Supplementary Information

One-Pot Bifunctionalization of Silica Nanoparticles Conjugated with Bioorthogonal Linkers: Application in Dual-modal Imaging

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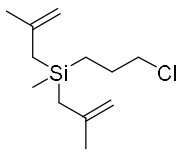
I. Experimental procedures

General Information. All reactions were conducted using oven-dried glassware under an atmosphere of argon (Ar). All commercially available reagents and anhydrous solvents were obtained from Sigma Aldrich, TCI, Alfa, Junsei, Samchun, DaeJung Chemical and were used without further purification. Solvents CH_2Cl_2 was dried and distilled following usual protocols. The following chemicals for the synthesis of silica nanoparticles were used as received: tetraethyl orthosilicate (TEOS, 98.0%) from Daejung; L-lysine(98%) from Sigma Aldrich. Deionized water (DI water) produced on-site with a minimum resistivity of 18.2 MΩ·cm was used in all experiments. Organic solvents were evaporated with reduced pressure using a rotary evaporator. Reactions were followed by TLC analysis using silica gel 60 F_{254} with fluorescent indicator using UV lamp and $KMnO_4$ solution with heat as visualizing agents. Flash chromatography was carried out using Merck silica gel 60 (0.063-0.200 mm) and Kanto silica gel 60N (spherical, neutral). The ^{1}H NMR spectra and ^{13}C NMR spectra were measured with Bruker AVANCE III HD 400. ^{1}H NMR chemical shifts are expressed in parts per million (δ) downfield to $CHCl_3$ (δ = 7.26), ^{13}C NMR chemical shifts are expressed in parts per million (δ) relative to the central $CDCl_3$ resonance (δ = 77.0). Coupling constants in ^{1}H NMR are in Hz. The following abbreviations were used to designate multiplicities: s= singlet, d= doublet, t= triplet, q= quartet, dd=doublet of doublets, m= multiplet. $CDCl_3$ was used as NMR solvent and standard material TMS (tetramethylsilane) wasn't contained. LC/MS analyses were performed on Agilent 6125 SQ LCMS system.

3-chloropropyldimethallylmethylsilane (2)[1]



2

10% wt. $H_2PtCl_6 \cdot xH_2O$ in 2-propanol (0.05 mL) and dichloromethylsilane (3 mL, 29 mmol) was added at room temperature, and the mixture was stirred until it became homogeneous. Diethyl ether (2.3 mL) was

added into the reaction mixture and the reaction temperature was raised to 40 °C. After dropwise addition of allyl chloride (2.3 mL, 30 mmol), the mixture was stirred for 12 hours at 60 °C. After the reaction, all volatiles were evaporated. The crude product 3-chloropropyl dichloromethylsilane was obtained. 3-chloropropyldichloromethylsilane was used in the next step without further purification.

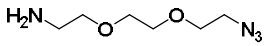
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.59 (t, J = 6.5 Hz, 2H), 1.97 (m, 2H), 1.25 (m, 2H), 0.8(s, 3H).

To the mixture of crude 3-chloropropyldichloromethylsilane was added dropwise into excess methallyl magnesium chloride solution in THF and the reaction mixture was stirred for 4 hours at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl, and it was extracted with Et_2O. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The desired product was isolated flash column chromatography on silica gel to afford the product **2** (1.65 mg, 24.6%) as colorless liquid.

R_f = 0.5, *n*-hexane, $KMnO_4$ stain.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.62 (s, 2H), 6.50 (s, 2H), 3.50 (t, J = 6.9 Hz, 2H), 1.81 (m, 2H), 1.72 (s, 6H), 1.59 (s, 4H), 0.71(m, 2H), 0.07(s, 3H).

2-(2-(2-azidoethoxy)ethoxy)ethan-1-amine (3)[2]



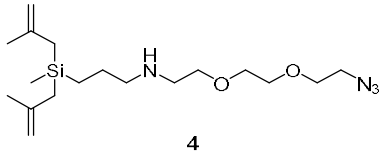
3

To a solution of 1,2-bis(2-azidoethoxy)ethane (200 mg, 1 mmol) in EtOAc (3 mL) and HCl (1 N, 2 mL) at room temperature was added PPh_3 (262 mg, 1 mmol) dropwise. The reaction mixture was stirred for 12 hours at room temperature. HCl (1N, 10 mL) was added into the reaction mixture, and the mixture was extracted with EtOAc (3 x 15 mL) to remove unreacted 1,2-bis(2-azidoethoxy)ethane. NaOH solution was added until the reaction mixture become pH = 14. The mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford the title compound **3** (104 mg, 60%) as a colorless liquid.

R_f = 0.25, Dichloromethane/MeOH = 20:1 (v/v %), Ninhydrin stain.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.68 (m, 6H), 3.54 (t, J = 5.2 Hz, 2H), 3.41 (t, J = 5.0 Hz, 2H), 2.89 (t, J = 5.1 Hz, 2H).

N-(2-(2-(2-azidoethoxy)ethoxy)ethyl)-3-(methylbis(2-methylallyl)silyl)propan-1-amine (4)



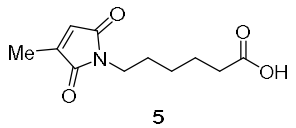
4

To a solution of **3** (800 mg, 4.59 mmol) in acetonitrile (5.7 mL) at room temperature was added **2** (265 mg, 1.15 mmol) and K_2CO_3 (318 mg, 2.3 mmol). The reaction mixture was stirred for 72 hours at 80 °C. The reaction mixture was stirred for 6 h at room temperature. The reaction mixture was quenched with water (10 mL), extracted with CH_2Cl_2 (3 x 15 mL), and washed with brine. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel to afford the title compound **4** (246 mg, 58%) as colorless liquid.

R_f = 0.3, Dichloromethane/MeOH = 10:1 (v/v %), $KMnO_4$ stain.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.62 (s, 2H), 4.52 (s, 2H), 3.68 (m, 6H), 3.54 (t, J = 5.2 Hz, 2H), 3.41 (t, J = 5.0 Hz, 2H), 2.83 (t, J = 5.2 Hz, 2H), 2.64 (t, J = 7.3 Hz, 2H), 1.73 (s, 6H), 1.60 (s, 4H), 1.55 (m, 2H), 0.60 (m, 2H), 0.07 (s, 3H); ^{13}C NMR (100 MHz; $CDCl_3$): δ 143.4, 108.9, 70.6, 70.4, 70.1, 53.2, 50.7, 49.1, 29.7, 25.6, 25.4, 24.1, 11.5, -4.5; HRMS(ESI) (m/z): $[M+H]^+$ calcd for $C_{18}H_{36}N_4O_2Si$ 369.2685 found 369.2683.

6-(3-Methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoic acid (5)[3]



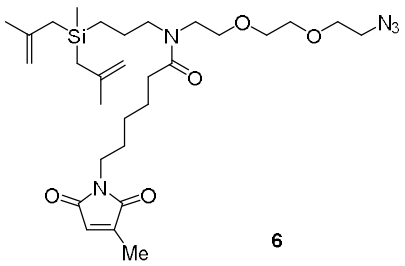
5

To a solution of 6-aminohexanoic acid (1 g, 7.62 mmol) in AcOH (6.1 mL) at room temperature was added citraconic anhydride (0.75 mL, 8.38 mmol). The reaction mixture was stirred for 4 h at 100 °C. The reaction mixture was stirred for 6 h at room temperature. The reaction mixture was quenched with water (10 mL), extracted with CH_2Cl_2 (3 x 15 mL), and washed with brine. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel to afford the title compound **5** (1.5 g, 90%) as white solid.

R_f = 0.5, *n*-hexane/EtOAc = 1:1 (v/v %), $KMnO_4$ stain.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.33 (d, J = 1.8 Hz, 1H), 3.52 (t, J = 7.2 Hz, 2H), 2.37 (t, J = 7.4 Hz, 2H), 2.10 (d, J = 1.8 Hz, 3H), 1.65 (m, 4H), 1.36 (m, 2H).

N-(2-(2-(2-azidoethoxy)ethoxy)ethyl)-6-(3-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-(3-(methylbis(2-methylallyl)silyl)propyl)hexanamide (6)



6

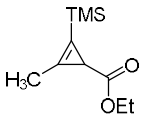
To a solution of **4** (555 mg, 1.49 mmol) in anhydrous CH_2Cl_2 (15 mL) at room temperature was added **5** (370 mg, 1.64 mmol), DMAP (184 mg, 1.49 mmol), and EDCI (320 μL, 1.80 mmol). The reaction mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with water (10 mL), extracted with CH_2Cl_2 (3 x 15 mL), and washed with brine. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel to afford the title compound **6** (677 mg, 78%) as colorless liquid.

R_f = 0.3, *n*-hexane/EtOAc = 1:2 (v/v %), $KMnO_4$ stain.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.32 (d, J = 1.8 Hz, 1H), 4.63 (m, 2H), 4.51(m, 2H), 3.65 (m, 8H), 3.51 (m, 4H), 3.40 (m, 2H), 3.30 (m, 2H), 2.32 (m, 2H), 2.09 (d, J = 1.8 Hz, 3H), 1.64 (m, 16H), 1.35 (m, 2H), 0.53

(m, 2H), 0.08 (m, 3H); ^{13}C NMR (100 MHz; $CDCl_3$): δ 172.8, 172.6, 171.8, 170.9, 154.5, 143.2, 143.0, 127.2, 109.0, 108.8, 70.8, 70.7, 70.6, 70.3, 70.1, 70.0, 69.4, 69.4, 52.2, 50.6, 49.4, 47.5, 45.8, 37.8, 37.7, 32.9, 32.8, 28.5, 26.7, 26.6, 25.7, 25.6, 25.4, 24.9, 23.3, 21.8, 11.1, 11.0, 10.9, -4.4, -4.5; HRMS(ESI) (m/z): $[M+Na]^+$ calcd for $C_{29}H_{49}N_5O_5SiNa$ 598.3400. found 598.3400.

Ethyl 2-methyl-3-(trimethylsilyl)cycloprop-2-ene-1-carboxylate (S1)[4]

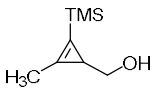


The flask was charged with $Rh_2(OAc)_4$ (20 mg, 0.04 mmol), CH_2Cl_2 (17 mL) and filled with argon. Trimethylsilyl acetylene (1.3 mL, 8.76 mmol) was added to the flask slowly with stirred. Ethyl diazoacetate **7** (500 mg, 4.38 mmol) was then added via syringe pump at a rate of 1.0 mL/h. After the addition was complete, the mixture was stirred for 1 hour and concentrated by rotary evaporation. The desired product was isolated flash column chromatography on silica gel to afford the title compound **S1** (439 mg, 50.5%) as colorless liquid.

R_f = 0.4, *n*-hexane/Et_2O = 15:1 (v/v %), $KMnO_4$ stain.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (m, 2H), 2.15 (s, 3H), 1.93 (s, 1H), 1.19 (t, J = 7.1 Hz, 3H), 0.15 (s, 9H).

(2-Methyl-3-(trimethylsilyl)cycloprop-2-en-1-yl)methanol (8)[4]



8

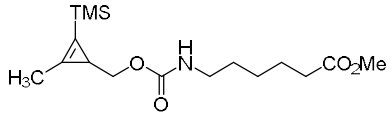
To a solution of ethyl 2-methyl-3-(trimethylsilyl)cycloprop-2-ene-1-carboxylate (770 mg, 3.88 mmol) in anhydrous Et_2O (20 mL) at 0 °C was added 1.0 M DIBAL-H in toluene (8 mL, 7.7 mmol) dropwise. The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was quenched with saturated

Rochelle's salt solution (20 mL), extracted with Et_2O (3 x 15 mL), and washed with brine. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford the title compound **8** (677 mg, 78%) as colorless liquid.

R_f = 0.4, *n*-hexane/EtOAc = 5:1 (v/v %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.51 (q, J =2.0 Hz, 2H), 2.23(s, 3H), 1.58 (t, J = 4.6 Hz, 1H), 0.18 (s, 9H).

Methyl 6-((((2-methyl-3-(trimethylsilyl)cycloprop-2-en-1-yl)methoxy)carbonyl)amino) hexanoate (9)



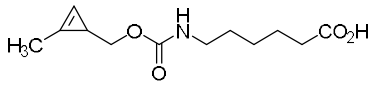
9

To a solution of **8** (100 mg, 0.64 mmol) in anhydrous THF (4.2 mL) at room temperature was added CDI (115 mg, 0.70 mmol). The reaction mixture was stirred for 3 h at room temperature. The volatile compounds were removed under reduced pressure. The crude material was dissolved in DMF (1.3 mL), and $MeO_2C(CH_2)_5NH_3Cl$ **S2** (128 mg, 0.70 mmol) and triethylamine (0.18 mL, 1.28 mmol) were added. The resulting solution was stirred at 50 °C for 12 h. The reaction mixture was quenched with water (10 mL), extracted with CH_2Cl_2 (3 x 15 mL), and washed with brine. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel to afford the title compound **9** (73 mg, 35%) as colorless liquid.

R_f = 0.3, *n*-hexane/EtOAc = 2:1 (v/v %), $KMnO_4$ stain.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.64 (br s, 1H), 3.91 (m, 2H), 3.68 (s, 3H), 3.19 (q, J = 6.7 Hz, 2H), 2.33 (t, J = 7.4 Hz, 2H), 2.20 (s, 3H), 1.70 (m, 3H), 1.55 (m, 3H), 1.39 (m, 2H), 0.17 (s, 9H); ^{13}C NMR (100 MHz; $CDCl_3$): δ 174.0, 157.0, 134.6, 111.0, 73.3, 51.5, 40.7, 33.9, 29.8, 26.2, 24.6, 18.6, 13.3, -1.2; LRMS(ESI) (m/z): $[M+Na]^+$ calcd for $C_{16}H_{29}NNaO_4Si$ 350.2 found 350.1.

6-((((2-Methylcycloprop-2-en-1-yl)methoxy)carbonyl)amino)hexanoic acid (11)



11

To a solution of **9** (216 mg, 0.66 mmol) in MeOH (2.2 mL) at 0 °C were added a solution of KOH (111 mg, 1.98 mmol) in H_2O (0.6 mL). After the reaction mixture was stirred for 3 hours, aqueous 1M HCl (1 mL) was added dropwise (it should be confirmed that pH is around 1). The organic phase was extracted with CH_2Cl_2 (3 x 10 mL), washed with brine and dried over $MgSO_4$. The combined organic layers were evaporated under reduced pressure to afford the crude acid, which was used in the next step without further purification.

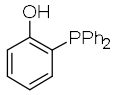
R_f = 0.2, *n*-hexane/EtOAc = 1:2 (v/v %), $KMnO_4$ stain.

To the crude solution, THF (6.6 mL), TBAF (2 mL) was added at room temperature and stirred for 2 hours. Then reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL) and was dried with $MgSO_4$. The organic solvent was evaporated in the reduced pressure to afford the title compound **11** (110 mg, 74%) as white liquid. The crude mixture was used without further purification.

R_f = 0.2, *n*-hexane/EtOAc = 1:3 (v/v %), $KMnO_4$ stain.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.58 (s, 1H), 4.70 (br s, 1H), 3.94 (d, J = 4.2 Hz, 2H), 3.20 (d, J = 4.0 Hz, 2H), 2.38 (t, J = 7.4 Hz, 2H), 2.15 (s, 3H), 1.67 (m, 3H), 1.54 (m, 2H), 1.40 (m, 2H).

2-(diphenylphosphaneyl)phenol (13)[5]



13

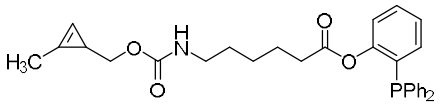
Before the reaction, DMAc was degassing using Ar gas about 1h. A mixture of ortho-iodophenol (1 g, 4.54 mmol), diphenylphosphine (0.8 mL, 4.54 mmol), palladium (II) acetate (10 mg, 0.045 mmol) and sodium acetate (0.4 g, 4.99 mmol) in anhydrous DMAc (15 mL) was stirred under nitrogen at 110°C for 2h. The solution was extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was dried over $MgSO_4$ and concentrated

in *vacuo.* The desired product was isolated flash column chromatography on silica gel to afford the product **13** as a white solid (800 mg, 63%).

R_f = 0.3, *n*-hexane/Dichloromethane = 1:2 (v/v %), $KMnO_4$ stain.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.37 (m, 11H), 7.01 (dt, J = 5.6 Hz, 13.1 Hz, 2H), 6.92 (t, J = 7.4 Hz, 1H), 6.67 (br, 1H).

2-(Diphenylphosphaneyl)phenyl 6-((((2-methylcycloprop-2-en-1-yl)methoxy)carbonyl) amino)hexanoate (14)



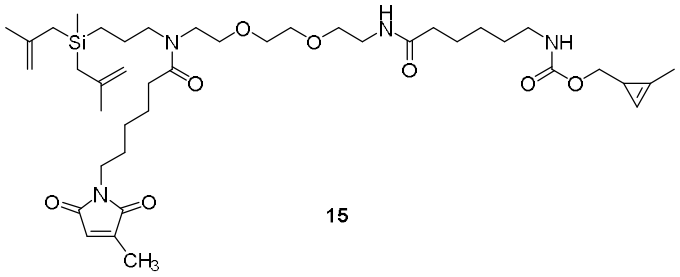
14

To a solution of carboxylic acid **11** (175 mg, 0.725 mmol) in CH_2Cl_2 (6.6 mL) at room temperature was added **13** (202 mg, 0.725 mmol), EDCI (140 µL, 0.792 mmol), DMAP (80 mg, 0.66 mmol). Under argon atmosphere, the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was quenched with water (10 mL), extracted with CH_2Cl_2 (3 x 15 mL), and washed with brine. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel to afford the title compound **14** (677 mg, 78%) as white liquid.

R_f = 0.3, *n*-hexane/EtOAc = 3:1 (v/v %), $KMnO_4$ stain.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.36 (m, 11H), 7.16 (dd, J = 5.4, 11.5 Hz, 2H), 6.82 (m, 1H), 6.58 (s, 1H), 4.65 (s, 1H), 3.95 (d, J = 4.6 Hz, 2H), 3.16 (q, J = 6.2 Hz, 2H), 2.28 (t, J = 7.4 Hz, 2H), 2.15 (d, J = 0.8 Hz, 3H), 1.66 (t, J = 4.6 Hz, 1H), 1.34 (m, 4H), 1.29 (q, J = 5.2 Hz, 2H); ^{13}C NMR (100 MHz; $CDCl_3$): δ 171.3, 156.9, 152.8, 152.7, 135.7, 135.6, 134.1, 133.9, 133.7, 130.2, 130.1, 129.90 129.0, 128.6, 128.6, 126.1, 22.6, 120.8, 102.2, 72.1, 40.7, 33.8, 29.7, 26.1, 24.1, 17.3, 11.7; HRMS(ESI) (m/z): $[M+Na]^+$ calcd for $C_{30}H_{32}NO_4PNa$ 524.1966 found 524.1964.

(2-methylcycloprop-2-en-1-yl)methyl (2,4-dimethyl-8-(6-(3-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl)-4-(2-methylallyl)-18-oxo-11,14-dioxa-8,17-diaza-4-silatricos-1-en-23-yl)carbamate (15)



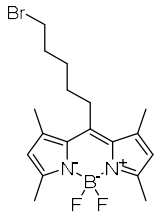
15

To a solution of **14** (145 mg, 0.28 mmol) in THF (1.4 mL) at room temperature was added azide **6** (165 mg, 0.286 mmol). After the reaction mixture was stirred for 12 h at 40 °C, water (15 µL) was added and stirred at room temperature for 3 hours. The reaction mixture was quenched with water (5 mL), extracted with CH_2Cl_2 (3 x 10 mL), and washed with brine. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel to afford the title compound **15** (114 mg, 51%) as colorless liquid.

R_f = 0.3, Dichloromethane/MeOH = 20:1 (v/v %), $KMnO_4$ stain.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.58 (s, 1H), 6.32 (d, J = 1.7 Hz, 1H), 6.15 (m, 1H), 4.79 (s, 1H), 4.64 (s, 2H), 4.51 (s, 2H), 3.93 (d, J = 4.7 Hz, 2H), 3.57 (m, 14H), 3.30 (m, 2H), 3.18 (q, J = 6.5 Hz, 2H), 2.33 (m, 2H), 2.23 (m, 2H), 2.15 (s, 3 H), 2.09 (d, J = 1.6 Hz, 3H), 1.74 (s, 6H), 1.61 (s, 15H), 1.35 (m, 4H), 0.54 (m, 2H), 0.08 (m, 3H); ^{13}C NMR (100 MHz; $CDCl_3$): δ 173.0, 172.7, 171.9, 170.94 157.1, 145.5, 143.2, 143.0, 127.2, 120.8, 109.1, 108.9, 102.2, 72.1, 70.9, 70.5, 70.2, 70.0, 69.1, 70.0, 53.4, 52.3, 49.2, 47.5, 45.8, 40.8, 39.1, 37.83, 37.8, 36.4, 33.0, 32.9, 29.8, 28.5, 26.7, 26.6, 26.4, 25.7, 25.6, 25.49 25.3, 24.9, 23.4, 21.9, 17.3, 11.7, 11.2, 11.1, 11.0, -4.3, -4.4; HRMS(ESI) (m/z): $[M+Na]^+$ calcd for $C_{41}H_{68}N_4O_8SiNa$ 795.4704 found 795.4702.

8-(5-Bromopentyl)-4,4-difluoro-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene (S3)[6]



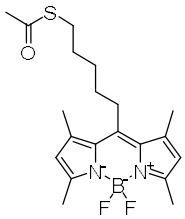
S3

To a solution of 6-bromohexanoyl chloride (0.717 mL, 4.68 mmol) in CH_2Cl_2 (46 mL) at 0 °C was added 2,4-dimethylpyrrole (1.1 mL, 10.3 mmol) dropwise. The reaction mixture was stirred for 7 h at room temperature. The mixture was then cooled again to 0 °C and Et_3N (1.96 mL, 14 mmol) was added dropwise. After 30 min, boron trifluoride etherate (2.89 mL, 23.4 mmol) was added and the mixture was stirred at room temperature for 6 hours. The reaction mixture was quenched with water (10 mL), extracted with CH_2Cl_2 (3 x 30 mL), and washed with brine. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel to afford the title compound **S3** (591 mg, 32%) as orange solid.

R_f = 0.3, *n*-hexane/Dichloromethane = 1:1 (v/v %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.08 (s, 2H), 3.46 (t, J = 6.5 Hz, 2H), 2.98 (m, 2H), 2.53 (s, 6H), 2.44 (s, 6H), 1.95 (t, J = 6.5 Hz, 2H), 1.68 (m, 4 H).

S-(5-(5,5-difluoro-1,3,7,9-tetramethyl-5H-4l4,5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2] diazaborinin-10-yl)pentyl) ethanethioate (S4)[6]



S4

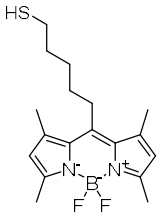
The BODIPY-bromide **S3** (500 mg, 1.26 mmol) was dissolved in acetone (25 mL), and potassium thioacetate (173 mg, 1.51 mmol) were added. The solution was stirred under reflux for 3h. The mixture was

extracted with DCM. The organic layers were dried over $MgSO_4$ and concentrated in *vacuo* to afford the title compound **S4** as an orange-colored residue (480 mg, 97%), which was used for the next step without further purification.

R_f = 0.4, *n*-hexane/ Dichloromethane = 1:1 (v/v %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.07 (s, 2H), 2.94 (m, 4H), 2.53 (s, 6H), 2.43 (s, 6H), 2.36(s, 3H), 1.64 (m, 6H), 1.68 (m, 4 H).

5-(5,5-difluoro-1,3,7,9-tetramethyl-5H-4l4,5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2] diazaborinin-10-yl)pentane-1-thiol (BODIPY-thiol, 16)[6]



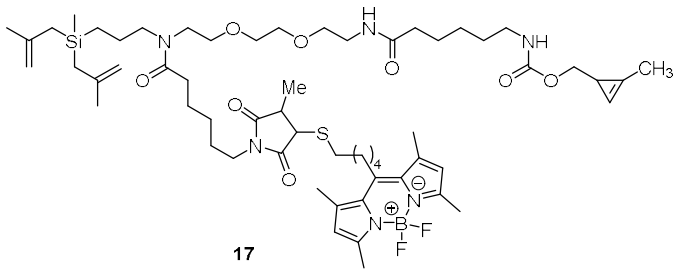
6

The **BODIPY-thioacetate S4** (300 mg, 0.76 mmol) was suspended in MeOH (15 mL) and degassing using Ar gas about 1h. After 1 hour, potassium carbonate (158 mg, 1.15 mmol) was added, and the solution was gently warmed to 30 °C (heating above 40 °C must be avoided since it leads to increased disulfide formation). The solution was stirred for 4 h under an argon atmosphere. The solution was extracted with DCM. The organic layers were dried over $MgSO_4$ and concentrated in *vacuo.* The desired product was isolated flash column chromatography on silica gel to afford the title compound **16** (130 mg, 48%) as an orange solid.

R_f = 0.3, *n*-hexane/Dichloromethane = 1:1 (v/v %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.07 (s, 2H), 2.98 (t, J = 7.9 Hz, 2H), 2.59 (q, J = 7.2 Hz, 2H), 2.53 (s, 6H), 2.44 (s, 6H), 1.66 (m, 6H), 1.36 (t, J = 7.8 Hz, 1H); LRMS(ES-API): $[M+H]^+$ calcd for $C_{18}H_{26}BF_2N_2S$ 351.2 found 351.1

Multimodal linker-Bodipy (17)

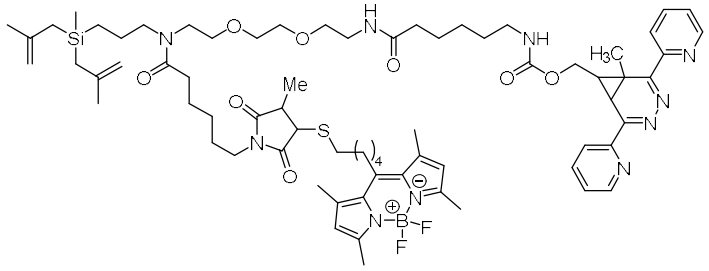


17

To a solution of **15** (41 mg, 0.053 mmol) in CH_3CN (0.5 mL), **16** (18.6 mg, 0.053 mmol) and TEA (7 µL) was added at room temperature. The mixture was stirred for 1 h. The solution was extracted with DCM. The organic layers were dried over $MgSO_4$ and concentrated in *vacuo*. The desired product was isolated flash column chromatography on silica gel to afford the title compound **17** (47 mg, 80%) as an orange solid. R_f = 0.3, Dichloromethane/MeOH = 20:1 (v/v %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.56 (s, 1H), 6.17 (s, 1H), 6.05 (s, 2H), 4.81 (s, 1H), 4.62 (s, 2H), 4.50 (s, 2H), 3.91 (d, J = 4.6 Hz, 2H), 3.54 (m, 14H), 3.27 (m, 2H), 3.16 (q, J = 6.5 Hz, 2H), 2.94 (m, 2H), 2.77 (m, 2H), 2.51 (s, 6H), 2.41 (s, 6H), 2.35 (t, J = 7.5Hz, 1H), 2.28 (t, J = 7.5Hz, 1H), 2.20 (m, 2H), 2.13 (d, J = 0.6Hz, 3H), 1.72 (s, 6H), 1.57 (m, 17H), 1.36 (m, 6H), 0.52 (t, J = 8.5 Hz, 2H), 0.07 (s, 1.8H), 0.05 (s, 1.2H); LRMS(ES-API): $[M+Na]^+$ calcd for $C_{59}H_{93}BF_2N_6O_8SSiNa$ 1145.6 found 1145.6.

Multimodal linker-Bodipy-Tetrazine (19)



19

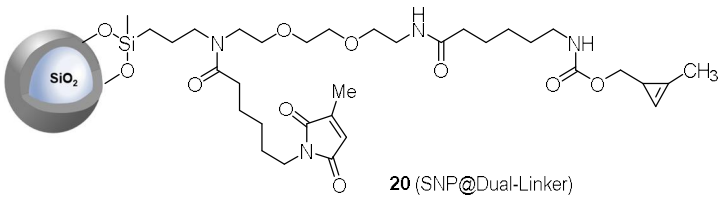
To a solution of **17** (22.8 mg, 0.02 mmol) in CH_3CN (0.2 mL), tetrazine **18** (4.8 mg, 0.02 mmol) was added at room temperature. The mixture was stirred for 3 hours at room temperature. The reaction mixture was quenched with water (1 mL), extracted with CH_2Cl_2 (3 x 10 mL), and washed with brine. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel to afford the title compound **19** (23.5 mg, 87%) as orange solid.

R_f = 0.25, Dichloromethane/MeOH = 20:1 (v/v %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.71 (d, J = 4.2 Hz, 0.7H), 8.68 (d, J = 4.2 Hz, 1.4H), 8.51 (d, J = 8.0 Hz, 0.7H), 8.47 (d, J = 8.0 Hz, 0.3H), 8.10 (d, J = 7.9 Hz, 0.6H), 8.06 (d, J = 7.9 Hz, 0.3H), 7.80 (m, 2H), 7.38 (m, 2H), 6.13 (s, 1H), 6.03 (s, 2H), 5.02 (s, 0.3H), 4.86 (s. 0.6H), 4.60 (m, 2), 4.48 (d, J = 0.8 Hz, 2H), 3.75 (m, 1H), 3.50 (m, 14H), 3.24 (m, 4H), 3.01 (q, J = 6.3 Hz, 1H), 2.93 (m, 2H), 2.74 (m ,4H), 2.50 (s, 6H), 2.39 (d, J = 3.1 Hz, 6H), 2.32 (t, J = 7.5 Hz, 0.7H), 2.26 (t, J = 7.5 Hz, 1.4H), 2.13 (t, J = 7.1 Hz, 2H), 2.02 (d, J = 7.3 Hz, 2H), 1.70 (d, J = 4.1 Hz, 6H), 1.57 (m, 24H), 1.34 (m, 6H), 0.50 (m, 2H), 0.05 (s, 2H), 0.03(s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 178.6, 174.1, 173.0, 172.7, 154.0, 149.2, 148.8, 146.1, 143.1, 140.3, 136.8, 136.7, 131.5, 125.4, 124.8, 122.2, 121.8, 109.2, 109.0, 77.4, 71.1, 70.6, 70.3, 70.1, 69.3, 69.1, 60.0, 53.5, 52.4, 49.4, 47.6, 47.5, 45.9, 44.0, 42.8, 40.8, 39.3, 38.9, 38.8, 36.5, 33.1, 32.9, 32.0, 31.8, 31.5, 31.0, 29.8, 29.6, 29.4, 28.9, 28.8, 28.4, 27.6, 26.7, 26.5, 26.4, 25.8, 25.7, 25.5, 25.3, 25.0, 24.1, 23.5, 23.2, 22.8, 22.0, 16.6, 15.9, 14.6, 14.2, 11.6, 11.3, 11.2, 2.0, -4.2, -4.3; HRMS(ESI): $[M+Na]^+$ calcd for $C_{71}H_{101}BF_2N_{10}O_8SSiNa$ 1353.7253; found 1353.7247.

Synthesis of SNP 20

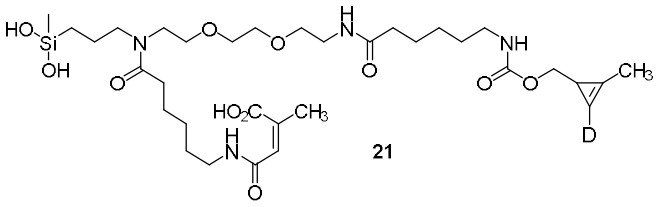
SNP@Dual-linker (20)



Bismethallylsilane **15** (30 mg, 0.039 mmol) and $Sc(OTf)_3$ (1 mg, 1 μmol) were added to silica (20 mg) dispersed in CH_3CN (6 mL). The mixture was stirred at room temperature for 90 minutes and then centrifuged. The supernatant was discarded and the remaining material was treated with fresh CH_3CN and H_2O, and sonicated for 20 minutes. The washing process was repeated three times. TLC was used to confirm whether unreacted **15** remained or not. The aggregation of **SNP 20** was confirmed by DLS analysis.

Hydrolysis of SNP 20 under basic condition

(*Z*)-20-(3-(dihydroxy(methyl)silyl)propyl)-30-methyl-1-(2-methylcycloprop-2-en-1-yl-3-d)-3,10,21,28-tetraoxo-2,14,17-trioxa-4,11,20,27-tetraazahentriacont-29-en-31-oic acid (21)



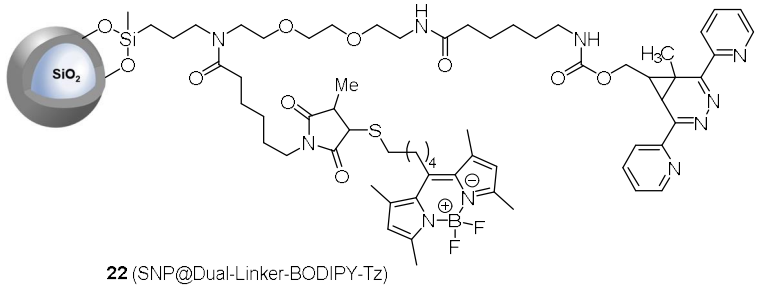
To a dispersed solution of **20** (12.5 mg) in D_2O (350 μL) was added an aqueous solution of NaOD (30 wt% at D_2O, 50 μL). The mixture was sonicated for 30 min and then stirred at 45 °C for 3 h. The reaction mixture was cooled to room temperature, which was analyzed by DLS to confirm whether there are any remaining particles. Potassium phthalate monobasic was added to the resulting solution as an internal standard, which was analyzed by NMR instrument.

^{1}H-NMR (400 MHz, D_2O, a mixture of isomers): δ 5.65 (s, 0.05H), 5.35 (s, 1H), 3.71 (m, 2H), 3.45 (m,

17H), 3.34 (m, 1H), 3.13 (m, 4H), 2.97 (t, J = 6.8 Hz, 2H), 2.89 (t, J = 6.1 Hz, 2H), 2.23 (t, J = 7.4 Hz, 2H), 2.05 (t, J = 7.2 Hz, 2H), 1.90 (s, 2H), 1.76 (s, 2.4H), 1.72 (d, J = 5.2 Hz, 0.6H), 1.38 (m, 6H), 1.30 (q, J = 7.0 Hz, 4H), 1.14 (m, 5.2H), 0.97 (t, J = 7.1 Hz, 12H), 0.18 (m, 2H), -0.26 (s, 2H), -0.27 (s, 1H). LRMS(ESI) (m/z): $[M+Na]^+$ calcd for $C_{33}H_{57}DN_4NaO_{11}Si$ 738.4 found 738.4.

One pot procedure for the synthesis of SNP 22

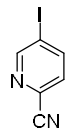
SNP@Dual-linker-Bodipy-Tz (22)



22 (SNP@Dual-Linker-BODIPY-Tz)

To a dispersed solution of **20** (10 mg) in CH_3CN (4 mL) were added BODIPY-thiol **16** (1 mg, 3.0 μmol) and Et_3N (2 μL, 1.0 μmol). After the mixture was stirred at room temperature for 30 min, tetrazine **18** (0.7 mg, 3.0 μmol) was added and the resulting mixture was stirred at room temperature for additional 3 h. The mixture was centrifuged, the supernatant was discarded, and the remaining material was dispersed in CH_3CN and sonicated for 10 minutes. This washing process was repeated three times (or until no unreacted **16** or **18** was not detected by TLC).

5-Iodopicolinonitrile (23)[7]



23

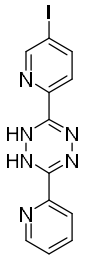
To a solution of $TsOH{\cdot}H_2O$ (958 mg, 5.04 mmol) in CH_3CN (6.7 mL), 5-amino-pyridine-2-carbonitrile (200 mg, 1.68 mmol) was added. The resulting suspension was cooled to 5 °C. A solution of $NaNO_2$ (232 mg,

3.36 mmol) and KI (724 mg, 4.37 mol) in 1.5 mL of water was added slowly in small portions. Vigorous gas evolution and foaming was observed during the addition. After addition, the brown/black mixture was stirred 10 min and was then warmed to room temperature and stirred for 4 h. The mixture was added saturated $NaHCO_3$ solution until pH 9-10 and saturated sodium thiosulfate solution until the solution changed from a dark red to light orange in color. And then, the solution was stirred for 30 min and extracted with EtOAc. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The residue was purified by flash column chromatography on silica gel to afford product **23** as white powder (234 mg, 62%).

R_f = 0.55, *n*-hexane/EtOAc = 4:1 (v/v %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (d, J = 1.4 Hz, 1H), 8.19 (dd, J = 8.1, 2.1 Hz, 1H), 7.46 (dd, J = 8.1, 0.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 157.5, 145.6, 132.7, 129.4, 116.9, 98.3.

3-(5-iodopyridin-2-yl)-6-(pyridin-2-yl)-1,2-dihydro-1,2,4,5-tetrazine (24)[7]



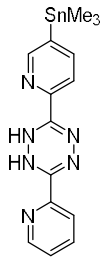
24

A Round-bottom flask was charged with picolinonitrile (190 mg, 1.83 mmol), **23** (100 mg, 0.43 mmol), and sulfur (28 mg, 0.87 mmol) and purged with argon. A solution of 50-64 % hydrazine hydrate (447 µL, 7.17 mmol) and absolute EtOH (1.7 mL) were added to the flask which was then sealed and refluxed for 2h. The reaction mixture was cooled to room temperature and extracted with DCM. The organic layers were dried over $MgSO_4$, filtered, and the desired product isolated by flash column chromatography on silica gel to afford product **24** as orange powder (73 mg, 46%).

R_f = 0.40, *n*-hexane/EtOAc = 4:1 (v/v %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (s, 1H), 8.61 (s, 1 H), 8.57 (d, J = 4.6 Hz, 1H), 8.40 (s, 1H), 8.06 (t, J = 7.6 Hz, 2H), 7.83 (d, J = 8.4 Hz, 1H), 7.77 (t, J = 7.7 Hz, 1H), 7.36 (t, J = 6.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 154.6, 148.4, 147.4, 146.6, 146.5, 146.2, 145.2, 137.0, 125.1, 122.9, 121.5, 95.0.

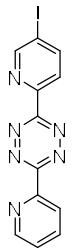
3-(pyridin-2-yl)-6-(5-(trimethylstannyl)pyridin-2-yl)-1,2-dihydro-1,2,4,5-tetrazine (25)[7]



25

A solution of 1,1,1,2,2,2-hexamethyldistannane (90 mg, 0.27 mmol) in dry THF (2 mL) was added to a pressure tube which was purged with argon. A solution of $Pd(PPh_3)_4$ (3.2 mg, 2.7 µmol) in THF (1 mL) were added to the reaction vessel at room temperature for 5 min, and a solution of **24** (50 mg 0.14 mmol) in THF (1.5 mL) was added under argon. The reaction vessel was heated at 110 °C for 4h. The vessel was cooled to room temperature and the mixture was extracted with DCM. The organic layers were washed with brine, dried over $MgSO_4$, filtered, and the solvent removed by rotary evaporation. The desired product was isolated flash column chromatography on silica gel to afford product **25** as orange crystal (54 mg, 98%). R_f = 0.33, *n*-hexane/EtOAc = 4:1 (v/v %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (s, 1H), 8.64 (s, 1H), 8.56 (m, 2H), 8.04 (d, J = 7.9 Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.75 (td, J = 7.4, 0.3 Hz, 1H), 7.35 (td, J = 5.8, 0.2 Hz, 1H).



26

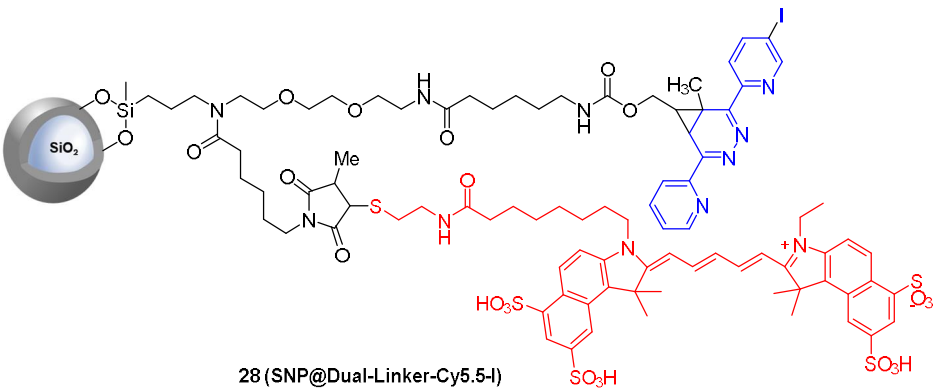
3-(5-iodopyridin-2-yl)-6-(pyridin-2-yl)-1,2,4,5-tetrazine (26) [7].

A 5 mg/mL solution (500 µL) containing iodogen in 5% acetic acid/acetonitrile was added to a vial containing stannyl tetrazine **25** (1 mL from a 10 mg/mL solution, in acetonitrile). The mixture was combined with aqueous sodium iodide and stirred for 5 min. And then, the solution was added an additional aliquot (2.8 mL) of the iodogen solution and stirred for a further 15 min. The reaction was quenched with aqueous sodium thiosulfate and extracted with DCM. The organic layers were combined, washed with brine, dried over MgSO4, filtered, and the solvent removed by rotary evaporation. The desired product was isolated by flash column chromatography on silica gel to afford product **26** as purple solid (5 mg, 56%).

R_f = 0.30, *n*-hexane/EtOAc = 1:2 (v/v %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (d, J = 1.5 Hz, 1H), 8.98 (d, J = 4.3 Hz, 1 H), 8.74 (d, J = 7.9 Hz, 1H), 8.51 (d, J = 8.3 Hz, 1H), 8.34 (dd, J = 8.3, 1.9 Hz, 1H), 8.00 (td, J = 7.8, 1.4 Hz, 1H), 7.58 (dd, J = 7.0, 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.0, 163.9, 157.3, 151.2, 150.0, 148.9, 146.1, 137.6, 126.8, 125.8, 124.7, 98.3.

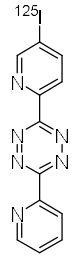
SNP@Dual-Linker-Cy5.5-Iodo tetrazine (28)



28 (SNP@Dual-Linker-Cy5.5-I)

Following the same procedure used for the synthesis of SNP **22**, to a dispersed solution of **20** (12.8 mg) in CH_3CN (4 mL) were added Cy5.5 dye **27** (1.0 mg, 1.0 μmol) and Et_3N (1.0 μL, 0.5 μmol). After the mixture was stirred at room temperature for 30 min, tetrazine **26** (1.0 mg, 2.8 μmol) was added and the resulting mixture was stirred at room temperature for additional 1 h. The mixture was centrifuged, the supernatant was discarded, and the remaining material was dispersed in EtOH and sonicated for 10 minutes. This washing process was repeated three times (or until no unreacted **26** or **27** was not detected by TLC) to afford bifunctional SNP **28** (cold SNP) as a dispersion in EtOH.

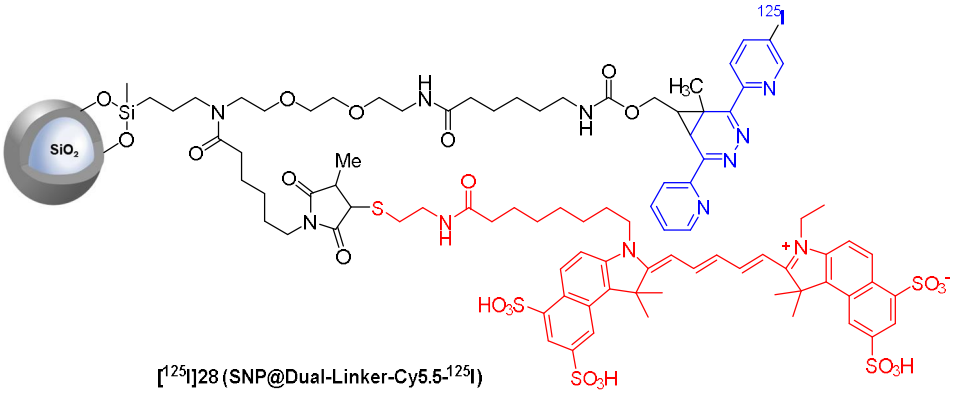
3-(5-(iodo-^{125}I)pyridin-2-yl)-6-(pyridin-2-yl)-1,2,4,5-tetrazine ([^{125}I]26)[7]



26

A 5 mg/mL solution (29.3 μL) containing iodogen in 5% acetic acid/acetonitrile was added to a vial containing stannyl tetrazine **25** (58.7 μL from a 10 mg/mL solution, in acetonitrile). The mixture was combined with aqueous sodium iodide [I-125] (41 μL, 74 MBq) that was obtained from a 0.1 M NaOH solution. The mixture was agitated for several seconds by hand and allowed to stand for 5 min. To this we added an additional aliquot (164.5 μL) of the iodogen solution and allowed the mixture to stand for a further 15 min. The reaction mixture was quenched with aqueous sodium thiosulfate (100 μL, 0.1 M) and extracted with dichloromethane (100 μL). The organic solvent was separated and evaporated at room temperature to afford product **[^{125}I]26**.

SNP@Dual-Linker-Cy5.5-^{125}I tetrazine([^{125}I]28)



Following the same procedure used for the synthesis of SNP **22**, to a dispersed solution of **20** (5 mg) in CH_3CN (2 mL) were added Cy5.5 dye **27** (1.0 mg, 1.0 µmol) and Et_3N (1.0 µL, 0.5 µmol). After the mixture was stirred at room temperature for 30 min, tetrazine **[^{125}I]26** (0.7 mg, 3.0 µmol) was added and the resulting mixture was stirred at room temperature for additional 1 h. The mixture was centrifuged, the supernatant was discarded, and the remaining material was dispersed in EtOH and sonicated for 10 minutes. This washing process was repeated three times (or until no unreacted **[^{125}I]26** or **27** was not detected by TLC) to afford bifunctional SNP **[^{125}I]28** as a dispersion in EtOH. For biodistribution study, the solvent was replaced by water using centrifugation followed by solvent exchange and sonication.

Synthetic procedure of 40-50 nm size of silica nanoparticles (SNPs)

150 mL of DI water and 0.16 g of L-lysine are added to 500 mL polypropylene bottle, stirred in an oil bath at 90 °C, and the temperature is adjusted. After, 20 g of TEOS in added to proceed with the 24 hours reaction. And then 45 g of TEOS is added to the reaction for 24 hours. Finally, an additional 40 g of TEOS is added to the reaction for 24 hours. After synthesis the solution is sufficiently cooled to room temperature. Filtering with a filter paper, check the concentration, and storage solution.

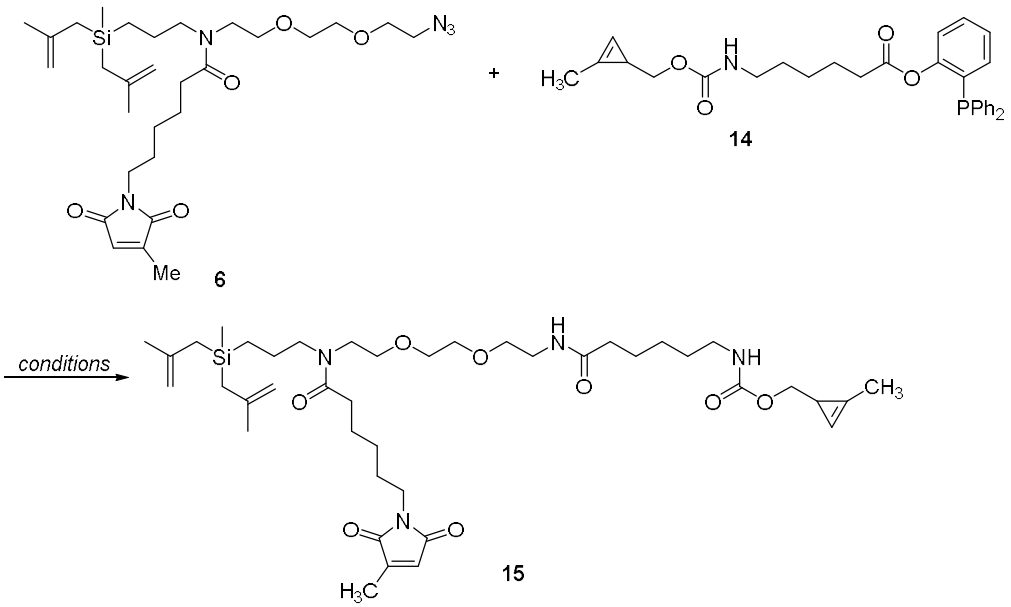
II. Image Acquisitions

All protocols were approved by the Institutional Animal Care and Use Committee of the Seoul National University Bundang Hospital (IACUC number BA-2009-304-085-04). The Ji Seok Young Research Center is fully accredited by the AAALAC. All animals were cared for in accordance with the ILAR Guide for the Care and Use of Laboratory Animals 8th Edition.

We acquired SPECT/CT images and fluorescence images immediately after, 24 hours, 48 hours after intravenous injection of ^{125}I and Cy 5.5 dye conjugated silica nanoparticle (**28**, 100 μCi) via mouse tail vein. The activity of silica nanoparticle was measured with dose calibrator, before and after injection. For SPECT/CT images acquisition, animal SPECT/CT scanner (NanoSPECT/CT; Bioscan Inc., Washington DC, USA) was used with a high-resolution static scan of the mouse head was acquired in helical scanning mode in 24 projections after 60 min using a four-head scanner with 4 × 9 (1.4 mm) pinhole collimators. The energy window was set at 140 keV ± 15 %. The SPECT image acquisition was followed using CT in the same position. For fluorescence images acquisition, IVIS Lumina III (PerkinElmer, Waltham, Massachusetts, USA) was used. The analysis software PMOD (Version 4.2, Technologies, Zurich, Switzerland) was used for the images analysis. The CT images were used for creating each organ volume of interest (VOI). We measured the activity of each organ using the VOI of each organ, respectively.

III. Optimization reaction conditions of traceless Staudinger reaction

Table S1. Optimization reaction conditions of traceless Staudinger reaction



entry[a]	H_2O (equiv.)	solvent	temp (°C)	time (h)	yield (%)[b]
1	-	THF (0.05 M)	rt	4	No reaction[c]
2	100	THF (0.05 M)	rt	4	No reaction[c]
3	50	DMF (0.175 M)	rt	4	No reaction[c]
4	50	DMF (0.175 M)	50	4	No reaction[c]
5	20	THF (0.1 M)	40	24	15[d]
6	10	THF (0.2 M)	40	24	20[d]
7	10	CH_3CN (0.2 M)	40	24	No reaction[d]
8	10	dioxane (0.2 M)	40	24	No reaction[d]
9	5	THF (0.2 M)	40	24	41[d]
10	3	THF (0.2 M)	40	24	54[d]
11	1	THF (0.2 M)	40	24	52[d]

[a]The reaction was performed with 1:1 ratio of azide **6** and phosphine **14**. [b]Isolated yield. [c]H_2O was initially added. [d]H_2O was added after the reaction proceeded for 12 h.

IV. Optical properties and kinetic study for 19

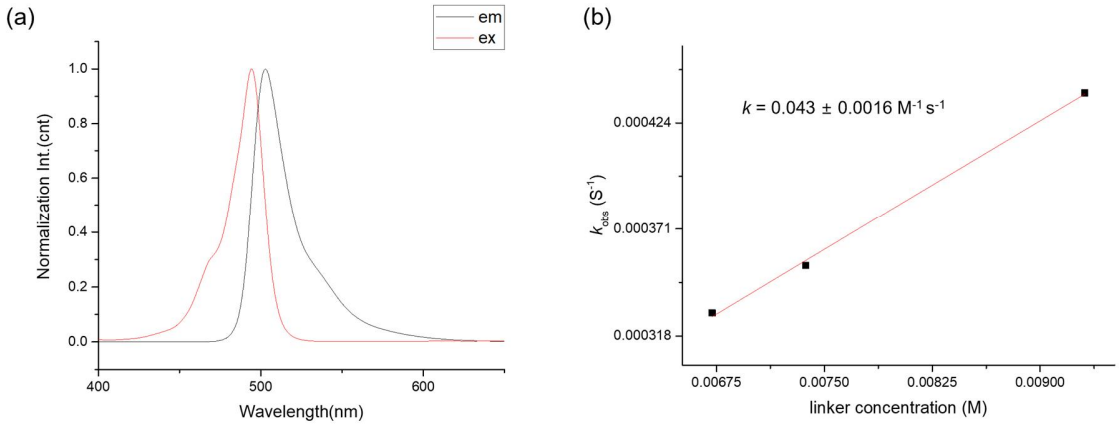
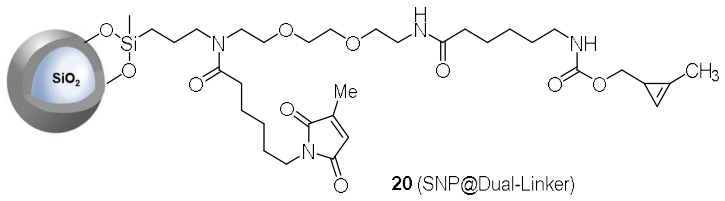


Figure S1. (a) Normalized excitation and emission spectra of **19** in CH_3CN. (λ_{ex} 494 nm and λ_{em} 503 nm). (b) Determination of the rate constant for the reaction of **17** with **18** in CH_3CN. The rate constants (k_{obs}) were plotted against different concentrations with the slope taken as the second-order rate constant.

V. Calculation of surface coverage of 20 by NMR experiments



20 (SNP@Dual-Linker)

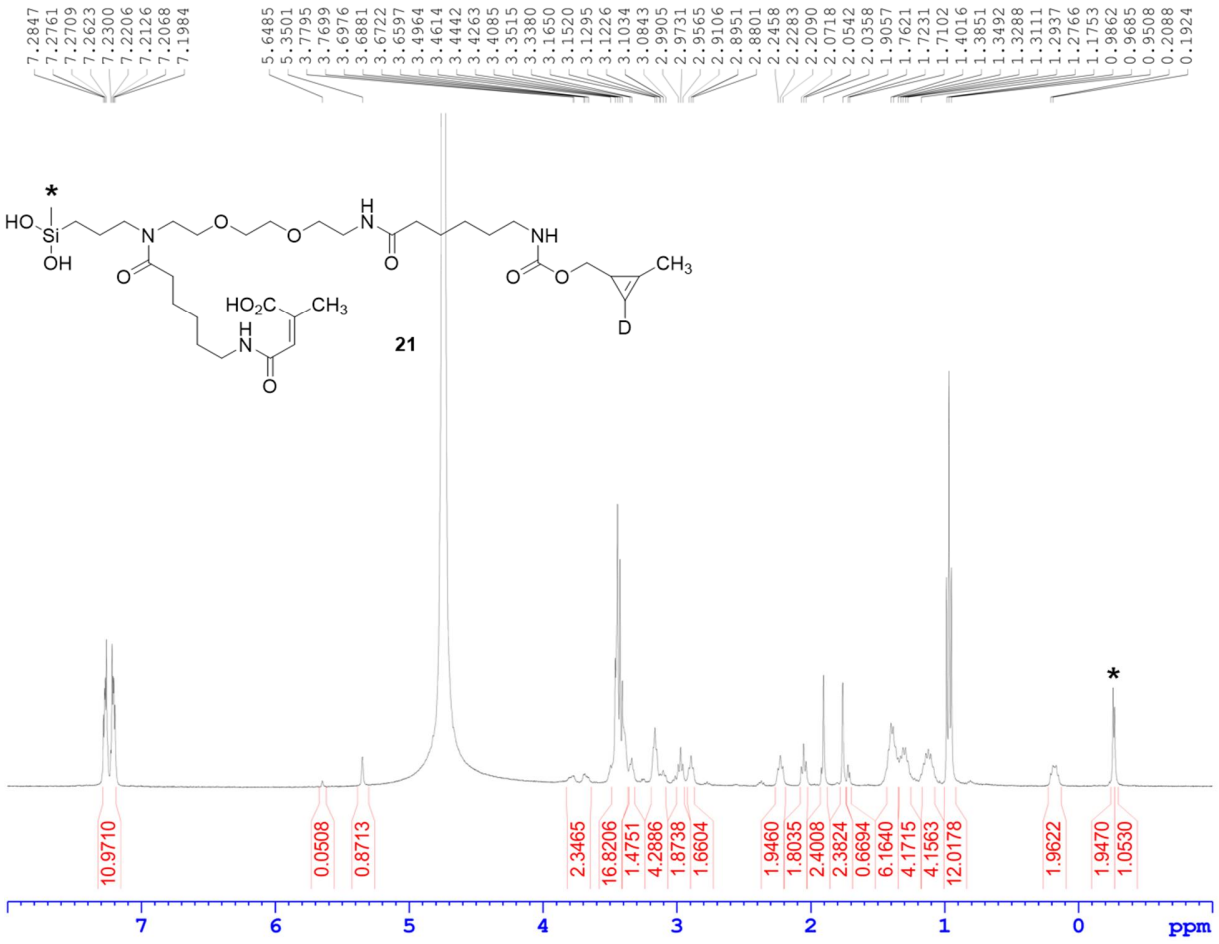
After hydrolysis of SNP **20** with NaOD solution, the NMR spectrum of the compound **21** was obtained according to the above-mentioned procedure. The following assumptions were made in all calculation and applied across all the work presented.

- All particles are perfect spheres of the same size.
- The density of all particles is the same and equal to $2 g/cm^3$
- DLS and SEM gives an accurate description of true size

The mass of modified silica nanoparticle: 12.5 mg

The mass of internal standard (potassium phthalate monobasic): 0.6 mg

From the mean particle size, we calculated the area ($A = 4\pi r^2$) and volume ($V = 4/3\pi r^3$) of the particles. The mass of a particle was calculated from the density and the calculated volume, allowing the quantification of the number of particles per gram of material. With the number of particles per gram, and the area of an individual particle, we determined the total area (m^2) per gram. The concentration of the functionalized compound (mol/m^2) can then be obtained from the total area and the value obtained by NMR (mol/g). From the product between the total area (m^2) and the concentration of the functionalized compound (mol/m^2), we obtained the total number of moles of the functionalized compound and, from this, the corresponding number of molecules. By dividing the number of molecules by the total area, we obtain the number of molecules per nm^2.



^{1}H NMR of compound 21 (400 MHz, $CDCl_3$)

VI. Characterization of cold SNP 28

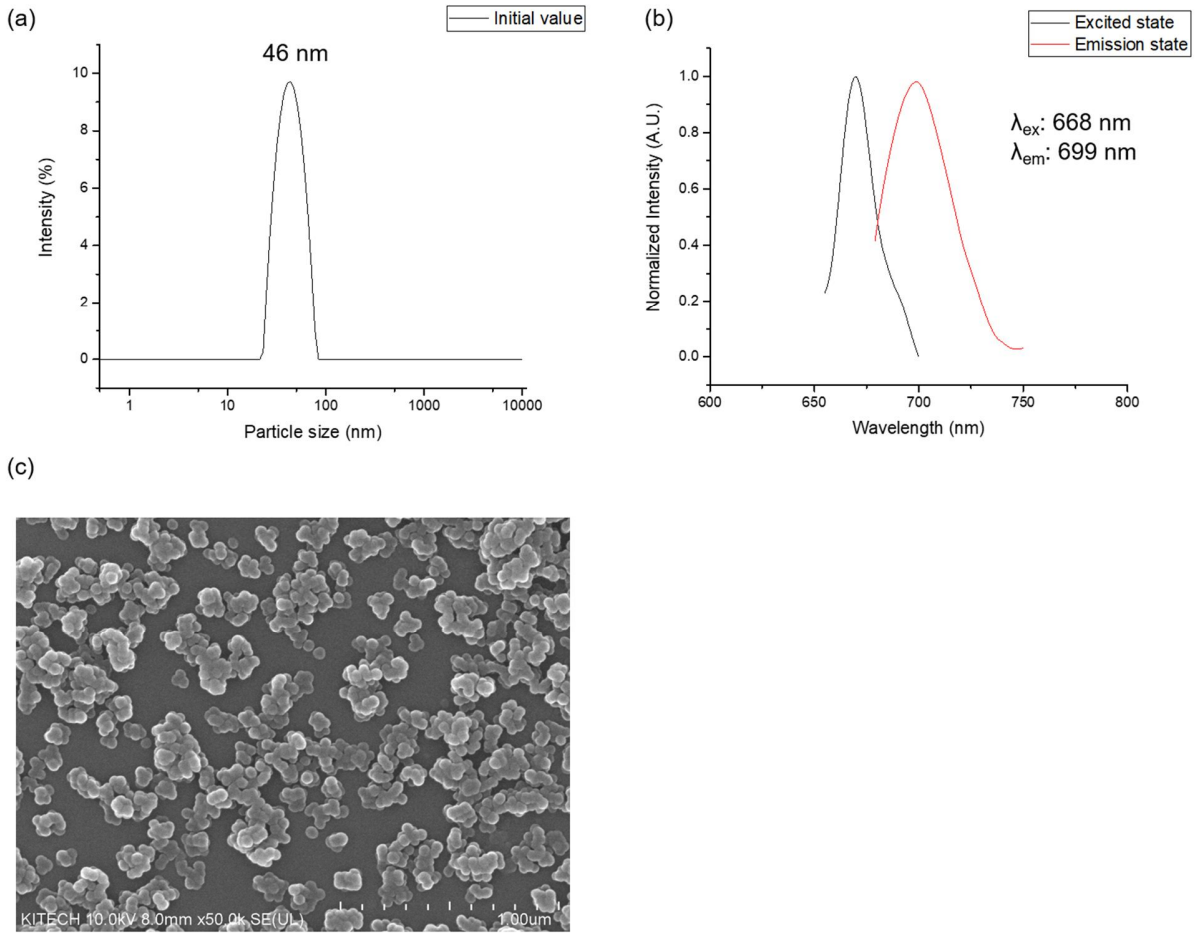


Figure S2. Characterization of cold SNP **28**. (a) DLS graph; (b) Excitation and emission spectra of **28**; (c) SEM image

VII. Stability of cold SNP 28 under physiological conditions

Methods: A solution of SNP **28** in water (100 μL, 1 mg/mL) was added in three different environments; (1) D.I water, (2) 1X PBS buffer, (3) 10 % FBS buffer (100 μL). The complex was incubated at 37 ℃. After 3 hours, the residue was centrifuged by 13,000 rpm for 15 minutes. And then, the supernatant was exchanged with H_2O and sonicated for 5 minutes. The procedures were repeated at least three times.

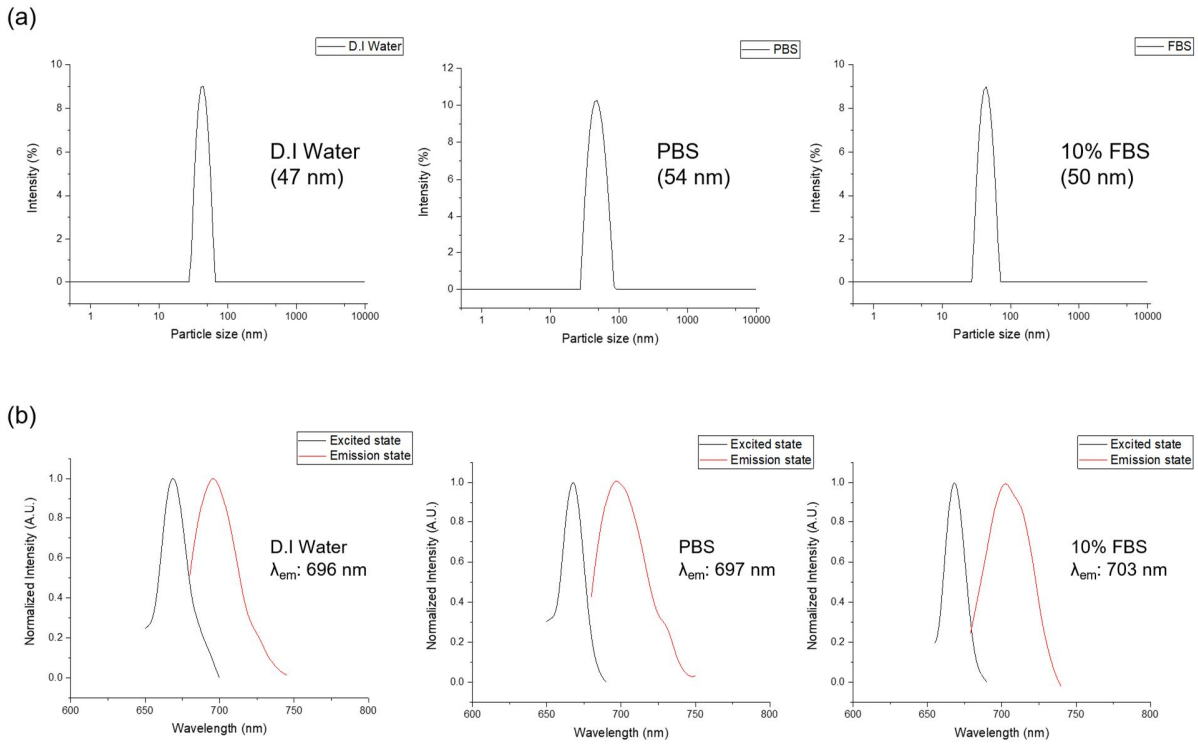
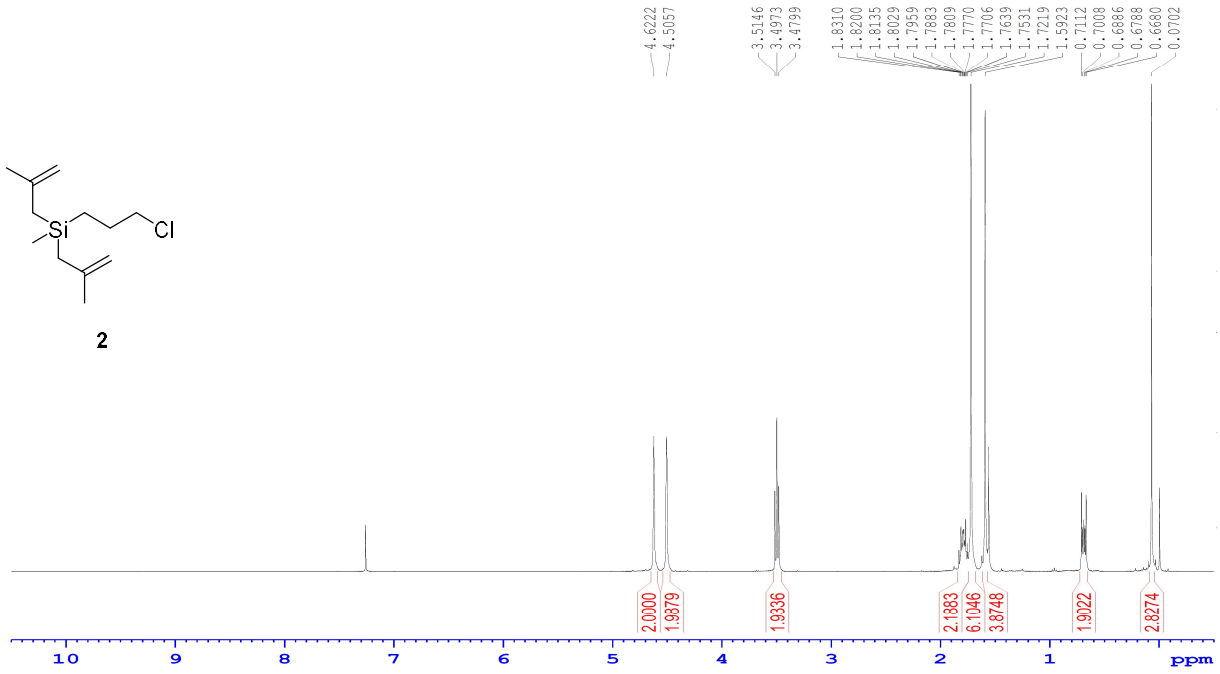


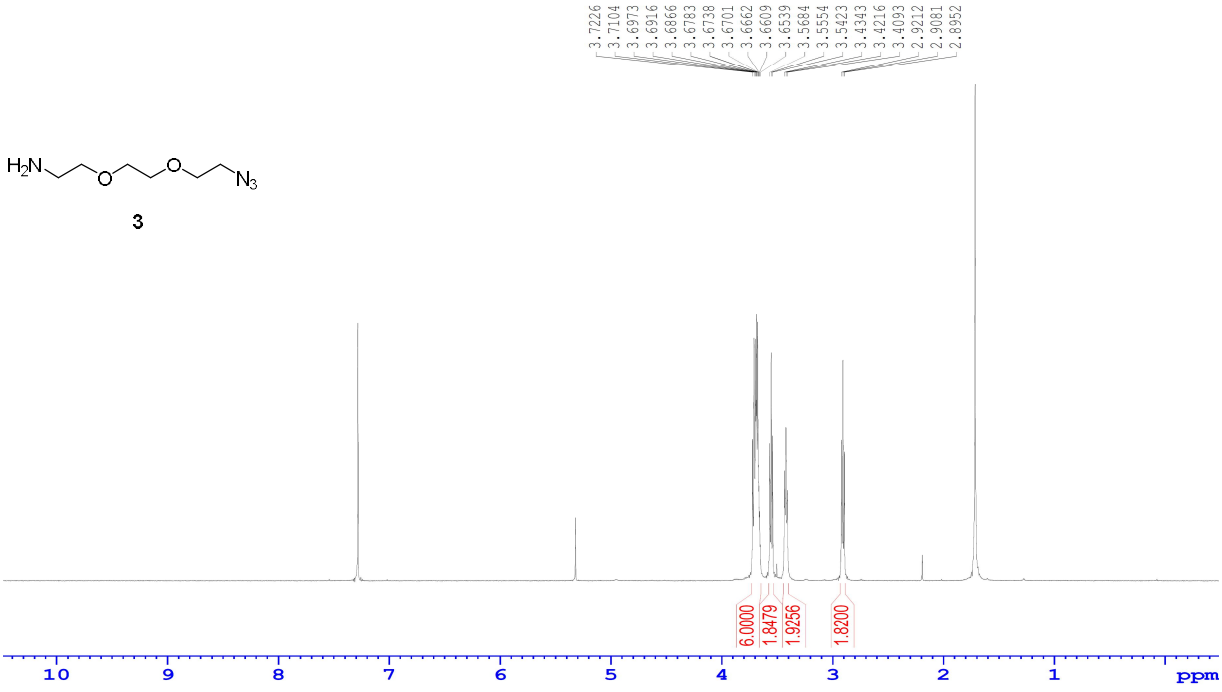
Figure S3. Stability of cold SNP **28** after incubation of cold SNP **28** in three different media for 3h. (a) Hydrodynamic radius measured by DLS; (b) Excitation/emission spectra of cold SNP **28**.

VIII. NMR Spectra



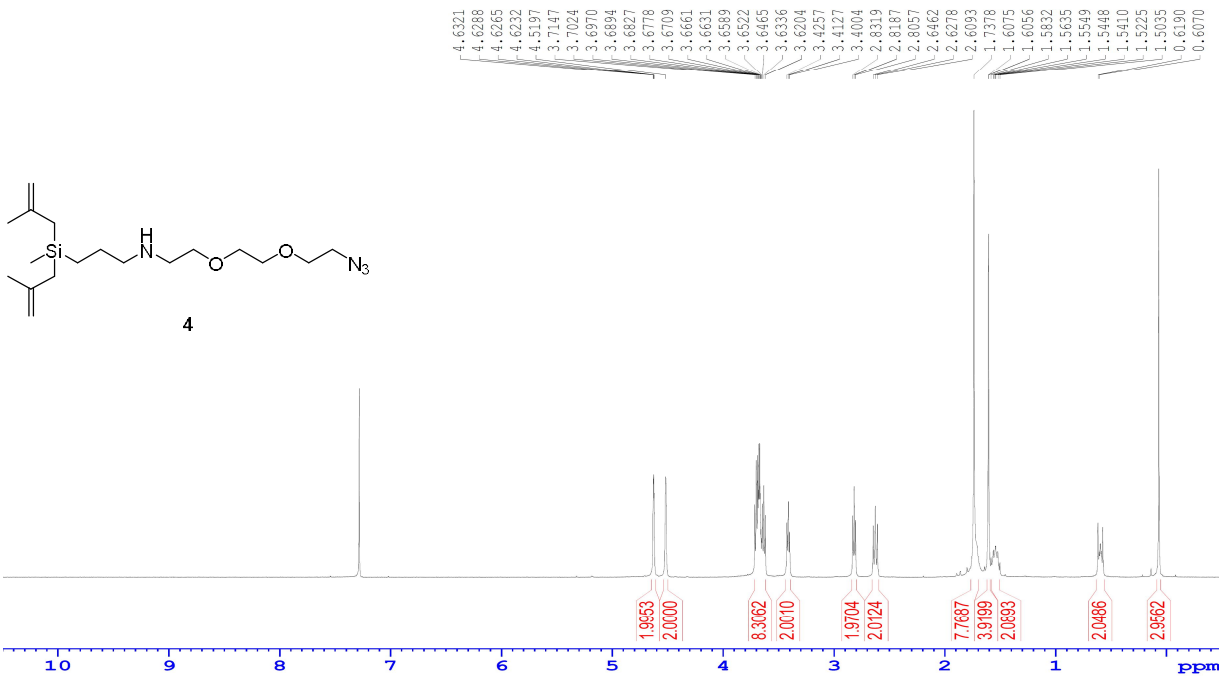
2

^{1}H NMR of compound 2 (400 MHz, $CDCl_3$)

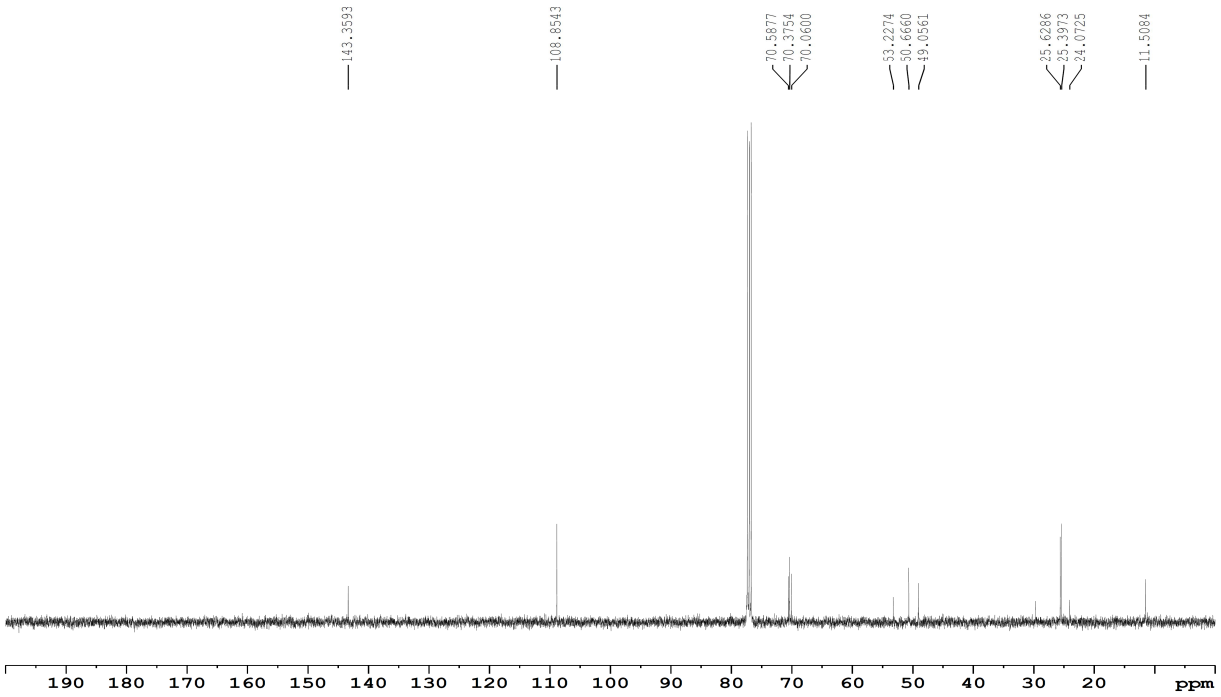


3

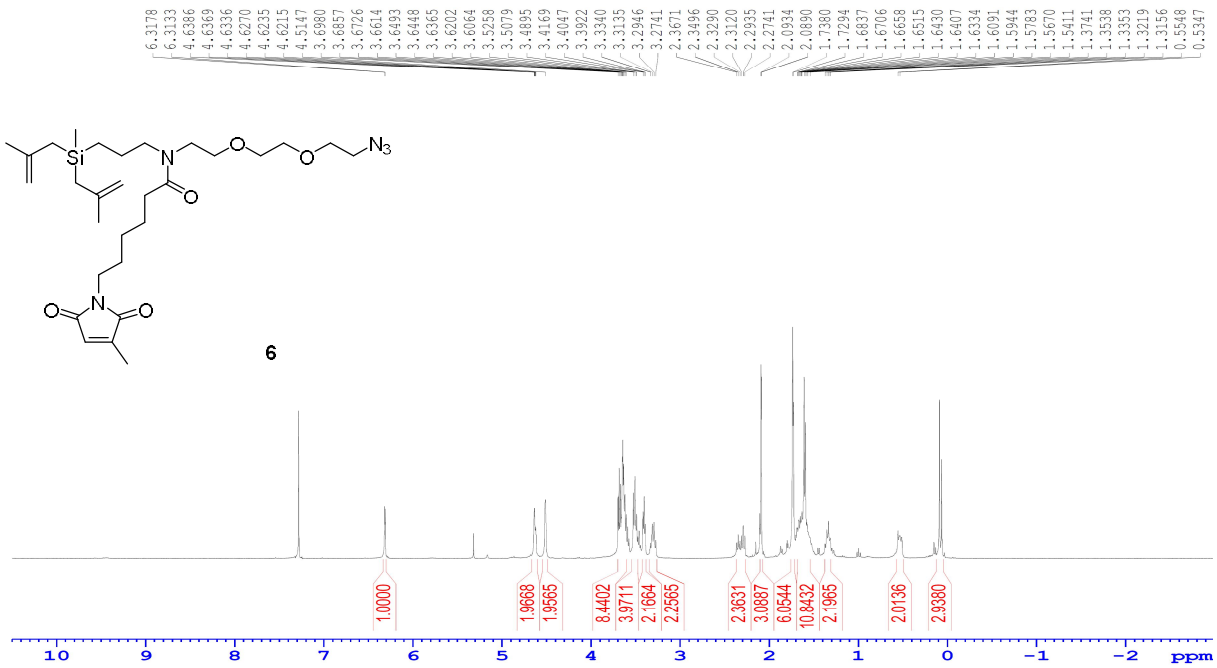
^{1}H NMR of compound 3 (400 MHz, $CDCl_3$)



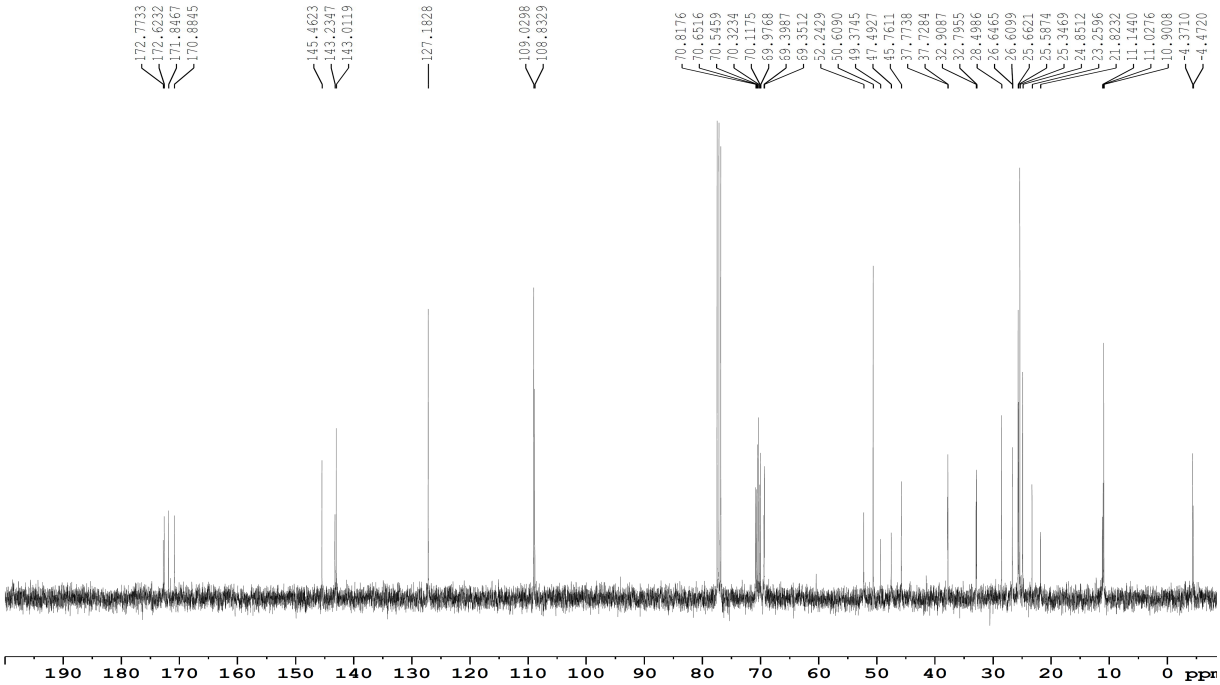
^{1}H NMR of compound 4 (400 MHz, $CDCl_3$)



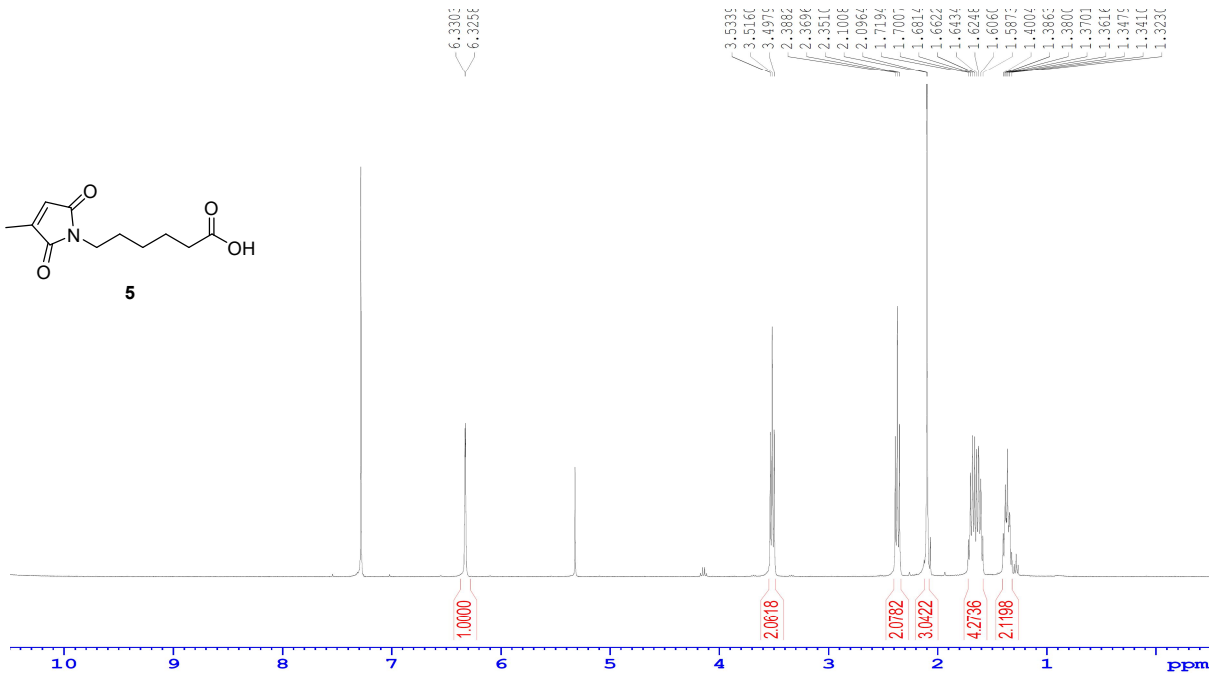
^{13}C NMR of compound 4 (100 MHz, $CDCl_3$)



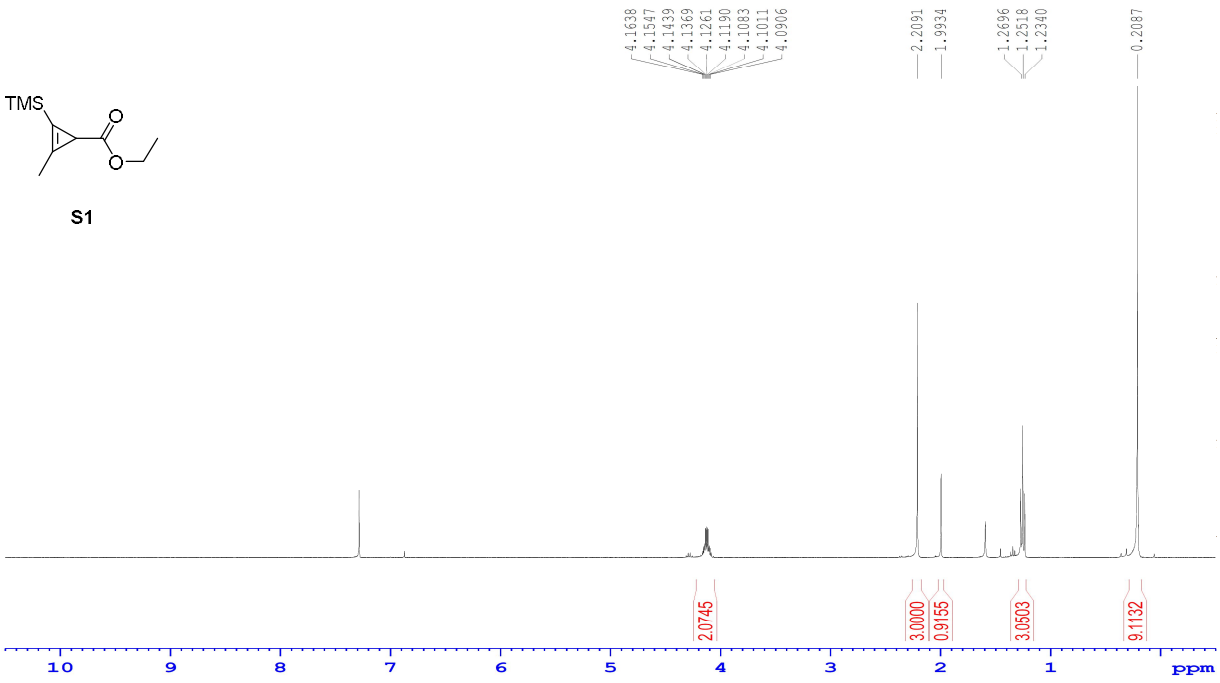
^{1}H NMR of compound 6 (400 MHz, $CDCl_3$)



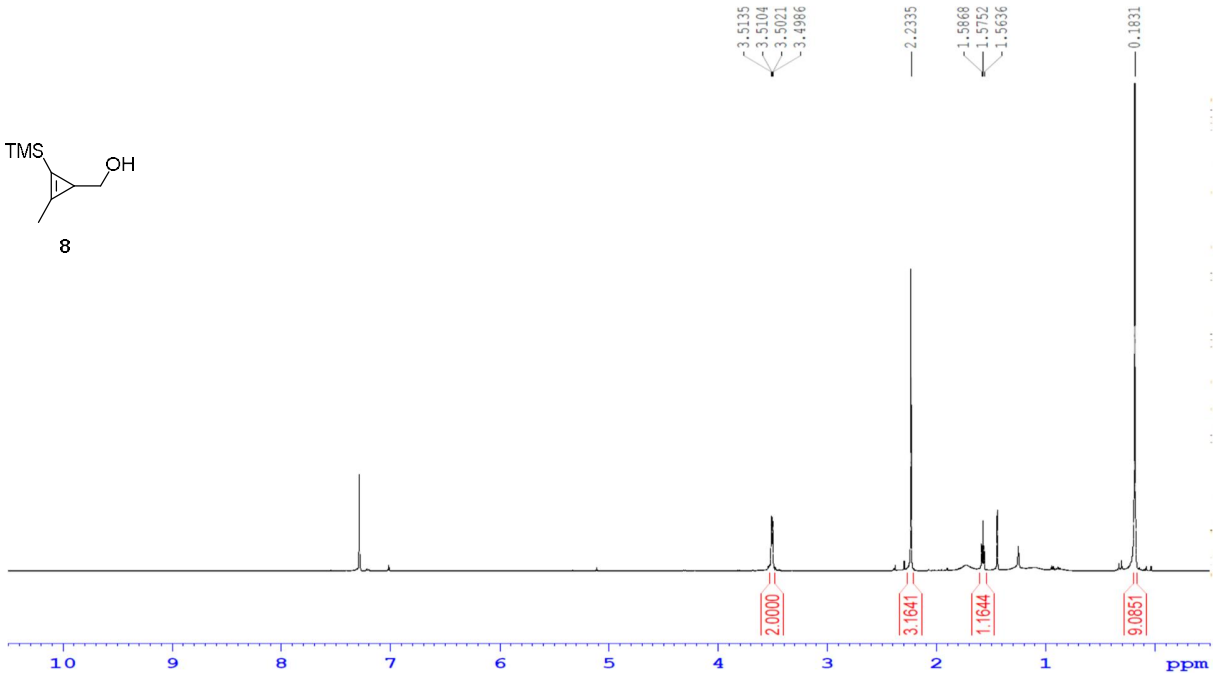
^{13}C NMR of compound 6 (100 MHz, $CDCl_3$)



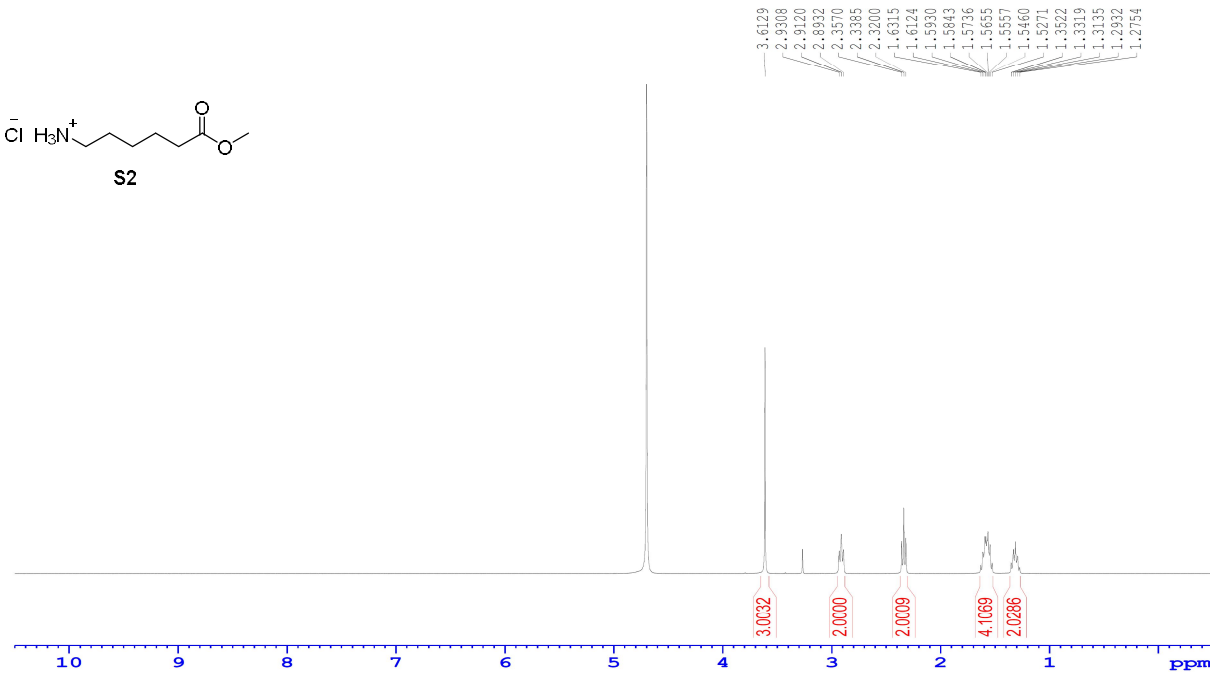
^{1}H NMR of compound 5 (400 MHz, $CDCl_3$)



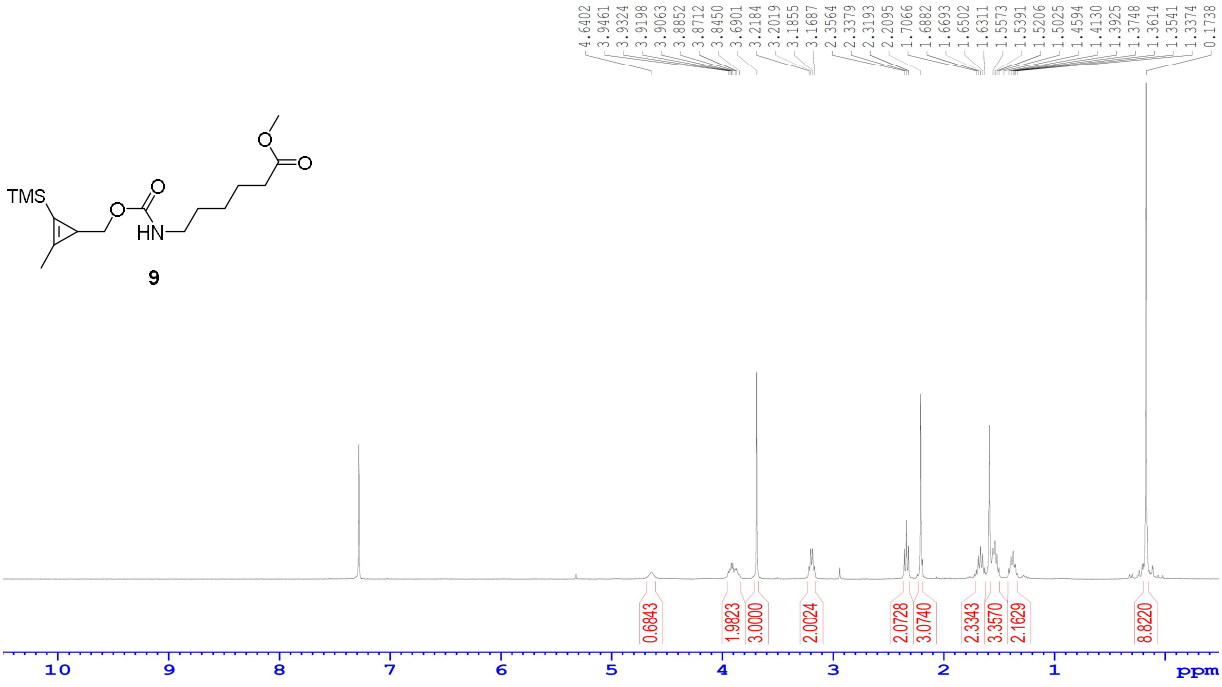
^{1}H NMR of compound S1 (400 MHz, $CDCl_3$)



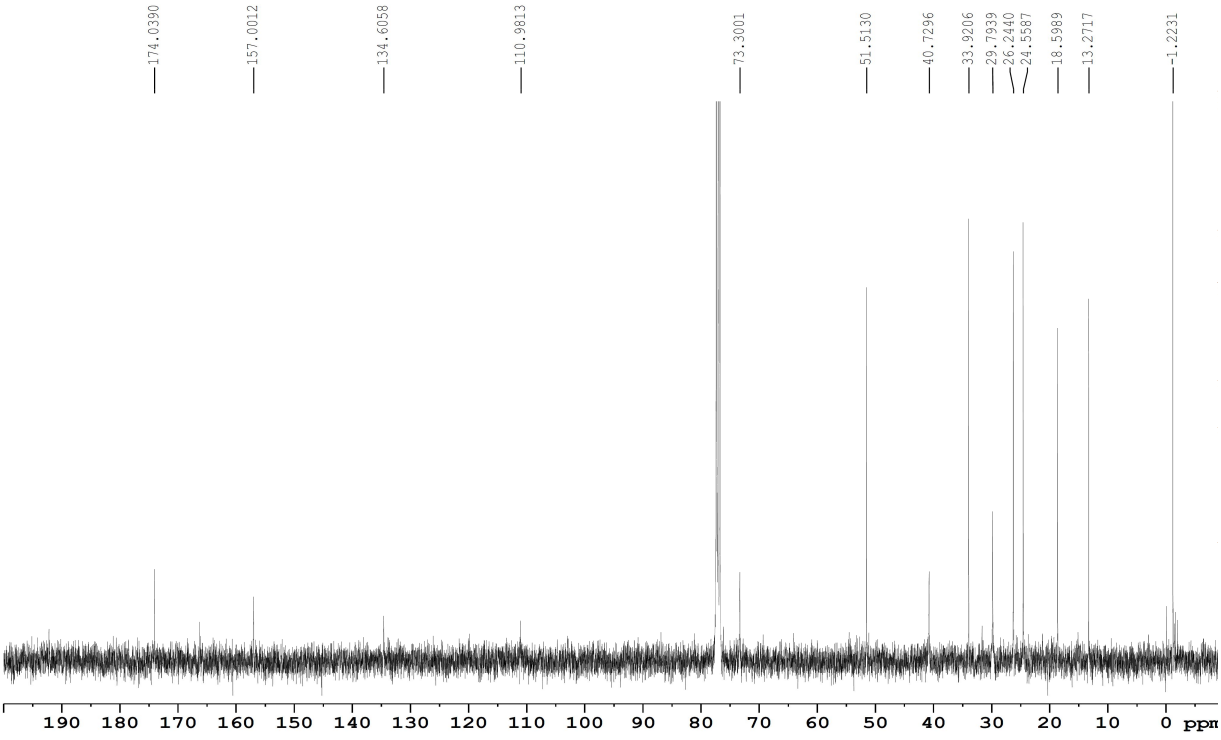
^{1}H NMR of compound 8 (400 MHz, $CDCl_3$)



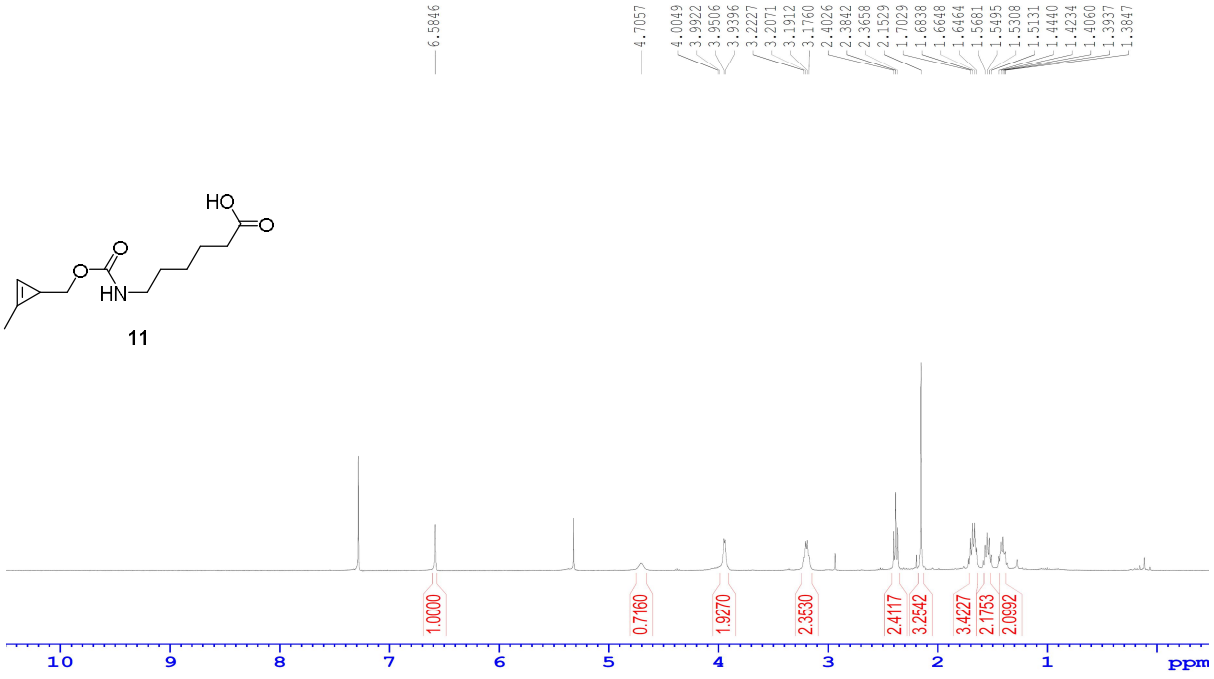
^{1}H NMR Spectrum of $H_2N(CH_2)_5CO_2Me$•HCl S2 (400 MHz, D_2O)



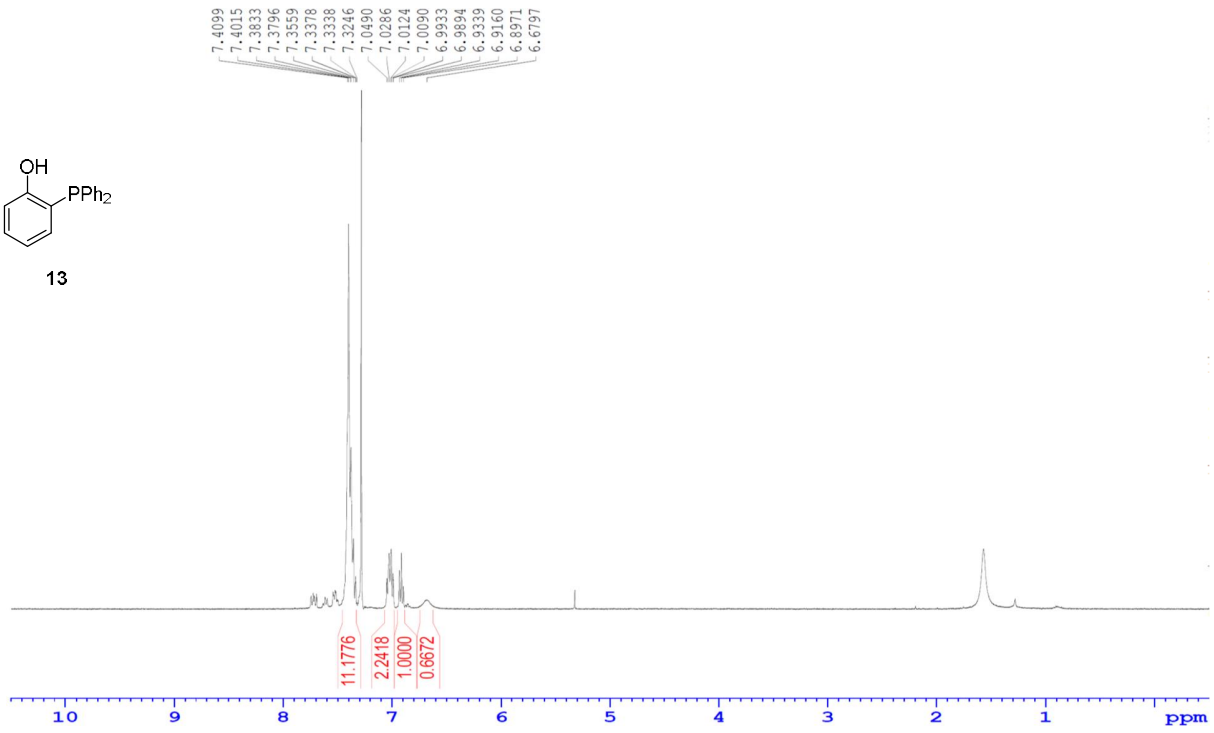
^{1}H NMR of compound 9 (400 MHz, $CDCl_3$)



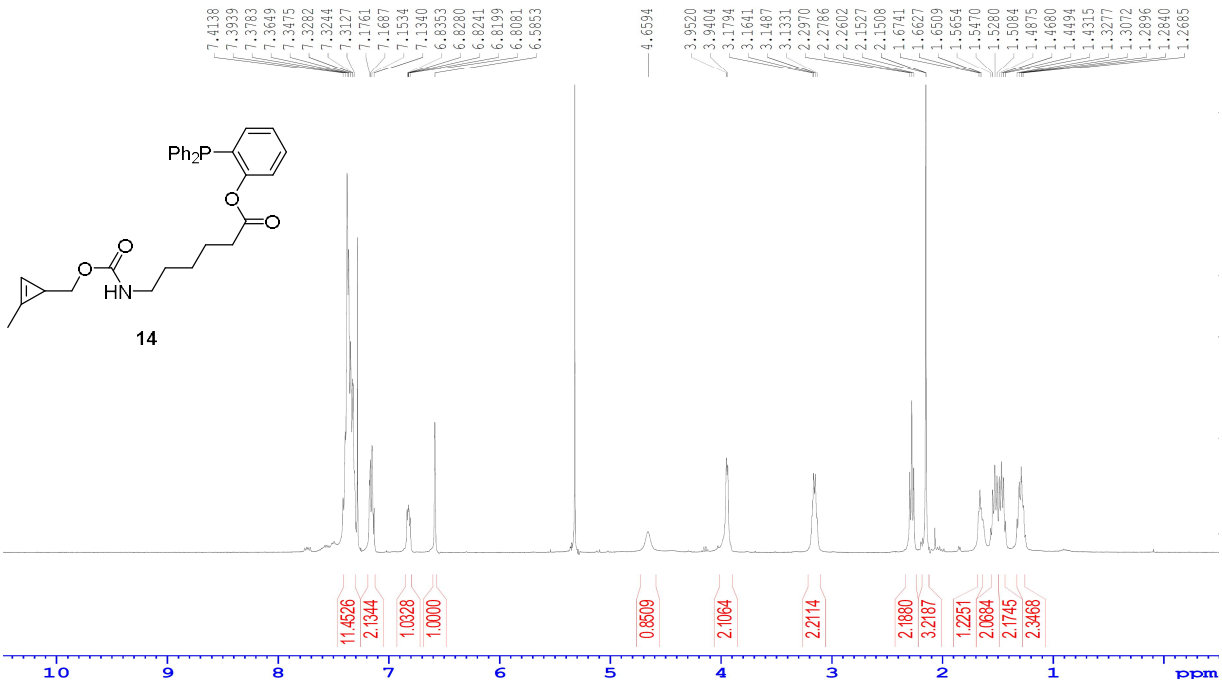
^{13}C NMR of compound 9 (100 MHz, $CDCl_3$)



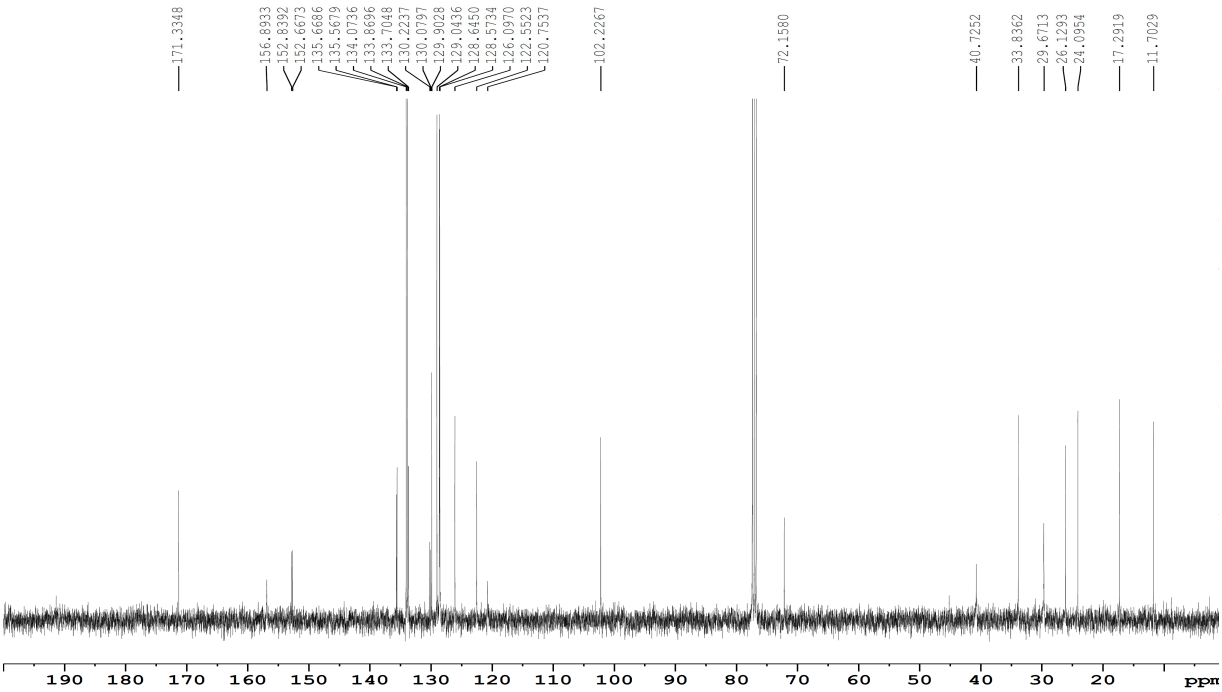
^{1}H NMR of compound 11 (400 MHz, $CDCl_3$)



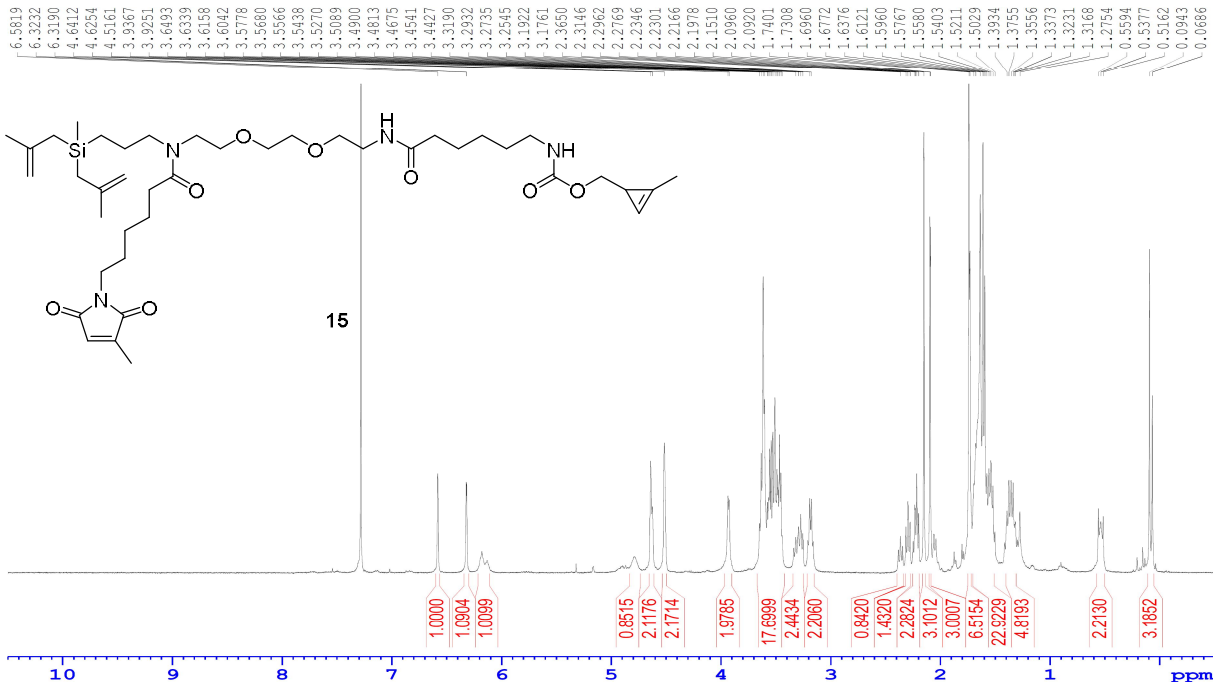
^{1}H NMR of compound 13 (400 MHz, $CDCl_3$)



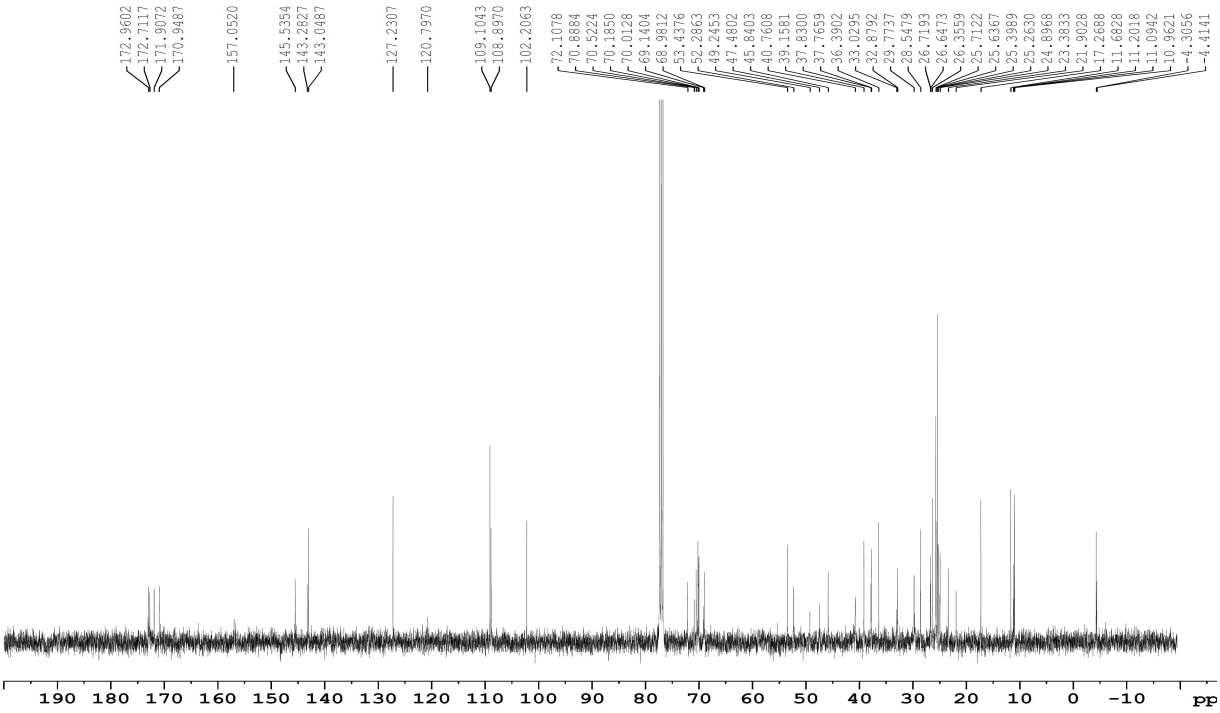
^{1}H NMR of compound 14 (400 MHz, $CDCl_3$)



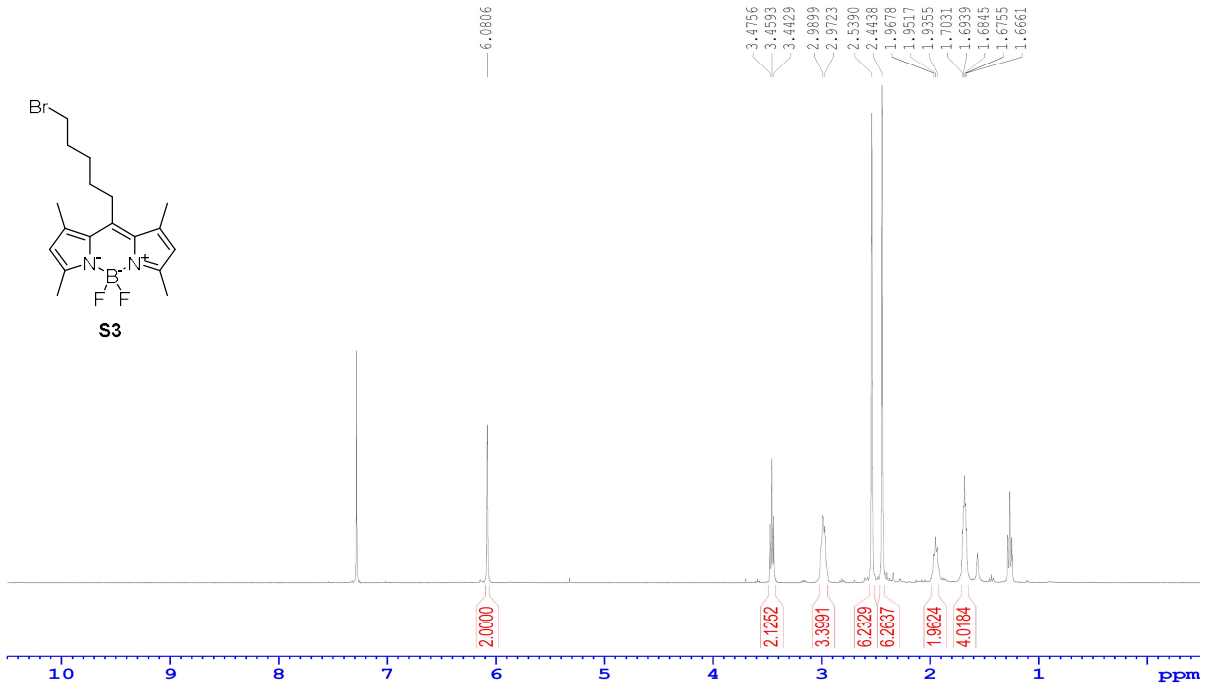
^{13}C NMR of compound 14 (100 MHz, $CDCl_3$)



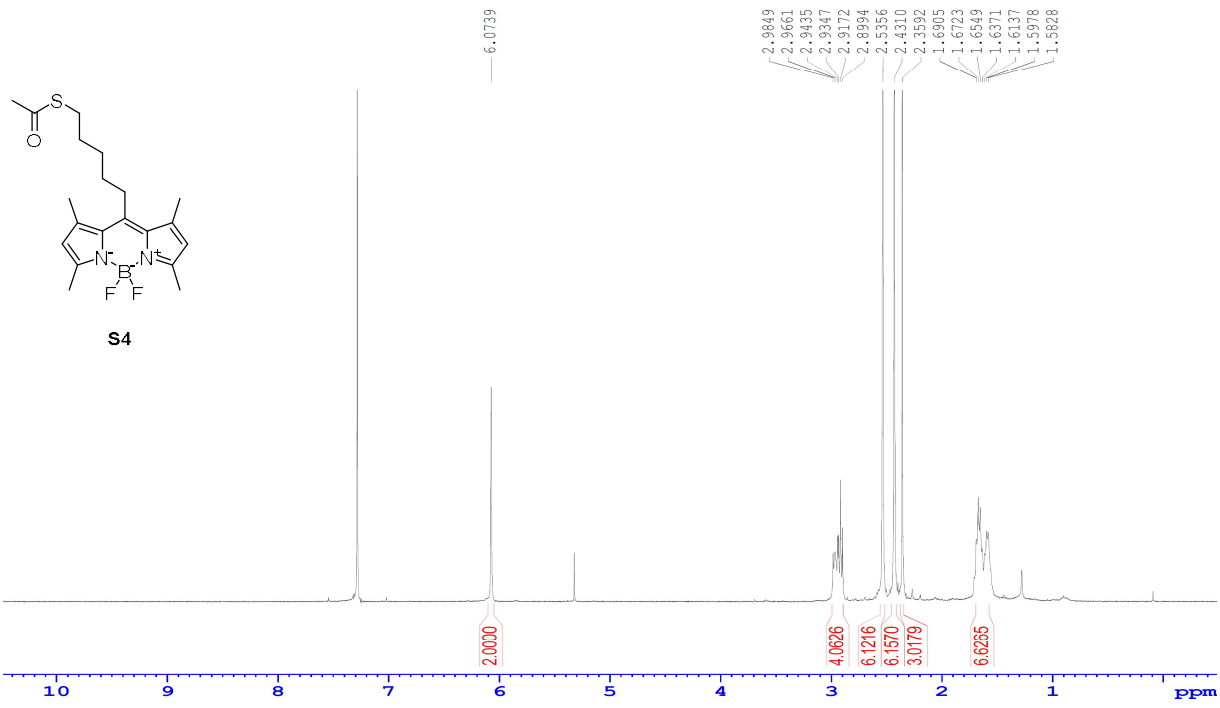
^{1}H NMR of compound 15 (400 MHz, $CDCl_3$)



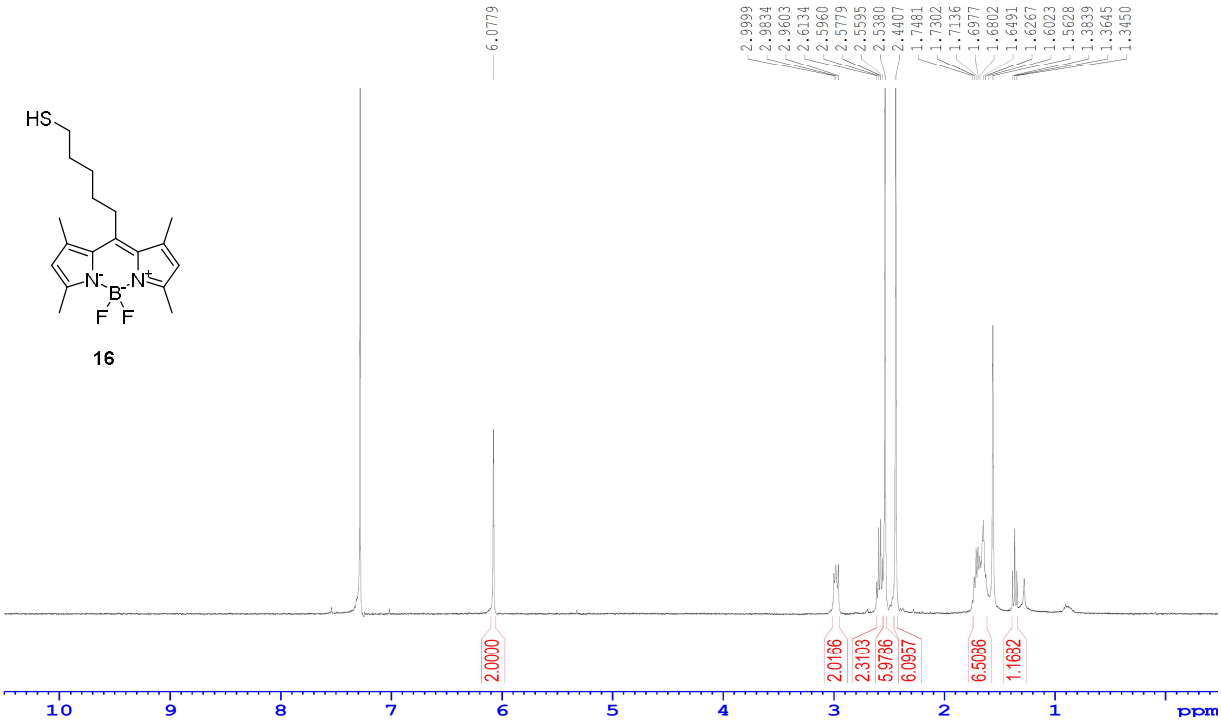
^{13}C NMR of compound 15 (100 MHz, $CDCl_3$)



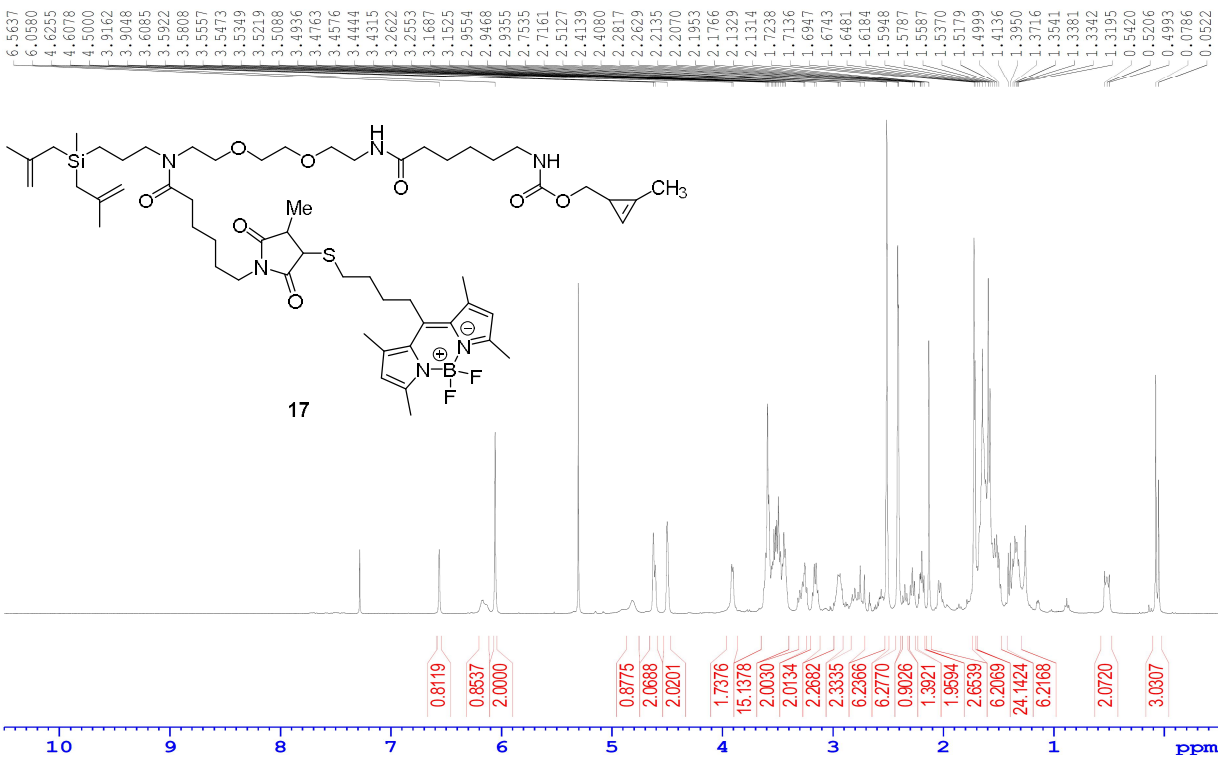
^{1}H NMR of compound S3 (400 MHz, $CDCl_3$)



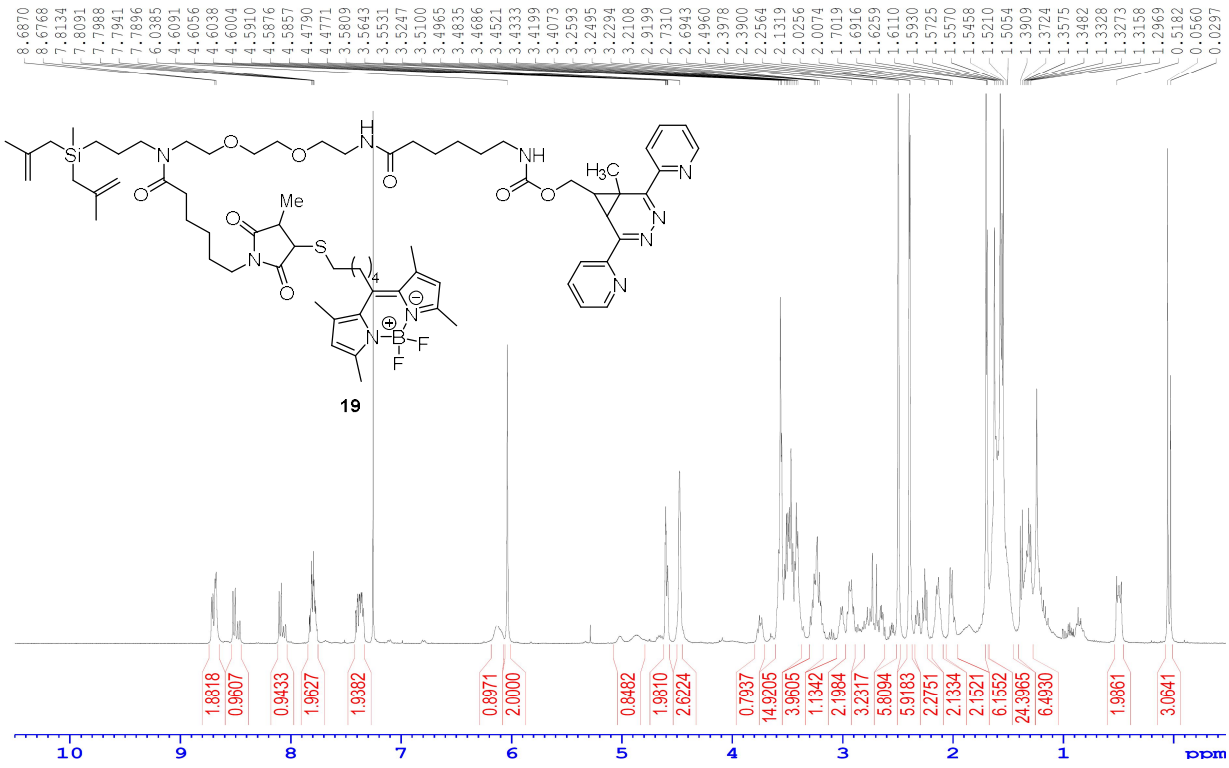
^{1}H NMR of compound S4 (400 MHz, $CDCl_3$)



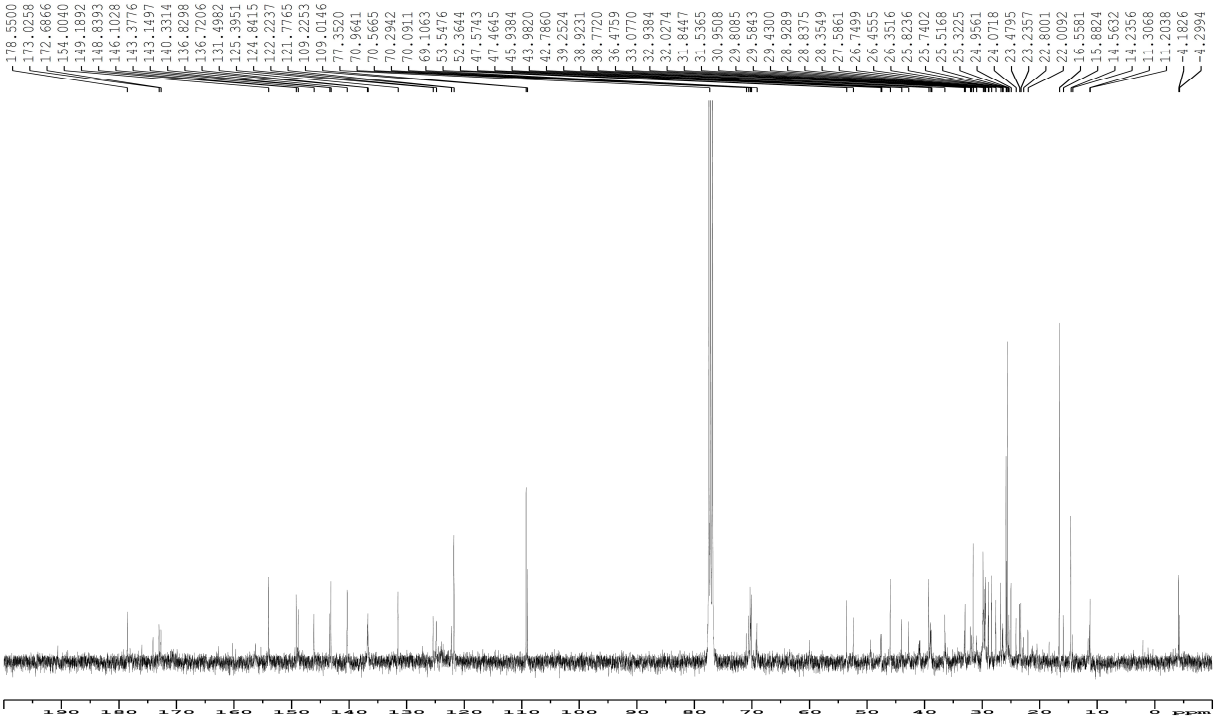
^{1}H NMR of compound 16 (400 MHz, $CDCl_3$)



^{1}H NMR of compound 17 (400 MHz, $CDCl_3$)



^{1}H NMR of compound 19 (400 MHz, $CDCl_3$)



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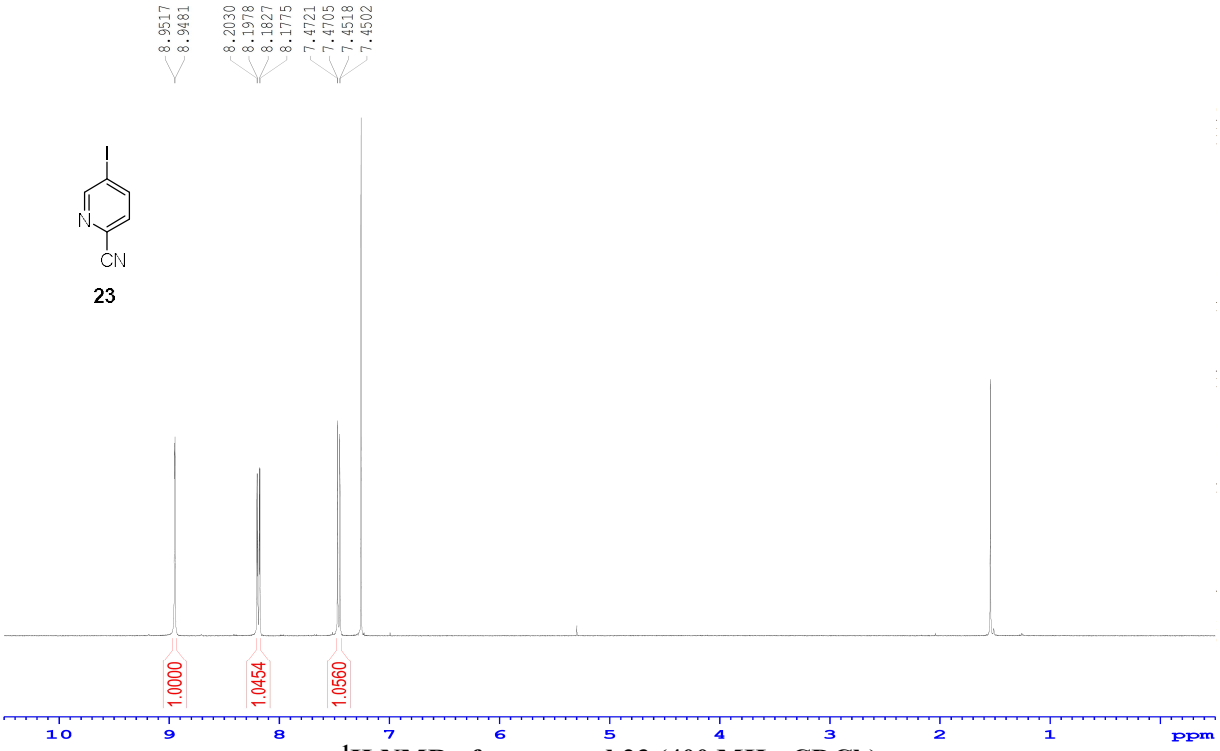
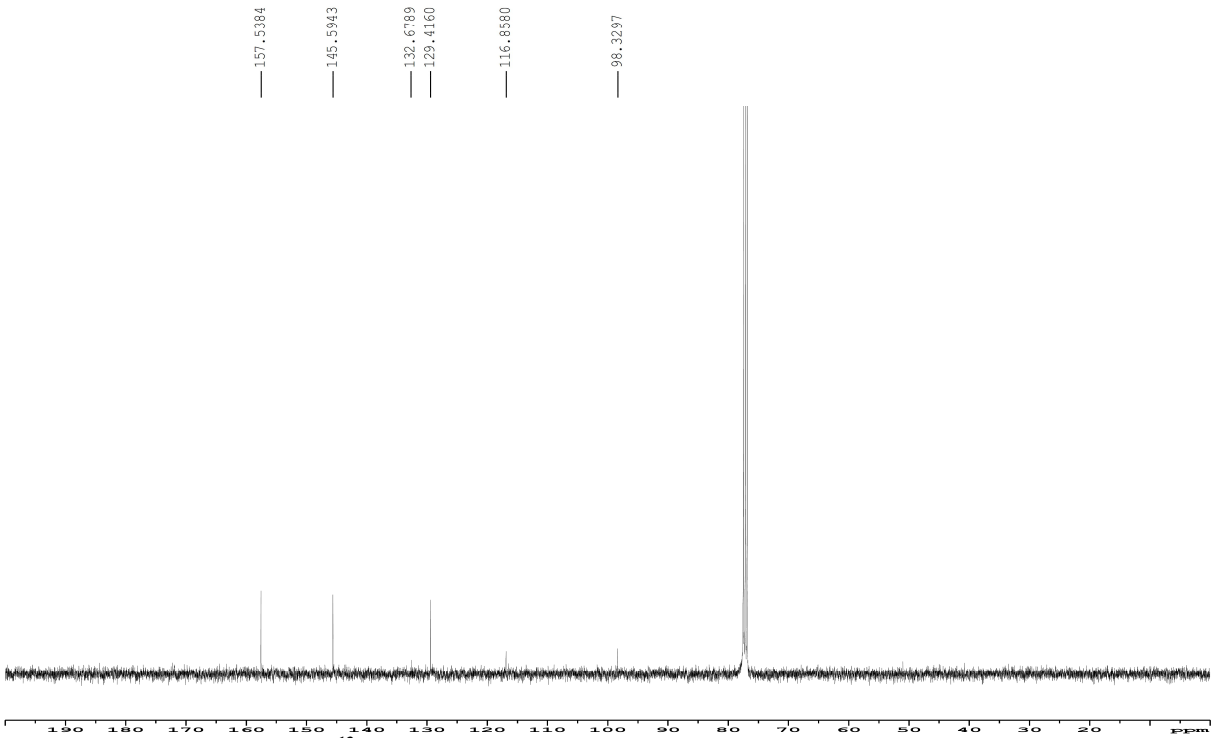
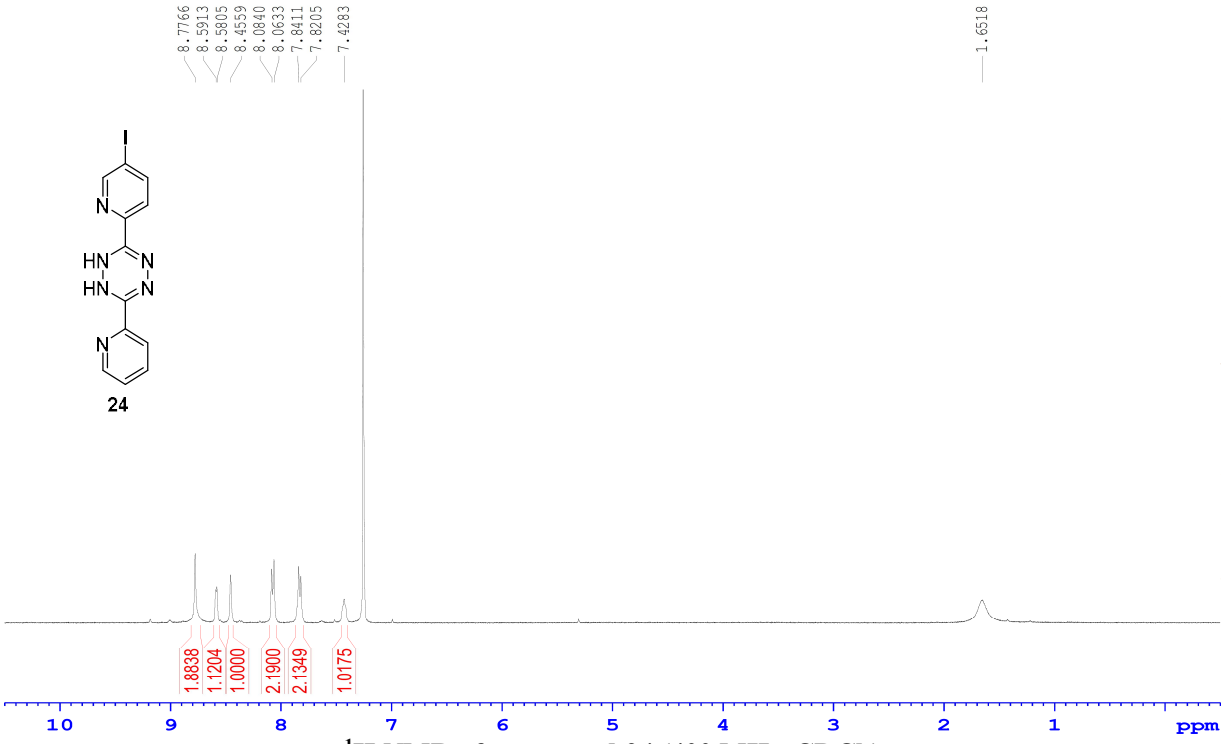


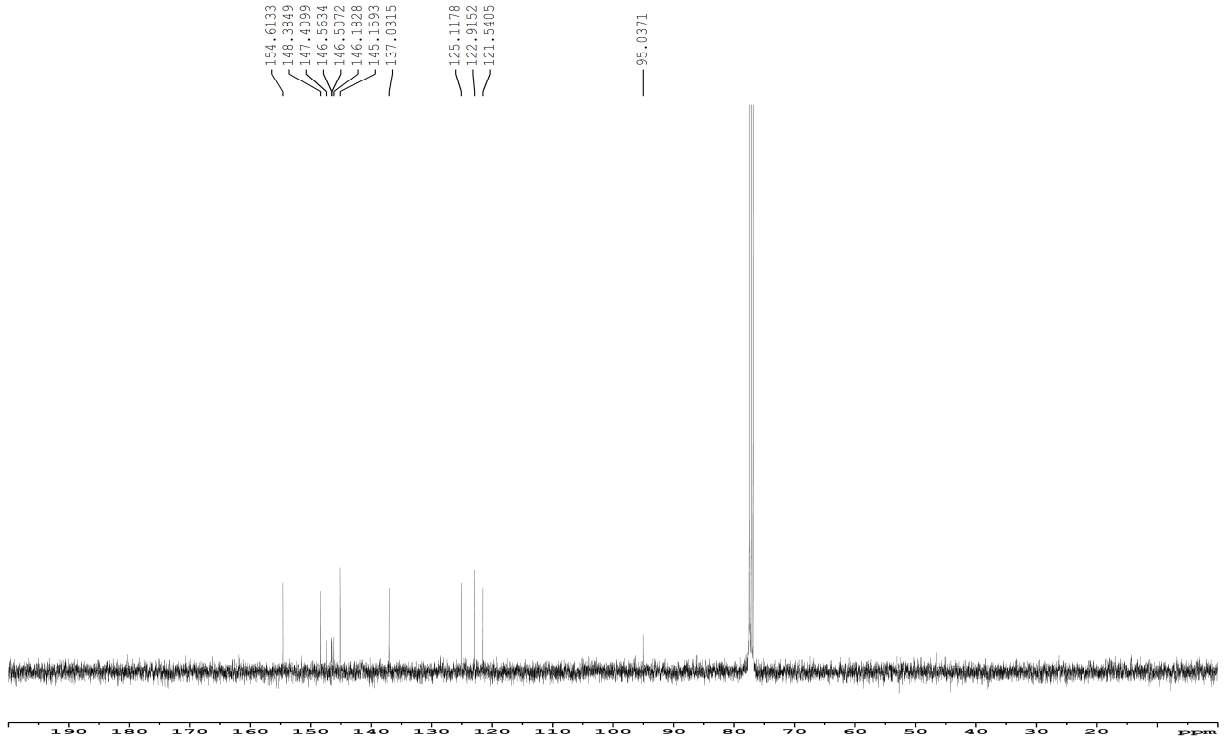
^{1}H NMR of compound 23 (400 MHz, $CDCl_3$)



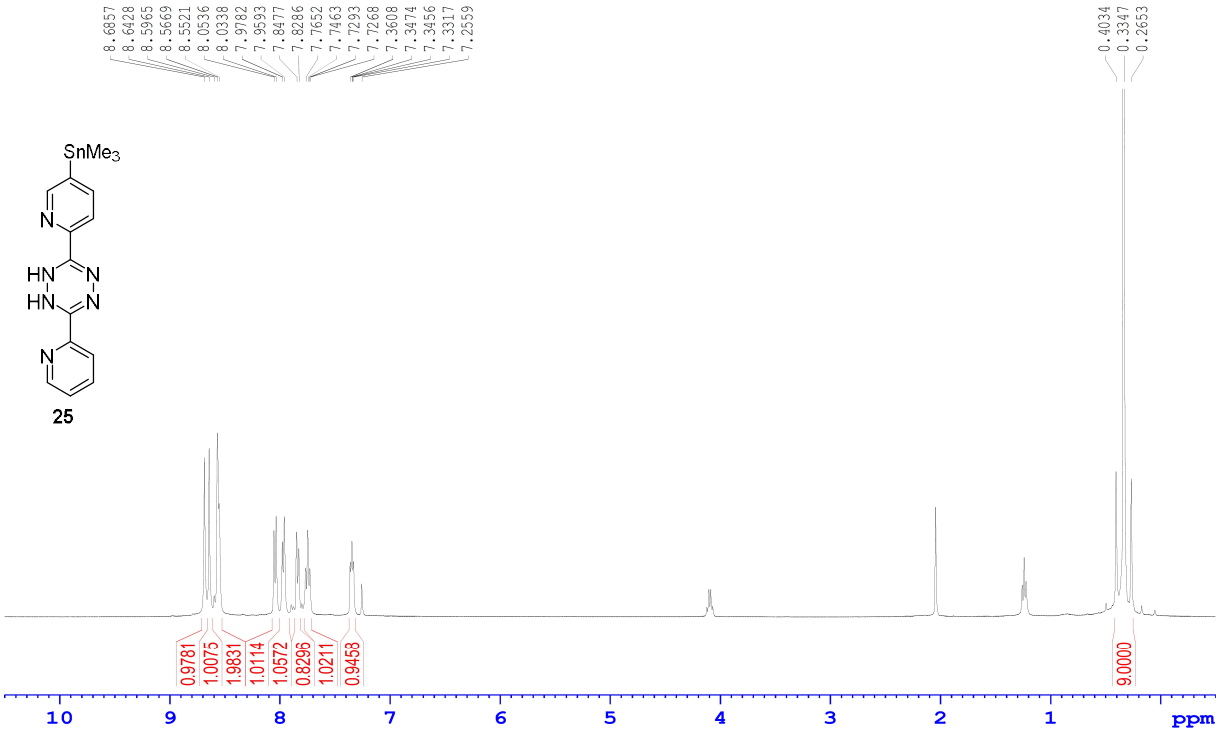
^{13}C NMR of compound 23 (100 MHz, $CDCl_3$)



^{1}H NMR of compound 24 (400 MHz, $CDCl_3$)



^{13}C NMR of compound 24 (100 MHz, $CDCl_3$)



^{1}H NMR of compound 25 (400 MHz, $CDCl_3$)

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