One-step synthesis of [^{18}F]cabozantinib for use in positron emission tomography imaging of c-Met.

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Abstract

Cabozantinib is an FDA approved kinase inhibitor for the treatment of medullary thyroid cancer and advanced renal cell carcinoma, which exerts its therapeutic effect by inhibiting, among others, the tyrosine kinase c-Met. Non-invasive imaging techniques are becoming increasingly important clinically to ensure drug efficacy, staging, monitoring and patient stratification. PET isotope labelled tyrosine kinase inhibitors have, for the same reason, potential as PET tracers for imaging of various cancers. Based on cabozantinib, we synthesized the novel boronic acid pinacol ester **4** as a labelling precursor, where the boronic ester moiety replaces the fluorine native to this kinase inhibitor. By this we wanted to explore whether recently developed Cu-mediated fluorination methods are adaptable to more complex substrates and thereby provide easy access to [^{18}F]cabozantinib directly. Hydrolysis was implemented before preparative purification due to challenges with on-column hydrolysis of the precursor **4**, and [^{18}F]cabozantinib was obtained in ≥ 99 % radiochemical purity and in 2.8±0.05 % (n=4) isolated decay corrected yield in a synthesis time of 90 minutes. The molar activity of representative batches was determined to be 17±8 GBq/μmol.

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Introduction

Kinase alterations have emerged as one of the most important factors for why cancers proliferate and metastasize, and are therefore viewed as a central oncological drug target.[1] This has led to substantial research activity to understand the function and to inhibit the action of various kinases.[2] To date, 34 kinase inhibitors are approved by the U.S. Food and Drug Administration (FDA),[3,4] and despite challenges regarding resistance and relapse in patients, the field is developing and expanding. Although only a small portion of the human kinome has been studied in detail, many kinases have been shown to be key regulators of important oncogenes. The tyrosine kinase c-Met plays a central role in many cancer types, e.g. lung, colon and gastric cancer,[5] by affecting cell proliferation, motility and invasion.[6] Hepatocyte growth factor (HGF) binds extracellular to the c-Met receptor, which then leads to several downstream events. Importantly, it has been observed that c-Met is frequently amplified in metastatic tumors.[5] This suggest its role in the proliferation of cancer cells throughout the body, and further emphasize the importance of therapeutics inhibiting the c-Met pathway, as metastasis is the primary cause of cancer related deaths. Therefore, considerable efforts have been made towards inhibiting this target.[7] To date, two c-Met drugs have been clinically approved, which are crizotinib (to treat subtypes of non-small cell lung cancer) and cabozantinib (to treat medullary thyroid cancer and advanced renal cell carcinoma). The structures of these drugs are shown in Figure 1.

Positron emission tomography (PET) has a valuable role to play in making personalized medicine a clinical reality. To be able to exclude a patient population that is unlikely to respond to a specific therapeutic treatment through the use of companion diagnostics might be of great value, since it enables individually tailored therapy regimen to be identified. Due to potential severe side-effects of kinase inhibitors, high development cost, and patient-unique drug resistance, the correct kinase inhibitor regimen is imperative. By using PET, the target expression for a certain drug can be assessed *in vivo*, and this could give vital clinical information resulting in a more targeted and effective treatment. Several of the FDA-approved kinase inhibitors have in recent years been labelled with positron emitting nuclides and investigated as PET tracers.[8,9] Overexpression of c-Met in several tumors[5] motivates the use of PET, and studies have been performed with a small-molecule,[10] a monoclonal antibody[11] and HGF itself.[12] Cabozantinib is an attractive candidate for labelling with either fluorine-18 or carbon-11 as it contains two positions that are readily available for labelling, a methoxy group and a fluorine, as shown in Figure 2. An advantage of using exactly the same structure for the radiopharmaceutical as the approved drug is that pharmacology, toxicity and metabolism are already known, which should promote more rapid clinical translation.

For cabozantinib, ^{11}C-labelling of the methoxy group is feasible from the demethylated precursor using e.g. [^{11}C]CH_3I. However, with its short half-life (20 min), carbon-11 is not as attractive for regular clinical applications and off-site distribution. Introduction of fluorine-18 into the aromatic ring is expected to be impractical by a direct S_NAr reaction due to the electron donating nature of the anilide. An alternative strategy could be a multiple step procedure starting with ^{18}F-labelling of dinitrobenzene, subsequent reduction to the aniline and acylation. This method was recently reported in the patent literature.[13] However, such a multi-step radiosynthesis is time consuming and inherently challenging to automate.

Methods for introducing fluorine-18 directly in electron-rich aryls, as is the case for cabozantinib, has recently been developed.[14] One method utilizes boronic acid pinacol esters as substrates in copper mediated reactions with [^{18}F]fluoride to give the ^{18}F-labelled products in one step, both with electron releasing and electron donating groups present.[15,16] Many boronic acid pinacol esters are commercially available, aryl borylation chemistry is well established and the utility of these precursors for [^{18}F]fluorination chemistry should be straight-forward to implement. This one-step procedure simplifies and opens new chemical avenues for both old and new PET-tracers, including cabozantinib. So far, this method has seen limited use outside the inventing research group[17,18,19], and it remains to see whether it is robust enough to be applicable to a wider selection of substrates using GBqs of [^{18}F]fluoride.

Herein, we report the chemical synthesis of the boronic acid pinacol ester precursor **4** and a one-step, automated radiosynthesis of [^{18}F]cabozantinib.

Results and discussion

The desired BPin precursor **4** was synthesized over four steps, in an overall yield of 14 %, as shown in Scheme 1. Carboxylic acid **1** was obtained from reaction of commercial cyclopropane-1,1-dicarboxylic acid and 4-aminophenylboronic acid pinacol ester. 6,7-dimethoxyquinolin-4-ol was reacted with 1-fluoro-4-nitrobenzene to yield quinoline **2**. This was followed by reduction of the nitro group to the aniline **3**, which was then coupled with the carboxylic acid **1** to give the precursor **4**.

The reaction of **4** with [^{18}F]fluoride was performed as shown in Scheme 2a, using the same protocol as previously reported.[15] Initially, a test reaction was conducted by adding an aliquot (40 μL, 13 MBq) of [^{18}F]KF/K_{222} in acetonitrile to a reaction vial containing **4** and $Cu(OTf)_2(py)_4$ in *N*,*N*-dimethylformamide (DMF). Analytical HPLC of the reaction mixture after 20 minutes at 120 °C showed that the reaction conditions indeed gave the radiolabelled product, confirmed by co-elution with non-radioactive cabozantinib. Radio-TLC indicated a conversion yield of 36 %, and radio-HPLC revealed that [^{18}F]cabozantinib was the only radioactive species besides unreacted [^{18}F]fluoride. The observed yield was in the expected range, and no further optimization was attempted at this scale.

To be useful as a method to produce [^{18}F]cabozantinib for small-animal PET-studies, and eventually for clinical use, the chemistry must allow for higher amounts of radioactivity and be amenable to automation. Therefore, a full-scale experiment using 15 GBq of activity was performed. This time, a change from DMF to *N*,*N*-dimethylacetamide (DMA) as solvent and a higher catalyst loading (1.4 equivalents) was used, consistent with optimisations made to the method in later publications.[16] After semi-preparative HPLC the isolated yield was only 0.7 % (decay corrected yield). As much as 40 % of the activity was remaining in the reaction vial or on the Chromafix® PS-HCO_3 column. Modifying the preconditioning (using oxalate solution) and the elution (using more K_2CO_3) of the column, resulted in only 13 % loss of activity, with the decay corrected yield increasing to 2.8 %. HPLC analysis of the purified fraction containing [^{18}F]cabozantinib revealed a relatively high contamination of several non-radioactive impurities (see supporting information, figure S8). The identity of the main contamination was identified as **5** (Figure 2b), the boronic acid of **4,** using LC-MS. Boronic acid pinacol esters are in general considered to a be stable class of compounds, but hydrolysis has been shown to occur for some derivatives, and possibly yield problems in purifications.[20,21] The precursor **4** has the longest retention time of all species in the reaction

mixture, and on-column hydrolysis to the more hydrophilic and faster eluting **5** will result in contamination throughout the semi-preparative run. Different eluents (gradients with acetonitrile or ethanol) and additives (NH_4COOH) were investigated to improve the on-column stability of **4**, however, with little success. A pre-purification hydrolysis strategy of **4** was then considered, and heating in phosphate buffer (pH 7.4) at 100 ºC for 10 minutes indicated a complete hydrolysis. When implementing hydrolysis before preparative HPLC in the automated synthesis, [^{18}F]cabozantinib was obtained in ≥ 99 % radiochemical purity with a decay corrected yield of 2.8±0.05 % and molar activity 17±8 GBq/μmol (n=4). As can be seen in Figure 3, trace amounts of **5** was still present, however this was quantified using HPLC to only 15 μg (0.17 % of the amount **4** added). These results indicate that also more complex ^{18}F-labelled tracers are available in a one-step reaction with this protocol. However, the observed hydrolysis of the precursor in this case, with subsequent challenges during purification, is a potential drawback with the method.

Conclusions

The FDA-approved tyrosine kinase inhibitor cabozantinib was synthesized as its ^{18}F-labelled analogue using a one-step procedure from the boronic acid pinacol ester precursor **4** in 2.8±0.05 % yield and with a molar activity of 17±8 GBq/μmol (n=4). The precursor was synthesized over four steps. The applied method proved to produce [^{18}F]cabozantinib as the sole radioactive species, although in low yield. Non-radioactive impurities due to hydrolysis of **4** prompted us to explore a pre-column hydrolysis strategy which improved the chemical purity of the final product. It is apparent that some boronic acid pinacol ester substrates are prone to hydrolysis using this method, which may lead to challenges during HPLC purification. Despite the low yield, a total of around 280±15 MBq (n=4) of [^{18}F]cabozantinib was isolated, which are suitable for applications in small-animal PET-studies. After reformulation, [^{18}F]cabozantinib will be tested as a potential companion PET tracer for cabozantinib in relevant tumor models.

Experimental

General

All chemicals were purchased from Sigma–Aldrich or Fluorochem and used without further purification. Air and/or moisture sensitive reactions were performed under argon atmosphere with dried solvents and reagents. TLC was performed on Merck silica gel 60 F_{254} plates, and visualized using UV light at 312 nm or 365 nm, a phosphomolybdic acid solution (12 g phosphomolybdic acid in 250 mL EtOH) or a potassium permanganate solution (1,5 g $KMnO_4$, 10 g K_2CO_3, 2,5 mL 5M $NaOH/H_2O$, 200 mL H_2O). Column chromatography was performed with silica gel (pore size 60 Å, 230–400 mesh particle size) purchased from Fluka. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AVIII HD 400 instrument (400/101 MHz). Chemical shifts (δ) are reported in parts per million, and coupling constants are reported in Hertz (Hz).The residual proton solvent resonance in ^{1}H NMR ($CDCl_3$ at δ 7.27, DMSO-d_6 at δ 2.50) and the residual carbon solvent resonance in ^{13}C NMR ($CDCl_3$ at δ 77.16 ppm and DMSO-d_6 at δ 39.52) are used as reference. Accurate mass determination (HRMS) in positive or negative mode was performed on a Waters Prospec Q instrument, ionized by electrospray (ESI). LC-MS was performed on a Thermo Finnigan LCQ Deca XP Plus and preparative HPLC was

performed on a Waters Delta Prep 4000, using a gradient from 20% to 80 % acetonitrile in water, collecting fractions of 10 mL/minute.

Precursor and cabozantinib synthesis

1-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamoyl)cyclopropanecarboxylic acid (**1**)
Triethylamine (0.30 mL, 2.2 mmol) was added via syringe to a solution of cyclopropane-1,1-dicarboxylic acid (0.210 g, 1.6 mmol) in tetrahydrofuran (THF) (6 mL) at 0 ºC. The solution was then stirred for 15 minutes at 0 ºC, before $SOCl_2$ (0.12 mL, 1.6 mmol) was added via syringe. After another 15 minutes of stirring, 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (390 mg, 1.78 mmol) in THF (3 mL) was added via cannula at 0º C, and the solution was then stirred at ambient temperature for 20 h. The crude mixture was diluted with ethyl acetate (EtOAc) (20 mL), washed with water (2x10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated on a rotary evaporator. Work-up was performed under neutral conditions, and with no further purifications, to prevent possible hydrolysis of the pinacol ester. The title compound was achieved as an off white solid (0.53 g, 99 % crude yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.62, (s, 1H), 7.77 (d, 2H, *J* = 8.4 Hz), 7.55 (d, 2H, *J* = 8.4 Hz), 1.94-1.92 (m, 2H), 1.83-1.80 (m, 2H), 1.34 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 177.75, 166.83, 140.49, 135.90, 119.63, 119.35, 83.94, 26.54, 25.00, 22.18. HRMS (ESI-) m/z calcd. for $C_{17}H_{21}NO_5B$ [M-H]-: 330.1518 , found 330.1519.

6,7-dimethoxy-4-(4-nitrophenoxy)quinolone (**2**)
Cs_2CO_3 (3.68 g, 11.3 mmol) and 6,7-dimethoxyquinolin-4-ol (0.94 g, 4.57 mmol) were weighed out in a round-bottom flask, added 10 mL DMF and 5 mL MeCN, and stirred for 15 minutes. 1-fluoro-4-nitrobenzene (1.49 g, 10.5 mmol) in 10 mL 1:1 DMF:MeCN was then added, and the reaction mixture was stirred for 20 h at 55 ºC. The crude mixture was diluted with EtOAc (80 mL), washed with water (4x40 mL) and brine (40 mL), dried over $MgSO_4$ and concentrated on a rotary evaporator, and then purified by column chromatography (Hep:EtOAc (4:1) → Hep:EtOAc:MeOH (10:10:1). The title compound was achieved as a light yellow solid (0.486 g, 33%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.62 (d, 1H, *J* = 5.2 Hz), 8.32 (d, 2H, *J* = 9.2 Hz), 7.47 (s, 1H), 7.36 (s, 1H), 7.26, (d, 2H, *J* = 9.2 Hz), 6.69 (d, 1H, *J* = 5.2 Hz), 4.06 (s, 3H), 4.0 (s, 3H).

4-((6,7-dimethoxyquinolin-4-yl)oxy)aniline (**3**)
Iron (0.488 g, 8.74 mmol), NH_4Cl (0.511 g, 9.53 mmol) and **2** (0.233, 0.714 mmol) were weighed out in a round-bottom flask, and added water (10 mL) and EtOH (15 mL). The reaction mixture was stirred for 3 h at 70 ºC, and then cooled, filtered through Celite and washed with EtOAc (20 mL). The aqueous phase was extracted with EtOAc (2x15 mL), and the combined organic phases were washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated on a rotary evaporator. The title compound was achieved as a light brown solid (0.176 g, 83 %), and used without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.45 (d, 1H, *J* = 5.5 Hz), 7.58 (s, 1H), 7.42 (s, 1H), 6.99 (d, 2H, *J* = 8.8 Hz), 6.77 (d, 2H, *J* = 8.8 Hz), 6.43 (d, 1H, *J* = 5.5 Hz)

N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)phenyl)-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropane-1,1-dicarboxamide (**4**)
The acid **1** (0.135 g, 0.407 mmol), 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU) (0.184 g, 0.484 mmol) and DMF (2 mL) were placed in a round bottom flask, and then added *N*,*N*-diisopropylethylamine (DIPEA)

(0.13 mL, 0.746 mmol). The aniline **3** (0.128 mg, 0.432 mmol) dissolved in DMF (4 mL) was added after 10 minutes, and the mixture was stirred for 20 h at room temperature. The mixture was then diluted with EtOAc (30 mL), washed with water (4x10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated on a rotary evaporator. This solid was further purified on a preparative HPLC, and the title compound was achieved as a white solid (123 mg, 50 %). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.42 (s, 1H), 8.87 (s, 1H), 8.47 (d, 1H, J = 5.2 Hz), 7.79 (d, 2H, *J* = 8.4 Hz), 7.63 (d, 2H, *J* = 8.8 Hz), 7.54 (s, 1H), 7.53 (d, 2H, *J* = 8.4 Hz), 7.41 (s, 1H), 7.16 (d, 2H, *J* = 8.8 Hz), 6.45 (d, 2H, *J* = 5.2 Hz), 4.04 (s, 3H), 4.03 (s, 3H), 1.73-1.70 (m, 2H), 1.67-1.64 (m, 2H), 1.34 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.23, 168.87, 160.79, 153.01, 151.12, 149.69, 148.99, 147.04, 139.92, 135.98, 134.94, 122.61, 121.77, 119.59, 116.24, 107.97, 103.57, 99.63, 83.98, 56.32, 56.27, 29.67, 25.01, 17.67. HRMS (ESI+) m/z calcd. for $C_{34}H_{37}N_3O_7B$ [M+H]+: 610.2719, found 610.2722.

N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**cabozantinib**)
1-((4-fluorophenyl)carbamoyl)cyclopropanecarboxylic acid[22] (0.146 g, 0.654 mmol), HATU (0.415 g, 1.09 mmol) and DMF (5 mL) were placed in a round-bottom flask, and then added DIPEA (0.26 mL, 1.49 mmol). **3** (0.157 g, 0.53 mmol) dissolved in DMF (5 mL) was added after 10 minutes. The mixture was stirred for 20 h at room temperature. The mixture was then diluted with EtOAc (30 mL), washed with water (4x10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated on a rotary evaporator. This solid was further purified on a preparative HPLC. The title compound was achieved as a white solid (0.112 g, 42 %). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.20 (s, 1H), 8.74 (s, 1H), 8.46 (d, 1H, *J* = 6.4 Hz), 7.99 (s, 1H), 7.79 (d, 2H, *J* = 8.8 Hz), 7.63 (s, 1H), 7.50-7.47 (m, 2H), 7.18 (d, 2H, *J* = 8.8 Hz), 7.02 (t, 2H, *J* = 8.8 Hz), 6.68 (d, 1H, *J* = 6.4 Hz), 4.13 (s, 3H), 4.09 (s, 3H), 1.83-1.81 (m, 2H), 1.69-1.67 (m, 2H). ^{13}C NMR (101 MHz, CDCl3): δ 170.08, 169.04, 165.83, 159.99 (d, J=246 Hz), 156.86, 151.90, 148.70, 141.46, 138.70, 137.12, 133.15 (d, J=3 Hz), 123.24 (d, J=8 Hz), 122.95, 121.65, 116.20, 115.87 (d, J=23 Hz), 102.67, 101.13, 100.05, 57.37, 56.74, 29.21, 18.23.

Radiochemistry

General
[^{18}F]fluoride was produced from the ^{18}O(p,n)^{18}F nuclear reaction on a GE PETtrace 880 cyclotron. Radiosynthesis and azeotropic drying was performed on a ScanSys chemistry module (Værløse, Denmark). Radio-HPLC analyses were performed using an Agilent system (1100 series) with UV detection equipped in series with radiodetector (10 to 90 % acetonitrile in water (0.05 % TFA) over 10 minutes, ACE 3 µm C18-AR 50×4.6mm column, flow 1mL/min). Radio-TLC was performed using a Raytest MiniGita (Straubenhardt, Germany).

Small-scale reaction

[^{18}F]fluoride (~1 GBq) was separated from ^{18}O-enriched-water using a Chromafix® PS-HCO_3 ^{18}F cartridge and released with 900 µL of a solution of K_{222}/K_2CO_3 (Kryptofix® 222 (145 mg) and K_2CO_3 (29 mg) in 10 mL of acetonitrile/H_2O (4:1)) into a 3 mL V-vial. The Chromafix® PS-HCO_3 ^{18}F cartridge was preconditioned with 1 mL of 1 M oxalic acid solution, 10 mL of H_2O and 10 mL of air. The solution was dried with two cycles of azeotropic drying with acetonitrile (200 µl) under a flow of helium at 100 °C, and redissolved in anhydrous MeCN (0.6 mL). A 3 mL vial containing precursor **4** (21.8 mg, 0.036 mmol) and $Cu(OTf)_2(py)_4$ (3.9 mg, 0.0058 mmol) was added [^{18}F]KF/K_{222} in MeCN (40 µL). Anhydrous DMF (300 µL) was

added and the vial was purged with 10 mL of air using a syringe, and then heated at 120 °C for 20 min. The reaction was quenched by adding water (300 μL), and analysed by radio-TLC and HPLC.

Automated synthesis

[^{18}F]fluoride (~15 GBq) was separated from ^{18}O-enriched-water using a Chromafix® PS-HCO_3 ^{18}F cartridge and released with 900 μL of a solution of $K_{222}/K_2C_2O_4/K_2CO_3$ (Kryptofix® 222 (63 mg), $K_2C_2O_4$ (12 mg) and K_2CO_3 (2.5 mg) in 10 mL of acetonitrile/H_2O (4:1)) into a 3 mL V-vial placed in the reactor. The Chromafix® PS-HCO_3 ^{18}F cartridge was preconditioned with 10 mL of 0.06 M $K_2C_2O_4$ solution, 10 mL of H_2O and 5 mL of air. The solution was dried with two cycles of azeotropic drying with acetonitrile (200 μl) under a flow of helium at 100 °C. The 3 mL vial containing the dried [^{18}F]KF/K_{222} complex was added a solution of **4** (10 mg, 0.016 mmol) and $Cu(OTf)_2(py)_4$ (15 mg, 0.022 mmol) in anhydrous DMA (400 μL) and purged with 10 mL of air using a syringe. The mixture was heated at 120 °C for 20 min, after which, the reaction mixture was added 1.3 mL phosphate buffer (pH 7.4), and heated at 100 °C for 10 minutes. The crude mixture was then diluted with 1.3 mL of 40 % acetonitrile in water and loaded directly onto a HPLC loop and injected on a semi-prep HPLC column (Phenomenex Onyx 100x10 mm, 4 mL/min) using a gradient from 10 to 40 % EtOH in water (0.05 % TFA) over 20 minutes, monitored with UV- and radiodetector. An aliquot from the fraction collected around 20 minutes was analysed by analytical HPLC for product identity and molar activity measurements. Molar activity was calculated by comparing the UV absorption to a calibration curve of cabozantinib. Radio-TLC was used for further radiochemical purity measurements.

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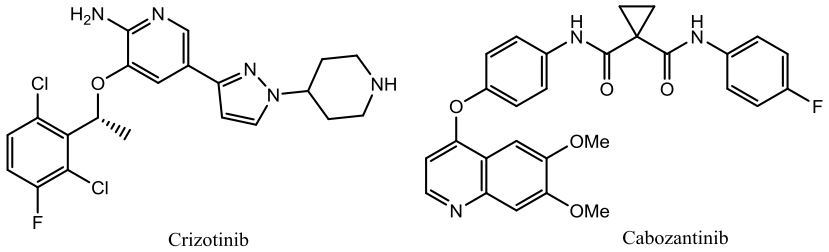


Figure 1: The structure of crizotinib and cabozantinib.

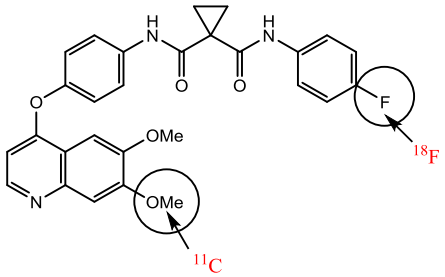
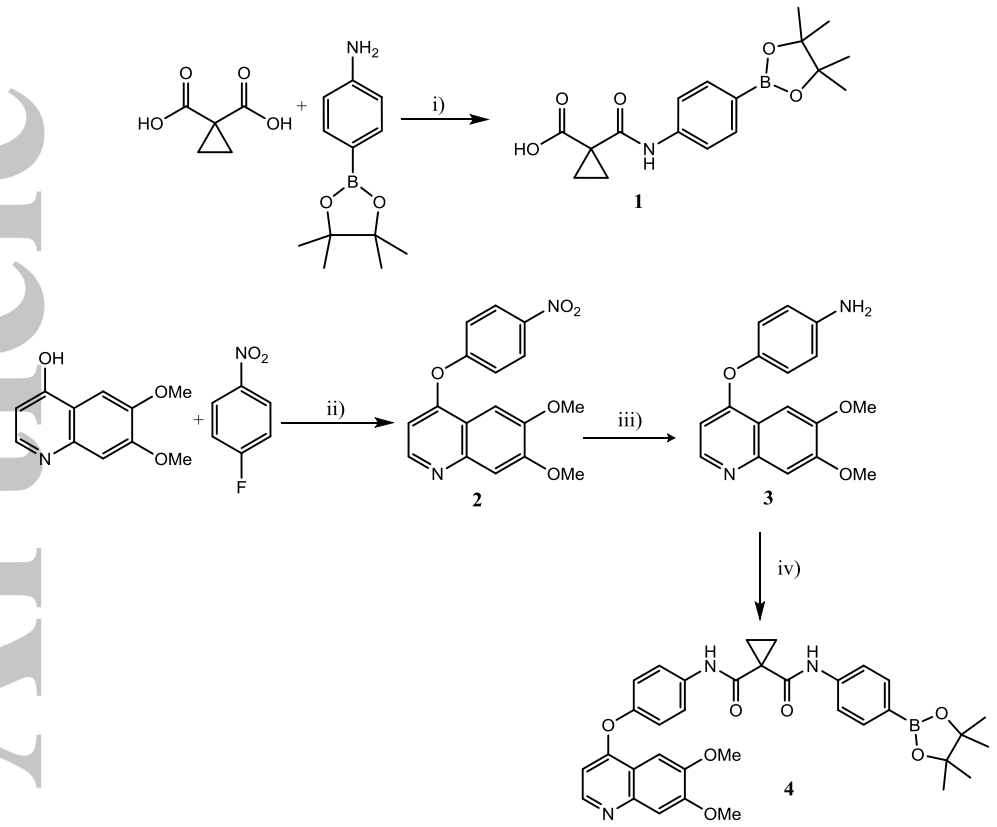
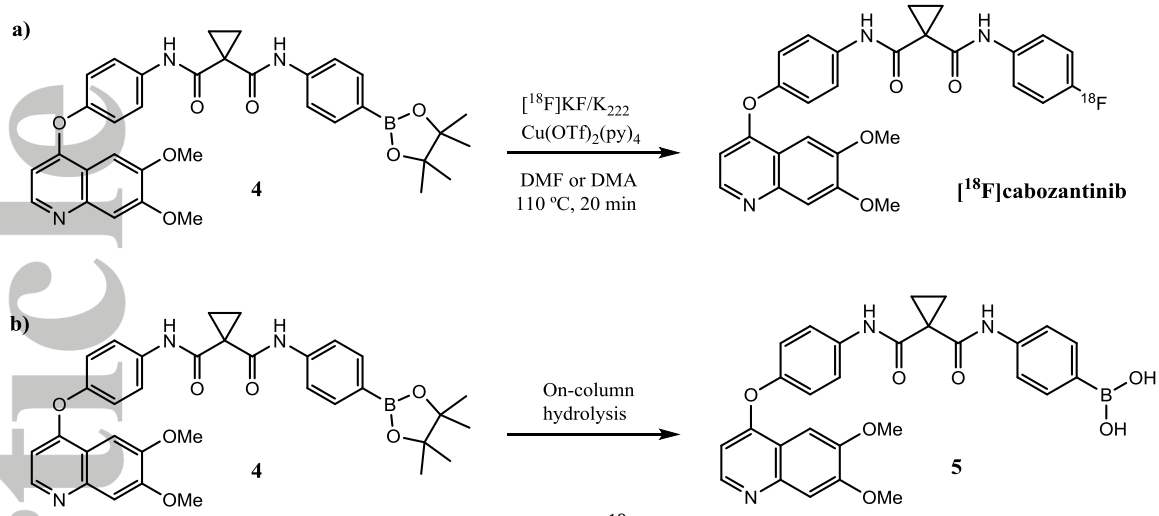


Figure 2: Cabozantinib with its two sites for isotopic labelling with either carbon-11 or fluorine-18.



Scheme 1: The synthesis of precursor **4**. i) NEt_3, $SOCl_2$, THF, rt, 99 %; ii) Cs_2CO_3, DMF, MeCN, 20 h, 55 ºC, 33 %; iii) Fe, NH_4Cl, EtOH, H_2O, 3 h, 70 ºC, 83 %; iv) **1**, HATU, DIPEA, DMF, rt, 20 h, 50 %.



Scheme 2: a) The radiochemical reaction yielding [^{18}F]cabozantinib from **4**. b) observed hydrolysis during purification produced the boronic acid **5**.

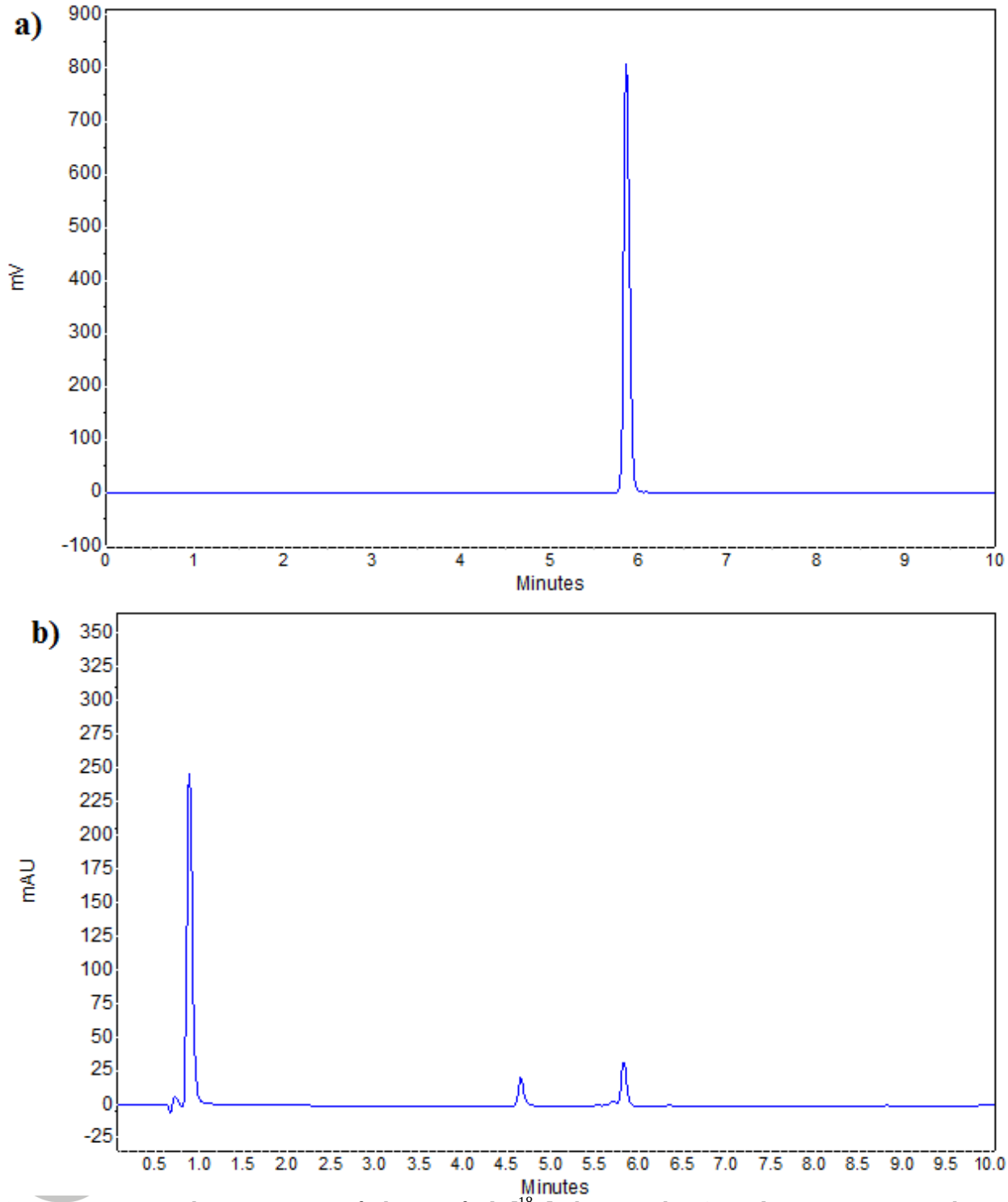


Figure 3: HPLC chromatograms of the purified [^{18}F]cabozantinib; a) Radioactive trace, with [^{18}F]cabozantinib at t_R = 5.8 min; b) UV-trace. The impurity from boronic acid **5** can be seen eluting at t_R = 4.6 min.