Supplementary Information

Rapid One-step ^{18}F-Labeling of Peptides via Heteroaromatic Silicon-Fluoride Acceptors

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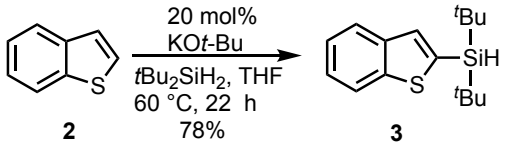
1. Materials and methods

All reagents and chemicals were purchased from commercial sources and used without further purification. DOTA-mono-NHS tris (*t*-Bu ester) (product number B-270) was purchased from Macrocyclics. Gastrin Tetrapeptide (H-Trp-Met-Asp-Phe-NH_2) (cas no [1947-37-1]) was purchased from Bachem Americas (product number H-3110). All deuterated solvents were purchased from Cambridge Isotope Laboratories. Unless otherwise noted, reactions were carried out in oven-dried glassware under an atmosphere of argon using commercially available anhydrous solvents. Solvents used for extractions and chromatography were not anhydrous. Silicon oil bath was used as the heating source for all reactions. Reactions and chromatography fractions were analyzed by thin-layer chromatography (TLC) using Merck precoated silica gel 60 F_{254} glass plates (250 μm) and visualized by ultraviolet irradiation, 2,4-dinitrophenyl hydrazine or potassium permanganate stain or ninhydrin stain. Flash column chromatography was performed using E. Merck silica gel 60 (230−400 mesh) with compressed air and ethyl acetate and *n*-hexane were used as eluent solvents. NMR spectra were recorded on a Bruker ARX 400 (400 MHz for ^{1}H; 100 MHz for ^{13}C) spectrometer. Chemical shifts are reported in parts per million (ppm, δ) using the residual solvent peak as the reference. The coupling constants, *J*, are reported in Hertz (Hz), and the multiplicity identified as the following: br (broad), s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). High-resolution electrospray mass spectrometry data was collected with a Waters LCT Premier XE time-of-flight instrument controlled by MassLynx 4.1 software. For some samples, high-resolution mass spectra were obtained on Thermo Scientific™ Exactive Mass Spectrometer with DART ID-CUBE. Samples were dissolved in methanol and infused using direct loop injection from a Waters Acquity UPLC into the Multi-Mode Ionization source. HPLC purifications were performed on a Knauer Smartline HPLC system with inline Knauer UV (210 or 254 nm) detector. Semi-preprative HPLC was performed using Phenomenex reverse-phase Luna column (10 × 250 mm, 5 μm) with a flow rate of 4 mL/min. Final purity of compounds was determined by analytical HPLC analysis performed with a Phenomenex reverse-phase Luna column (4.6 × 250 mm, 5 μm) with a flow rate of 1 mL/min. Compounds were identified by UV absorbance at 254 nm. All chromatograms were collected by a GinaStar (raytest USA, Inc.; Wilmington, NC, USA) analog to digital converter and GinaStar software (raytest USA, Inc.).

2. Experimental data

2.1 Synthesis and characterization of heteroarylsilanes

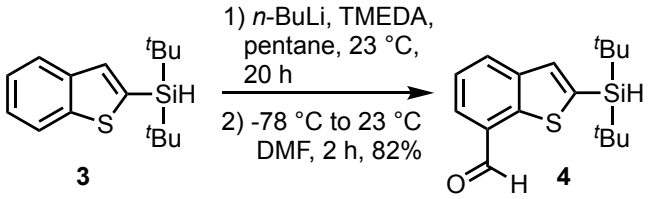
Heteroarylsilanes were synthesized according to literature procedure.[1] A representative example is described below.



benzo[*b*]thiophen-2-yldi-*tert*-butylsilane (3). To a vial containing benzothiophene (134.2 mg, 1 mmol), potassium *tert*-butoxide (22.5 mg, 0.2 mmol) and di-tert-butylsilane (0.59 mL, 3.0 mmol) was added THF (1.0 mL) inside a glovebox. The vial was sealed, taken outside the glovebox and stirred at 60 °C for 22 h. The reaction mixture was concentrated *in vacuo* and the crude residue was purified by silica gel column chromatography eluting with 100% hexane to afford **3** (214.0 mg, 78%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.87 (m, 1H), 7.86 – 7.82 (m, 1H), 7.58 (d, J = 0.7 Hz, 1H), 7.39 – 7.30 (m, 2H), 4.09 (s, 1H), 1.11 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 140.7, 135.0, 133.8, 124.2, 124.0, 123.4, 122.0, 29.4, 19.0. HRMS (APCI) *m/z* calcd for $C_{16}H_{24}FSSi$ $[M]^+$ 276.1368, found 276.1364.

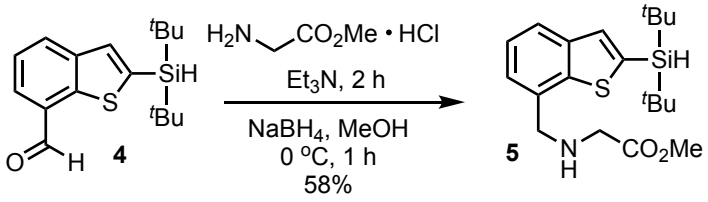
2.2 Synthesis of glycine ester HetSiFA 6



2-(di-*tert*-butylsilyl)benzo[*b*]thiophene-7-carbaldehyde (4). To a flame dried round bottom flask benzothiophene **3** (304.2 mg, 1.1 mmol), TMEDA (0.25 mL, 1.65 mmol) and pentane (3 mL) was added under a steady stream of argon. *n*-Butyllithium (2.5 M in hexanes, 0.66 mL, 1.65 mmol) was added dropwise such that the internal temperature remained between 22 and 25 °C. The

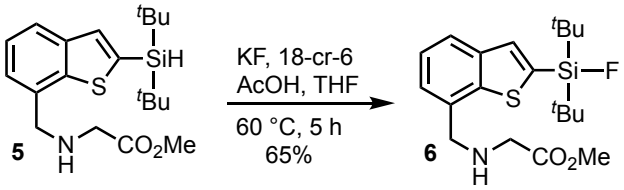
reaction mixture was stirred at room temperature for 20 h. The solution was then cooled to -78 °C (dry ice/acetone bath) and *N*,*N*-dimethylformamide (0.32 mL, 4.4 mmol) was added dropwise such that the temperature was kept at -78 °C. The resulting solution was allowed to stir at -78 °C for 1 h before it was brought to room temperature and stirred at 23 °C for additional 1 h. The dark colored reaction mixture was carefully quenched with saturated aqueous NH_4Cl (3 mL). The crude product was extracted with ethyl acetate (10 mL x 2) and combined organics were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 5% ethyl acetate in hexanes to afford aldehyde **4** (250 mg, 82%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 (s, 1H), 8.13 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.88 (dd, *J* = 7.2, 1.1 Hz, 1H), 7.67 (s, 1H), 7.57 (dd, *J* = 7.9, 7.2 Hz, 1H), 4.15 (s, 1H), 1.11 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 142.3, 141.0, 139.3, 132.6, 131.4, 130.6, 129.5, 124.0, 28.7, 19.0. HRMS (APCI) *m/z* calcd for $C_{17}H_{25}OSSi$ $[M+H]^+$ 305.1395, found 305.1400.



Methyl ((2-(di-tert-butylsilyl)benzo[b]thiophen-7-yl)methyl)glycinate (5): To a stirred solution of **4** (110 mg, 0.36 mmol) and glycine methyl ester hydrochloride (68 mg, 0.54 mmol) in methanol at 0 °C was added trimethylamine (0.075 mL, 0.54 mmol). The contents were stirred at 0°C for 30 min before warming to room temperature and stirring for 1.5 h. The reaction mixture was cooled to 0 °C and sodium borohydride (27 mg. 0.72 mmol) was added in one portion and the reaction was stirred at 0 °C for 1 hr. The reaction was quenched with water (1 mL) and the crude product was extracted into ethyl acetate (25 mL) and washed with a saturated brine solution. The residue was purified on silica gel column chromatography eluting with 20% ethyl acetate in hexanes to obtain desired product **5** as colorless oil (79 mg, 58% yield).

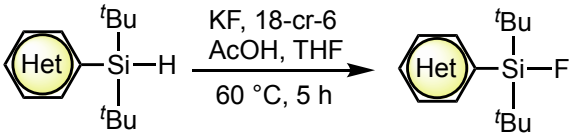
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, J = 5.0, 4.0 Hz, 1H), 7.61 (s, 1H), 7. 36-7.33 (m, 2H), 4.16 (s, 2H), 4.10 (s, 1H), 3.73 (s, 3H), 3.49 (s, 2H), 1.11 (s, 18H). ^{13}C NMR (100 MHz, CDCl3) δ 172.7, 142.9, 141.3 134.8, 134.1, 132.9, 124. 4, 123.4, 122. 6, 52.1, 51.8, 49.8, 28.7, 19.1. HRMS (APCI) *m/z* calcd for $C_{20}H_{32}NO_2SSi$ $[M+H]^+$ 378.1923, found 378.1911.



Methyl ((2-(di-tert-butylfluorosilyl)benzo[b]thiophen-7-yl)methyl)glycinate (6) : To a stirred solution of **5** (64 mg, 0.17 mmol), potassium fluoride (15 mg, 0.26 mmol) and 18-crown-6 (67 mg, 0.26 mmol) was added THF (2 mL) and acetic acid (0.030 mL, 0.51 mmol). The contents were stirred at 60 °C for 5 h. The crude residue was filtered and concentrated under reduced pressure. The crude product was purified on silica gel column chromatography eluting with 30% ethyl acetate in hexanes to obtain **6** as colorless oil (44 mg, 65% yield).

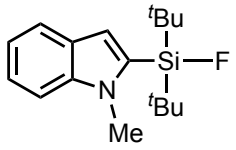
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, J = 6.2, 2.9 Hz, 1H), 7.67 (s, 1H), 7.38 (dd, J = 6.7, 4.2 Hz, 2H), 4.18 (s, 2H), 3.73 (s, 3H), 3.49 (s, 2H), 1.12 (d, *J* = 1.0 Hz, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 142.8, 141.0, 133.7 (d, J = 4 Hz), 133.2, 132.9, 124.6, 123.8 (d, *J* = 2.2 Hz), 122.9, 52.1, 51.8, 49.6 (d, *J* = 3.5 Hz), 27.0, 20.3 (d, *J* = 12.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -183.78. HRMS (APCI) *m/z* calcd for $C_{20}H_{31}NFO_2SSi$ $[M+H]^+$ 396.1829, found 396.1815.

2.3 General procedure for fluorination of heteroarylsilanes:



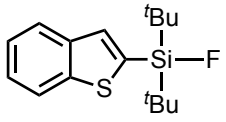
A round bottom flask containing the heteroarylsilane (0.22 mmol), potassium fluoride (0.33 mmol) and 18-crown-6-ether (0.33 mmol) was added THF (2 mL) and acetic acid (0.66 mmol) under

argon atmosphere. The reaction mixture was stirred at 60 °C for 5 h. After completion of the reaction, the crude mixture was filtered with dichloromethane and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 10-15% ethyl acetate in hexanes to afford the desired heteroarylfluorosilanes.



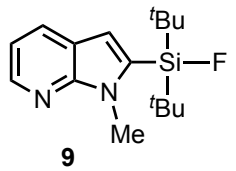
7

2-(di-*tert*-butylfluorosilyl)-1-methyl-1*H*-indole (7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.40 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.29 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.14 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 6.84 (s, 1H), 3.95 (d, *J* = 1.2 Hz, 3H), 1.14 (d, *J* = 1.2 Hz, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 128.2 (d, *J* = 1.4 Hz), 122.3, 120.8, 119.4, 112.4, 109.4, 33.1, 27.2, 20.9 (d, *J* = 12.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -181.04. HRMS (ESI) *m/z* calcd for $C_{17}H_{27}FNSi$ $[M+H]^+$ 292.1897, found 292.1895.



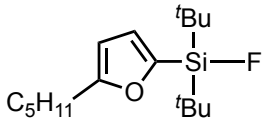
8

benzo[*b*]thiophen-2-yldi-tert-butylfluorosilane (8). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.88 (m, 2H), 7.87 (s, 1H), 7.41-7.33 (m, 2H), 1.13 (d, *J* = 1.1 Hz, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 140.4, 133.3 (d, *J* = 2.9 Hz), 133.1 (d, *J* = 16.4 Hz), 124.7, 124.2, 123.8, 122.1, 27.0, 20.3 (d, *J* = 12.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -183.95. HRMS (APCI) *m/z* calcd for $C_{16}H_{23}FSSi$ $[M+H]^+$ 294.1264, found 294.1263.



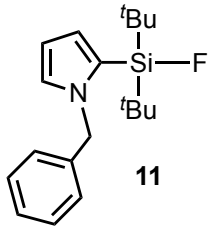
9

2-(di-*tert*-butylfluorosilyl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (9). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.94 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.07 (dd, *J* = 7.8, 4.7 Hz, 1H), 6.77 (s, 1H), 4.06 (d, *J* = 2.2 Hz, 3H), 1.11 (d, *J* = 1.0 Hz, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 144.8, 142.4, 129.7, 126.7, 120.8, 116.0, 115.4, 110.6, 32.0, 22.0, 20.8 (d, *J* = 11.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -181.45. HRMS (ESI) *m/z* calcd for $C_{17}H_{26}FN_2Si$ $[M+H]^+$ 293.1849, found 293.1852.



10

di-*tert*-butylfluoro(5-pentylfuran-2-yl)silane (10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, *J* = 3.1 Hz, 1H), 6.01 (d, *J* = 3.1 Hz, 1H), 2.66 (t, *J* = 7.5 Hz, 2H), 1.69 – 1.61 (m, 2H), 1.35 – 1.29 (m, 4H), 1.07 (d, *J* = 1.1 Hz, 18H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 151.4 (d, *J* = 23.3 Hz), 123.5, 104.7, 31.3, 28.0, 27.8, 26.8, 22.4, 20.0 (d, *J* = 12.4 Hz), 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -187.21. HRMS (APCI) *m/z* calcd for $C_{17}H_{32}FOSi$ $[M+H]^+$ 299.2206, found 299.2212.

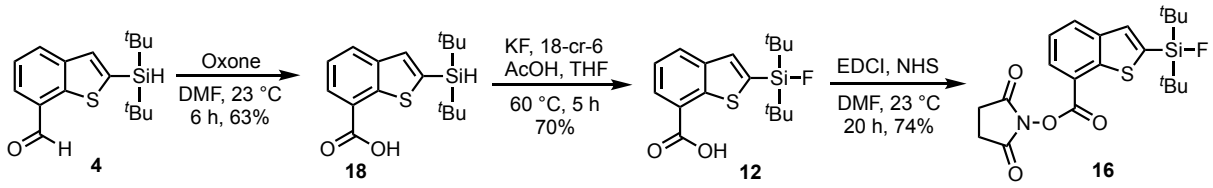


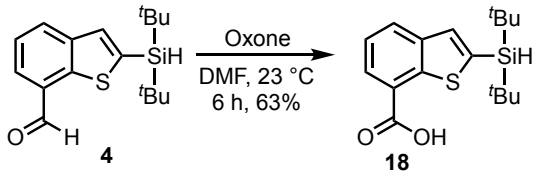
11

1-benzyl-2-(di-*tert*-butylfluorosilyl)-1*H*-pyrrole (11). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.20 (m, 3H), 7.05 (dd, *J* = 16.6, 7.0 Hz, 2H), 6.91 (dd, *J* = 2.3, 1.4 Hz, 1H), 6.54 (td, *J* = 4.0, 1.4 Hz, 1H), 6.30 – 6.24 (m, 1H), 5.28 (s, 2H), 1.02 (d, *J* = 1.0 Hz, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 128.4 (d, *J* = 5.4 Hz), 127.2, 126.9, 126.7, 120.1 (d, *J* = 6.0 Hz), 108.6, 53.4, 27.2, 20.9 (d, *J* = 12.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -187.63. HRMS (APCI) *m/z* calcd for $C_{19}H_{29}FNSi$ $[M+H]^+$ 318.2053, found 318.2059.

2.4 Synthesis of *N*-hydroxysuccinimide ester HetSiFA 16

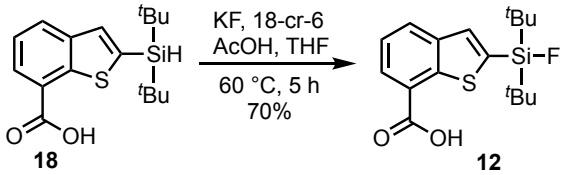
Scheme S1. Synthetic route towards HetSiFA **16**





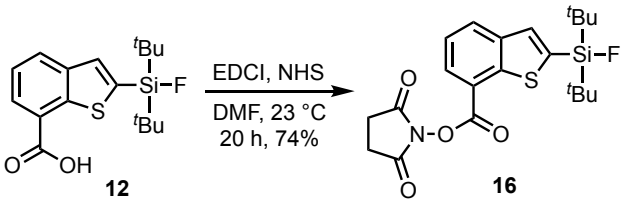
2-(di-*tert*-butylsilyl)benzo[*b*]thiophene-7-carboxylic acid (18).[2] To a 10 mL round-bottom flask containing *N,N*-dimethylformamide (2 mL) and aldehyde **4** (128 mg, 0.42 mmol), was added Oxone® (135 mg, 1.05 mmol) in one portion and stirred at room temperature for 6 hrs. The reaction mixture was diluted with 1 M HCl (1 mL) and ethyl acetate (10 mL). The organic layer was washed with brine, dried over sodium sulfate and the solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography eluting with hexanes:ethyl acetate (70:30, v/v) to obtain the desired acid **18** (84 mg, 63%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, J = 7.5, 1.2 Hz, 1H), 8.10 (dd, J = 7.9, 1.2 Hz, 1H), 7.66 (s, 1H), 7.49 (t, J = 7.7 Hz, 1H), 4.14 (s, 1H), 1.14 (s, 18H). ^{13}C NMR (100 MHz, CDCl3) δ 171.5, 144.5, 142.3, 138.3, 133.1, 129.0, 128.0, 123.9, 123.2, 28.7, 19.1. HRMS (APCI) *m/z* calcd for $C_{17}H_{23}O_2SSi$ $[M-H]^-$ 319.1194, found 319.1200.



2-(di-*tert*-butylfluorosilyl)benzo[*b*]thiophene-7-carboxylic acid (12). A round bottom flask containing carboxylic acid **18** (70 mg, 0.22 mmol), potassium fluoride (19 mg, 0.33 mmol) and 18-crown-6-ether (87 mg, 0.33 mmol) was added THF (2 mL) and acetic acid (0.04 mL, 0.66 mmol) under argon atmosphere. The reaction mixture was stirred at 60 °C for 5 hrs. After completion of the reaction, crude mixture was filtered with dichloromethane and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 30% ethyl acetate in hexane to afford the desired product **12** (52 mg 70%) as an off-white solid.

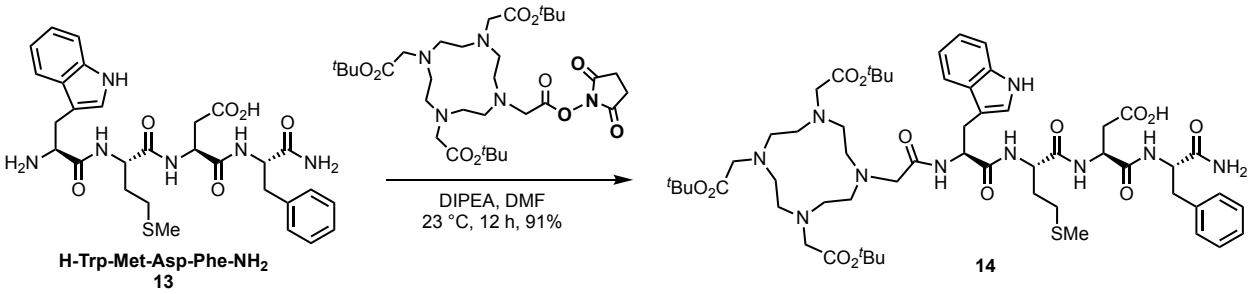
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 7.4, 1.0 Hz, 1H), 8.14 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.74 (s, 1H), 7.52 (t, *J* = 7.7 Hz, 1H), 1.15 (d, *J* = 0.7 Hz, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 144.3, 141.9, 136.5 (d, *J* = 16.1 Hz), 132.7 (d, *J* = 2.9 Hz), 129.4, 128.4, 124.1, 123.3, 27.0, 20.2 (d, *J* = 12.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -183.85. HRMS (APCI) *m/z* calcd for $C_{17}H_{22}FO_2SSi$ $[M-H]^+$ 337.1099, found 337.1099.



2-(di-*tert*-butylfluorosilyl)benzo[*b*]thiophene-7-carboxylic acid *N*-succinimidyl ester (16). To a stirred solution of carboxylic acid **12** (10 mg, 0.03 mmol) in DMF (0.12 mL) at 0 °C, EDC.HCl (9 mg, 0.05 mmol) and *N*-hydroxysuccinimide (3.8 mg, 0.03 mmol) was added. The contents were stirred at room temperature for 20 h followed by extraction into dichloromethane. The organic phase was washed with brine, concentrated under reduce pressure and filtered through a short silica gel plug using 20% ethyl acetate in hexane to obtain NHS-ester **16** (9.5 mg 74%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (dd, *J* = 7.5, 1.1 Hz, 1H), 8.19 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.74 (s, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 1.11 (d, *J* = 1.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 161.5, 144.9, 141.9, 136.8, 132.9 (d, *J* = 2.8 Hz), 130.5, 128.4, 124.2, 118.8, 26.9, 25.7, 20.2 (d, *J* = 12.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -183.96. HRMS (APCI) *m/z* calcd for $C_{21}H_{26}FNO_4SSi$ $[M^+]$ 435.1330, found 435.1329.

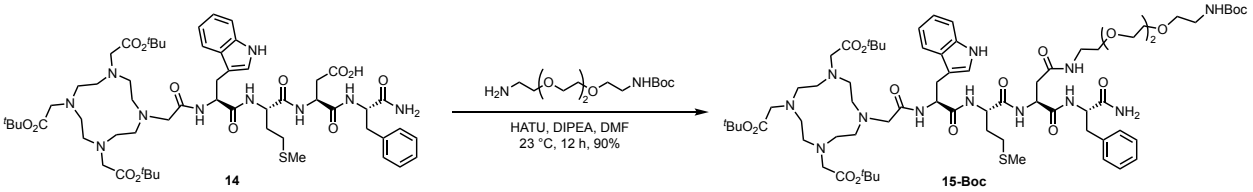
2.5 Synthesis of benzothiophene-peptide conjugates



H-Trp-Met-Asp-Phe-NH_2
13

14

tris(*t*-butyl)DOTA-Gastrin conjugate (14). To a stirred solution of gastrin tetrapeptide (H-Trp-Met-Asp-Phe-NH_2) **13** (7.31 mg, 12.25 µmol) in DMF (0.15 mL) was added DOTA-mono-NHS tris(*t*-Bu ester) (10 mg, 12.25 µmol) and DIPEA (4.2 µL, 24.50 µmol) at 0 °C. Reaction mixture was stirred at room temperature for 12 h. The crude product was purified by semi-preparative reverse phase HPLC (10% to 90% CH_3CN in water (both with 0.1% TFA) over 30 minutes, 4 mL/min flow rate; UV 220 nm). The product fractions were lyophilized to obtain desired peptide conjugate **14** (12.8 mg, 91%) as a white solid. The identity of the conjugate was confirmed by HRMS. HRMS (ESI) *m/z* calcd for $C_{57}H_{87}N_{10}O_{13}S$ $[M+H]^+$ 1151.6175, found 1151.6178.

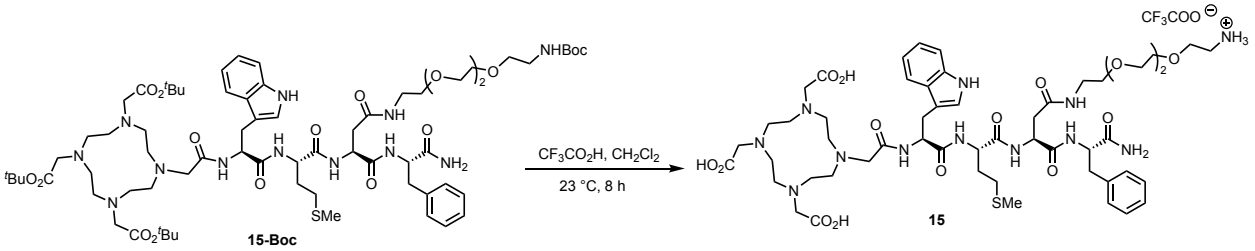


14

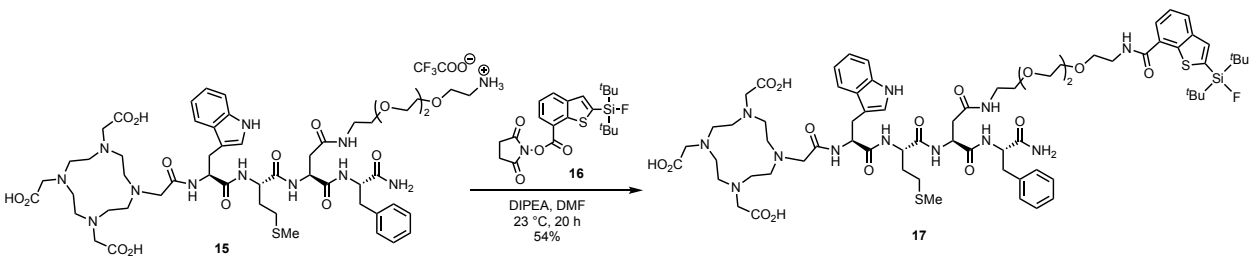
15-Boc

***N*-boc-PEGylated tris(*t*-butyl)DOTA-Gastrin conjugate (15-Boc).** To a solution of peptide conjugate **14** (14 mg, 12.16 µmol) in DMF (0.2 mL) cooled to 0- 4 °C (in ice bath), was added HATU (5.54 mg, 14.59 µmol). The contents were stirred at 0 - 4 °C for 5 min. To the reaction mixture, was added tert-butyl (2-(2-(2-(2-aminoethoxy) ethoxy)ethoxy)ethyl)carbamate (7.12 mg, 14.59 µmol) and DIPEA (6.3 µL, 36.47 µmol) and the reaction was stirred at room temperature for 18 hrs. The crude reaction was purified by semi-preparative HPLC (10% to 90% CH_3CN in water (both with 0.1 % TFA) over 30 minutes, 4 mL/min flow rate; UV 220 nm). The product fractions were lyophilized to get PEGylated peptide conjugate **15-Boc** (15.7 mg, 90%) as a white solid. The identity of the conjugate was confirmed by HRMS. HRMS (ESI) *m/z* calcd for

$C_{70}H_{112}N_{12}O_{17}SNa$ $[M+Na]^+$ 1447.7886 found 1447.7916 , and $[M/2+H]^{2+}$ calcd 713.4067, found 713.4096.



PEGylated DOTA-Gastrin conjugate (15). Boc protected peptide conjugate **15-Boc** (15.4 mg) was taken in dichloromethane (0.2 mL) and trifluoroacetic acid (0.5 mL) and stirred at room temperature for 8 h. The solvent was evaporated under reduced pressure and crude residue was used in the following reaction without any purification. HRMS (ESI) *m/z* calcd for $C_{53}H_{81}N_{12}O_{15}S$ $[M+H]^+$ 1157.5665, found 1157.5687.



Benzothiophene-SiFA-peptide conjugate (17). To a stirred solution of PEGylated DOTA-Gastrin conjugate **15** (6 mg, 4.76 μmol) in 150 μL DMF and 2.5 μL DIPEA was added *N*-hydroxysuccinimidyl ester **16** (2 mg, 4.53 μmol) at 0 °C. The crude reaction was stirred at room temperature for 20 h. The crude residue was purified by semi-preparative HPLC (10% to 90% CH_3CN in water (both with 0.1 % TFA) over 30 minutes, 4 mL/min flow rate; UV 220 nm). The product fractions were lyophilized to afford benzothiophene-SiFA-peptide conjugate **17** (3.7 mg, 54%) and recovered NHS-ester **16**. The identity of the conjugates were confirmed by HRMS. HRMS (ESI) calcd for $C_{70}H_{101}FN_{12}O_{16}S_2Si$ $[M-H]^-$ 1475.6580 found 1475.6617 and *m/z* calcd for $C_{70}H_{101}FN_{12}O_{16}S_2Si$ $[M/2+H]^{2+}$ 739.3399, found 739.3410.

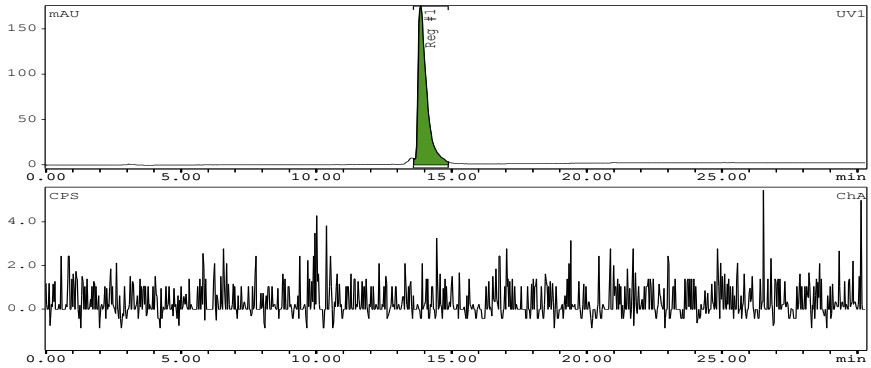


Figure S1: **Analytical HPLC chromatograph of purified benzothiophene-SiFA-peptide conjugate 17.** HPLC mobile phase: 10% acetonitrile in water (both with 0.1% TFA) to 90% over 18 min then 95% acetonitrile up to 25 min with flow rate 1.2 mL/min at UV 254 nm.

3. Radiochemistry

3.1 General Materials and Methods

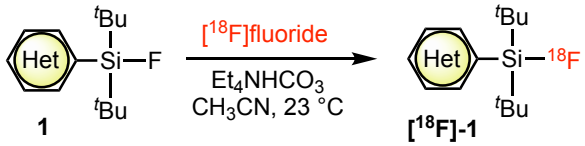
No-carrier-added [^{18}F]fluoride was produced by the ^{18}O(p,n)^{18}F nuclear reaction in a Siemens RDS-112 cyclotron at 11 MeV using a 1 mL tantalum target with havar foil. The solvents and reagents were commercially available and used without further purification. HPLC grade acetonitrile and trifluoroacetic acid were purchased from Fisher Scientific. Anhydrous acetonitrile, dimethyl sulfoxide and tetraethylammonium bicarbonate were purchased from Sigma-Aldrich. Sterile product vials were purchased from Hollister-Stier. QMA-light Sep-Paks and tC18 light cartridges were purchased from Waters Corporation. Radio-TLCs were analyzed using a miniGITA***** TLC scanner. HPLC purifications were performed on a Knauer Smartline HPLC system with inline Knauer UV (254 nm) detector and gamma-radiation coincidence detector and counter (Bioscan Inc.). Semi-preprative HPLC was performed using Phenomenex reverse-phase Luna column (10 × 250 mm, 5 µm) with a flow rate of 4 mL/min. Final purity and identity of compounds were determined by analytical HPLC analysis performed with a Phenomenex reverse-phase Luna column (4.6 × 250 mm, 5 µm) with a flow rate of 1.2 mL/min or 1 mL/min. All chromatograms were collected by a GinaStar (Raytest) analog to digital converter and GinaStar software.

Preparation of [^{18}F]tetraethylammonium fluoride ([^{18}F]TEAF)

Dry [^{18}F]TEAF was prepared using an ELIXYS automated radiosynthesizer (Sofie Biosciences). [^{18}F]Fluoride was delivered to the ELIXYS in [^{18}O]H_2O (1 mL) via nitrogen gas push and trapped on a QMA cartridge to remove the [^{18}O]H_2O. Trapped [^{18}F]fluoride was subsequently eluted into the reaction vial using a solution containing Et_4NHCO_3 (1.8-2.0 mg, ~10 µmol) in acetonitrile and water (1 mL, 8:2) (QMA cartridge was flipped before elution step). Contents in the reaction vial were evaporated by heating the vial to 110 °C while applying a vacuum for 3.5 min, with stirring. Acetonitrile (1.3 mL) was passed through the QMA cartridge to wash remaining activity into the reaction vial. The combined contents in the reaction vial were dried by azeotropic distillation (heating to 110 °C under vacuum) for 2 min. Anhydrous acetonitrile (1.3 mL) was directly added to the reaction vial and azeotropic distillation was repeated once more until dryness, approximately 3-4 min. The reaction vial was cooled to 30 °C under nitrogen pressure and acetonitrile (1 mL) was added to provide anhydrous [^{18}F]TEAF which was used for subsequent reactions.

Note: In some cases, an alternate protocol using methanol as the eluent was employed to obtain dry [^{18}F]TEAF. Briefly, the QMA cartridge washed with 1 mL methanol followed by 5 mL air. [^{18}F]Fluoride was trapped on the QMA and eluted with a solution of tetraethylammonium bicarbonate (1.5-2 mg) in methanol (0.8 mL, cartridge was flipped while elution). Additional methanol (0.8 mL) was eluted through the QMA and the methanol was evaporated at 70 °C, under vacuum to obtain dry [^{18}F]TEAF.

3.2 Isotopic exchange reactions and characterization of ^{18}F-labeled compounds



General experimental procedure: Isotopic exchange reactions were conducted in 1 mL Eppendorf tube containing hetroarylfluorosilanes **1** in dry acetonitrile (3 mM stock solution, 50 µL). To the Eppendorf tube, was added 0.5 - 1 mCi of [^{18}F]TEAF in 100-150 µL of dry acetonitrile and the contents were left at room temperature for 2 min without stirring. An aliquot of the crude reaction mixture was spotted on a silica gel coated TLC plate, developed in a glass chamber using

acetonitrile (100 %) or acetonitrile:water (95:5) as the eluent and analyzed by radio-TLC using a miniGITA* TLC scanner. The radiochemical conversion (RCC) was calculated by dividing the integrated area of the ^{18}F-fluorinated product peak by the total integrated area of all peaks on the TLC and multiplying by 100 to convert to percentage units. Isotopic exchange and purity was confirmed by analytical HPLC by co-injecting with the ^{19}F-reference standard (UV absorbance at 254 nm). An aliquot of the crude reaction mixture (10 μL) was added to the ^{19}F-reference standard (1 mg/mL) in acetonitrile (10 μL) and the sample was injected into the analytical HPLC.

3.3 Optimization Screening

High base vs Low Base. [^{18}F]TEAF was obtained by eluting fluoride ion with high base or low base, following the protocol described above. Elution with high base led to the formation of hydrolyzed products as seen in analytical HPLC (UV impurities) and the radiochemical conversions dropped over time.

Table S1. Reactions were conducted with HetSiFA **6** using 50 μmol Et_4NHCO_3.

High Base					
Concentration nmol (run)	**2 min**	**5 min**	**15 min**	**30 min**	**60 min**
150(1)	93.45	88.15	83.25	78.24	74.23
150(2)	94.67	88.12	82.24	76.14	70.12
150(3)	96.46	89.14	81.47	75.49	71.35
Average	94.86	88.47	82.32	76.62	71.9
Standard Dev.	1.51	0.58	0.89	1.43	2.11
100(1)	95.73	90.12	81.12	75.23	70.25
100(2)	94.23	90.26	79.53	73.15	69.42
100(3)	94.38	89.92	78.47	75.24	68.28
Average	94.78	90.1	79.70	74.54	69.32
Standard Dev.	0.83	0.17	1.33	1.20	0.98
50(1)	88.15	85.21	78.21	72.12	68.36
50(2)	88.2	84.56	77.63	71.25	66.72
50(3)	85.21	81.03	76.41	70.52	65.23
Average	87.18	83.60	77.41	71.29	66.77
Standard Dev.	1.71	2.25	0.92	0.80	1.57

Table S2. Reactions were conducted with HetSiFA **6** using 5.75 μmol Et_4NHCO_3.

Low Base			
Concentration nmol (run)	**2 min**	**15 min**	**30 min**
150(1)	92.84	94.11	95.39
150(2)	94.33	96.11	95.66
150(3)	92.21	92.05	97.45
150(4)	94.67	---	---
Average	93.51	94.09	96.16
Standard Dev.	1.18	2.03	1.11
100(1)	92.13	91.21	91.82
100(2)	92.77	93.1	93.39
100(3)	92.12	93.85	93.69
100(4)	89.92	90.85	92.53
Average	91.74	92.25	92.85
Standard Dev.	1.25	1.45	0.84
50(1)	88.97	93.44	95.43
50(2)	89.52	94.48	93.83
50(3)	90.83	93.85	93.03
Average	89.77	93.92	94.09
Standard Dev.	0.95	0.523	1.22
10(1)	83.52	87.52	93.51
10(2)	82.54	85.86	92.26
10(3)	85.52	88.87	90.94
Average	83.86	87.42	92.23
Standard Dev.	1.52	1.50	1.29

Table S3. Reactions were conducted with HetSiFA **12**.

Et_4NHCO_3 mg (µmol)	Elution solvent	Elution efficiency (%)	Time (min)[b]	RCC (%)
9.0 (47.1)	Acetonitrile/water	96	2 15 30	93 85 65
5.0 (26.2)	Acetonitrile/water	78	2 15 30	90 80 75
4.0 (20.9)	Methanol	50[a]	2 15 30	88 82 76
2.0 (10.5)	Methanol	35[a]	2 15 30	92 90 90
2.0 (10.5)	**Acetonitrile/water**	**64[a]**	**2** **15** **30** **60**	**95** **97** **97** **95**
1.5 (7.8)	Acetonitrile/water	60[a]	2	91
1.1 (5.8)	Acetonitrile/water	55[a]	2	88

[a]QMA cartridge was flipped to elute in the opposite direction as [^{18}F]fluoride was trapped. [b]Reactions were conducted with 150 nmol HetSiFA **12** and left at room temperature without stirring.

Table S4. Stability screen of HetSiFA **[^{18}F]-12** in acetonitrile with 1.8 mg (9.4 µmol) Et_4NHCO_3 used for elution.

Time (min)	RCC (%)[a]
2	95
5	96
15	97
30	97
60	97

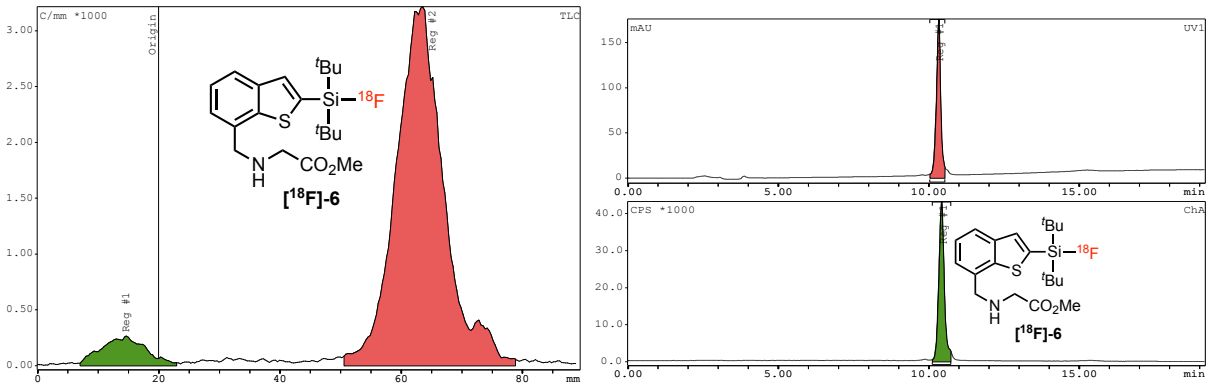
[a]Reaction was conducted at room temperature.

Table S5. Effect of precursor concentration of HetSiFA **12** on RCC.

Precursor amount (nmol)	RCC (%)[a]
5	58
25	83
50	86
100	94
150	**96**

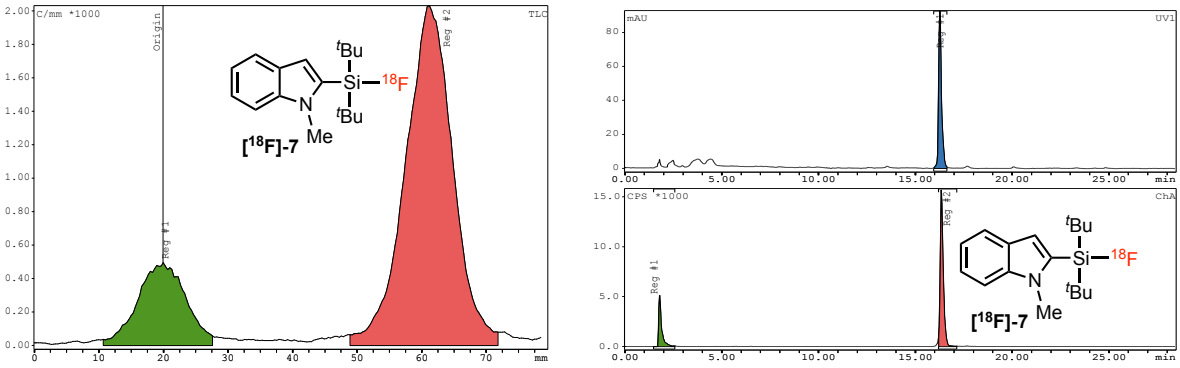
[a]Reaction conditions: Et_4NHCO_3 (1.8 mg, 9.4 µmol) in 150 µL acetonitrile. RCCs were obtained after 2 min standing at room temperature.

3.4 Radio-TLC/Radio-HPLC analysis of ^{18}F-labeled HetSiFAs



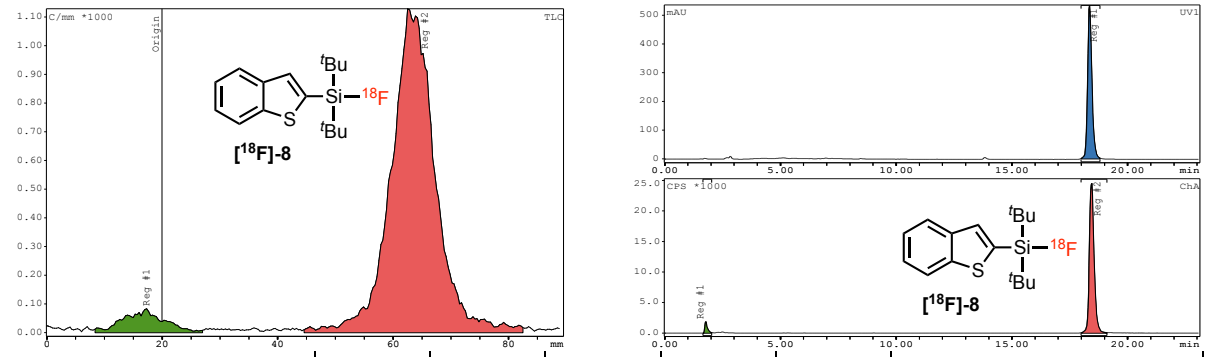
Run	1	2	3	4	**mean**	**Standard deviation**
Radio TLC yield (%)	92	93	92	90	92	1

Figure S2. Isotopic exchange and characterization of methyl ((2-(di-tert-butylfluorosilyl)benzo[b]thiophen-7-yl)methyl)glycinate ([^{18}F]-6). Radio-TLC scan (left). Radio-HPLC (right) with 254 nm UV trace of ^{19}F reference standard (upper chromatogram) and radioactivity trace of reaction mixture (lower chromatogram). HPLC mobile phase: 30% Acetonitrile in water (both with 0.1% TFA) to 90% acetonitrile in water over 10 min; then to 95 % acetonitrile in water from 13 min to 18 min.



Run	1	2	3	4	**mean**	**Standard deviation**
Radio TLC yield (%)	82	82	80	78	81	2

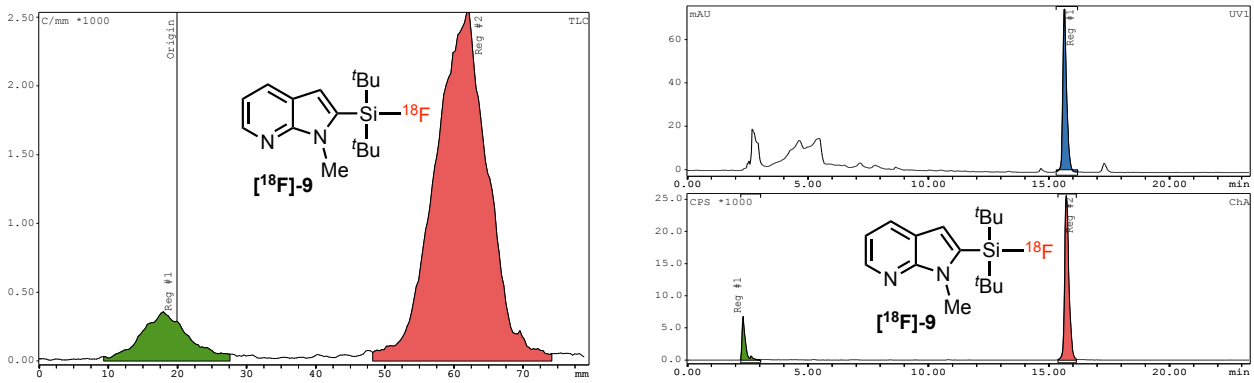
Figure S3. Isotopic exchange and characterization of 2-(di-*tert*-butylfluorosilyl)-1-methyl-1*H*-indole ([^{18}F]-7). Radio-TLC scan (left). Radio-HPLC (right) with 254 nm UV trace of ^{19}F reference standard (upper chromatogram) and radioactivity trace of reaction mixture (lower chromatogram). HPLC mobile phase: 10% Acetonitrile in water to 95% acetonitrile in water over 8 min; then to 95 % acetonitrile in water from 8 min to 25 min.



Run	1	2	3	4	**mean**	**Standard deviation**
Radio TLC yield (%)	93	91	90	89	91	1

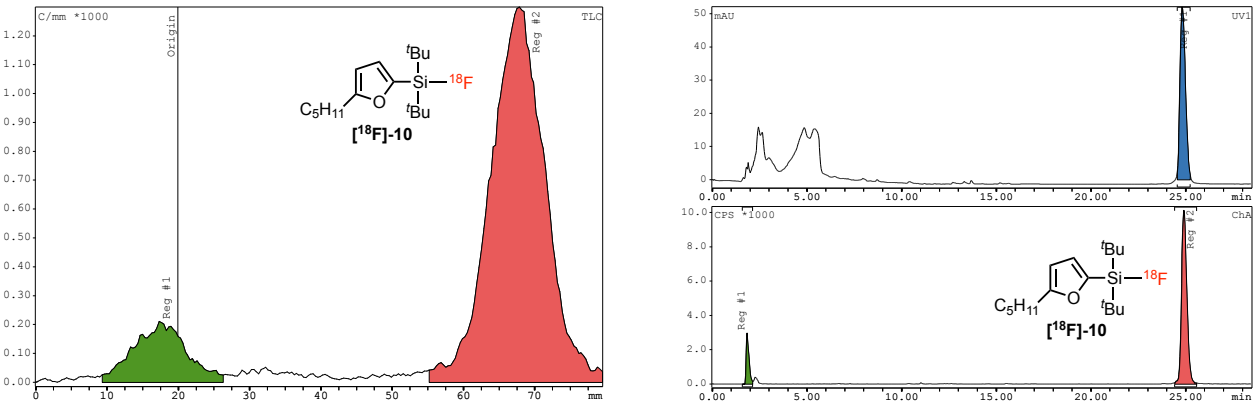
Figure S4. Isotopic exchange and characterization of benzo[*b*]thiophen-2-yldi-tert-butylfluorosilane ([^{18}F]-8). Radio-TLC scan (left). Radio-HPLC (right) with 254 nm UV trace of ^{19}F reference standard (upper chromatogram) and radioactivity trace of reaction mixture (lower

chromatogram). HPLC mobile phase: 10% Acetonitrile in water to 95% acetonitrile in water over 8 min; then to 95 % acetonitrile in water from 8 min to 25 min.



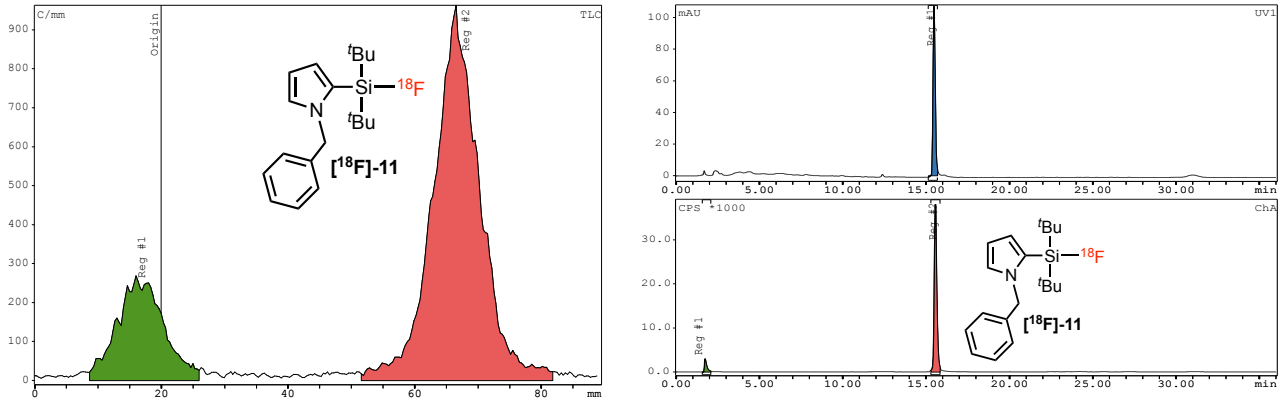
Run	1	2	3	**mean**	**Standard deviation**
Radio TLC yield (%)	89	87	86	87	1

Figure S5. Isotopic exchange and characterization of 2-(di-*tert*-butylfluorosilyl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine ([^{18}F]-9). Radio-TLC scan (left). Radio-HPLC (right) with 254 nm UV trace of ^{19}F reference standard (upper chromatogram) and radioactivity trace of reaction mixture (lower chromatogram). HPLC mobile phase: 10% Acetonitrile in water to 95% acetonitrile in water over 10 min; then to 95 % acetonitrile in water from 10 min to 25 min.



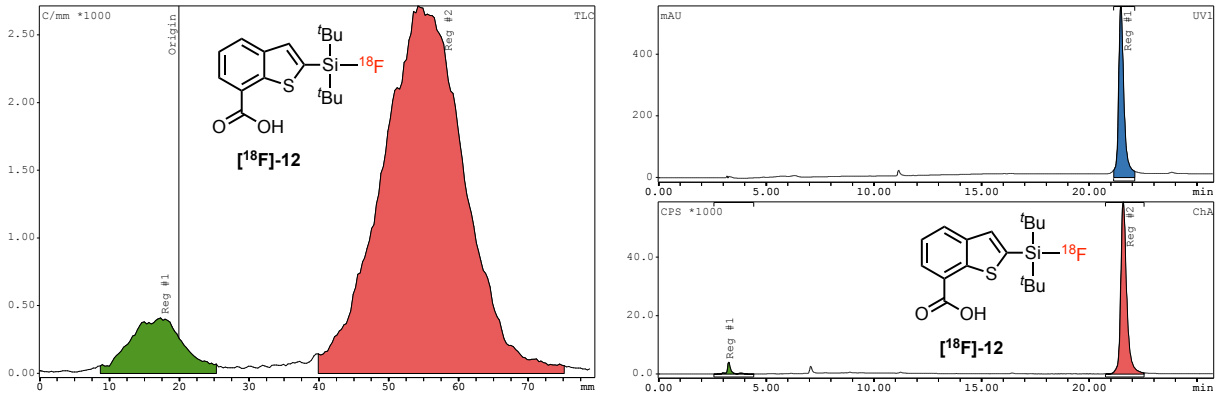
Run	1	2	3	**mean**	**Standard deviation**
Radio TLC yield (%)	87	88	90	88	2

Figure S6. Isotopic exchange and characterization of di-*tert*-butylfluoro(5-pentylfuran-2-yl)silane ([^{18}F]-10). Radio-TLC scan (left). Radio-HPLC (right) with 254 nm UV trace of ^{19}F reference standard (upper chromatogram) and radioactivity trace of reaction mixture (lower chromatogram). HPLC mobile phase: 10% Acetonitrile in water to 95% acetonitrile in water over 10 min; then to 95 % acetonitrile in water from 10 min to 25 min.



Run	1	2	3	**mean**	**Standard deviation**
Radio TLC yield (%)	78	80	84	81	3

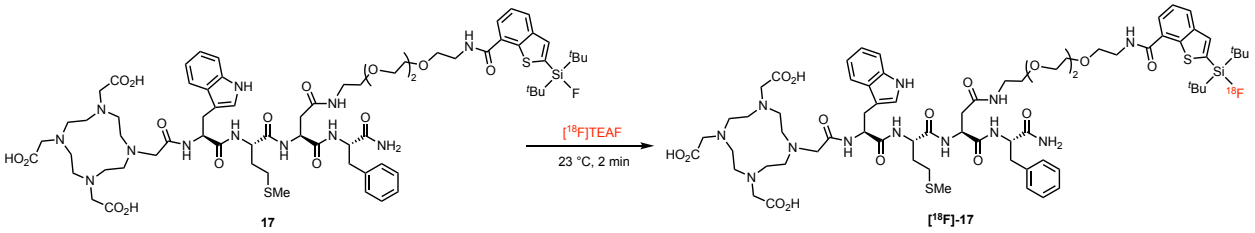
Figure S7. Isotopic exchange and characterization of 1-benzyl-2-(di-*tert*-butylfluorosilyl)-1*H*-pyrrole ([^{18}F]-11). Radio-TLC scan (left). Radio-HPLC (right) with 254 nm UV trace of ^{19}F reference standard (upper chromatogram) and radioactivity trace of reaction mixture (lower chromatogram). HPLC mobile phase: 10% Acetonitrile in water to 95% acetonitrile in water over 8 min; then to 95 % acetonitrile in water from 8 min to 25 min.



Run	1	2	3	4	5	6	7	8	9	10	11	12	13	14	**mean**	**Standard deviation**
Radio TLC yield (%)	88	88	89	95	90	94	92	88	91	87	93	91	89	86	90	3

Figure S8. Isotopic exchange and characterization of 2-(di-*tert*-butylfluorosilyl)benzo[*b*]thiophene-7-carboxylic acid ([^{18}F]-12). Radio-TLC scan (left). Radio-HPLC (right) with 254 nm UV trace of ^{19}F reference standard (upper chromatogram) and radioactivity trace of reaction mixture (lower chromatogram). HPLC mobile phase: 10% Acetonitrile in water to 95% acetonitrile in water over 12 min; then to 95 % acetonitrile in water from 12 min to 25 min.

3.5 Automated radiolabeling of benzothiophene-SiFA-Peptide conjugate 17



Using an ELIXYS radiosynthesis module, benzothiophene-SiFA-Peptide conjugate **17** in acetonitrile (1 mM solution, 250 µL) was added to anhydrous [^{18}F]TEAF (~ 12 mCi) and contents were kept at 23 ^{o}C for 2 min without stirring. The crude mixture was diluted with 10 mL 0.01 M HEPES (pH = 4) and passed through a C18 cartridge to afford **[^{18}F]-17**. Residual solvent and [^{18}F]fluoride were removed by flushing the C18 cartridge with water (~2 mL). **[^{18}F]-17** was eluted with ethanol (250 - 500 µL) and diluted with saline to a final formulation of 5-8% ethanol in saline.

Table S6. Isotopic exchange of peptide conjugate **17** to afford **[^{18}F]-17**.

Et_4NHCO_3 mg (µmol)[a]	Initial [^{18}F]TEAF for IEX reaction (mCi)	Final Activity after formulation (mCi)	% RCC[b]	% RCY[c] (isolated, non-decay corrected)
1.8 (9.4)	11.5	7.5	95	65
1.8 (9.4)	12.5	6.6	93	53
1.5 (7.8)	11.2	6.2	95	55
			94 ± 1	**58 ± 6**

[a]Standard elution with acetonitrile:water as described above
[b]RCC determined by radio-TLC, before formulation
[c]Isolated RCY calculated after formulation; formulation was not optimized

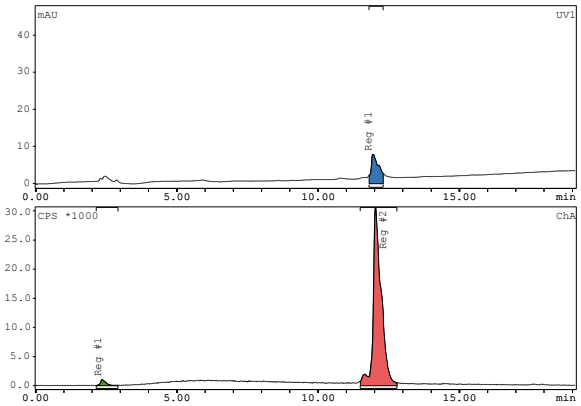


Figure S9. Crude [^{18}F]-17. Radio-HPLC with 254 nm UV trace (top) and radioactivity trace (lower) of crude reaction mixture after 2 min. HPLC mobile phase: 10% acetonitrile in water (both with 0.1% TFA) to 95% over 15 min then 95% acetonitrile up to 25 min with flow rate 1.2 mL/min.

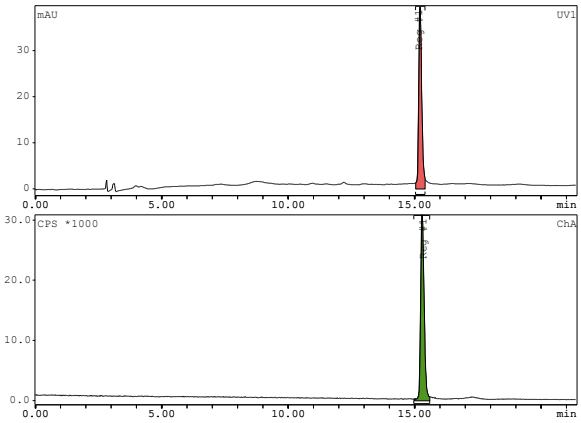


Figure S10. Formulated [^{18}F]-17 . Radio-HPLC of formulated peptide **[^{18}F]-17** with 254 nm UV trace (top) and radioactivity trace (lower). HPLC mobile phase: 10% acetonitrile in water (both with 0.1% TFA) to 90% over 18 min then to 95% acetonitrile at 25 min with flow rate 1.2 mL/min.

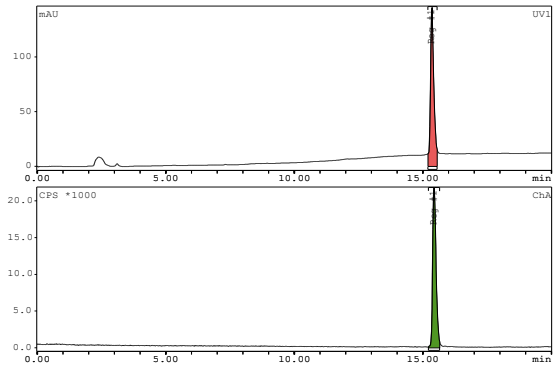
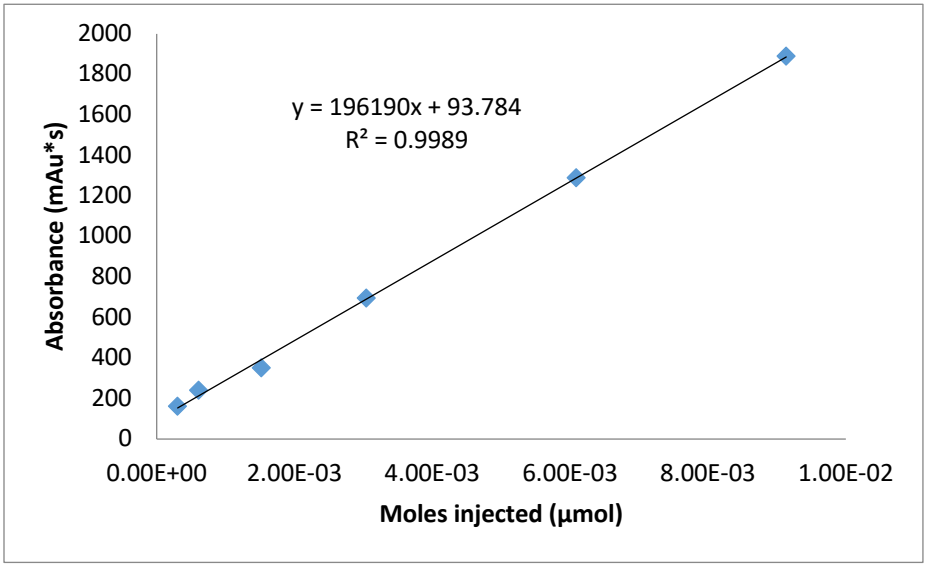


Figure S11. Co-injection of formulated [^{18}F]-17 with reference standard. Radio-HPLC with 254 nm UV trace of reference standard **17** (top) and radioactive trace of **[^{18}F]-17** (lower). HPLC mobile phase: 10% acetonitrile in water (both with 0.1% TFA) to 90% over 18 min then to 95% acetonitrile at 25 min with flow rate 1.2 mL/min.

3.6 Molar Activity of benzothiophene-SiFA-Peptide conjugate [^{18}F]-17

A calibration curve was generated from standard solutions of **17**, by measuring the UV absorbance at different concentrations. The activity of **[^{18}F]-17** injected divided by the concentration of the product measured from the calibration curve afforded the molar activity. The molar activity of **[^{18}F]-17** was calculated to be 0.032 ± 0.015 Ci/μmol.



Volume Injected (μL)	Activity Injected (μCi)	Absorbance (mAu*s)	Moles from Curve (μmol)	Specific Activity (Ci/μmol)
25	65	789	3.54E-03	1.83E-02
25	50	392	1.52E-03	3.29E-02
10	70	331	1.21E-03	5.79E-02
25	85	632	2.74E-03	3.10E-02
60	100	1024	4.74E-03	2.11E-02

4. MicroPET/CT in vivo imaging experiments

4.1 Methods

Animal studies were approved by the UCLA Animal Research Committee and carried out according to the guidelines of the Department of Laboratory Animal Medicine at UCLA. Female C57BL6 mice were injected intravenously via tail vein with approximately 2.2 MBq (60 μCi) of **[^{18}F]-17**. Animals were kept warm on heating pads throughout the imaging procedures. At 1 and 2 h after tracer injection, mice were anesthetized with 2% isoflurane in oxygen and placed in dedicated Genisys8 imaging chambers for PET/CT imaging on the Genisys8 PET/CT (Sofie Biosciences). PET scans were acquired for 10 min with an energy window of 150-650 keV reconstructed using ML-EM, followed by CT acquisition. All PET images were corrected for CT-based photon attenuation, detector normalization and radioisotope decay (scatter correction was not applied) and converted to units of percent injected dose per gram (%ID/g). Images were analyzed by drawing regions-of-interest (ROI) in select tissues using AMIDE v1.0.5.[3]

Organ	1 h	2 h
GI	107 ± 24	122 ± 48
Bladder	35 ± 12	30 ± 7
Gallbladder	33 ± 14	28 ± 9
Bone (knee)	8.0 ± 0.65	8.2 ± 0.56
Liver	5.0 ± 0.07	2.4 ± 0.47
Kidney	2.9 ± 0.62	2.2 ± 0.38
Heart	2.0 ± 0.25	1.2 ± 0.26
Brain	0.44 ± 0.06	0.33 ± 0.03
Muscle	0.36 ± 0.06	0.27 ± 0.11

Table S7. Biodistribution of **[^{18}F]-17** in C57BL6 mice following PET quantification (%ID/g), 1 and 2 h post-injection.

5. References

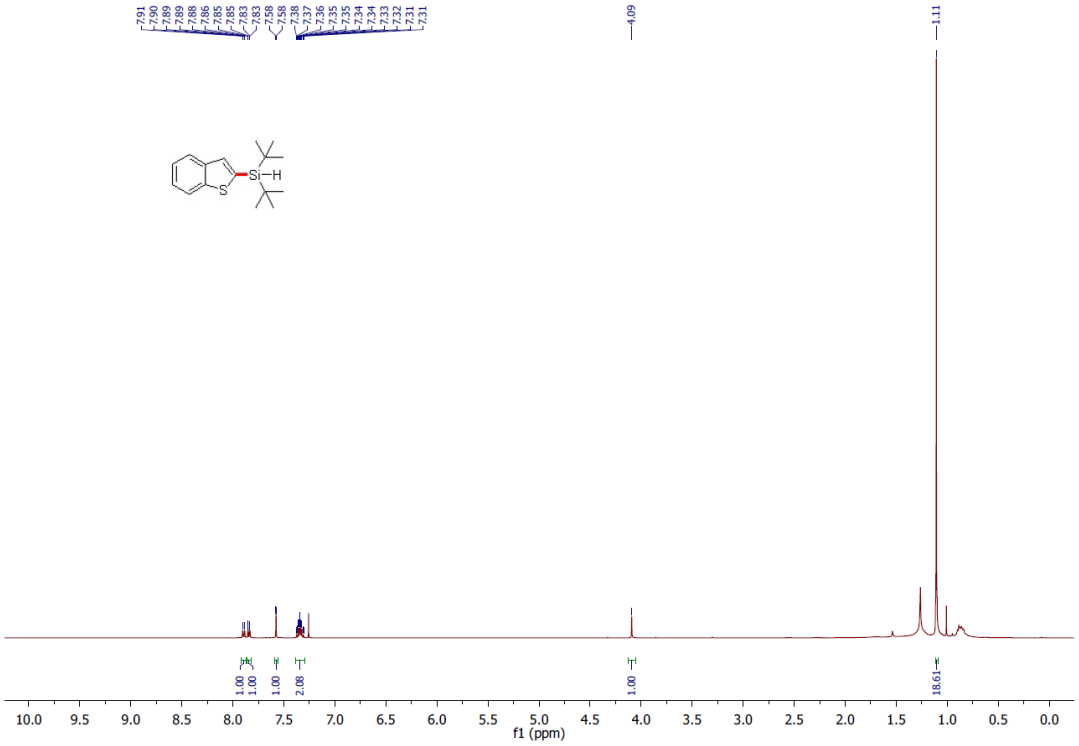
1. Toutov, A. A.; Liu, W.-B.; Betz, K. N.; Fedorov, A.; Stoltz, B. M.; Grubbs, R. H., Silylation of C–H bonds in aromatic heterocycles by an Earth-abundant metal catalyst. *Nature* **2015,** *518*, 80.

2. Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B., Facile Oxidation of Aldehydes to Acids and Esters with Oxone. *Org. Lett*. **2003**, *5*, 1031.

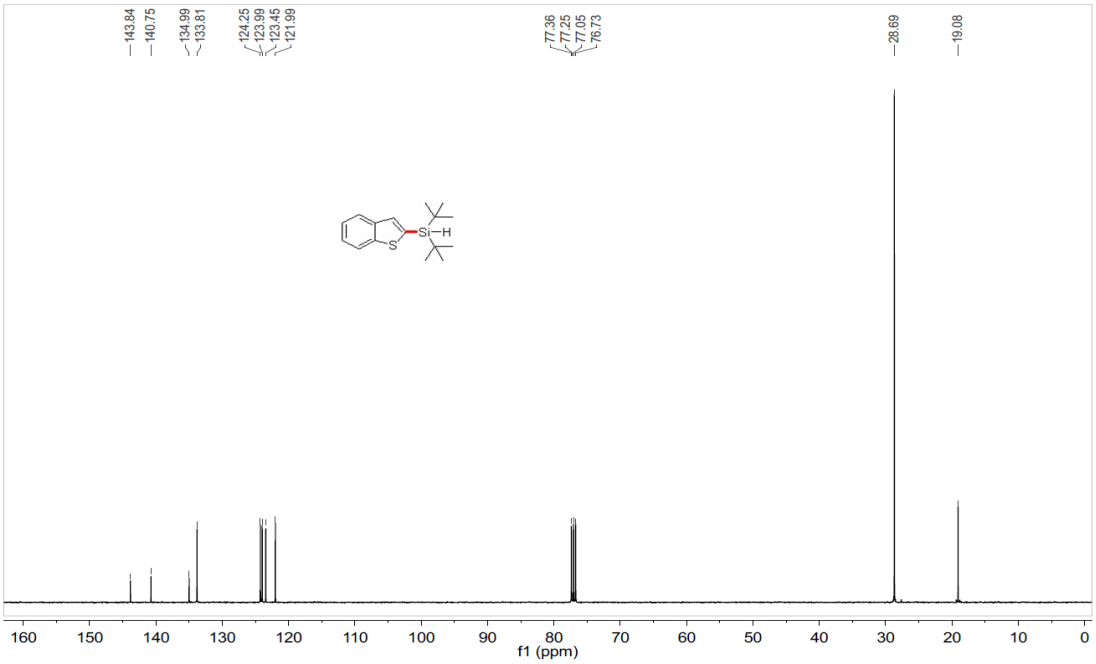
3. Loening, A.; Gambhir, S. S., AMIDE: a free software tool for multimodality medical image analysis. *Mol. Imaging* **2003,** *3*, 131.

6. NMR Spectra

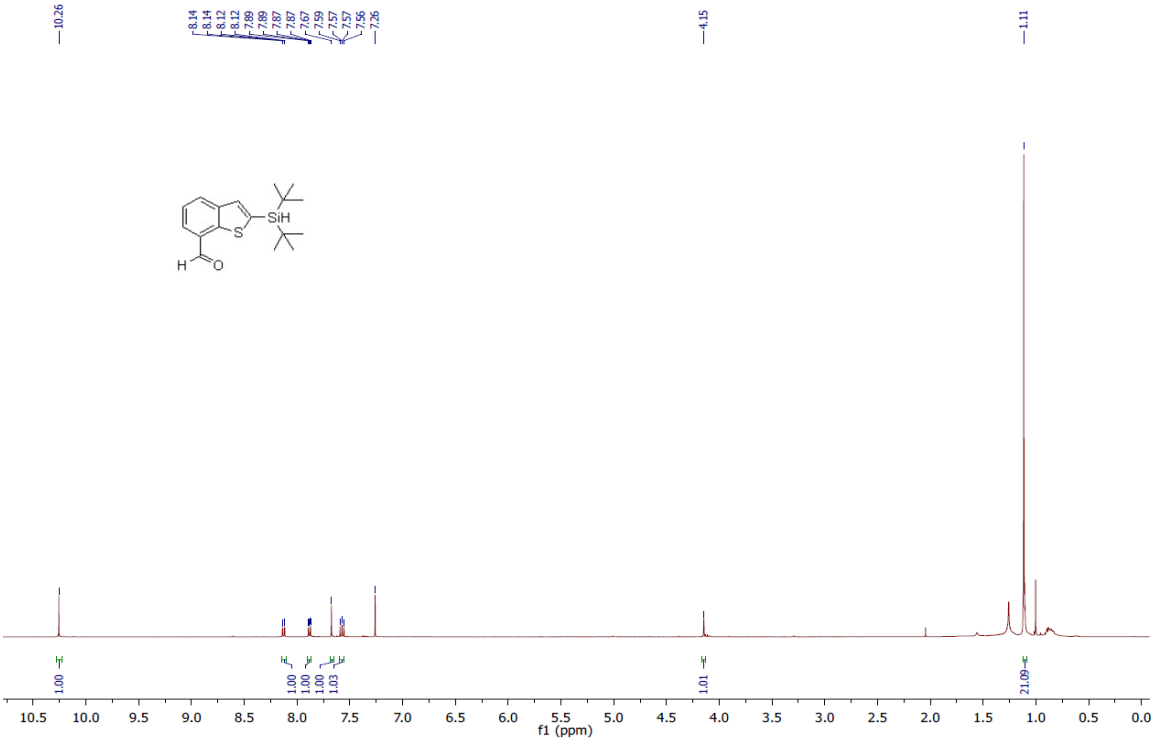
^{1}H NMR for **3** (400 MHz, $CDCl_3$)



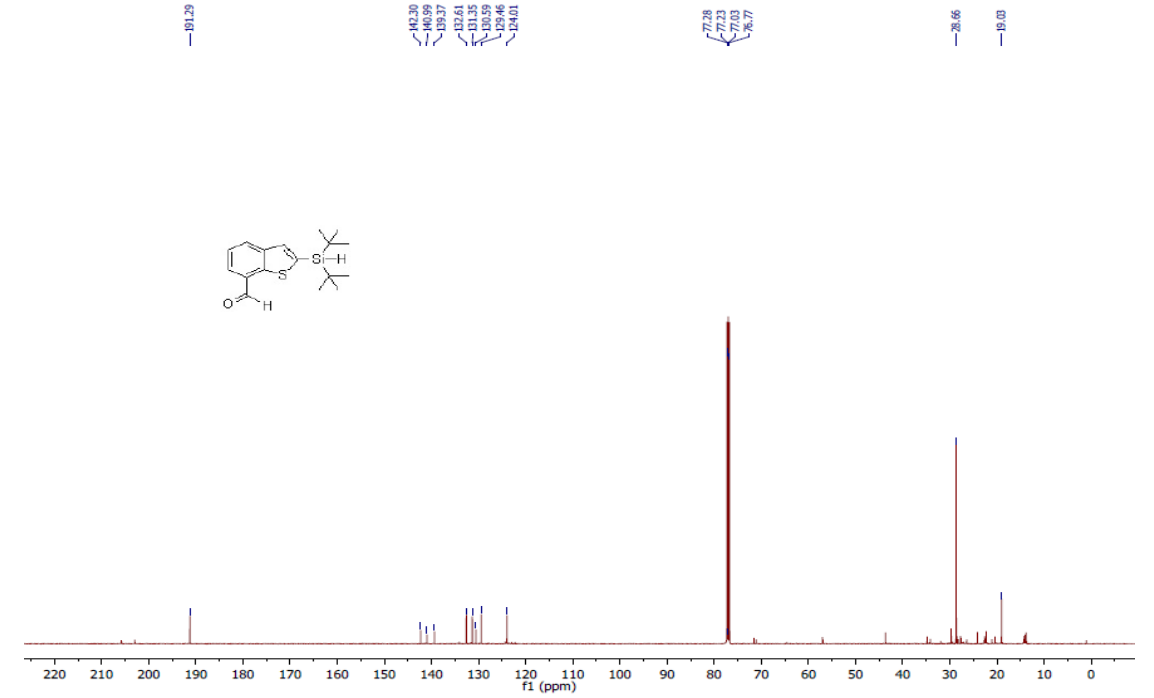
^{13}C NMR for **3** (100 MHz, $CDCl_3$)



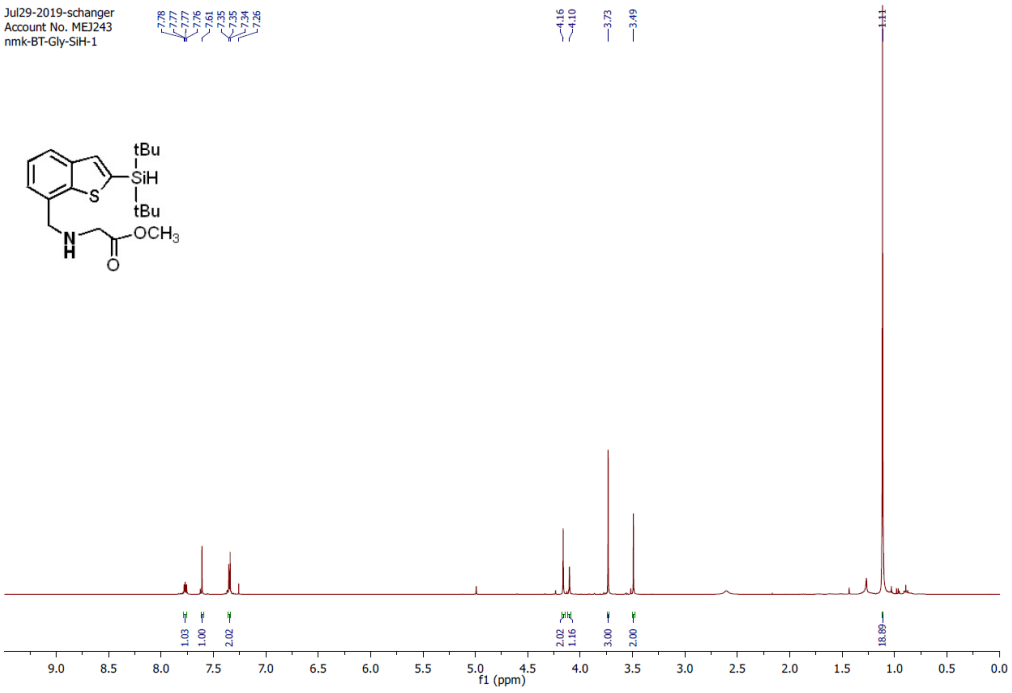
^{1}H NMR for **4** (400 MHz, $CDCl_3$)



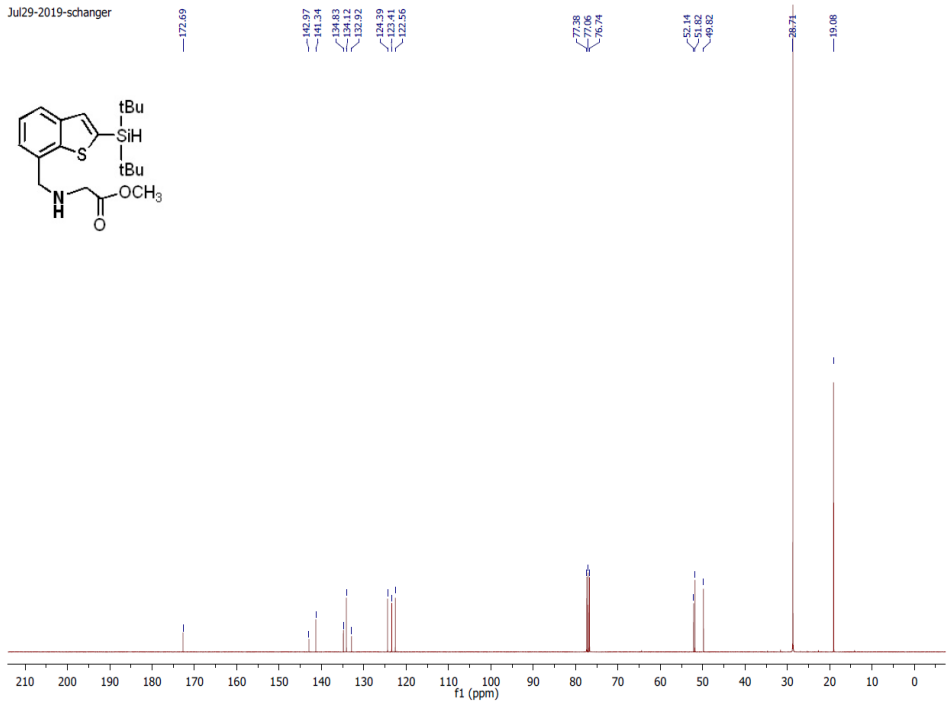
^{13}C NMR for **4** (100 MHz, $CDCl_3$)



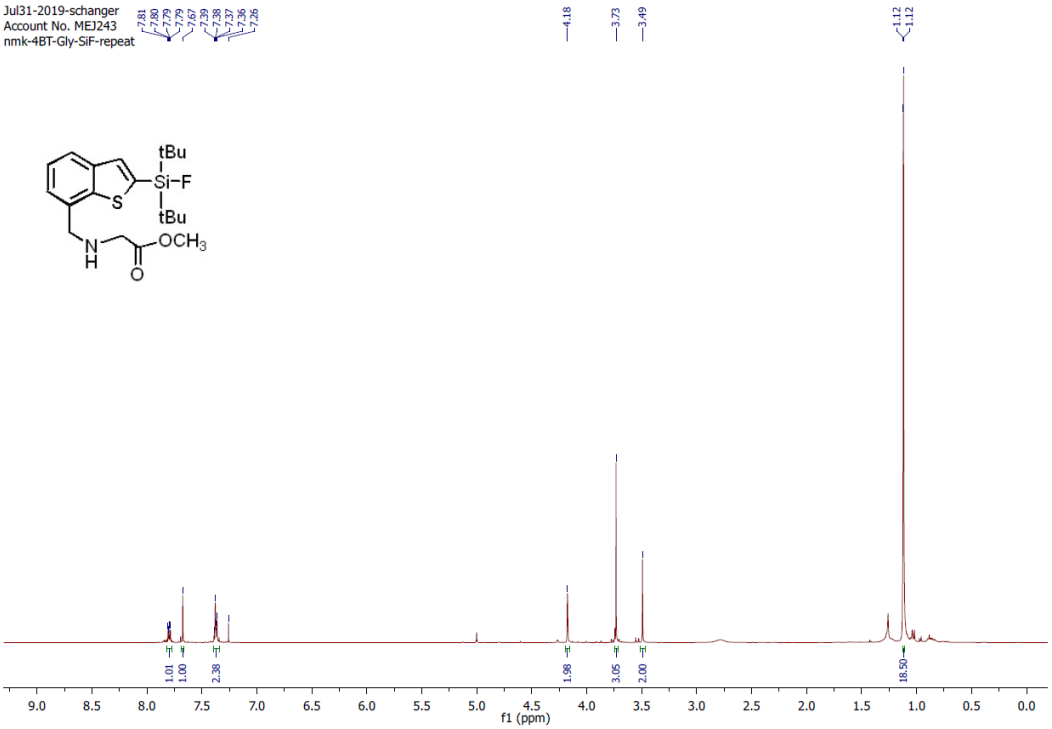
^{1}H NMR for **5** (400 MHz, $CDCl_3$)



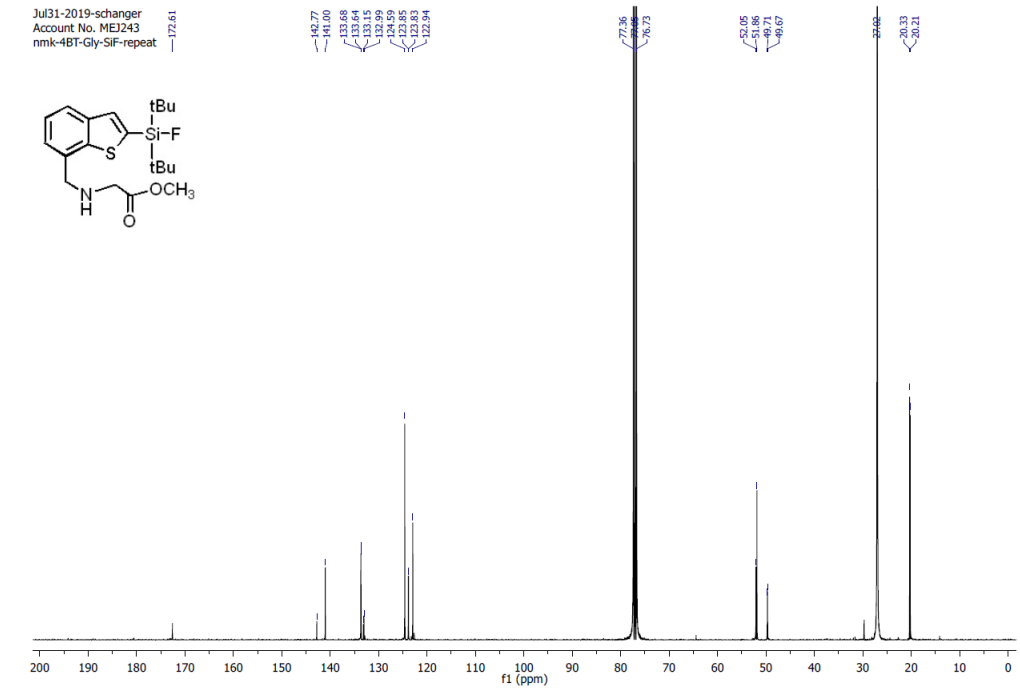
^{13}C NMR for **5** (100 MHz, $CDCl_3$)



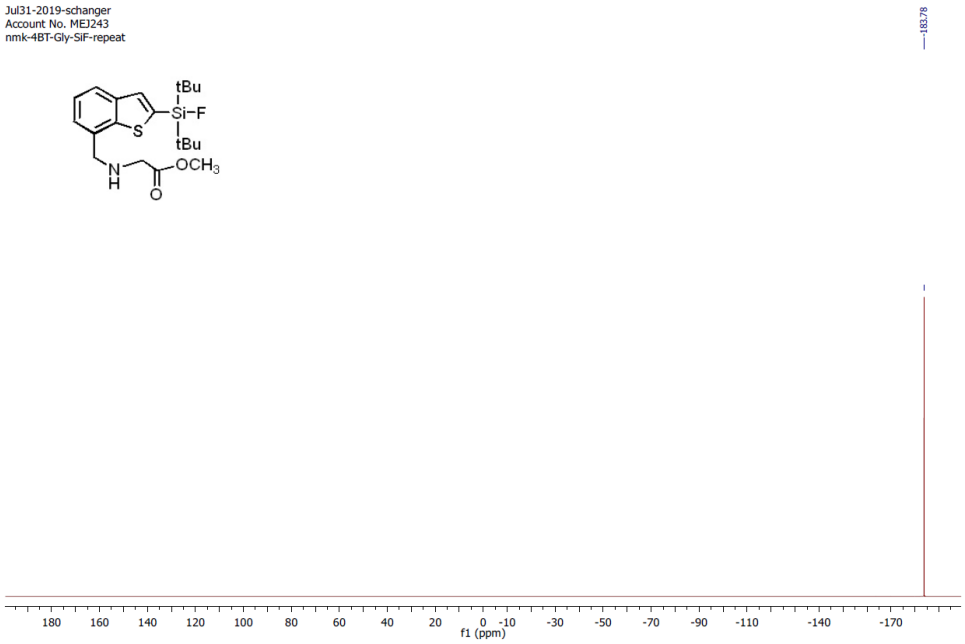
^{1}H NMR for **6** (400 MHz, $CDCl_3$)



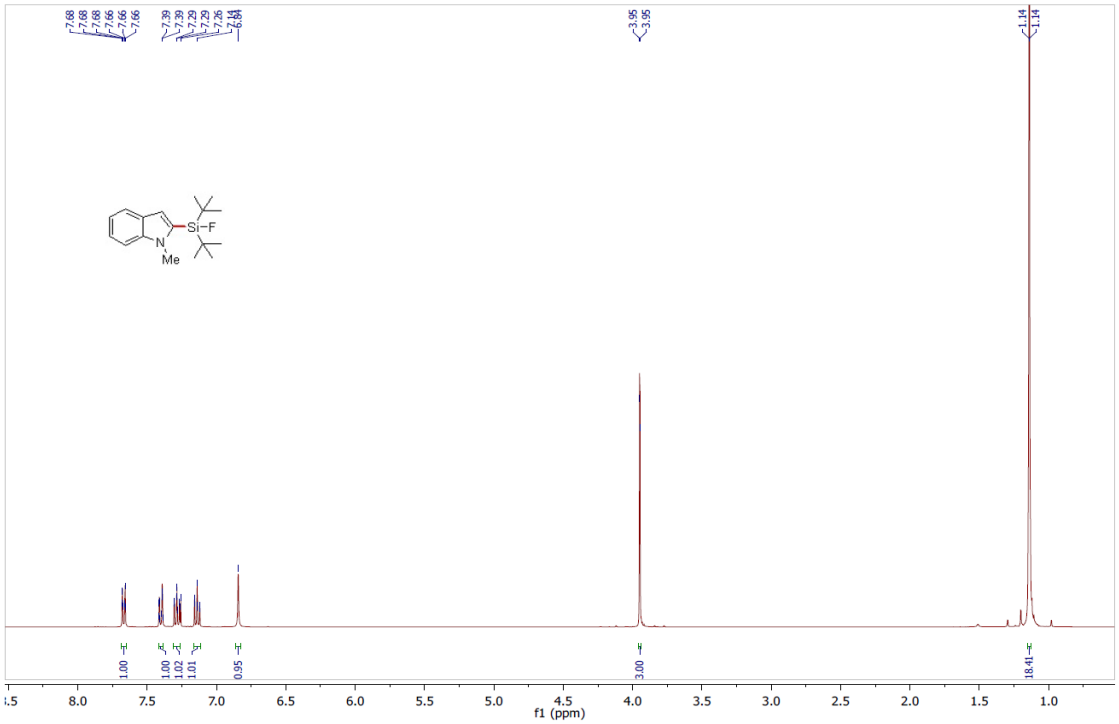
^{13}C NMR for **6** (100 MHz, $CDCl_3$)



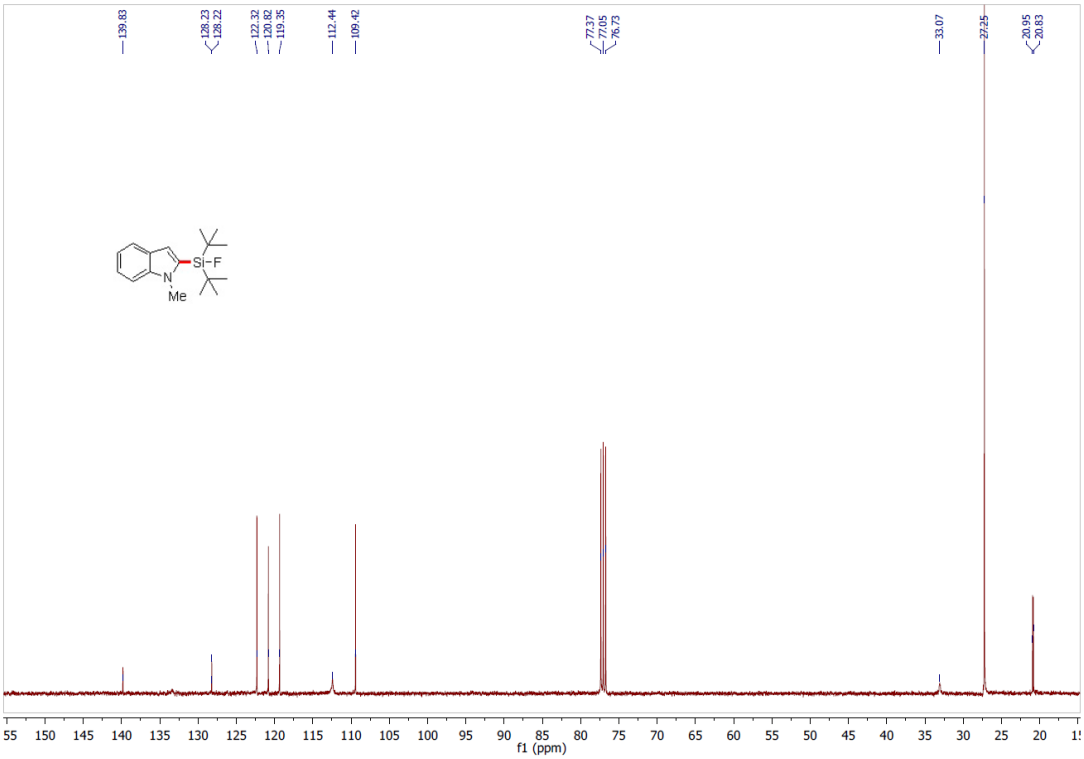
^{19}F NMR for **6** (376 MHz, $CDCl_3$)



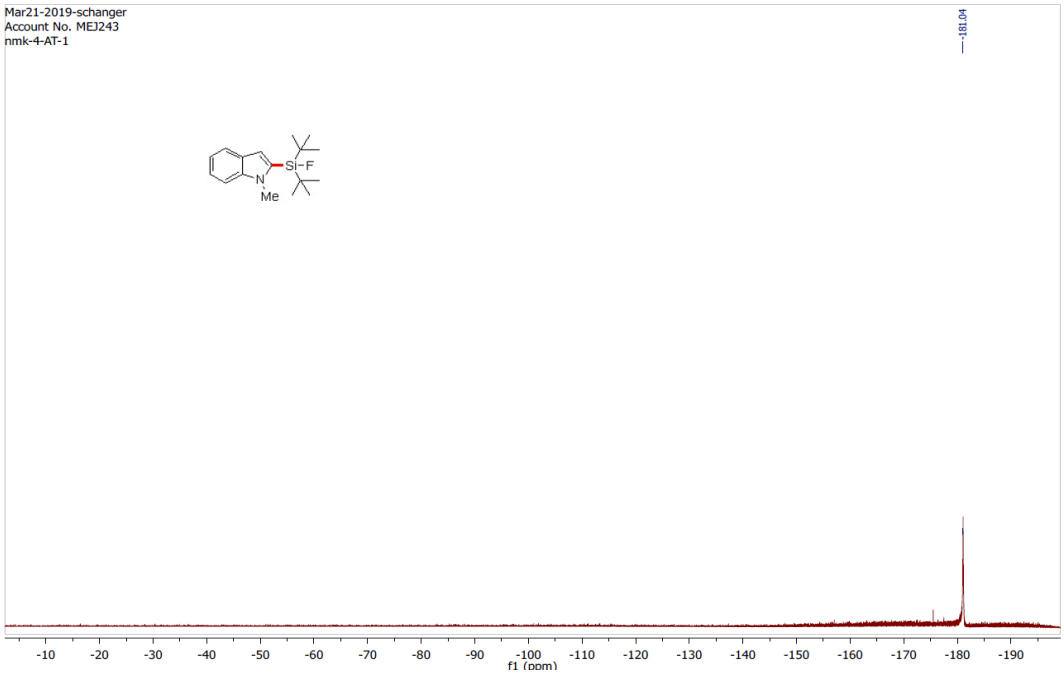
^{1}H NMR for **7** (400 MHz, $CDCl_3$)



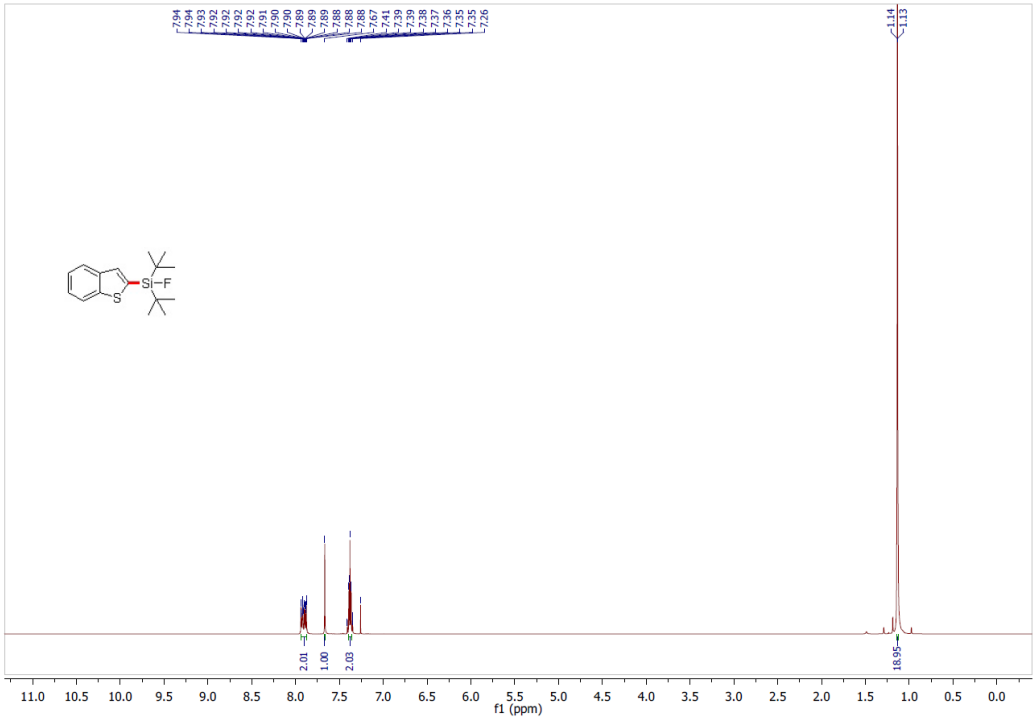
^{13}C NMR for **7** (100 MHz, $CDCl_3$)



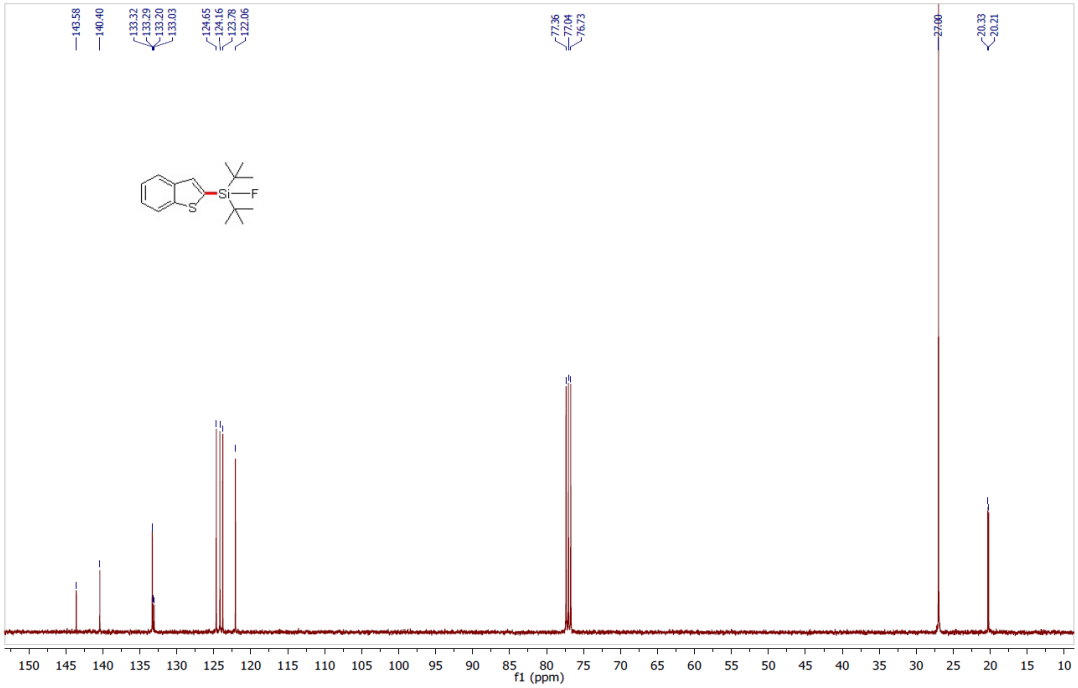
^{19}F NMR for **7** (376 MHz, $CDCl_3$)



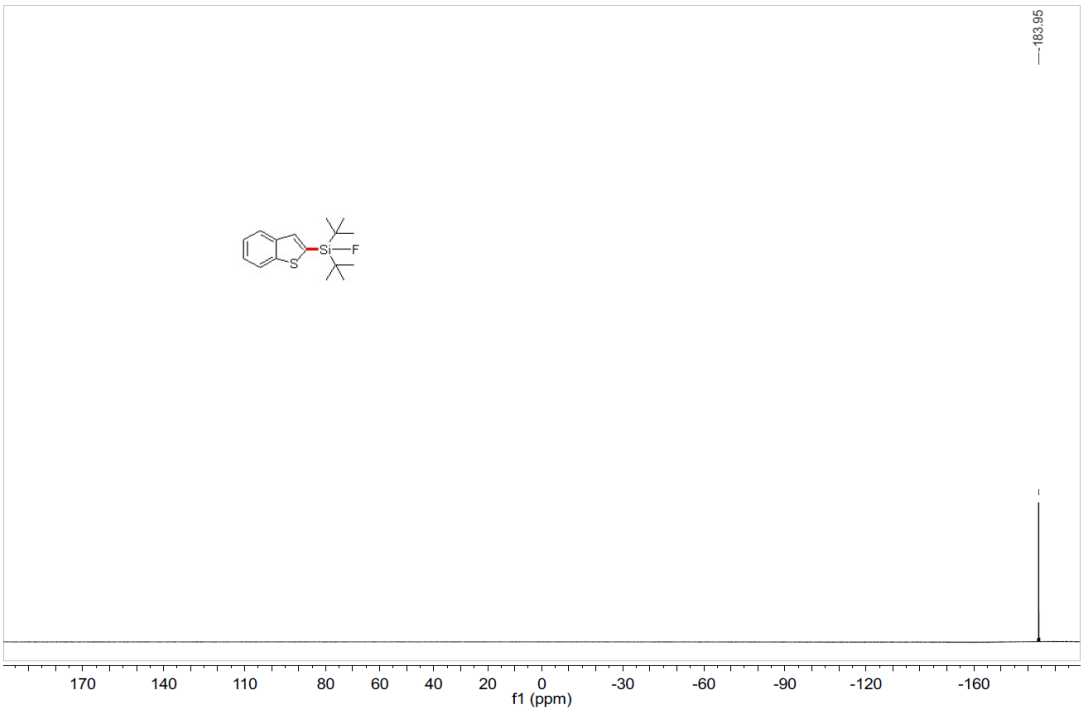
^{1}H NMR for **8** (400 MHz, $CDCl_3$)



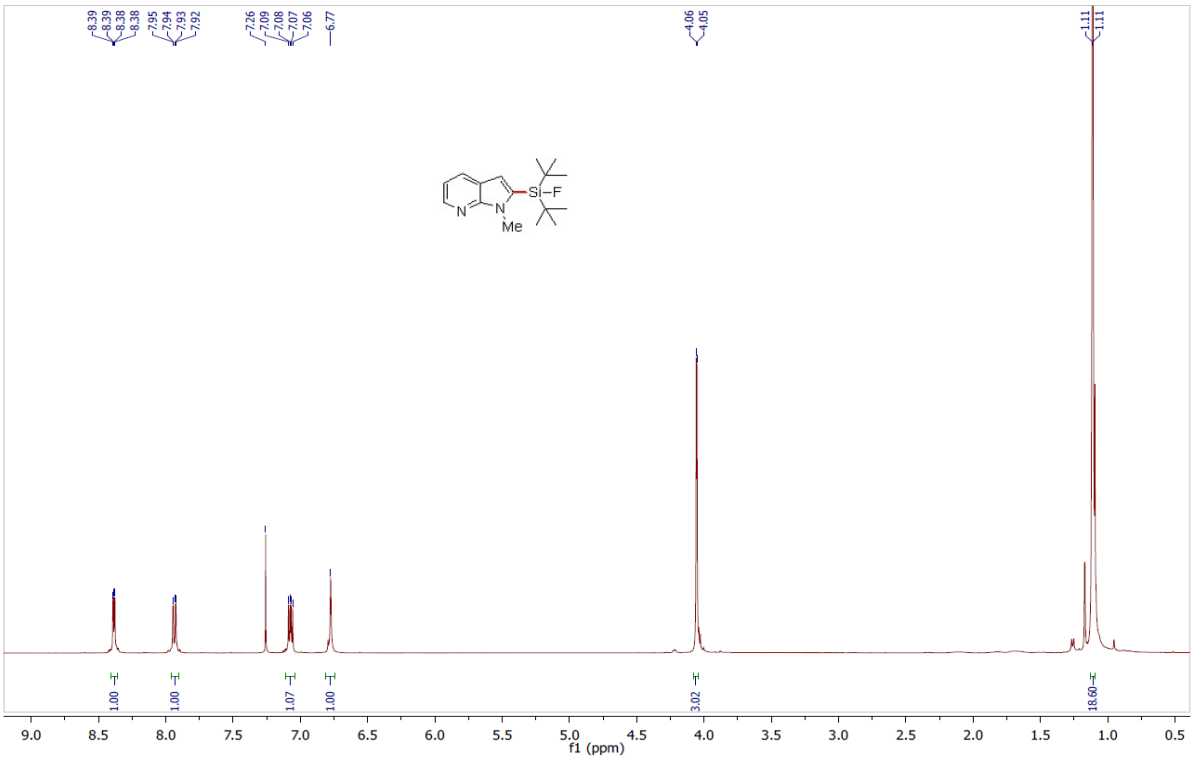
^{13}C NMR for **8** (100 MHz, $CDCl_3$)



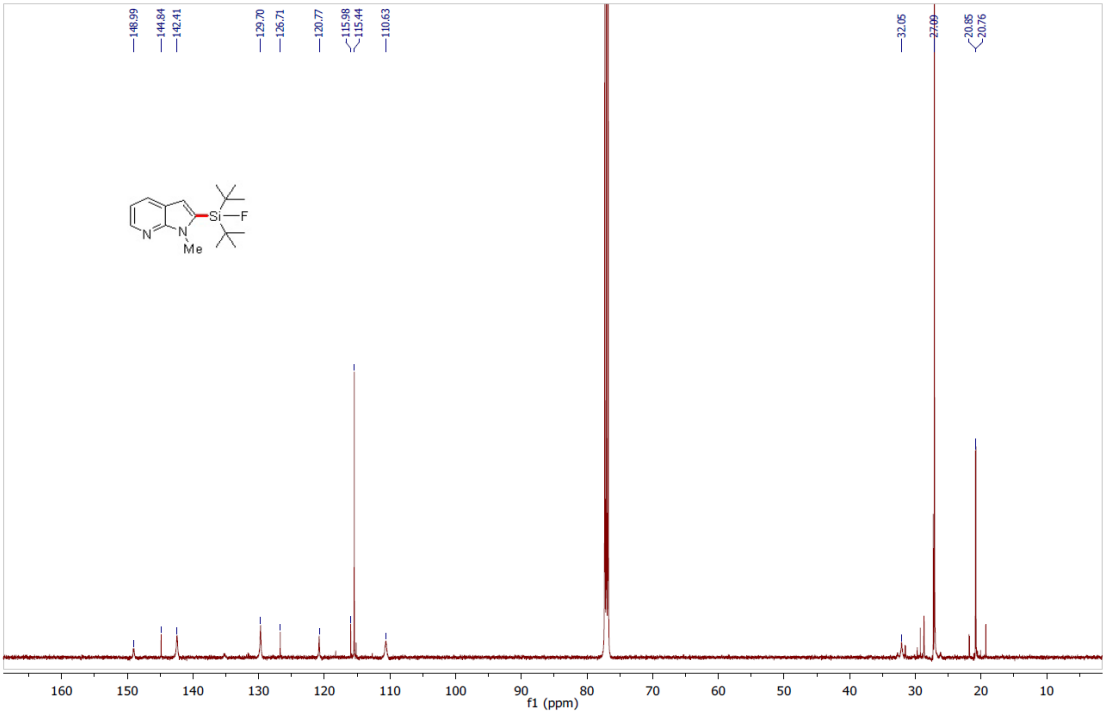
^{19}F NMR for **8** (376 MHz, $CDCl_3$)



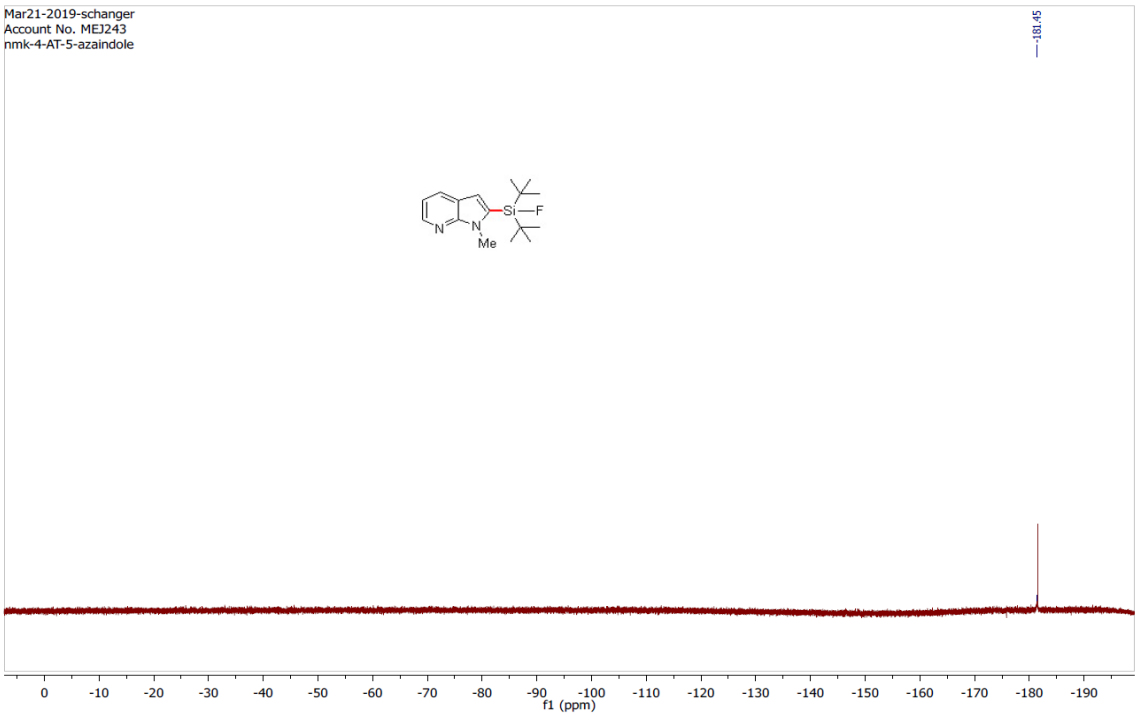
^{1}H NMR for **9** (400 MHz, $CDCl_3$)



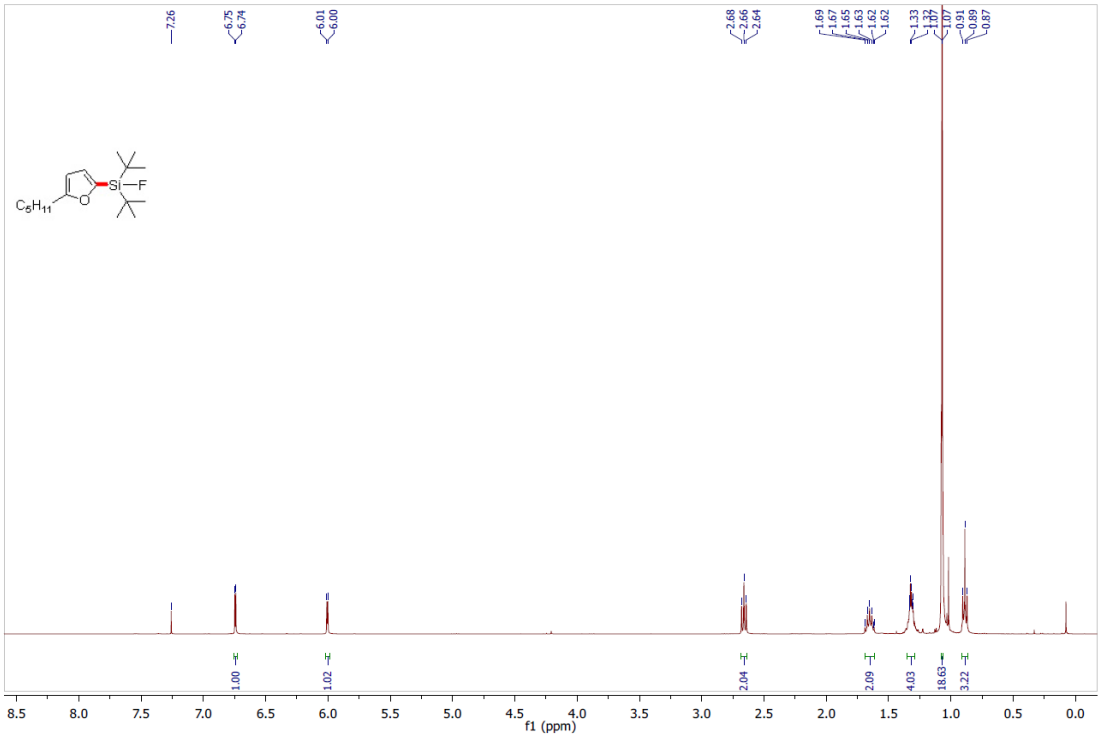
^{13}CNMR for **9** (100 MHz, $CDCl_3$)



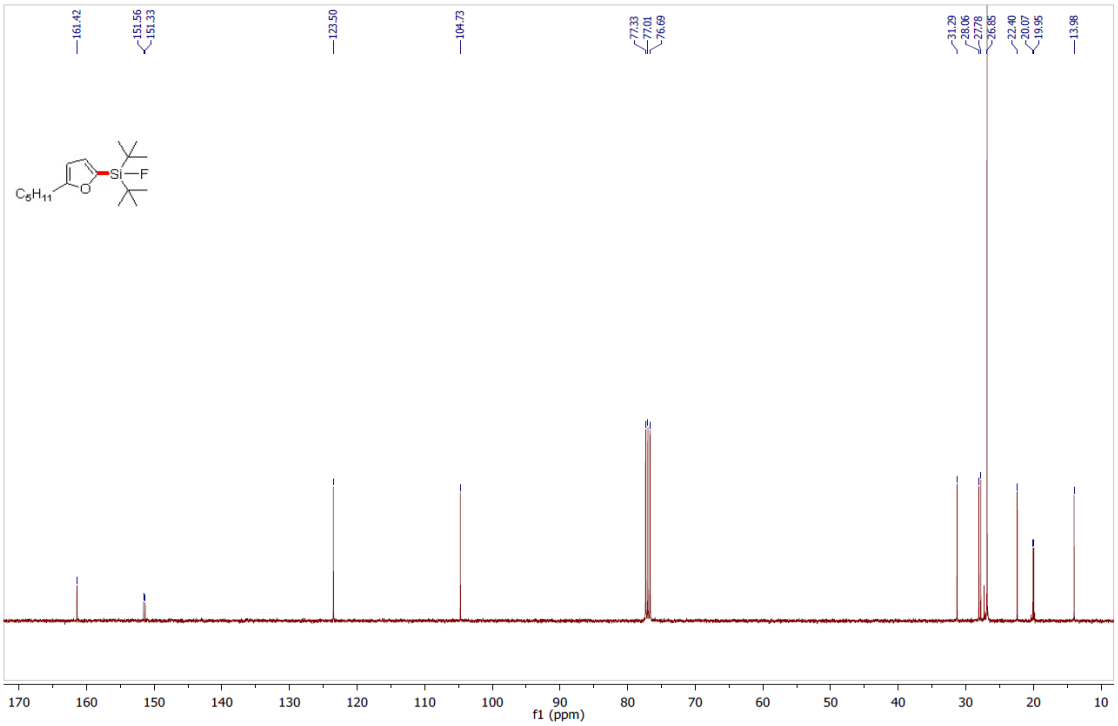
^{19}F NMR for **9** (376 MHz, $CDCl_3$)



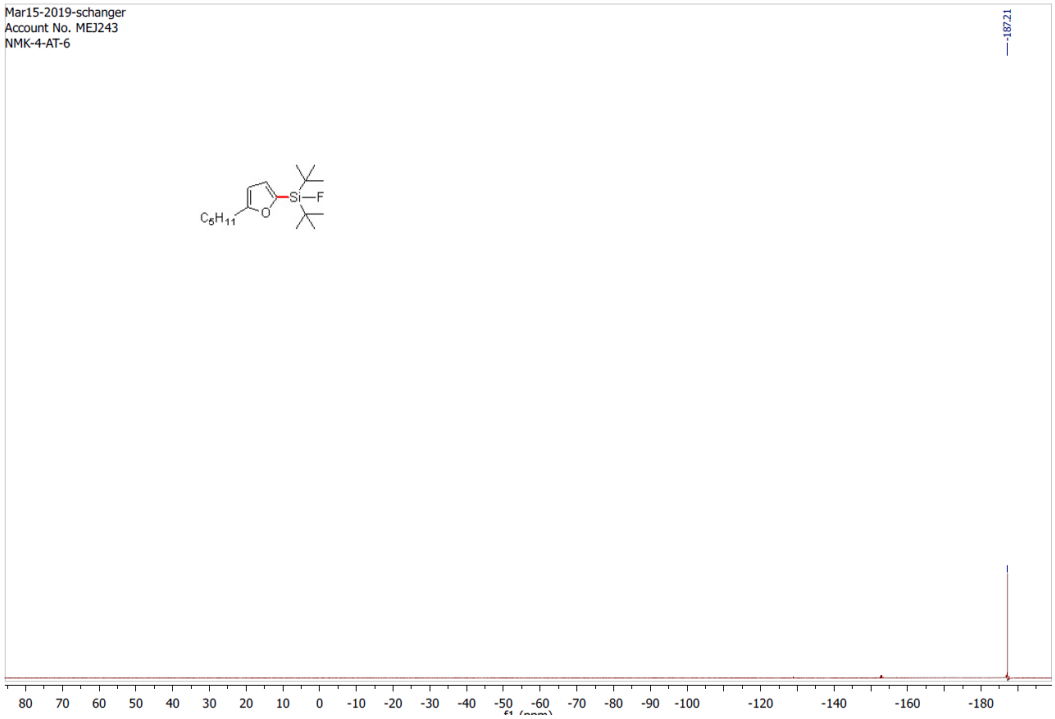
^{1}H NMR for **10** (400 MHz, $CDCl_3$)



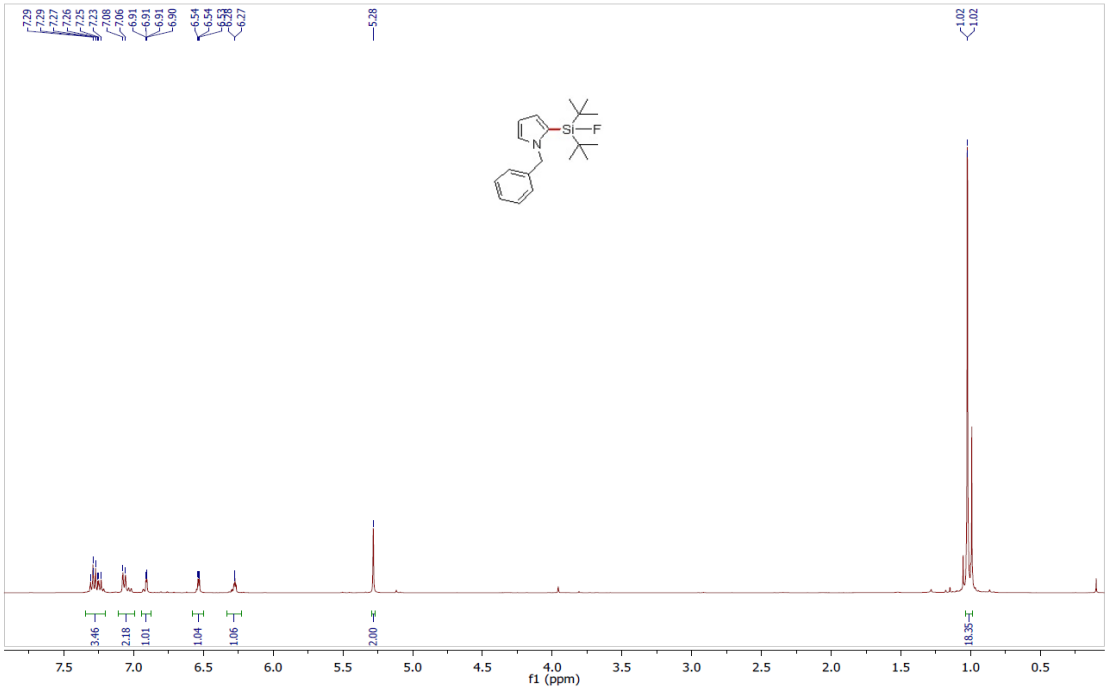
^{13}C NMR for **10** (100 MHz, $CDCl_3$)



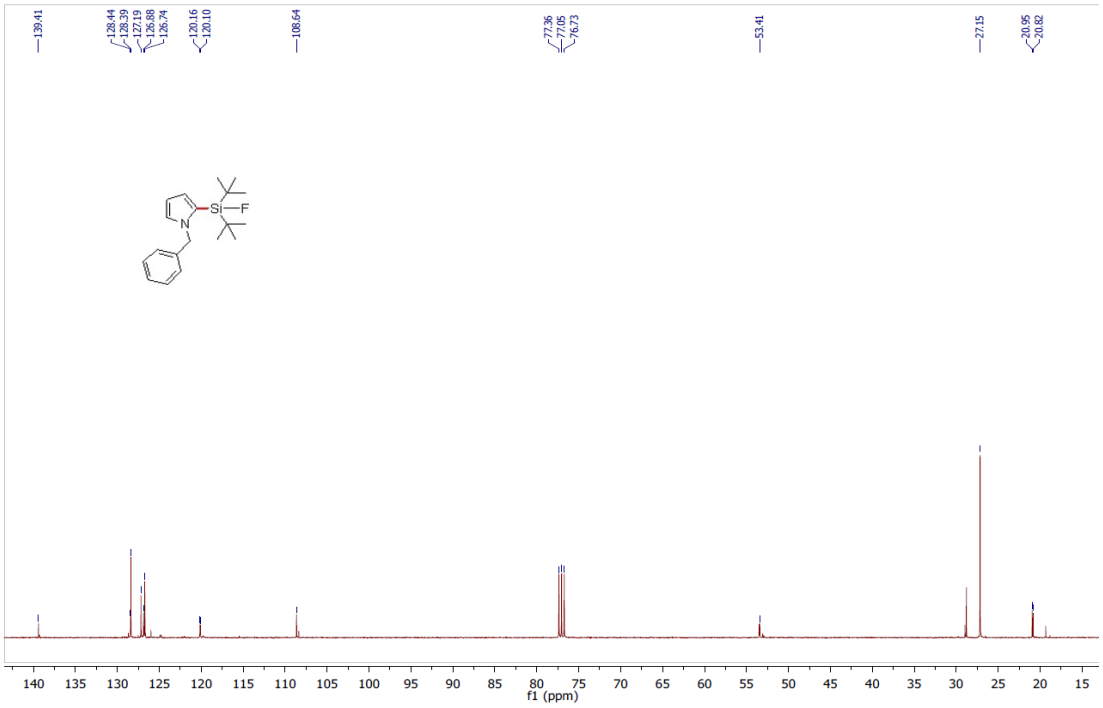
^{19}F NMR for **10** (376 MHz, $CDCl_3$)



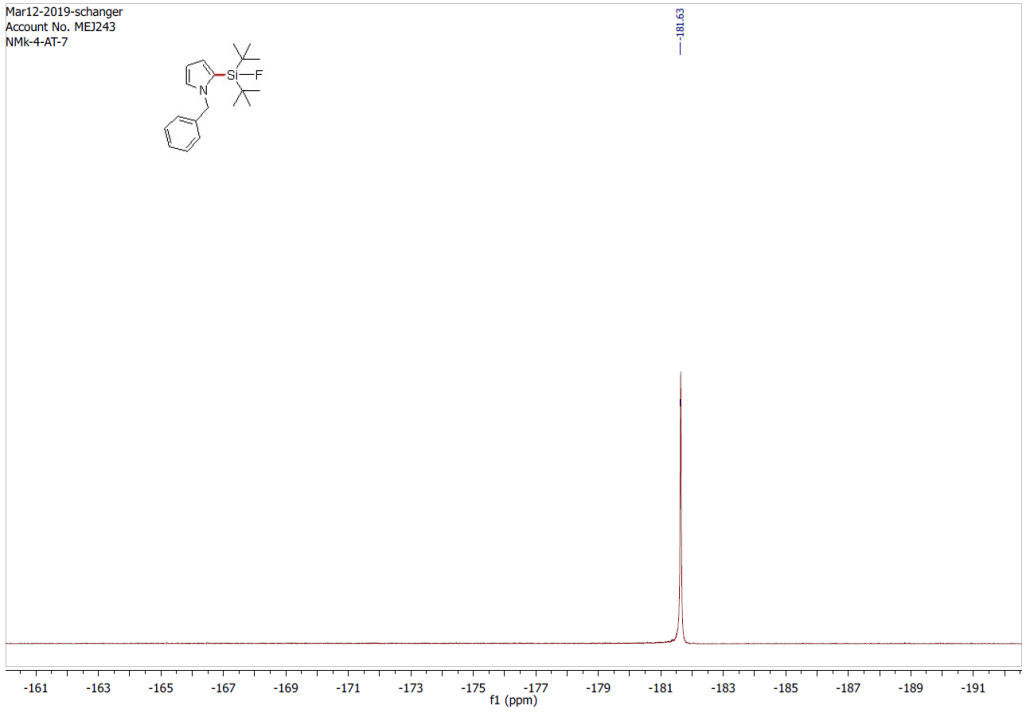
^{1}H NMR for **11** (400 MHz, $CDCl_3$)



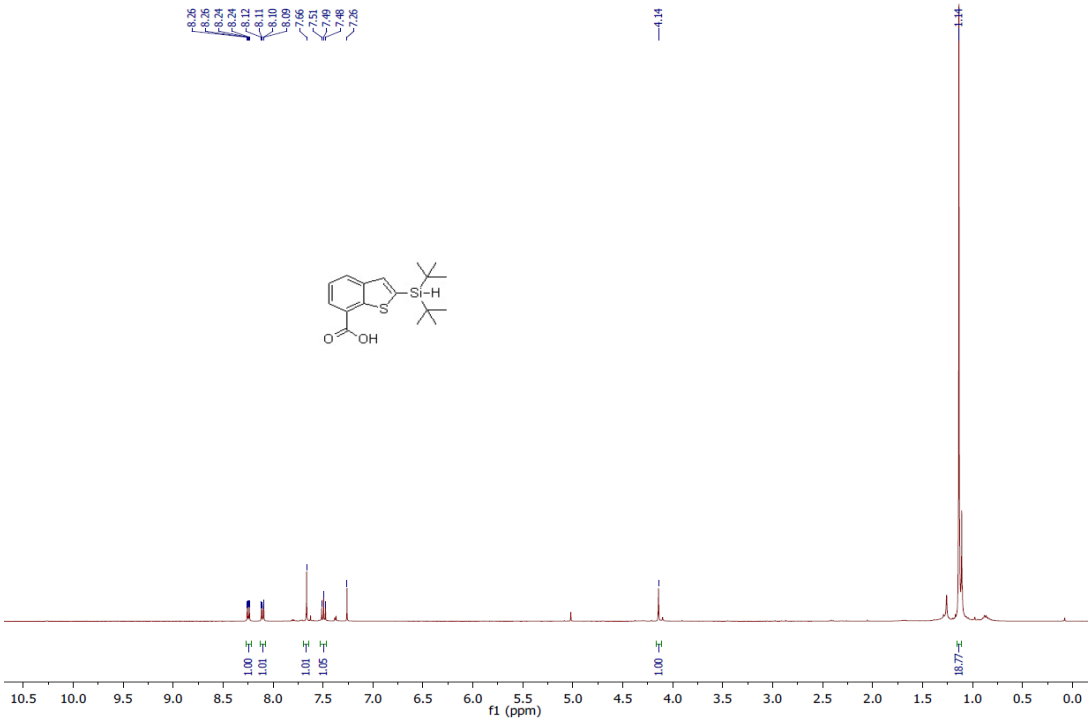
^{13}C NMR for **11** (100 MHz, $CDCl_3$)



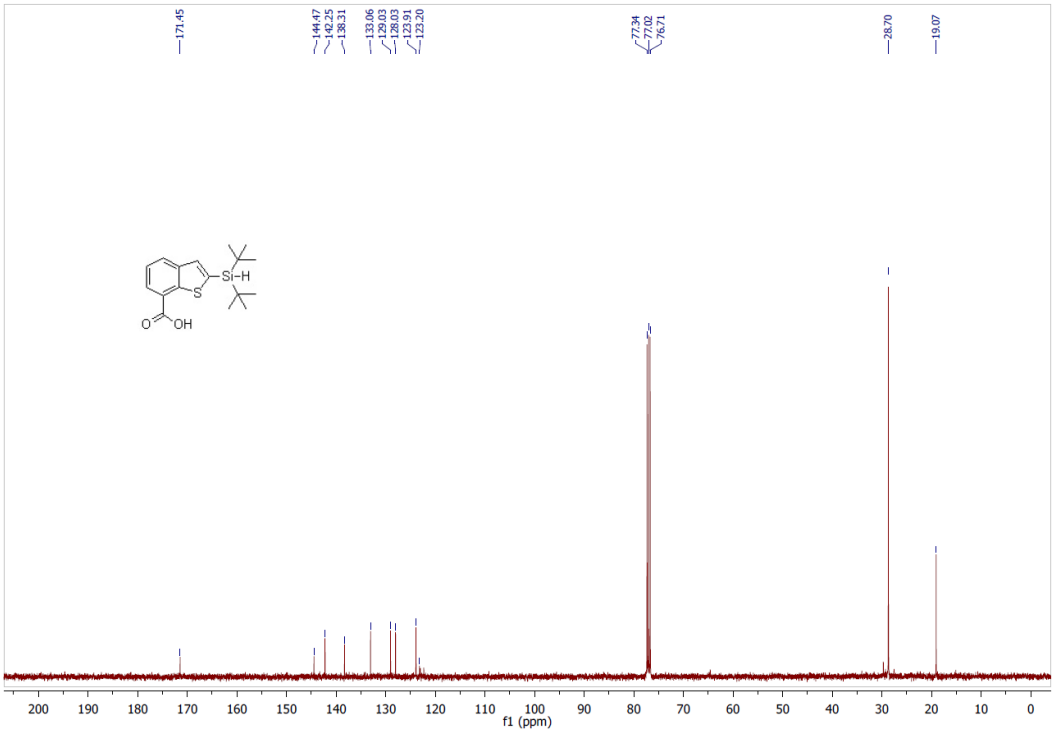
^{19}F NMR for **11** (376 MHz, $CDCl_3$)



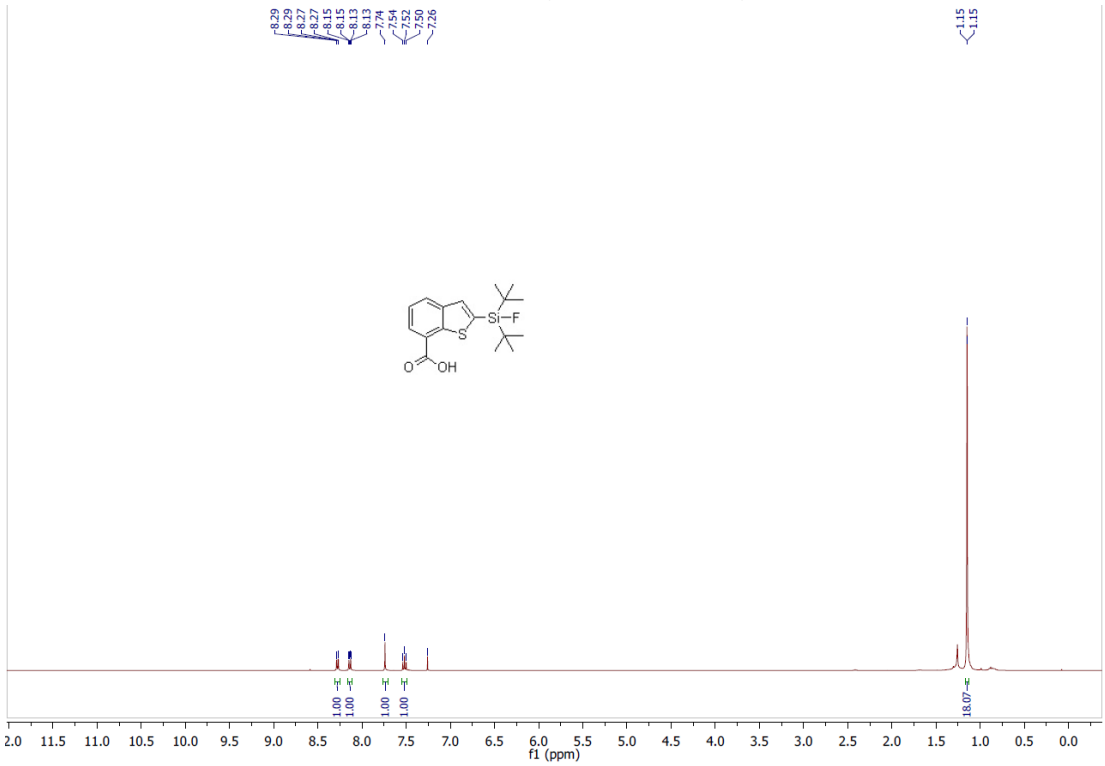
^{1}H NMR for **18** (400 MHz, $CDCl_3$)



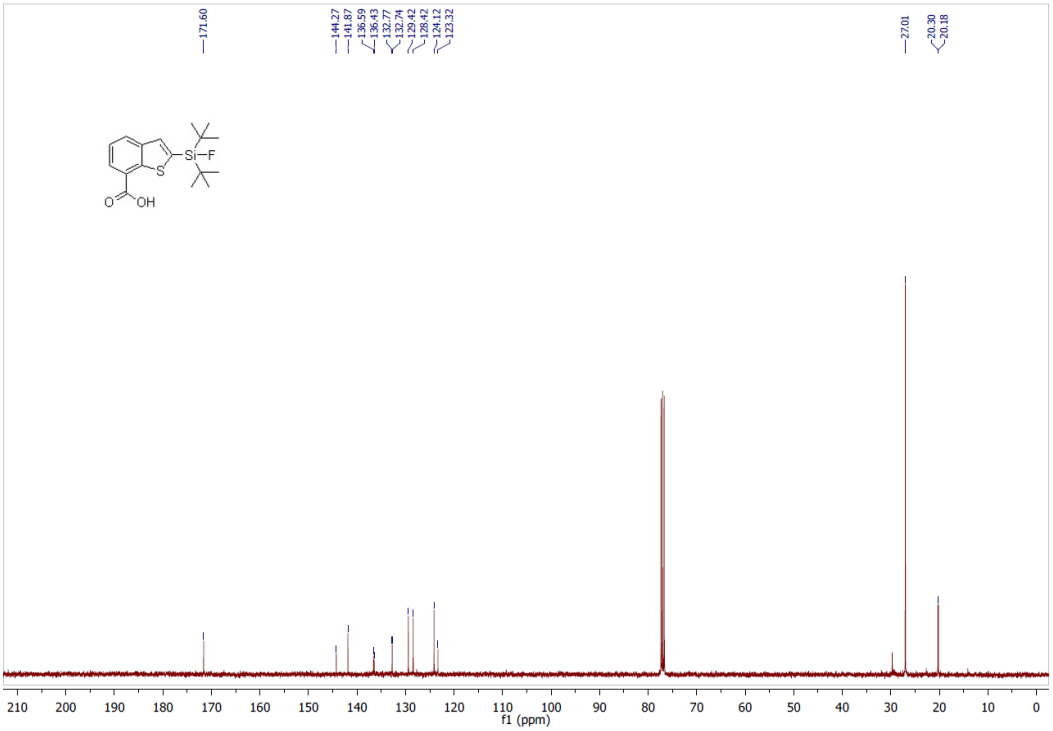
^{13}C NMR for **18** (100 MHz, $CDCl_3$)



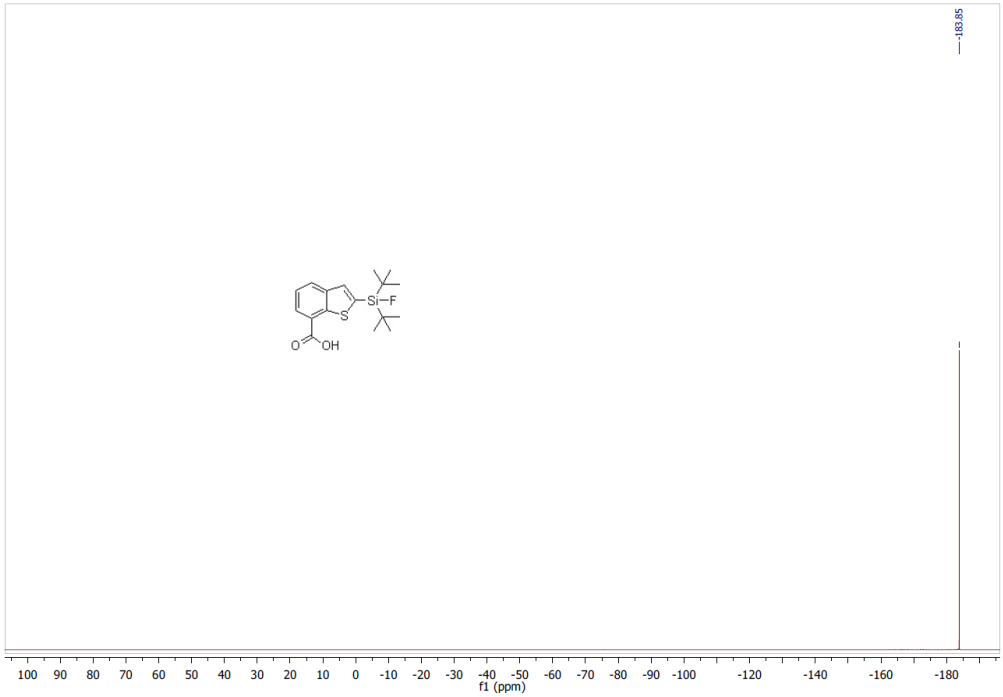
^{1}H NMR for **12** (400 MHz, $CDCl_3$)



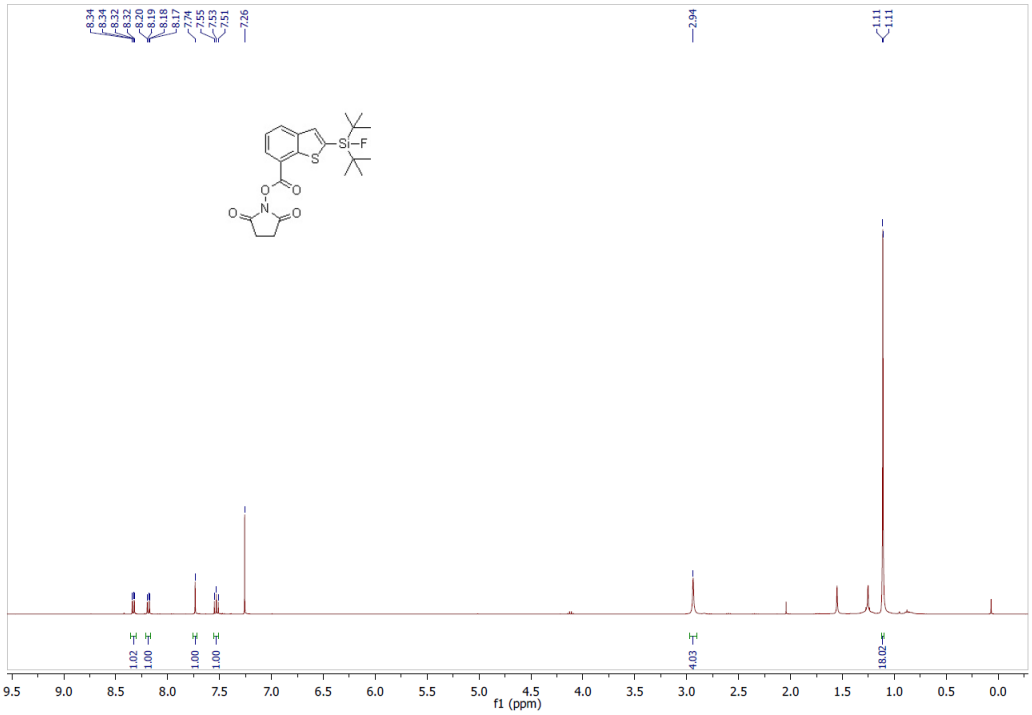
^{13}C NMR for **12** (100 MHz, $CDCl_3$)



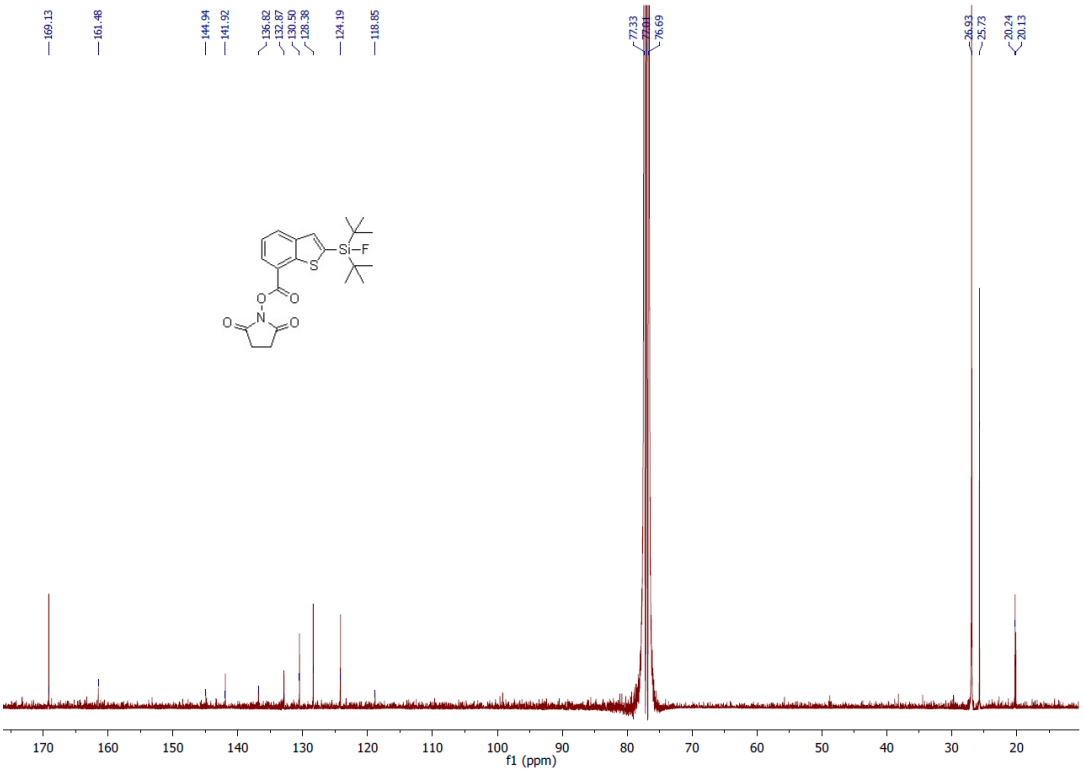
^{19}F NMR for **12** (376 MHz, $CDCl_3$)



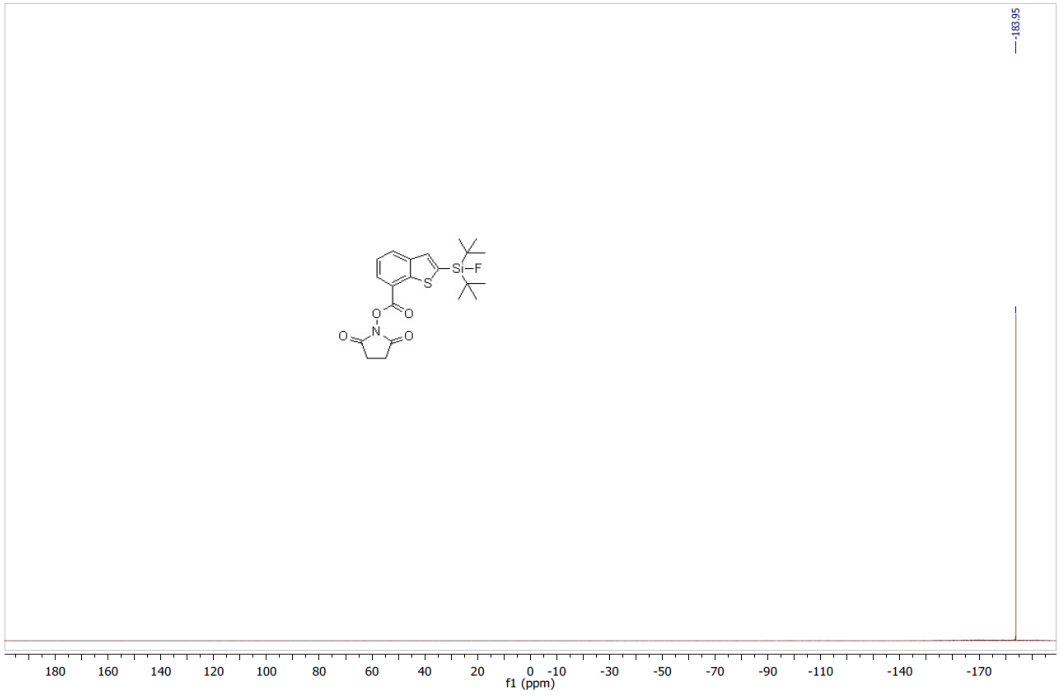
^{1}H NMR for **16** (400 MHz, $CDCl_3$)



^{13}C NMR for **16** (100 MHz, $CDCl_3$)

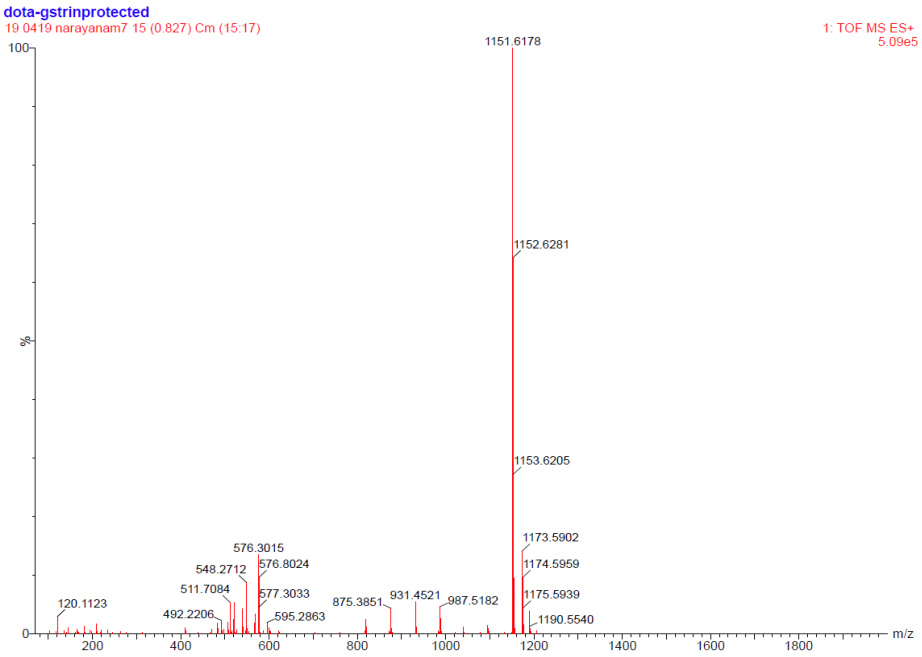


^{19}F NMR for **16** (376 MHz, $CDCl_3$)

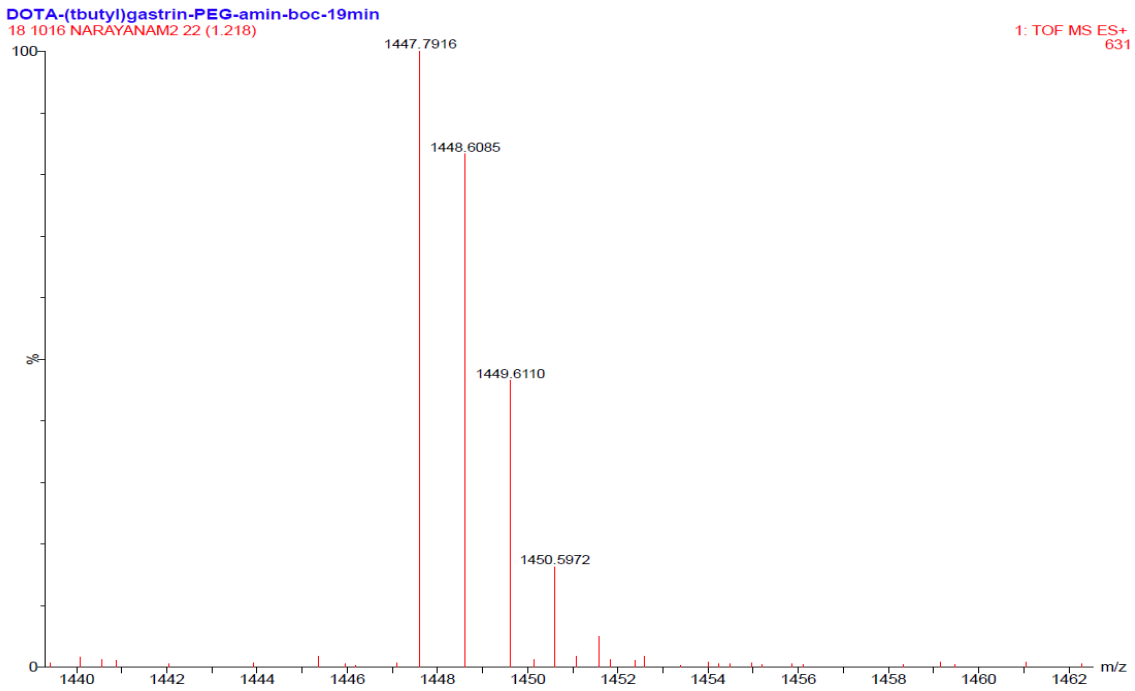


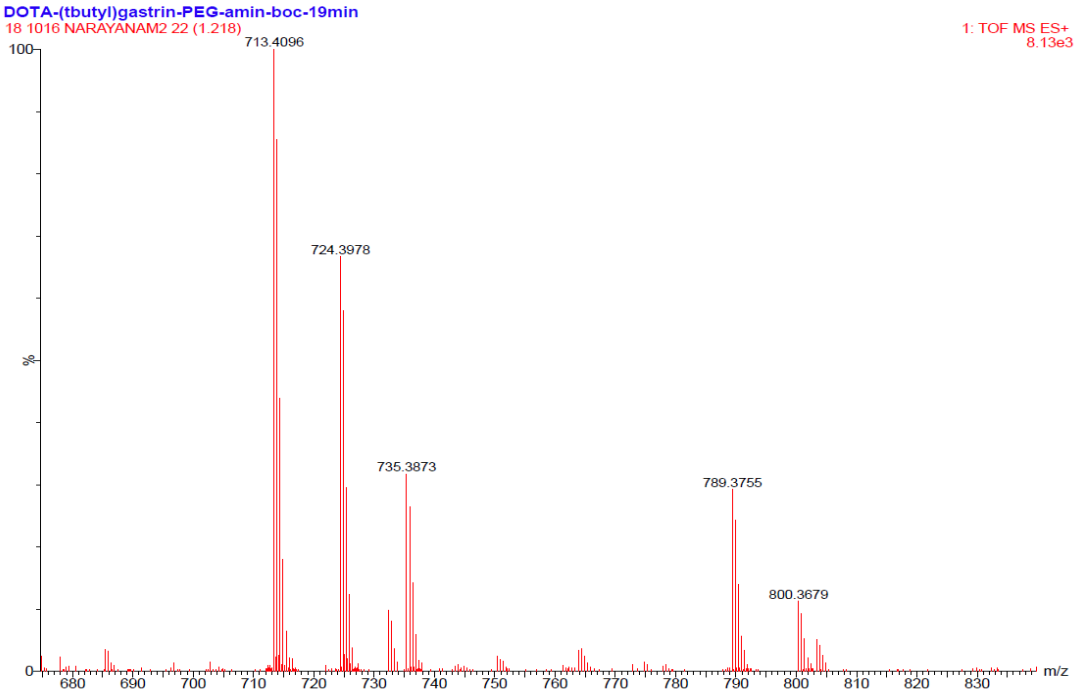
7. HRMS

tris(*t*-butyl)DOTA-Gastrin conjugate (14)

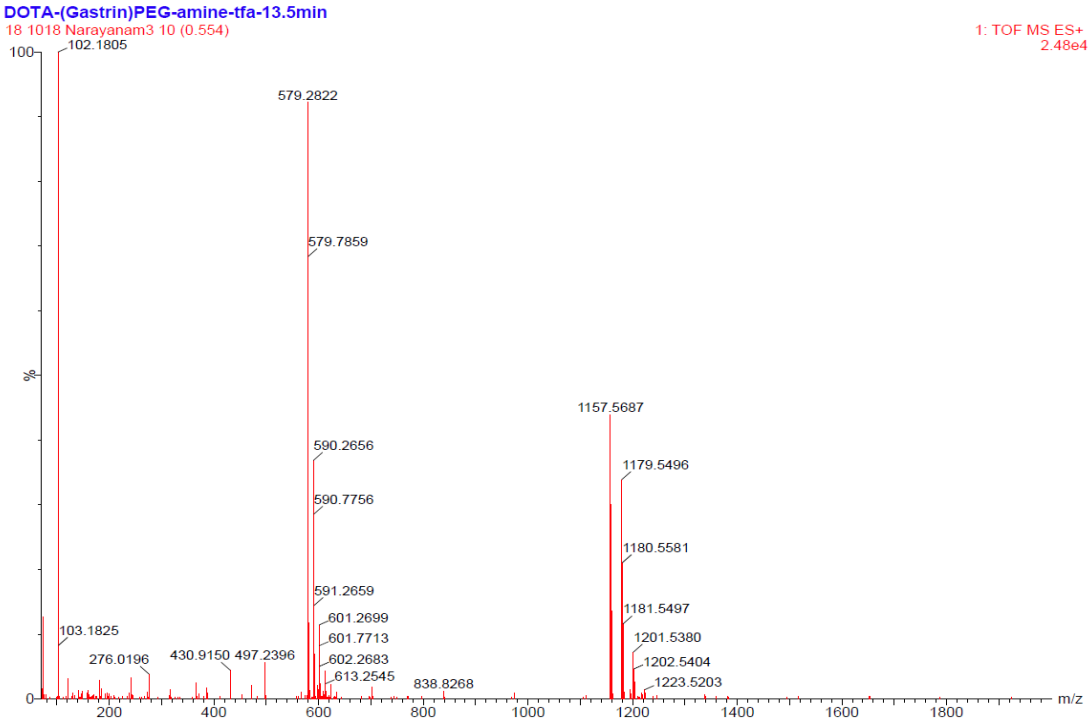


N-boc-PEGylated tris(*t*-butyl)DOTA-Gastrin conjugate (15-Boc).





PEGylated DOTA-Gastrin conjugate (15).



Benzothiophene-SiFA-peptide conjugate (17)