Journal of Radioanalytical and Nuclear Chemistry (2020) 326:1281–1287
https://doi.org/10.1007/s10967-020-07376-2

Thermochromatographic separation of ^{45}Ti and subsequent radiosynthesis of [^{45}Ti]salan

Kai Giesen[1] · Ingo Spahn[1] · Bernd Neumaier[1]

Received: 30 June 2020 / Published online: 10 October 2020

Abstract

Due to its favorable decay properties, the non-standard radionuclide ^{45}Ti is a promising PET isotope for tumor imaging. Additionally, titanium complexes are widely used as anti-tumor agents and ^{45}Ti could be used to study their in vivo distribution and metabolic fate. However, although ^{45}Ti can be obtained using the ^{45}Sc(p,n)^{45}Ti nuclear reaction its facile production is offset by the high oxophilicity and hydrolytic instability of Ti^{4+} ions in aqueous solutions, which complicate recovery from the irradiated Sc matrix. Most available ^{45}Ti recovery procedures rely on ion exchange chromatography or solvent extraction techniques which are time-consuming, produce large final elution volumes, or, in case of solvent extraction, cannot easily be automated. Thus a more widespread application of ^{45}Ti for PET imaging has been hampered. Here, we describe a novel, solvent-free approach for recovery of ^{45}Ti that involves formation of [^{45}Ti]$TiCl_4$ by heating of an irradiated Sc target in a gas stream of chlorine, followed by thermochromatographic separation of the volatile radiometal chloride from co-produced scandium chloride and trapping of [^{45}Ti]$TiCl_4$ in a glass vial at − 78 °C. The recovery of ^{45}Ti amounted to $76 \pm 5\%$ ($n = 5$) and the radionuclidic purity was determined to be $>99\%$. After trapping, the [^{45}Ti]$TiCl_4$ could be directly used for ^{45}Ti-radiolabeling, as demonstrated by the successful radiosynthesis of [^{45}Ti][Ti(2,4-salan)].

Keywords ^{45}Ti · Separation · Thermochromatography · Ti-complexes · Radiolabeling · Radio metal complexes

Introduction

Discovery of the anticancer activity of cisplatin and its clinical introduction in the 1970s have spurred interest into metal based antitumor compounds with less side effects and increased effectiveness against a broad range of cancers [1, 2]. Titanium(IV) complexes like budotitane, titanocene dichloride and their derivatives are effective against various cancer cell lines but failed in in vivo clinical trials [3–6], most likely due to their rapid (within seconds) hydrolysis under physiological conditions [7]. A more promising class of titanium-based drugs with hydrolytic half-lives in the range of hours is based on tetradentate diaminobis(phenolato) ligands (salans) [8]. Their titanium complexes selectively induce apoptotic cell death [9] and display strong antitumor properties in vitro and in tumor-bearing mice [10, 11]. Further studies on their distribution, uptake and mechanism of action rely on imaging techniques such as positron emission tomography (PET), which allows for non-invasive assessment of the biological fate of radiolabeled drugs while they distribute in vivo. The titanium isotope ^{45}Ti has a half-life of 3.1 h, a high positron branching ratio ($\beta^+ = 84.8\%$) and low maximum positron energy ($E_{\beta+max} = 439$ keV), negligible secondary gamma emission and a low β end point energy of 1.04 MeV, making it an ideal candidate for use in PET studies [12–14]. However, while the radiometal can be produced by transmutation of naturally monoisotopic scandium with low energy protons [15, 16], ^{45}Ti radiochemistry is hampered by the high oxophilicity ($\theta = 1.0$) and hydrolytic instability of Ti^{4+} ions in aqueous environments, which necessitate the use of strongly acidic conditions [17, 18]. Solid phase extraction of ^{45}Ti dissolved in acidic solutions by ion exchange chromatography is time-consuming, cannot easily be automated and often results in non-reactive titanyl species that are unsuitable for production of titanium complexes [19, 20]. A number of approaches have been proposed to circumvent these problems, which include the use of hydroxamate resins and oxalic acid elution [21], trapping of ^{45}Ti on a diol-functionalized resin followed

---

✉ Ingo Spahn
i.spahn@fz-juelich.de

[1] Institut für Neurowissenschaften und Medizin (INM-5), Forschungszentrum Jülich GmbH, 52428 Jülich, Germany

by on-resin radiosynthesis [22] and continuous liquid–liquid extraction of the radioisotope with a guaiacol/anisole mixture to obtain a ^{45}Ti containing organic phase that can be used for radiolabeling [23, 24]. Here, we describe an alternative, solvent-free "one-pot" method that is based on thermochromatographic separation of ^{45}Ti from an irradiated Sc target and consecutive radiotitanation of a salan ligand, thereby obviating the need for organic solvents, solid phase extraction or on-column chelation chemistry.

Experimental

Materials

Dry tetrahydrofurane (THF), N,N-diisopropylethylamine (DIPEA) (99.5%), 2,4-dimethylphenol (98%) and thin layer chromatography (TLC) plates were purchased from Sigma-Aldrich (Germany). N,N′-bis(2-hydroxyethyl)ethylendiamine (95%) was purchased from ABCR GmbH (Germany). Scandium ingots were purchased from Smart Elements GmbH (Austria). Chlorine gas (5.0) was obtained from Linde Gas (Germany). All chemicals were used without further purification. Mass flow controllers were bought from Bronkhorst Deutschland Nord GmbH (Germany) (EL-FLOW Select 300 mL/min for inert gases, LOW-ΔP-FLOW 60 mL/min for chlorine gas). Mass flow conversions were done using the Fluidat database (Bronkhorst Nord GmbH, Germany). Glassware for the separation system was manufactured at the Central Institute of Engineering, Electronics and Analytics (ZEA-1) at Forschungszentrum Jülich.

Analytical instrumentation

Gamma spectroscopy was performed with ORTEC gamma-ray spectrometers (AMETEK GmbH, Germany), which were energy and efficiency calibrated with certified radiation point sources (Co-60, Ba-133, Eu-152, Ra-226) from the Physikalisch-Technische Bundesanstalt (Germany). To monitor the separation process, a Geiger–Müller–Tube (VacuTec GmbH, Germany) was used. Radio-TLC measurements were performed on $60F_{254}$ silica plates (Merck, Germany) with methanol as mobile phase and recorded using a Packard Instant Imager (Packard Instrument Company, USA). The radioactivity detection limit (LOD) was determined by serial dilution and amounted to ≤ 3 Bq for an exposure time of 30 min. Radio-HPLC was performed on an Azura P 4.1 s pump with an Azura UVD 2.1 s UV/VIS detector (Knauer Wissenschaftliche Geräte GmbH, Germany) and an EG & G Ortec ACE NaI(Tl) radioactivity detector with photomultiplier (EG & G Ortec, USA). The radioactivity detection limit was determined by serial dilution and amounted to 0.3 kBq. Co-elution experiments of radioactive and non-radioactive complexes were performed with a flow rate of 1 mL/min using $H_2O/MeOH/CH_3COOH$ (27/73/0.07, v/v/v) as the mobile and Synergi Fusion 4 µ RP 80 Å, 250 × 4.6 mm (Phenomenex Inc., Germany) as the RP stationary phase. The UV detection wavelength for all measurements was 240 nm. NMR spectra were measured on a Varian Inova 400 spectrometer (Agilent Technologies, Germany) with 400.1 MHz (^{1}H-NMR) and 100.62 MHz (^{13}C-NMR). High-resolution mass spectrometry (HRMS) was performed using a hybrid linear ion trap FT-ICR mass spectrometer LTQ-FT Ultra (Thermo Fisher Scientific, Germany) equipped with a 7 T superconducting magnet. The electrospray ionisation (ESI) source was operated in the positive mode. Low-resolution mass spectrometry was measured using a Finnigan Automass Multi spectrometer (Thermoquest, Germany). ^{45}Sc concentrations in solution were determined by inductively coupled plasma mass spectrometry (ICP-MS) using an Agilent 7500 instrument with quadrupole mass analyzer and collision cell (Agilent Technologies, Germany). The instrument was operated with helium as collision gas to minimize spectral interferences by cluster ions. Quantification was performed by external calibration using Rh as the internal standard.

Radionuclide production

Titanium-45 was produced from discs of metallic scandium (0.35 ± 0.1 g) by the ^{45}Sc(p,n)^{45}Ti nuclear reaction. As target material scandium of 99.99% purity was used (Smart-Elements GmbH, Austria). The material came in form of small ingots, which were rolled to plates of 0.6 mm. From those plates circular target of 13 mm were cut and put into a copper target holder to be irradiated at the solid target station of the BC1710 [30]. The target was irradiated with 8.2–16.9 MeV protons at 1.5 µA for 30 min using the Baby Cyclotron BC1710 at the INM-5 (Forschungszentrum Jülich). To minimize coproduction of ^{44}Sc (half-life: 3.9 h), ^{44m}Sc (half-life: 58 h) and ^{44}Ti (half-life: 60 y), two Ni foils with a thickness of 125 µm each were used to degrade the proton energy to approximately 12 MeV. For initial optimization studies, irradiation was performed without degradation of the proton beam, so that ^{44}Sc and ^{44m}Sc could be used to radiometrically monitor the separation process and determine the radiochemical purity of the product.

Radionuclide separation system

The separation set-up (Fig. 1) consisted of a quartz glass reaction chamber that was connected to the main gas line via a Young valve and could be heated to temperatures of up to 1000 °C by a model MTF 12/39/250 heating oven (Carbolite Gero GmbH, Germany), a borosilicate glass tube condenser that could be heated to 400 °C, a

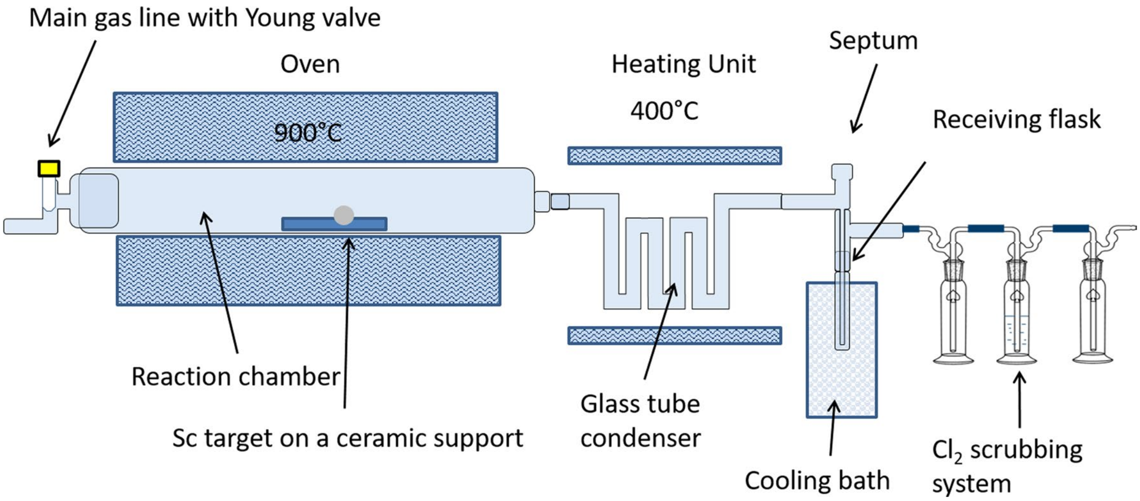


Fig. 1 Schematic representation of the separation setup

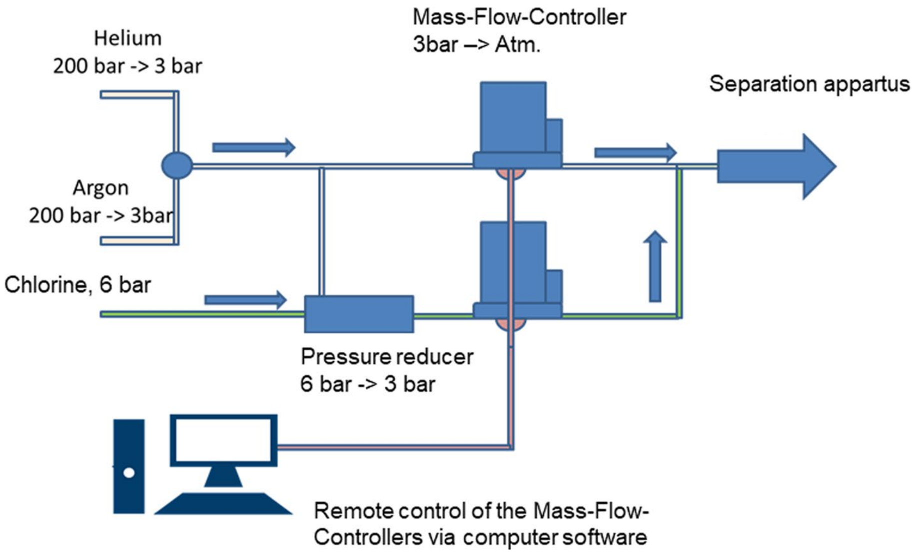
receiving flask that could be cooled down to − 79 °C by an acetone/CO_2 cooling bath and a chlorine scrubbing system with 20% sodium hydroxide solution. Various gas mixtures were supplied to the setup by two mass flow controllers (Fig. 2).

The ground glass joint connecting the reaction chamber and the condenser was sealed with a polytetrafluoroethylene sealing ring to obviate the need for high vacuum grease which could have absorbed or contaminated the product. In addition, the upper part of the receiving flask was equipped with a septum, which allowed for addition of reagents during the radiosynthesis that was performed immediately after the separation process.

Thermochromatographic separation of ^{45}Ti from scandium

For isolation of titanium-45, the irradiated Sc matrix was placed into the reaction chamber, which was flushed with helium (125 mL/min) and heated to 900 °C. When the reaction temperature was reached, the chamber was flushed with a mixture of chlorine (15 mL/min) and helium (110 mL/min) gas to form the halides [^{45}Ti]$TiCl_4$ and $ScCl_3$ respectively. As the gaseous mixture of metal chlorides reached the condenser, $ScCl_3$ (boiling point ~ 975 °C) resublimed while [^{45}Ti]$TiCl_4$ (boiling point ~ 136 °C) passed further and condensed in the receiving flask. A Geiger–Müller counter was used to monitor the separation process. When the collection of [^{45}Ti]$TiCl_4$ was complete, the addition of chlorine and heating were discontinued, the temperature of the receiving

Fig. 2 Scheme of the mass-flow-controller setup



flask was raised to − 30 °C and the system was flushed with helium for 10 min to remove excess chlorine. Optimal reaction conditions (temperature, chlorine concentration and gas flow) were determined experimentally as described in more detail in the results section and supporting information.

Synthesis of 6,6′-((ethane-1,2-diylbis((2-hydroxyethyl)azanediyl))bis(methylene))bis(2,4-dimethyl-phenol) (2,4-salanH$_4$)

740 mg (1 eq, 5.0 mmol) 1,2-bis(2-aminoethoxy)ethane, 122 mg 2,4-dimethylphenol (2 eq, 10.0 mmol) and 500 mg paraformaldehyde (3.3 eq, 16.7 mmol) were dissolved in methanol and refluxed for 12 h. The organic solvent was removed under reduced pressure and the crude product recrystallized from diethylether/petrolether to obtain the target compound as white crystals. (251 mg, yield: 12%). *^{1}H-NMR* (400 MHz, $CDCl_3$): δ 6.89 (br, 2 h, Ar), 6.65 (s, 2 h, Ar), 3.82–3.76 (m, 2 h, CH_2), 3.71 (s, 4 h, CH_2), 2.75 (s, 4 h, CH_2), 2.23 (s, 6 h, CH_3), 2.22 ppm (s, 6 h, CH_3). *^{13}C-NMR* (101 MHz, $CDCl_3$): 152.3, 131.0, 128.3, 127.3, 125.0, 121.0, 58.9, 57.2, 54.8, 50.8, 20.4, 15.7 ppm. *HRMS*: m/z calculated for $[M+H]^+$ $C_{24}H_{37}N_2O_4$: 417.27533, found: 417.27481 $[M+H]^+$.

Synthesis of titanium complex [Ti(2,4-salan)]

Under argon atmosphere, 150 mg 6,6′-((ethane-1,2-diylbis((2-hydroxyethyl)azanediyl))bis-(methylene))-bis(2,4-dimethylphenol) (2,4-salanH$_4$) was dissolved in 25 ml dry THF and 139 mg titanium isopropoxide was added to the solution. After stirring for 15 min the organic solvent was removed under reduced pressure and the product was obtained as light yellow solid (220 mg, yield: 99%). *^{1}H-NMR* (400 MHz [D$_6$]DMSO): δ 6,86 (s, 2 h, Ar), 6,78 (s, 2 h, Ar), 4,45–4,25 (m, 4 h, CH_2), 3,79 (br, *J* = 18,0 4 h, CH_2), 3,51 (d, *J* = 8,6 Hz, 2 h, CH_2), 3,23 (br, 2 h, CH_2), 3,12 (d, *J* = 8,9 Hz, 2 h, CH_2), 2,85 (d, *J* = 9,5 Hz, 2 h, CH_2), 2,18 (s, 6 h, CH_3), 2,12 (s, 6 h, CH_3). *HRMS*: m/z calculated for $[M+H]^+$ $C_{24}H_{33}O_4N_2Ti$: 461.19198, found: 461.19148 $[M+H]^+$.

Radiosynthesis of [^{45}Ti][Ti(2,4-salan)]

2 mg 2,4-salanH$_4$ and 20 µl of DIPEA in 2 mL anhydrous THF were added to the receiving flask containing the isolated [^{45}Ti]TiCl$_4$ and allowed to react for 5 min at − 30 °C, after which the mixture was analyzed by HPLC. For purification of the radiolabeled complex, the reaction mixture was diluted with H_2O (30 mL) and loaded onto a SepPak C18 RP cartridge (Waters GmbH, Germany). The cartridge was washed with a mixture of $H_2O/MeOH/CH_3COOH$ (4/1/0.005 mL) and the product eluted with MeOH (3 mL).

Results and discussion

Routine production of ^{45}Ti by proton bombardment of natural scandium resulted in high radionuclidic purity and good yields. The latter amounted to about 290 MBq for a typical bombardment with 12 MeV protons and 1.5 µA current for 30 min of beam time. When choosing 16.9 MeV incident proton energy, a typical bombardment of 1.5 µA for 30 min produced a batch yield of 360 MBq and the product was composed of 87% ^{45}Ti, 12% ^{44}Sc and 1% ^{44m}Sc. These production yields are comparable to those reported by Vavere et al. [19]. For isolation of the radiometal and formation of radiolabeled complexes, we developed a solvent-free "one-pot" procedure that involves (1) formation of [^{45}Ti]TiCl$_4$ by reaction of the cyclotron-irradiated scandium target with chlorine gas, (2) isolation of [^{45}Ti]TiCl$_4$ by thermochromatographic separation of the resulting metal chlorides and (3) direct reaction of isolated [^{45}Ti]TiCl$_4$ with a chelating ligand to form the radiometal complex.

Preparation of [^{45}Ti]TiCl$_4$ by high-temperature chlorination of irradiated Sc

To avoid the formation of titanyl species, [^{45}Ti]TiCl$_4$ for PET radiochemistry has almost exclusively been produced by dissolving irradiated scandium targets with concentrated hydrochloric acid. Recovery of the radiometal chloride from acidic solutions involves arduous separation chemistry, which has limited a more widespread application of ^{45}Ti for PET imaging. To circumvent these problems, we investigated high-temperature chlorination, which has long been used for commercial $TiCl_4$ production from rutile (TiO_2) or ilmenite (FeO–TiO_2) feedstocks [25]. To this end, we first examined whether [^{45}Ti]TiCl$_4$ could be produced and separated from the irradiated target under conditions that minimize formation of scandium chlorides. However, preliminary experiments with non-irradiated targets treated with 100% Cl_2 demonstrated that formation of $ScCl_3$ starts to occur at temperatures above 600 °C which is still below the 850–1050 °C typically used for chlorination of titanium ores [25]. Also, no formation of [^{45}Ti]TiCl$_4$ was observed when an irradiated target was chlorinated at 550 °C. When the temperature was increased to 750 °C, some formation of [^{45}Ti]TiCl$_4$ took place but isolation was hampered by an exothermic reaction of the scandium with Cl_2, which contaminated the whole separation apparatus. To avoid this exothermic reaction, a series of optimization experiments was performed with a fixed reaction temperature of 900 °C and a total gas flow rate of 100 mL/min while varying the concentration of chlorine. For these experiments, irradiation of the Sc target was deliberately performed without degradation of the proton beam, so that ^{44}Sc and ^{44m}Sc could be used to radiometrically monitor the separation. As illustrated in Table 1, ^{45}Ti recovery under these conditions was maximal (53%) when the chlorine concentration was 12%. In a second set of optimization experiments, temperature and chlorine concentration were fixed at 900 °C and 12% while the total gas flow rate was varied (Table 2). The results showed that highest recovery rates could be obtained with total gas flow rates between 100 and 150 mL/min, whereas recovery decreased at lower or higher rates (Table 2). Finally, we examined the influence of reaction temperature on recovery of ^{45}Ti with the total flow rate fixed to 125 mL/min and a Cl_2 concentration of 12%. The recovery of [^{45}Ti]$TiCl_4$ decreased as the temperature was lowered to 850 °C (Table 3), presumably because $ScCl_3$ formation on the surface of the target prevented reaction of the radiometal with Cl_2. Better results (53% recovery) were obtained at 900 °C, a temperature at which sublimation of $ScCl_3$ was sufficient to prevent its accumulation on the surface of the target. If the temperature was further increased to 1000 °C, the recovery yield decreased again by 13%, most likely reflecting the thermal decomposition of [^{45}Ti]$TiCl_4$ at that temperature [26, 27].

Thermochromatographic separation and purification of [^{45}Ti]$TiCl_4$

As noted above and consistent with previous reports [28, 29], appreciable transition of $ScCl_3$ to the gas phase was observed at temperatures above 850 °C, requiring its removal from the gaseous mixture of metal chlorides. This was initially attempted with fritted glass, which proved to have several disadvantages. Apart from loss of product on the large surface area of the frit, re-sublimation of $ScCl_3$ tended to clog the system, which could potentially result in dangerous pressure build-up. Therefore, a simple condenser made of a 100 cm borosilicate spiral coil that was heated to 400 °C and served as the vapor–condensate path was used instead. In initial experiments with argon as the inert gas, no separation could be achieved since $ScCl_3$ was transported to the receiving flask. In contrast using helium as the inert gas, $ScCl_3$ resublimed in the condenser and was effectively retained, while [^{45}Ti]$TiCl_4$ passed through and could be collected in the receiving flask. A temperature of − 78° was chosen to condense the radiometal chloride (boiling point 136 °C) while avoiding formation of solid Cl_2 (melting point − 101.5 °C) in the receiving flask. Once the collection of [^{45}Ti]$TiCl_4$ was complete, remaining Cl_2 (boiling point − 34.04 °C) could be easily removed by increasing the temperature to − 30 °C and flushing the trapping vessel with helium gas for 10 min. Tracer experiments with ^{44}Sc and gamma-ray spectroscopy showed that negligible ^{44,44m}Sc activities were found in the isolated ^{45}Ti fraction. Additionally, ICP-MS measurements of Sc in the product fraction confirmed that only traces of Sc (0.005 mg (0.1 ppm)) were transported to the trapping vessel.

Table 1 Influence of Cl_2 concentration on ^{45}Ti recovery

Cl_2 (%)	^{45}Ti recovery (%)[a]
6	42
9	42
12	53
18	45

Reaction temperature and total gas flow rate were 900 °C and 100 mL/min

[a] Relative to the cumulative activity of ^{45}Ti, ^{44m}Sc and ^{44}Sc at the start of the separation process

Table 2 Influence of total gas flow rate on ^{45}Ti recovery

Total gas flow (mL/min)	^{45}Ti recovery (%)[a]
75	38
100	53
125	54
150	53
200	31

Reaction temperature and Cl_2 concentration were 900 °C and 12%

[a] Relative to the cumulative activity of ^{45}Ti, ^{44m}Sc and ^{44}Sc at the start of the separation process

Table 3 Influence of reaction temperature on ^{45}Ti recovery

Temperature (°C)	^{45}Ti recovery (%)[a]
850	42
900	53
1000	40

Total gas flow rate and Cl_2 concentration were 125 mL/min and 12%

[a] Relative to the cumulative activity of ^{45}Ti, ^{44m}Sc and ^{44}Sc at the start of the separation process

Finally, the optimized reaction conditions were used for the separation of pure ^{45}Ti, produced by degrading the proton energy for irradiation of the Sc target to approximately 12 MeV (see Experimental section). This allowed precise quantification of ^{45}Ti recovery by simply dividing the recovered activity of ^{45}Ti by the total starting activity. On average, recovery of ^{45}Ti amounted to 76 ± 5% (n = 5). The separation process was conducted within 2 h, corresponding to a non-decay-corrected (n.d.c.) recovery of 48 ± 3% (n = 5) (Table 4). The amount of non-radioactive Ti was analyzed by ICP-MS to be less than 1 µg/L in the final reaction volume.

Radiosynthesis of [^{45}Ti][Ti (2,4-salan)]

To confirm that the isolated [^{45}Ti]$TiCl_4$ can be directly employed for radiolabeling, it was reacted with the hexadentate ligand 2,4-salan to produce a [^{45}Ti][Ti(2,4-salan)] complex (Fig. 3). To this end, 2,4-salan and DIPEA were dissolved in dry THF, added to the receiving flask containing the purified [^{45}Ti]$TiCl_4$ and allowed to react for 5 min at − 30 °C. HPLC of the reaction mixture with co-injection of the non-radioactive reference compound confirmed the identity of the product and the absence of radioactive byproducts (Fig. 4). However, radio-TLC revealed up to 50% of an unidentified byproduct, presumably [^{45}Ti]TiO_2, which may have formed due to traces of H_2O present in the reaction mixture. From the starting activity used for this reaction, 50% could be recovered from the receiving vessel for further purification. The radiochemical yield (RCY) obtained after isolation of the radiocomplex via solid phase extraction amounted to 15 ± 7% (n = 7).

Table 4 Duration of specific separation steps and recovery of ^{45}Ti

Separation step	Time (min)
Heating	45
Separation	60
Removal of excess chlorine	10
Total	115
Production ^{45}Ti ^{45}Sc(p,n)^{45}Ti, 12MeV→0	390 MBq/(µA.h)
Recovery	76 ± 5% (n = 5)
Recovery n.d.c.	48 ± 3% (n = 5)

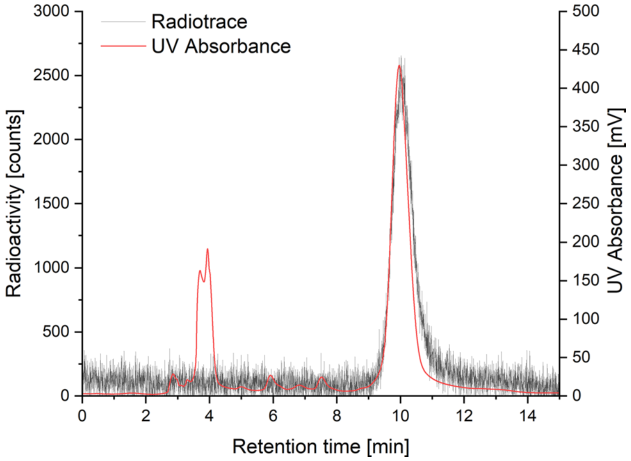


Fig. 4 HPLC chromatogram of [^{45}Ti][Ti(2,4-salan)] with coinjected reference compound. Mobile phase: $H_2O/MeOH/CH_3COOH$, 27/73/0.07, vol/vol/vol. Stationary phase: Synergy Fusion RP, flow = 1 mL/min. The UV-peaks at ≈ 4 min correspond to protonated excess ligand and base

Conclusions

In this work a radioseparation method of no-carrier-added [^{45}Ti]$TiCl_4$ from Sc is described. ^{45}Ti was produced by proton irradiation of a metallic Sc target followed by thermochromatographic separation in a chlorine gas stream. The separated [^{45}Ti]$TiCl_4$ could be used directly for the preparation of the radiometal complex [^{45}Ti][Ti(2,4-salan)] in radiochemical yields of 10–20%. This simple separation technique obviates the need for complex separation chemistry and may contribute to a more widespread application of ^{45}Ti-labeled compounds in imaging applications.

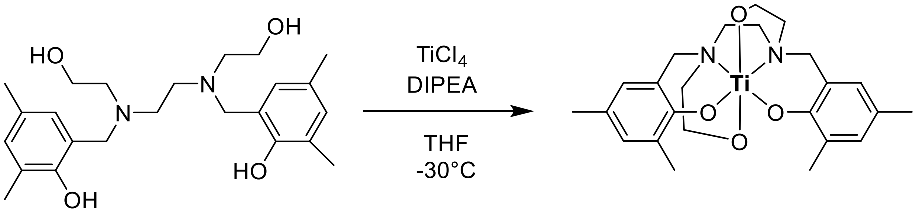
Acknowledgements The authors are grateful to Mr. S. Spellerberg for technical assistance, and to Mr. M. Holzgreve and Mr. I. Montag for all cyclotron-irradiations. Further thanks go to F. Neumaier for his assistance in the preparation of this manuscript.

Funding Open Access funding enabled and organized by Projekt DEAL.

Compliance with ethical standards

Conflict of interest No conflict of interests is reported.

Fig. 3 Formation of [^{45}Ti][Ti(2,4-salan)] complex by radiolabeling of 2,4-salanH_4 with [^{45}Ti]$TiCl_4$ and DIPEA



References

1. Gaynor D, Griffith DM (2012) The prevalence of metal-based drugs as therapeutic or diagnostic agents: beyond platinum. Dalton Trans 41:13239–13257
2. Mjos KD, Orvig C (2014) Metallodrugs in medicinal inorganic chemistry. Chem Rev 114:4540–4563
3. Schilling T, Keppler KB, Heim ME, Niebch G, Dietzfelbinger H, Rastetter J, Hanauske A-R (1995) Clinical phase I and pharmacokinetic trial of the new titanium complex budotitane. Invest New Drugs 13:327–332
4. Lümmen G, Sperling H, Luboldt H, Otto T, Rübben H (1998) Phase II trial of titanocene dichloride in advanced renal-cell carcinoma. Cancer Chemother Pharmacol 42:415–417
5. Strohfeldt K, Tacke M (2008) Bioorganometallic fulvene-derived titanocene anti-cancer drugs. Chem Soc Rev 37:1174–1187
6. Meléndez E (2002) Titanium complexes in cancer treatment. Crit Rev Oncol Hematol 42:309–315
7. Toney JH, Marks TJ (1985) Hydrolysis chemistry of the metallocene dichlorides M(.eta.5-C5H5)2Cl2, M = titanium, vanadium, or zirconium. Aqueous kinetics, equilibria, and mechanistic implications for a new class of antitumor agents. J Am Chem Soc 107:947–953
8. Immel TA, Groth U, Huhn T (2010) Cytotoxic titanium salan complexes: surprising interaction of salan and alkoxy ligands. Chem A Eur J 16:2775–2289
9. Immel TA, Debiak M, Groth U, Bürkle A, Huhn T (2009) Highly selective apoptotic cell death induced by halo-salane titanium complexes. ChemMedChem 4:738–741
10. Immel TA, Groth U, Huhn T, Öhlschläger P (2011) Titanium salan complexes displays strong antitumor properties in vitro and in vivo in mice. PLoS ONE 6:e17869
11. Immel TA, Grützke M, Späte A-K, Groth U, Öhlschläger P, Huhn T (2012) Synthesis and X-ray structure analysis of a heptacoordinate titanium(iv)-bis-chelate with enhanced in vivo antitumor efficacy. Chem Commun 48:5790–5792
12. Kuhn S, Spahn I, Scholten B, Coenen HH (2015) Positron and γ-ray intensities in the decay of ^{45}Ti. Radiochim Acta 103:403–409
13. Burrows TW (2008) Nuclear data sheets for A = 45. Nucl Data Sheets 109:171–296
14. Chaple LF, Lapi SE (2018) Production and use of the first-row transition metal PET radionuclides ^{43,44}Sc, ^{52}Mn, and ^{45}Ti. J Nucl Med 59:1655–1659
15. Sadeghi M, Enferadi M, Nadi H (2011) ^{45}Ti, a candidate for positron emission tomography: study of the cyclotron production. Radiochemistry 53:411–414
16. Fazaeli Y, Aboudzadeh M, Aardaneh K, Kakavand T, Bayat F, Yousefi K (2014) A new approach to targetry and cyclotron production of ^{45}Ti by proton irradiation of ^{45}Sc. Nucl Technol Radiat Prot 29:28–33
17. Kepp KP (2016) A quantitative scale of oxophilicity and thiophilicity. Inorg Chem 55:9461–9470
18. Kislik V (2002) Competetive complexation/solvation theory of solvent extraction. II. Solvent extraction of metals by acidic extractants. Sep Sci Technol 37:2623–2657
19. Vāvere AL, Laforest R, Welch MJ (2005) Production, processing and small animal PET imaging of titanium-45. Nucl Med Biol 32:117–122
20. Kislik V, Eyal A (1993) Acidity dependence of Ti(IV) extraction: a critical analysis. Solvent Extr Ion Exch 11:258
21. Gagnon K, Severin GW, Barnhart TE, Engle JW, Valdovinos HF, Nickles RJ (2012) ^{45}Ti extraction using hydroxamate resin. In: AIP conference proceedings , vol 1509, p 211
22. Severin GW, Nielsen CH, Jensen AI, Fonslet J, Kjær A, Zhuravlev F (2015) Bringing radiotracing to titanium-based antineoplastics: solid phase radiosynthesis, PET and ex vivo evaluation of antitumor agent [^{45}Ti](salan)Ti(dipic). J Med Chem 58:7591–7595
23. Pedersen KS, Imbrogno J, Fonslet J, Lusardi M, Jensen KF, Zhuravlev F (2018) Liquid–liquid extraction in flow of the radioisotope titanium-45 for positron emission tomography applications. React Chem Eng 3:898–904
24. Søborg Pedersen K, Baun C, Michaelsen Nielsen K, Thisgaard H, Ingemann Jensen A, Zhuravlev F (2020) Design, synthesis, computational, and preclinical evaluation of natTi/45Ti-labeled urea-based glutamate PSMA ligand. Molecules 25:1104
25. Bordbar H, Yousefi AA, Abedini H (2017) Production of titanium tetrachloride (TiCl4) from titanium ores: a review. Polyolefins J 4:149–173
26. Teyssandier F, Allendorf MD (1998) Thermodynamics and kinetics of gas-phase reactions in the Ti–Cl–H system. J Electrochem Soc 145:2167–2178
27. Herzler J, Roth P (2002) High-temperature decomposition of TiCl4 based on Cl-concentration measurements. Proc Combust Inst 29:1353–1359
28. Biltz W, Klemm W (1923) Über die elektrolytische Leitfähigkeit geschmolzenen Scandiumchlorids. Z für Anorg Allg Chem 131:22–26
29. Voigt A, Biltz W (1924) Über das elektrolytische Leitvermögen geschmolzener chloride. Z für Anorg Allg Chem 133:277–305
30. Spellerberg S, Scholten B, Spahn I, Bolten W, Holzgreve M, Coenen HH, Qaim SM (2015) Target development for diversified irradiations at a medical cyclotron. Appl Radiat Isot 104:106–112