SUPPLEMENTARY INFORMATION

Therapeutic efficacy of ^{211}At-radiolabeled 2,6-diisopropylphenyl azide in mouse models of human lung cancer

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Keywords: acrolein; aryl azide; dipolar cycloaddition; in vivo synthesis; targeted α-particle therapy

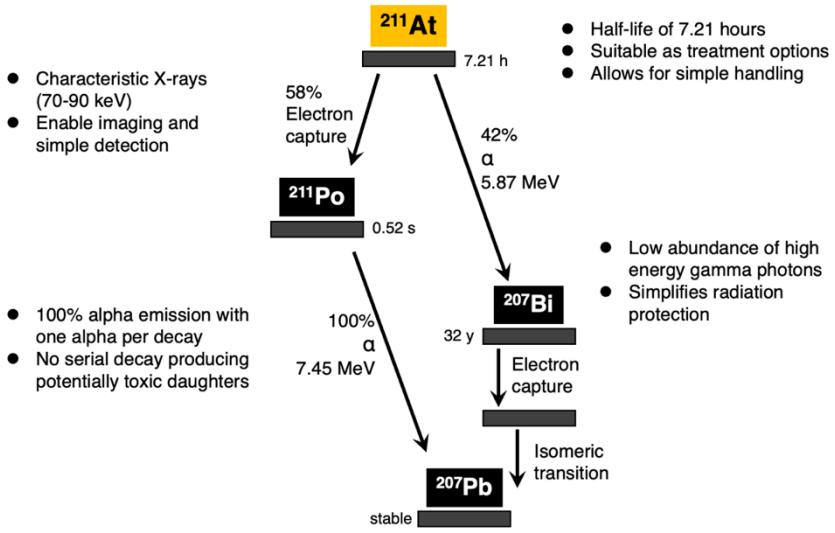


Fig. S1 Physical properties and scheme for the nuclear decay of ^{211}At.

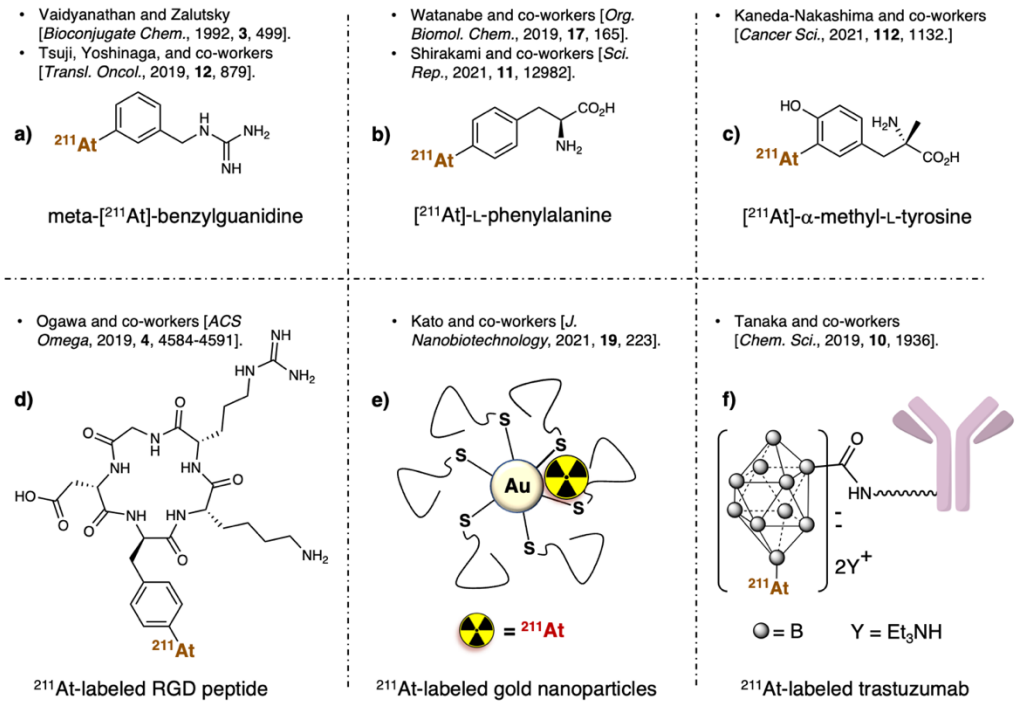


Fig. S2 (a) The meta-[^{211}At]-benzylguanidine shows an antitumor effect on pheochromocytoma xenograft tumors. (b) [^{211}At]-L-phenylalanine and (c) [^{211}At]-α-methyl-L-tyrosine have a high binding affinity for the cancer-specific L-type amino acid transporter 1 (LAT1). Other groups developed ^{211}At combined with (c) RGD peptide or (d) gold nanoparticles. (e) Previous work from our group to utilize ^{211}At-labeled trastuzumab.

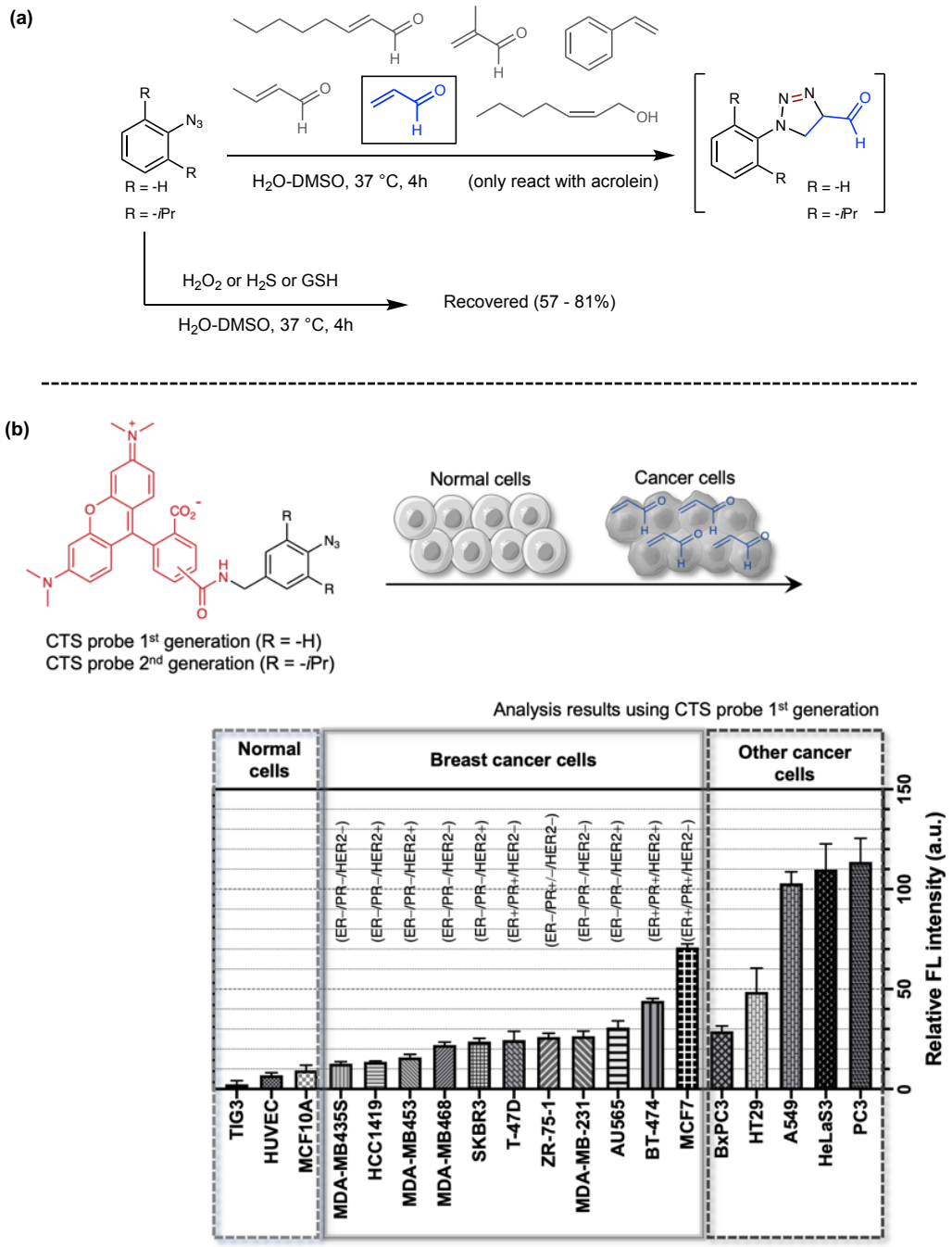


Fig. S3 (a) Our previous work (ACS Sens., 2016, 1, 623; *Chem. Sci*., 2021, **12**, 5438): phenyl azide reacts selectively towards acrolein under physiological conditions. No noticeable products were found when it was reacted with other α,β-unsaturated aldehydes (*e.g*., methacrolein, crotonaldehyde, *trans*-2-octenal) or reactive olefin (e.g., cis-2-heptanol, styrene). Furthermore, we found that phenyl azide is stable toward in vivo oxidating and reducing agents, such as H_2O_2, H_2S, and GSH. (b) Our previous work (*Adv. Sci*., 2019, **6**, 1801479; *Bull. Chem. Soc. Jpn.*, 2022, **95**, 421): acrolein levels in various human cells were determined using a CTS probe. The fluorescence intensity corresponds to the level of acrolein in cells.

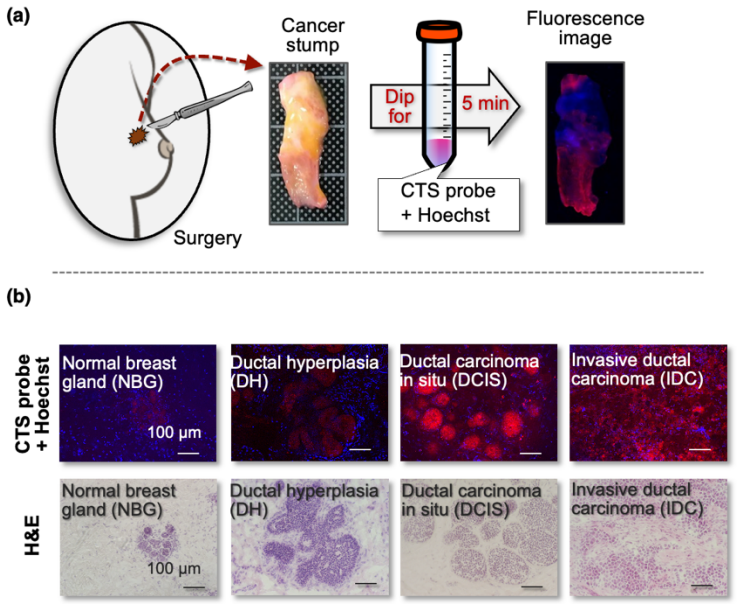
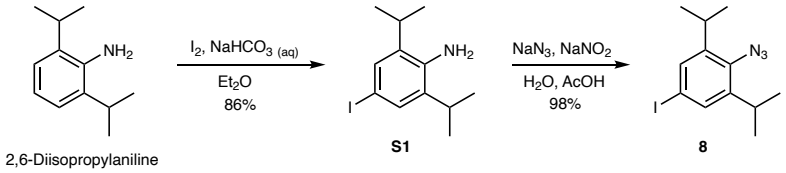


Fig. S4 Our previous work (*Adv. Sci.*, 2019, **6**, 1801479; *Eur. J. Surg. Oncol.*, 2022, **48**, 1520): (a) CTS probes distinguish cancer and normal tissue from patients with breast cancer with high selectivity and sensitivity. (b) Morphology of normal breast gland (NBG), ductal hyperplasia (DH), ductal carcinoma in situ (DCIS), and invasive ductal carcinoma (IDC) labeled with 20 μM of CTS probe 1st generation at 200x magnification. The cancer morphology detected was consistent with the morphology in images stained with H&E (hematoxylin and eosin) in frozen sections.

Chemical synthesis. All commercially available reagents were used without further purification. The preparative separation was performed by column chromatography on Merck Silica gel 60 (230–400 mesh). High-resolution mass spectrometry (HRMS) was recorded on micrOTOF-QIII. ^{1}H, ^{13}C, and ^{119}Sn NMR spectra were recorded on the Bruker Ascend 400 NMR spectrometer. Unless otherwise mentioned, $CDCl_3$ was used as a solvent, and chemical shifts were represented as δ-values relative to the internal standard TMS. Bu_3SnCl was used as a standard for the ^{119}Sn measurement, and its chemical shift was adjusted to 153.0 ppm (*Ref*: A. Ariza-Roldán, M. López-Cardoso, H. Tlahuext, G. Vargas-Pineda, P. Román-Bravo, M. Acevedo-Quiroz, P. Alvarez-Fitz and R. Cea-Olivares, *Inorg. Chim. Acta*, 2022, **534**, 120810). *Caution*: Azide-containing compounds are presumed to be potentially explosive. Although we have never experienced such an explosion with the azide compounds used in this study, all manipulations should be carefully carried out in a hood.

Synthesis of analog compound **8**

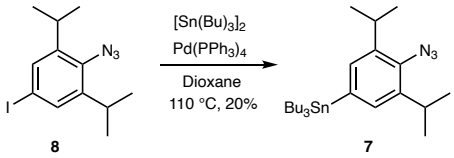


2,6-Diisopropylaniline **S1** **8**

*Synthesis of 4-iodo-2,6-diisopropylaniline **S1**:* Iodine (10.9 g, 42.8 mmol, 1.21 eq) was added to a solution of 2,6-diisopropylaniline (5.64 g, 35.2 mmol, 1.0 eq) in saturated aqueous $NaHCO_3$ and Et_2O (1:1) (350 mL, [2,6-diisopropylaniline] = 0.1 M). After being stirred for 40 minutes at ambient temperature, $Na_2S_2O_3{\cdot}H_2O$ (8.66 g) was added, and the mixture was stirred for 10 minutes. The resulting mixture was extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated to dryness under reduced pressure and then purified by smart flash column chromatography on silica gel using a gradient of eluents [n-hexane/EtOAc (49:1 to 77:23)] to give the desired 4-iodo-2,6-diisopropylaniline **S1** as a red-black oil (9.25 g, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.27 (s, 2H), 3.73 (bs, 2H, NH_2), 2.84 (hept, J = 6.7 Hz, 2H), 1.24 (d, J = 6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 140.23, 135.16, 131.87, 81.25, 28.02, 22.38; ESI-HRMS m/z calcd for $C_{12}H_{19}IN$ ($[M+H]^+$) 304.0557, found 304.0558.

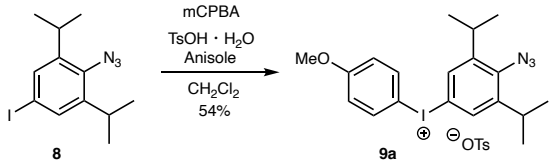
*Synthesis of analog compound **8**:* Sodium nitrite (539 mg, 7.82 mmol, 2.20 eq) was slowly added to a mixture of compound **S1** (1.08 g, 3.55 mmol, 1.0 eq) and sodium azide (461 mg, 7.09 mmol, 2.0 eq) dissolved in acetic acid and distilled water (6:1) (35 mL, [**S1**] = 0.1 M) at 0 °C. After stirring for 4 hours at 0 °C, a saturated aqueous solution of $NaHCO_3$ was added until the mixture achieved a pH of 7. The mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel using an eluent (n-hexane) to give the desired analog compound **8** as a yellow oil (1.14 g, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.42 (s, 2H), 3.28 (hept, J = 6.7 Hz, 2H), 1.24 (d, J = 6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ145.66, 135.47, 133.42, 92.42, 28.89, 23.49.

Synthesis of tributyltin precursor **7**

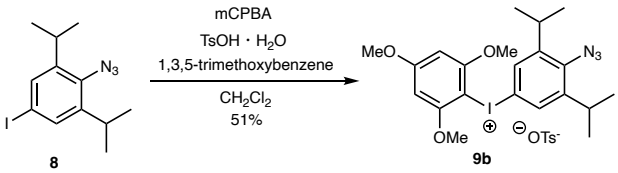


*Synthesis of tributyltin precursor **7***: Bis(tributyltin) (850 µL, 1.70 mmol, 1.14 eq) and $Pd(PPh_3)_4$ (50.5 mg, 0.04 mmol, 0.03 eq) were added to compound **8** (492 mg, 1.49 mmol, 1.00 eq) in anhydrous dioxane (8.4 mL, [**8**] = 0.18 M). The mixture was refluxed with stirring for 16 hours under an argon atmosphere. After cooling to ambient temperature, the suspension was filtered through Celite, and the filtrate was concentrated to dryness under reduced pressure. The obtained crude was filtered through silica gel (K_2CO_3 10 wt%) using an eluent (n-hexane) and then purified by reversed-phase HPLC to give the desired tributyltin precursor **7** as a colorless oil (139 mg, 20% yield). Conditions of reversed-phase HPLC (Shimadzu): Column, Cosmosil $5C_{18}$-AR-300 (Nacalai Tesque, Inc.) 4.6 × 250 mm; Mobile phase A, H_2O; B, MeCN; Flow rate 1 mL/min (Pump LC-20AD); UV detection at 254 nm (UV/vis detector SPD-20AV). Isocratic elution, 0-25 min at 100% B. The desired tributyltin precursor **7** was eluted at 14 minutes. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.20 (s, 2H), 3.34 (hept, J = 6.7 Hz, 2H), 1.59–1.50 (m, 6H), 1.39 – 1.30 (m, 6H), 1.28 (d, J = 6.9 Hz, 12H), 1.07–1.02 (m, 6H), 0.89 (t, J = 7.3 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 142.11, 140.29, 135.51, 132.07, 29.27, 28.94, 27.49, 23.72, 13.86, 9.86; ^{119}Sn NMR (149 MHz, $CDCl_3$, 25 °C) δ -44.90.

Synthesis of aryliodonium salt precursor **9a** and **9b**



*Synthesis of aryliodonium salt precursor **9a***: mCPBA (1.31 g, 5.25 mmol, 1.12 eq) was added to compound **8** (1.55 g, 4.69 mmol, 1.00 eq) in CH_2Cl_2 (47 mL, [**8**] = 0.1 M). After stirring for 4 hours at ambient temperature, TsOH·H_2O (1.01 g, 5.33 mmol, 1.14 eq) and anisole (1.00 mL, 9.25 mmol, 1.97 eq) were added. The mixture was stirred for another 30 minutes. The resulting mixture was extracted with $CHCl_3$ and washed with H_2O. The solution was removed azeotropically with toluene under reduced pressure. The obtained residue was washed with n-hexane and Et_2O to give the desired aryliodonium salt precursor **9a** as a white solid (1.55 g, 54%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.86 (d, J = 9.0 Hz, 2H), 7.62 (s, 2H), 7.57 (d, J = 8.2 Hz, 2H), 7.05 (d, 2H), 6.88 (d, J = 9.1 Hz, 2H), 3.82 (s, 3H), 3.26 (hept, J = 6.8 Hz, 2H), 2.31 (s, 3H), 1.17 (d, J = 6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 162.66, 147.36, 142.82, 139.57, 138.70, 137.30, 130.47, 128.61, 126.13, 117.69, 113.31, 103.80, 55.79, 29.41, 23.20, 21.42; ESI-HRMS m/z calc for $C_{19}H_{23}IN_3O$ ($[M]^+$) 436.0880, found 436.0884.



*Synthesis of aryliodonium salt precursor **9b***: mCPBA (464 mg, 1.85 mmol, 1.17 eq) was added to compound **8** (523 mg, 1.59 mmol, 1.00 eq) in CH_2Cl_2 (16 mL, [**8**] = 0.1 M). After stirring for 4 hours at ambient temperature, TsOH·H_2O (339 mg, 1.78 mmol, 1.12 eq) and 1,3,5-trimethoxybenzene (567 mg, 3.37 mmol, 2.12 eq) were added. The mixture was stirred for another 1 hour. The resulting mixture was extracted with $CHCl_3$ and washed with H_2O. The solution was removed azeotropically with toluene under reduced pressure. The obtained residue was washed with n-hexane and Et_2O to give the desired aryliodonium salt precursor **9b** (540 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.70 (d, J = 8.2 Hz, 2H), 7.66 (s, 2H), 7.09 (d, J = 7.8 Hz, 2H), 6.17 (s, 2H), 3.90 (s, 6H), 3.87 (s, 3H), 3.26 (hept, J = 6.8 Hz, 2H), 2.32 (s, 3H), 1.18 (d, J = 6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 167.08, 157.47, 146.91, 143.23, 139.40, 138.35, 130.22, 128.58, 126.19, 113.72, 107.57, 84.56, 56.95, 56.63, 29.36, 23.24, 21.43; ESI-HRMS m/z calc for $C_{21}H_{27}IN_3O_3$ ($[M]^+$) 496.1092, found 496.1092.

Production of ^{211}At (s*ee also Fig. S5*).

According to the procedure described,[1,2] the radioisotope of ^{211}At was produced in the nuclear reaction of ^{209}Bi(α,2n)^{211}At. A metallic ^{209}Bi target (chemical purity: > 99.999%, typical thickness: 20 mg cm^{-2}) was prepared by vacuum evaporation on an aluminum plate. The Bi target was placed at 15° inclines to the beam axis. The 29.0 MeV beam was delivered from the RIKEN AVF cyclotron; the beam energy on the center of the target surface was calculated to be 28.0 MeV with the SRIM-2013 program.[3] To obtain ^{211}At with a high radionuclidic purity, the beam energy was controlled to 28–29 MeV using electrostatic pickups to prevent the production of ^{210}At ($t_{1/2}$ = 8.1 hours), which decays to a highly toxic α emitter ^{210}Po ($t_{1/2}$ = 138 days). The typical beam intensities were 10–20 μA. During irradiation, the target was cooled with the circulating water (1.5 L min-1) and He Gas (30 L min-1). The beam axis was continuously rotated in a 3-mm diameter at 2 Hz to avoid local heating of the ^{209}Bi target using a waggling beam electromagnet on the beamline of the AVF cyclotron. The Bi targets were irradiated for several hours to produce a maximum of 1 GBq of ^{211}At.

After the irradiation, the ^{209}Bi target was placed on a copper tray in a quartz tube (28 mm i.d. $\times$ 200 mm length) and heated up to 850 °C using an electric furnace. ^{211}At sublimated from the target material was extracted from the quartz tube to a PFA tube (1 mm id $\times$ 1 m length) through a quartz capillary (2 mm i.d. $\times$ 130 mm length) with an O_2 gas flow at a flow rate of 10 mL min^{-1}. The PFA tube was cooled at –96 °C in ethanol to collect the gaseous ^{211}At. After distillation for 15 minutes at 850 °C, the quartz capillary was removed from the quartz tube. Subsequently, the inside of the quartz capillary and the PFA trap tube were washed with 300–400 μL of $CHCl_3$ to recover ^{211}At. The chemical yield of ^{211}At was determined by γ spectrometry using a Ge detector. The radionuclidic purity (Fig. S5) was determined by α-particle spectrometry (Si detector) and γ-ray spectrometry (Ge detector).[4]

The chemical yields of ^{211}At were approximately 80%. The radionuclidic purity of the ^{211}At solution was $>$ 99.9%, and the atomic ratio of ^{210}At/^{211}At was $< 1.0\times10^{-5}$ at the end of irradiation. Moreover, a maximum of 181 MBq of ^{211}At was used for the radiolabeling experiment. The obtained dry ^{211}At is pure, satisfies medical requirements, and is acceptable for clinical application.

Ref: (1) N. Sato, S. Yano, A. Toyoshima, H. Haba, Y. Komori, S. Shibata, K. Watanabe, D. Kaji, K. Takahashi and M. Matsumoto, *RIKEN Accel. Prog. Rep*., 2017, **50**, 262; (2) S. Yano, N. Sato, A. Toyoshima, H. Haba, Y. Komori, S. Shibata, K. Takahashi and M. Matsumoto, *RIKEN Accel. Prog. Rep*., 2017, **50**, 263; (3) J. F. Ziegler, M. D. Ziegler, J. P. Biersack, *Nucl. Instrum. Meth. Phys. Res. B*, 2010, **268**, 1818. (4) Y. Wang, N. Sato, T. Yokokita, D. Mori, S. Usuda and H. Haba, *RIKEN Accel. Prog. Rep*., 2019, **53**,192.

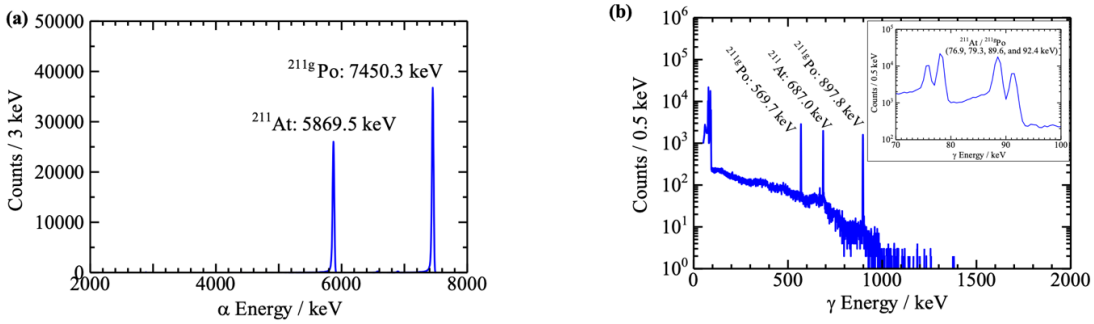
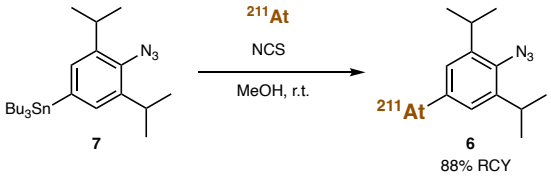


Fig. S5 Typical (a) α-ray and (b) γ-ray spectra of the purified ^{211}At from the ^{209}Bi target.

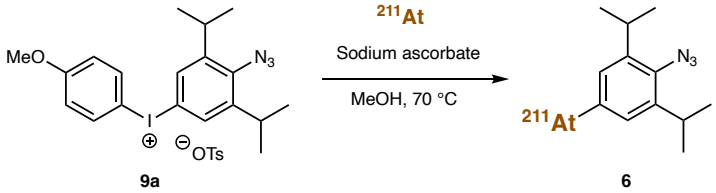
Synthesis of ADIPA **6** from tributyltin precursor **7**



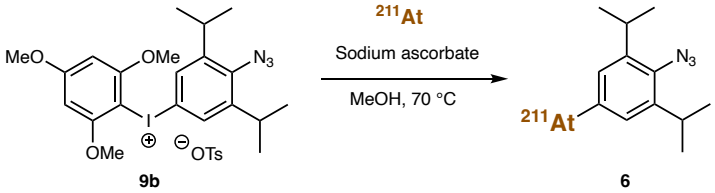
*Synthesis of ADIPA **6** (Fig. 2)*: A 300 μL of ^{211}At (88 MBq) in MeOH solution was divided equally into two portions. One portion of the solution (150 μL) was mixed with 50 μL of 40 mM NCS in MeOH to give 200 μL of $^{211}At^{+}$ solution (normalized radioactivity = 44 MBq) in MeOH. Subsequently, 50 μL of the $^{211}At^{+}$ solution (normalized radioactivity = 11.4 MBq) were moved into a 1.5 mL Eppendorf tube, mixed with 100 μL of 10 mM tributyltin precursor **7** in MeOH and 50 μL of 1% AcOH in MeOH, and then was incubated at ambient temperature for 30 minutes. The reaction mixture was purified by reversed-phase HPLC to give ADIPA **6** (normalized radioactivity = 10.1 MBq, 88% RCY). The radioactivity levels were determined using a Ge detector by determining the counting rates for the most abundant γ-rays emitted in the decay of ^{211}At and its daughter, ^{211}Po. Reversed-phase HPLC systems: pump LC-20AD, autosampler SIL-20AC, PDA detector SPD-M20A(Shimadzu), and γ detector GABI Star. Condition of reversed-phase HPLC: Column, Cosmosil 5C_{18}-AR300 (Nacalai Tesque, Inc.) 4.6 x 250 mm; Mobile phase A, H_2O; B, MeCN; Gradient elution, 0–1 min at 80% B, 1–5 min at 80–100% B, 5–18 min at 100% B; Flow rate at 1 mL/min; UV detection at 254 nm. ADIPA **6** was eluted at 12 minutes.

*Preparation of ADIPA **6** for animal experiments (Fig. 3)*: To the 160 μL of ^{211}At (167 MBq) in MeOH solution was added 50 μL of 40 mM NCS in MeOH, 50 μL of 20 mM tributyltin precursor **7** in MeOH, and 40 μL of 1% AcOH in MeOH. The mixture was stirred for 40 minutes at ambient temperature. Approximately 150 μL of the solution (normalized radioactivity = 90 MBq) was purified by reversed-phase HPLC. The obtained fraction was evaporated by using GBCS-mini-I, Techno Sigma (40 °C, 90 minutes) to give ADIPA **6** (normalized radioactivity = 63.2 MBq, 70% RCY; real-time radioactivity = 38.4 MBq). Subsequently, the purified product was dissolved in DMSO : Tween 80 : PBS (192.2 μL : 9.6 μL : 172.0 μL) to give 1.92 mL of ADIPA **6** (real-time radioactivity: 38.4 MBq) ready to be used for animal experiments. Other radioactivity concentrations of ADIPA **6** solution for animal experiments were prepared from this solution by further dilution with an appropriate volume of DMSO : Tween 80 : PBS (10 : 0.5 : 89.5) solution. All radioactivity measurements were corrected for decay.

Synthesis of ADIPA **6** from *aryliodonium salt **9a** or **9b*** (*see also Fig. S6*)



*Synthesis of ADIPA **6** from aryliodonium salt precursor **9a***: A 300 μL of ^{211}At (88 MBq) in MeOH solution was divided equally into two portions. One portion of the solution (150 μL) was mixed with 150 μL of 20 mM sodium ascorbate in H_2O to give 300 μL of $^{211}At^-$ solution (normalized radioactivity = 44 MBq) in 50% MeOH. Subsequently, 50 μL of the $^{211}At^-$ solution (normalized radioactivity = 7.19 MBq) were moved into a 1.5 mL Eppendorf tube, mixed with 100 μL of 10 mM aryliodonium salt precursor **9a** in MeOH and 50 μL MeOH, and then was incubated at 70 °C for 30 minutes. The reaction mixture was purified by reversed-phase HPLC to give ADIPA **6** (41% RCY).



*Synthesis of ADIPA **6** from aryliodonium salt precursor **9b***: A 300 μL of ^{211}At (88 MBq) in MeOH solution was divided equally into two portions. One portion of the solution (150 μL) was mixed with 150 μL of 20 mM sodium ascorbate in H_2O to give 300 μL of $^{211}At^-$ solution (normalized radioactivity = 44 MBq) in 50% MeOH. Subsequently, 50 μL of the $^{211}At^-$ solution (normalized radioactivity = 7.22 MBq) were moved into a 1.5 mL Eppendorf tube, mixed with 100 μL of 10 mM aryliodonium salt precursor **9b** in MeOH and 50 μL MeOH, and then was incubated at 70 °C for 30 minutes. The reaction mixture was purified by reversed-phase HPLC to give ADIPA **6** (48% RCY).

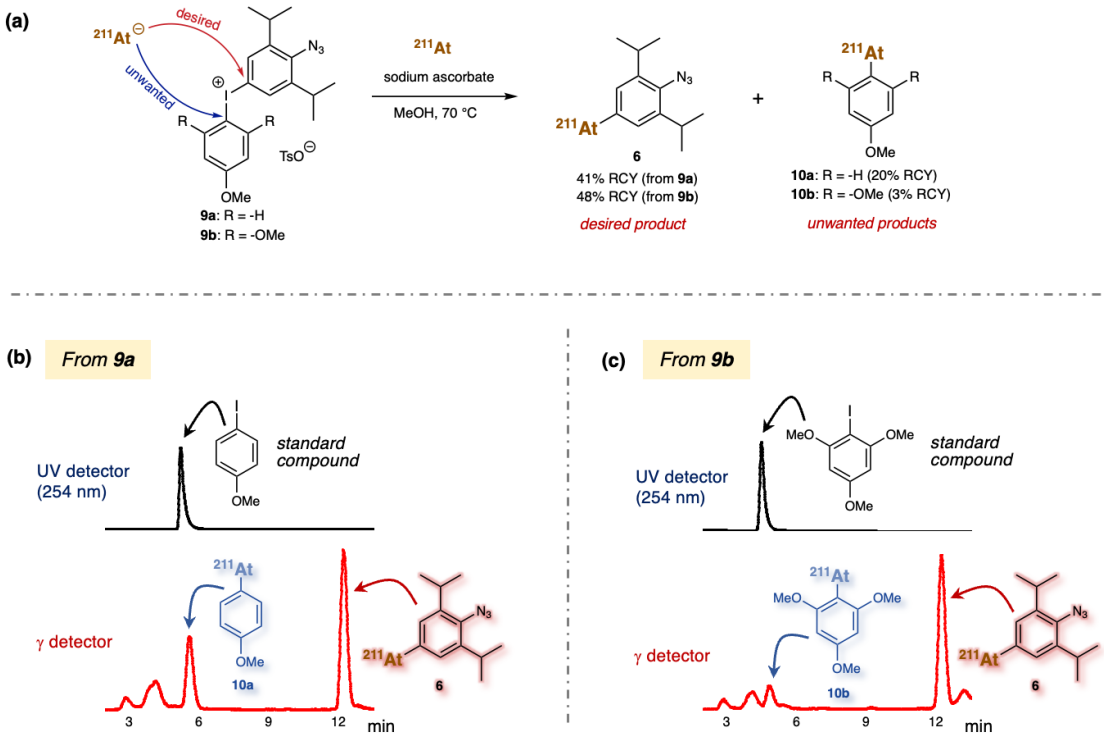
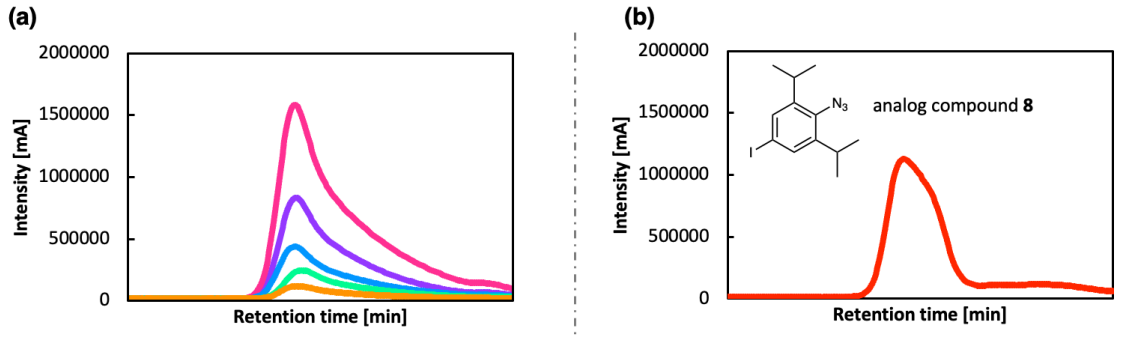


Fig. S6 Nucleophilic substitution of aryliodonium salts **9a** or **9b** with At^- species gave the desired ADIPA **6** and unwanted product **10a** or **10b**, respectively. The presence of unwanted products **10a** and **10b** were confirmed by comparing the retention time of HPLC analysis with the standard compounds. Condition of reversed-phase HPLC: Column, Cosmosil 5C_{18}-AR300 (Nacalai Tesque, Inc.) 4.6 x 250 mm; Mobile phase A, H_2O; B, MeCN; Gradient elution, 0–1 min at 80% B, 1–5 min at 80–100% B, 5–18 min at 100% B; Flow rate at 1 mL/min; γ detector GABI Star; UV detection at 254 nm. The radioactivity levels were determined using a Ge detector by determining the counting rates for the most abundant γ-rays emitted in the decay of ^{211}At.

Solubility test (*see Fig. S7*).

The solubility of ADIPA **6** in PBS (10% DMSO, 0.5% Tween 80) was examined by analogy to the solubility of compound **8** in the solvent systems. The analog compound **8** (2.4 mM) in PBS (10% DMSO, 0.5% Tween 80) was subjected to reversed-phase HPLC analysis. The solubility of compound **8** solutions was determined by comparing the observed chromatogram peak area to the calibration curve. The calibration curve was obtained from the HPLC analysis of the various concentration of compound **8** in DMF. The calibrated concentration of the treated compound **8** is similar to the prepared 2.4 mM solution in PBS (10% DMSO, 0.5% Tween 80), suggesting a good solubility of compound **8** in the solvent systems. This result indicates that ADIPA **6** has good solubility in PBS (10% DMSO, 0.5% Tween 80).



	Concentration (mM)	Peak area
Standard (compound **8** in DMF)	- 5 mM	36783950
	- 2.5 mM	18074965
	- 1.25 mM	9372938
	- 0.625 mM	5030848
	- 0.3125 mM	2331233
- Compound **8** in PBS (10% DMSO, 0.5% Tween 80)		17509808

Fig. S7 (a) HPLC analysis of the various concentrations of compound **8** in DMF. (b) HPLC analysis of the prepared compound **8** in PBS (10% DMSO, 0.5% Tween 80). (c) Peak area data of the HPLC analysis. (d) The calibrated concentration of the treated compound **8** is similar to the prepared 2.4 mM solution in PBS (10% DMSO, 0.5% Tween 80). Condition of reversed-phase HPLC: Column, Cosmosil 5C_{18}-AR300 (Nacalai Tesque, Inc.) 4.6 x 250 mm; Mobile phase A, H_2O; B, MeCN; Gradient elution, 0–1 min at 80% B, 1–5 min at 80–100% B, 5–18 min at 100% B; Flow rate at 1 mL/min; UV detection at 254 nm.

Stability test for ADIPA 6 (*See Fig. S8*).

*Stability of ADIPA **6** in PBS*: The ADIPA **6** (3.68 MBq/mL) in PBS (10% DMSO, 0.5% Tween 80, 1% sodium ascorbate) was incubated at 37 °C. At various time intervals (0.5, 1, 1.5, 2, and 15 hours), the solution was subjected to reversed-phase HPLC analysis.

*Stability of ADIPA **6** in mouse serum*: 20% mouse serum (77% PBS, 2% DMSO, 1% sodium ascorbate) was used to prepare ADIPA **6** (0.20 MBq/mL). The solutions were incubated at 37 °C for certain periods (0.5 and 15 hours). Then, the incubation was stopped by adding MeOH, the mixtures were centrifuged (HITACHI himacCT15, 4 °C, 14000xg, 15 minutes), and the resulting supernatants were subjected to reversed-phase HPLC analysis. *Conditions of the HPLC*: Column, Cosmosil 5C_{18}-AR300 (Nacalai Tesque, Inc.) 4.6 x 250 mm; mobile phase A, 0.1% TFA in H_2O; mobile phase B, 0.1% TFA in CH_3CN; gradient elution, 0–1 min at 80% B, 1–5 min at 80–100% B, 5–18 min at 100% B; flow rate at 1 mL/min; γ detector GABI Star. The ADIPA **6** was eluted at 12 minutes.

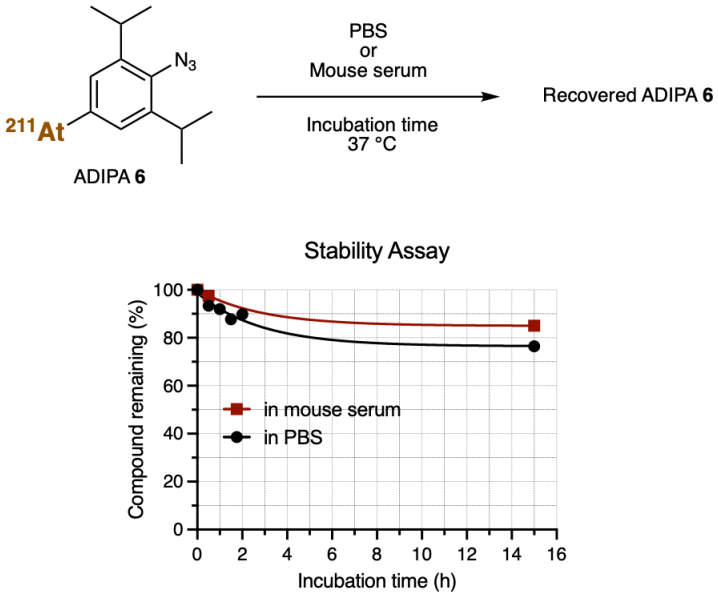


Fig. S8 The ADIPA **6** was incubated at 37 °C in PBS and mouse serum. At specific time intervals, the samples were analyzed using RP-HPLC, and the peak areas on the chromatogram were measured to observe compound degradation. The results showed that the ADIPA **6** remained stable even when incubated in PBS (76% at 15 h) or mouse serum (85% at 15 h).

Cellular uptake assay for ADIPA 6 (*see Fig. S9*).

A549 cell was seeded in 24-well plates (200,000 cells/well) and incubated for 24 h. The cultured medium was aspirated, and cells were washed with 2% DMSO/DMEM containing 1 w/v% sodium ascorbate (500 µL). The cells were treated with 4 kBq/500 µL of ADIPA **6** and incubated for 10, 60, 120, and 240 min at 37 °C. The supernatant was collected, and the cells were washed thrice with 2% DMSO/DMEM containing 1 w/v% sodium ascorbate (500 µL). The cells were then lysed with 1 mL lysis buffer (1 w/v% SDS in 200 mM NaOH aq., 1 mL) for 15 min at 37 °C. The lysate was collected by scrapping the wells and washed with 2% DMSO/DMEM containing 1 w/v% sodium ascorbate (500 µL) twice. The radioactivity levels of the lysate were measured using a Ge detector by determining the counting rates for the most abundant γ-rays emitted in the decay of ^{211}At. All radioactivity measurements were corrected for decay.

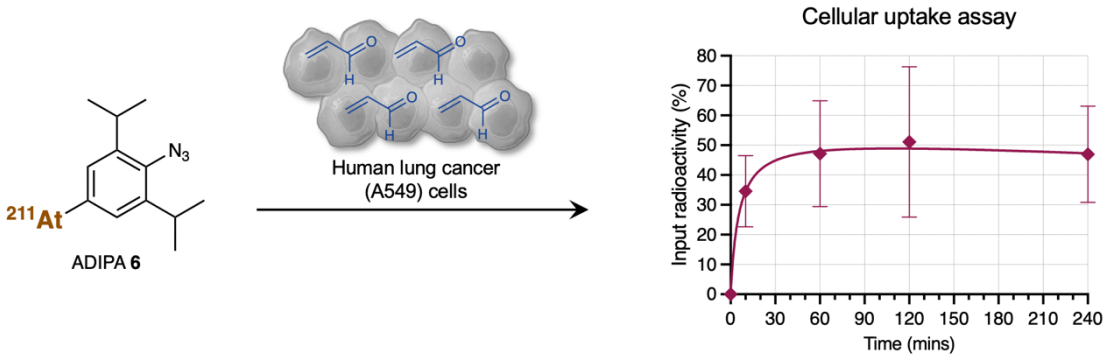
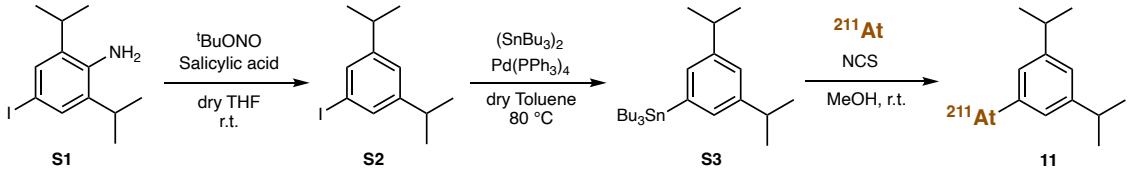


Fig. S9 Cellular uptake of the ADIPA **6** to the A549 cells was determined by measuring the radioactivity levels of the lysate. The results indicated that ADIPA **6** is easily taken up by cells, with a rate of 35% in just 10 minutes of incubation, and increased to 47% after 60 minutes.

Synthesis of 3,5-diisopropylphenyl astatine **11**



*Synthesis of 3,5-diisopropyphenyl iodine **S2***: ^{t}BuONO (489 μL, 4.22 mmol, 1.20 eq) and salicylic acid (48.7 mg, 0.352 mmol, 0.10 eq) were added to compound **S1** (1.07 g, 3.52 mmol, 1.00 eq) in dry-THF (11.7 mL, [**S1**] = 0.1 M). The reaction mixture was stirred under an argon atmosphere at ambient temperature for 4 hours. The resulting mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated to dryness under reduced pressure. The crude was used for the next reaction without further purification. A small portion was purified by HPLC for NMR measurements. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.38 (d, J = 1.6 Hz, 2H), 7.01 (t, J = 1.6 Hz, 1H), 2.81 (hept, J = 6.6 Hz, 2H), 1.22 (d, J = 6.9 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 151.36, 133.10, 124.54, 94.86, 34.13, 24.03. (*Ref*: D. Felipe-Blanco, F. Alonso and J. C. Gonzalez-Gomez, *Adv. Synth. Catal*., 2017, **359**, 2857).

*Synthesis of tributyltin precursor **S3***: Bis(tributyltin) (2.72 mL, 5.43 mmol, 3.00 eq) and $Pd(PPh_3)_4$ (66.7 mg, 0.0577 mmol, 0.032 eq) were added to the crude of compound **S2** (522 mg, 1.81 mmol, 1.00 eq) in dry-toluene (3.6 mL, [**S2**] = 0.50 M). The mixture was stirred for 3 hours under an argon atmosphere. After cooling to ambient temperature, the suspension was filtered through Celite, and the filtrate was concentrated to dryness under reduced pressure. The obtained crude was filtered through silica gel (K_2CO_3 10 wt%) and washed using n-hexane and then purified by reversed-phase HPLC to give the desired tributyltin precursor **S3** as a colorless oil (43.3 mg, 6% yield) Conditions of reversed-phase HPLC (Shimadzu): Column, Cosmosil 5C_{18}-AR-300 (Nacalai Tesque, Inc.) 20 × 250 mm; Mobile phase A, H_2O; B, MeCN; Flow rate 10 mL/min (Pump LC-20AP); UV detection at 254 nm (UV/vis detector SPD-20AV). Isocratic elution, 0-35 min at 100% B. The desired tributyltin precursor **S3** was eluted at 30 minutes. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.14 (d, J = 1.8 Hz, 2H), 7.02 (t, J = 1.8 Hz, 1H), 2.88 (hept, J = 6.6 Hz, 2H), 1.62 – 1.52 (m, 6H), 1.40 – 1.31 (m, 6H), 1.27 (d, J = 6.9 Hz, 12H), 1.11 – 1.00 (m, 6H), 0.91 (t, J = 7.3 Hz, 9H); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ 147.98, 141.71, 132.23, 124.51, 34.36, 29.30, 27.55, 24.26, 13.86, 9.74; ^{119}Sn NMR (149 MHz, $CDCl_3$, 25 °C) δ -47.96.

*Synthesis and preparation of 3,5-diisopropylphenyl astatine **11** for animal experiments (Figs. S10 and S14)*: To the 150 μL of ^{211}At (9.5 MBq) in MeOH solution was added 50 μL of 40 mM NCS in MeOH, 50 μL of 20 mM tributyltin precursor **S3** in MeOH, and 40 μL of 1% AcOH in MeOH. The mixture was stirred for 30 minutes at ambient temperature. 190 μL of the solution (normalized radioactivity = 9.5 MBq) was purified by reversed-phase HPLC. The obtained fraction was evaporated by using GBCS-mini-I, Techno Sigma (40 °C, 50 minutes) to give 3,5-diisopropylphenyl astatine **11** (normalized radioactivity = 8.3 MBq, 87% RCY; real-time radioactivity = 6.0 MBq). Subsequently, the purified product was dissolved in DMSO : Tween 80 : PBS (85.2 μL : 4.26 μL : 763 μL) to give 852 μL of 3,5-diisopropylphenyl astatine **11** (real-time radioactivity: 8.3 MBq) ready to be used for animal experiments. Other radioactivity concentrations of 3,5-diisopropylphenyl astatine **11** solutions for animal experiments were prepared from this solution by further dilution with an appropriate volume of DMSO : Tween 80 : PBS (10 : 0.5 : 89.5) solution. Reversed-phase HPLC systems: pump LC-20AD, autosampler SIL-20AC, PDA detector SPD-M20A(Shimadzu), and γ detector GABI Star. Condition of reversed-phase HPLC: Column, Cosmosil 5C_{18}-AR300 (Nacalai Tesque, Inc.) 4.6 x 250 mm; Mobile phase A, H_2O; B, MeCN; Gradient elution, 0–1 min at 80% B, 1–5 min at 80–100% B, 5–18 min at 100% B; Flow rate at 1 mL/min; UV detection at 254 nm. The 3,5-diisopropylphenyl astatine **11** was eluted at 11 minutes.

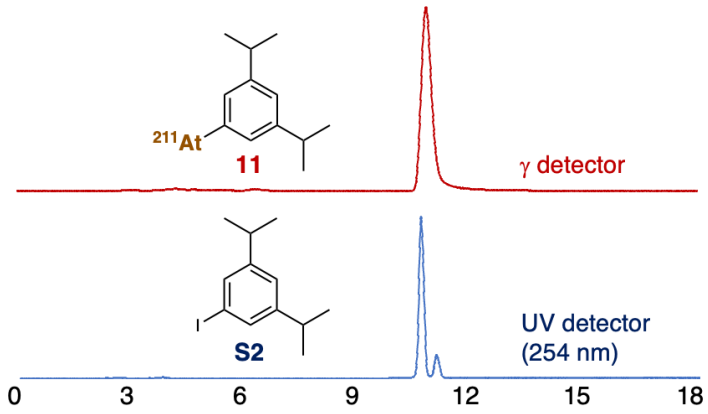


Fig. S10 HPLC analysis of synthesized 3,5-diisopropylphenyl astatine **11** (red line, monitored by the γ detector) and analog compound (3,5-diisopropyphenyl iodine) **S2** (blue line, monitored by UV detector at 254 nm) shows identical retention time (11 minutes). Condition of reversed-phase HPLC: Column, Cosmosil 5C_{18}-AR300 (Nacalai Tesque, Inc.) 4.6 x 250 mm; Mobile phase A, H_2O; B, MeCN; Gradient elution, 0–1 min at 80% B, 1–5 min at 80–100% B, 5–18 min at 100% B; Flow rate at 1 mL/min; γ detector GABI Star; UV detection at 254 nm. The radioactivity levels were determined using a Ge detector by determining the counting rates for the most abundant γ-rays emitted in the decay of ^{211}At.

Stability test for 3,5-diisopropylphenyl astatine 11 (*see Fig. S11*).

*Stability of 3,5-diisopropylphenyl astatine **11** in PBS*: The compound **11** (0.57 MBq/mL) in PBS (10% DMSO, 0.5% Tween 80, 1% sodium ascorbate) was incubated at 37 °C. At various time intervals (0.5, 1, 1.5, 2, and 15 hours), the solution was subjected to reversed-phase HPLC analysis.

*Stability of 3,5-diisopropylphenyl astatine **11** in mouse serum*: Mouse serum diluted to 20% (v/v) in PBS : DMSO (78 : 2) was used to prepare compound **11** (0.25 MBq/mL). The solutions were incubated at 37 °C for certain periods (0.5 and 15 hours). The incubation was stopped by adding MeOH, the mixtures were centrifuged (HITACHI himacCT15, 4 °C, 14000xg, 15 minutes), and the resulting supernatants were subjected to reversed-phase HPLC analysis. *Conditions of the HPLC*: Column, Cosmosil 5C_{18}-AR300 (Nacalai Tesque, Inc.) 4.6 x 250 mm; mobile phase A, 0.1% TFA in H_2O; mobile phase B, 0.1% TFA in CH_3CN; gradient elution, 0–1 min at 80% B, 1–5 min at 80–100% B, 5–18 min at 100% B; flow rate at 1 mL/min; γ detector GABI Star. *Compound **11*** was eluted at 11 minutes. All radioactivity measurements were corrected for decay.

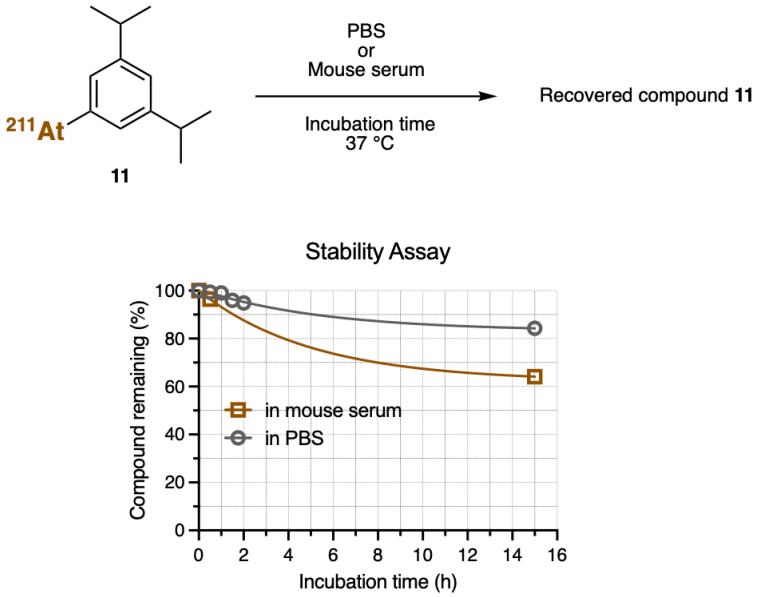


Fig. S11 The 3,5-diisopropylphenyl astatine **11** was incubated at 37 °C in PBS and mouse serum. At specific time intervals, the samples were analyzed using RP-HPLC, and the peak areas on the chromatogram were measured to observe compound degradation. The results showed that the 3,5-diisopropylphenyl astatine **11** remained stable even when incubated in PBS (84% at 15 h) or mouse serum (64% at 15 h).

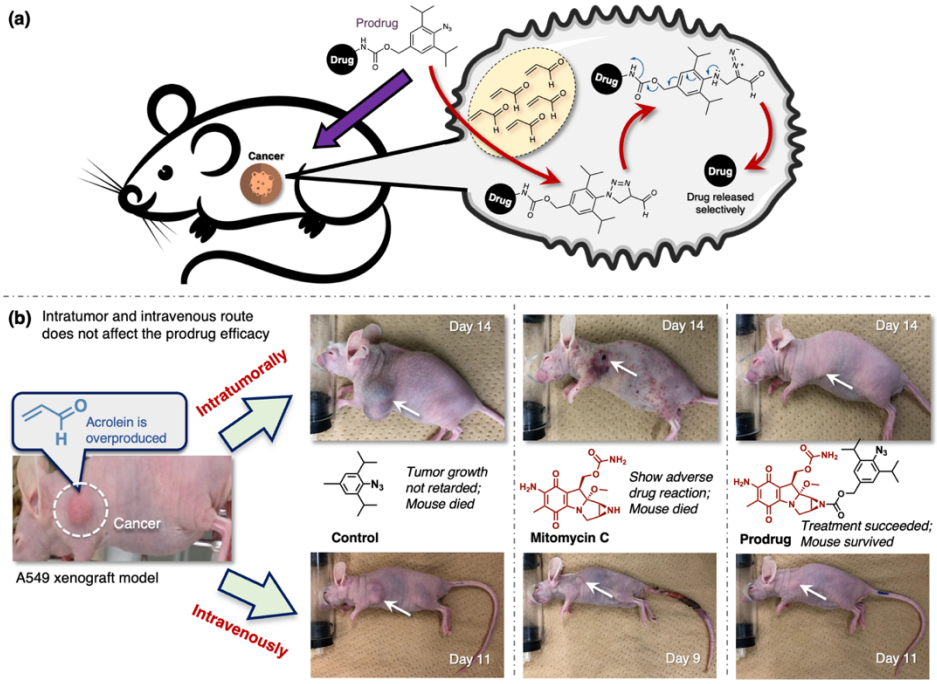


Fig. S12 (a) Our previously reported prodrug activation strategy in living mice (*Chem. Sci.*, 2021, **12**, 5438). (b) A549 cell-bearing xenograft nude mice were treated intratumorally or intravenously with control compound, mitomycin C (toxic drug), and prodrug. The prodrug showed high selectivity in treating cancer. Moreover, differences in administration (intratumoral or intravenous injection) do not affect its efficacy.

Animal experiments.

All animal experiments were approved by RIKEN's Animal Ethics Committee (W2019-2-049). For all injections and tumor measurements, mice were anesthetized with 2% isoflurane in oxygen at a 2.5–3.0 L/minute flow rate.

Statistics: All quantitative results are expressed as mean and standard deviation. Indicators of statistical significance were unpaired two-tailed Student's t-test or two-way analysis of variance (ANOVA) with Tukey's correction for multiple comparisons analyses. All statistical analyses were performed using a GraphPad PRISM (version 9.5.1, GraphPad Software, Inc., California, USA). Statistical significance was defined as a *P*-value < 0.05.

Cell lines and reagents: A549 cells were obtained from our stock kept in liquid nitrogen. They were cultured in Dulbecco's Modified Eagle's medium (DMEM) (Wako-Fujifilm, Japan) supplemented with 10% fetal bovine serum (FBS) (Biowest, France) and 1% penicillin-streptomycin (Gibco, Saint Aubin, France). The cells were then incubated at 37 °C in a 5% CO_2 humidified atmosphere.

A549-bearing mice xenograft models (*see also Fig. S13*)*:* The A549 (human lung) cancer xenograft tumors were established in 5-week-old female nude mice (BALB/cAJcl-nu/nu) by subcutaneous injection of 7.66 x 10^6 cells in 100 µL of cold 50% Matrigel in unnourished DMEM into the right shoulder. Tumor growth was then monitored. The mice were kept in a controlled temperature, salinity, and aeration room with sufficient food and water for 12 h a day and 12 h a night. After the tumor reached 150–250 mm^3 (approximately 24 days), the A549 tumor-bearing mice were ready for radiotherapy.

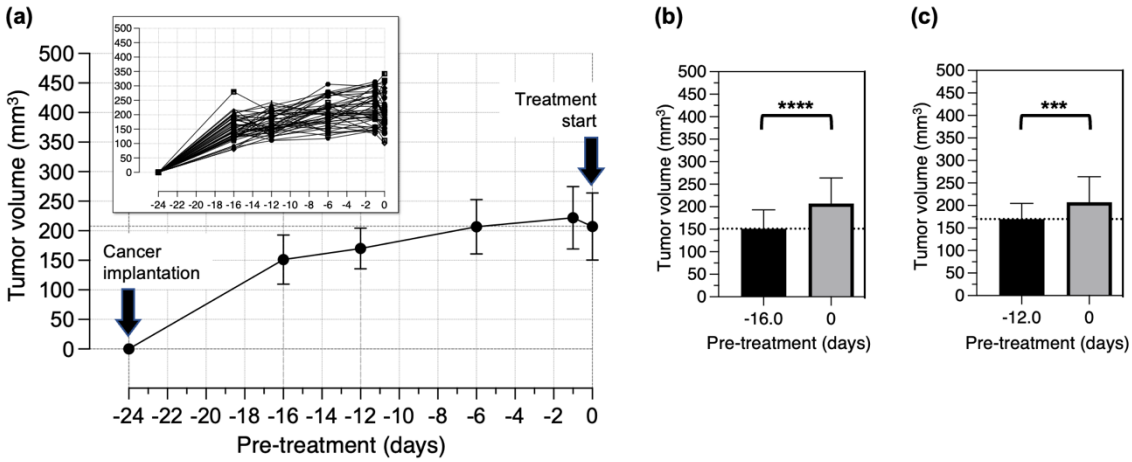


Fig. S13 (a) Tumor growth plots for A549 (human lung) cancer implanted in the nude mouse. The main graph presents the mean value (±SD) of relative tumor growth for 45 mice implanted with 7.66 x 10^6 cells in 100 µL. The inset presents the individual relative tumor growth for each of the 45 mice. (b) Intragroup comparison at day -16 and 0 before treatment. (c) Intragroup comparison at day -12 and 0 before treatment. P value is determined using a two-tailed Student's test. $^{***}P < 0.001$, $^{****}P < 0.0001$.

*Treatment of tumor-bearing mice with 70 kBq of ADIPA **6** (intratumorally and intravenously), 200 kBq of Na[^{211}At], and vehicle (see Fig. 3, Fig. S16, Fig. S17, Table S1, and Table S2):* The mice were randomized into four groups (double-blind) and treated with the corresponding compound or control. The first group was intratumorally injected with 10 μL of PBS (10% DMSO, 0.5% Tween 80) (n = 6) as vehicle control. The second group was intratumorally injected with 10 μL of 200 kBq Na[^{211}At] (n = 6). The third group was intratumorally injected with 10 μL of 70 kBq of ADIPA **6** (n = 6). Finally, the fourth group was intravenously injected with 100 μL of 70 kBq of ADIPA **6** (n = 6). The mice's tumor volume and body weight were recorded within a specific time period using the equation $V = W^2 \times L / 2$, where W and L represented the minor and major lengths of the tumor, respectively. When the tumor reached 2000 mm^3, the mice were sacrificed, and survival rates were calculated using the Kaplan-Meier method.

Table S1 Two-way ANOVA with Tukey's correction was performed to test group tumor growth differences. The difference between the vehicle-treated and ADIPA **6**-treated groups was significant starting eight days after treatment. The considerable increase continued throughout the experiment (see manuscript Fig. 3b). Vehicle = PBS (10% DMSO, 0.5% Tween 80). n.s. = not significant.

Post-treatment (days)	Vehicle (intratumorally) vs ADIPA **6** (70 kBq, intratumorally)		Vehicle (intratumorally) vs ADIPA **6** (70 kBq, intravenously)		ADIPA **6** (70 kBq, intratumorally) vs ADIPA **6** (70 kBq, intravenously)	
	Summary	Adjusted *P* value	Summary	Adjusted *P* value	Summary	Adjusted *P* value
1	n.s.	0.9870	n.s.	0.8466	n.s.	0.9632
2	n.s.	0.9948	n.s.	0.9605	n.s.	0.9946
3	n.s.	0.9737	n.s.	0.9597	n.s.	0.9999
6	n.s.	0.6453	n.s.	0.5970	n.s.	0.9998
7	n.s.	0.1181	n.s.	0.1051	n.s.	>0.9999
8	**	0.0051	**	0.0019	n.s.	0.9922
9	***	0.0006	***	0.0009	n.s.	0.9994
10	***	0.0003	***	0.0006	n.s.	0.9990
12	****	<0.0001	****	<0.0001	n.s.	0.9903
14	****	<0.0001	****	<0.0001	n.s.	0.9980
16	****	<0.0001	****	<0.0001	n.s.	0.9987
19	****	<0.0001	****	<0.0001	n.s.	0.7919
21	****	<0.0001	****	<0.0001	n.s.	0.3064
23	****	<0.0001	****	<0.0001	n.s.	0.2182
26	****	<0.0001	****	<0.0001	**	0.0072

Table S2 Two-way ANOVA with Tukey's correction was performed to test group tumor growth differences. The difference between the Na[^{211}At]-treated group and ADIPA **6** treated group was significant starting 12 days after treatment, and the considerable increase continued throughout the experiment (see manuscript Fig. 3b). Vehicle = PBS (10% DMSO, 0.5% Tween 80). n.s. = not significant.

Post-treatment (days)	Na[^{211}At] (intratumorally) vs ADIPA **6** (70 kBq, intratumorally)		Na[^{211}At] (intratumorally) vs ADIPA **6** (70 kBq, intravenously)		Na[^{211}At] (200 kBq, intratumorally) vs Vehicle (intratumorally)	
	Summary	Adjusted *P* value	Summary	Adjusted *P* value	Summary	Adjusted *P* value
1	n.s.	0.9861	n.s.	0.8431	n.s.	>0.9999
2	n.s.	0.8837	n.s.	0.7600	n.s.	0.9617
3	n.s.	0.8643	n.s.	0.8317	n.s.	0.9852
6	n.s.	0.6472	n.s.	0.5988	n.s.	>0.9999
7	n.s.	0.5386	n.s.	0.5060	n.s.	0.8119
8	n.s.	0.5258	n.s.	0.3567	n.s.	0.1989
9	n.s.	0.2903	n.s.	0.3539	n.s.	0.1378
10	n.s.	0.1076	n.s.	0.1473	n.s.	0.2673
12	*	0.0308	n.s.	0.0688	n.s.	0.1322
14	*	0.0180	*	0.0301	n.s.	0.2467
16	**	0.0010	**	0.0018	n.s.	0.4090
19	***	0.0002	**	0.0067	n.s.	0.1129
21	****	<0.0001	****	<0.0001	n.s.	0.6586
23	****	<0.0001	****	<0.0001	*	0.0121
26	****	<0.0001	****	<0.0001	*	0.0184

Biodistribution studies (see Fig. 3f): Na[^{211}At] (200 kBq) or ADIPA **6** (70 kBq) was administered to the mouse via intratumoral (n = 3) or intravenous (n = 3) injection. After 18 h, the mice were sacrificed, and the organs or tissues of interest were harvested and weighed. Then the distributed radioactivity was quantified using a Ge detector by determining the counting rates for the most abundant γ-rays emitted in the decay of ^{211}At. The radioactivity of each sample was presented as a percentage of the injected dose per gram of tissue (%ID/g). All radioactivity measurements were corrected for decay.

Treatment of tumor-bearing mice with control compounds (see Figs. S14 and S17): The mice were randomized (double-blind) into two groups and treated with the corresponding compounds. The first group was intratumorally injected with 10 µL of 70 kBq 3,5-diisopropylphenyl astatine **11** (n = 6). The second group was intratumorally injected with 5 µL of 2,6-diisopropylphenyl azide **1** [120 nmol in saline (10% DMSO, 40% EtOH), 1.2 mg/kg, n = 6], then one hour later intravenously injected with 100 µL of 70 kBq ADIPA **6**. The mice's tumor volume and body weight were recorded within a specific time period using the equation $V = W^2 \times L/2$, where W and L represented the minor and major lengths of the tumor, respectively. When the tumor reached 2000 mm^3, the mice were sacrificed, and survival rates were calculated using the Kaplan-Meier method. The result was compared to the group treated with 10 µL of 200 kBq Na[^{211}At] (see also Fig. 3). 2,6-diisopropylphenyl azide **1** was prepared according to the previously reported method (*Chem. Sci.*, 2021, **12**, 5438).

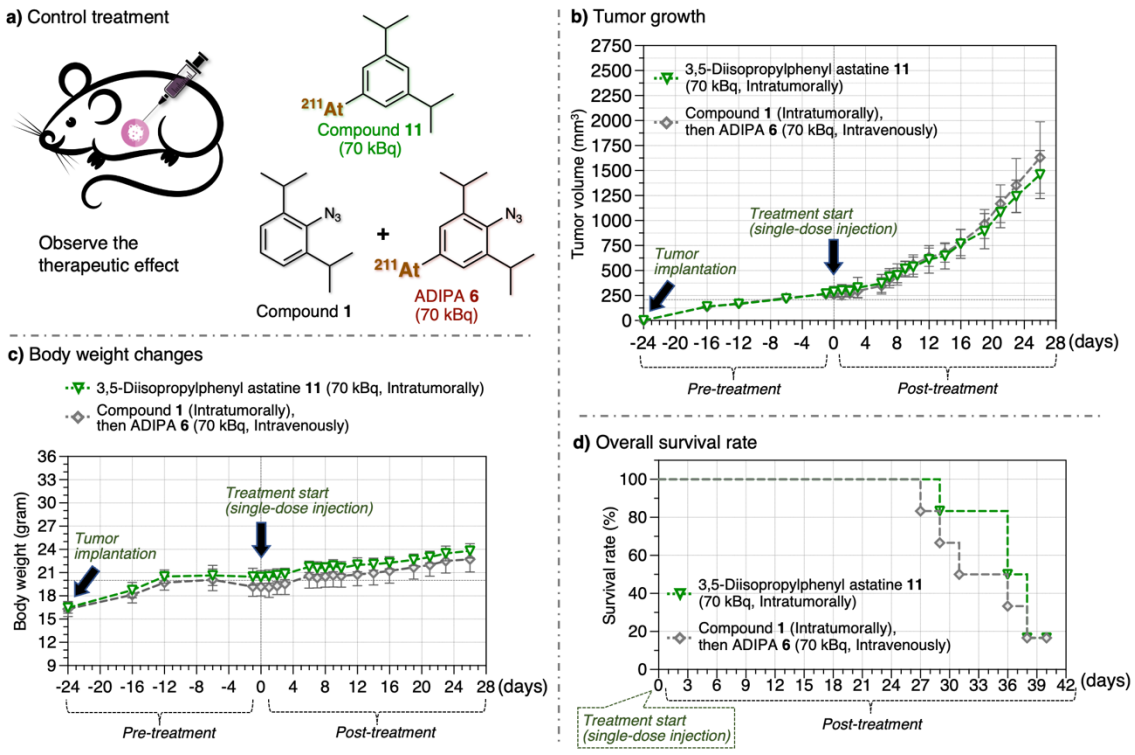


Fig. S14 (a) A549 cell-bearing xenograft nude mice were treated with compound **11** (70 kBq, administered intratumorally) or ADIPA **6** (70 kBq, administered intravenously) with pretreatment using compound **1** (120 nmol, administered intratumorally). The compounds were administered in a single-dose injection. Subsequently, the (b) tumor growth levels, (c) body weight changes, and (d) survival rates were observed (*n*=6). Data are represented as mean value ± SD. See Figs. S17 for representative photos. Dashed green line = 3,5-diisopropylphenyl astatine **11** treated mouse group; Dashed grey line = 2,6-diisopropylphenyl azide **1** and ADIPA **6** co-treated mouse group.

Intratumoral therapy using various concentrations of ADIPA ***6*** *(Figs. S15, S18, S19, and Table S3):* The mice were randomized (double-blind) into four groups and treated with the corresponding compound. The first group was intratumorally injected with 10 μL of 60 kBq of ADIPA **6** (n = 4). The second group was intratumorally injected with 10 μL of 100 kBq of ADIPA **6** (n = 4). The third group was intratumorally injected with 10 μL of 160 kBq of ADIPA **6** (n = 4). Finally, the fourth group was intratumorally injected with 10 μL of 300 kBq of ADIPA **6** (n = 4). The mice's tumor volume and body weight were recorded within a specific time period using the equation $V = W^2 \times L/2$, where W and L represented the minor and major lengths of the tumor, respectively. When the tumor reached 2000 mm^3, the mice were sacrificed, and survival rates were calculated using the Kaplan-Meier method.

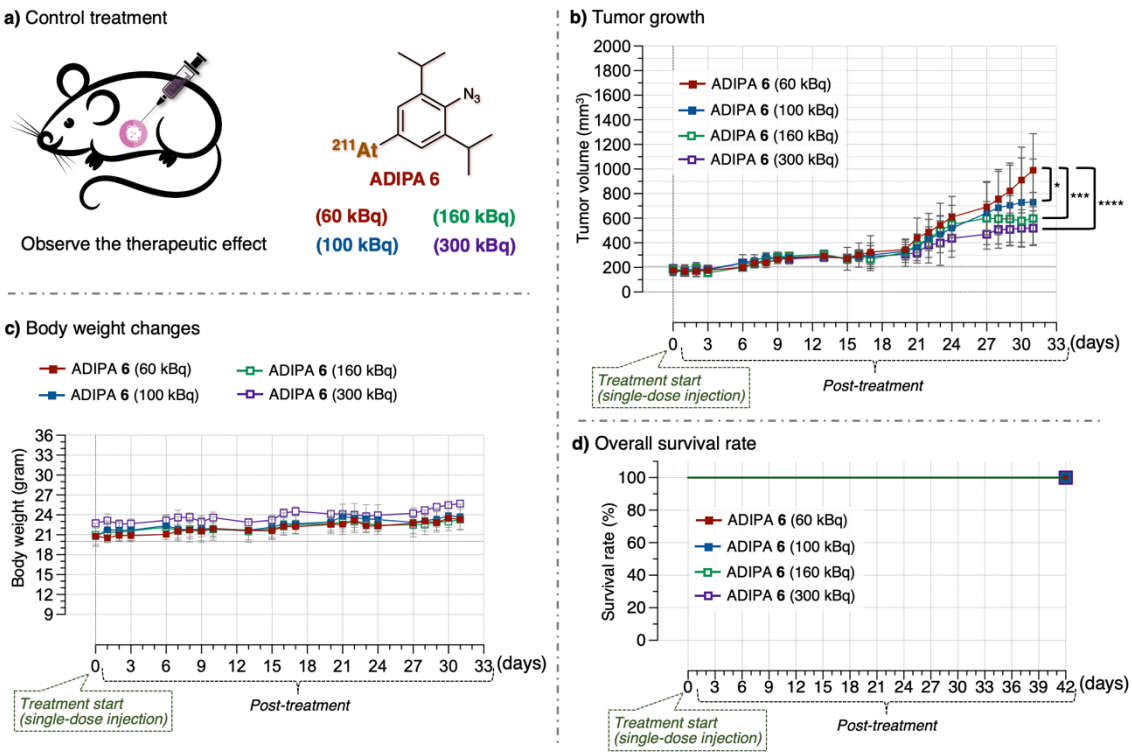


Fig. S15 (a) A549 cell-bearing xenograft nude mice were treated with various concentrations of ADIPA **6** (60 kBq, 100 kBq, 160 kBq, 300 kBq). The compounds were administered intratumorally in a single-dose injection. Subsequently, the (b) tumor growth levels, (c) body weight changes, and (d) survival rates were observed (*n*=4). Data are represented as mean value ± SD. See Figs. S18 and S19 for representative photos, and Table S3 for tumor growth differences test results. P values were determined using a two-way ANOVA (with Tukey's correction for multiple comparisons between groups). n.s.=not significant, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$.

Table S3 Two-way ANOVA with Tukey's correction was performed to test group tumor growth differences. The difference between the 60 kBq ADIPA **6** treated group with 100 kBq, 160 kBq, and 300 kBq ADIPA **6** treated group was significant starting 28 days after treatment. It increased throughout the experiment (see also Fig. S15). n.s.=not significant.

Post-treatment (days)	ADIPA **6** (60 kBq) vs ADIPA **6** (100 kBq)		ADIPA **6** (60 kBq) vs ADIPA **6** (160 kBq)		ADIPA **6** (60 kBq) vs ADIPA **6** (300 kBq)	
	Summary	Adjusted *P* value	Summary	Adjusted *P* value	Summary	Adjusted *P* value
20	n.s.	0.9989	n.s.	0.9962	n.s.	0.9776
21	n.s.	0.8289	n.s.	0.9093	n.s.	0.5443
22	n.s.	0.9363	n.s.	0.9318	n.s.	0.6580
23	n.s.	0.8353	n.s.	0.9540	n.s.	0.3706
24	n.s	0.7529	n.s.	0.9081	n.s.	0.2311
27	n.s.	0.9501	n.s.	0.7477	n.s.	0.0749
28	n.s.	0.8560	n.s.	0.2821	*	0.0332
29	n.s.	0.5770	n.s.	0.0622	**	0.0038
30	n.s.	0.1893	**	0.0017	***	0.0001
31	*	0.0247	***	0.0001	****	<0.0001

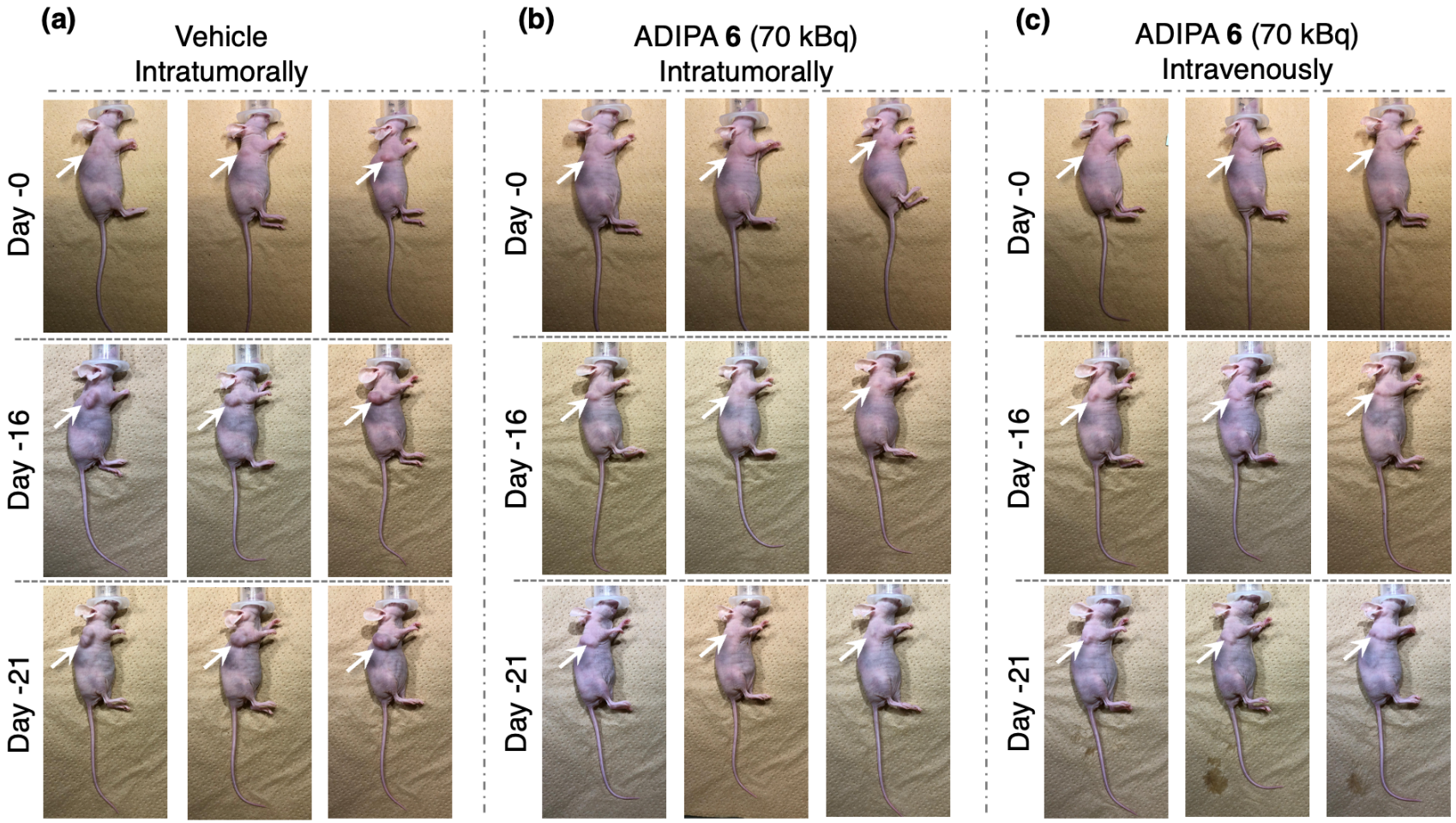


Fig. S16 Representative photos. A549 cell-bearing xenograft nude mice were treated with (a) vehicle [PBS (10% DMSO, 0.5% Tween 80), administered intratumorally], (b) ADIPA **6** (70 kBq, administered intratumorally), and (c) ADIPA **6** (70 kBq, administered intravenously). The photos were taken before the treatment, day 16 post treatment, and day 21 post treatment. The arrow shows the tumor location.

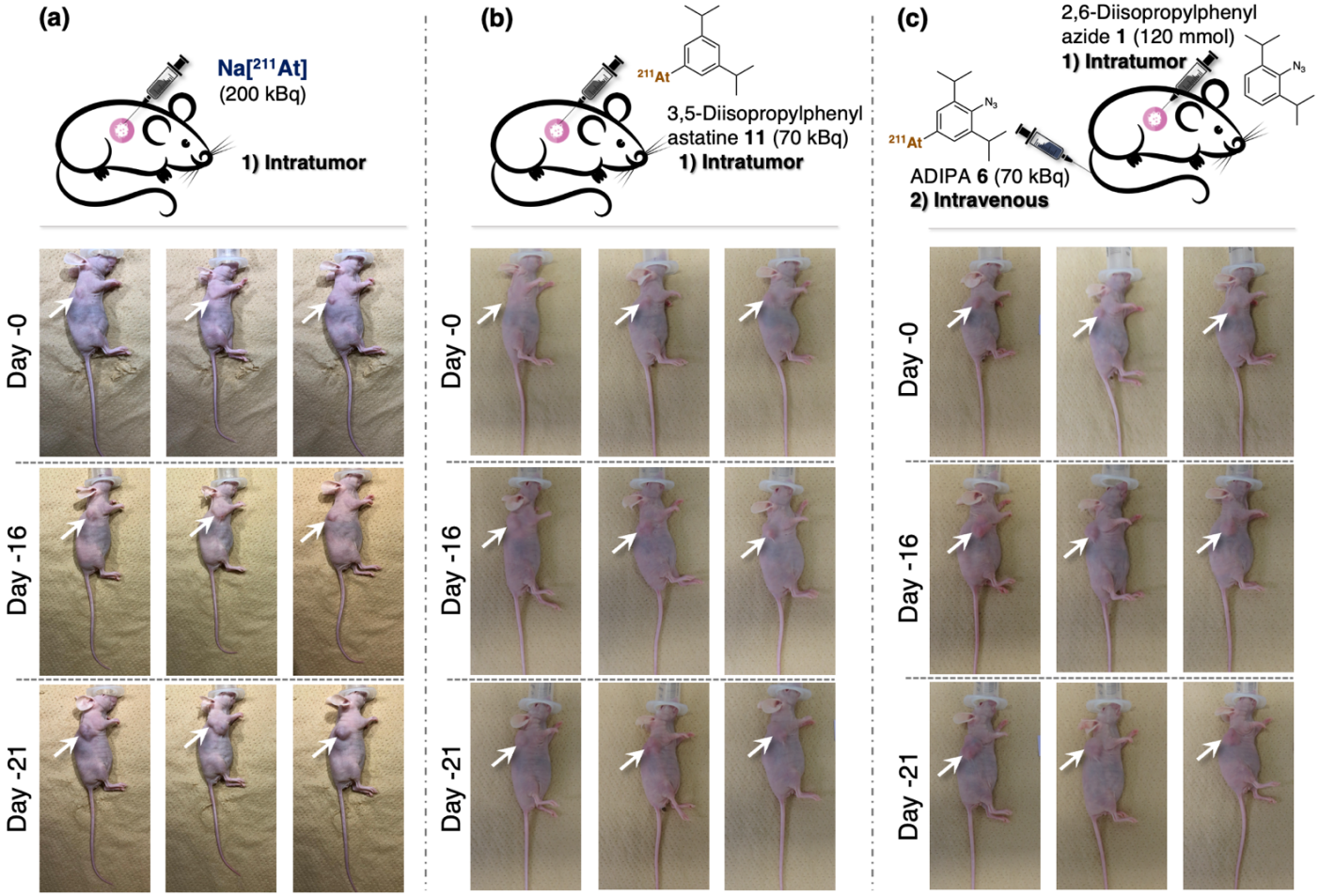


Fig. S17 Representative photos. A549 cell-bearing xenograft nude mice were treated with (a) Na[^{211}At] (200 kBq, administered intratumorally), (b) 3,5-diisopropylphenyl astatine **11** (70 kBq, administered intratumorally), and (c) 2,6-diisopropylphenyl azide **1** (120 nmol, administered intratumorally) and then with ADIPA **6** (70 kBq, administered intravenously) after 1 hour. The photos were taken before the treatment, day 16 post treatment, and day 21 post treatment. The arrow shows the tumor location.

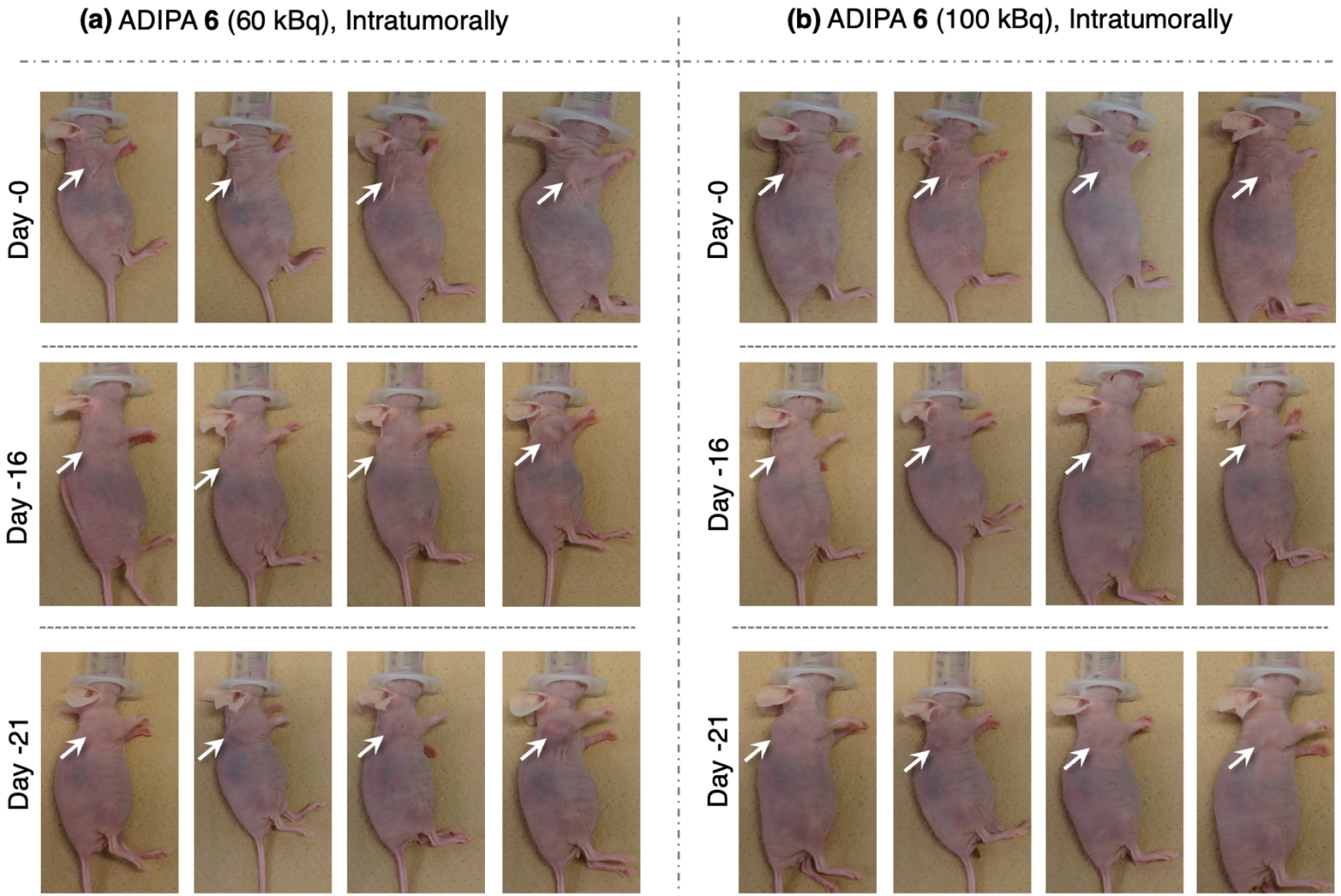


Fig. S18 Representative photos. A549 cell-bearing xenograft nude mice were treated intratumorally with ADIPA **6** (a) 60 kBq, (b) 100 kBq. The photos were taken before the treatment, day 16 post treatment, and day 21 post treatment. The arrow shows the tumor location.

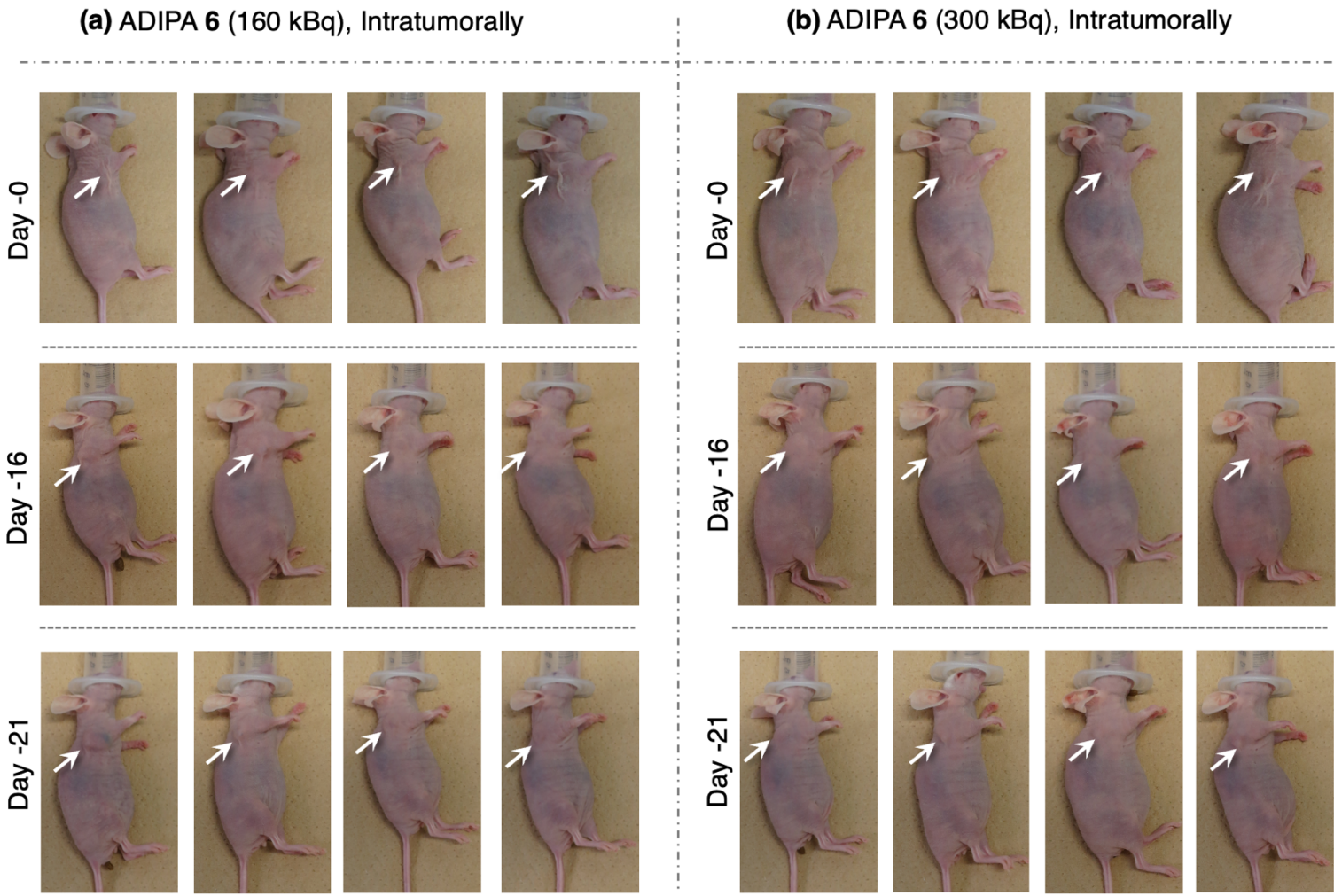
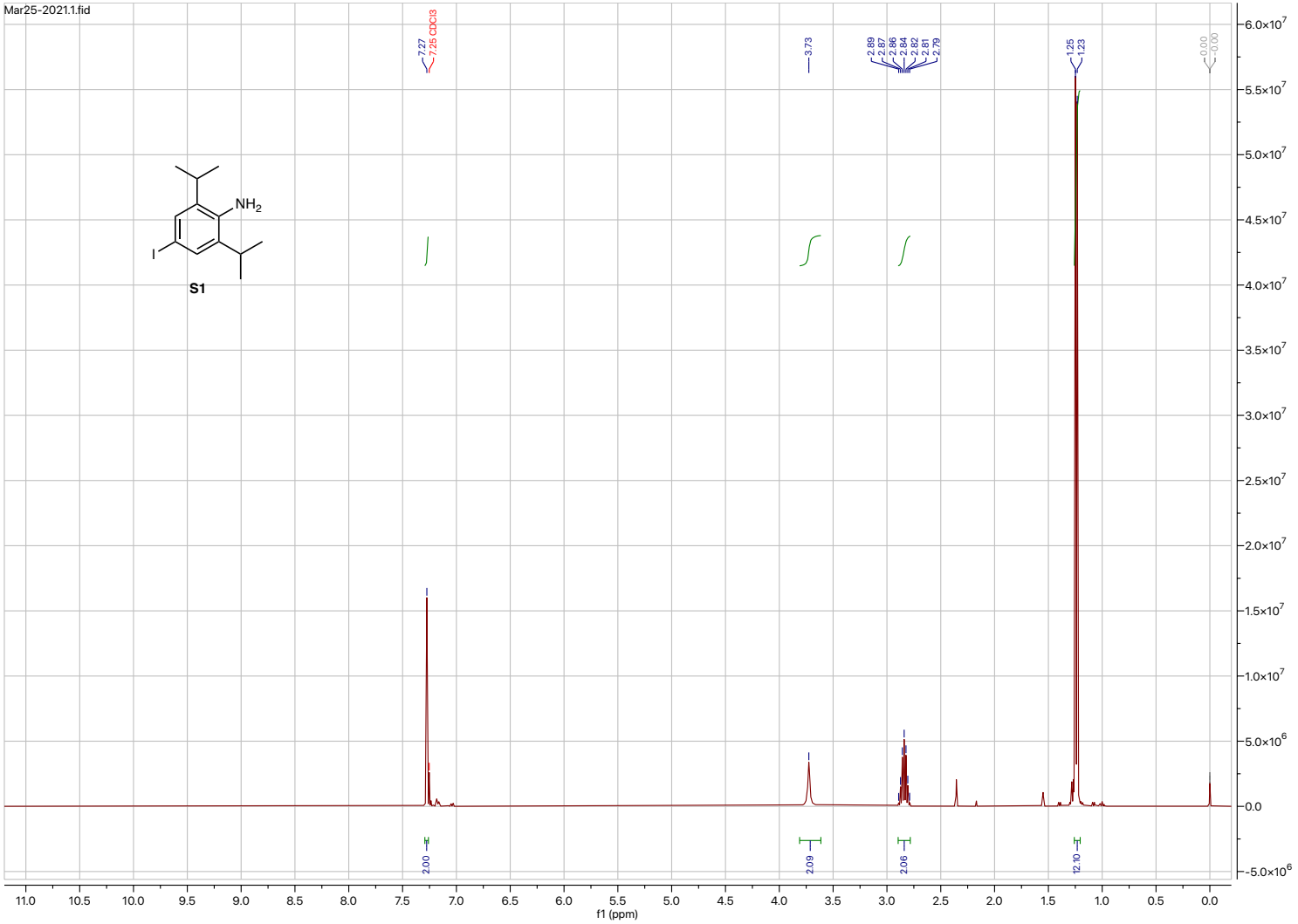
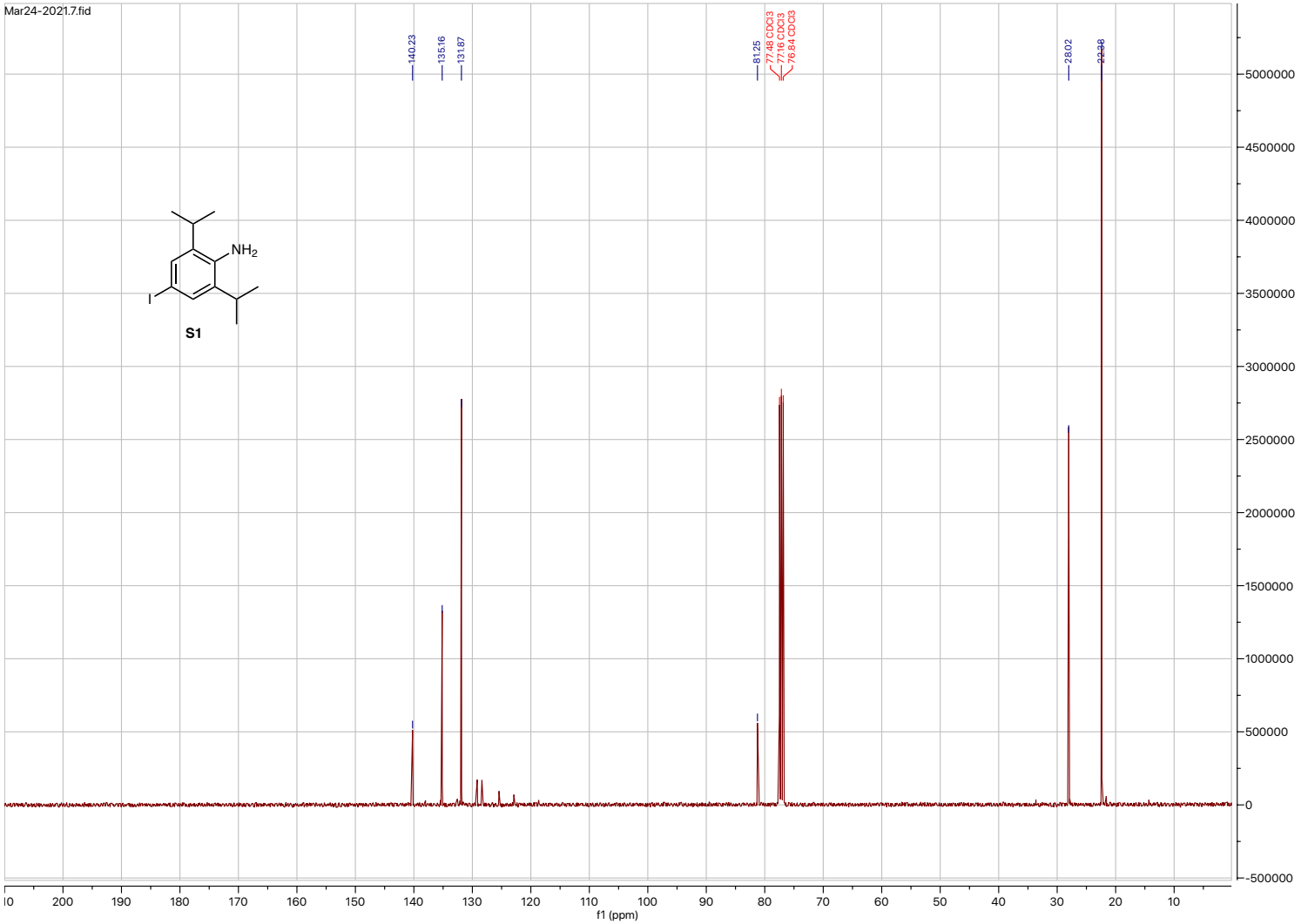


Fig. S19 Representative photos. A549 cell-bearing xenograft nude mice were treated intratumorally with ADIPA **6** (a) 160 kBq, (b) 300 kBq. The photos were taken before the treatment, day 16 post treatment, and day 21 post treatment. The arrow shows the tumor location.

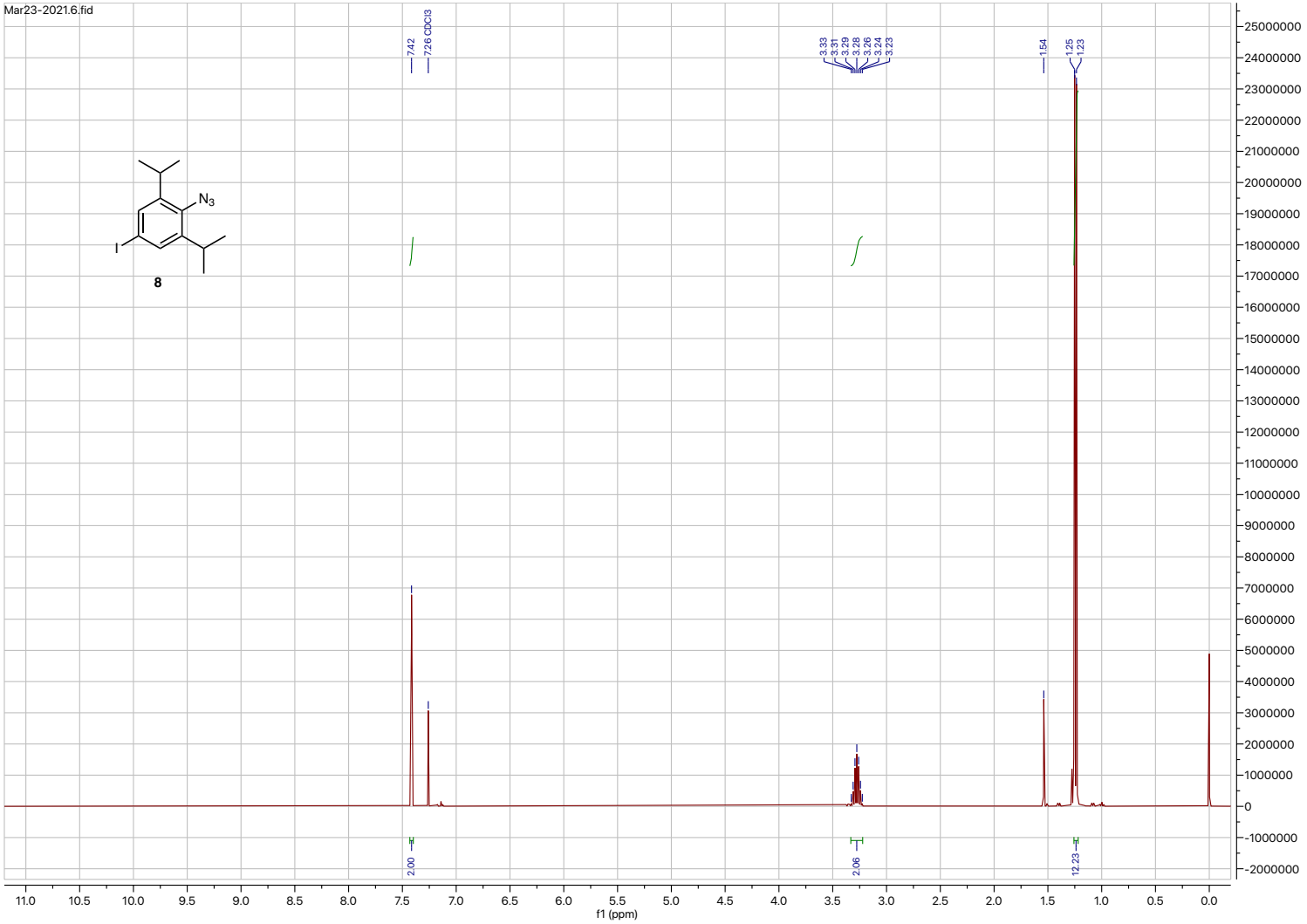
^{1}H-NMR in $CDCl_3$



^{13}C-NMR in $CDCl_3$



^{1}H-NMR in $CDCl_3$



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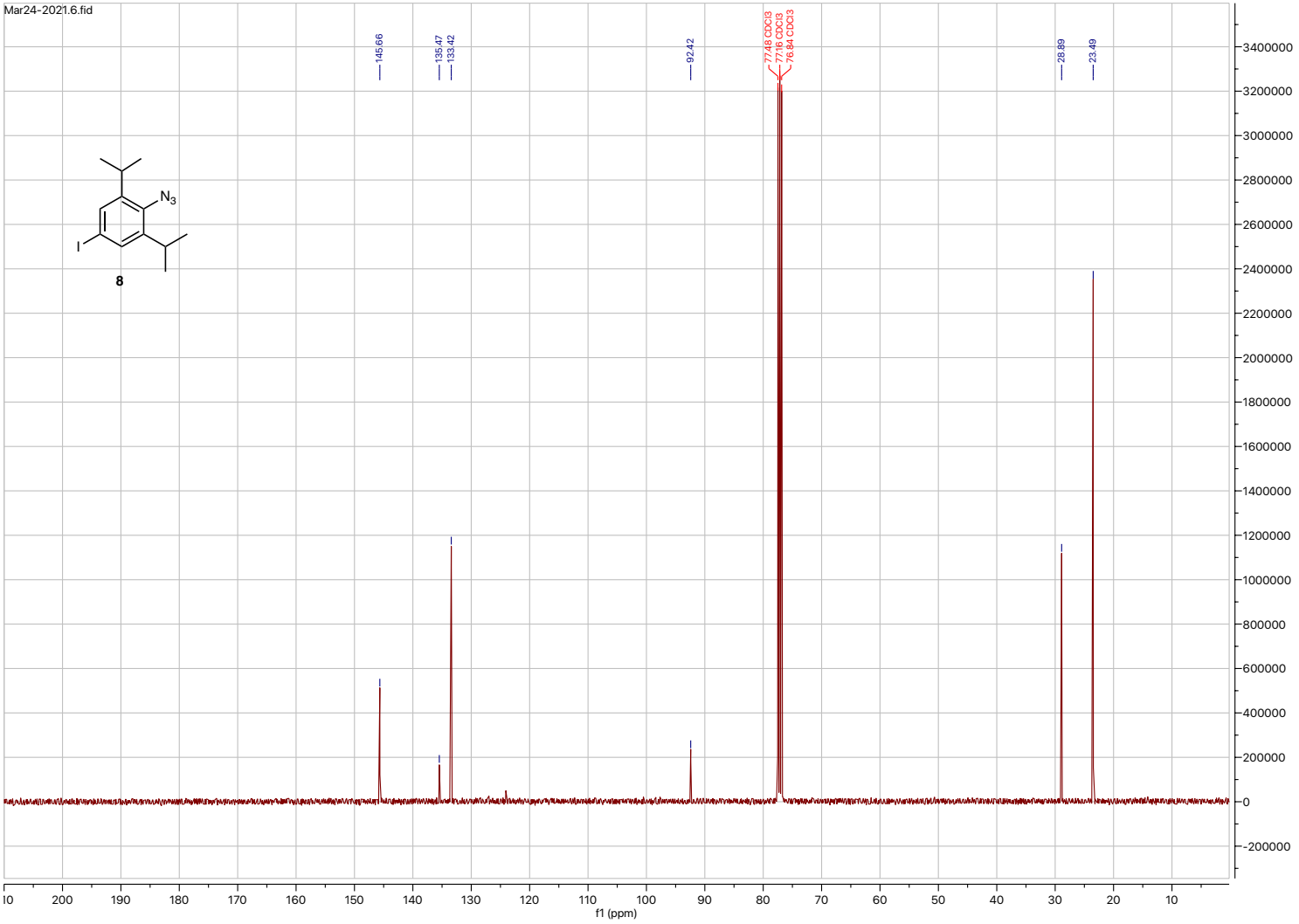

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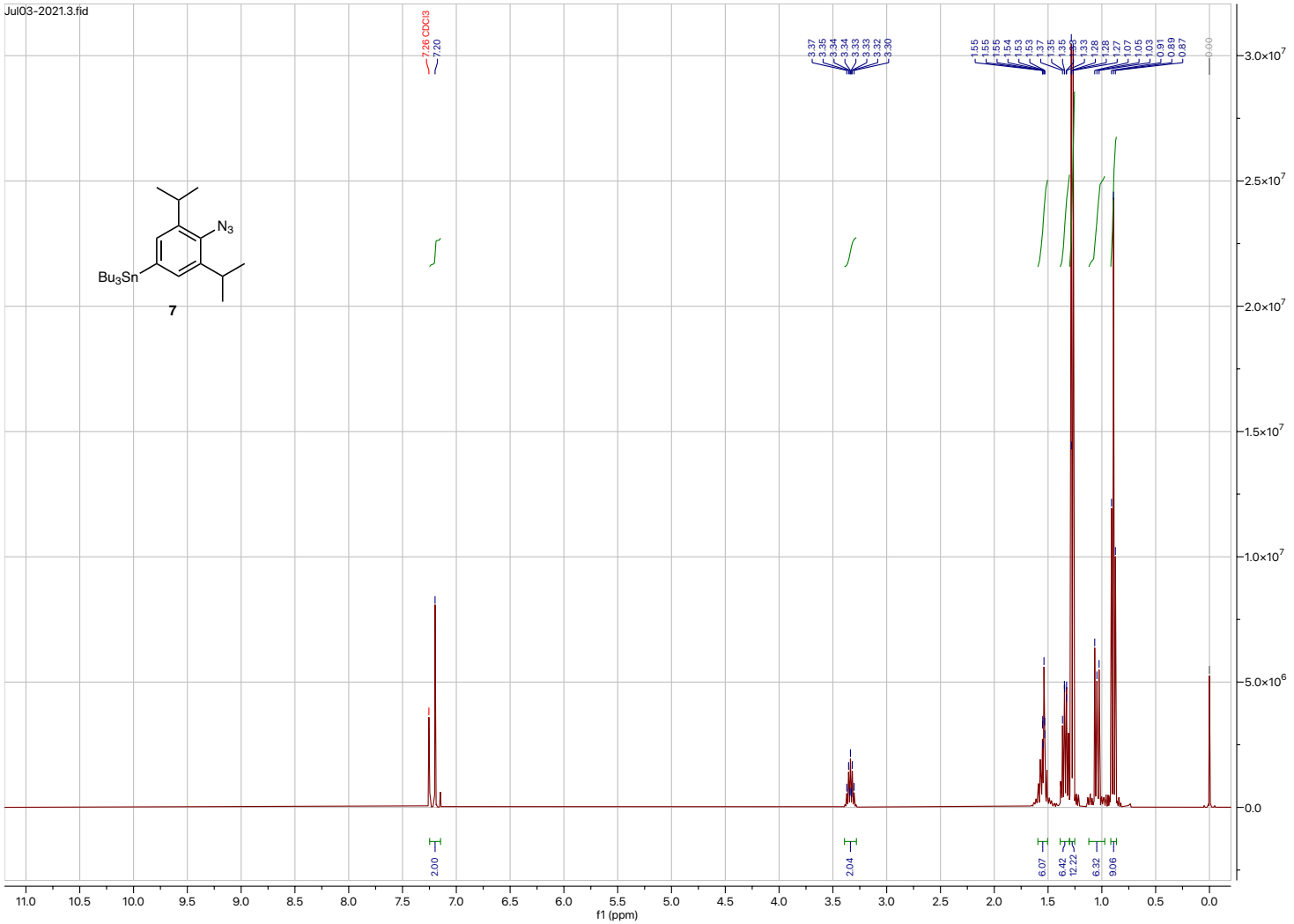

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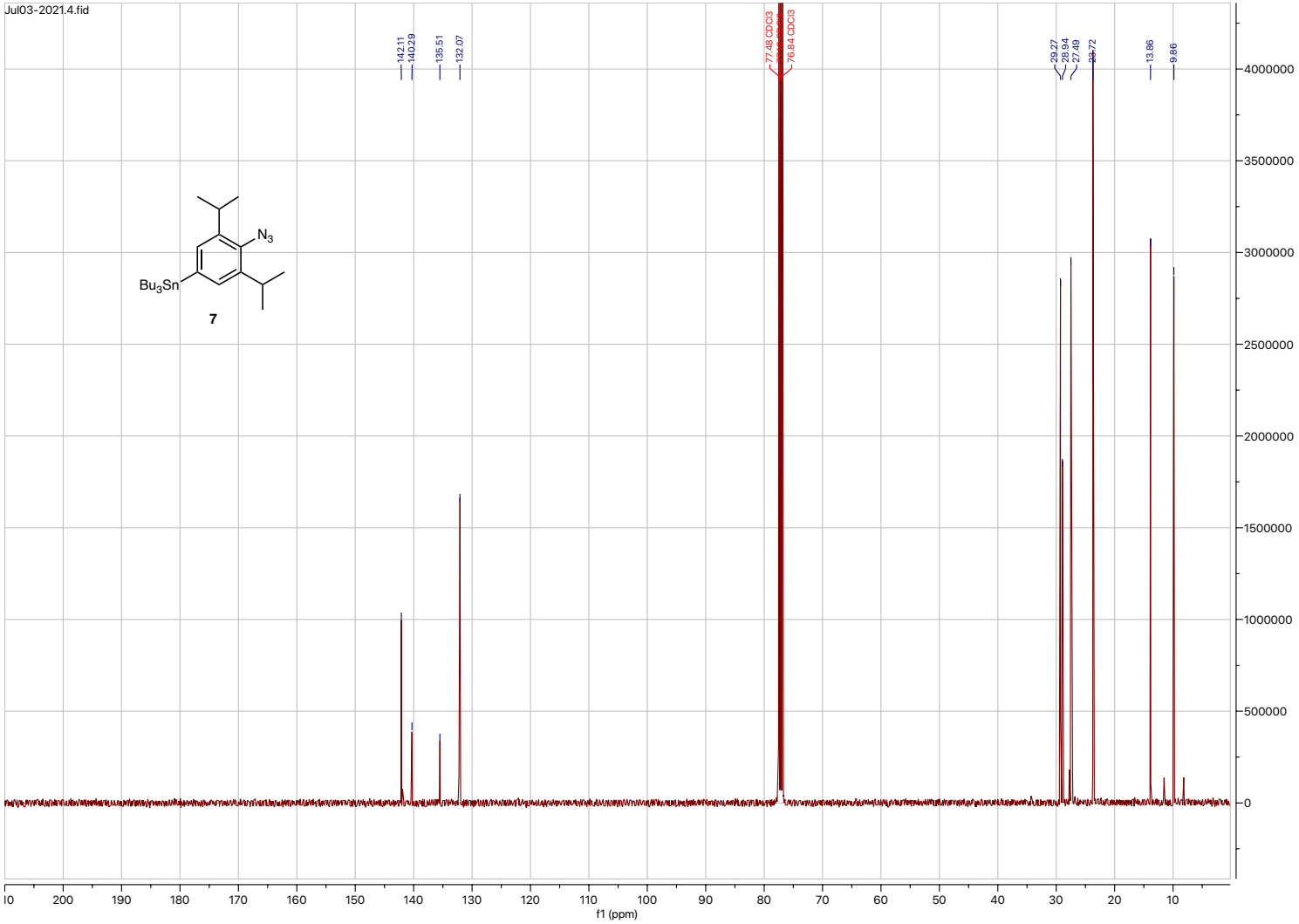
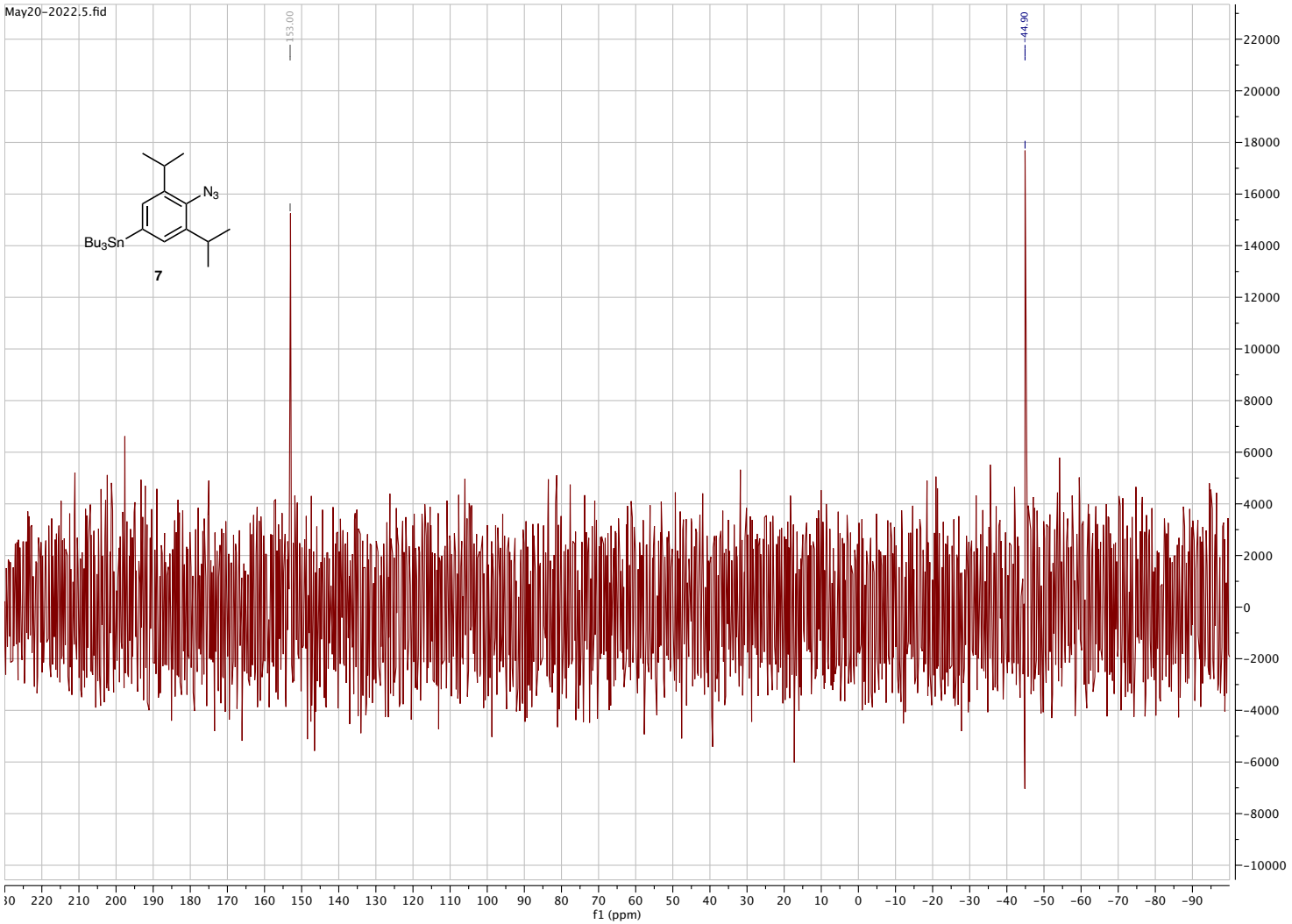
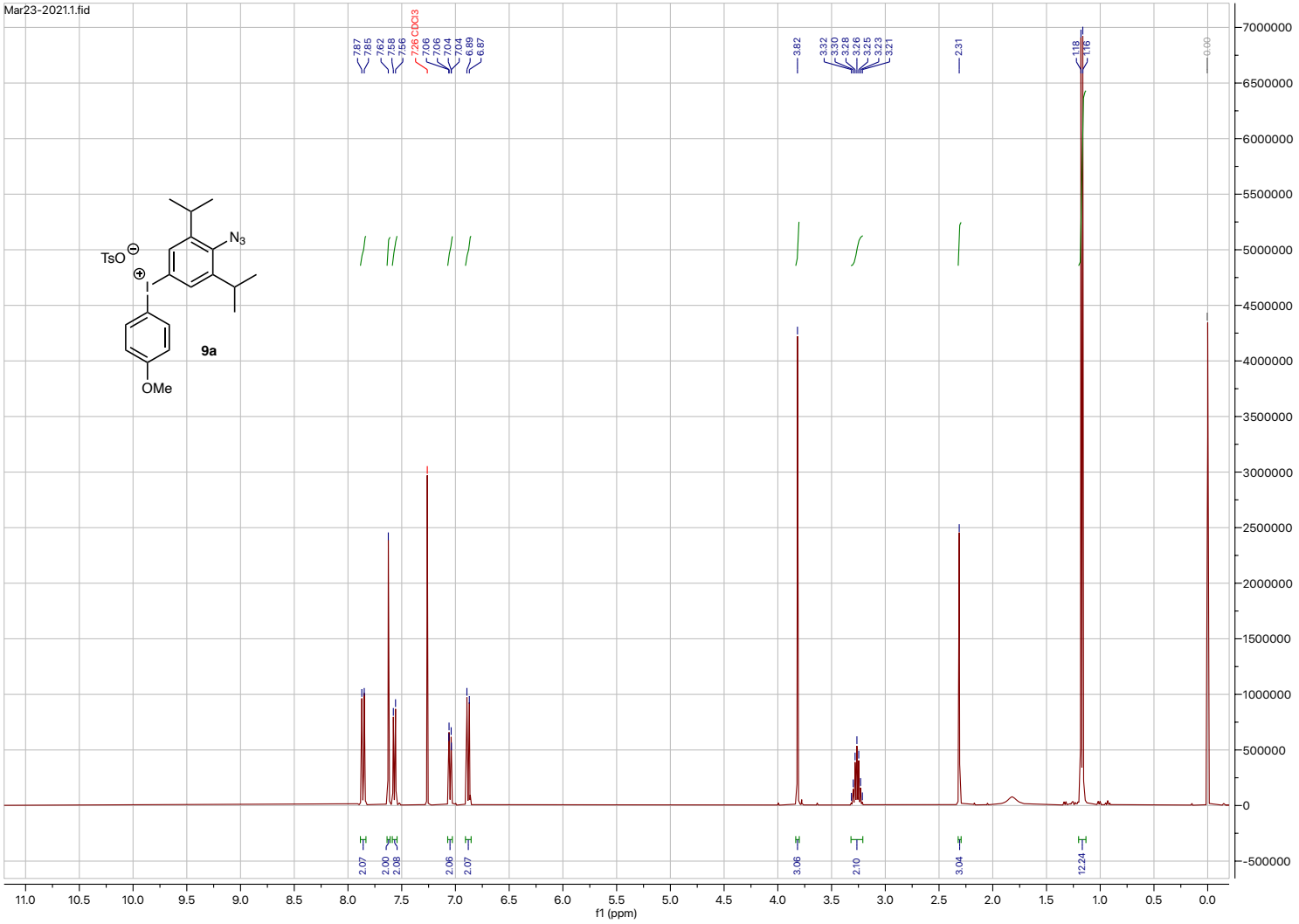


^{119}Sn-NMR in $CDCl_3$



^{1}H-NMR in $CDCl_3$



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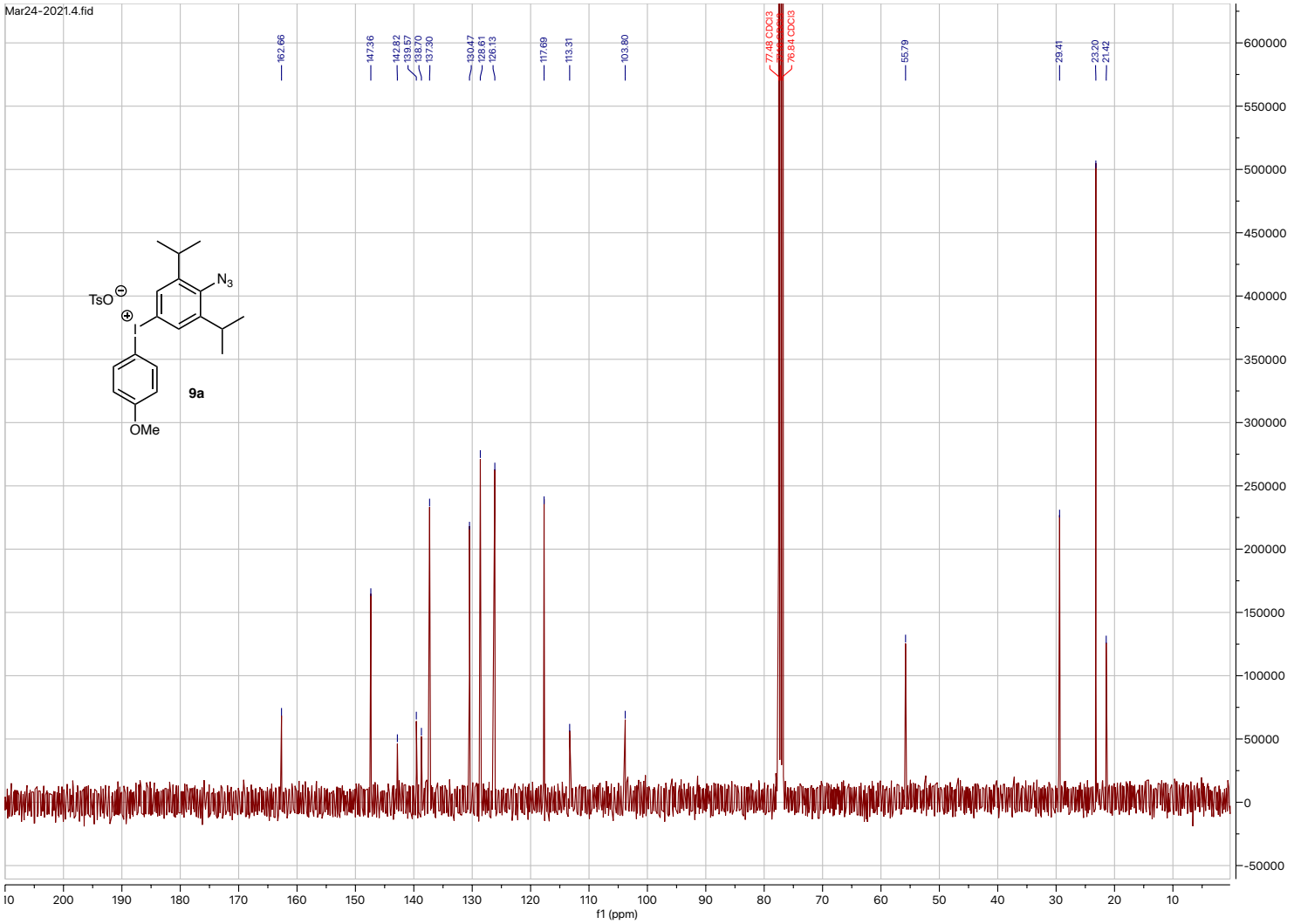

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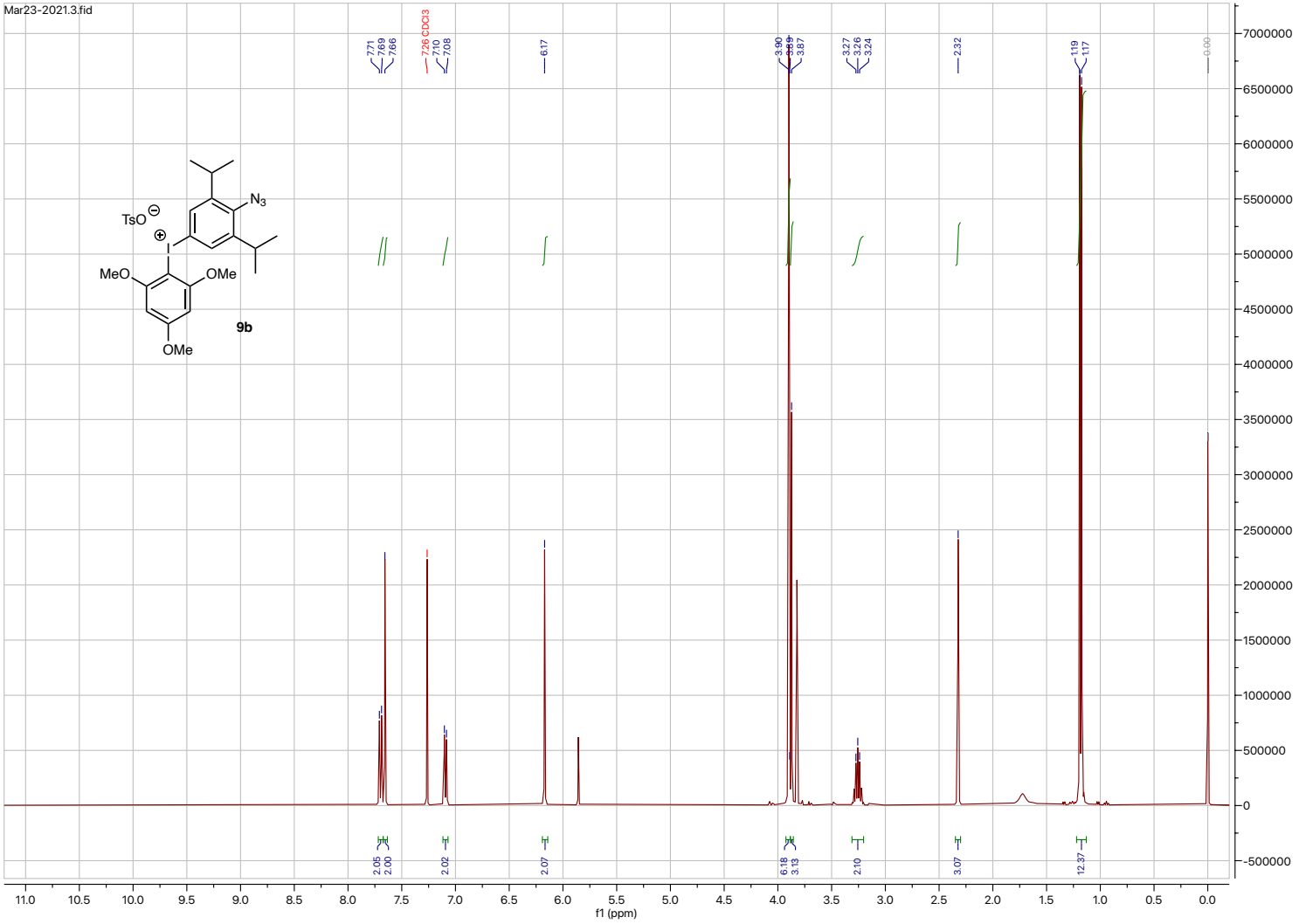

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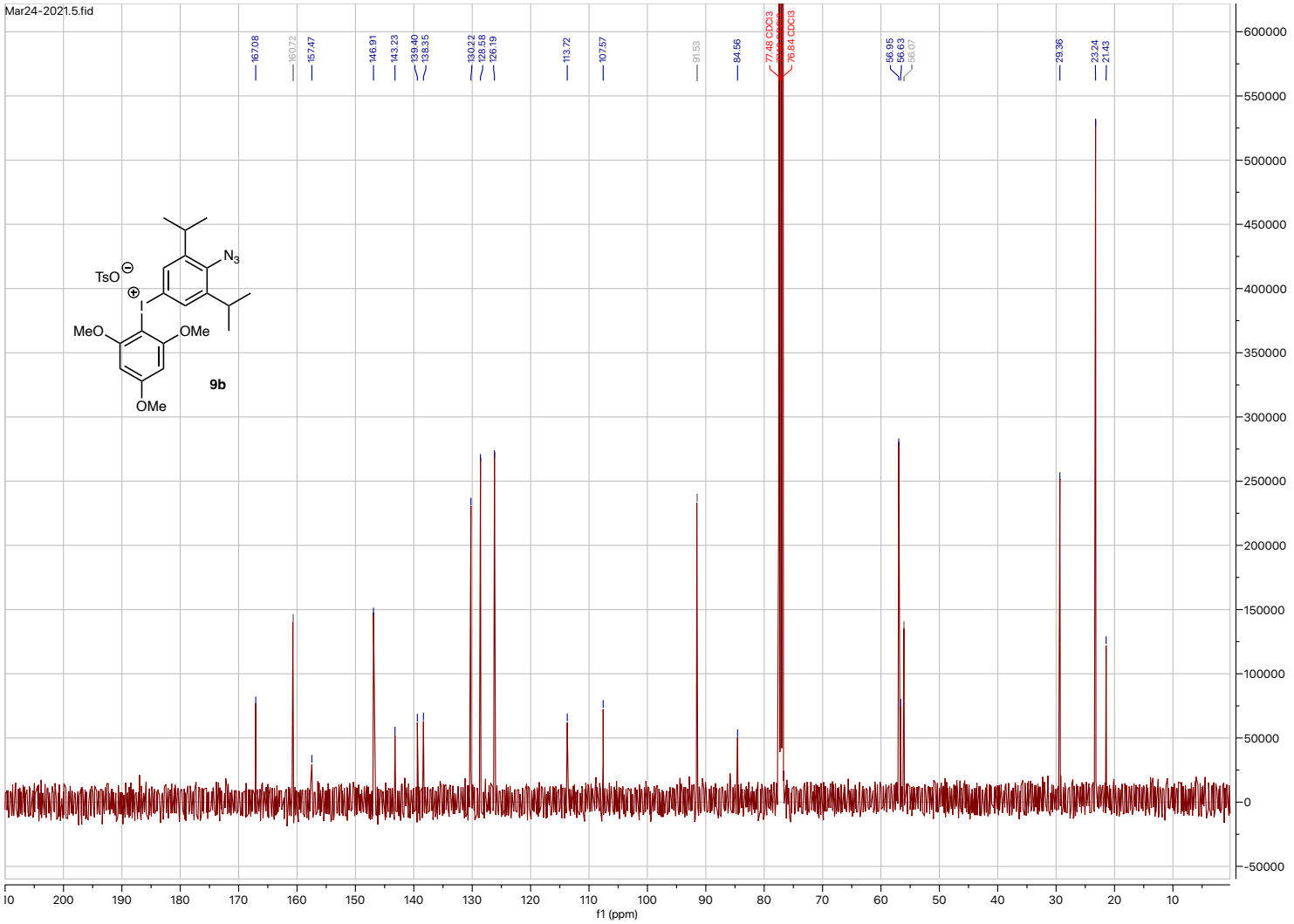
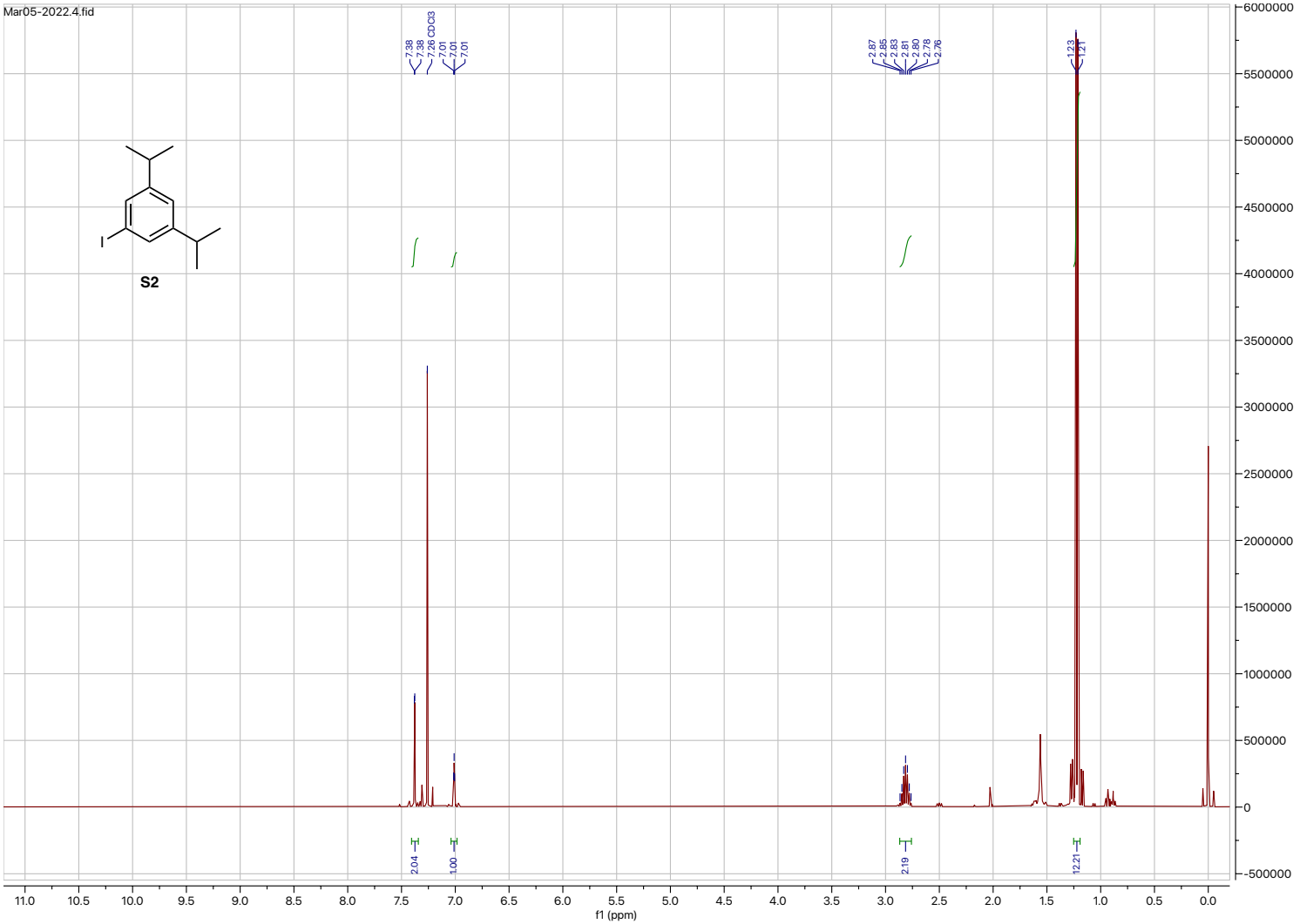


^{1}H-NMR in $CDCl_3$



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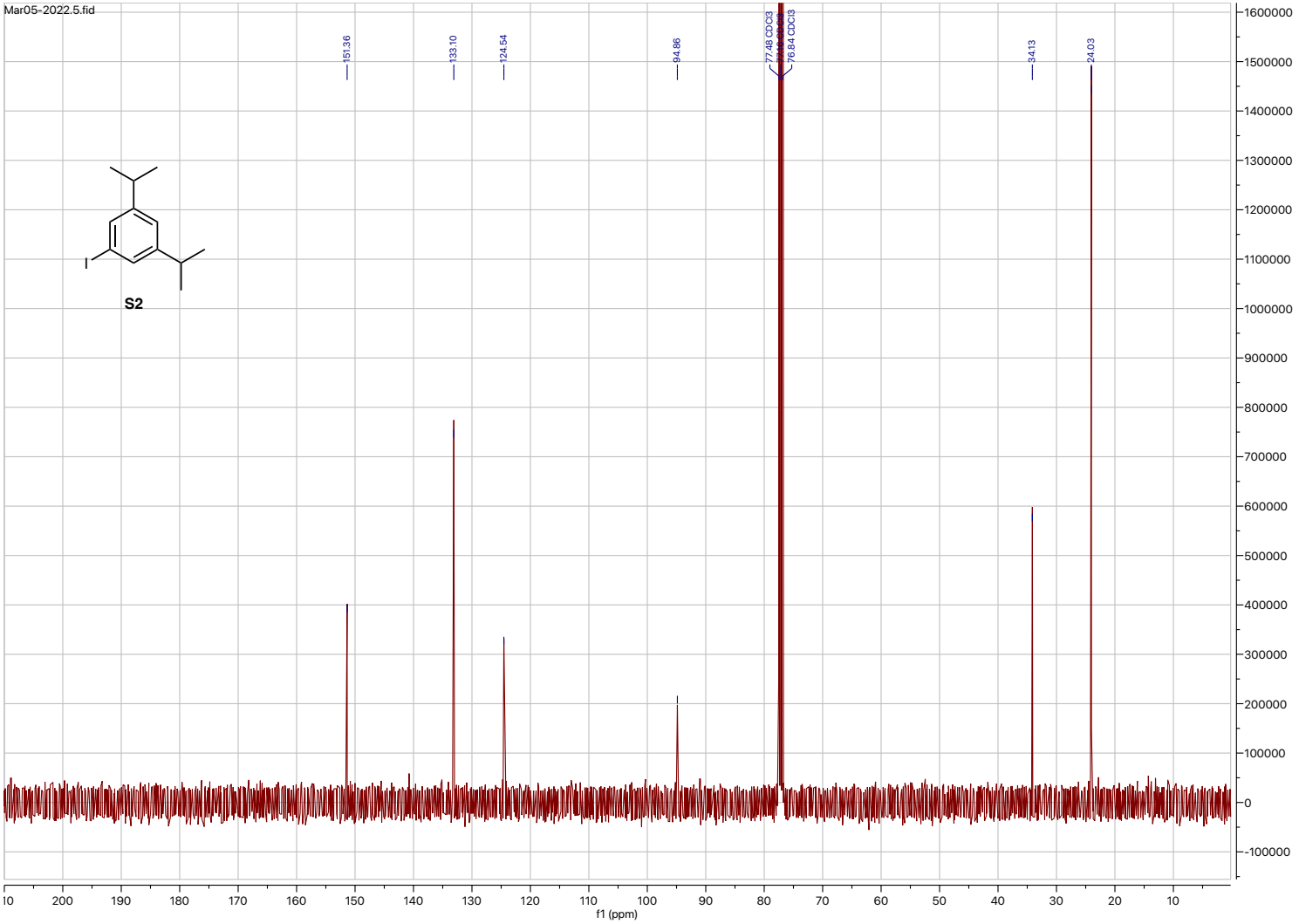

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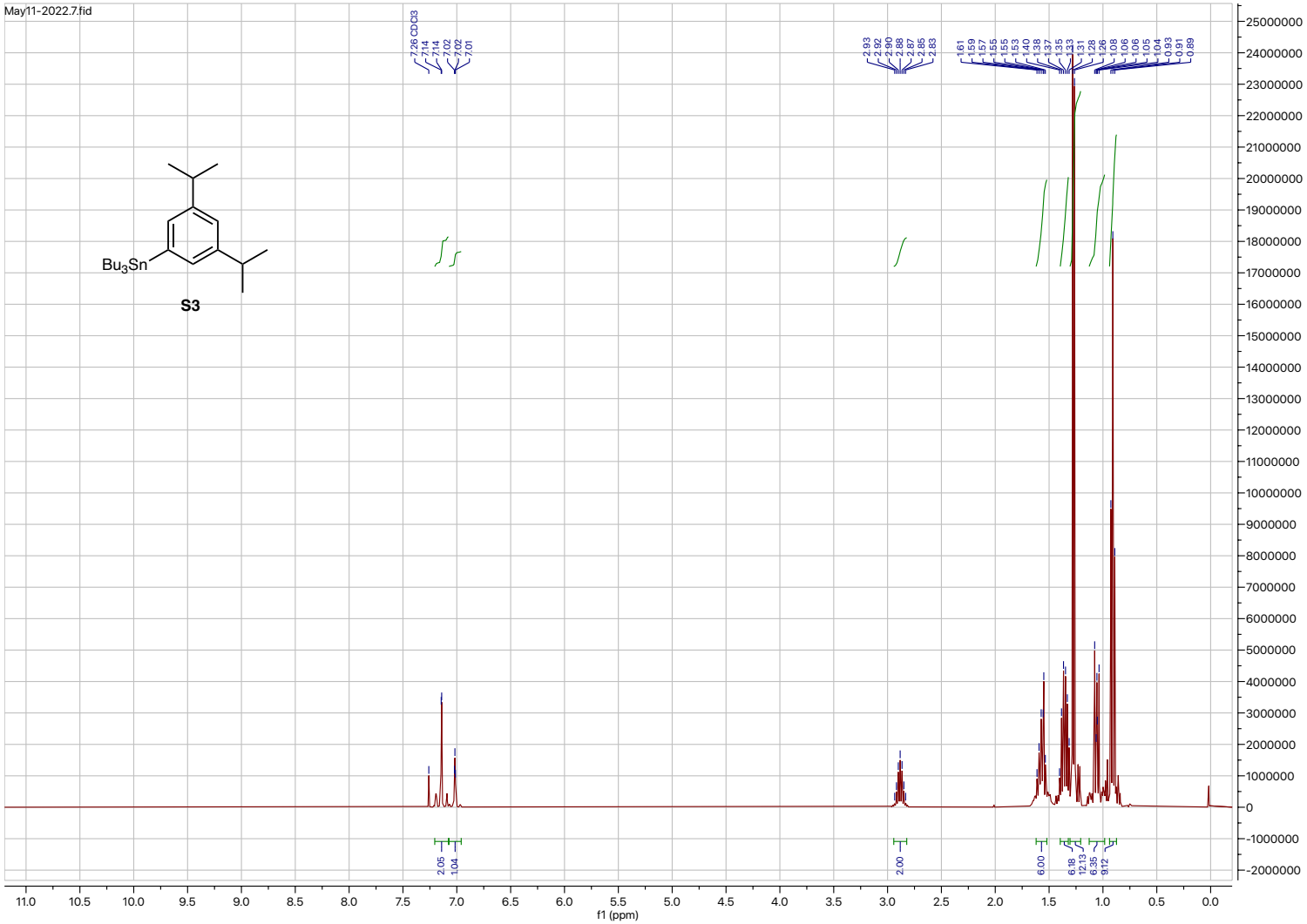

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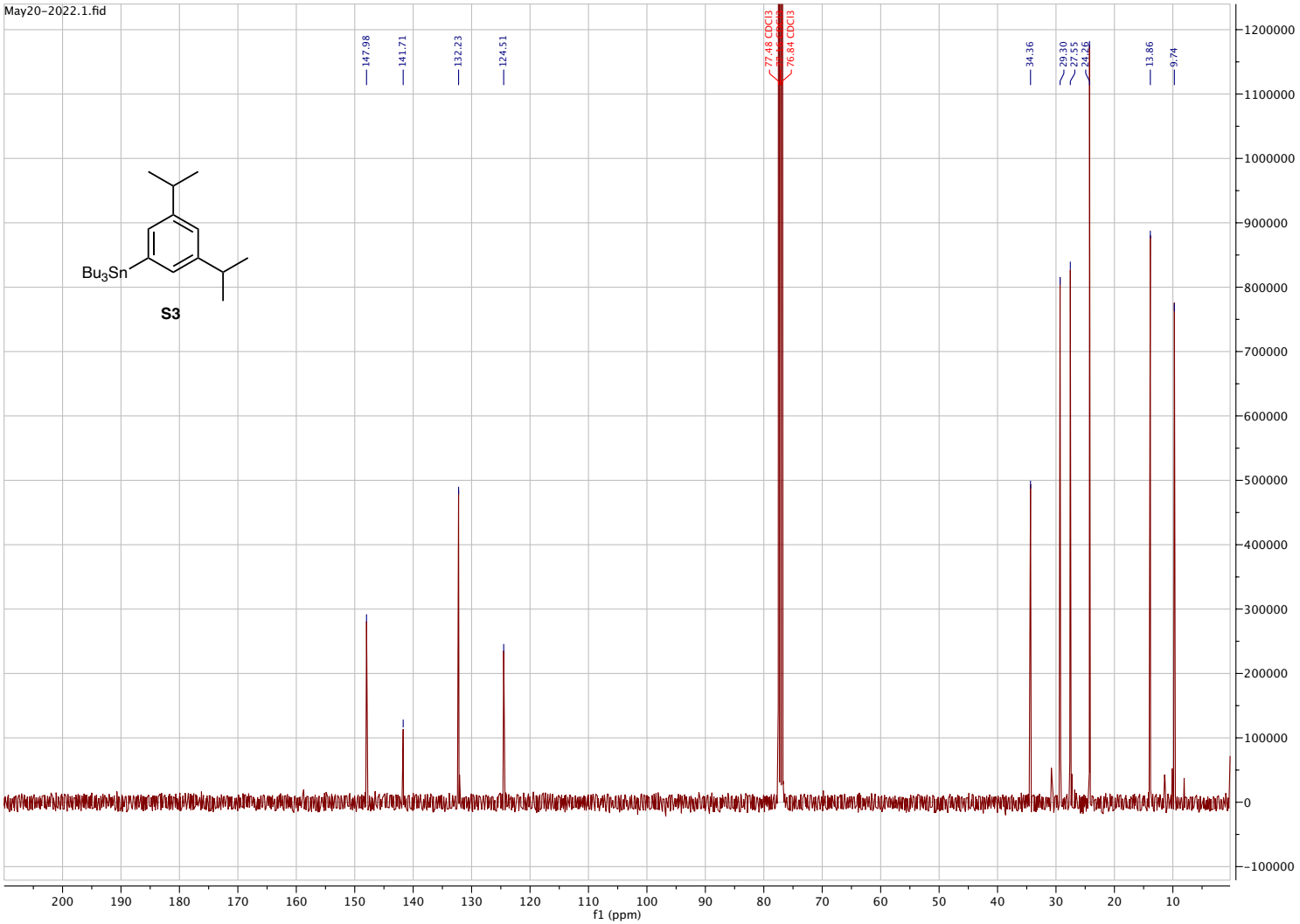

^{119}Sn-NMR in $CDCl_3$