different melflufen analogues.^a ^a Unless otherwise stated, to $\mathbf{3}$ (30 μmol , 1.0 equiv.) and $[\text{Cu}(\text{OTf})_2(\text{py})_4]$ (3 μmol , 0.1 equiv.) in DMF (150 μL) was added $[^{18}\mathbf{F}]\text{KF}/\text{K}_{222}$ (in ~ 30 μL MeCN). Under air at 110 $^{\circ}\text{C}$ for 20 min. Carried out twice ($n = 2$). ^b In DMA; carried out once.



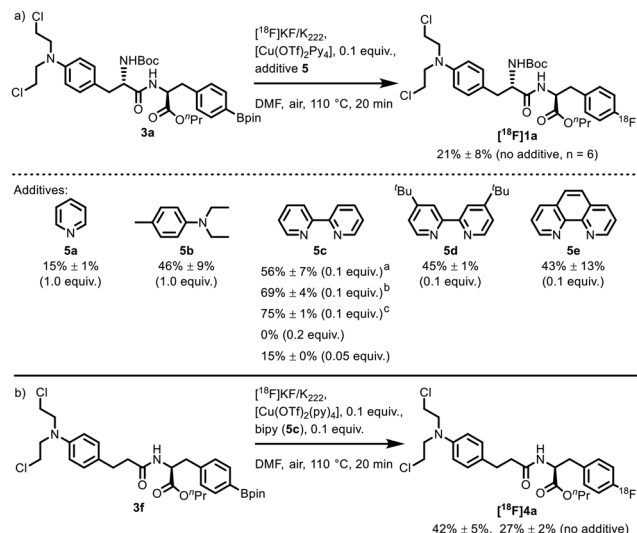


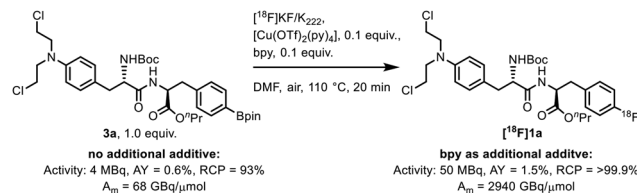
Fig. 4 ^{18}F -labelling of **3a** and **3f** in the presence of N-ligands. ^a Reaction was carried out 3 times ($n = 3$). ^b Reaction time was 10 min. ^c Reaction time was 5 min. Reactions were carried out twice ($n = 2$).

required. Indeed, addition of diethyl-toluidine (**5b**) led to a significant improvement of the RCC to 46%. Ligand **5b** is a structural analogue of the bis(2-chloroethyl)amino moiety, and thus the improved RCC suggested that prevention of the coordination to nitrogen in the bis(2-chloroethyl)amino group possibly has a beneficial effect on the outcome of the ^{18}F -labelling. Subsequently, we applied the strongly coordinating bidentate ligand bipyridyl (bpy) (**5c**). We expected a much stronger metal-coordination by bpy **5c** than by the monodentate ligands **5a** and **5b**. Therefore, initially, only 0.1 equivalents of **5c** were applied instead of the 1 equivalent that was used for **5a** and **5b**. When 0.1 equivalents of **5c** were used with respect to **3a** (1 : 1 ratio with respect to $[\text{Cu}(\text{OTf})_2(\text{py})_4]$), the RCC for ^{18}F **1a** was increased to 56%. When the reaction time was reduced to 10 and 5 minutes, a further slight improvement in the RCC occurred (69 and 75%). Using higher or lower amounts of **5a** as an additive led to a sharp decrease in the RCC. The inhibitory effects of using 0.2 equivalents of **5c** (2 : 1 ratio with respect to $[\text{Cu}(\text{OTf})_2(\text{py})_4]$) indicated that probably two bpy ligands coordinated to copper, blocking the substrate coordination.

We also attempted to use a couple of analogues of bipyridyl **5c**, such as **5d** and **5e**. These also performed well but the RCC was slightly lower (43–45%). A further control experiment with **3f** was also performed (Fig. 4b). This compound lacks the Boc-protected amino group. As mentioned, under the standard optimized conditions, the **3f** \rightarrow ^{18}F **4a** conversion proceeded with 27% RCC (Scheme 1d). However, on addition of bpy (**5c**), the RCC was increased to 42%, indicating the beneficial effect of **5c** in the presence of the bis(2-chloroethyl)amino moiety.

Isolation of ^{18}F **1a** with and without bpy as an additive

Next, we isolated ^{18}F **1a** from reactions conducted under various conditions (Scheme 2). Using the optimized con-



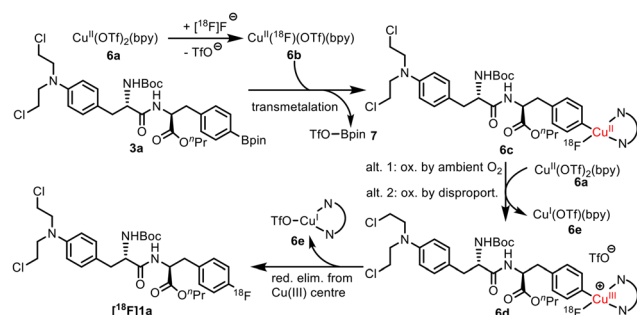
Scheme 2 ^{18}F -Labelling of melflufen derivative **3a** with subsequent isolation. ^a To **3a** (30 μmol , 1.0 equiv.), $[\text{Cu}(\text{OTf})_2(\text{py})_4]$ (3 μmol , 0.1 equiv.) and $[\text{Cu}(\text{OTf})_2(\text{py})_4]$ (3 μmol , 0.1 equiv.) in DMF (150 μL) was added ^{18}F KF/K_{222} (in $\sim 30 \mu\text{L}$ MeCN) under air at 110 $^{\circ}\text{C}$ for 20 min.

ditions, starting with 3.4 GBq of ^{18}F KF , the melflufen analogue radiotracer ^{18}F **1a** could be isolated with 1.5% activity yield (AY), >99.9% radiochemical purity (RCP) and 2940 $\text{GBq } \mu\text{mol}^{-1}$ molar activity (A_m). We showed that upon addition of bpy (**5c**), the AY and A_m could be significantly improved.

Suggested mechanism of the CMRF reaction of **3a**

Based on our results and literature studies,^{4b,5a} we suggest a mechanism for the above presented CMRF reaction of **3a** (Scheme 3). Initially, the copper complex **6a** bearing bpy **5c** undergoes ligand exchange to give the copper- ^{18}F F complex **6b**. The boronate precursor **3a** probably undergoes transmetalation with **6b** to give the organometallic species **6c**. The reductive elimination of fluoride from the low-valent $\text{Cu}(\text{II})$ - ^{18}F F complex **6c** is probably prohibitively slow. However, disproportionation^{5a} by another $\text{Cu}(\text{II})$ complex may result in the $\text{Cu}(\text{III})$ species **6d**. Alternatively, oxygen from ambient air may oxidize $\text{Cu}(\text{II})$ to $\text{Cu}(\text{III})$. This may explain the beneficial effects of conducting the reaction under air. A facile reductive elimination from the $\text{Cu}(\text{III})$ - ^{18}F F complex **6d** results in product ^{18}F **1a**.

Thus, application of the σ -donor bpy ligand **5c** has at least two beneficial effects for the studied CMRF reaction. In the presence of **5c** coordinated to the metal center, the oxidation of $\text{Cu}(\text{II})$ to $\text{Cu}(\text{III})$ is probably facilitated,^{7b} and in addition, bpy may prevent the coordination of the nitrogen atom of the bis(2-chloroethyl)amino moiety to the copper mediator.



Scheme 3 Suggested mechanism of the copper-mediated radiofluorination of the melflufen derivative **3a** in the presence of the bidentate ligand bpy (**5c**).



Conclusions

We have studied the ^{18}F -labelling of alkylating anticancer drug analogues with copper-mediated boron to fluorine exchange reactions. The target molecule bears three different types of nitrogen-containing functional groups. The alkylating bis(2-chloroethyl)amino pharmacophore of these drug-like substances showed the strongest inhibitory effect on the late-stage labelling. Application of bidentate nitrogen ligands led to significant improvement of the ^{18}F -labelling efficiency. These studies will hopefully help our colleagues to develop new copper-mediated fluorination reactions in the presence of reactive nitrogen-containing pharmacophores.

Experimental

General information

Reagents were purchased from commercial suppliers and used without further purification, unless otherwise stated. Solvents were purchased from commercial suppliers and dried using a Vacuum Atmospheres Solvent Purifier system. For column chromatography, silica gel (40–63 μm) from VWR Chemicals was used. TLC was performed with a suitable solvent system on aluminium sheets 60 F254 pre-coated with silica gel from Merck KGaA. UV active components were visualized by UV fluorescence using a UV-lamp (254 nm). ^1H -, ^{13}C - and ^{19}F -NMR spectra were recorded using a DPX-400 (400 MHz) spectrometer from Bruker. The spectra were recorded in CDCl_3 (internal standard: 7.26 ppm, ^1H ; 77.16 ppm, ^{13}C), $\text{DMSO}-d_6$ (internal standard: 2.50 ppm, ^1H ; 39.52 ppm, ^{13}C) or CD_3OD (internal standard: 3.31 ppm, ^1H ; 49.00 ppm, ^{13}C). High resolution mass data (HRMS) were obtained by using a MicroTOF® from Bruker with the electron spray ionisation (ESI) technique. Specific optical rotation α was measured with an Autopol IV® polarimeter from Rudolph Research Analytical ($l = 1\text{ dm}$). The unit of α is $^\circ\text{ ml (g dm)}^{-1}$ and the unit of concentration (c) is g per 100 ml.

Radiofluorination

Radiofluorinations were carried out in dry conical glass vials. For all reactions, solvents, such as dry DMF and dry MeCN, were purchased from commercial suppliers and stored in an N_2 -filled glovebox. ^{18}F Fluoride was produced through bombardment of ^{18}O oxygen-enriched water with protons by the $^{18}\text{O}(\text{p,n})^{18}\text{F}$ nuclear reaction in a cyclotron (Scanditronix MC-17). ^{18}F Fluoride was trapped on an anion exchange cartridge (quaternary methyl ammonium, Sep-Pak® Accell Plus QMA Light from Waters) after preconditioning with K_2CO_3 solution (10 ml, 0.5 M, aq.) and deionized water (10 ml). The radiofluorinated compounds were characterised by comparing the radio-HPLC signal with the UV-HPLC signal of an authentic ^{19}F -reference. Radiochemical conversions (RCC) were determined from a small aliquot of the reaction mixture by analytical radio HPLC (rHPLC). The analytical radio HPLC was performed using an Agilent 1260 Infinity II with a UV-detector

($\lambda = 254\text{ nm}$) in series with a Flow-Count PMT radioactivity detector system from Eckert & Ziegler, using a small aliquot ($\sim 10\text{ }\mu\text{l}$) diluted in a solution of $\text{MeCN}:\text{H}_2\text{O} = 1:1$ ($\sim 500\text{ }\mu\text{l}$). The analysis was performed using a C-18 reversed phase column (Phenomenex, Kinetex 2.6 μm , 100 \AA , $100 \times 4.6\text{ mm}$) and an eluent gradient system of ammonium formate (50 mM aq.)/MeCN (1.5 ml min^{-1} flow; linear increase 30% to 90% MeCN 0–10 min; isocratic 10–12 min; linear decrease 90% to 30% MeCN 12–13 min).

Typical procedure for ^{18}F -labelling

A dry 1 ml V-shaped vial containing a magnetic stirring bar was charged with the boronate substrate (30 μmol , 1.0 equiv.) and the copper mediator $[\text{Cu}(\text{OTf})_2(\text{py})_4]$ (9 μmol , 0.3 equiv.). The vial was sealed before the addition of dry DMF (150 μl). It was stirred vigorously until all components were dissolved ($\sim 30\text{ s}$). A solution of $^{18}\text{F}[\text{K}]\text{F}/\text{K}_{222}$ in dry MeCN ($\sim 300\text{ MBq}$ in $\sim 30\text{ }\mu\text{l}$) was added through the septum to the reaction mixture before it was heated and stirred at $110\text{ }^\circ\text{C}$ for 20 min. An aliquot ($\sim 10\text{ }\mu\text{l}$) was removed and added to a solution of $\text{MeCN}:\text{H}_2\text{O} = 1:1$ ($\sim 500\text{ }\mu\text{l}$) for radio HPLC analysis.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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