Electronic Supplementary Information

RGD-conjugated Two-photon Absorption Near-IR Emitting Fluorescent Probes for Tumor Vasculature Imaging

Xiling Yue,[1] Alma R. Morales,[2] Grace W. Githaiga,[1] Adam W. Woodward,[1] Simon Tang,[1] Junko Sawada,[3] Masanobu Komatsu,[3] Xuan Liu,[4] Kevin D. Belfield*[5]

[1]Department of Chemistry, University of Central Florida, P.O. Box 162366, Orlando, FL 32816, USA

[2]Institute of Chemical Sciences and Engineering, Swiss Federal Institute of Technology of Lausanne, Lausanne, Switzerland

[3]Sanford-Burnham Medical Research Institute at Lake Nona, Orlando, FL 32827, USA

[4]Department of Electrical and Computer Engineering, New Jersey Institute of Technology, University Heights, Newark, NJ 07102, USA

[5]College of Science and Liberal Arts, New Jersey Institute of Technology, University Heights, Newark, NJ 07102, USA

Synthetic Details of Intermediate compounds:

Synthesis of 7-bromo-9*H*-fluorene-2-carbaldehyde (A). Fluorene aldehyde (3.6 g, 18.53 mmol) was dissolved in propylene carbonate (45 mL) and the reaction mixture was heated at 60 °C under N_2. NBS (4.94 g, 27.81 mmol) was added to the mixture and reaction was kept at 60 °C for 18 h. The reaction mixture was cooled down and poured into distilled water; the precipitated was collected by filtration and washed several times with water. Recrystallization in EtOH provided a white solid (4.28 g, 85% yield). mp = 167-168 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 10.06 (s, 1H), 8.05 (s, 1H), 8.00 -7.87 (m, 2H), 7.79- 7.63 (m, 2H), 7.63 - 7.50 (m, 1H), 3.98 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 191.95, 146.77, 146.50, 143.31, 139.26, 135.37, 130.45, 129.87, 128.60, 125.87, 122.51, 122.28, 120.24, 36.63. HRMS (DART, $[M+NH_4]^+$) calcd for $C_{14}H_9BrO^+$ 290.0175, found. 290.0166.

Synthesis of 2-(7-bromo-9*H*-fluoren-2-yl)-5,5-dimethyl-1,3-dioxane (B). 7-Bromo-9*H*-fluorene-2-carbaldehyde (4 g, 14.70 mmol) and 2, 2-dimethyl,1,3- propandiol (3.06 g, 29.4 mmol) were dissolved in benzene (52 mL), then catalytic amount of *p*-toluenesulfonic acid (0.026 mg) was added into the reaction mixture. The reaction was kept at reflux for 6 h using a Dean Stark trap. After completion the solvent was removed under reduced pressure obtaining a yellow solid. The solid was purified by recrystallization in EtOH affording a white solid (4.76 g, 90% yield). mp = 210-211 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.78 -7.68 (m, 2H), 7.69 -7.59 (m, 2H), 7.50 (dddd, *J* = 8.0, 5.7, 1.6, 0.7 Hz, 2H), 5.46 (s, 1H), 3.88 (s, 2H), 3.80 (dt, *J* = 11.2, 1.4 Hz, 2H), 3.69 (dq, *J* = 11.2, 1.1 Hz, 2H), 1.33 (d, *J* = 0.8 Hz, 3H), 0.82 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 145.62, 143.01, 141.32, 140.37, 137.56, 129.88, 128.30, 125.28, 122.76, 121.32, 120.64, 119.74, 101.94, 77.75, 36.72, 30.28, 23.11, 21.91. HRMS (DART, $[M+H]^+$) calcd for $C_{19}H_{19}BrO_2^+$ 359.0641, found. 359.0639.

Synthesis of 7-(5,5-dimethyl-1,3-dioxan-2-yl)-*N*,*N*-diphenyl-9*H*-fluoren-2-amine (C). To a Schlenk tube equipped with a magnetic stir bar was added diphenylamine (2.6 g, 15.38 mmol), $Pd_2(dba)_3$ (0.45 g, 0.49 mmol), dppf (0.55 g, 0.99 mmol), 2-(7-bromo-9*H*-fluoren-2-yl)-5,5-dimethyl-1,3-dioxane (5.05 g, 14.03 mmol) and toluene (85 mL) under nitrogen. The reaction mixture was degassed for 10 min and sodium *tert*-butoxide (4.3 g, 44.74) was added. The reaction was stirred at 110 °C, while the progress of the reaction was monitored by TLC. Upon the disappearance of 2-(7-bromo-9*H*-fluoren-2-yl)-5,5-dimethyl-1,3-dioxane the reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The product was purified by column chromatography on silica gel eluting with 4:1 hexanes/ ethyl acetate providing yellow solid (4.82 g, 73% yield). mp = 166-167 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.74 - 7.62 (m, 3H), 7.49 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.34 -7.20 (m, 5H), 7.14 (dd, *J* = 7.8, 2.0 Hz, 5H), 7.03 (tt, *J* = 7.3, 1.2 Hz, 2H), 5.48 (s, 1H), 3.87 - 3.77 (m, 4H), 3.71 (dd, *J* = 11.1, 1.5 Hz, 2H), 1.36 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 148.01, 147.06, 145.06, 143.24, 142.21, 136.29, 129.22, 125.10, 124.73, 124.15, 123.31, 122.61, 122.58, 121.04, 120.62, 119.09, 102.25, 77.87, 77.78, 36.89, 30.29, 23.14, 21.93. HRMS (ESI, $[M+H]^+$) calcd for $C_{31}H_{29}NO_2^+$ 448.2271, found. 448.2284.

Synthesis of 7-(5,5-dimethyl-1,3-dioxan-2-yl)-9-(2-(2-ethoxyethoxy)ethyl)-*N*,*N*-diphenyl-9*H*-fluoren-2-amine (D). A solution of 7-(5,5-dimethyl-1,3-dioxan-2-yl)-*N*,*N*-diphenyl-9*H*-fluoren-2-amine (3.62 g, 7.66 mmol) in dry THF (55 mL) was treated under nitrogen at -78 ^{o}C with *n*-BuLi (1.6 M in hexanes, 6 mL) over 10 min period. After addition, the temperature was allowed to rise to room temperature and stirring continued for 1 h. The mixture was then cooled to -78 °C and treated with a solution of 1-bromo-2-(2-ethoxyethoxy)ethane (1.23 mL, 8.05 mmol) in THF (5 mL). The temperature was then allowed to rise to room temperature and the mixture was stirred overnight. The yellow solution was poured into distilled water, and extracted with CH_2Cl_2. Solvent was evaporated *in vacuo* yielded yellow oil. Purification was

carried out by column chromatography using hexanes/ethyl acetate (4:1) to give colorless oil (3.88 g, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.72 -7.57 (m, 3H), 7.49 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.31 - 7.16 (m, 5H), 7.19 -6.98 (m, 7H), 5.45 (s, 1H), 4.03 (t, *J* = 6.4 Hz, 1H), 3.85 - 3.77 (m, 2H), 3.70 (d, *J* = 11.0 Hz, 2H), 3.5-3.3 (m, 8H), 2.28-2.10 (m, 2H) 1.34 (s, 3H), 1.19 (t, J = 6.8 Hz, 3H), 0.83 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 148.76, 147.96, 147.23, 147.08, 141.39, 136.46, 135.47, 129.22, 125.32, 124.18, 123.29, 122.68, 122.21, 120.58, 119.07, 102.24, 77.76, 77.75, 70.19, 69.70, 68.41, 66.62, 44.43, 32.85, 30.27, 23.15, 21.93, 15.16. HRMS (ESI, $[M+H]^+$) calcd for $C_{37}H_{41}NO_4^+$ 564.3108, found. 564.3110.

Synthesis of 3-(2-(5,5-dimethyl-1,3-dioxan-2-yl)-7-(diphenylamino)-9-(2-(2-ethoxyethoxy)ethyl)-9*H*-fluoren-9-yl)propanenitrile (E). 7-(5,5-Dimethyl-1,3-dioxan-2-yl)-9-(2-(2-ethoxyethoxy)ethyl)-*N*,*N*-diphenyl-9*H*-fluoren-2-amine (3.79 g, 6.72 mmol) was dissolved in dioxane (20 mL) at room temperature. The solution was degassed under vacuum and nitrogen, and then reaction mixture was treated with 40% aqueous solution of Triton B (0.12 mL). After addition the mixture turned from yellow light to brown reddish color. The resulting solution was then treated with acrylonitrile (0.70 g, 13.26 mmol) over a 5 min period. The reaction temperature was maintained between 30 to 40 ^{o}C by occasional cooling with ice-water throughout the addition period. The red solution thus obtained was then stirred at room temperature for 16 h. The reaction mixture was poured into distilled water. Extraction with CH_2Cl_2 afforded orange oil. The crude product was purified by column chromatography using hexanes/ethyl acetate (3:2) as eluent to afford 3.75 g of colorless oil, which solidified (90% yield). mp = 54-55 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.61 (d, *J* = 7.8 Hz, 1H), 7.58 -7.49 (m, 2H), 7.46 (d, *J* = 1.4 Hz, 1H), 7.34 -7.25 (m, 3H), 7.19 -6.99 (m, 9H), 5.44 (s, 1H), 3.89-3.76 (m, 2H), 3.76 (d, *J*= 11.2 Hz, 2H), 3.45 (q, *J*= 6.8, 7.2 Hz, 2H), 3.40 -3.32 (m, 2H), 3.28 - 3.24 (m, 2H), 2.89 (ddd, *J* = 7.9, 6.3, 1.2 Hz, 2H), 2.49 -2.16 (m, 4H), 1.63-1.50 (m, 2H), 1.35 (s, 3H), 1.17 (t, *J* = 7.0 Hz, 3H), 0.84 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 148.62, 148.26, 147.67, 146.70, 141.28, 137.43, 134.71, 129.54, 129.37, 126.36, 125.06, 124.44, 123.54, 123.17, 121.07, 120.65, 119.57, 119.38, 118.13, 101.86, 77.75, 70.12, 69.64, 67.22, 66.59, 52.34, 38.81, 35.60, 30.28, 23.20, 21.93, 15.12, 11.92. HRMS (ESI, $[M+H]^+$) calcd for $C_{40}H_{44}N_2O_4^+$ 617.3374, found. 617.3381.

Synthesis of 3-(2-(5,5-dimethyl-1,3-dioxan-2-yl)-7-(diphenylamino)-9-(2-(2-ethoxyethoxy)ethyl)-9*H*-fluoren-9-yl)propanoic acid (F). A mixture of 3-(2-(5,5-dimethyl-1,3-dioxan-2-yl)-7-(diphenylamino)-9-(2-(2-ethoxyethoxy)ethyl)-9*H*-fluoren-9-yl)propanenitrile (3.35 g, 5.43 mmol), ethylene glycol (140 mL), and aqueous solution of NaOH (3M, 17 mL), was heated to reflux for 12 h. Ethylene glycol was removed under vacuum distillation obtaining a yellow oil. The oil was added into water and extracted with CH_2Cl_2. The crude product was purified via column chromatography using hexanes/ethyl acetate (1:1) as eluent to afford yellow oil, which solidified (3.03 g, 88% yield). mp = 59-60 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.58 (dd, *J* = 7.8, 0.6 Hz, 1H), 7.55 - 7.41 (m, 3H), 7.30 - 7.18 (m, 4H), 7.15 - 7.06 (m, 5H), 7.06 - 6.96 (m, 3H), 5.41 (s, 1H), 3.88 - 3.72 (m, 2H), 3.67 (d, *J* = 10.8 Hz, 2H), 3.38 (m, 2H), 3.31 - 3.15 (m, 2H), 2.95 (t, *J* = 7.3 Hz, 2H), 2.82 (dd, *J* = 8.4, 7.2 Hz, 2H), 2.40 - 2.08 (m, 4H), 1.69 -1.45 (m, 2H), 1.33 (d, *J* = 0.8 Hz, 3H), 1.24 - 1.10 (m, 3H), 0.82 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 178.19, 150.35, 148.34, 147.81, 147.70, 141.29, 136.88, 135.17, 129.22, 125.58, 124.14, 123.39, 122.75, 121.06, 120.73, 119.11, 118.72, 102.18, 77.70, 69.99, 69.62, 67.44, 66.55, 52.30, 38.93, 35.31, 30.25, 29.37, 23.18, 21.92, 15.09. HRMS (ESI, $[M+H]^+$) calcd for $C_{40}H_{45}NO_6^+$ 636.3320, found. 636.3325.

Synthesis of 3-(2-(diphenylamino)-9-(2-(2-ethoxyethoxy)ethyl)-7-formyl-9*H*-fluoren-9-yl)propanoic acid (G). 3-(2-(5,5-Dimethyl-1,3-dioxan-2-yl)-7-(diphenylamino)-9-(2-(2-ethoxyethoxy)ethyl)-9*H*-fluoren-9-yl)propanoic acid (2.78 g, 4.37 mmol) was dissolved in CH_2Cl_2:H_2O (150 mL, 1:1) at room temperature. To the mixture TFA (10 mL) was added drop wise at room temperature. The reaction mixture was then stirred for 6 h at room temperature under nitrogen. After completion the reaction mixture was poured

into distilled water and organic phase was separated and washed several times with water (until pH was near to neutral), dried over $NaSO_4$ and concentrated. Purification was carried out by silica gel chromatography using hexanes/ethyl acetate (3:2) affording yellow oil (2.10 g, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.01 (s, 1H), 7.90 - 7.83 (m, 2H), 7.72 (d, J = 8.2 Hz, 1H), 7.60 (d, J = 8.3 Hz, 1H), 7.38 - 7.24 (m, 3H), 7.20 - 7.00 (m, 9H), 3.42 (q, J = 7.0 Hz, 2H), 3.35 (t, J = 4.8 Hz, 2H), 3.28 - 3.19 (m, 2H), 2.95- 2.81 (m, 2H), 2.50 - 2.18 (m, 4H), 1.80 -1.43 (m, 2H), 0.96 - 0.79 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 191.88, 178.10, 151.33, 149.35, 148.94, 147.36, 147.13, 134.58, 133.14, 130.78, 129.42, 124.81, 123.67, 123.55, 122.62, 121.94, 119.34, 117.33, 70.05, 69.62, 67.29, 66.57, 52.37, 38.86, 34.64, 28.89, 15.07. HRMS (ESI, $[M+H]^+$) calcd for $C_{35}H_{35}NO_5^+$ 550.2588, found. 550.2599.

Synthesis of 7-(5,5-dimethyl-1,3-dioxan-2-yl)-9,9-di(3,6,9,12,15,18,21,24,27,30-decaoxadotriacontyl)-*N*,*N*-diphenyl-9*H*-fluoren-2-amine (I). To a solution of 7-(5,5-dimethyl-1,3-dioxan-2-yl)-*N*,*N*-diphenyl-9*H*-fluoren-2-amine (1 g, 2.23 mmol) in DMF (25 mL), NaH (0.16g, 6.69 mmol) was added to the mixture under N_2. The mixture was stirred at room temperature for 30 min. Successively, a PEG tosylate derivative (3.39 g, 4.90 mmol) was added and the reaction was stirred for 48 h. After quenching the reaction with water, the solution was extracted with CH_2Cl_2. The combined organic fractions were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2/MeOH 9/1) to give colorless oil (2.65 g, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.54 - 7.48 (m, 1H), 7.29 - 7.25 (m, 2H), 7.21 -7.16 (m, 1H), 7.05 - 6.92 (m, 4H), 6.91 - 6.79 (m, 5H), 6.79 - 6.67 (m, 3H), 5.15 (s, 1H), 3.53 – 3.30 (m, 85H), 2.04 - 1.90 (m, 4H), 1.04 (s, 3H), 0.99 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 150.45, 148.54, 147.52, 147.27, 140.44, 136.84, 134.60, 129.02, 125.32, 124.11, 123.77, 122.58, 120.71, 120.48, 118.73, 101.72, 77.81, 70.36, 70.28, 70.25, 70.19, 70.04, 66.58, 58.65, 42.54, 29.97, 23.19, 21.70. HRMS-MALDI-DTL: High resolution MS shows a series of ions centered around m/z 1356 $[C_{35}H_{37}NO_2(C_2H_4O)_{20}]^+$ which are fragments related to the various ethoxylate oligomers that differ by Δm/z 44, an ethoxy unit.

Synthesis of 7-(diphenylamino)-9,9-di(3,6,9,12,15,18,21,24,27,30 decaoxadotriacontyl)-9*H*-fluorene-2-carbaldehyde (J). 7-(5,5-Dimethyl-1,3-dioxan-2-yl)-9,9-di(3,6,9,12,15,18,21,24,27,30-decaoxadotriacontyl)-*N*,*N*-diphenyl-9*H*-fluoren-2-amine) (1.5 g, 1.083 mmol) was dissolved in CH_2Cl_2:H_2O (35 mL, 1:1) at room temperature. To the mixture TFA (1.6 mL) was added dropwise at room temperature. The reaction mixture was then stirred for 6 h at room temperature under nitrogen. After completion the reaction mixture was neutralized with $NaHCO_3$ solution and organic phase was separated, dried over $NaSO_4$ and concentrated. Purification was carried out by silica gel chromatography using CH_2Cl_2/MeOH (9:1) affording yellow oil (1.15 g, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.98 (s, 1H), 7.96 (m, 1H), 7.79 - 7.73 (m, 2H), 7.62 (d, J = 8.3 Hz, 1H), 7.31 (d, J = 8.1 Hz, 2H), 7.29 - 7.21 (m, 3H), 7.21 - 7.16 (m, 1H), 7.15 - 6.94 (m, 6H), 3.79 - 3.44 (m, 80H), 2.62 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 191.83, 151.85, 149.63, 149.12, 147.37, 134.51, 132.86, 129.77, 129.37, 127.91, 124.99, 124.69, 123.56, 122.57, 121.79, 119.22, 117.63, 70.58, 70.54, 70.50, 70.48, 70.45, 70.43, 70.20, 66.82, 58.96, 39.15. HRMS-MALDI-DTL: High resolution MS shows a series of ions centered around m/z 1269 $[C_{30}H_{27}NO_2(C_2H_4O)_{20}]^+$ which are fragments related to the various ethoxylate oligomers that differ by Δm/z 44, an ethoxy unit.

Synthesis of 7-bromo-9,9-dihexyl-9H-fluorene-2-carbaldehyde (L). *n*-BuLi (12.5mL, 1.6M in hexane) was added dropwise to a dry THF solution (50 mL) of 2, 7-dibromo-9,9-dihexyl-9H-fluorene (10 g, 20.32 mmol) under nitrogen and at -78 ^{o}C. 2.4 mL of DMF was then added to the solution after stirring for 1 h. The solution was then stirred for 2 h. And the solution then brought to room temperature and quenched with distilled H_2O until the pH was neutral. The solution was then extracted with toluene three times, dried with anhydrous magnesium sulfate and the solvent removed under reduced pressure to give a

yellow green solution. The crude product was purified by column chromatography using silica gel (hexanes:ethyl acetate 7:3) to yield colorless oil (6.16 g, 69%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.04 (s, 1H), 8.03 – 7.74 (m, 3H), 7.77 – 7.53 (m, 1H), 7.60 – 7.33 (m, 2H), 1.97 (qdd, *J* = 13.5, 10.9, 5.5 Hz, 4H), 1.36 – 0.87 (m, 12H), 0.74 (t, *J* = 7.1 Hz, 6H), 0.55 (ddt, *J* = 17.9, 13.8, 6.5 Hz, 4H).^{13}C NMR (101 MHz, $CDCl_3$) δ 192.58, 154.64, 151.53, 146.72, 138.93, 135.99, 130.94, 130.81, 126.84, 123.49, 123.47, 122.62, 120.47, 55.99, 40.48, 31.81, 29.90, 24.08, 22.90, 14.33.

Synthesis of 7-(diphenylamino)-9,9-dihexyl-9H-fluorene-2-carbaldehyde (M). A mixture of 7-bromo-9,9-dihexyl-9H-fluorene-2-carbaldehyde(5g, 11.6mmol), diphenylamine (2.88 g, 17.03 mmol), $Pd(OAC)_2$ (0.061g, 0.27mmol), P(*t*-Bu)$_3$ (0.121 g ,0.60 mmol) and Cs_2CO_3 (5.53 g 16.98 mmol) in 40 mL dry toluene was degassed for 15 min. The mixture was then stirred and heated at 120 ^{0}C for 48 h in a vial with a screw cap. The reaction mixture was then cooled to room temperature and filtered to form yellow-brownish oil, which was purified using column chromatography (hexanes:CH_2Cl_2 1:1) to yield a yellow oil (4.86g, 81%). δ H (400 MHz, Chloroform-d) 0.40 – 0.77 (4 H, dd, J 18.5, 6.1), 0.72 – 0.89 (6 H, t, J 7.1), 0.89 – 1.40 (12 H, m), 1.72 – 2.06 (4 H, dd, dd, J 39.6, 13.3, 11.4, 5.0), 6.88 – 7.10 (3 H, m), 7.10 – 7.22 (5 H, m), 7.22 – 7.48 (4 H, m), 7.46 – 7.67 (1 H, d, J 8.2), 7.67 – 7.79 (1 H, d, J 8.1), 7.79 – 7.99 (2 H, m), 9.89 – 10.23 (1 H, s).^{13}C NMR (101 MHz, $CDCl_3$) δ 192.65, 154.07, 151.68, 149.25, 148.03, 147.90, 134.88, 134.43, 131.18, 129.67, 124.76, 123.49, 123.25, 123.18, 122.07, 119.50, 118.62, 55.54, 40.42, 37.48, 33.13, 32.31, 31.87, 31.62, 30.42, 30.09, 30.05, 29.92, 29.75, 27.47, 24.14, 23.08, 23.05, 22.91, 20.12, 14.50, 14.39

Synthesis of methyl 6-bromohexanoate (O). 6-Bromohexanoic acid (0.3 g, 1.53 mmol) was dissolved in methanol and a catalytic amount of H_2SO_4 (0.03 mL) was added and the reaction was refluxed overnight. Upon complexion of the reaction, methanol was removed and the crude product washed with aqueous $NaHCO_3$, brine and extracted with diethyl ether to yield yellow oil (0.29 g, 91%), and the product was used without further purification. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.70 – 3.46 (m, 3H), 3.43 – 3.13 (m, 2H), 2.35 – 2.09 (m, 2H), 1.92 – 1.67 (m, 2H), 1.57 (ddt, *J* = 10.0, 7.4, 4.1 Hz, 2H), 1.39 (tdd, *J* = 8.4, 6.6, 2.5 Hz, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 174.14, 51.82, 34.10, 33.84, 33.76, 32.70, 27.95, 24.37, 24.21.

Synthesis of methyl 6-(4-formyl-2,6-dimethoxyphenoxy)hexanoate (P). A two neck pear shape flask was charged with 3, 5-dimethoxy-4-hydroxybenzaldehyde (1.0 g, 5.47 mmol), bromoalkanoic acid (1.25 g, 5.97 mmol), and DMF (17 mL). The flask was flushed with nitrogen and the reaction mixture heated at 85 ^{o}C for 30 min. Anhydrous K_2CO_3 (1.33 g, 9.62 mmol) was added in portions and the reaction further heated at 85 ^{o}C overnight. The mixture was let to cool to room temperature and then poured into 100 mL of distilled water and the product extracted with CH_2Cl_2 to form yellow oil .The crude product was purified by silica column chromatography using hexanes/ethyl acetate (1:1) to give (1.3 g, 80%) of the product. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.97 – 9.55 (m, 1H), 7.23 – 6.84 (m, 2H), 4.11 – 3.87 (m, 2H), 3.91 – 3.69 (m, 7H), 3.69 – 3.43 (m, 4H), 2.95 – 2.65 (m, 2H), 2.23 (t, *J* = 7.4 Hz, 2H), 1.82 – 1.09 (m, 7H) 13C NMR (101 MHz, CDCl3) δ 13.90, 13.93, 17.85, 17.89, 20.23, 24.89, 24.94, 24.99, 25.64, 25.68, 27.15, 27.19, 27.57, 27.83, 27.96, 27.99, 30.01, 30.05, 30.42, 31.30, 34.30, 50.40, 51.64, 53.83, 55.64, 56.43, 56.51, 73.43, 73.52, 106.05, 106.99, 107.03, 124.93, 130.39, 131.90, 143.23, 143.84, 153.94, 153.99, 154.13, 154.17, 174.35, 176.40, 191.39.

Synthesis of 6-(4-formyl-2,6-dimethoxyphenoxy)hexanoic acid (Q). A mixture of the ester derivative, (0.15 g, 0.48 mmol) and (*n*-$Bu_3Sn)_2O$ (0.57 g, 0.96 mmol) in benzene was heated at reflux and after 24 h. HCl (0.5 M, 2 mL) was added. The organic phase was washed with 5% $NaHCO_3$, extracted with ethyl acetate and dried over Na_2SO_4. The crude product was purified on silica gel using hexanes/ethyl acetate

(7:3) to yield the product (0.14g, 70%). δ H (400 MHz, Chloroform-d) 1.29 – 1.86 (10 H, m), 2.01 – 2.46 (2 H, tt, *J* 7.8, 3.9), 3.66 – 3.89 (6 H, m), 3.89 – 4.16 (2 H, td, *J* 6.6, 3.8), 6.91 – 7.13 (2 H, m), 9.61 – 9.91 (1 H, m).^{13}C NMR (101 MHz, $CDCl_3$) δ 191.48, 179.74, 174.48, 154.21, 143.33, 131.94, 131.91, 107.10,73.66, 73.56, 56.54, 51.79, 34.84, 34.35, 30.13, 30.08, 28.26, 28.16, 28.05, 27.65, 27.33, 27.00, 26.59, 25.78, 25.72, 25.54, 24.98, 18.55, 18.48, 16.77, 15.06, 14.98, 13.96, 13.86.

Cytotoxicity Assay

U87MG cells (for **1a** and **2a**) or HCT116 cells (for **3a** and **3b**) were seeded in 96-well plates (Corning, USA) at a concentration of 5 × 10^3 cells/well and incubated for 48 h. Stock solutions of **1a**, **2a**, **3a** and **3b** were diluted into 1.56 µM, 3.12 µM, 6.25 µM, 12.5 µM, 25 µM, and 50 µM from stock solutions. Cells were then incubated with diluted probes for an additional 24 h. Viability was then determined with the CellTiter 96® AQueous One Solution Reagent (Promega, USA).

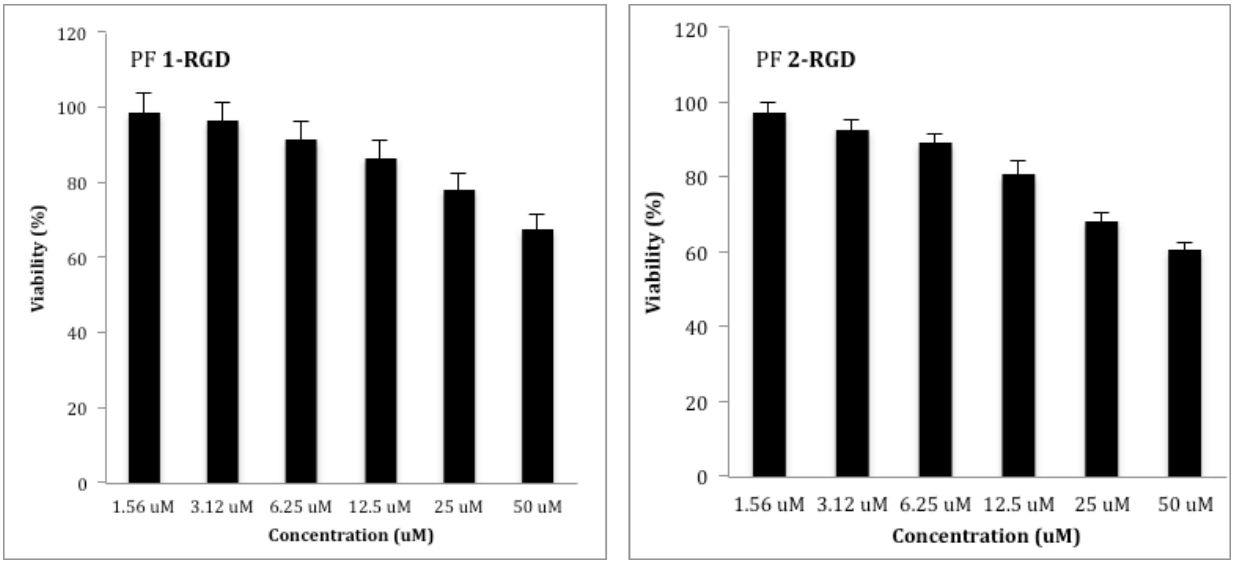

Figure S1. Viability of U87MG cells after 24 h incubation with RGD-conjugated probes.

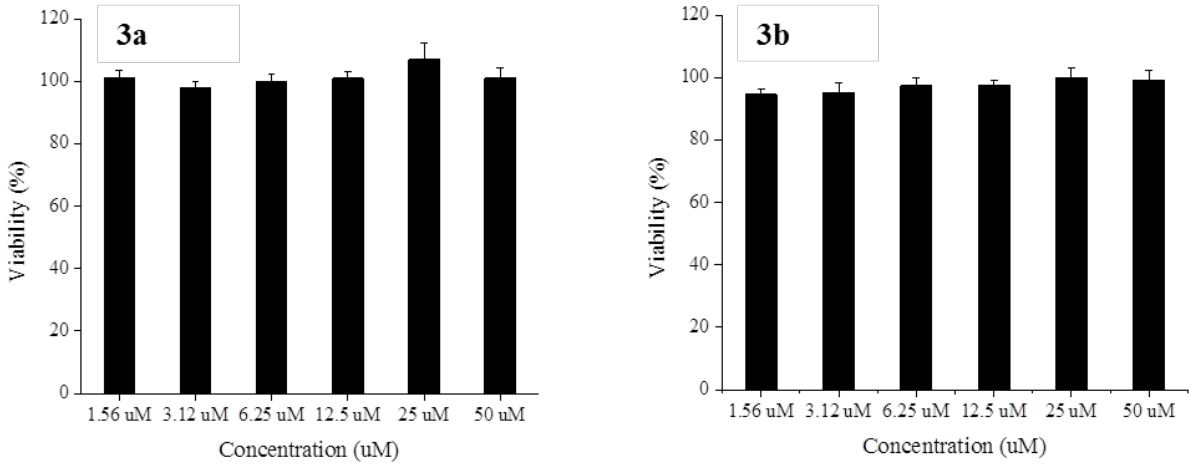

Figure S2. Viability of HCT116 cells after 24 h incubation with organic nanoparticles.

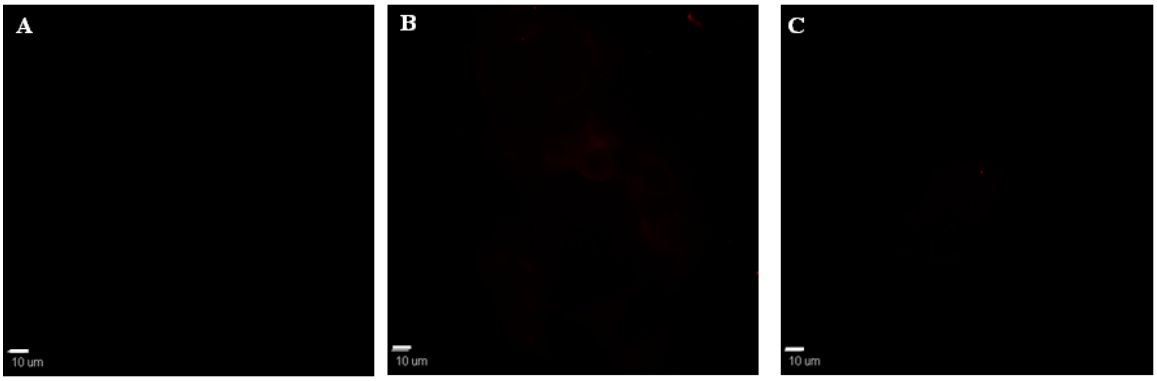

Figure S3. Negative control fluorescent images for RGD-conjugated structure **1a** (B) and **2a** (D) in MCF-7 cells. (A) Untreated U87MG cells; (B) MCF-7 cells incubated with **1a** for 1 h; (C) MCF-7 cells incubated with **2a** for 1h.

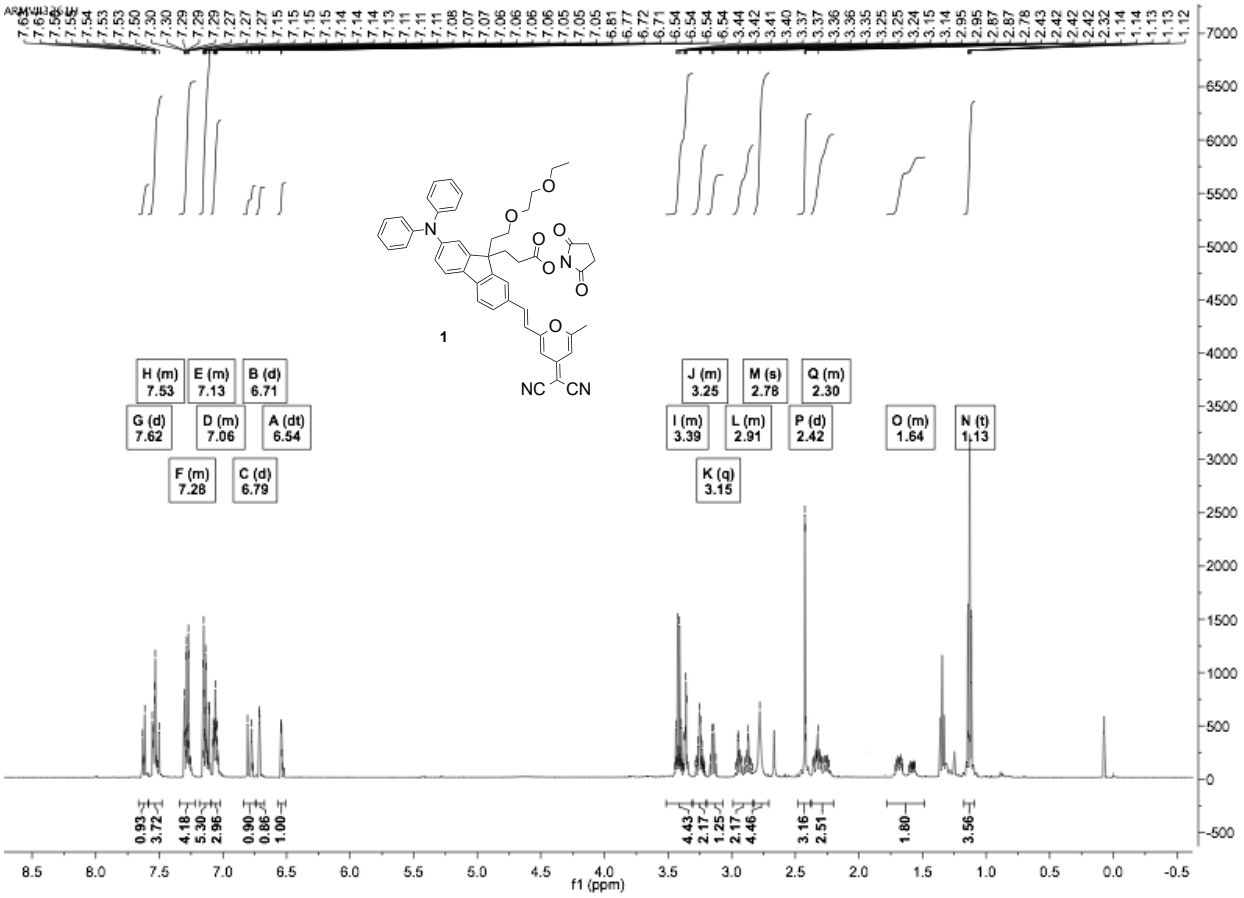

Figure S4. ^{1}H NMR of compound **1** in $CDCl_3$.

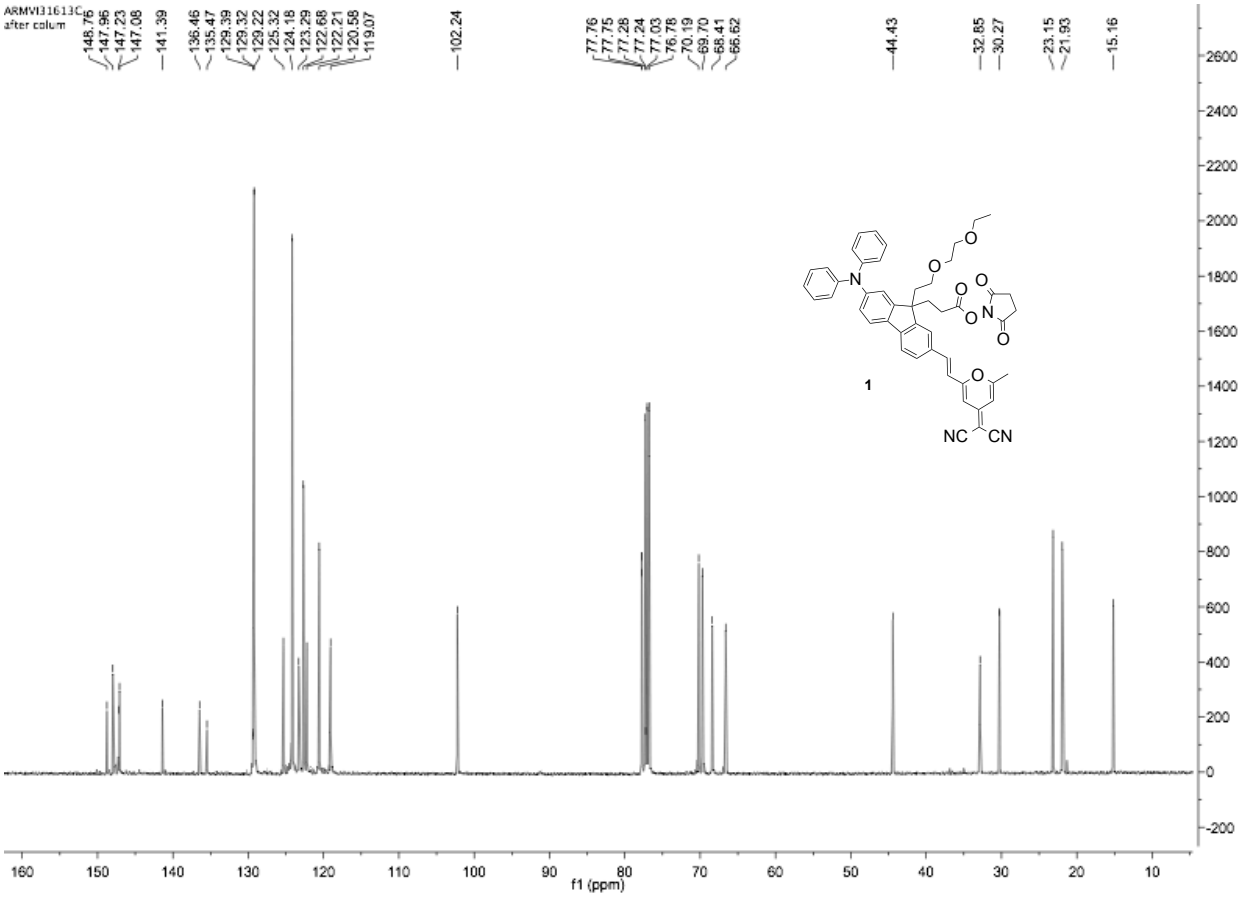

Figure S5. ^{13}C NMR of compound **1** in $CDCl_3$.

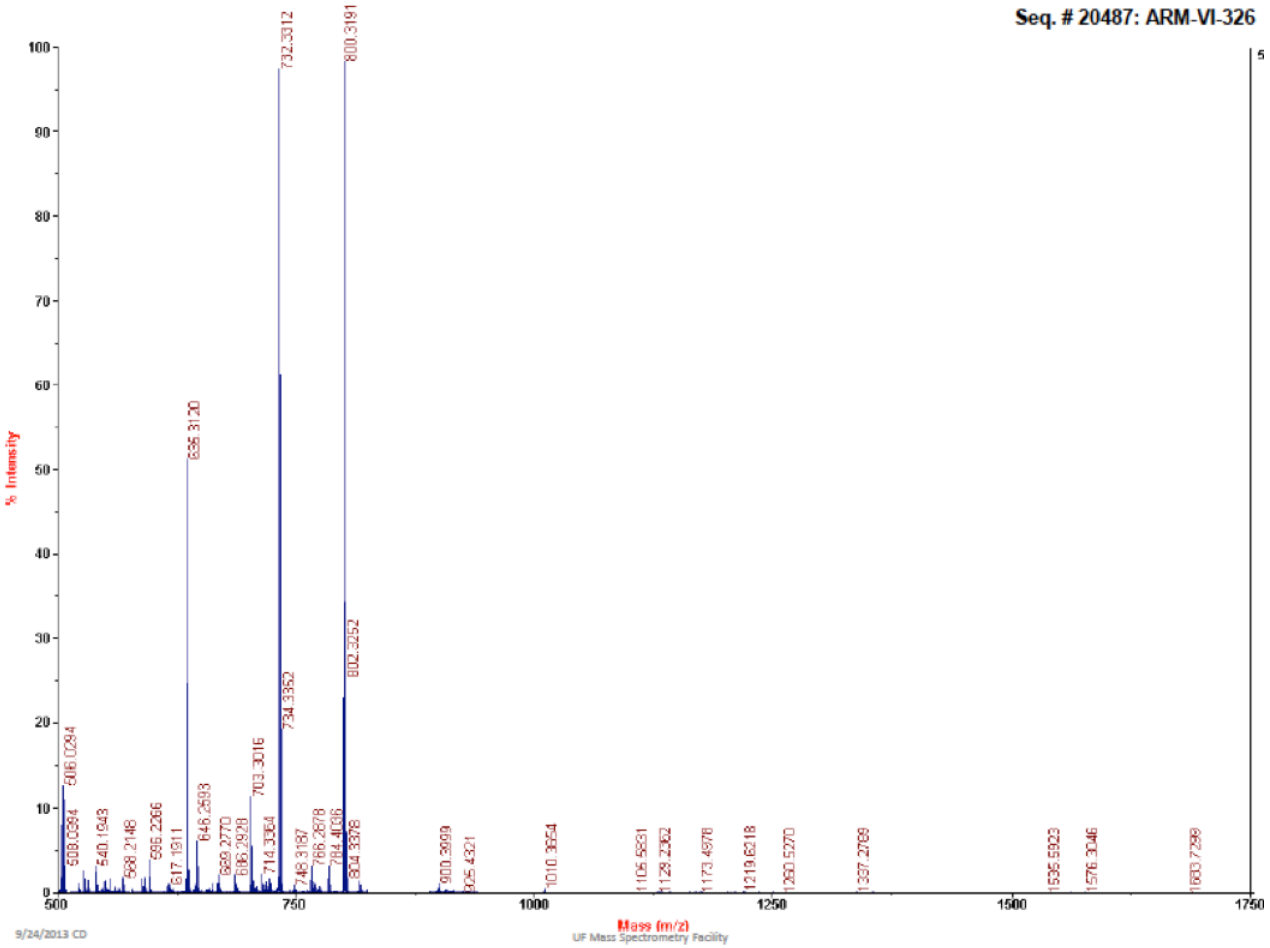

Figure S6. HRMS of Compound **1**

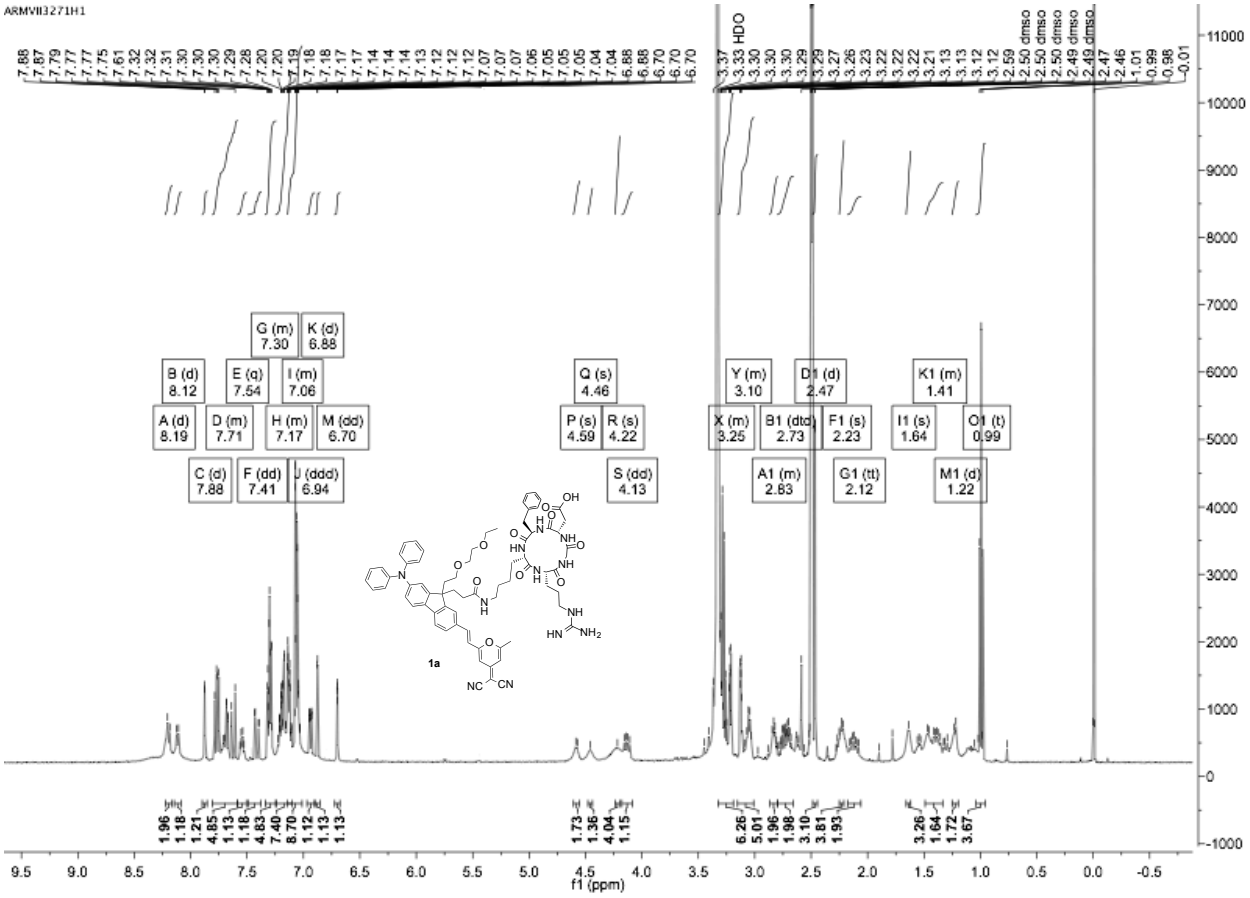

Figure S7. ^{1}H NMR of compound **1a** in DMSO-d_{6}.

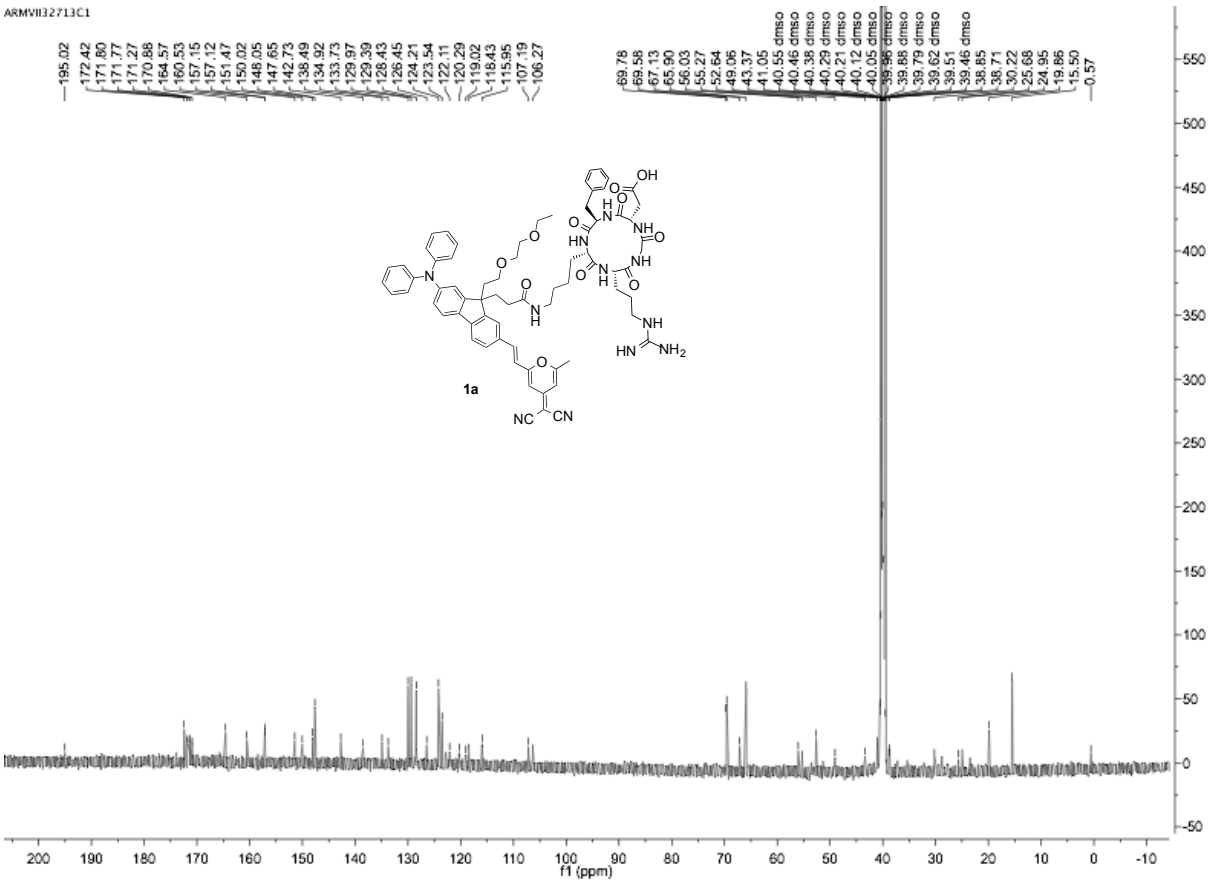

Figure S8. ^{13}C NMR of compound **1a** in DMSO-d_6.

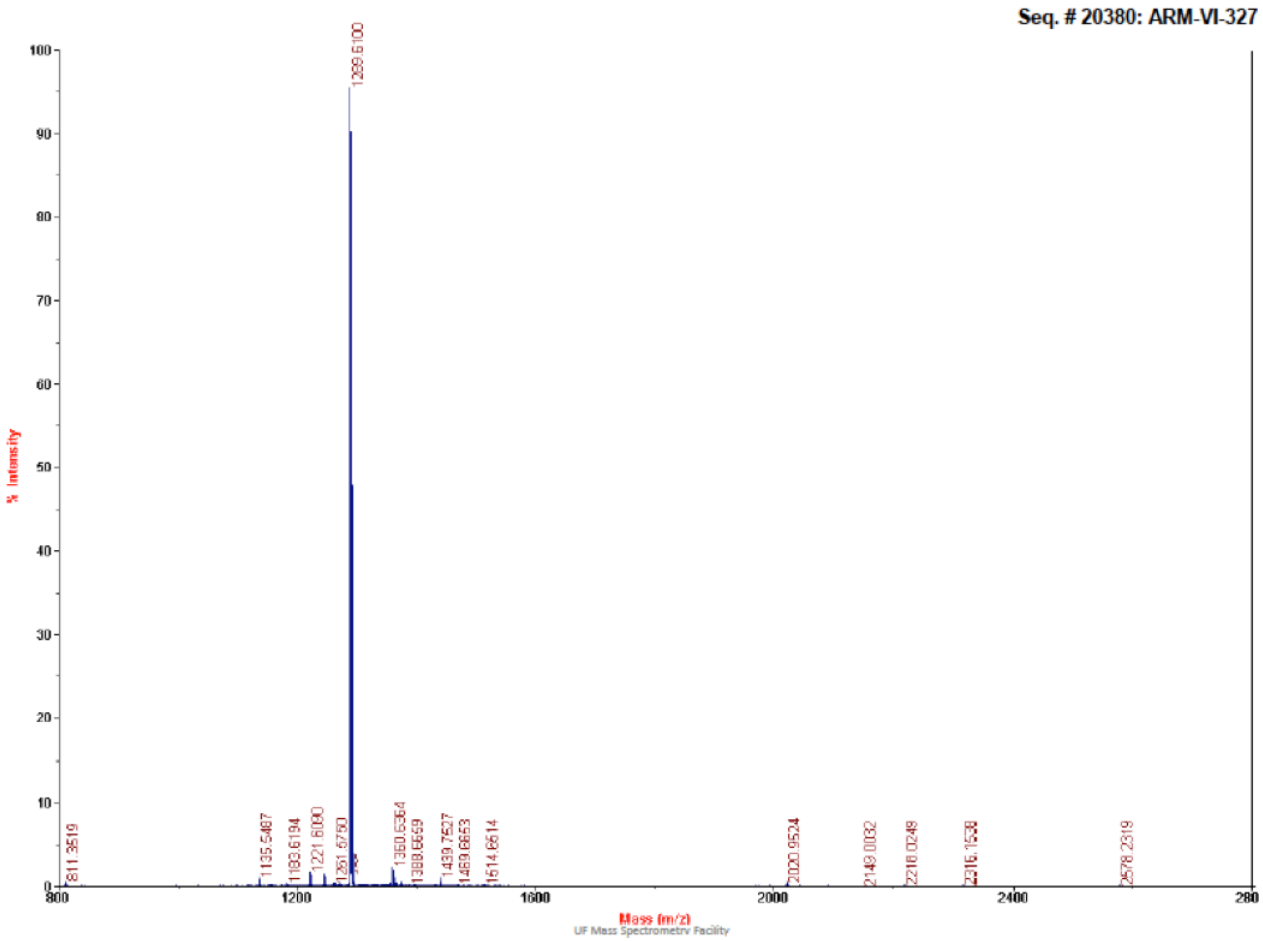

Figure S9. HRMS of Compound **1a**

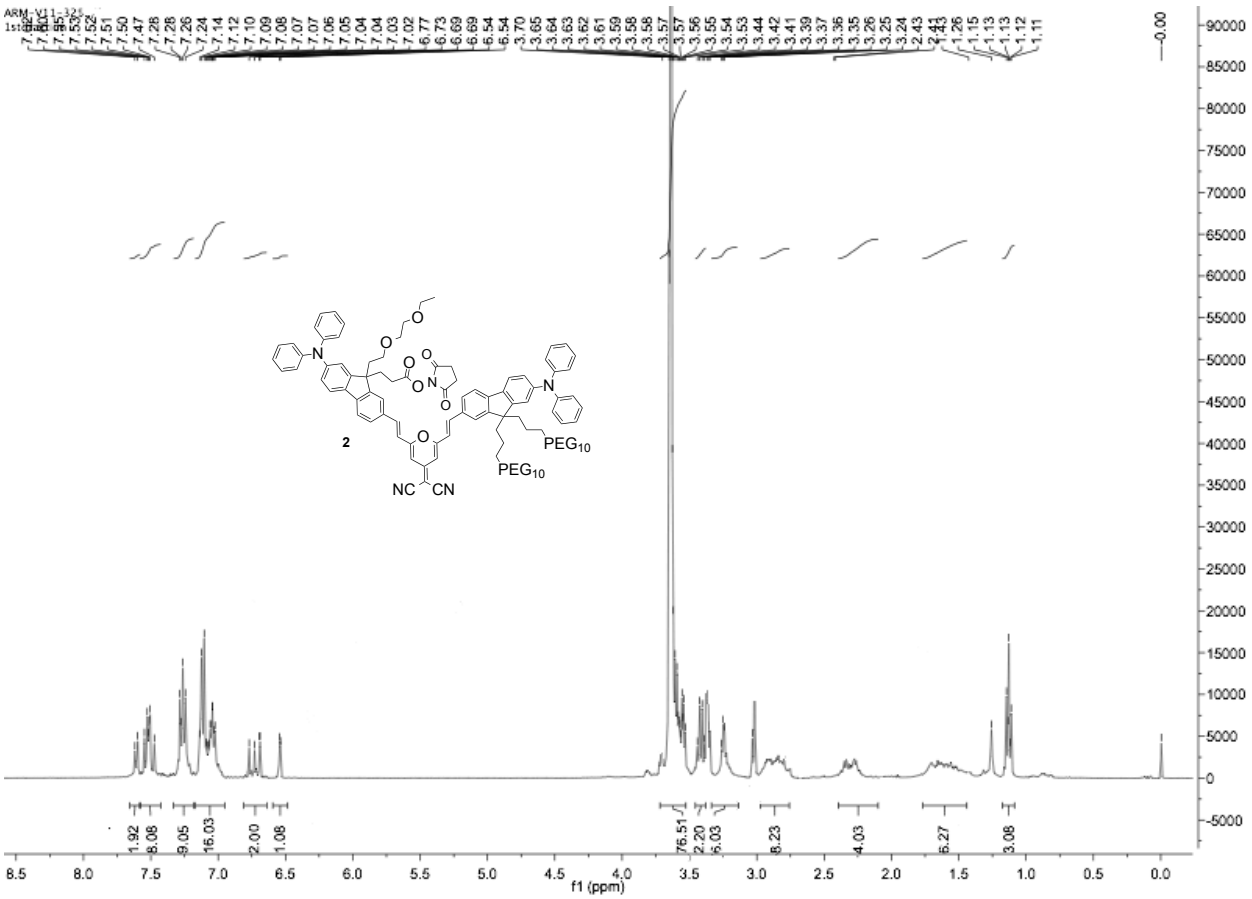

Figure S10. ^{1}H NMR of compound **2** in $CDCl_3$

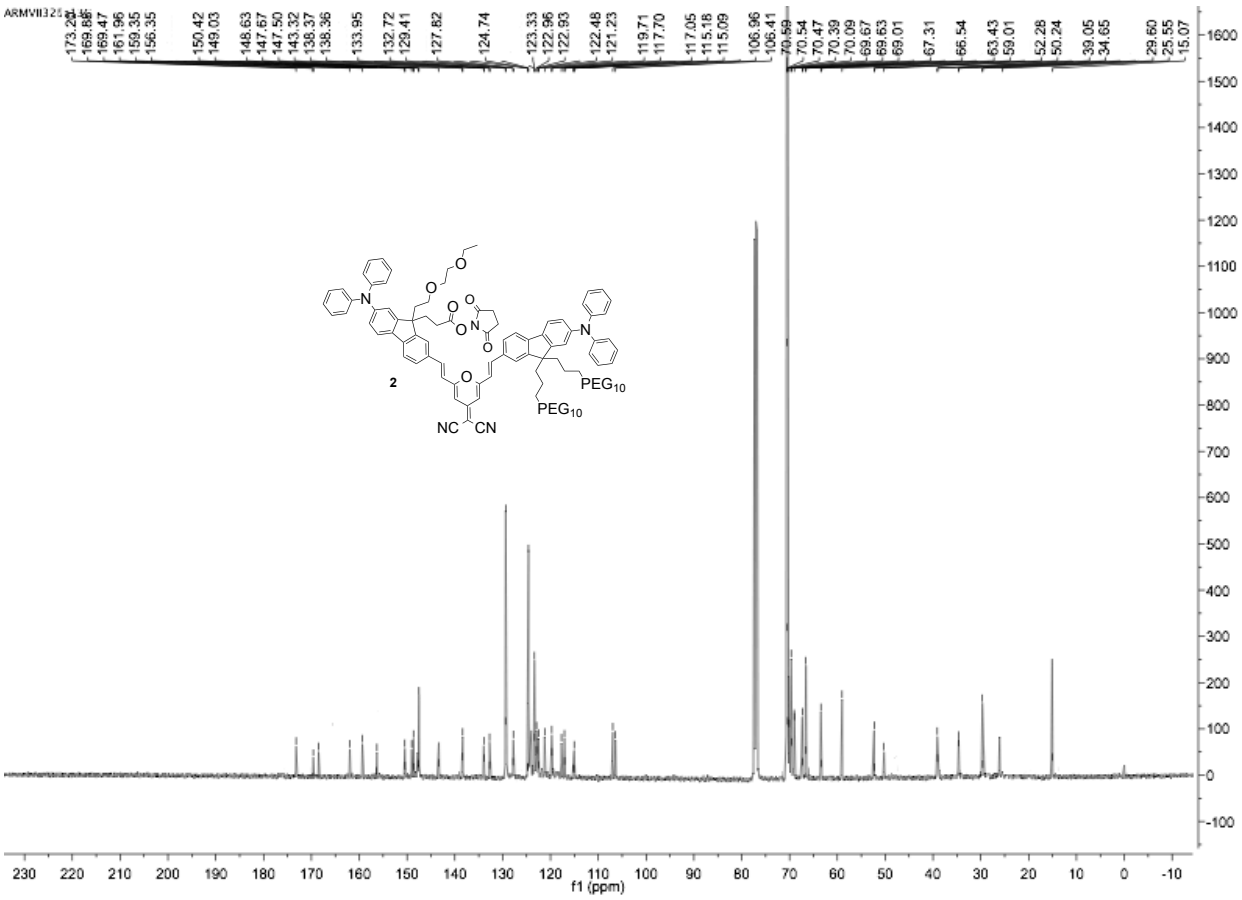

Figure S11. ^{13}C NMR of compound **2** in $CDCl_3$

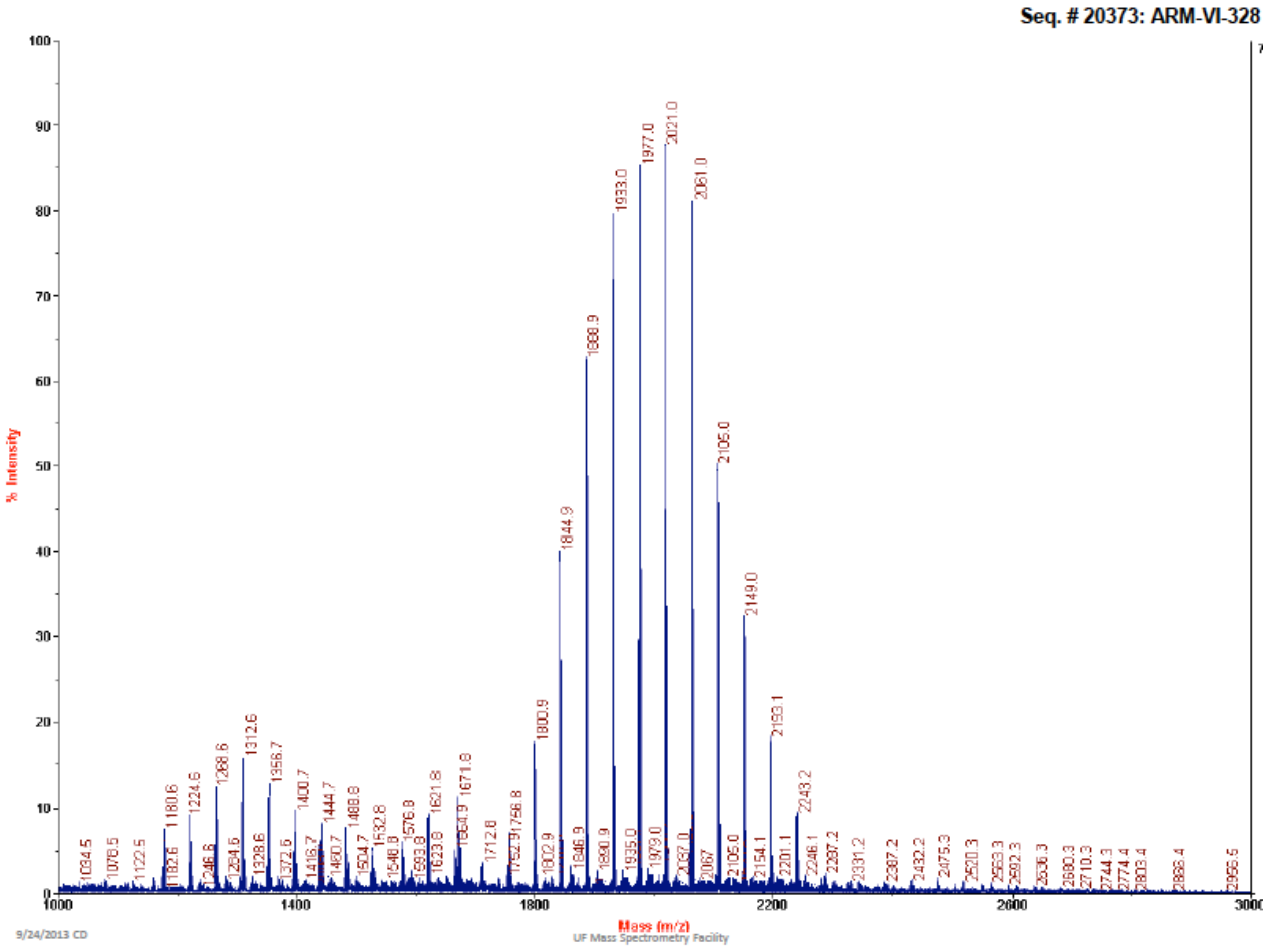

Figure S12. HRMS of Compound **2**

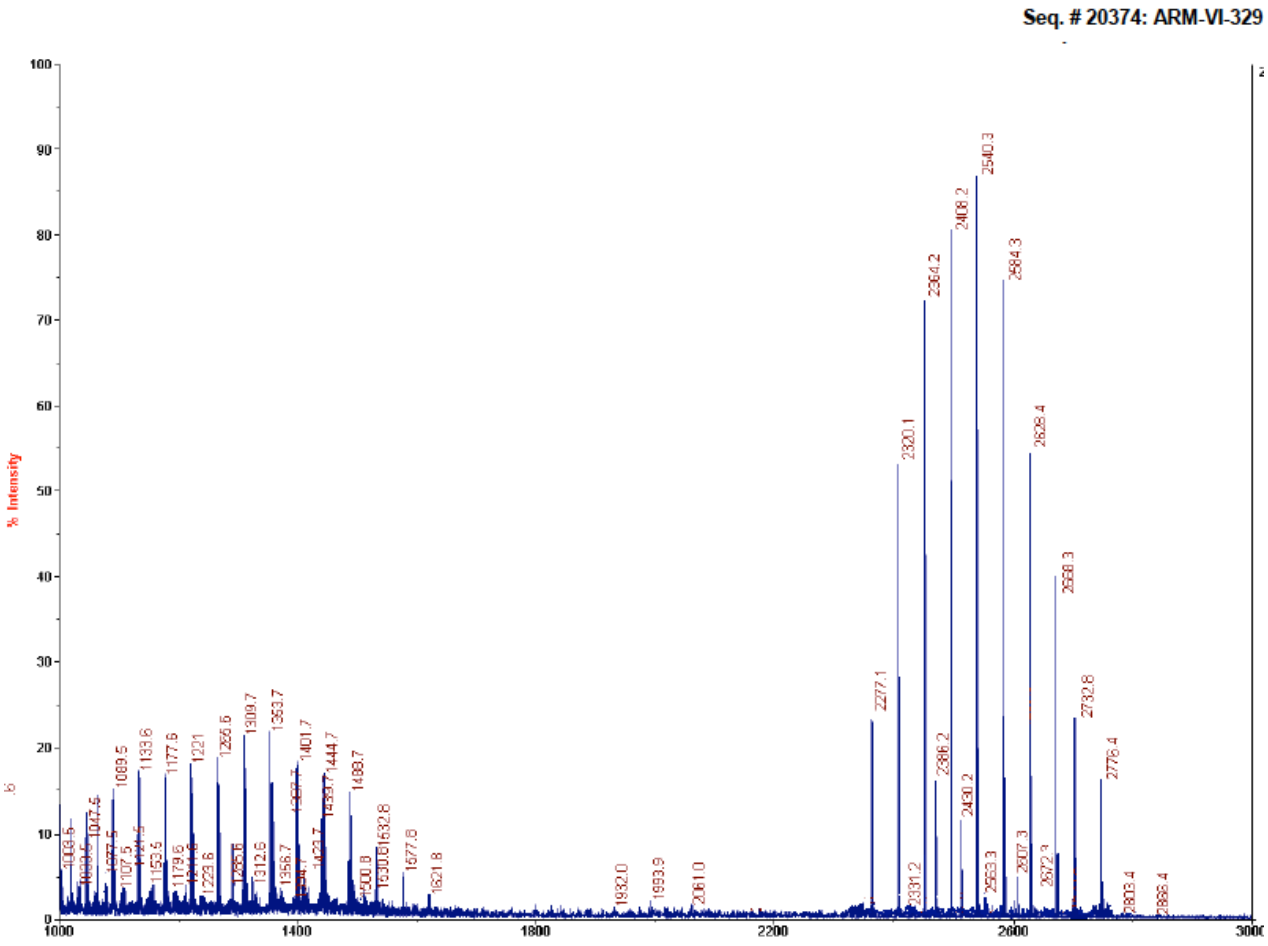

Figure 13. HRMS of Compound **2a**

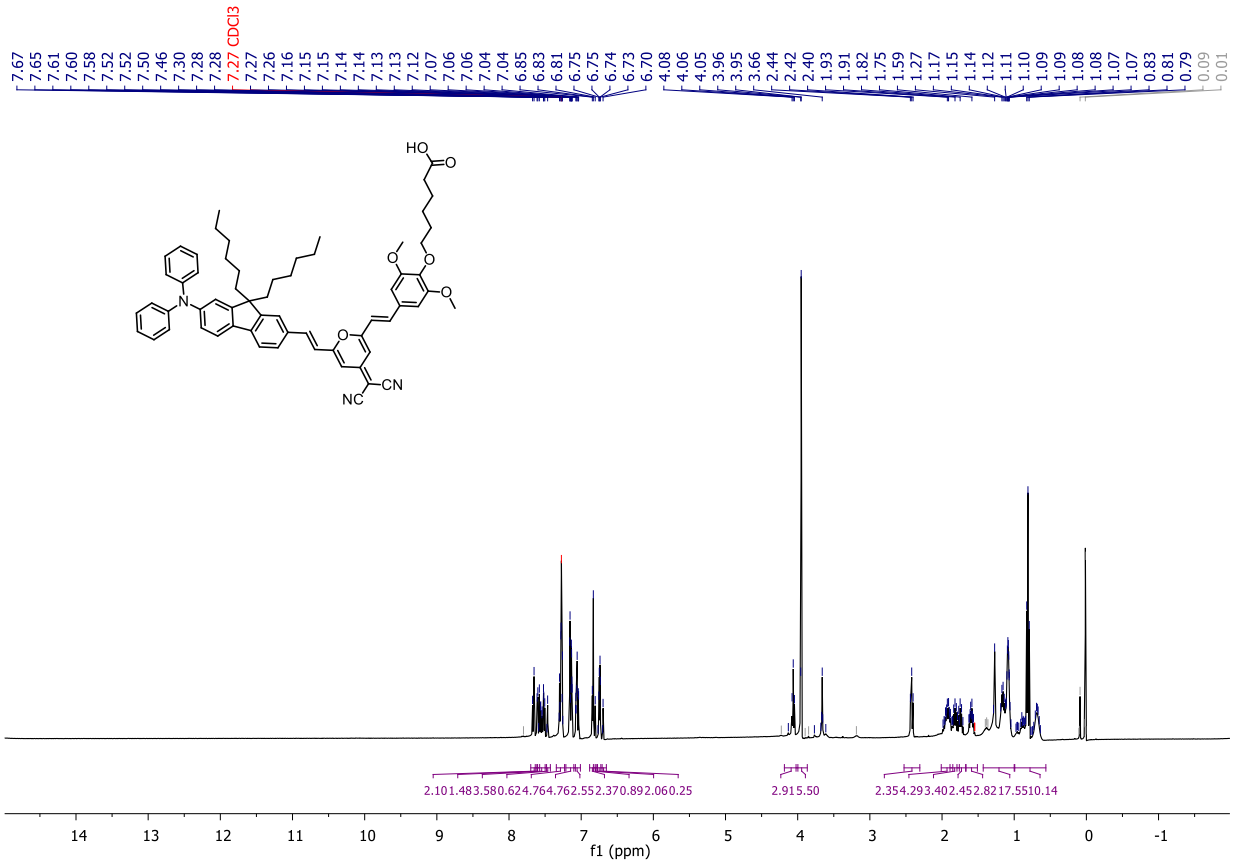

Figure S14. ^{1}H NMR of compound **3** in $CDCl_3$.

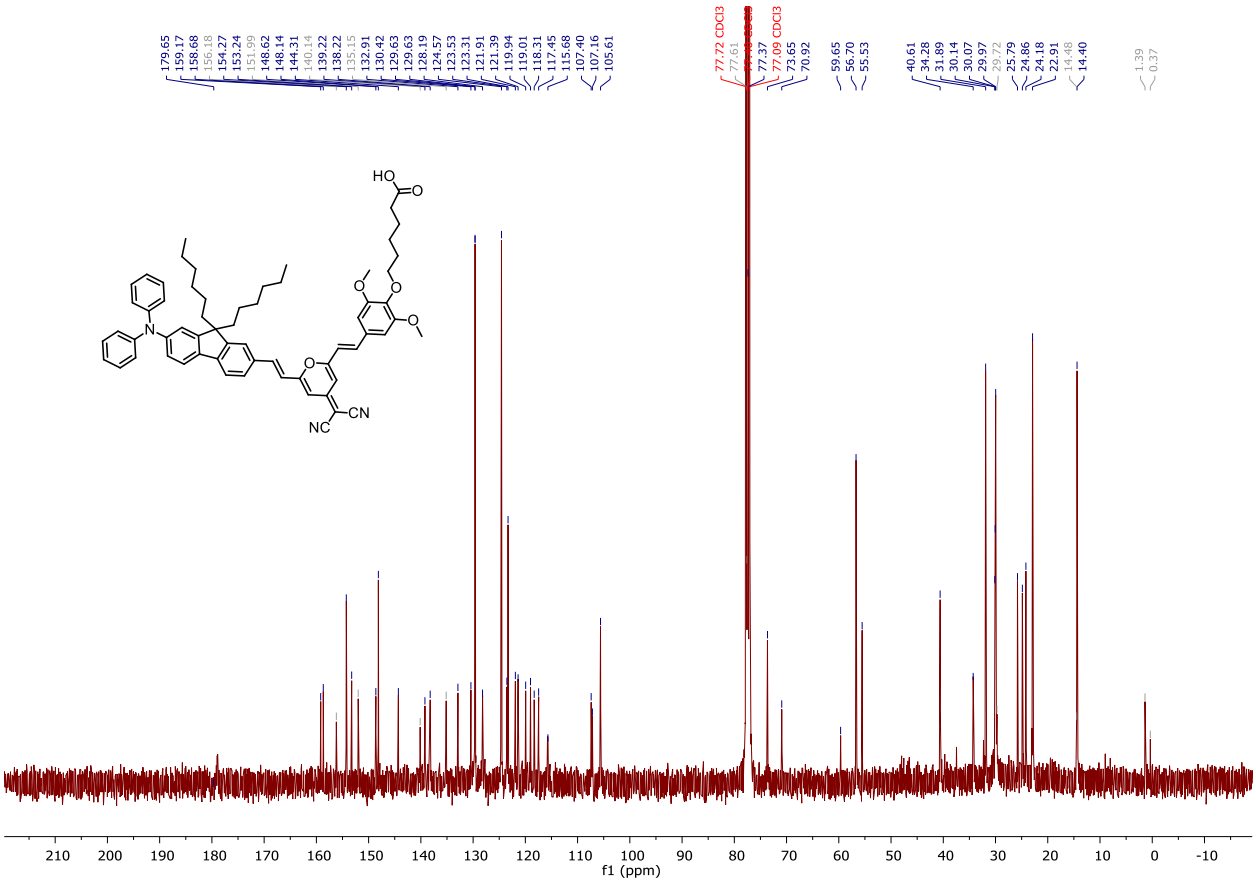

Figure S15. ^{13}C NMR of compound **3** in $CDCl_3$.

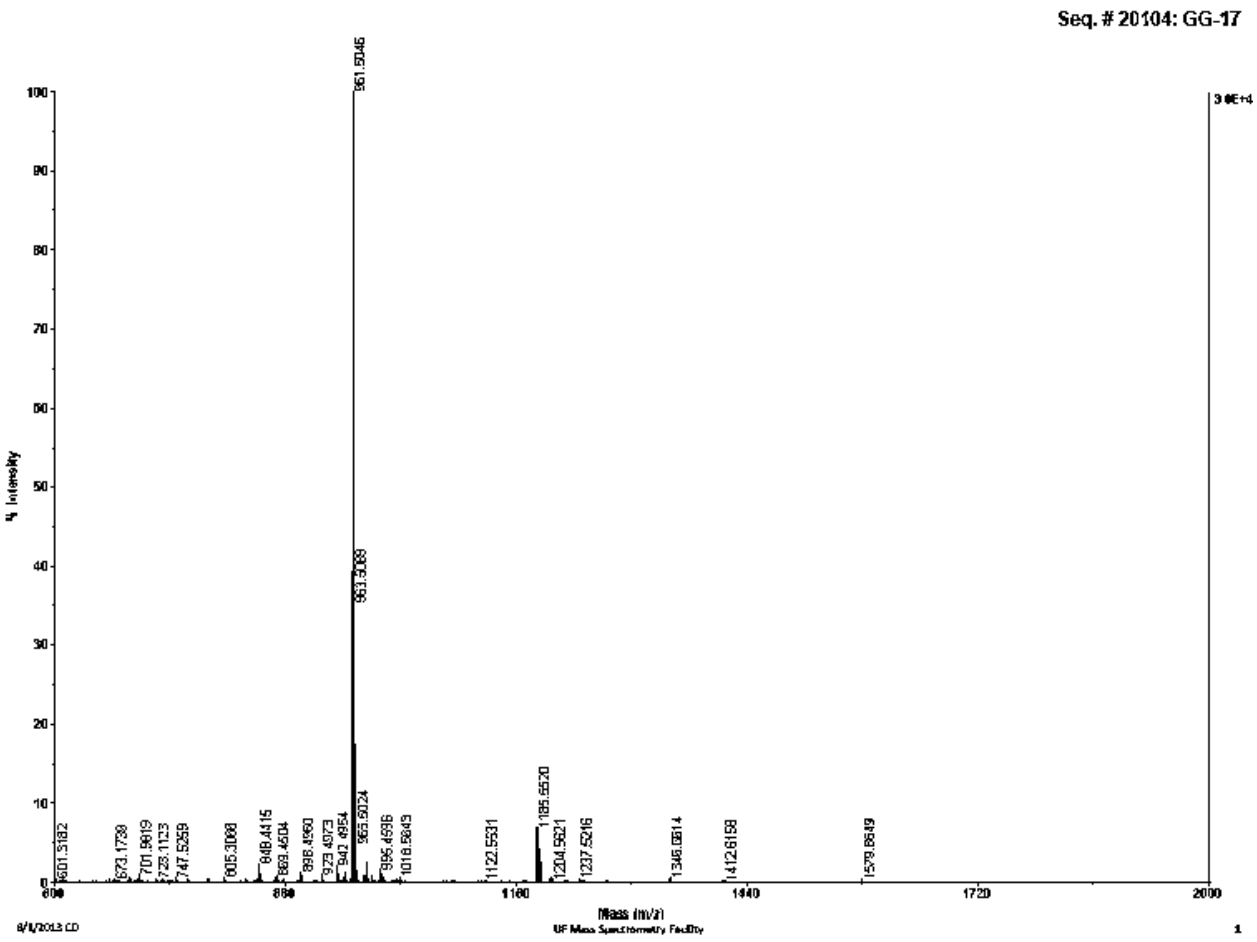

Figure S16. Mass spectrum of compound **3**.